LEE A. FLEISHER • STANLEY ROSENBAUM

COMPLICATIONS IN ANESTHESIA

THIRD EDITION

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All experienced educators realize that those whom we teach are also our own most enthusiastic and involved teachers. So we dedicate this volume to our residents at Penn and Yale, who have been our students, our teachers, and our colleagues.

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Preface

"Complications are the natural byproduct of the search for perfection"

The third edition of *Complications in Anesthesia,* like the two previous editions, is designed to provide practitioners of anesthesia and critical care medicine with a comprehensive source of information for a large number of complications they might be faced in clinical practice. The first two editions were edited by John L. Atlee, MD, who established an outstanding framework for addressing complications using a highly structured format of a case synopsis, problem analysis, management, and prevention. In the current edition, the chapters have been grouped into Preoperative Conditions, Procedure-Related Complications, Intraoperative Agents and Potential Complications, Equipment-Related Complications, Perioperative Events, and Pediatric Perioperative Events.

While many of these individual chapter topics were covered in previous editions, the vast majority of the authors have changed, and new topics have been added. The editors wish to acknowledge Dr. Atlee and the previous edition authors; some of the chapters were based upon their contributions to the previous edition.

It is our hope that this approach to the treatment of complications in anesthesia and critical care will serve as a reference for those currently in practice and as a tool for residents to learn how to both prepare for and manage complications.

Lee A. Fleisher
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1 Adrenal Insufficiency

Jonathan T. Ketzler • Douglas B. Coursin

Case Synopsis

A 68-year-old, 5-foot 10-inch, 100-kg man develops refractory hypotension toward the end of a laparotomy to remove the left colon because of recurrent diverticulitis and suspected peridiverticular abscess. The patient remains intubated at the end of the procedure and is taken to the intensive care unit (ICU), where a pulmonary artery catheter is placed and transthoracic echocardiogram (TTE) is obtained. The pulmonary artery occlusion pressure is 6 mm Hg, systemic vascular resistance is 475 dynes/cm^5, cardiac output is 10 L/min, and cardiac index is 6 L/min/m^2. TTE shows a hyperdynamic left ventricle with end-systolic cavity obliteration, a small hypercontractile right ventricle, and a small inferior vena cava with marked respiratory variations. The patient is mechanically ventilated and has a heart rate of 128 beats per minute in sinus rhythm and blood pressure of 88/42 mm Hg on infusions of norepinephrine 0.1 μg/kg per minute, epinephrine 0.1 μg/kg per minute, and vasopressin 0.03 units per minute. The patient's medical history is remarkable for hypertension and type 2 diabetes chronically treated with lisinopril and glucophage, respectively. Both were withheld on the day of surgery. Shortly after his admission to the ICU, a diagnostic test was performed and a new medication was added to the therapeutic regimen. After several hours the patient was hemodynamically stable and vasopressors had been discontinued.

PROBLEM ANALYSIS

Definition

Adrenal insufficiency (AI) is a relatively rare but potentially life-threatening condition that can be quiescent until unmasked by medical stressors such as sepsis, traumatic insults, hemorrhagic shock, or surgical stress.

Sir Thomas Addison described primary AI in 1855. Approximately a century later Harvey Cushing developed the concept of secondary AI. Causes for primary and secondary AI are listed in Box 1.1.

The hypothalamic-pituitary-adrenocortical (HPA) axis (Fig. 1.1) regulates the amount of cortisol released by the adrenals. The cycle begins with the release of corticotropin-releasing factor (CRF) from the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH then stimulates the release of cortisol from the adrenal cortex at a rate of about 20 mg/day. Cortisol (or a synthetic analog) acts on the hypothalamus to inhibit the release of CRF and on the anterior pituitary to inhibit the release of ACTH. The associated diurnal variation in cortisol release peaks in the morning and midafternoon and then tapers off to a nadir in the evening. Although normal adults secrete about 5 to 10 mg/m^2 of cortisol (or hydrocortisone) each day, during periods of acute stress the adrenal cortex can secrete as much as 100 mg/m^2 per 24 hours.

Primary adrenal insufficiency is rare and is a result of adrenal destruction or surgical resection. Causes include autoimmune etiologies, trauma, hemorrhage, infection, infiltrative disease, or surgical removal. Secondary adrenal insufficiency develops with any process that involves the hypothalamus or pituitary and interferes with CRF and/or ACTH secretion. Tertiary adrenal insufficiency may be brought about by adrenal atrophy due to acute or chronic glucocorticoid therapy. Patients with adrenal atrophy may show no symptoms of AI; however, when subjected to the stress of even modest surgery or acute illness, these patients may develop life-threatening symptoms of AI.

Along with the classification of AI as a primary or secondary process, there is now recognition of absolute or relative AI. Classic Addison disease due to autoimmune destruction of the adrenals is an example of primary, absolute AI. In contrast, the normal stress-induced increase in cortisol production may be blunted during life-threatening illnesses (e.g., sepsis) in some patients owing to relative AI. Alternatively, there may be down-regulation of cortisol binding and adrenergic receptors despite the normal stress-induced increase in steroidogenesis, another explanation for relative AI. Etomidate transiently inhibits normal adrenal steroidogenesis (see Box 1.1) and appears to result in relative AI in critically ill patients. It is no longer used as a continuous infusion for sedation in the critically ill because of its reported deleterious impact on survival. Finally, as illustrated in the case synopsis, relative AI may underlie life-threatening hemodynamic instability. However, if it is recognized as such and treated with stress doses of glucocorticoids, this process may be reversed.

Recognition

The presentation of acute AI varies from a gradual onset over many days in a patient who is not stressed to a sudden fall in blood pressure associated with major stress such as an operation, trauma, or infection. Hypotension associated with AI can be severe and refractory to treatment. Chronic AI can be insidious and nonspecific in onset and remain undiagnosed for months. The prevalence of signs and symptoms associated with AI is detailed in Table 1.1. The most specific sign of primary AI is hyperpigmentation of the skin and mucosal surfaces caused by the high levels of corticotropin resulting from decreased cortisol feedback.

BOX 1.1 Causes of Adrenal Insufficiency

Primary Adrenal Insufficiency

- Autoimmune
  - Polyglandular autoimmune syndrome types I and II
- Infectious
  - Tuberculosis
  - Histoplasmosis
  - Blastomycosis
  - Coccidiomycosis
  - Cryptococcosis
  - Human immunodeficiency virus
  - Cytomegalovirus
  - *Mycobacterium avium-intracellulare*
  - Cryptococcus
  - Toxoplasmosis
  - Kaposi sarcoma
- Fibrosis
- Infarction
- Adrenal hemorrhage
  - Waterhouse-Friderichsen syndrome
  - Lupus anticoagulant
  - Antiphospholipid antibodies
  - Immune thrombocytopenic purpura
  - Heparin induced
  - Thrombocytopenia
  - Anticoagulants
- Metastatic disease
  - Lung
  - Gastric
  - Breast
  - Malignant melanoma
  - Lymphoma
- Drugs
  - Decreased steroid synthesis
    - Metyrapone
    - Aminoglutethimide
    - Mitotane
    - Etomidate*
    - Ketoconazole
  - Increased steroid catabolism
    - Rifampin
    - Dilantin
    - Phenobarbital
- Familial
  - Familial glucocorticoid deficiency
  - Adrenoleukodystrophy
  - Adrenomyeloneuropathy
- Iatrogenic
  - Bilateral surgical removal
  - Bilateral embolization

Secondary Adrenal Insufficiency

- Exogenous steroid administration (often referred to as tertiary or iatrogenic)
- Pituitary or hypothalamic diseases
  - Infiltrative tumor (adenoma)
  - Sarcoid
  - Hemorrhage
  - Autoimmune
- Isolated ACTH deficiency
- Surgical
  - Pituitary surgery
  - Removal of a functioning adrenal adenoma

*Still unproven and therefore speculative.
ACTH, Adrenocorticotropic hormone.

Because primary AI (Addison disease) develops from failure of the adrenal gland itself, there is evidence of both glucocorticoid and mineralocorticoid deficiencies. Because secondary AI develops from an interruption of the HPA axis that stimulates the adrenal glands to secrete cortisol, but spares the gland itself, it presents as pure glucocorticoid deficiency. In this case the patient may also have hyponatremia; this is not related to sodium excretion but rather to water intoxication secondary to an elevated level of antidiuretic hormone, as well as a primary defect in free water excretion related to glucocorticoid deficiency.

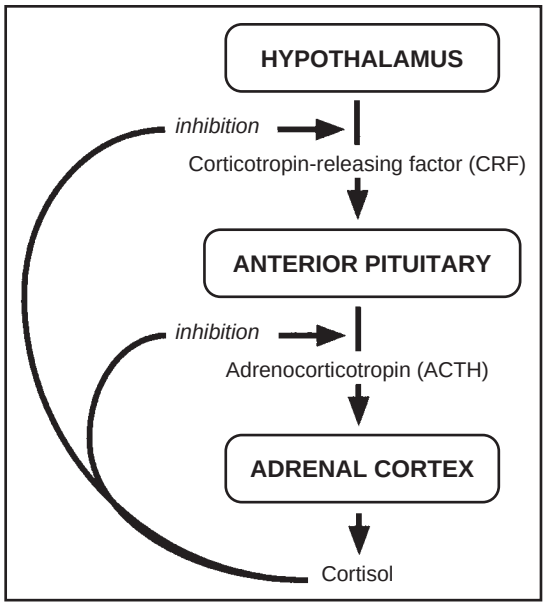

Fig. 1.1 Hypothalamic-pituitary-adrenocortical axis.

TABLE 1.1 Prevalence of Signs and Symptoms of Chronic Adrenal Insufficiency

Signs and Symptoms	Prevalence (%)
Weakness and fatigue	74–100
Weight loss	56–100
Hyperpigmentation	92–96
Hypertension	59–88
Hyponatremia	88–96
Hyperkalemia	52–64
Gastrointestinal symptoms	56
Postural dizziness	12
Adrenal calcification	9–33
Hypercalcemia	6–41
Muscle and joint pain	6
Vitiligo	4

Data from De Rosa G, Corsello SM, Cecchin L, et al: Clinical study of Addison's disease. *Exp Clin Endocrinol* 90:232-242, 1987.

Hypotension can be a common finding in both chronic and acute AI. Hypotension associated with acute AI has been reported as high-output circulatory failure with hallmarks of elevated cardiac output and index, low or normal pulmonary artery occlusion pressure, and decreased systemic vascular resistance. The pathogenesis of such hypotension is unknown but may include a combination of three possible mechanisms: (1) impairment of the direct effect of glucocorticoids on vascular smooth muscle, (2) loss of the "permissive" glucocorticoid effect on catecholamine synthesis and action, and (3) a decrease in the effects of glucocorticoids on vasoactive peptides. Dehydration can also be a factor in the hypotension associated with acute and chronic AI.

Risk Assessment

procedure or severe illness. Patients with certain comorbid diseases such as asthma, inflammatory bowel disease, collagen vascular disease, and rheumatoid arthritis may have received corticosteroids within 1 year, and the HPA axis can be suppressed by a relatively modest dose of exogenous steroids administered for as short a period as 7 to 10 days. Except for low-dose prednisone (less than 5 mg/day) and alternate-day regimens, chronic administration of corticosteroids suppresses the HPA axis, and recovery of its function can take up to 12 months. Normalization of pituitary function comes first; adrenocortical function returns more gradually.

The reported incidence of perioperative AI is between 0.01% and 0.7%. A report by Rivers and colleagues suggested that older patients may have a greater risk of relative AI. The incidence during septic shock also appears to be significant, and steroid replacement therapy has been reported to significantly improve outcome in a selected subpopulation of such patients. The 2013 Surviving Sepsis Guidelines suggest not using intravenous hydrocortisone as a treatment in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, they suggest intravenous hydrocortisone alone at a dose of 200 mg per day without any further testing.

Even though there are ample case reports of hypotension and even death secondary to AI, there are also many reports of patients on chronic glucocorticoid therapy who underwent various surgeries without perioperative glucocorticoid coverage. Most of these patients had uneventful perioperative courses, probably because they had normal perioperative biochemical indices of HPA function. This suggests that a historical assessment of glucocorticoid administration alone is unreliable.

Historically, endocrine evaluation was necessary in patients with suspected adrenal failure. A random screening cortisol level less than 25 μg/dL is abnormal when measured during the stress of an acute illness. A low cortisol level (less than 25 μg/dL) during a stressful illness or following stressful surgery mandates further evaluation. Major trauma and surgical stress usually result in a twofold to threefold increase in plasma cortisol levels, with levels returning to normal 4 to 5 days after the stress. Levels may remain increased if there are complications.

Historically, the cosyntropin stimulation test was the "gold standard" for evaluating adrenal function in critically ill patients. Current recommendations, however, are to initiate treatment especially in refractory septic shock without testing if life-threatening AI is suspected. After injection of 250 μg of cosyntropin, cortisol levels are compared with baseline levels at 30 and 60 minutes. There is controversy regarding interpretation of these tests and even over the amount of cosyntropin used in the test. Because of this, many experts say that if life-threatening AI is strongly suspected, treatment should not be delayed for diagnostic testing. Dexamethasone provides glucocorticoid coverage without interfering with cosyntropin studies.

Implications

An acute adrenal crisis can occur spontaneously or in response to significant emotional or physiologic stress. Stressors may include extreme psychological stress, trauma, withdrawal from alcohol or opioids, infection, general anesthesia, or surgery. During such times of stress, the patient is unable to secrete adequate amounts of cortisol to maintain hemodynamic stability.

MANAGEMENT

Because AI can progress rapidly, early recognition and intervention are essential to improve outcome. Adrenal crisis is a medical emergency, and treatment cannot be delayed for extensive diagnostic studies. Therapy is directed toward rapidly increasing the circulating levels of cortisol. Without such treatment, even symptomatic treatment for volume depletion and electrolyte imbalance is inadequate.

If AI is suspected, serum electrolytes, complete blood count, glucose, blood urea nitrogen, and creatinine are analyzed to assess for sodium depletion, potassium retention, and hypoglycemia.

During adrenal crisis, patients can lose up to 20% of their circulating intravascular volume. This can result in hypovolemic shock and tissue hypoperfusion, both of which can lead to lactic acidemia. Therefore rapid infusion of intravenous fluid is started to correct dehydration and hypovolemia. Normal saline is the initial fluid of choice. Subsequent treatment of electrolyte abnormalities, volume deficits, and hypoglycemia can be guided by laboratory measurements and the patient's response to treatment.

If a patient is known to have AI, replacement therapy should be individualized, depending on the degree of surgical or medical stress. For patients at high risk who undergo major procedures or have life-threatening injuries or illnesses, hydrocortisone 100 mg can be given, with additional intravenous doses of 50 to 100 mg every 6 to 8 hours (see also Chapter 25). Such doses can usually be rapidly tapered as the patient's clinical condition improves. If the patient has no known history of AI, dexamethasone 4 to 10 mg can be given as an intravenous bolus. Dexamethasone does not interfere with the measurement of serum cortisol levels, so diagnostic tests can still be performed. However, because dexamethasone has no aldosterone activity, fludrocortisone, an oral mineralocorticoid, may also be needed, but may interfere with accurate serum cortisol determination.

Patients usually respond quickly to initial therapies, and improvement is usually seen within several hours. Adrenal dysfunction has been shown to be present in as many as 70% of patients with septic shock, and the outcome can be significantly improved with replacement therapy in 20% of such patients. Finally, because 40% to 65% of critically ill patients have high plasma renin activity, previous recommendations did not include the administration of a mineralocorticoid. Based on more recent data, some experts now advise the addition of fludrocortisone 50 μg/day or greater by mouth or enteral tube in patients with sepsis-induced relative AI.

PREVENTION

There are many ways to approach the administration of steroids in stressed patients with suspected adrenal suppression. Some studies suggest tailoring the dose of hydrocortisone to the magnitude of the stress. Others advocate testing the HPA axis in patients at risk for AI. This is done using the cosyntropin stimulation test, which is easy and safe. However, there is controversy over how to interpret the test and even over what dose of cosyntropin to use. Some advocate the use of a more physiologic dose (e.g., 1 μg) instead of the currently recommended 250 μg for stimulation. Because the risk of steroids is so small in most stressed patients, most authorities suggest the use of stress doses in any patient at risk for AI. Because cortisol production under extreme stress is as great as 200 mg/day, hydrocortisone can be administered in 50-mg intravenous doses every 6 hours for 2 days or as a continuous infusion of 200 mg/day for 2 days (see also Chapter 25). In the absence of continued stress, these doses can be tapered to 50 mg every 8 hours for 1 to 2 days and then stopped, or continued at 25 mg every 8 hours for 1 to 2 days and then stopped. How steroids are tapered must be determined on a case-by-case basis, depending on the amount and duration of stress in patients with likely adrenal suppression. Finally, some have reported better outcomes with weight-related dosing for the treatment of chronic AI.

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2 Alzheimer's Disease

Robert A. Whittington • Roderic G. Eckenhoff

Case Synopsis

A 78-year-old woman, living independently at home, falls and sustains a hip fracture. She is admitted to the hospital, and the medical history reveals only hypertension, for which she takes hydrochlorothiazide. Cleared for surgery, she undergoes a 3-hour hip arthroplasty under general endotracheal anesthesia with isoflurane with no complications. She experiences moderate blood loss (900 mL) but no episodes of hypotension or hypoxemia. After extubation, she is noted to be delirious in the postanesthesia care unit. Her delirium waxes and wanes over the next 24 to 36 hours, and she is discharged to a rehabilitation facility on postoperative day 5. Her course in rehab is difficult, with the staff noting depression, forgetfulness, and inattention. Her family describes her as being "very different" from before her fall, although they do admit, in retrospect, that she had been getting a "little forgetful." She is discharged to home, where it becomes apparent that she cannot perform the activities of daily living, and she is transferred to an assisted care facility. After 6 months, with no improvement, and a formal evaluation by a geriatric neurologist, including a lumbar puncture for cerebrospinal fluid (CSF) biomarkers, she is diagnosed with dementia of the Alzheimer type.

PROBLEM ANALYSIS

Recognition

Older patients present for surgery with a number of preexisting comorbidities, and among the most common are the age-related neurodegenerative disorders. There are a large number of these disorders, often with overlapping neuropathology and symptomatology, but Alzheimer's disease (AD) is the most prevalent. It is estimated that 10% of Americans over 65 years of age have AD, and 30% of those over 85 have the disorder. The neuropathology responsible for the disease is thought to start more than 20 years before diagnosis. For example, in the earliest stages, the protein amyloid beta begins to aggregate extracellularly in specific areas of the brain. This can occur slowly over years and is thought to gradually deplete the levels circulating in the CSF—forming the basis of one of the primary diagnostic tests for AD. At some stage the amyloidopathy begins to promote tau detachment from microtubules and its aggregation into intracellular filaments called neurofibrillary tangles. This latter process appears to be more cytotoxic than the amyloidopathy and is associated with both enhanced neuroinflammation and cell loss (neurodegeneration). The excess tau, perhaps released from dying neurons, ends up in the CSF forming the other feature of the CSF diagnostic test. Only at this later stage, when there is clear tauopathy and significant cell loss, apparent on magnetic resonance scans as thinning cortical and hippocampal gray matter layers, do changes in cognitive ability become noticeable.

Cognitive changes are noted initially in memory and executive function, but extend to other domains as well as sensory function as the neurodegeneration progresses. Clinically, AD is divided into two primary stages: mild cognitive impairment (MCI) (termed *mild neurocognitive disorder* in DSM-5) and Alzheimer's disease (AD) or dementia (termed *major neurocognitive disorder* in DSM-5). Each of these stages is being further divided based largely on recent advances in biomarkers. Diagnosis and staging is currently based on three primary modalities: neuropsychological testing, CSF biomarkers, and amyloid positron emission tomography (PET). Newer forms of imaging (e.g., tau) and perhaps blood-based biomarkers will add significantly to the diagnosis and staging in the near future.

This scenario represents the progression of the "late-onset" or sporadic form of AD, but a much rarer form is observed in people 30 to 50 years of age, almost always due to specific mutations in elements of the amyloid pathway. There exist other genetic risk factors for early acceleration of the sporadic form of AD, most notably the ApoEε4 allele.

The neurodegenerative disorders present two primary sets of concerns in the perioperative setting. The first regards the changes in management required for the patient with neurodegeneration, and the second regards the impact of the perioperative period on the trajectory of disease neuropathology.

MANAGEMENT

Preoperative

The first issue involves informed consent. If the patient already carries a diagnosis of AD or major neurocognitive disorder (NCD), the consent will be provided by a spouse, family member, or other authorized caregiver. However, a large number of patients will carry a diagnosis of MCI or mild NCD, or simply be undiagnosed. Before attempting to obtain informed consent from the AD patient, the anesthesiologist must make sure that any readily correctable hearing and visual deficits are treated before proceeding with this important assessment and discussion. Although currently rarely done, administration of a screening assessment might be considered for all patients over age 65. Patients who fail the screen should then be more fully evaluated and consent obtained as indicated by the diagnosis. Information on preexisting

cognitive function is also essential as it has been found to be the strongest predictor of delirium and postoperative NCDs. Should time exist, the concept of *prehabilitation*—a program of exercise, nutrition, and socialization—may be useful to optimize both cognitive and functional outcomes. Medications, including cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and/or memantine, should be continued.

In addition, it is not uncommon for many of these patients to be treated with a variety of antidepressants, antipsychotics, anticonvulsants, and mood stabilization medications. Hence, given the high probability of polypharmacy in these patients, it is imperative that the anesthesiologist consider interactions between these medications and various anesthetics, sedatives, and adjunct medications used during the perioperative period.

Intraoperative

Intraoperatively, evidence for optimal anesthetic approaches is weak at best, although some evidence suggests that total intravenous anesthesia has a lower risk of poor cognitive outcomes. The AD patient is thought to be more sensitive to all anesthetics, although few rigorous studies have appeared. Electroencephalographic monitoring of sedation depth remains controversial, but many studies suggest that avoidance of deep anesthesia reduces delirium and postoperative neurocognitive complaints. Drugs to avoid include benzodiazepines, diphenhydramine, certain psychotropics such as haloperidol, and central anticholinergic drugs. Should sedatives be required, the α_2-adrenergic agonist dexmedetomidine may be better tolerated. Because a presumed mechanism of neurodegeneration is neuroinflammation, antiinflammatory drugs such as dexamethasone have been tested in clinical trials, but without any evidence of benefit.

Avoidance of abnormal physiology (hemodynamics, gas exchange, metabolism, hypothermia) may be more critical in these patients because of the lack of reserve and blunted compensatory mechanisms. Some investigators have advocated the use of cerebral oximetry or blood flow devices toward this end. Nontherapeutic hypothermia should be avoided, as this can potentiate the central nervous system–depressant effects of anesthesia; furthermore, preclinical studies have demonstrated that hypothermia can increase tau phosphorylation and perhaps even accelerate neurofibrillary pathology.

Postoperative

Postoperatively, aggressive remobilization, sensory restoration (e.g., eyeglasses, hearing aids), resocialization (e.g., family members), and the insurance of sleep and nutrition are thought to accelerate return to normal functional and cognitive activities. Those patients with preoperative cognitive impairment are at highest risk of needing these interventions. Beneficial pharmacologic interventions, other than resuming their preoperative regimen, have not been reported. Protocols for the minimization of delirium are available and should be followed as possible.

Effect of the Perioperative Period on the Trajectory of Neurodegeneration

The preceding discussion deals primarily with the perioperative implications of taking care of patients with neurodegenerative diseases. There is another side to this discussion: Is the perioperative period itself a risk factor for the acceleration or subsequent development of AD? This remains an open, controversial topic. Over the last decade, there has been a steady increase in preclinical in vivo and in vitro evidence demonstrating that anesthesia and surgery can each independently affect the amyloid, tau, and apoptotic pathways mentioned in the background section.

Despite this preclinical evidence, definitive high-level epidemiologic evidence demonstrating that anesthesia and surgery actually lead to the subsequent progression of AD in humans has not been reported. Indeed, the literature on this topic is primarily defined by multiple retrospective studies that both support and refute an association between surgery and anesthesia and subsequent AD. These clinical data should be interpreted with caution, as many of these studies have low statistical power, lack randomization, and lack adequate, well-matched control groups.

Nevertheless, there have been some small, prospective clinical studies demonstrating postoperative changes in CSF levels of Aβ and tau; moreover, some of these biomarker changes have been demonstrated to mimic levels observed in patients with known AD. Again, these studies are characterized by the same weaknesses as previously mentioned, so clinical relevance is still uncertain. Nevertheless, expected advances in biomarker technology should allow the impact of anesthesia and surgery exposure on the progression of AD to be determined.

Aside from the consent issues touched on earlier, there is the additional issue of whether to inform patients and their families that the perioperative experience may actually worsen their cognitive abilities. Although the evidence for persistent cognitive decline (more than 3 months) is not strong, it is likely to be of higher incidence than many of the risks that patients are routinely informed of, such as stroke, myocardial infarction, and death. Therefore we believe that patients and their families should be forewarned that cognitive abilities may decline postoperatively, that the causes are multifactorial and unclear, but that in the majority of cases it resolves in weeks to months.

In summary, the patient with MCI or Alzheimer's disease represents a significant challenge for perioperative care. At the least, screening assessment of cognition for patients older than 65 should routinely occur, and all patients should be informed of the risk of cognitive disorders postoperatively. Patients with existing neurodegenerative diseases should be considered vulnerable to many aspects of perioperative care, especially postoperative delirium and other cognitive disorders, and should be aggressively remobilized and reoriented in the postoperative period. No specific intraoperative measures or drugs have been validated with level 1 evidence as constituting best practices.

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3 Chemical Dependency: Nonopioids

Mark S. Gold • William S. Jacobs

Case Synopses

Alcohol

Dr. P is a 60-year-old white male anesthesiologist with a 40-year history of alcohol abuse. Five years ago, he was questioned about alcohol on his breath before starting an 8:00 AM case. He immediately took a blood alcohol concentration (BAC) test, which was below detectable limits, and proceeded with the case. Two years later, the operating room staff thought they detected the smell of alcohol on his breath; that time, his BAC was 0.12. Dr. P denied having had anything to drink since midnight but admitted to drinking vodka tonics the night before. He was referred to the state physician's health program (PHP), where he was evaluated by an addictionologist certified by the American Board of Addiction Medicine. Dr. P successfully completed an intensive outpatient program and then entered into a monitoring agreement with the PHP. He actively participated in the facilitated group meetings and attended 12-step meetings but did not get a sponsor or work the steps. Random urine testing was negative until 1 month ago. Dr. P had had three drinks after his wife retired for the night and was selected for a random urine drug screen the following morning. He notified the PHP facilitator of his relapse before the positive result was reported.

Tobacco

Dr. K is a 62-year-old white male anesthesiologist with a 100 pack-year history of cigarette smoking. He has smoked two packs a day since age 12 and has suffered from chronic bronchitis and chronic obstructive pulmonary disease for at least the past 12 years. He has made numerous attempts to stop smoking—including cold turkey, hypnosis, and nicotine patch—without success. He now believes that he is "too old" to quit. He slipped on a wet floor in the operating room last week and fell against the anesthesia machine. Since then, he has had left-sided chest pain at the site of the impact and had a lateral chest film taken today. He read the film himself and saw a cavitating lesion in the right upper lobe.

Cannabis

Dr. B is a 28-year-old black male anesthesiologist who joined a prestigious private practice after finishing his chief residency at a major university anesthesiology program. He immediately became a favorite of many surgeons and operating room staff. He was seen smoking cigars on his way home on a number of occasions. After 6 months in private practice, he purchased a new car that was valued at over $100,000. The following Friday, after finishing his cases and leaving the hospital, he was arrested for misdemeanor possession of marijuana and drug paraphernalia after a police officer saw his car pulled to the side of the road. Dr. B was caught with six rolled "joints." The incident was discovered by his partners within 24 hours, and he was given the option to self-report to the state PHP or have his partners report him to the state Board of Medicine. He was evaluated and found to have a long history of polysubstance dependence that had evolved into cannabis dependence and alcohol abuse. He was treated in a long-term residential treatment program and entered into a 5-year monitoring agreement with the PHP. His license was placed on probation for 2 years after treatment and then restored to unencumbered active status. He returned to private practice after completing residential treatment.

Cocaine

Dr. W is a 44-year-old white male anesthetist who was reported to his state PHP after being seen snorting a white powder, presumed to be cocaine, in the men's room during the hospital Christmas party. He was contacted 2 days after the party and denied any drug abuse. A urine drug screen was requested immediately, and Dr. W reluctantly complied. It was positive for benzyleconine, a cocaine metabolite. Dr. W was not allowed to continue working and, after reporting to his state PHP, had an evaluation by an addiction psychiatrist and was admitted to a residential substance abuse treatment program. After successfully completing the formal program, he entered into a 5-year monitoring and advocacy agreement with the state PHP.

PROBLEM ANALYSIS

Definition

Nonopiate abuse and dependence are common among health care professionals. Alcohol and tobacco are the most commonly abused chemical substances, but marijuana is the most commonly abused illicit chemical substance in the general population.

It is widely believed that tobacco, alcohol, and marijuana are the most commonly abused substances among physicians. Alcohol dependence appears to be as common among physicians as among their age-, sex-, and socioeconomic-matched controls. Cannabis abuse is common among medical students and younger physicians; however, with the aging baby boomers and the recent changes in state laws related to cannabis, the incidence in older physicians is rising. Alcohol dependency is more common among older physicians. Although the abuse of other illicit or licit substances, such as cocaine, is not as prevalent, it may cause significant impairment and have detrimental effects on the lives of health care providers, their patients, and their families. Although the diversion and abuse of prescription drugs by physicians and other health care personnel are also a concern, this problem is not discussed here.

Substance use disorders can have a number of negative effects, including severe medical and legal implications. Chemical dependence can impair function in relation to acute intoxication, drug-seeking behavior, chronic dependence, and substance withdrawal. In this chapter, we focus on the recognition of nonopiate dependence—specifically alcohol, tobacco, marijuana, and cocaine. Also, we consider behaviors associated with such substance use, the diagnosis of dependence, its implications, and the management and prevention of substance dependency.

Recognition and Risk Assessment

Diagnosis

Several screening tests are available for the diagnosis of substance abuse, such as the CAGE and AUDIT programs for alcohol; these have now been modified for marijuana abuse. Clinical diagnosis of substance abuse is often difficult because denial and lying are part of the disease of addiction. Denial is the hallmark of many initial clinical interviews. Physicians may admit to use, but only on occasion. They may quote the *New York Times* or *High Times* to defend their use, as opposed to a respected medical, addiction, or psychiatric text or journal. They may actually say that marijuana smoke is not dangerous to one's health and deny any similarities to tobacco smoking or secondhand smoke. Among health care professionals, direct observation of drug use, possession, inappropriate procurement of drugs, or signs and symptoms of intoxication or withdrawal can help make the diagnosis. The diagnosis of a substance use disorder is based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria. The medical history and physical examination, along with confirmatory laboratory testing, are useful for diagnosis. Although there could be other reasons for changes in personality, family problems, infertility (males), withdrawal from social activities, and impaired ability to perform professional duties, a positive drug test moves a substance use disorder to the top of the differential diagnosis.

Physicians rarely refer themselves to addiction specialists for drug abuse or dependence problems. Laboratory testing is the gold standard for confirming substance use and is also helpful during treatment. Drug testing cannot detect all marijuana, cocaine, or other illicit drug users, however. Random testing does not detect all substances of abuse and may not detect infrequent use. For example, even daily users have only a 50% probability of testing positive in any given month when urine testing is done eight times per year. Urine testing is standard for the evaluation and treatment of substance abuse; detection times for some common drugs of abuse are given in Table 3.1. There have also been advances in the testing of other biologic substrates, including hair, nails, sweat, and oral fluid. Thin-layer chromatography and enzyme-linked antibody testing are the most comprehensive, inexpensive, and widely used drug screening tests, but combined gas chromatography with mass spectroscopy for confirmation is the gold standard for drug testing. Marijuana impairment must be diagnosed with blood tetrahydrocannabinol (THC) concentrations because the usual test for cannabis use screens for THC metabolite, which may remain positive for weeks after regular use. The window of detection for alcohol use may be extended from hours to several days by testing for alcohol metabolites ethylglucuronide and ethyl sulfite in urine. True random drug testing should be a mandatory part of all health care provider health programs.

TABLE 3.1 Substance Detection Time in Urine

Substance	Detection Times
Amphetamines	Up to 24 hours
Barbiturates	5–10 days
Benzodiazepines	5–7 days
Cannabinoids	1–3 days; greater with chronic use
Cocaine	1–3 days
Opiates	1–3 days
Phencyclidine	Up to 3 days

Laboratory tests may also help in the diagnosis of a chronic substance abuse problem, but they are usually performed late in the course of the disease. Heavy consumption of alcohol (e.g., one bottle of wine a day) for a few months almost always results in macrocytosis (mean corpuscular volume between 100 and 110 fL), even before anemia occurs. Alcohol-related liver disease may be reflected in abnormal serum γ-glutamyltransferase, aspartate transaminase, and alanine transaminase levels. In fact, unlike in other liver diseases, aspartate transaminase may be more than two times greater than alanine transaminase when alcoholic hepatitis is present. The Food and Drug Administration has also approved a test that measures serum carbohydrate-deficient transferrin to identify long-term excessive alcohol use.

Alcohol and Tobacco

Symptoms of alcohol or tobacco dependence include the following:

- Impaired control over use
- Preoccupation with obtaining the substance
- Continued use, despite adverse consequences
- Distorted thinking, especially denial of substance dependency
- Development of tolerance to the effects
- Withdrawal symptoms when use is discontinued

Although no specific constellation of symptoms is specific for the diagnosis of alcohol use disorder, physical examination findings consistent with alcohol abuse are elevated blood pressure, evidence of physical harm from falls or accidents, tremors, obstructive lung disease (due to concurrent tobacco use), and unexplained tachycardia, hepatosplenomegaly, or peripheral neuropathy. In contrast to alcohol, the health consequences of tobacco dependence generally take years to develop and are related primarily to lung cancer or chronic pulmonary disease. Quitting smoking has immediate positive health effects, reduces the risk for adverse consequences over time, and increases the smoker's life expectancy (see http://www.cancer.org for more details).

TABLE 3.2 Signs and Symptoms of Acute Cocaine Intoxication and Chronic Cocaine Abuse or Dependence

ACUTE COCAINE INTOXICATION		CHRONIC COCAINE ABUSE OR DEPENDENCE	
Signs	**Clinical Symptoms**	**Physical and Mental Symptoms**	**Behavioral and Social Signs**
Sociability—most users become overly "chatty" at low doses	Blood pressure changes	Anxiety, delirium, depression, hallucinations, insomnia, memory loss, confusion, slurred speech, reflex changes, blackouts, acute vision changes, incoordination, dizziness, tremors, impotence	Car and boat accidents
Hypervigilance	Breathing difficulties	Hypertension, irregular heartbeat, bradycardia	Problems with family or job (e.g., tardiness, absenteeism)
Impaired judgment	Dilated pupils	Bronchitis, lingering colds and flu symptoms, frequent respiratory tract infections	Legal or financial problems
Grandiose thinking and plans	Mental confusion	Bumps and bruises due to falls	Increased reliance on drugs
Increased anxiety and tension	Muscle weakness	Craving for sweets or avoidance, loss of appetite, poor nutrition, liver enlargement	Passive-aggressive behavior, suicidal thoughts or gestures, violent or aggressive behavior, suspiciousness
Quick mood changes	Tachycardia, chest pain	Increased or reduced alcohol or drug tolerance	
Increased libido	Nausea or vomiting	Red, puffy face; red, swollen nasal mucosa	
	Psychomotor agitation or retardation, seizures		
	Sweating or chills		

Cocaine

A number of clinical and behavioral signs and symptoms of cocaine use are usually evident. Some are related to acute intoxication, and others appear after chronic use or during withdrawal (Table 3.2). Although cocaine is more commonly abused as a "street drug" (snorted as powder or smoked as crack), it is also used medicinally as a topical anesthetic and vasoconstrictor (e.g., in awake oral or nasal intubation as well as ear/nose/throat surgery and rarely as a topical local anesthetic in combination with tetracaine and adrenaline). If so, health care professionals may have access to unadulterated cocaine, similar to fentanyl and other highly potent narcotics. Street cocaine is often adulterated or "cut" with other substances that have the potential to cause additional harm.

Marijuana

In the 1960s and 1970s, marijuana was perceived as a safe and natural drug that produced a "high" (euphoria) without the risk of negative side effects or addiction. Some young physicians still do not believe that marijuana dependence is possible and may smoke marijuana more frequently than cigarettes. Dependence on marijuana is related to the THC concentration in its smoke and the duration of use; signs of marijuana withdrawal can be provoked by the administration of a THC antagonist. Today, the THC concentration in marijuana has been increased to produce greater highs and encourage repeat use. Researchers at Harvard and Columbia have shown that with this increased potency, chronic marijuana use can lead to tolerance, dependence (even subhuman animal species will self-administer THC), and a distinct withdrawal syndrome that may not peak for weeks after cessation. Marijuana is now one of the leading substances of abuse in persons referred for the treatment of substance abuse.

As defined in DSM-5, marijuana intoxication begins with a feeling of being "high." Symptoms vary but generally include grandiosity, euphoria, and inappropriate laughter. Acute use also causes difficulty with concentration and complex thought processes; distorted sensory and time perception; lethargy and sedation; and impaired judgment, memory (especially short-term memory), and motor performance. Marijuana use sometimes provokes anxiety and panic, which may require treatment. During and after intoxication, there is generally increased appetite, red eyes, dry mouth, and increased heart rate. High-potency cannabis has been associated with first-case psychosis and significantly increased risk for lifetime psychotic disorders. As these effects subside, there is often depressed mood, anger, irritability, or social withdrawal. Cannabis oil, which is now in clinical trials, appears to be an effective treatment for refractory pediatric seizures as well as psychotic disorders. The long-term health effects of marijuana smoke are difficult to determine because persons who use marijuana often use tobacco products as well. Recent studies have shown, however, that there are many carcinogens in marijuana smoke, which actually has 50% higher levels of tar and carcinogens than tobacco smoke does. Also, case-control studies have linked marijuana smoke to head and neck cancers.

People who become dependent on marijuana usually use it daily, often for months or years. When they try to stop using it, they often cannot do so for longer than 30 days. They are also easily angered by questions about their marijuana use because they are psychopathologically attached to the substance. Often, this has a negative impact on their health, families, and careers. Moreover, they may choose parties, social contacts, or friends on the basis of whether marijuana is going to be available, and they may spend many hours each day thinking about using marijuana and later recovering from the effects. Further, they may smoke cigarettes or take psychostimulants in an attempt to reverse the effects of marijuana on their memory or performance. Dependence interferes with family life and work, but use continues despite the development of chronic problems, such as a smoker's cough or psychological problems (e.g., excessive sedation resulting from repeated use of high doses, anxiety/panic, or even psychosis), or social and legal consequences.

Implications

Maladaptive behavior problems are usually the first sign of chemical dependency. However, these often are not attributed to drug abuse until after an addiction is recognized. Health care professionals are generally better equipped than others to hide and deny substance abuse. Most often, family and social problems related to use occur far in advance of problems on the job. Health care professionals who are using drugs may experience changes in mood, energy level, and the ability to concentrate. They also miss work or arrive late. They may use the drug more often and at inappropriate times, taking more frequent breaks than their colleagues. In addition, they may have alcohol on their breath or smell of tobacco or marijuana smoke. Often family and friends become aware of the drug-seeking, drug-acquiring, and drug-consuming behaviors before patients and other physicians recognize the problems.

Chemical-dependent health care professionals often have problems in their interpersonal relationships, and they are exposed to significant professional risk in terms of medical credentialing and licensure, as well as criminal investigations. A physician might come to attention by propositioning a prostitute or experiencing money problems related to gambling or purchasing drugs. However, these are late-stage behaviors. Early detection requires a high degree of suspicion both at the workplace and at home. Usually deteriorating job performance is

the last thing to be affected, and health care workers use this as a way to deny that they have a drug problem. Common severe complications from drug abuse include accidents, head injuries, memory failure, financial collapse, sexually transmitted diseases, seizures, depression, impulsivity, suicidal thinking, and suicide attempts.

Negative affective symptoms (e.g., anhedonia), depression, and dysphoria are symptoms associated with the cessation of almost all drugs of abuse. The chemical withdrawal syndrome specific to the drug of choice may be another sign of chronic use and dependence. The desire for the drug is probably greatest during withdrawal, because the addicted person wishes to alleviate unpleasant withdrawal symptoms. Health care professionals who abuse or become dependent on drugs have higher rates of depression, which may lead to suicide without intervention and treatment.

Alcohol and Tobacco

Alcohol and tobacco are the most widely used drugs. Alcohol is generally considered safe and may even have a beneficial effect when used in moderation. However, there are no established moderate or safe levels of tobacco use. People who smoke often drink, and those who abuse alcohol usually use tobacco; thus dependence on both alcohol and tobacco is common. Tobacco smoking is the leading cause of death among alcoholics. Alcohol can also be potent and dangerous, causing more death and personal destruction than any other drug except for tobacco. Each year, alcohol misuse causes more than 100,000 deaths and injury to more than 2 million people; tobacco is reportedly directly responsible for more than 400,000 deaths annually.

Cocaine

The pathologic attraction to cocaine can be intense, with many experts agreeing that it is the most intense among the substances of abuse. Although specific medical management of withdrawal symptoms is usually unnecessary, discontinuation is clinically significant and difficult to manage outside of a hospital or other highly controlled environment. Craving for cocaine, anhedonia, feelings of helplessness, and drive for the drug make relapse likely. Animal self-administration models suggest that the amount of work or punishment an animal will expend or endure for a dose of cocaine is greater than for most other drugs.

Once the physician addict discontinues the drug, treatment can begin. We have reported on cocaine sniffing, cocaine injecting, and even crack addiction among physicians. Cocaine addiction is so profound and relapse so common that the DSM had to change the diagnostic criteria to allow addiction to be diagnosed in the absence of significant signs and symptoms of tolerance or physical dependence. Addicted physicians often sign contingency contracts, agree to random and at least biweekly urine testing, and are sent to inpatient and residential treatment facilities.

Marijuana

Possessing, smoking, growing, and purchasing marijuana are all illegal according to U.S. federal law. Physicians who do so are a phone call or two away from losing their licenses. This usually does not occur, however. Their spouses, their children, or angry patients may call an anonymous tip line to report their behavior. Marijuana use may bring doctors into contact with other illicit drugs, leading to further experimentation. Sometimes, marijuana smoking or the use of other illicit substances brings physicians into contact with drug dealers and other criminals. Physicians are usually undertrained for this social network and may be easily blackmailed or robbed by their dealers or new "friends."

TABLE 3.3 Pharmacologic Treatment for Nonopioid Dependency

Substance	Pharmacologic Treatment
Alcohol	Antabuse—deters drinking by causing painful symptoms when alcohol is used
	Naltrexone—likely reduces craving and may reduce pleasurable effects of alcohol
	Acamprosate—reduces craving for alcohol and prevents relapse
Tobacco	Nicotine replacement: gum, patch, inhaler, spray
	Detoxification: bupropion (Zyban, Wellbutrin)—originally prescribed as an antidepressant but now used primarily for smoking cessation
Marijuana	Maintenance: Marinol—in clinical trials
	Antagonist: Rimonblat—in clinical trials
Cocaine	Definitive: none at present
	Supportive: antidepressants, mood stabilizers (e.g., lithium)

MANAGEMENT

Changes in thinking and behavior, along with a positive drug test, are usually taken as definitive evidence of substance abuse by hospital staffs, physician employment groups, and state physician health monitoring programs. Detoxification with management of withdrawal symptoms to abstinence, followed by involvement in 12-step fellowships and therapeutic communities, remain the treatment of choice for professional health care addicts. It is important to note that detoxification/withdrawal management is not sufficient treatment. Numerous treatment programs are designed to meet the special needs of addicted health care professionals. There are also a number of pharmacologic therapies that may be useful in the treatment of alcohol, tobacco, marijuana, and cocaine dependence (Table 3.3). Physicians have the best outcomes when there is long-term follow-up with contingency management, frequent random drug testing, 12-step group attendance, and individual follow-up with a psychiatrist and treatment facilitator.

Alcohol and Tobacco

Both psychosocial and pharmacologic therapies can help in overcoming alcohol and tobacco addiction. Some of these can be purchased over the counter (e.g., nicotine replacements), but others require a prescription. For alcohol, a number of pharmacologic therapies have been approved for use in the United States, including disulfiram (Antabuse), naltrexone, and acamprosate.

Cocaine

Treatment for cocaine dependence includes both residential and outpatient approaches. One primary approach is behavioral intervention. After stabilization, recovery begins with a learning process of breaking old habits, breaking ties with cocaine-using friends, and identifying "triggers" that increase the desire to use cocaine; once these triggers are identified, patients are encouraged to restructure their lifestyles to avoid them. Cognitive-behavioral coping skills provide another alternative that, in the short term, focuses on helping cocaine-addicted individuals become abstinent through a learning process. This therapy is compatible with a range of other treatments, such as pharmacotherapy. Active membership in 12-step programs, such as Narcotics Anonymous and Cocaine Anonymous, is one of the most beneficial tools for continued abstinence from cocaine and other drugs of abuse. For addicted health care professionals, regular random drug testing, a contract with contingencies, and chronic follow-up care improve the

long-term success of treatment. It is imperative that any positive drug tests be promptly identified and that any necessary changes in treatment plans be made quickly. Waiting can be associated with a rapid and complete relapse. Finally, cocaine abstinence and long-term use are associated with depression, suicidal ideation, and suicide attempts; thus cocaine-dependent physicians must be closely monitored.

Marijuana

Treatments under study include use of the synthetic marijuana dronabinol (Marinol). This is similar to the use of methadone for heroin addicts. Cannabidiol may be beneficial in reducing withdrawal and reducing THC-induced high. Relapse prevention is an important factor in the successful treatment of marijuana dependence. Recovering addicts must change their behaviors and be able to resist social and environmental cues for continued drug use. Psychosocial treatments, such as cognitive-behavioral therapy, can be successful. Pharmacologic therapies under study may be useful as maintenance therapy.

PREVENTION

Prevention of substance abuse and dependence starts with abstinence—that is, no experimentation. Physicians are well educated and are therefore used as examples of the limitations of knowledge as a protective factor against addiction. Drug use, abuse, and dependence are now observed in medical students and house staff, not just in older practicing physicians. Physicians who have learned to balance their lives and manage their stress, anxiety, and workplace problems without drugs should mentor medical students to help them learn to do the same. Addiction among health care professionals is a significant public health problem that requires intervention. The health care professions must be considered safety-sensitive positions, similar to airline pilots. Without treatment, addiction leads to harm to self, family, and patients. At least 15% of all physicians will become markedly impaired sometime during their careers; however, there continues to be a dearth of research on the primary prevention of substance abuse and dependence among health care providers.

Generally, the best way to prevent drug dependence is to prevent drug use in the first place. For example, there is a strong genetic risk for alcohol dependence among those who have a positive family history, especially among first-degree relatives. Such persons should refrain from using alcohol. Prevention of exposure to drugs and drug use during early childhood and adolescence is key to reducing later dependence. Prevention efforts and appropriate training should also be a focus in medical schools and other health care professional educational programs to minimize the risk of future chemical dependency problems. If primary prevention has failed, there is still the opportunity for early intervention. Random drug testing while in training can act as a deterrent to initial use just as it has been shown to do in the military and Department of Transportation. Some leading institutions, such as Massachusetts General Hospital, have incorporated random testing into their substance abuse policy and now routinely test residents and house staff.

Even if dependence has developed, we know that treatment works, especially for physician addicts, who have remarkably positive 5-year outcomes. Treatment can prevent or reduce the incidence of a number of adverse health outcomes.

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Chemical Dependency: Opioids

4

Mark S. Gold • William S. Jacobs

Case Synopsis

A 38-year-old anesthesiologist is found unresponsive and cyanotic in the call room after failing to return from a break in the case of a patient undergoing a craniotomy for tumor. Both fresh and recent venipuncture sites are found on his left forearm, along with a 1-mL insulin syringe and a rubber tourniquet.

PROBLEM ANALYSIS

Definitions

The American Medical Association defines an impaired physician as "one unable to fulfill professional or personal responsibilities due to psychiatric illness, alcoholism or drug dependency." This definition is in stark contrast to that for a professional athlete or a pilot, who is defined as impaired if "he or she is unfit for duty, shows up at work under-the-influence, or with residual effects."

Recognition

Although drug testing is not mentioned in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), it is used to support clinical diagnosis because in addictive disorders, history from the patient is unreliable. A medical history with collateral information and physical examination coupled with confirmatory laboratory testing are needed to diagnose drug addiction. Direct observation of a health professional using drugs, obviously under the influence, diverting drugs as evidenced by inappropriately carrying or procuring drugs, or having withdrawal symptoms should trigger such an evaluation. The intensity and timing of opioid withdrawal depends on the particular opioid used and the dose and frequency of use. Abrupt withdrawal from opioids usually results in yawning, runny nose and eyes, anxiety, diffuse body aches, sleep disturbances, nausea, vomiting, diarrhea, goose flesh or piloerection, dilated pupils, diaphoresis, increased vital signs (pulse rate, respiratory rate, blood pressure), and a delusional fear that death will occur without opiates. These symptoms are associated with a very strong drive for the drug. Many anesthesiologists initiate opioid use taking them orally or snorting diverted liquid opioids but usually rapidly progress to intravenous use. Track marks and other physical evidence of parenteral use may be found on examination of an opioid-addicted anesthesiologist. Most anesthesiologists, however, are quite adept at using small-gauge needles and finding discreet intravenous injection sites. Because of a "conspiracy of silence," often loved ones, physicians, and other professional colleagues will be in denial themselves that opioid addiction is the explanation for the aberrant behavior that the addict exhibits. Frequently the addiction will progress until an overdose situation leaves no other explanation. Addiction medicine professionals and experienced addicts recognize that a protracted withdrawal syndrome, which may last for months and include episodes of sweats, night terrors, dysphoria, drug craving, and malaise, generally follows the acute withdrawal phase with its dramatic symptoms.

Laboratory diagnosis is the gold standard for confirmation of drug use. Drug testing is available and reliable when the correct methodology is used and the correct specimen for the particular opioid being abused is tested. Urine is the most commonly tested specimen. Point-of-care immunoassay testing provides immediate presumptive screening results. Thin-layer chromatography is the most inexpensive and commonly used comprehensive test. Gas chromatography with mass spectroscopy is the most exact confirmatory testing method. Hair or nail testing provides a much longer window of detection of drug use and should be part of comprehensive evaluations of suspected opioid-addicted anesthesiologists, especially if urine testing results are negative. It is crucial to specifically request testing for synthetic opioids such as fentanyl and its analogs because the usual standard drug test for opiates only screens for morphine, codeine, hydrocodone, and hydromorphone.

Risk Assessment

Opiates have been important analgesics and drugs of abuse for centuries. With the availability of parenterally administered opiates and the invention of the hypodermic syringe, opiate addiction and withdrawal distress became major issues following the American Civil War, with morphine addiction being known as soldier's disease. The shift in the prescribing paradigm for oral opioids in this country from the mid-1990s through the present has created a full-blown opioid epidemic. Drug addiction is a disorder characterized by craving, compulsive drug use, continued use despite adverse consequences, and relapses or failed attempts to cut down with tolerance and withdrawal symptoms with cessation of drug use especially in the case of opioids.

The concept of drug tolerance was originally based on the observation that opioids lose their physiologic effects with repeated use. As tolerance develops, drug-dependent subjects progressively increase the dose of the drug to achieve the originally experienced euphoric effects. In the psychopharmacologic context, tolerance is an organism's adaptive response to supraphysiologic levels of an exogenous substance. A major consequence of this adaptation is that on cessation of drug use, the physiologic adaptations remain unopposed and induce a physiologic withdrawal syndrome specific to the class of

drug. After chronic opioid use, cessation can induce a severe physical withdrawal syndrome including diarrhea, hypertension, tachycardia, vomiting, and muscle cramps. Depression, dysphoria, or negative affective symptoms (e.g., anhedonia) are associated with the cessation of almost all drugs of abuse, including opioids. Depression and suicide are common comorbidities with drug abuse and dependence, especially after intervention. Anesthesiologists have both the knowledge and means of successfully completing a suicide attempt, and a safety plan should be in place to reduce this risk, especially from the time of intervention until the time of admission for addiction treatment.

Addiction among health professionals is a significant public health problem. Health care professionals are in safety-sensitive occupations. Without intervention and treatment, impaired professionals harm themselves, their families, and their patients. Although treatment outcomes for physician addicts are remarkably positive, there is a dearth of research on the primary prevention of substance abuse and dependence in this population. Researchers have studied opioid-addicted physicians for decades, reported on the use of clonidine and naltrexone in this population, and followed them for many years after detoxification and initial formal treatment. Although physicians are overrepresented among prescription drug addicts, their rates of alcohol abuse and dependence are similar to those of appropriately matched controls.

All medical schools and hospitals encounter cases of physician opioid abuse, dependence, and overdose. However, they attribute these events to poor self-regulation or ease of drug access. Substance abuse and addiction appears to be an occupational hazard among physicians, especially anesthesiologists. To become a physician, one must be a high achiever throughout high school and college to obtain the required grades and test scores for medical school admission. Additionally, potential physicians must continue to excel throughout medical school to gain internships and residencies.

Physicians seem unlikely candidates for opioid injection and self-administration. However, they are 30 to 100 times more likely to become addicted to narcotics than the general population. One study estimated that 12.5% of male physicians are drug dependent, compared with 0.1% of men in the general population. Although alcohol-related disorders and cigarette smoking rates were comparable between physicians and other Harvard University graduates, physicians had higher rates of drug use and prescription drug abuse, depression, depression with substance abuse, and suicide than other age- and sex-matched professionals. At least 15% of all physicians will become markedly impaired during their careers. Stress and access have dominated the theories for physician use and dependence, but basic scientists who conduct research with cocaine or narcotics do not usually use these drugs themselves. Not all medical subspecialties are equally represented among physicians with substance use disorders (Fig. 4.1). Anesthesiologists administer highly potent anesthetics including extremely potent opioids to patients; they work in a confined space around the patient's head and are exposed in the workplace to discarded drugs (e.g., opioids, propofol, benzodiazepines) that affect the brain, emotions, and behavior. This exposure sensitizes their brains to these highly addictive drugs such that if they are then used by the sensitized anesthesiologist, addiction develops more rapidly than it would otherwise.

Fentanyl and its analogs deserve special mention as a risk to anesthesiologists. Fentanyl abuse, overdose deaths, and addiction had been limited to health care professionals for many years due primarily to access. Fentanyl is a narcotic analgesic developed in the early 1960s by Janssen Pharmaceutica in Belgium. Like morphine, fentanyl is an opioid receptor agonist that preferentially binds μ-opioid receptors. Fentanyl's chemical structure, however, is distinct from that of morphine analogs, which explains why it is not picked up by standard urine opiate dug testing. Fentanyl is 50 to 100 times more potent than morphine. Also, new and more potent fentanyl analogs have been developed. The most potent is 3-methylfentanyl, which is about 6000 times as potent as morphine and 600 times as potent as heroin. Unfortunately, these potent analgesics also have an extremely high abuse potential and have been associated with a large number of drug overdose deaths. Between 1979 and 1988, 108 drug overdose deaths were related to fentanyl analogs in California alone. The extremely potent respiratory depressant effects of fentanyl account for the high number of overdose deaths. It has been reported that fentanyl concentrations vary between 1 and 10 ng/mL in the body fluids of those dying of fentanyl overdose, which is very low compared with the concentrations identified in other opioid overdose death. For example, free morphine concentrations in heroin overdose deaths vary between 462 and 1350 ng/mL. In 2004, prescription methadone, OxyContin-like analgesics, and fentanyl were more likely to cause an overdose death in Florida than was heroin.

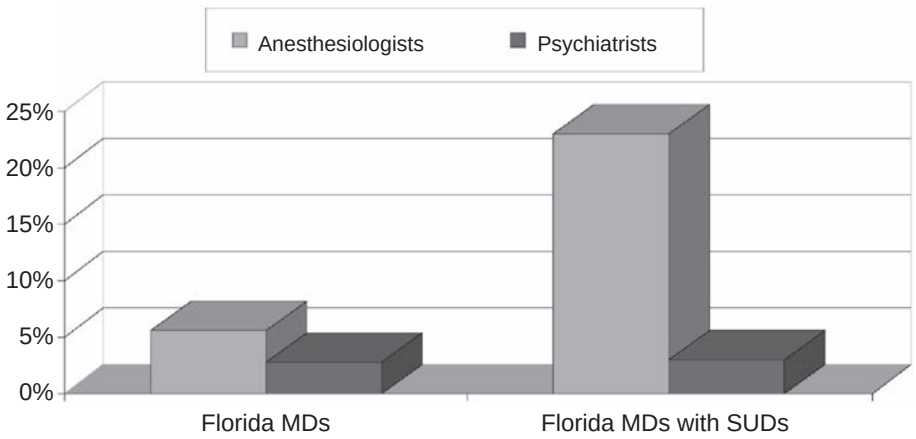

Fig. 4.1 Substance use disorders (SUDs) among anesthesiologists and psychiatrists in Florida.

Implications

At the onset of treatment, a full medical and psychiatric evaluation helps predict the long-term outcome. Intravenous drug abuse is associated with a number of medical conditions, including bacterial or viral endocarditis, hepatitis, acquired immunodeficiency syndrome, tuberculosis, cellulitis, cerebritis, wound abscess, sepsis, arterial thrombosis, renal infarction, and thrombophlebitis. The most common severe complications from intravenous drug use, however, are accidents, head injuries, memory failure, sexually transmitted diseases, seizures, depression, suicidal thinking, and suicide attempts. Opioid addiction is associated with a very high death rate, with an annual incidence of about 10 per 1000 persons among those who are untreated. Death is most often due to overdose, accidents, injuries, or general medical complications. In some places, violence accounts for more opioid-related deaths than does overdose or human immunodeficiency virus infection. Beyond these medical issues, physician addicts are exposed to significant career risk in medical credentialing and licensure, as well as marital and other personal problems.

MANAGEMENT

After appropriate intervention and admission to treatment, detoxification to abstinence is the treatment of choice for physician addicts; replacement or maintenance treatments (e.g., methadone or buprenorphine) are not used for this class of addicts. In the detoxification phase, clonidine not only provides an effective nonopiate treatment for opiate withdrawal but also allows a rapid progression from opiate dependence to maintenance, especially when coupled with the opioid receptor blocker naltrexone. Together, clonidine and naltrexone reduce the detoxification process to a matter of a few days. This combination is rapidly becoming the new standard of treatment, along with naltrexone maintenance, therapeutic communities, 12-step fellowship, individual and group therapy with recovering peers, management of co-occurring psychiatric and medical conditions, and minimum 5-year monitoring after initial formal treatment.

Despite the chronic nature of the disease of addiction and the low long-term recovery rates seen in the general population, the treatment of physicians in specialized physician programs has been remarkably efficacious. Whereas most treatment programs for addicts continue to be shortened, physician and health care provider treatment programs have been extended to include inpatient, residential, and rehabilitation phases. Using these techniques, long-term treatment outcomes for physicians are far better than those reported for similarly diagnosed addicts in the general population. In the most recent study of randomly selected Physician Recovery Network physician addicts at 5 years, 91.4% had returned to work. This rate is comparable to the results of other studies of physician addicts. When the subset of addicted anesthesiologists was broken out and examined, they did equally well compared with nonanesthesia specialties. Anesthesiologists who were addicted to intravenous opioids have historically been recommended not to return to a work setting where intravenous opioids were used; however, with the routine use of depo naltrexone, that paradigm has changed. In summary, good management options exist to care for physicians (especially anesthesiologists) addicted to opioids and allow them to obtain meaningful recovery and return to their professional duties and careers.

PREVENTION

Our research confirms other studies' findings that anesthesiologists have an increased rate of opioid use disorders. Left untreated, addiction has numerous adverse health consequences for anesthesiologists, as well as their patients and families. Early detection is critical to prevent overdose death and make treatment more successful. For prevention and early detection, strong consideration should be given to true random testing for all anesthesia personnel.

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Chronic Opioid Use

5

Taras Grosh • Michael A. Ashburn

Case Synopsis

A 38-year-old woman is transported to the emergency department (ED) via ambulance following a motor vehicle crash. Her medical history is notable for hypothyroidism, as well as a history of an intravenous (IV) opioid use disorder diagnosed at the age of 25. Her opioid use disorder is managed with medication-assisted treatment (MAT), which was started 10 years ago. She is currently receiving buprenorphine/naloxone 8 mg/2 mg twice daily. Following her evaluation in the ED, she is diagnosed with a femur fracture and scheduled for urgent surgical correction.

PROBLEM ANALYSIS

Definition

The use of opioids to treat chronic noncancer pain has increased significantly over the last 15 years, despite very limited evidence to document its safety or efficacy. As the use of prescription opioids has increased, so has the misuse and abuse of prescription opioids. Addiction to prescription drugs, most often opioids, has skyrocketed, and more people than ever are dying from the adverse effects of opioids. Misuse and abuse of prescription drugs is commonly associated with the dramatic rise of heroin abuse and the subsequent rise in heroin overdose deaths.

Tolerance develops following chronic use of many drugs, including opioids. *Tolerance* can be defined as a change in a patient's response to a medication over time such that an increased dose is needed to achieve the same effect. Opioids are associated with differential tolerance, in that tolerance to the various effects of opioids (i.e., analgesia, ventilation, sedation, constipation) appears to develop at different rates and to different degrees. Tolerance to the analgesic effects can occur quickly, whereas tolerance to the effects of opioids on ventilation occurs more slowly and to a lesser degree than observed with analgesia. As a result, aggressive up-titration of opioids to achieve analgesia in an opioid-tolerant patient appears to have an *increased* risk of respiratory-related complications compared with patients who have not been exposed to opioids. The Food and Drug Administration defines opioid tolerance as being present when a patient has received at least 60 mg a day of morphine or morphine equivalents for at least 1 week.

Addiction is a term that remains in common use, although the term has been replaced as a diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) with the term *substance use disorder.* The American Society of Addiction Medicine defines *addiction* as

> a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include the following: *Impaired control over drug use, craving, compulsive use and continued use despite harm.* [emphasis added]

The diagnostic criteria for opioid use disorder were revised in the DSM-5 (see Box 4.1 in Chapter 4). The new diagnosis attempts to capture the essence of addiction while avoiding categorizing patients properly using chronic opioids under physician supervision as having an addiction disorder.

When discussing chronic opioid therapy, an important concept to understand is how to properly quantify daily opioid dose. A common method for doing this is through the use of "morphine equivalent dose" (MED). The total daily opioid dose is determined, then the dose is expressed in MED using an opioid conversion table. The patient's MED may be used to guide proper opioid prescribing and may be predictive of the patient's postoperative pain experience.

Recognition

A careful history and physical examination is essential to guide clinical decision making. It is important to carefully determine what medications the patient is taking. Likewise, it is critical for the physician to carefully determine the current opioid dose and if the opioid dose has recently been started or is chronic.

Patients with chronic pain conditions and patients with substance use disorders both have an increased risk of mental health disorders, including depression and anxiety disorders. In addition, patients with substance use disorders are more likely than the general population to have a history of posttraumatic stress disorder, as well as an Axis II disorder. The presence of these conditions may affect perioperative care, as will the use of medications to treat these conditions.

Risk Assessment

Patients taking chronic opioids at the time of surgery are more likely to experience poorly controlled pain following surgery. The presence of differential tolerance following chronic opioid use, combined with complaints of poor pain control, likely increases the risk of respiratory-related complications including respiratory arrest and death following aggressive use of systemic opioids to treat pain. Risk of harm is increased significantly if benzodiazepines are administered in combination with opioids.

Patients with sleep-disordered breathing, including obstructive sleep apnea (OSA) or central sleep apnea, are at increased risk of compromised ventilation following the administration of systemic opioids. There may be an increased risk for central sleep apnea in patients receiving greater than 100 mg/day MED of chronic opioids. OSA is often present but not diagnosed or properly treated. Therefore many providers are advocating for perioperative screening for OSA and increased monitoring and intervention to ensure proper oxygenation and ventilation in patients identified to be at high risk for OSA. Likewise, early identification of patients on high doses (greater than 80–100 MED) of opioids may allow for institution of monitoring and early intervention when indicated.

Implications

There is growing evidence in the literature that outcomes following elective surgery may be compromised in patients on high doses of chronic opioids. For example, patients taking more than 80 mg MED of chronic opioids often report poor acute and chronic pain control and no or limited improvement in physical functioning following joint replacement surgery. Therefore early identification of patients on chronic opioids and consideration of efforts to decrease the prescribed dose of opioids preoperatively may lead to improved outcomes following surgery.

Patients receiving chronic opioids are at high risk for the development of opioid withdrawal symptoms if opioids are abruptly discontinued. The time to onset of withdrawal symptoms varies with the pharmacokinetics of the consumed opioid (Table 5.1). Although not usually life threatening, opioid withdrawal symptoms can be very distressing, and when unrecognized can lead to extensive unnecessary medical evaluation when the symptoms present following surgery. Patients on chronic opioids will, of course, experience severe pain following surgery if their chronic opioids are not continued following surgery. Therefore it is important to identify patients on chronic opioids before surgery and put into place a proactive plan to avoid opioid withdrawal and treat anticipated pain as best as one can.

Buprenorphine is a partial mu agonist that binds tightly to the mu receptor. Although buprenorphine provides opioid analgesia, this analgesia may have a ceiling effect. The presence of buprenorphine may limit the usefulness of administration of other opioid analgesics, and as a result, effective analgesia may not be obtained following opioid administration in patients already taking buprenorphine. Patients receiving buprenorphine MAT have been reported to have improved perioperative pain control if rotated from buprenorphine to methadone or a short-acting opioid before surgery.

MANAGEMENT

Preoperative Care

Determine Current Opioid Dose and Calculate MED

Patient report (e.g., "I've been prescribed oxycodone 15 mg every 4 hours as needed") is *not* sufficient to determine MED. Rather, one must determine the actual opioid dose that is being consumed. This information may not be reliably obtained from the patient or his or her family, and other sources may need to be accessed to confirm opioid dosing. Opioid dose confirmation may be obtained by review of the medical record or the state prescription drug monitoring program (PDMP), or by contacting the patient's pharmacy. When determining MED, it is important to determine daily opioid dose, then carefully calculate the MED via use of a validated opioid conversion table.

TABLE 5.1 Time Course of Opioid Withdrawal

Opioid	Onset	Peak Intensity	Duration
Meperidine	2–6 hours	6–12 hours	4–5 days
Fentanyl			
Morphine	6–12 hours	36–72 hours	7–10 days
Heroin			
Methadone	24–48 hours	3–21 days	6–7 weeks

Modified from Mitra S, Sinatra R: Perioperative management of acute pain in the opioid-dependent patient. *Anesthesiology* 101(1):212-227, 2004.

TABLE 5.2 Multimodal Analgesia Systemic Medication Options

Medication	Commonly Used Doses
Acetaminophen	650 mg–1 g q6-8h PO/IV
NSAIDs (COX-2, ibuprofen, ketorolac)	Celebrex 200 mg q12h PO
	Ibuprofen 800 mg q6h PO
	Ibuprofen 400 mg q6h IV
	Ketorolac 15–30 mg q6h PO × 5 days
Anticonvulsants	Gabapentin 900–1200 mg daily PO
	Pregabalin 300–600 mg daily PO
NMDA antagonist	Ketamine 0.1–0.5 mg/kg IV
	Ketamine 125–500 μg/kg/h IV

COX-2, Cyclooxygenase-2; *NMDA*, *N*-methyl-D-aspartate; *NSAIDs*, nonsteroidal antiinflammatory drugs. Note: Patients should be reassessed weekly and weaned/discontinued, as long as symptoms do not persist, to lowest possible dose.

Determine Risk for Respiratory Compromise Caused by Other Concurrent Sedatives

The risk of respiratory compromise is significantly increased when opioids are used in combination with other centrally acting sedatives. Patients are often prescribed opioids in combination with benzodiazepines. As abrupt discontinuation of benzodiazepines can lead to life-threatening withdrawal, benzodiazepines may need to be continued perioperatively if they can be tapered and discontinued in advance of elective surgery.

As a potent central depressant, ethanol, when combined with an opioid, causes greater respiratory depression than either alone. As expected, this is more pronounced in the elderly population. The physician should exercise extreme caution when prescribing concomitant opioids to patients with a history of ethanol abuse.

Determine Risk for Respiratory Compromise Caused by Concurrent OSA or Central Sleep Apnea (CSA)

Screen patients for OSA, and consider patients taking MED greater than 100 mg/day to be at risk for OSA unless they have had a sleep study while on high doses of opioids to rule out sleep-disordered breathing.

Determine whether the patient is a candidate for preventive care (see later discussion).

Create a Pain Treatment Plan as Part of the Anesthetic Plan That Includes Multimodal Analgesia Whenever Possible (Table 5.2)

Consult a pain specialist early if indicated. Pain therapy considerations should include the following:

- The administration of scheduled acetaminophen unless contraindicated.
- The administration of scheduled nonsteroidal antiinflammatory drug (with appropriate monitoring) unless contraindicated.

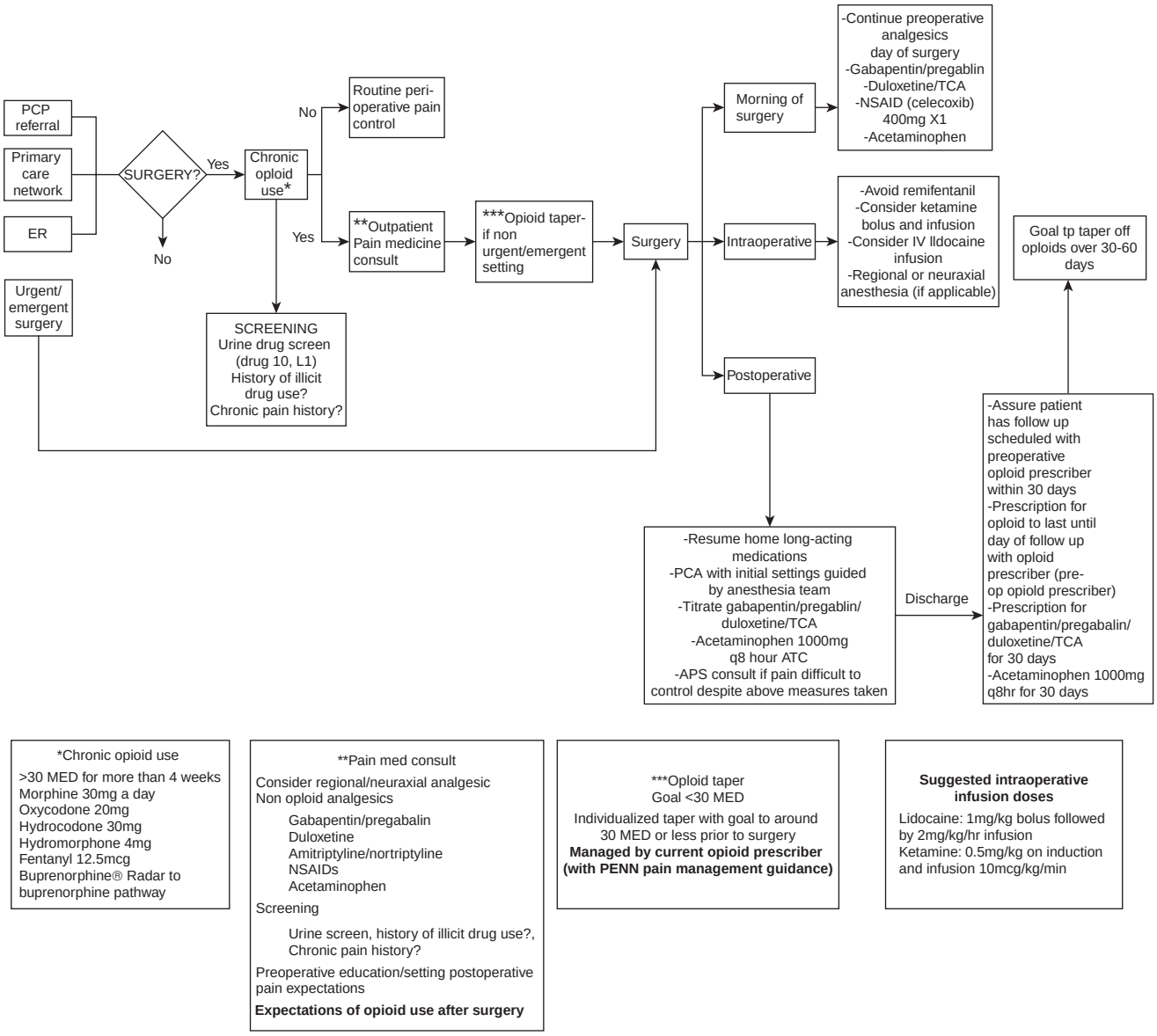

Fig. 5.1 University of Pennsylvania pathway for opioid-tolerant patients scheduled for elective spine surgery.

- Consideration of the administration of either gabapentin or pregabalin.
- Aggressive use of regional anesthetic and analgesic techniques whenever possible. This may include the placement of an epidural or peripheral nerve catheter.
- Continuation of opioids at a dose to match chronic MED to avoid opioid withdrawal.
- Development of a plan, including proper patient placement following surgery for monitoring for adequacy of ventilation following surgery.

Establish Reasonable Expectations With the Patient, Family, Surgery, and Nursing

Patients on chronic opioids should understand that they likely will experience increased pain following the procedure and that aggressive use of opioids is not likely to lead to improved pain control, but rather would more likely lead to significant risk of harm. Reassure patients that they will be treated with dignity and respect and that everything possible will be done to treat their pain, but that they ultimately will more likely than not have periods of increased pain.

Patients with an opioid use disorder will require careful consultation and coordination of their pain care with their addiction treatment team. It is critical that the treatment plan includes clear planning with regard to opioid prescribing at discharge with a scheduled early return visit to the addiction treatment team.

Intraoperative Care

Whenever possible, consider the use of regional anesthetic techniques as part of the anesthetic. Ensure that opioids are administered at proper MED to avoid the development of opioid withdrawal during surgery.

Consider the administration of the following:

- Wound infiltration of long-acting local anesthetics
- IV infusion of lidocaine (1 mg/kg bolus followed by 2 mg/kg/h infusion)
- IV infusion of ketamine (0.5 mg/kg on induction followed by 10 μg/kg/min infusion)

Postoperative Care

- Continue opioid administration at proper MED to avoid withdrawal.
- Continue administration of scheduled acetaminophen, nonsteroidal antiinflammatory drug, and gabapentenoid if indicated.
- Continue regional analgesia for as long as possible during the immediate postoperative period.
- Establish proper monitoring for adequacy of ventilation in patients receiving systemic opioids, especially in patients identified to have or be at high risk for sleep-disordered breathing.
- Use systemic opioid analgesic carefully, recognizing that because of differential tolerance it is not likely possible to achieve analgesic using opioids alone without compromising ventilation.
- In patients with an untreated substance use disorder, obtain a psychiatry evaluation to offer proper treatment for the substance use disorder immediately following hospital discharge.
- Establish and implement a plan for opioid prescribing at the time of discharge. This should include a plan for prescribing opioids for a limited number of days, then referral to the pain specialist or addiction specialist for that physician to take over and monitor ongoing opioid prescribing.

PREVENTION

Perioperative pain care and patient outcomes may be improved with preoperative pain specialist consultation well before scheduled elective surgery. This would allow for careful coordination of care with the addiction specialist in patients on MAT, rotation from buprenorphine to methadone or another opioid when indicated, and opioid taper in patients receiving opioids for chronic noncancer pain in advance of scheduled surgery. A perioperative pain treatment plan can then be created and documented to guide clinical decision making at the time of surgery, and reasonable patient and family expectations can be discussed.

More globally, institutions may wish to develop a standardized patient care pathway for the care of patients receiving buprenorphine who present for surgery, as well as a care pathway for patients on chronic opioids who present for surgery (Fig. 5.1). Such pathway development will allow for education of the care team and the development of a standardized process of care to administer novel infusions at the time of surgery (such as ketamine), as well as the development and implementation of a process to monitoring patients at high risk for compromise of ventilation following surgery.

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6 Dialysis-Dependent Patients

Klaus D. Torp

Case Synopsis

A 43-year-old African American male gas station attendant is scheduled for emergency exploratory laparotomy after sustaining an abdominal stab wound in an attempted robbery. He is dialysis dependent and awaiting renal transplantation. His last hemodialysis was 52 hours earlier. He is awake and alert. His blood pressure is 102/90 mm Hg; heart rate, 114 beats per minute; and respiratory rate, 24 breaths per minute. His hemoglobin level is 8.2 g/dL after receiving 3 units of packed red blood cells; the serum potassium level before the transfusion was 6.0 mEq/L. While cricoid pressure is applied, anesthesia is induced with etomidate, fentanyl, and rocuronium. Soon after the operation begins, the surgeon complains of difficulty in achieving hemostasis. The T waves on the monitor are tall and peaked.

PROBLEM ANALYSIS

Definition

Chronic kidney disease (CKD) is defined by the National Kidney Foundation as either kidney damage (defined as abnormalities of either imaging studies or laboratory values) or a decrease in glomerular filtration rate to less than 60 mL/min/1.73 m^2 and goes often unnoticed in the early stages. Urine albumin spot checks often serve as a marker for kidney damage from which an albumin/creatinine ratio (ACR) is calculated. The different stages of CKD can be found in Table 6.1.

In 2012, approximately 637,000 patients were affected by end-stage renal disease (ESRD) in the United States, with an estimated incidence of about 353 per 1 million persons (which ranges by 66% across the different regions in the United States) and are slightly declining since 2009 and a prevalence of 1943 per 1 million (ranging across regions by 33%, which represents a slight increase from 2011). The prevalence rate for African Americans is about 4 times higher compared with Caucasians, and Hispanics have a 60% higher prevalence rate than non-Hispanics. Although the incidence rates have been stable for most age groups, they decreased dramatically in the older age groups of greater than 65, which, combined with the increase in prevalence in all age groups, especially the population over 65 (by 30%–50%), suggests longer survival in ESRD patients. About 45% of patients who start hemodialysis have diabetes listed as primary diagnosis, followed by hypertension in 30% and glomerulonephritis in 7%. The remainder is made up by the more rare diseases such as polycystic kidney disease, immunoglobulin A (IgA) and IgM nephropathies, systemic lupus erythematosus, Wegener granulomatosis, multiple myeloma, amyloidosis, and AIDS nephropathy, just to name a few. These patients tend to be younger and are less likely to present with the typical comorbidities of the dialysis patient. In 2012 approximately 100,000 patients initiated treatment for ESRD with hemodialysis or peritoneal dialysis, and 2800 patients received preemptive renal transplantation. Chronic dialysis is usually required when glomerular filtration rate (GFR) falls below 20 mL/min. It is indicated for volume overload refractory to diuretic therapy, severe metabolic acidosis, hyperkalemia, seizures, or other neurologic symptoms, as well as pericarditis, and is usually started when the blood urea nitrogen exceeds 100 mg/mL or creatinine approaches 10 mg/dL. Regardless of the cause, ESRD results in abnormalities in virtually all organ systems and therefore has important implications for patients undergoing surgery (Box 6.1). The abnormalities result from both a failure to excrete urea and other end products of metabolism and a loss of metabolic and endocrine functions normally performed by the kidney.

Recognition

Perioperative complications of ESRD are listed in Box 6.2. One of the frequent acute life-threatening perioperative complications of ESRD is hyperkalemia. It is frequently associated with acidosis and with trauma due to the release of potassium from damaged tissue and hematomas. Hyperkalemia can cause progressive cardiac conduction defects, ending in ventricular fibrillation or, less commonly, asystole (Table 6.2). Electrocardiographic changes also depend on the chronicity and the rate of rise of serum potassium.

An increased propensity to bleeding occurs frequently in uremia because of an acquired defect in primary hemostasis. Tests of coagulation factors are typically normal, although a slight reduction in platelet counts may be seen. The pathogenesis is multifactorial, and the major defects involve decreased platelet–vessel wall adhesion and platelet-platelet interactions manifested by impaired aggregation in response to epinephrine, adenosine diphosphate, collagen, and fibrinogen. Platelets from uremic patients release less adenosine triphosphate and serotonin and display reduced cyclooxygenase activity. The activation-dependent receptor function of the glycoprotein IIb-IIIa complex is defective in uremia, as shown by decreased binding of both von Willebrand factor (vWF) and fibrinogen to stimulated platelets. Nitric oxide (NO) and prostacyclin also limit the activation of platelets.

Tests of decreased platelet function can range from the gold standard highly labor-intensive light transmission aggregometry to automatic analyzers with short turnaround times such as the Platelet Function Analyzer (PFA-100, Siemens Medical Solutions, Erlangen, Germany), Multiplate whole blood platelet aggregometry (Roche, Switzerland), or thromboelastographic methods such as TEG with

TABLE 6.1 Classification of Chronic Kidney Disease

CKD Stage	Abnormalities
1	eGFR ≥90 mL/min/1.73 m^2 *and* ACR ≥30 mg/g
2	eGFR 60–89 mL/min/1.73 m^2 *and* ACR ≥30 mg/g
3	eGFR 30–59 mL/min/1.73 m^2
4	eGFR 15–29 mL/min/1.73 m^2
5	eGFR ≤15 mL/min/1.73 m^2

CKD, Chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *ACR,* albumin/creatinine ratio.

BOX 6.1 Clinical Abnormalities in End-Stage Renal Disease

- Nervous system
  - Sleep disorders
  - Motor weakness
  - Polyneuritis
  - Asterixis
  - Seizures
  - Coma
- Hematologic system
  - Anemia
  - Increased fragility of red blood cells
  - Platelet dysfunction with bleeding
  - Thrombosis
- Metabolic and endocrine systems
  - Glucose intolerance
  - Hyperparathyroidism
  - Hypogonadism
- Immunologic system
  - Increased susceptibility to infection
- Integumentary system
  - Pruritus
- Cardiovascular system
  - Hypertension
  - Hypotension
  - Cardiomyopathy
  - Diastolic dysfunction
  - Left ventricular hypertrophy
  - Congestive cardiac failure
  - Pericarditis
- Gastrointestinal system
  - Gastrointestinal bleeding
  - Pancreatitis
- Acid-base balance and electrolytes
  - Anion gap metabolic acidosis
  - Hyperkalemia
  - Hyponatremia
  - Hypermagnesemia or hypomagnesemia
  - Hyperphosphatemia
- Musculoskeletal system
  - Renal osteodystrophy (osteoporosis, osteomalacia)

BOX 6.2 Perioperative Complications of End-Stage Renal Disease

- Hyperkalemia
- Bleeding
- Cardiovascular dysfunction
- Hypertension/hypotension
- Congestive heart failure
- Ischemia
- Sepsis
- Graft thrombosis

TABLE 6.2 Electrocardiographic Changes With Progressive Hyperkalemia

K^+ (mEq/L)	Electrocardiographic Abnormality
5.0	Usually none or tenting of T waves
6.0	Tall and peaked T waves
7.0	Prolonged PR interval with depressed ST segments
8.0	Auricular arrest with "sine wave" QRS complex
9.0	Ventricular fibrillation

Platelet Mapping (Haemonetics, Braintree, MA, USA) or ROTEM (TEM Intl., Munich, Germany), just to name a few. Although simple and easily obtained, the cutaneous bleeding time has been abandoned by many institutions because of inaccurate prediction of bleeding risk and high operator-dependent variability. Despite the bleeding tendency in patients with ESRD, markers of hypercoagulability such as an elevated vWF activity and elevated thromboelastographic amplitudes are frequently noted. In fact, ESRD patients receive antiplatelet agents to prevent thrombosis of atrioventricular grafts, as well as for their cardiovascular disease, which in turn can also contribute to the bleeding tendency.

Cardiovascular dysfunction is common in patients with ESRD. This is not surprising given the high prevalence of hypertension, left ventricular hypertrophy, and coronary artery disease in patients on chronic dialysis. In addition, diminished responsiveness of cardiac α- and β-adrenergic receptors due to autonomic dysfunction results in poor compensatory responses to acute hemodynamic changes. Pulmonary hypertension can be present in up to 40% of patients with ESRD and arteriovenous fistulae.

Hypoxemia and disequilibrium syndrome are two complications of which the anesthesiologist should be aware that occur either during or soon after dialysis. Hypoxemia is more common when acetate rather than bicarbonate is used in the dialysate and is due to a combination of CO_2 unloading and complement activation-induced pulmonary inflammation. The hypoxemia is usually transient. Disequilibrium is caused by rapid removal of urea and other osmotically active agents, while the blood-brain barrier prevents its rapid removal from brain cells, which become relatively hypertonic. Fluid diffuses into brain cells along the osmotic gradient, and cerebral edema may result.

Risk Assessment

Patients who are dialysis dependent and undergo major surgical procedures have a higher perioperative mortality rate than patients with normal renal function. The mortality rate is particularly high for patients undergoing open-heart surgery (approximately 12% compared with 2.9% in the nondialysis population). The risk of major surgery is related to abnormalities directly attributable to ESRD, as well as to the underlying disease process, such as hypertension. Diastolic dysfunction is as frequently a cause of congestive heart failure in dialysis patients as is dilated cardiomyopathy; therefore, in individuals with ESRD, a relatively small excess of ingested sodium chloride and water can lead to a large increase in left ventricular end-diastolic pressure, resulting in pulmonary edema. The probability of having angina or a myocardial infarction requiring hospitalization is 10% per year, and cardiac disease accounts for about 45% of deaths in patients on dialysis. Anemia and hypertension are independent predictors of mortality. Although the all-cause mortality rate of patients with ESRD has improved over the past few years, the life expectancy of dialysis patients in their thirties to fifties is still only about one-third of that of the general population.

Anesthetic drugs, such as succinylcholine, that increase serum potassium levels after an intubating dose can contribute to the risk of death; however, in ESRD patients with a normal preprocedure potassium level, that risk does not seem to be higher and should not be withheld if indicated. The need for multiple blood transfusions also will increase serum potassium levels (1 unit of blood can contain up to 70 mEq/L of potassium), as will acidosis resulting from periods of hypoperfusion or a failure to adequately compensate for increasing metabolic acidosis with an increase in minute ventilation. Drug accumulation and overdoses can occur due to reduced renal clearance of the drug itself or its active metabolites, which is mostly a concern with repeat dosing. However, increased unbound fractions of drugs due to decreased proteins in the plasma can also lead to overdosing, with the initial dose leading to the need for dose a reduction in highly protein-bound medications such as midazolam, alfentanil, or barbiturates.

Altered neutrophil and monocyte function, as well as impaired lymphocyte activation, may increase the risk of infections in patients with ESRD, who are also at high risk for colonization with bacterial pathogens due to multiple health care facility visits.

All general anesthetic techniques have the potential to reduce renal perfusion and can adversely affect any residual renal function, which can still be a very important contributor to the patient's health. No volatile anesthetic has been shown to be superior to either each other or to total intravenous anesthesia.

Implications

The potential for serious life-threatening problems relating to electrolyte, coagulation, and acid-base problems is ever present and is further compounded by the underlying and coexistent diseases, especially serious cardiovascular abnormalities.

MANAGEMENT

General principles useful in the management of all ESRD patients undergoing surgery regardless of its etiology are listed in Box 6.3.

Vascular Access in Dialysis-Dependent Patients

Invasive hemodynamic monitoring is often used in these patients due to their frequent comorbidities in addition to the need for intravenous access to administer blood and vasoactive substances. Peripheral vascular access can be difficult to obtain and central venous access can also be challenging due to thrombosis of the vessels after multiple previous dialysis catheter placements, making the use of ultrasound to guide assessment of vascular patency before draping the patient, as well as live needle guidance during the procedure, a valuable clinical tool. In emergency situations, accessing an arteriovenous fistula or a dialysis catheter should be weighed very carefully against the risk and the severe consequences of thrombosis or infection of the graft or catheter.

BOX 6.3 General Management of Patients Undergoing Surgery

- Dialysis within 24 hours of surgical procedure
- Serum potassium in the normal range
- Serum bicarbonate of 20 mEq/L or higher desirable
- Euvolemic or minimally hypovolemic before surgical procedure
- Hematocrit around 30%
- Potassium-free fluid; wash red blood cells to minimize transfused potassium load
- Caution with use of succinylcholine
- Choose drugs that do not depend on renal elimination; adjust (decrease) dosages of drugs that depend on renal metabolism or that are highly protein bound.
- Use strict aseptic techniques when placing intravascular devices.
- Identify and adequately protect functioning shunts during surgical procedures.
- Attention to padding of pressure points

Treatment of Hyperkalemia

The management of acute hyperkalemia can be divided into three steps. The first-line treatment is directed at antagonizing the adverse effects of potassium by administering calcium, followed by shifting potassium into the intracellular space, either through stimulation of the Na/K ATPase or by following an electric gradient. The third step consists of removal of whole body potassium through dialysis or the use of exchange resins (Table 6.3).

Treatment of Bleeding in Uremic Patients

Treatment with erythropoietin and/or infusion of washed red blood cells has been shown to significantly shorten the bleeding time in uremic patients when the hematocrit was raised above 30%. Erythrocytes enhance platelet function by releasing adenosine diphosphate, by increasing platelet–vessel wall contact by displacing platelets away from the axial flow and toward the vessel wall, and by inactivating the inhibitors of platelet aggregation such as prostacyclin and NO. Infusion of desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), which has less pressor effect than vasopressin, stimulates the release of vWF from endothelial cells, and this may be the reason for its therapeutic effect in uremia. Administered intravenously or subcutaneously at a dose of 0.3 μg/kg in 50 mL of normal saline over 15 to 30 minutes, it shortens the bleeding time in 50% to 100% of uremic patients. This correction occurs in 30 to 60 minutes and lasts for about 4 hours, correlating with an increase in the plasma concentration of vWF and an increase in the proportion of the higher-molecular-weight multimers of vWF. Tachyphylaxis typically occurs after the second dosage of DDAVP, possibly because of depletion of endothelial multimer stores. Cryoprecipitate, which is rich in factor VIII/vWF, also can be used at an initial dose of 10 to 20 units. The onset of action is similar to that of desmopressin, but the beneficial effects persist for 24 to 36 hours.

Conjugated estrogen (Premarin) (0.6 mg/kg/day intravenously for 5 days) is effective before elective major operations, and beneficial effects persist for 3 to 4 weeks.

TABLE 6.3 Treatment of Acute Hyperkalemia

Mechanism	Intervention
Antagonism of potassium effect	Calcium chloride or calcium gluconate 1–2 g slow IV push
Intracellular shift of potassium (effective within 30 minutes)	Moderate hyperventilation
	Insulin 20 units/dextrose 50 g IV infusion over 20–30 minutes
	Sodium bicarbonate, 50–100 mEq IV
	Albuterol, 10 mg (nebulized)
	Epinephrine, 0.01 μg/kg/min IV
Potassium removal from the body	Sodium polystyrene sulfonate (Kayexalate) (30 g of sodium polystyrene sulfonate in 100 mL of 20% sorbitol) and administered via a nasogastric tube (30 g) or rectally (30–60 g) (exchanges potassium for sodium, which may lead to pulmonary edema)
	Emergency hemodialysis (intraoperative if required); risk of hypotension, bleeding

Hemodialysis significantly ameliorates platelet dysfunction and should, if necessary, be used within 24 hours of the intended operation. However, studies have shown that hemodialysis may transiently worsen platelet function, an effect that seems to be reversed the day after dialysis. Tranexamic acid can also be used when these treatments are not effective; however, it can accumulate in renal failure.

PREVENTION

Complications of ESRD in the perioperative period are best prevented by communicating with the nephrologist caring for the patient to plan dialysis the day before the operation and arrange for dialysis in the immediate postoperative period or intraoperatively if required. There is increasing evidence that the aggressive treatment of hypertension in the period preceding initiation of dialysis is a potent intervention to decrease subsequent cardiovascular mortality. Similarly, early treatment of anemia is recommended because this may delay or prevent left ventricular hypertrophy and may reduce bleeding problems. Prevention and treatment of acidosis (serum bicarbonate greater than 20 mEq/L) to establish an acid buffer can help reduce the risk of hyperkalemia. After major surgery, these changes in approach have the potential to reduce the serious morbidity and mortality rates associated with ESRD in the future and improve outcome.

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7 Do-Not-Resuscitate Orders in the Operating Room

Gail A. Van Norman

Case Synopsis

An 86-year-old woman presents as an add-on operating room case late one afternoon for treatment of a hip fracture suffered in a fall at home. She lives independently with home assistance. She is clearly competent and articulate and states that she is a "DNR" and does not want resuscitation measures in the operating room if her "heart stops." She reasons that her likelihood of returning to independence in the event of a cardiac arrest is small, and she does not want to risk long-term disability. The anesthesiologist and orthopedic surgeon demand that she suspend her DNR for the surgery. She refuses. Finally, the anesthesiologist states that he will not anesthetize her unless she suspends her DNR because being able to resuscitate her is "a necessary part of the anesthesia." Ultimately, she angrily agrees to the suspension of her DNR. The surgery is uneventful.

PROBLEM ANALYSIS

Definition

Closed-chest cardiac massage for treatment of cardiopulmonary arrest was first described in 1960 by Kouwenhoven and colleagues, and enthusiastically embraced by the health care profession. Despite Kouwenhoven's report of a 70% survival-to-discharge rate following cardiopulmonary resuscitation (CPR), subsequent studies revealed that survival rates were dismal. Concerns about universally applying CPR in the inpatient setting were fueled by rising costs of hospitalization and intensive care unit (ICU) treatment, and public concerns that not all postresuscitation lives were worth living.

Beginning in the 1970s, legal precedents (e.g., the cases of Karen Ann Quinlan and Nancy Cruzan) were established, and subsequently reaffirmed by the U.S. Supreme Court, that patients could refuse any medical treatments, including life-sustaining treatments, so long as they were of legal age and mentally competent to do so. Passage of the Patient Self-Determination Act of 1990 in the United States established federal law protecting the rights of patients to refuse life-sustaining treatments and threatening federal defunding of any medical institution that did not honor these rights (Box 7.1).

Despite well-defined legal rights to refuse resuscitation, many physicians experience conflicts when patients who have do-not-resuscitate (DNR) orders present for anesthesia and surgery. Cardiopulmonary arrest and resuscitation measures have different medical implications in the operating room (OR) than in other hospital areas. Respiratory arrest on the hospital ward, for example, is a "defining event." Immediate recognition and effective intervention, including possible intubation and mechanical ventilation, are needed to prevent death or permanent injury. Treatment of cardiac arrest may include cardiovascular pharmacologic support, direct current countershock, CPR, and mechanical circulatory support. When a patient has a DNR order without further specification, many patients and physicians expect that the directive prohibits many if not all of such interventions.

In the OR, however, elements of these interventions can represent a part of normal anesthetic care. Anesthetic agents can suppress respiration, requiring respiratory assistance up to and including intubation and mechanical ventilation. Common and predictable variations in hemodynamics can require administration of pharmacologic support, and indeed such interventions are in the very nature of anesthetic care.

Anesthesiologists present several common arguments for rescinding DNR orders in the operating room: (1) outcomes from CPR are more favorable in the OR than in other hospital locations; (2) anesthesia is "nothing but ongoing resuscitation," and it cannot clearly be distinguished from other resuscitative measures; and (3) patients who have DNR orders should also forgo invasive procedures, because it does not make sense to offer invasive surgery to a patient who also wants to be allowed to die.

Outcomes from CPR remain poor, despite decades of efforts to improve overall survival. Survival-to-discharge of out-of-hospital cardiac arrest has been determined to be roughly 6%. Multiple studies demonstrate that less than half of patients survive initially following in-hospital cardiac arrest, and overall survival to discharge is 6% to 26.5%, although recent increases in survival are somewhat offset by a concomitant increase in percentage of survivors discharged to hospice or long-term care. Survival of in-hospital cardiac arrest is associated with a significant rate of substantial neurologic injury. In one study, about 42% of survivors overall experienced significant neurologic impairment.

Cardiac arrest in the noncardiac, nontrauma OR is a relatively rare event, occurring in around 3 in 10,000 anesthetics overall. When we look at outcomes of cardiac arrests that occur in the OR during noncardiac surgery, we find more favorable, yet still surprisingly consistent and grim, statistics. Approximately 60% of patients survive the first hour following cardiac arrest in the OR. At least one study found that 46% of immediate survivors (around 36% of the total) will die later in the hospitalization, often in the ICU. Only 37% of those who survive to discharge have "good" cerebral function. In short, cardiac arrest in the noncardiac surgery patient in the OR is accompanied by more

BOX 7.1 Provisions of H.R. 4449—The Patient Self-Determination Act of 1990, Section 1395cc

Defines "advance directive" as a written instruction (e.g., living will or durable power of attorney for health care) recognized under state law and regarding provision of care when the individual is incapacitated.

Providers must maintain policies and procedures concerning advance directives in adults.

Each patient must receive written information regarding the following:

- Their rights to accept or refuse treatment
- Their rights to formulate an advance directive
- The written policies of the facility regarding implementation of the patient's rights

For hospitals, skilled nursing facilities, and hospices this information must be provided on admission.

There must be documentation in each patient's medical record about the existence of any advance directive.

The facility cannot condition the provision of care or otherwise discriminate against a patient based on whether an advance directive exists.

The facility must assure compliance with state law regarding advance directives.

The facility must provide education for staff and community regarding issues with advance directives.

favorable, albeit still poor, long-term outcomes than arrest elsewhere in the hospital. The most recent review by Kalkman of anesthesia-related cardiac arrest and CPR reports slightly better but still notably poor outcomes: immediate survival of about 41.6%, followed by 32% to 55.7% survival for 1 to 24 hours, followed by subsequent survival of 45.3% to 66.8% at follow-up after discharge. The authors of the review feel that this suggests a viable survival rate of about 25%. They did not determine the *quality* of survival in this group. We can conclude that survival after cardiac arrest in the OR is better than out-of-hospital cardiac arrest, or even than cardiac arrest experienced in other areas of the hospital, but is still surprisingly poor.

The statement that anesthesia is "nothing but ongoing resuscitation," however, is very difficult to defend because it depends on a manipulative and misleading use of the term "resuscitation." Physicians and patients use the word "resuscitation" to describe very different events, and physicians use the term variously to describe significantly different circumstances with different implications. "Fluid resuscitation" means something very different than CPR, for example. Stating that anesthesia is "nothing but resuscitation" wrongfully implies that anesthesia care is an uncontrolled, near-death experience from which anesthesiologists are constantly rescuing their patients, and that cardiac arrest is a common occurrence during anesthesia, such that CPR is a normative procedure for most anesthetics, instead of the extreme and rare complication that anesthesiologists strive diligently to avoid.

Patients generally refer to a very specific event when they elect DNR orders—the event of complete cardiac arrest—and often describe it clearly as "when my heart stops." They perceive that cardiac arrest is usually a terminal event from which the likelihood of recovery to previous function is limited, *and they are correct.* We know that the majority of patients suffering cardiac arrest in the OR in fact do not survive to discharge, and that many are significantly injured even when they do.

Finally, it is not appropriate to deny patients treatments that may reasonably improve their remaining quality of life, even if that remaining life is short, simply because they will not agree to other invasive and potentially injurious procedures (e.g., CPR) that are rarely needed. To do so not only goes against the basic principle of medicine to ease suffering, but it is coercive.

Ethical Considerations

Basic principles of Western medical ethics are to respect and promote patient autonomy, to "do good" (beneficence), and "avoid harm" (nonmaleficence). Gone are the "old days" in which medical ethics dictated that preservation of life was the preeminent ethical principle and that the physician had a duty to dictate to patients the treatments that would be most likely to accomplish that goal.

The principle of respect for patient autonomy requires that, once a sufficiently informed and competent patient is apprised of the relevant information, his or her decision regarding consent or refusal of various treatments should be followed. The fact that outcomes for CPR in the OR differ significantly from other scenarios warrants review with the patient to determine the patient's decision in light of the special circumstances of the OR. However, the decision to forgo resuscitative care still rests with the patient. Physician perceptions about resuscitation can be affected by personal values, unrealistic expectations, interpersonal conflicts, unconscious motivations, fear of professional failure, and fear of legal retribution—all of which have little to do with the patient's needs. *Ethically as well as legally, only the patient or someone whom the patient has designated to speak for him or her can consent to or refuse treatments.*

Legal Considerations

Although the legal rights of patients to make health care decisions including refusal or cessation of life-sustaining care have long been established, studies have repeatedly shown that physicians understand advance directives poorly and that physician practice is inconsistent with advance directives in over half of cases.

Many physicians are unaware that federal law protects a patient's right to refuse life-sustaining care, and even fewer appreciate that resuscitation despite the presence of a patient's advance directive not to resuscitate may place them in legal peril. In some cases, courts have found that the plaintiffs had grounds to seek prosecution for battery, which is a harmful or offensive unconsented touching that occurs directly or indirectly. Note that "battery" does not require that there be any direct hostility or even physical injury involved. Also note that battery is a crime.

"Wrongful living" has been proposed as a tort for cases in which a patient's recognized right to refuse treatment has been violated when treatment results in "the unwanted extension of life." The legal concept that the plaintiff in such cases may be entitled to damages has been slow to gain traction, due to the reluctance of courts to find continued life "a compensable harm"; however, the idea is recently attaining new consideration. In addition, compliance with the federal Patient Self-Determination Act of 1990 (see also Chapter 24) is a condition of participation in the federal Medicare and Medicaid Programs (see Box 7.1). A health care facility that fails to comply with the law's requirements can be penalized and/or excluded from Medicare and Medicaid. Over the last 10 years, at least two health care facilities have had judgments against them from the Centers for Medicare and Medicaid Services. Administrative law judges have upheld state disciplinary board sanctions of medical providers who fail to comply with patient's advance directives, such as resuscitating patients with DNR orders, up to and including revocation of the practitioner's medical license. Furthermore, courts have decided that patients may be entitled to recover medical expenses arising from such unwanted treatments. In 2011 in *Callsion v. Hillcrest Healthcare System* in Oklahoma, the courts refused to dismiss a complaint of battery in a case in which a hospital continued intubation of a patient in violation of his advance directive and family's wishes. The hospital later settled out of court. Several other court cases suggest that, in the face of a validly executed DNR order, plaintiffs may have constitutional grounds to receive relief. Finally, in 2006 the American Civil Liberties Union brought suit against an orthopedic surgery center that required patients to sign a document acknowledging that the facility "does not honor requests

for 'Do Not Resuscitate' status and/or Advance Directives or Living Wills." The case was ultimately settled out of court, but the implication is that there is a substantial legal risk when physicians use coercive tactics (e.g., denial of anesthesia and surgery) against patients who have DNR orders and other advance directives. In addition, substantial monetary awards, although uncommon, have been made in cases where patients' advance directives, including DNR orders, have been violated. This was exemplified in the case of Brenda Young, a woman who suffered severe neurologic injury after an unwanted resuscitation, whose family was awarded $16.5 million (later reduced to $1.4 million on appeal).

In 1993 the American Society of Anesthesiologists developed and published Ethical Guidelines for Management of Patients with Do-Not-Resuscitate Orders and Other Orders Limiting Medical Treatments. They advise anesthesiologists to have informed discussions with patients or their decision makers regarding outcomes of treatments in the OR, and to respect patient decisions regarding such treatments. Providers who cannot for personal reasons respect patient wishes should withdraw from providing care and find a substitute provider who can. In 1994 the American College of Surgeons and the Association of Operating Room Nurses followed suit, paraphrasing the ASA guidelines. In addition, the Joint Commission requires that appropriate policies and procedures be implemented that maximize respect for patient wishes regarding refusal of resuscitation.

Recognition

It is important to identify patients coming to the OR who have DNR orders; the presence of advance directives should be a standard question for all patients presenting for anesthesia and surgery. Every anesthesia practice should have procedures and policies in place to define how DNR orders in the OR will be handled. These policies must be consistent with ethical standards of care and with law, bearing in mind that federal law, legal precedent, and professional guidelines support patients' rights to have their DNR order followed even in the OR, after the patient and/or their decision makers are properly informed of the outcomes.

Resolution

In our case scenario, we are confronted with a clearly competent patient who wishes to have her DNR order followed in the OR. Unfortunately, the providers erroneously believe that they can demand that the patient rescind her order, and even resort to coercion (the threat to deny her life-altering surgery) to accomplish their aims. In coercing the patient to rescind her order against her will, they violated a primary principle in medical ethics to respect the decision of an autonomous patient. Not only is the DNR rescission invalid ethically and legally, but the surgical consent itself is called into question, because consent for some potential measures in the OR was coerced.

This situation should not be confused with refusing to perform a procedure in which a patient refusal literally renders the procedure either below any standard of care or impossible to perform. The provider may reasonably refuse to proceed with a thoracotomy, for example, if the patient refuses an intubation that is a necessary and elementary part of the surgery each time it is performed.

This case is all the more tragic in that the physicians are insisting on the right to perform a procedure that is extremely unlikely to benefit the patient and has a high likelihood of producing great harm. The patient actually has made a realistic appraisal of her outcomes, should CPR be necessary: Studies suggest that she would have minimal chance of survival to discharge and, if she did survive, would likely suffer neurologic injuries that would end her independence.

Ethical principles require physicians to respect patient autonomy in medical decision making. Legal precedents up to and including decisions by the U.S. Supreme Court have consistently iterated that patients have the legal right to refuse any medical treatments, including life-sustaining ones. In this case an appropriate course of action would have been for the anesthesiologist and surgeon to discuss with the patient the more favorable outcomes of CPR in the OR and determine what measures, if any, the patient would accept for treatment if her "heart stops." After such a discussion, if the patient wishes to have her DNR continued, this should be documented in the chart. If the patient decides to suspend her DNR order, plans should be made to reinstate the order after surgery (usually after discharge from the postanesthesia care unit).

PREVENTION

When a case like this uncovers gaps in knowledge and practice, it is likely that the individual practitioners involved are not the only physicians who have imperfect knowledge of the ethical and legal "landscape." Not only should one outcome of this case be education of the involved providers, but the education should address the entire group practice with regard to the appropriate ethical and legal approaches when such situations arise. Policies and procedures should be developed and published to the practitioners that standardize an appropriate approach when patients with DNR orders present for anesthesia and surgery.

Policies should include the following steps:

- Determine whether the patient presenting for anesthesia and surgery has an advance directive, such as a DNR order.
- Discuss the order with the patient and/or the patient's appropriate decision makers, including risks and benefits of resuscitation in the OR.
- Document any changes to the DNR order, if any, in the medical record.
- Inform other members of the OR team of the presence of a DNR order, and discuss how it will be managed in the OR.
- If questions arise about the validity of a DNR order, the institutional ethics committee or legal counsel can be of help.
- If the provider cannot respect a patient's wishes to continue a DNR order in the perioperative period, the provider should withdraw and refer the patient to a colleague who can.
- In emergencies, endeavor to determine whether an advance directive exists. If no directive exists, or the validity of the directive is in question, proceed with the best medical care, as far as possible respecting what is known about the patient's wishes.
- If a patient wishes to rescind his or her DNR order in the perioperative period, the DNR order should be reinstated postoperatively, usually following discharge from the postanesthesia care unit.

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8 Drugs Affecting the Renin-Angiotensin System

Laura Stover

Case Synopsis

A 95-kg, 70-year-old man is scheduled to have a left internal carotid endarterectomy. He takes amlodipine (5 mg/day) and irbesartan (150 mg/day), an angiotensin II receptor antagonist, for hypertension. He took his usual doses of both medications on the morning of surgery. Preoperative tests included a transthoracic echocardiogram that showed normal left ventricular systolic function and septal hypertrophy. Blood pressure and heart rate immediately before induction of anesthesia were 150/70 mm Hg and 56 beats per minute, respectively. After receiving 900 mL of crystalloid, he was induced with sufentanil (10 μg), propofol (150 mg), and rocuronium (50 mg), with subsequent endotracheal intubation and anesthetic maintenance with oxygen and air (40:60) and desflurane (0.7 minimum alveolar concentration [MAC]). Two minutes after induction, his blood pressure fell to 80/44 mm Hg. Despite repeated intravenous blouses of ephedrine (50 mg total), his blood pressure was 47/30 mm Hg 4 minutes after induction.

PROBLEM ANALYSIS

Definition and Recognition

Renin-angiotensin system (RAS) antagonists include both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists. These drugs are used to treat hypertension and heart failure in selected patients. ACE inhibitors and angiotensin II receptor antagonists cause a blockage of the RAS that can adversely affect hemodynamics during anesthesia and surgery. Although anesthesia is not invariably associated with hemodynamic instability in RAS-blocked patients, unexpected episodes of refractory hypotension have been reported. Also, RAS antagonists, specifically ACE inhibitors, have been associated with potentially life-threatening angioedema of the head and neck.

The RAS plays an essential role in the regulation of vascular tone and extracellular fluid volume. As shown in Fig. 8.1, sympathetic stimulation via β_1-adrenergic receptors, renal artery hypotension, and decreased sodium delivery to the distal tubules stimulate the release of renin by the kidney. Renin is a proteolytic enzyme that cleaves to the circulating substrate angiotensinogen to form angiotensin I, which has little intrinsic pharmacologic activity. Angiotensin I is converted immediately to angiotensin II via a reaction catalyzed by ACE, which is present in vascular endothelium and lung tissue.

In the short term (i.e., intraoperatively), angiotensin II contributes to vascular homeostasis by increasing vascular (especially arteriolar) tone. It acts directly on angiotensin II receptors and indirectly by enhancing sympathetic adrenergic function to increase vascular tone, which is necessary to maintain adequate perfusion pressure in patients with hypovolemia or reduced cardiac output. In the longer term (e.g., hours to days), angiotensin II contributes to vascular homeostasis by its effect on extracellular fluid volume. It causes the adrenal cortex to release aldosterone, a hormone that acts on the kidneys to increase sodium and fluid retention. Angiotensin II also stimulates the release of vasopressin (i.e., antidiuretic hormone) from the posterior pituitary, which causes the kidneys to increase fluid retention. Blocking angiotensin II–mediated increased vascular tone and relative reduction of intravascular volume in patients receiving RAS antagonists chronically may cause refractory hypotension after induction of anesthesia.

Angioedema of the oropharynx or larynx has been recognized as an unusual complication of ACE inhibitor therapy. ACE inhibitor–induced angioedema usually manifests spontaneously within hours to days of initiation of treatment and has been described in association with anesthesia and endotracheal intubation. Edema of the tongue is commonly the presenting symptom, with involvement of the face, lips, floor of the mouth, pharynx, glottis, or larynx frequently observed.

The precise mechanism of angioedema formation is uncertain. Because it is likely mediated by the kallikrein-bradykinin system, it is probably a biochemical rather than an immunologic phenomenon. Bradykinin is a potent vasodilator that increases vascular permeability and produces tissue edema. Kinase II (which is identical to ACE) is the major tissue enzyme responsible for the breakdown of bradykinin. ACE inhibitors inhibit kinase II to prevent bradykinin breakdown. Angioedema associated with ACE inhibitor therapy may therefore be a result of inhibition of bradykinin inactivation by kinase II.

Recognition

Hypotension

Recognition of RAS antagonist therapy as a contributor to hypotension relies on the exclusion of other intraoperative events that may produce hypotension. A heightened index of suspicion in patients chronically treated with these drugs, especially in those with left ventricular diastolic dysfunction, is justified. The temporal relationship

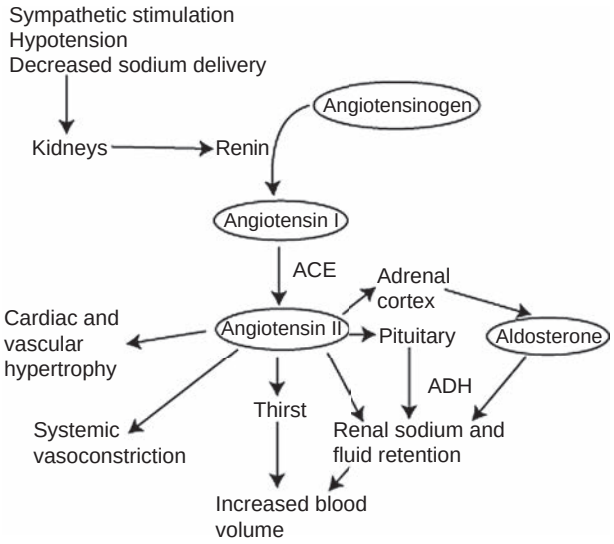

Fig. 8.1 The renin-angiotensin system. *ACE,* Angiotensin-converting enzyme; *ADH,* antidiuretic hormone.

between cardiovascular instability and induction of anesthesia in patients chronically treated with RAS antagonists, along with the failure of ephedrine or phenylephrine in usual doses to resolve the hypotension, makes RAS antagonists a likely cause of hypotension.

Angioedema

Recognition of ACE inhibition as the cause of angioedema relies on the exclusion of other perioperative events associated with swelling of the head and neck (e.g., allergy, anaphylaxis), as well as the knowledge that angioedema can occur (though infrequently) with ACE inhibitors. When it does occur, angioedema is usually temporally related to the initiation of ACE inhibitor therapy.

Risk Assessment

Hypotension

A number of patient factors modify the risk of severe hypotension with the induction of anesthesia in those treated with RAS antagonists. Patients treated with other antihypertensive agents in combination with an RAS antagonist are more likely to have refractory hypotension on induction. Likewise, the combination of RAS antagonists and other vasodilator drugs (e.g., amiodarone) increases the risk of hypotension. Patients with "complete" RAS blockade, which is associated with high doses and recent administration, are more likely to be unstable on induction. Patients with a history of severe hypertension, especially those with left ventricular diastolic dysfunction (which amplifies the dependence of cardiac output on preload), are also at increased risk for refractory hypotension. Short-term preoperative RAS inhibition (1 to 2 days) in normotensive or mildly hypertensive subjects is less likely to result in refractory hypotension on induction. Patients who continue therapy until the day of surgery are also at increased risk. One review found that the incidence of hypotension on induction of anesthesia in patients with a history of severe hypertension was 75% to 100% when ACE inhibitors were continued until the day of surgery.

Angioedema

Angioedema involving the oropharynx or larynx is an unusual complication of ACE inhibitor therapy, occurring on average in 0.1% of patients taking captopril, lisinopril, or enalopril; the incidence in patients taking enalapril may be slightly higher (0.2%) than in those taking the other two drugs. Patients are at highest risk within the first week of starting an ACE inhibitor; a retrospective study of 36,000 patients receiving enalapril showed that 60% to 70% of cases of angioedema occurred within this period. However, angioedema has occurred suddenly after months to years of therapy, and about 20% of known cases of angioedema occurring in this context may involve severe symptoms (e.g., dyspnea, stridor, laryngospasm). Unfortunately, there are no characteristics to predict which patients will progress to life-threatening airway compromise.

Implications

Concerning the risk for refractory hypotension on induction of anesthesia in patients taking RAS antagonists, there is no consensus on continuing or discontinuing the drug in the immediate preoperative period. For this class of drugs, the elimination half-life does not necessarily predict the duration of action, making recommendations with respect to perioperative dosing difficult.

MANAGEMENT

Hypotension

If RAS blockade contributes significantly to refractory hypotension after induction of anesthesia, therapy relies on the prompt restoration of adequate systemic vascular resistance and venous tone with phenylephrine or vasopressin, as well as increased intravenous fluid administration. Remedial actions for managing hypotension related to RAS antagonists include discontinuing or reducing the dose of other agents that might contribute to hypotension. Advanced cardiovascular life support protocols should be invoked in the event of cardiovascular collapse.

Angioedema

Most occurrences of ACE inhibitor–induced angioedema are mild and resolve spontaneously with discontinuation of the drug. However, swelling may progress rapidly to include the posterior pharynx or larynx, causing partial or complete upper airway obstruction. The symptoms may progress despite aggressive therapy and may recur hours after apparent resolution. Angioedema caused by ACE inhibitors can be fatal.

Management ranges from simply stopping the ACE inhibitor to endotracheal intubation or tracheostomy. Mild cases confined to the anterior tongue or lips generally resolve with discontinuation of the drug and administration of intravenous diphenhydramine and corticosteroids. More severe cases involving the pharynx and associated with dysphagia may require subcutaneous epinephrine, tracheal intubation, or both. As with any evolving process involving the airway, the potential for life-threatening airway obstruction dictates close observation and prompt intervention. After resolution of the acute process, a note should be made in the patient's medical record of this potentially life-threatening adverse reaction to ACE inhibitor therapy, and the patient should receive appropriate counseling.

PREVENTION

As noted earlier, there is no consensus regarding the management of patients receiving RAS antagonist therapy in the immediate preoperative period. Discontinuation of RAS antagonists during this period reduces the risk for hypotension with anesthesia induction, provided

there is sufficient time to allow the return of RAS activity. However, any risk reduction may be at the expense of optimal therapy for hypertension or heart failure. Identifying patients at the greatest risk for severe hypotension (those with severe hypertension or those receiving high doses of RAS antagonists, RAS antagonists in combination with other antihypertensives, or RAS antagonists chronically), along with intravenous fluid loading before the induction of anesthesia, may reduce the risk for refractory hypotension. Such pretreatment combined with the early use of vasopressors for hypotension believed to be caused by RAS blockade will shorten the duration of hypotension. Consistent with the foregoing, frequent blood pressure measurement immediately after induction (direct arterial measurement may be necessary) contributes to the earlier detection of severe hypotension.

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HIV Infection and AIDS

9

Michael S. Avidan

Case Synopsis

A 34-year-old woman with known human immunodeficiency virus (HIV) infection and a recent diagnosis of acquired immunodeficiency syndrome (AIDS) with *Pneumocystis jirovecii* (previously *carinii*) pneumonia presents for elective cesarean section at 38 weeks' gestation. She has not been followed by health care clinicians during her pregnancy and has not been taking antiretroviral therapy. She is very short of breath and has a dry cough, and her peripheral arterial oxygen saturation is 84% on room air. She weighs 62 kg, and her height is 164 cm. Her tympanic temperature is 37.2° C. She is alert and oriented, with no localizing neurologic signs. Her blood pressure is 90/50 mm Hg; her heart rate is 115 beats per minute, with no respiratory variation; and her respiratory rate is 26 breaths per minute. Recent laboratory tests show a CD4 T-cell count of 186 cells/mL and an HIV viral load of 240,000 copies/mL.

PROBLEM ANALYSIS

Definition

AIDS was first described in 1981 in the United States. HIV and, despite major therapeutic advances in recent years, the AIDS pandemic still pose a major threat to global health. It is estimated that more than 40 million people worldwide are infected with HIV, which is thought to have caused more than 20 million deaths to date. The infection continues to spread apace, with the most rapid increases observed in southern and central Africa and in South Asia. The predominant mode of HIV transmission is heterosexual sex, and women represent a high proportion of new infections, including in developed countries.

Increasing numbers of patients presenting for surgery are HIV-seropositive or have AIDS. Anesthesiologists should be familiar with this disease and be aware of the impact of HIV on anesthesia. An understanding of the pathogenesis of HIV and an awareness of the possible drug interactions occurring with HIV therapy may help guide the choice of anesthetic technique. The possibility of nosocomial transmission of HIV highlights the need for anesthesiologists to enforce rigorous infection control policies to protect themselves, other health care workers, and their patients. Antiretroviral therapy decreases the rate of disease progression, but there is no cure available, nor is a vaccine likely in the foreseeable future. With marked advances in treatment, the emphasis has shifted to early initiation of multidrug therapy regardless of immune status, and ongoing treatment to achieve HIV viral suppression throughout life.

Recognition

HIV belongs to the family Retroviridae and the genus *Lentivirus.* Members of this genus are cytopathic (cell damaging), have long latent periods, and run a chronic course. When cases of AIDS first appeared, its pathogenesis was frustratingly elusive because the disease does not appear immediately on infection with HIV. There is a variable period during which the patient remains healthy but is viremic.

Acute seroconversion illness occurs with a high viral load soon after infection. After several months, there is a gradual decrease in the viremia as the immune response occurs. The viral load is often at a steady state as the rate of viral production equals the rate of destruction. Up to 98% of T-helper lymphocytes (CD4 T cells) are located in lymph nodes, which are the major site of viral replication and T-cell destruction. There is a gradual involution of the lymph nodes, with a concomitant decrease in CD4 T cells and an increase in viral load as the inexorable onset of AIDS occurs (Fig. 9.1).

Before 1995, prospects for the treatment of HIV were gloomy. Subsequently, the situation changed dramatically as a result of four factors:

1. Improved understanding of the pathogenesis of HIV infection
2. Availability of surrogate markers of immune function and plasma viral burden
3. Development of new and more powerful drugs, such as the protease inhibitors and nonnucleoside reverse transcriptase inhibitors
4. Completion of several large clinical end-point trials that conclusively demonstrated that antiretroviral combinations significantly delayed the progression of HIV disease to AIDS and improved survival

In more recent years, advances have further transformed the treatment of HIV with more drugs, fewer side effects, less toxicity, and less pill burden. It has also been established that early initiation of therapy, regardless of the host's CD4 T-cell count, renders the virus virtually undetectable, restores immune function, improves quality of life, prevents transmission, reduces HIV-associated morbidity, and lengthens survival. HIV has thus been rendered a less debilitating and ominous infection. Indeed there are real prospects for arresting the pandemic and potentially even eradicating HIV as a major infectious disease threat.

Risk Assessment

HIV is a virus found mainly in CD4 T cells, macrophages, and monocytes, and it requires a large infecting dose for transmission. HIV has been isolated from blood, cerebrospinal fluid, tears, saliva, semen, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, amniotic fluid, vaginal secretions, and breast milk. Modes of transmission

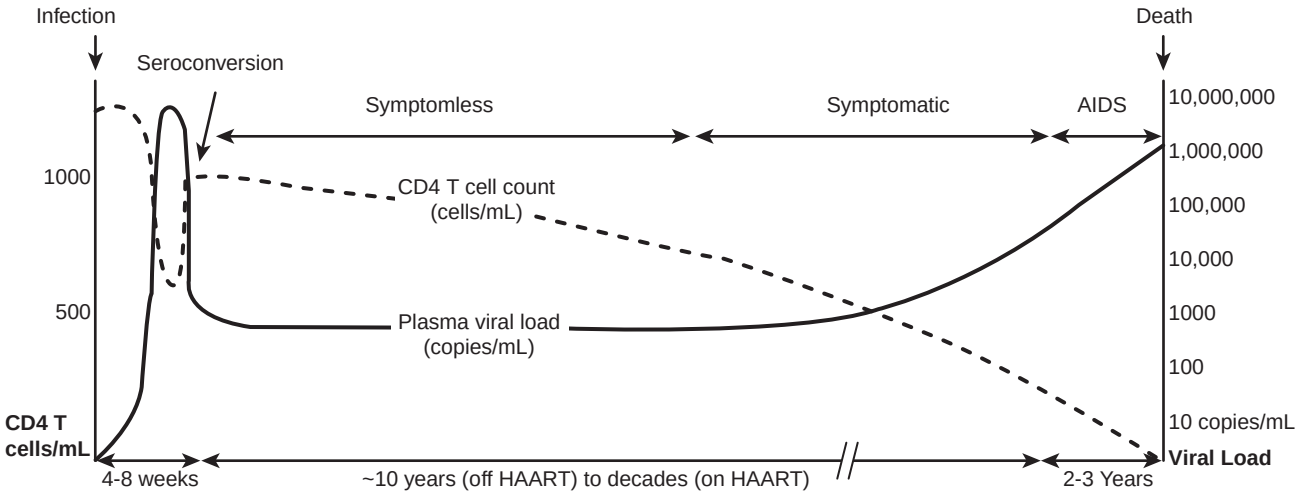

Fig. 9.1 Progression to acquired immunodeficiency syndrome (AIDS) of those infected with human immunodeficiency virus (HIV). Note that highly active antiretroviral therapy (HAART) greatly delays development of clinical AIDS.

are through oral, rectal, and vaginal sexual intercourse, blood product transfusion, shared intravenous needles, occupational acquisition, and vertical transmission from mother to child. The screening of blood products for HIV antibodies has reduced the risk of transfusion-associated infection (less than 1 per 750,000 donor units); the exact risk is difficult to quantify, however. Antibody screening fails to detect the virus in the so-called window period before antibody formation, which lasts about 3 months. Nuclear amplification is an alternative technique that has been adopted and allows for early virus detection.

Implications

Universal Precautions

Universal precautions for the prevention of transmission of blood-borne viruses were recommended in 1987 by the Centers for Disease Control. These precautions advise that every patient be regarded as potentially infected with a blood-borne virus.

Postexposure Prophylaxis

Following accidental exposure to a high-risk body fluid, such as a (hollow) needle-stick injury, postexposure prophylaxis (PEP) is recommended for health care workers. This should commence as soon as possible after the injury, ideally within 1 to 2 hours, but it can be considered up to 1 to 2 weeks after the injury. Very-high-risk exposures may be treated beyond this time with a view to modifying rather than preventing infection. A typical postexposure prophylaxis regimen of 4 weeks' duration is tenofovir plus emtricitabine/lamivudine plus raltegravir/dolutegravir. Such a regimen is excellent for PEP because of excellent tolerability, proven potency in HIV infection, and ease of administration.

MANAGEMENT

Antiretroviral Drug Therapy

Six major classes of antiretroviral agents are currently in use (Table 9.1):

1. Nucleoside analog reverse transcriptase inhibitors (NRTIs, approved in 1987) bind to the evolving viral DNA and prevent the completion of reverse transcription.
2. Protease inhibitors (PIs, 1996) inhibit the HIV protease, which cleaves the polyprotein precursors that ultimately make up the core proteins of the mature virions. PIs bind specifically to the active cleavage site.
3. Nonnucleoside reverse transcriptase inhibitors (NNRTIs, 1998) interfere with the transcriptional activity of reverse transcriptase by binding to it directly, downstream of the active catalytic site.
4. The fusion inhibitor (2003) enfuvirtide interferes binds to the first heptad-repeat (HR1) in the viral envelope glycoprotein gp41 and prevents conformational changes necessary for the fusion of the viral and human CD4 T lymphocyte cellular membrane.
5. The CCR5 antagonist (2007) maraviroc binds to human CCR5 receptor on the cell membrane of the CD4 T lymphocyte, thus blocking the interaction of the HIV gp120 and the CCR5 receptor, but only for CCR5-tropic HIV. It does not block viral entry of CXCR4 tropic HIV, and therefore it is necessary to determine that the infecting HIV strain is CCR5-topic before using this agent.
6. Integrase (strand transfer) inhibitors (INSTIs, 2007) block the integrase enzyme from catalyzing the formation of covalent bonds between the host and viral DNA, which prevents the incorporation of viral DNA into the host chromosome.

Table 9.1 lists examples of these major classes of antiretroviral agents currently in use, as well as routes of administration and common side effects. A typical antiretroviral regimen consists of three agents. Such combined therapy has been termed highly active antiretroviral therapy (HAART). In some circumstances, combinations of four or more drugs are used. The aim of therapy in treatment-naïve patients is to achieve an undetectable viral load and to improve and extend the length and quality of life. Based on favorable side-effect profile, minimal toxicity, and good efficacy, initial treatment for naïve patients frequently includes two NNRTIs and an INSTI. With multiple drug options available, the choice of therapy should also be guided by genotype resistance test results. The protease inhibitor, ritonavir, is often used at low dose as a pharmacokinetic booster (through cytochrome P450 inhibition) to increase the bioavailability of other protease inhibitors. Recently, preexposure prophylaxis (PrEP) has been shown to be effective in preventing HIV contraction for HIV-negative individuals who are at high risk, such as sex workers.

Side Effects of HAART Regimens

Numerous side effects and drug interactions complicate HAART regimens and decrease compliance. Patients may experience drug

TABLE 9.1 Major Classes of Antiretroviral Agents Currently in Use

Drug Name	Dosing	Common Side Effects
Nucleoside Analog Reverse Transcriptase Inhibitors		
Zidovudine (AZT/ZDV)	Oral/IV (twice daily)	Marked toxicity, bone marrow suppression (neutropenia), GI upset, headache
Didanosine (DDI)	Oral	Peripheral neuropathy, pancreatitis, diarrhea
Zalcitabine (DDC)	Oral	Peripheral neuropathy, pancreatitis, oral ulcers
Stavudine (D4T)	Oral	Peripheral neuropathy
Lamivudine (3TC)	Oral	Anemia, GI upset
Abacavir	Oral	GI upset, potentially fatal acute hypersensitivity (associated with the presence of the HLA-B*5701)
Tenofovir	Oral (once daily)	Renal dysfunction, osteomalacia
Emtricitabine	Oral	Headache, GI symptoms
Nonnucleoside Analog Reverse Transcriptase Inhibitors		
Nevirapine	Oral	Rash, hepatitis, increased liver enzymes
Delavirdine	Oral	Rash, increased liver enzymes
Efavirenz	Oral (once daily on empty stomach)	Dizziness, rash, dysphoria, increased liver enzymes, psychotic disturbances
Rilpivirine	Oral (once daily with food)	Rash, hepatitis
Protease Inhibitors		
Saquinavir	Oral	Diarrhea, raised transaminases, hyperlipidemia, cytochrome P-450 inhibition, arrhythmias
Indinavir	Oral + ≥1.5 L H_2O/24 hr	Nephrolithiasis, hyperbilirubinemia, hyperlipidemia, lipodystrophy, cytochrome P-450 inhibition
Ritonavir	Oral	GI upset, circumoral paresthesia, hyperlipidemia, lipodystrophy, cytochrome P-450 inhibition
Nelfinavir	Oral	Diarrhea, hyperlipidemia, lipodystrophy, cytochrome P-450 inhibition
Atazanavir	Oral (requires acidic pH for absorption)	Dyslipidemia, insulin resistance, hyperglycemia, lipodystrophy, cytochrome P-450 inhibition, P-R interval prolongation
Darunavir	Oral (with food and boosted by ritonavir)	Dyslipidemia, insulin resistance, hyperglycemia, lipodystrophy, cytochrome P-450 inhibition, GI symptoms, hepatotoxicity
Fosamprenavir	Oral (boosted by ritonavir)	Dyslipidemia, insulin resistance, hyperglycemia, lipodystrophy, cytochrome P-450 inhibition, rash, GI symptoms
Lopinavir	Oral (once daily coformulated with ritonavir)	Dyslipidemia, insulin resistance, hyperglycemia, lipodystrophy, cytochrome P-450 inhibition, GI symptoms, arrhythmias, hepatotoxicity
Tipranavir	Oral (high pill burden and requires ritonavir boost)	Dyslipidemia, insulin resistance, hyperglycemia, lipodystrophy, cytochrome P-450 inhibition, p-glycoprotein induction, hepatotoxicity, rash, GI symptoms
CCR5 Antagonist		
Maraviroc	Oral (twice daily)	Hepatotoxicity, upper respiratory tract infections, fever, orthostatic hypotension
Fusion Inhibitor		
Enfuvirtide	Injectable (subcutaneous twice daily)	Pain, erythema, induration, nodules, ecchymoses, hypersensitivity
Integrase Inhibitors		
Raltegravir	Oral (twice daily)	Headache, nausea, fatigue, rhabdomyolysis, myopathy
Elvitegravir	Oral (improved with food)	Only INSTI metabolized by CYP3A4 system, many drug interactions
Dolutegravir	Oral (once daily)	Headache, insomnia

Multiple drugs, even those in the same classes, can be helpful in the event of resistance.
GI, Gastrointestinal.

hypersensitivity reactions, causing fever, hypotension, and acute interstitial pneumonitis with respiratory failure. Concurrent use of zidovudine (which has fortunately largely been replaced with newer agents with fewer side effects) and corticosteroids may result in severe myopathy and respiratory muscle dysfunction. In addition, reports have documented several cases of respiratory failure related to HAART initiation and immune reconstitution resulting in a paradoxical worsening of *Pneumocystis* pneumonia; distinguishing this event from a superimposed respiratory infection is often clinically challenging. Of particular importance to anesthesiologists is that patients receiving HAART are subject to long-term metabolic complications, including lipid abnormalities and glucose intolerance, which may result in the development of diabetes, coronary artery disease, and cerebrovascular disease.

A syndrome resembling acute gram-negative sepsis has been reported in patients taking NRTIs. Lactic acidosis and hepatic steatosis are usually found. Patients develop high fever and can rapidly become confused and comatose. Nucleoside analog drugs may cause inhibition of DNA polymerase gamma, the sole DNA polymerase required for the replication of mitochondrial DNA. This in turn causes mitochondrial dysfunction and impaired aerobic cellular respiration. Inhibition of oxidative phosphorylation and derangement of respiratory chain enzymes have been implicated. Riboflavin has been suggested as a potential treatment. Unfortunately, most patients die despite intensive care unit (ICU) support.

HAART Drug Interactions

PIs, particularly ritonavir, are inhibitors of cytochrome P-450 (see Table 9.1). In contrast, drugs such as nevirapine are inducers of hepatic microsomal enzymes. These variable effects on liver enzymes complicate the dosing of drugs, including anesthetic and analgesic agents, many of which undergo hepatic metabolism.

Consequences of HIV

Initially HIV inevitably led to AIDS, which was universally fatal. With the advent of HAART, HIV was transformed into a chronic infection associated with morbidity from the infection and toxicity from the treatment. With further advances in HIV treatment, toxicity and

tolerability are diminished, and fewer treated patients exhibit organ system or infectious complications. Indeed, many people infected with HIV can expect to age normally and to die of causes unrelated to HIV infection or its treatment.

Respiratory Complications

Pneumocystis jirovecii pneumonia (PJP; formerly *Pneumocystis carinii* pneumonia [PCP]) does not usually occur until the CD4 T-cell count is less than 200 cells/mL. Breathlessness, night sweats, and weight loss are frequent complaints. The chest examination may be unremarkable, and the chest radiograph is normal in many instances. Complications include respiratory failure, pneumothorax, and chronic pulmonary disease.

The chest radiograph typically shows bilateral "ground-glass" shadowing. Pneumothoraces may be evident, and there may be multiple pneumatoceles. High-resolution computed tomography scanning reveals a ground-glass appearance even when the radiograph is normal. Lung function tests show reduced lung volumes with decreased compliance and diminished diffusing capacity for carbon monoxide. Oxygen saturation measurements during exercise may be more helpful than lung function tests. If PJP is suspected, fiberoptic bronchoscopy and bronchoalveolar lavage should be performed. The advantage of an early diagnosis compensates for the high frequency of negative examinations.

Combined high-dose sulfamethoxazole (100 mg/kg per day) with trimethoprim (20 mg/kg per day) remains the treatment of choice. Systemic steroid therapy, such as prednisolone 1 mg/kg per day, is advised for patients with low oxygen saturation values. Respiratory support and supplementary oxygen are invariably required. Use of continuous positive airway pressure can, in some instances, obviate the need for positive-pressure mechanical ventilation. The prognosis for patients who require mechanical ventilation despite adjunct corticosteroid therapy is poor. Further, the use of positive end-expiratory pressure may cause pneumothorax.

Cavitary lung disease can be due to a pyogenic bacterial lung abscess, pulmonary tuberculosis (TB), fungal infection, and *Nocardia* species. Kaposi sarcoma (KS) and lymphoma can also affect the lung. Adenopathy can lead to tracheobronchial obstruction or compression of the great vessels. Endobronchial KS may cause massive hemoptysis. HIV also directly affects the lungs, causing a destructive pulmonary syndrome similar to emphysema.

Disseminated TB is a potential cause of severe respiratory failure, and respiratory secretions should be examined routinely for acid-fast bacilli in AIDS patients with pulmonary infiltrates. Bacterial pneumonia *(Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa)* can also cause severe acute respiratory failure. Empirical antibacterial treatment to cover these microorganisms should be given when a bacterial agent is suspected. Outbreaks of multidrug-resistant TB have occurred in patients with HIV infection and in health care workers. Airborne transmission by inhalation of infective aerosols justifies appropriate isolation measures to protect medical staff and other patients from TB transmission.

Central Nervous System Complications

Neurologic disease ranging from AIDS dementia to infectious or neoplastic involvement may complicate AIDS. Three entities constitute mostly focal cerebral processes: cerebral toxoplasmosis, primary central nervous system (CNS) lymphoma, and progressive multifocal leukoencephalopathy. Focal lesions may increase intracerebral pressure, thereby precluding neuraxial anesthesia. Spinal cord involvement, peripheral neuropathy, and myopathy may occur with cytomegalovirus or HIV infection itself. Giving succinylcholine may be hazardous in this setting. *Cryptococcus neoformans,* HIV, and TB can cause meningitis. HIV infection is associated with autonomic neuropathy, and this can manifest as hemodynamic instability during anesthesia or in the ICU.

Cardiovascular Disease

Cardiac involvement in the course of HIV is common but is often clinically silent. Up to 50% of patients with HIV have abnormal echocardiographic findings at some point in their disease. Approximately 25% have pericardial effusions. Myocarditis is more common in advanced HIV and may be caused by toxoplasmosis, disseminated cryptococci, coxsackievirus B, cytomegalovirus, lymphoma, *Aspergillus* species, and HIV itself. Ventricular dilatation and cardiac dysfunction may result. With PIs, glucose intolerance and disorders of lipid metabolism are common. Aggressive generalized vascular disease, including cardiac and cerebral, may occur as a complication of antiretroviral therapy. If patients exhibit unexplained hypotension, adrenal insufficiency should be considered, because this may occur with advanced HIV infection.

Surgery and Anesthesia

HIV infection does not increase the risk for postprocedural complications, including death, up to 30 days after the procedure. Thus surgical intervention should not be limited because of HIV status and concern for subsequent complications. However, during anesthesia, tachycardia is more frequently seen in HIV-seropositive patients. Also, high fever, anemia, and tachycardia are more frequent postoperatively.

Several studies indicate that general anesthesia and opiates may impair immune function. Although this is likely of little clinical importance in healthy individuals, the implications for HIV-infected patients are not known. Immunosuppression due to general anesthesia occurs within 15 minutes of induction and may persist for as long as 3 to 11 days. Postoperative immunosuppression may last longer in inherently immunosuppressed patients and may predispose to the development of postoperative infections or facilitate tumor growth or metastasis.

In the current era of HAART, HIV is often not associated with opportunistic infections, but it is associated with chronic low-grade inflammation and early manifestation of diseases of aging. Therefore in patients who have been HIV positive for many years, there should be a higher index of suspicions for such conditions as coronary artery disease, cerebrovascular disease, diabetes, renal disease, and dementia.

Obstetric Patients

HIV and AIDS are common in women of childbearing age. In one study, zidovudine monotherapy was shown to dramatically reduce the incidence of vertical transmission of HIV from 25.5% to 8.3%. However, zidovudine monotherapy has limited long-term benefits because HIV resistance develops rapidly. Therefore in pregnancy, combination therapy is now believed to be preferable. With modern treatment regimens, transmission of HIV from mother to child can be virtually eliminated.

There are limited data on the use of PIs in pregnancy. A recent meta-analysis strongly suggested that cesarean section independently reduces the incidence of vertical transmission. Combined antiretroviral therapy and elective cesarean section reduce the rate of vertical transmission to 2%. However, cesarean section is a major surgical

intervention with well-known complications. There is a higher incidence of morbidity following cesarean compared with vaginal delivery, even in healthy women, including more prolonged and intense pain, longer duration of bed rest, increased blood loss, and more frequent venous thrombosis and wound infection. Many practitioners today do not recommend elective cesarean section to HIV-infected women who are compliant with antiretroviral therapy and have undetectable HIV viral loads. Unfortunately, HIV-positive women with low CD4 lymphocyte counts, whose infants would theoretically benefit most from cesarean delivery, are also those who are most likely to experience significant postoperative complications.

In a study of HIV-seropositive parturients receiving regional anesthesia, there were no infectious or neurologic complications related to the anesthetic or obstetric courses. In the immediate postpartum period, immune function measurements remained essentially unchanged, as did the severity of the disease. There have been concerns that epidural and lumbar puncture in HIV-seropositive patients may allow entry of the virus into the CNS. However, the natural history of HIV includes CNS involvement early in the clinical course, and expression of CNS infection varies widely.

Finally, epidural blood patches for the treatment of post–dural puncture headache have been reported as safe and effective in HIV-seropositive patients. Nevertheless, given the very small theoretical risk of introducing virus to the CNS, other analgesic strategies should be tried first.

Intensive Care Unit Complications

APACHE II scoring significantly underestimates mortality risk for HIV-seropositive patients admitted to a medical ICU with a total lymphocyte count less than 200 cells/mL. This is particularly true for those admitted with pneumonia or sepsis. There is a diverse range of indications for critical care in patients with HIV infection. Historically, respiratory failure due to PCP has been the most common reason for admission to an ICU, accounting for 34% of cases. Mechanical ventilation for PCP and other pulmonary disorders is associated with a mortality rate greater than 50%. In contrast, ICU admission and mechanical ventilation for nonpulmonary disorders are associated with a mortality rate less than 25%. In patients with septic shock, HIV infection is an independent predictor of poor outcome. In the era of HAART, fewer patients with HIV infection are admitted to ICUs with AIDS-defining illnesses such as PJP. In fact, many patients are now admitted with unrelated critical illnesses and are coincidentally found to be infected with HIV. Nonetheless, initiation of HAART in patients with PJP is known to improve outcome. However, this benefit must be weighed against problems associated with immune reconstitution, which may occur in septic patients when HAART is initiated.

PREVENTION

There is little specific information concerning the overall risk of anesthesia and surgery in HIV-seropositive patients. The American Society of Anesthesiologists' physical status assessment and the inherent surgical risk probably provide a measure of global risk. This information, when combined with the Centers for Disease Control and Prevention stage of HIV infection, the degree of immunosuppression, and the presence and severity of opportunistic infection or neoplasm, may offer the best predictor of global preoperative risk for HIV-seropositive patients. With regard to choice of anesthetic technique to minimize complications, regional anesthesia is the technique of choice, except in certain cases of neuropathies.

Finally, anesthesiologists and intensivists have contact with a broad range of patients, many of whom may be HIV-seropositive. Therefore rigorous adherence to infection control practices is imperative. Further, all clinicians should keep abreast of current knowledge about HIV therapy to ensure that their patients are receiving optimal treatment.

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10 Hypertensive Disorders of Pregnancy

Curtis L. Baysinger

Case Synopsis

A 27-year-old woman, at a gestational age of 37 weeks, is currently 4 cm cervical dilation and undergoing an induction of labor for worsening preeclampsia. Her blood pressure (BP) is 150/100 mm Hg after several doses of intravenous (IV) labetalol and she has 4+ patellar reflexes, right upper quadrant tenderness, and 4+ proteinuria. Her platelet count was 135,000/mm^3 on admission, but has decreased to 95,000/mm^3. She is receiving 1 g/h of IV magnesium sulfate ($MgSO_4$) and oxytocin augmentation. Her past obstetric history is significant for preeclampsia with her previous pregnancy, delivered at 35 weeks. She is morbidly obese with a body mass index of 41 kg/m^2. She and her obstetrician have requested epidural analgesia for labor.

PROBLEM ANALYSIS

Definition

In 2000 the National High Blood Pressure Education Program proposed four categories of hypertension associated with pregnancy, a categorization that has gained widespread acceptance. The Task Force on Hypertension in Pregnancy of the American College of Obstetricians and Gynecologists (ACOG) updated the content of the classification in 2013 and retained nearly the same four categories: gestational hypertension, preeclampsia (with and without severe features), chronic hypertension, and chronic hypertension with superimposed preeclampsia (Box 10.1).

Gestational hypertension occurs with elevated BPs after 20 weeks' gestation without other diagnostic features of preeclampsia. Preeclampsia occurs with and without severe features and is typically diagnosed by BPs greater than or equal to 140/90 mm Hg with proteinuria (Table 10.1). Preeclampsia with severe features is characterized by severe range BPs with or without other maternal organ dysfunction (see Table 10.1). Eclampsia is defined as the occurrence of seizures unrelated to a preexisting neurologic disorder that occur in women who are preeclamptic. Chronic hypertension is diagnosed with a BP greater than or equal to 140/90 mm Hg before 20 weeks' gestation or after 12 weeks following delivery. Chronic hypertension with superimposed preeclampsia is diagnosed with new-onset proteinuria, a marked increase of preexisting proteinuria or BP, or when other symptoms of organ dysfunction are noted. The HELLP syndrome is characterized by the presence of intravascular hemolysis, elevated liver enzymes (most often alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]), and low platelet count; it usually manifests earlier during pregnancy compared with other types of preeclampsia.

Recognition

Preeclampsia with severe features is defined when BP exceeds 160/100 mm Hg or the patient exhibits evidence of end-organ damage (see Table 10.1). Severe features can include the following:

- Pulmonary edema.
- Renal dysfunction. Although large proteinuria was previously used as a criterion for defining severe preeclampsia, recent work has not shown a significant relationship between the degree of proteinuria and pregnancy outcomes; therefore the degree of proteinuria has been dropped as a diagnostic feature for severe disease.
- Cerebral manifestations, including headache, visual changes, or seizures.
- Elevated liver enzymes with right upper quadrant pain (secondary to hepatic capsular distention).
- Thrombocytopenia with a platelet count less than 100,000/mm^3.

Intrauterine growth restriction, previously included, has been removed as a criterion.

The HELLP syndrome may occur with modest levels of BP elevation, and in 15% of cases BP can be normal. Diagnosis of preeclampsia in the parturient with preexisting chronic hypertension and renal disease can be very difficult; increases in urinary protein over time may be the only sign. It may be difficult to identify preeclampsia in parturients with acute cocaine intoxication, as both can present with seizures, pulmonary edema, proteinuria, and thrombocytopenia. However, the onset of seizures in women after 20 weeks' gestation with an elevated BP should be considered eclampsia until proven otherwise. Preeclampsia with severe features can present up to 2 weeks postpartum.

Risk Assessment

Gestational hypertension occurs in approximately 5% of pregnancies, and 50% of women with gestational hypertension before 30 weeks of pregnancy develop preeclampsia. Preeclampsia occurs in approximately 6% to 8% of all pregnancies in the United States, 25% of which will go on to develop preeclampsia with severe features. It accounts for 25% of all maternal deaths in the United States.

Several risk factors are associated with the development of preeclampsia (Box 10.2). Demographic factors, such as advanced maternal age and African American ethnicity, increase risk. Some obstetric conditions that increase its possibility are uterine overdistention (e.g., multiple gestations, polyhydramnios), trophoblastic disease, abnormal uterine artery Doppler studies obtained between 18 and 24 weeks' gestation, and previous histories of preeclampsia and placental abruption. Preexisting maternal diseases, such as obesity, diabetes, chronic hypertension, and collagen vascular disorders, convey higher risk for preeclampsia as well.

BOX 10.1 Classification of Hypertensive Disorders in Pregnancy

Gestational hypertension
Preeclampsia
  Preeclampsia
  Preeclampsia with severe features
Chronic hypertension
Chronic hypertension with superimposed preeclampsia

TABLE 10.1 Diagnostic Features of Preeclampsia

Type	Findings
Preeclampsia	• BP >140/90 mm Hg after 20 weeks' gestation • Proteinuria (300 mg in 24 hr, 1+ or 2+ by dipstick, protein/creatinine ratio >0.3)

Preeclampsia with severe features	• BP >160/110
	• Serum creatinine >1.1 mg/dL or a >2-times rise in baseline
	• Patient signs/symptoms of organ dysfunction
	  • Headaches/visual disturbances/seizures
	  • Pulmonary edema
	  • Thrombocytopenia (<100,000/mm^3)
	  • Abnormal liver function

BOX 10.2 Risk Factors for Preeclampsia

Demographic Factors
Advanced maternal age (>35 yr)
African American race

Concurrent Maternal Disease
Obesity
Preexisting hypertension
Diabetes
Renal disease
Antiphospholipid antibody syndrome
Vascular or connective tissue disorder
Angiotensin gene T235

Obstetric Conditions/History
Multiple gestations
Polyhydramnios
Molar pregnancy
Previous history of preeclampsia
In vitro fertilization
Nulliparity
Previous history of placental abruption, fetal growth restriction
Partner who fathered a previously preeclamptic pregnancy

Parturients who develop preeclampsia in the second trimester have worse obstetric outcomes compared with those who develop it after 34 weeks' gestation. These patients are more likely to have underlying chronic hypertension, renal disease, or a collagen vascular disorder than patients who develop preeclampsia later in gestation. Severe hypertension refractory to therapy, progressive thrombocytopenia or liver function abnormalities, oliguria, and a poor fetal environment (determined by nonstress testing or biophysical profile, particularly with an estimated fetal weight below the 5th percentile) are ominous signs. Doppler studies of umbilical arteries can help time delivery. Lack of diastolic flow, which progresses to an acute reversal of flow during diastole, is an indication for urgent delivery.

Currently, there is no single cost-effective screening test that reliably predicts preeclampsia, even in higher-risk populations. Despite advances in identifying and measuring biomarkers associated with preeclampsia (elevated soluble fms-like tyrosine kinase [sFLT1] and soluble endoglin [sEng]), scores combining abnormal levels of these makers with early Doppler studies of umbilical vessels lack sufficient positive predictive value to be useful for routine screening.

Preeclampsia evolves from a subclinical syndrome to overt disease over time. During an asymptomatic first stage, uterine spiral arteries fail to dilate as in normal pregnancies, so the fourfold increase in artery diameter and resultant low-resistance, high-flow state characteristic of typical uterine perfusion fails to develop. Decreased placental perfusion predisposes to fetal growth restriction in the symptomatic later stage. In addition, antiangiogenic factors, primarily sFLT1 and sEng, are released due to pathologic disruption of the normal immunologic cascade that promotes normal placental spiral artery development. Increased levels of sFLT1 and sEng reduce placental release of vascular endothelial growth factor and placental growth factor, which further retards normal placental vascular development. These placental factors also retard normal maternal endothelial repair and lead to maternal vascular damage and proteinuria, hypertension, cerebral vasospasm, and occasional liver dysfunction characteristic of the damage to target organs in preeclampsia. Additional inflammatory mediator release and lipid peroxidation by the placenta further promotes maternal endothelial damage. Instead of becoming less sensitive to vasoconstrictors as during normal pregnancy, the maternal vasculature becomes more sensitive, perhaps due to abnormally high levels of thromboxane compared with prostacyclin. The normal increases in renin, angiotensin II, and aldosterone fail to develop, most likely explained by failure of maternal endothelial cells to synthesize prostacyclin and nitric oxide. The generalized pathophysiology is one of widespread endothelial damage in the face of generalized vasoconstriction and activation of the coagulation system, including consumption of coagulation factors and platelets. Edema is attributed to salt and water retention, which is aggravated by decreased colloid osmotic pressure in the presence of proteinuria.

Implications

Maternal and neonatal morbidity increase with increased maternal age, an earlier gestational age at onset (especially when preeclampsia develops before 32 weeks' gestation), and preexisting maternal diabetes, renal disease, or thrombophilia. Generalized edema is not a diagnostic criterion, but is often severe and is of particular interest to anesthesia providers as it predicts airway and laryngeal edema. The risk of pulmonary edema is greatest after delivery when colloid osmotic pressure is lowest and affects approximately 3% of all women with preeclampsia. Most deaths due to preeclampsia result from intracranial hemorrhage or pulmonary edema.

Generalized cerebral edema can occur in women in association with a hyperdynamic and hyperfused cerebral vasculature. When present on magnetic resonance imaging (MRI), it conveys poor prognosis in the patient with a depressed sensorium. Computed tomographic and MRI studies of women several months after delivery may show small residual areas of cerebral infarction.

The cardiovascular system shows increased vascular tone and sensitivity to vasoconstrictors. Blood volume is reduced in most patients with preeclampsia compared with normotensive parturients. Sympathetic system activation most often leads to hyperdynamic hemodynamics in patients with severe preeclampsia with increased cardiac output and increased systemic vascular resistance. However, pulmonary artery catheter studies have revealed a subset of patients with reduced blood volume, depressed left ventricular function, and markedly increased systemic vascular resistance. This work has been corroborated in studies using transthoracic echocardiography (TTE). These observational case series also report a number of other abnormalities, including increased left ventricular mass, pericardial effusion, diastolic

dysfunction, and, rarely, ventricular dilation with depressed contractility. This later change is found most often in patients who present with other signs of cardiac failure.

Determining the typical maternal cardiovascular changes in preeclampsia has been difficult because most observational hemodynamic studies have been performed in women who were undergoing therapy. For example, depressed cardiac function in women who are hypovolemic often responds dramatically to volume expansion with increases in cardiac output of three to four times that of baseline, and judicious hydration is initiated almost immediately on hospitalization in most women. In addition, treatment with afterload reduction can dramatically improve depressed cardiac function, which in many studies had already begun in women with signs of cardiac failure. Most likely, the natural course starts with a hyperdynamic cardiovascular system with elevated systemic vascular resistance and central volume depletion and changes to one of more normal intravascular volume with signs of cardiac decompensation.

Thrombocytopenia secondary to consumptive coagulopathy occurs in 11% to 50% of patients with severe preeclampsia. Reduction in the platelet count to less than 100,000/mm^3 is associated with other coagulation abnormalities and occurs more often with HELLP syndrome. Intrinsic platelet dysfunction may also occur. However, patients with severe preeclampsia in whom the platelet count is greater than 100,000/mm^3 on admission are unlikely to develop a clinically significant thrombocytopenia, except in those with other signs of HELLP syndrome.

Oliguria may result from low cardiac filling pressures and often responds well to fluid challenge. Less often, oliguria is associated with depressed cardiac function and very high systemic vascular resistance. If so, afterload reduction is the treatment of choice.

Uteroplacental blood flow decreases as a result of uterine artery vasospasm. Exaggerated reductions in uteroplacental blood flow may occur when large amounts of vasopressors are used to treat hypotension, which may accompany the onset of neuraxial blockade.

Because many women have delivery early in gestation, preeclampsia is a common cause of preterm delivery in developed countries. Placental abruption is more common due to superficial placental development and postpartum hemorrhage is more common due to therapies for seizure prevention and BP treatment.

Women with a history of preeclampsia are at increased long-term risk for cardiovascular disease, including stroke and ischemic heart disease. The risk increases with increasing severity of preeclampsia. Some data suggest a reduced risk for solid cancers later in life.

MANAGEMENT

Obstetric Management

Obstetric management includes judicious delivery, prevention of seizures, fluid status optimization, and treatment of excessive increases in BP. The ACOG recommends that BPs of 160/110 be aggressively treated with the goal of reducing BP 15% to 25% to 120 to 160 mm Hg systolic and 80 to 105 mm Hg diastolic; lowering BP to "normal" may lead to uterine hypoperfusion. The goal of therapy is to reduce the risk for cerebral hemorrhage, placental abruption, or myocardial ischemia. The association of systolic pressures greater than 160 mm Hg with an increased risk for stroke has lead to an ACOG emphasis on systolic pressure reduction. Despite this, failure to recognize severe range BPs was found contributory in approximately 60% of deaths related to preeclampsia in one study.

In 2011 the ACOG recommended use of either labetalol or hydralazine as first-line therapies for the urgent treatment of hypertension; however, one recent trial showed that increasing doses of oral nifedipine more rapidly reduced BP and conveyed less risk for hypotension than IV labetalol. Despite the ACOG's recommendation, a recent systematic review suggests no clear advantage of a particular drug therapy over another, but notes that diazoxide, nimodipine, and $MgSO_4$ are inferior choices for BP control. $MgSO_4$ is ineffective as an antihypertensive agent because its vasodilatory effects are weak and transient. IV hydralazine is an older and effective therapy for the treatment of hypertension and is administered in doses of 5 to 10 mg every 15 minutes. Labetalol is given incrementally to a cumulative dose of 0.5 to 1 mg/kg.* Neither appear to have significant effects on neonatal heart rate or uterine blood flow. Dihydropyridine calcium channel blockers (e.g., nicardipine, nifedipine) also appear to be effective with little or no effect on labor and neonatal outcome, and are indicated for second-line therapy if labetalol and hydralazine are not effective. However, they have the theoretical potential to produce unexpected hypotension if used in patients also receiving $MgSO_4$. Calcium channel blockers should be avoided in women with known coronary artery disease or long-standing diabetes and aortic stenosis. Nitroglycerin administered by infusion may be effective in reducing BP, but its usefulness in the laboring women is limited by the marked uterine smooth muscle relaxation that accompanies its use.

Delivery is indicated in preeclampsia without severe features at a gestational age greater than 37 weeks; further expectant management is associated with poorer obstetric outcomes. Delivery is mandatory in women with preeclampsia with severe features if hypertension is uncontrolled after 24 to 48 hours of therapy, or with progressive renal dysfunction, severe thrombocytopenia, worsening coagulopathy, onset of fetal non–well-being, impending eclampsia, liver function values twice the upper limit of normal, or cardiopulmonary compromise. If possible, delivery is delayed for 48 hours after glucocorticoid administration to accelerate fetal lung maturity. Expectant management is safe if the BP is well controlled, laboratory parameters stabilize, and the fetal environment is reassuring. Delivery is indicated when gestational age reaches 34 weeks in women with severe disease, as further expectant management is associated with worse obstetric outcomes. Vaginal delivery should be attempted in all women with preeclampsia without severe features, and in most with severe disease.

Several studies have documented the effectiveness of $MgSO_4$ for the prevention of seizures. The British Eclampsia Trial Collaborative Group study of nearly 3 decades ago found a 52% reduction in seizure activity with $MgSO_4$. In this trial, $MgSO_4$ was superior to diazepam or phenytoin for seizure prevention, although the routine use of phenytoin is common outside the United States. $MgSO_4$ has the added benefit of improving fetal neurologic outcome in those neonates delivered preterm.

$MgSO_4$ does not appear to alter the duration of labor, interfere with coagulation, or significantly affect uterine blood flow in parturients with epidural blockade. It is given as a 4- to 6-g bolus with an infusion of 1 to 2 g/h, but no consensus exists on the ideal time to initiate treatment, the best loading and maintenance doses, or the optimal duration of therapy after delivery. Magnesium serum levels are checked every 8 hours to ensure therapeutic concentrations of 4 to 7 mg/dL. Loss of deep tendon reflexes precedes respiratory compromise with $MgSO_4$ toxicity and treatment with airway support, and IV calcium gluconate of 1 g over 10 minutes may be necessary.

*This bolus dose of IV labetalol is very high. With such doses, α-adrenergic blocking effects are expected to be more prominent, with β-blocking effects near the maximum clinical effect. The administration of such high doses would be contraindicated in women who present with signs and symptoms of congestive heart failure.

Anesthetic Management

Labor and Vaginal Delivery

The anesthetic management of the patient with preeclampsia without severe features differs little from that of normals. In women with severe disease, epidural analgesia provides superior pain relief and also has beneficial effects on placental blood flow. It can rapidly be converted to neuraxial anesthesia for emergency cesarean delivery. Judicious volume loading and incremental dosing of local anesthetics reduce the risk of significant hypotension.

Thrombocytopenia occurs in 15% to 20% of patients with preeclampsia with severe features. One should obtain a platelet count before performing neuraxial anesthesia in women with preeclampsia with severe features. Acute-onset thrombocytopenia is more ominous than the chronic variety; however, specific platelet count values that increase the risk for epidural hematoma are unknown. One retrospective study suggests that platelet counts less than 75,000/mm^3 are insensitive in predicting untoward events. Therefore it is prudent to consider tests for platelet activity (i.e., thromboelastography) when the platelet count is less than 75,000/mm^3, especially in patients with the HELLP syndrome. Similar to reduced platelet count, degrees of abnormality that increase the risk for central neurologic sequelae due to bleeding are unknown; however, a normal examination is reassuring. One should consider the risk of epidural block versus the benefits in patients with thrombocytopenia, balancing a risk for spinal bleeding versus the benefits of superior pain relief, salutary BP effects, the ability to expeditiously convert analgesic to anesthetic blocks for cesarean delivery, and avoidance of airway management if general anesthesia might be required for urgent delivery. It seems prudent to place epidural catheters early in labor before platelet counts fall below 100,000/mm^3; however, this increases the risk that a catheter might be retained for a considerable period after delivery while waiting for the coagulation status to improve.

Cesarean Delivery

Cesarean delivery can be accomplished with spinal, epidural, or general anesthesia. The use of neuraxial anesthesia avoids the hemodynamic responses associated with general anesthesia. Spinal (subarachnoid) block can be used safely in severely preeclamptic patients after judicious volume loading, and some evidence suggests that hypotension occurs less frequently with spinal anesthesia than in women without preeclampsia. Recent evidence-based reviews and prospective cohort studies comparing subarachnoid and epidural blocks in severely preeclamptic patients show that the BP effects and the need for vasopressors are similar. However, subarachnoid block for cesarean delivery is associated with statistically greater (but clinically insignificant) neonatal umbilical artery base deficit and lower pH values versus parturients who receive general anesthesia. Combined spinal-epidural anesthesia with lower-dose hyperbaric bupivacaine (7.5 mg) with fentanyl (25 μg) may offer the advantage of rapid onset with the ability to extend the anesthetic level and duration of block if necessary. Furthermore, it may reduce the risk of adverse hemodynamic changes compared with subarachnoid block with higher doses of local anesthetic.

The smaller needles used for subarachnoid block may convey less risk for spinal hematoma than the larger needles used for epidural anesthesia. However, epidural anesthesia with judicious incremental dosing may reduce the volume of fluid administration and the need for vasopressors. The use of large doses of vasopressor-containing local anesthetic solutions for epidural anesthesia is controversial. Some studies advocate their safety, but severe hypertension after their use has been reported.

General anesthesia should be reserved for emergency delivery, and airway edema may make endotracheal intubation difficult. A variety of small endotracheal tubes should be available, and management of a difficult airway should be anticipated. All patients should receive appropriate prophylaxis for pulmonary aspiration. Measures to reduce the BP increase accompanying tracheal intubation or light anesthesia should be available as pulmonary edema, cerebral edema, or intracranial hemorrhage may result from untreated hypertension. Sodium nitroprusside (SNP) is effective but must be titrated carefully due to the potential for severe hypotension. Direct arterial pressure monitoring is usually required when using SNP. Similarly, the effects of nitroglycerin are unpredictable (it is a primary venodilator, with a consequent drop in preload). IV nicardipine (15 to 30 μg/kg) may also be effective. Because it is arterioselective (i.e., has little effect on venous capacitance or preload), nicardipine is less likely to produce rapid declines in BP compared with SNP or nitroglycerin. Remifentanil in doses of 1 μg/kg has been recently shown to blunt the hypertensive responses associated with tracheal intubation. Although the drug is rapidly metabolized by both the mother and fetus, neonates may experience transient respiratory depression.

Propofol and etomidate are acceptable induction agents, and ketamine should generally be avoided. Succinylcholine is a good choice for muscle relaxation. Durations of both depolarizing and nondepolarizing agents may be prolonged in women who have received magnesium.

PREVENTION

Therapy with $MgSO_4$ reduces the risk of neonatal intraventricular hemorrhage and improves neurologic outcomes in preterm infants of preeclamptic mothers. There is no evidence that colloid is preferable to crystalloid for volume expansion, and some retrospective reviews of fluid management report that colloid administration is associated with increased maternal mortality. Antepartum dexamethasone increases the platelet count, which may allow the use of neuraxial analgesia or anesthesia in some patients with the HELLP syndrome.

No therapy has been shown to consistently reduce the incidence of preeclampsia. Studies of low-dose aspirin therapy to ameliorate the thromboxane/prostacyclin imbalance, dietary calcium supplementation in women with low dietary calcium intake, and the administration of other antioxidants such as vitamin C or E have failed to show consistent success. However, the ACOG recommends aspirin prophylaxis beginning at the end of the first trimester in women with a history of early-onset preeclampsia who delivered before 34 weeks' gestational age in a previous pregnancy.

Pulmonary artery pressure monitoring does not appear to improve maternal outcome and in most cases is not needed for the management of preeclampsia. One case series of routine pulmonary artery catheter monitoring in preeclamptic patients with severe features concluded that the data it provided did not alter clinical management. Nonetheless, patients with cardiopulmonary compromise or other appropriate indications should be considered for pulmonary artery pressure monitoring. Central venous pressure monitoring is usually not helpful. The use of TTE offers an exciting new way to monitor the hemodynamics of women with preeclampsia and may help direct therapy in women with hemodynamic compromise by measuring ventricular contractility, assessing intravascular volume status, and determining ejection fraction to differentiate preserved versus reduced ejection fraction heart failure.

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Hyperthyroidism: Thyroid Storm

11

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Case Synopsis

A 32-year-old woman undergoes emergent general anesthesia maintained with 1.2% isoflurane for fixation of a compound humeral fracture. Preoperative history is significant for anxiety and intolerance to heat. Physical examination is noteworthy for periorbital swelling; warm, moist skin with sweaty palms; and a noticeable midline lower neck mass consistent with an enlarged thyroid. Thirty minutes after induction, sinus tachycardia (128 beats per minute) with premature atrial contractions, arterial hypertension (195/100 mm Hg), and hyperpyrexia (core temperature 37.9° C despite a cool operating room environment) are noted. However, physical examination reveals the absence of muscle rigidity. The hemodynamic changes persist despite increasing the depth of anesthesia to 2% isoflurane supplemented with incremental doses of intravenous sufentanil.

PROBLEM ANALYSIS

Definition

Normal regulation and activity of thyroid hormone are summarized in the chapter on hypothyroidism. Increased circulating thyroid hormones lead to a hypermetabolic state. The following definitions apply to clinical syndromes of hyperthyroidism:

- *True hyperthyroidism* is thyroid gland hyperactivity with increased synthesis and secretion of thyroid hormone.
- *Thyrotoxicosis* refers to the clinical and biochemical manifestations of excess thyroid hormone. It affects 2% of women and 0.2% of men in the general population. Causes include thyroid gland hyperactivity, ectopic thyroid hormone synthesis, and iatrogenic causes.
- *Thyrotoxic crisis* or *thyroid storm* is a life-threatening complication of hyperthyroidism characterized by a severe, sudden exacerbation of thyrotoxicosis. Patients with uncontrolled hyperthyroidism presenting for surgical or trauma care are at considerable risk of developing thyrotoxicosis. Therefore it is critical that anesthesiologists carefully assess patients who may be at risk of thyroid storm before proceeding with anesthesia and surgery (Table 11.1).
- *Thyrotoxicosis factitia* refers to thyrotoxicosis without true hyperthyroidism (e.g., intentional ingestion of synthetic thyroid hormone, ectopic thyroid hormone production) and is associated with decreased endogenous synthesis of thyroid hormone.

Recognition, Risk Assessment, and Implications

History

Patients with undiagnosed hyperthyroidism often have a history of anxiety (occasionally progressing to psychosis or even coma), significant recent weight loss, heat intolerance, gastrointestinal disturbances (diarrhea, nausea, vomiting, abdominal pain), unexplained fever, muscle weakness, and tremor. Presentation is different in younger and older patients. Younger patients present with classic adrenergic symptoms (e.g., tachycardia, restlessness, or tremor). Older patients present with apathetic symptoms, such as depression, fatigue, and weight loss, and may not have adrenergic signs or symptoms. Thyroid storm is usually precipitated by a stressful event such as surgery, childbirth, infection, myocardial infarction, diabetic ketoacidosis, or major trauma.

Physical Examination Findings

Findings on physical examination that support the diagnosis of hyperthyroidism include the following symptoms (in decreasing order of frequency):

- Altered mental status (nervousness, agitation, anxiety, confusion, possible psychosis, or even coma)
- Sweating, heat intolerance
- Weight loss, fatigue, muscle weakness
- Increased appetite, diarrhea, other gastrointestinal symptoms
- Prominent, dry eyes
- Leg swelling

Signs of hyperthyroidism include the following (in decreasing order of frequency):

- Goiter—neck mass with potential airway compromise (Fig. 11.1)
- Sinus tachycardia (virtually 100% incidence) or associated tachyarrhythmias (Fig. 11.2)
- Warm, moist skin
- Muscle tremor
- Systolic hypertension, usually with a widened pulse pressure
- Atrial fibrillation, classically in the elderly (about 10% incidence)
- Enlarged thyroid and a possible thyroid bruit
- Ophthalmic signs, including exophthalmos, lid lag, lid retraction, periorbital swelling, and conjunctival injection
- Pretibial edema

Pathophysiology

The actual mechanism whereby thyrotoxicosis decompensates into thyroid crisis is poorly understood, but it most often develops after a stressful precipitating event. Whatever the cause, the resulting syndrome resembles prolonged, severe β-adrenergic agonist overdose. However, actual catecholamine concentrations generally are normal, despite the apparent hypermetabolic state.

TABLE 11.1 Diagnostic Criteria for Thyroid Storm

Criteria	Points	Criteria	Points
Thermoregulatory Dysfunction		Gastrointestinal-Hepatic Dysfunction	
Temperature (° F)		• Manifestation	
• 99.0–99.9	5	• Absent	0
• 100.0–100.9	10	• Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
• 101.0–101.9	15	• Severe (jaundice)	20
• 102.0–102.9	20		
• 103.0–103.9	25		
• ≥104.0	30		
Cardiovascular		Central Nervous System Disturbance	
Tachycardia (beats per minute)		Manifestation	
• 100–109	5	• Absent	0
• 110–119	10	• Mild (agitation)	10
• 120–129	15	• Moderate (delirium, psychosis, extreme lethargy)	20
• 130–139	20	• Severe (seizure, coma)	30
• ≥140	25		
Atrial fibrillation			
• Absent	0		
• Present	10		
Congestive heart failure		**Precipitant history**	
• Absent	0	Status	
• Mild	5	• Positive	0
• Moderate	10	• Negative	10
• Severe	20		
Scores totaled			
>45	Thyroid storm		
25–44	Impending storm		
<25	Storm unlikely		

From Burch HB, Wartofsky L: Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 22(2):263-277, 1993.

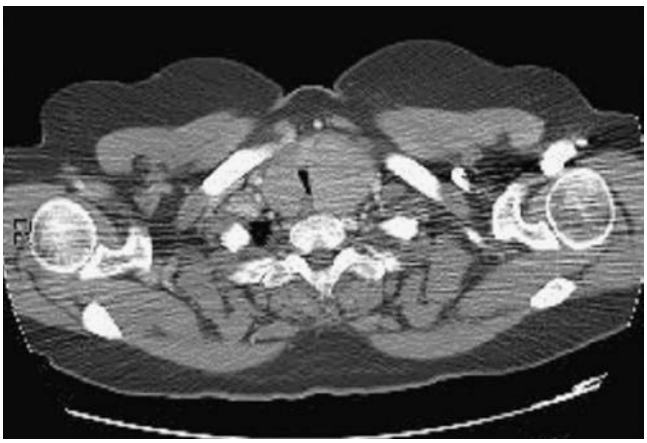

Fig. 11.1 Computed tomography scan (with intravenous contrast) of lower neck–upper thorax region reveals an enlarged thyroid gland (goiter) compressing the trachea and esophagus. Anesthetists must recognize the potential for significant airway compromise during induction of anesthesia in patients with large goiters in the neck and anticipate possible extension of the goiter to the retrosternal space. Up to 6% of tracheal intubations in patients anesthetized for thyroid surgery are difficult.

Cause

Undiagnosed hyperthyroidism (usually Graves' disease or toxic multinodular goiter) in a patient with major stress is the most common cause of thyroid storm. Another cause may be inadequate treatment in a known hyperthyroid patient. Disorders associated with thyrotoxicosis are listed in Box 11.1. Moreover, the many causes of thyrotoxicosis can be partially distinguished by a 24-hour radioactive iodine uptake study performed when the patient's condition is stable (Box 11.2).

Diagnosis

The diagnosis of thyroid storm is largely clinical (see Table 11.1). Corroboration and confirmation rely on thyroid studies with the following findings (Table 11.2):

- Elevated thyroxine (T_4)
- Elevated triiodothyronine (T_3)
- Decreased thyroid-stimulating hormone (TSH)

However, T_4 and T_3 concentrations may correlate poorly with the severity of clinical signs. Indeed, the Burch-Wartofsky-Score (see Table 11.1) is a point scale based solely on clinical and physical criteria that assesses the probability of thyrotoxicosis independently from the blood concentration of thyroid hormones. Other routine studies include a complete blood cell count, electrolyte levels, urinalysis, chest radiograph, and electrocardiogram. For instance, common associated laboratory abnormalities (present 5% to 20% of the time) include hypercalcemia, hypokalemia, hyperglycemia, hypocholesterolemia, microcytic anemia, lymphocytosis, granulocytopenia, hyperbilirubinemia, and increased alkaline phosphatase level. Last, a complete survey should look carefully for an infectious process.

Differential Diagnosis

Malignant hyperthermia must be considered simultaneously and treatment initiated if triggering anesthetic agents were used and clinical suspicion is high. This is especially true in children or when severe hypercarbia, acidosis, hyperkalemia, muscle rigidity, and increased creatine phosphokinase are present. Other hypermetabolic states such as sepsis, pheochromocytoma, or thyrotoxicosis without crisis, as well as neuroleptic malignant syndrome or serotonin syndrome, should be considered. Last, the differential diagnosis must include severe drug intoxication with either cocaine or amphetamines.

MANAGEMENT

Do not wait for laboratory results to begin treatment if there is sufficient clinical suspicion. Appropriate treatment includes general supportive measures; direct inhibition of thyroid hormone synthesis and thyroid hormone release, peripheral β-adrenergic activity, and peripheral conversion of T_4 to T_3; and regulation of intracellular calcium. If thyroid storm is refractory to standard treatment, special attempts should be made to remove circulating thyroid hormone.

General Supportive Measures

- Intravenous (IV) fluids to restore intravascular volume
- Acetaminophen for hyperthermia (avoid aspirin, because it displaces T_4 from thyroid-binding globulin, thereby increasing free T_4)

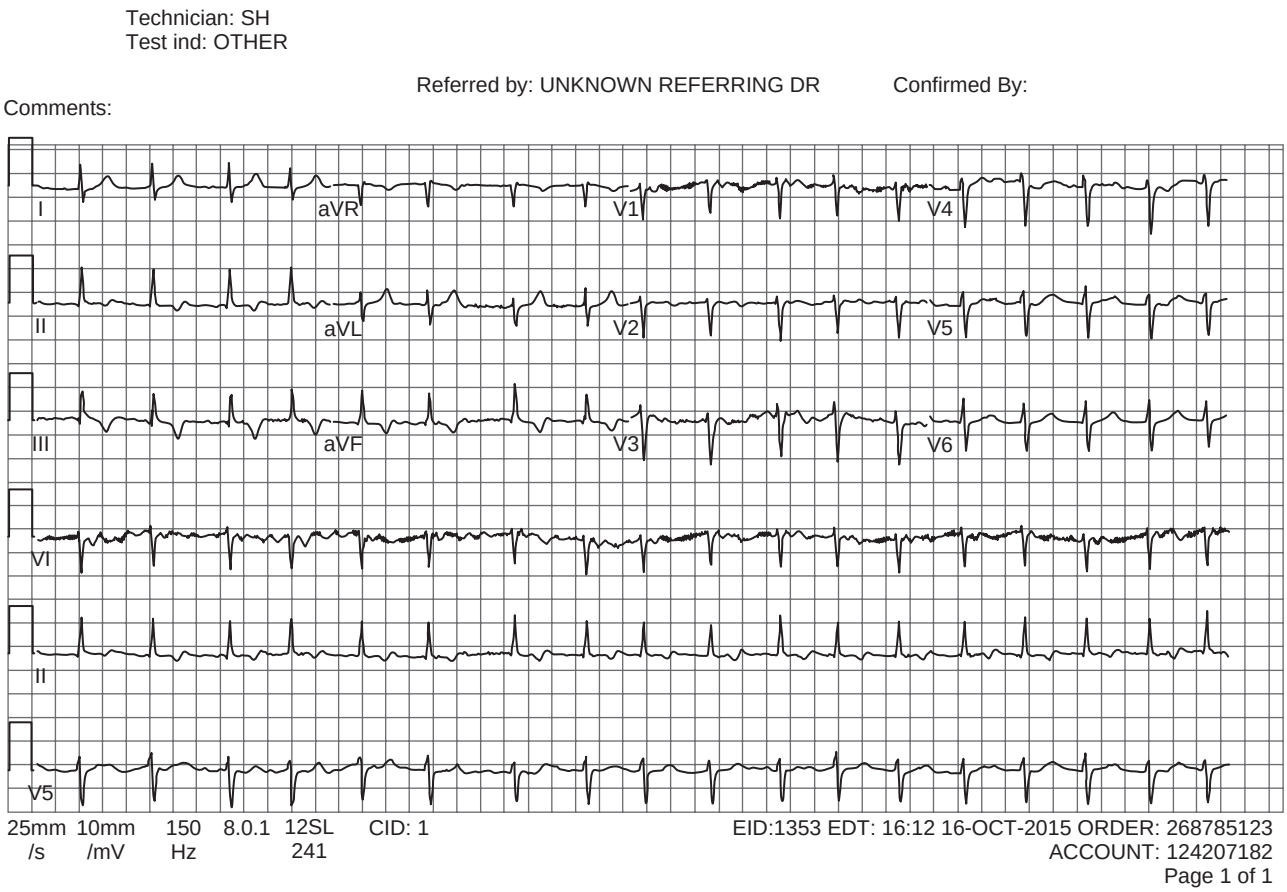

Fig. 11.2 Electrocardiogram (ECG) from a 71-year-old woman suffering from thyroid storm requiring mechanical ventilation and intensive care unit care. The ECG manifests characteristic changes of thyroid storm such as atrial fibrillation with rapid ventricular response (rate controlled with an esmolol infusion), nonspecific ST- and T-wave changes, and flipped T-waves probably indicative of concurrent inferior ischemia. At the time of this tracing, her thyroid function studies included FT3 = 9.7 [normal = 2.3–4.2 pg/mL]; FT4 = 3.4 [NL = 0.76–1.46 ng/dL]; and TSH <0.01 [NL = 0.40–4.0 mU/L].

BOX 11.1 Disorders Associated with Thyrotoxicosis

Graves' disease (may account for 85% of cases)
Toxic multinodular goiter
Toxic adenoma
Subacute thyroiditis
Neonatal thyrotoxicosis (consequent to maternal Graves' disease)
TSH-secreting pituitary tumor
Labor and childbirth
Hydatidiform mole
Metastatic (hyperfunctioning) thyroid carcinoma
Thyrotoxicosis factitia

TSH, Thyroid-stimulating hormone.

BOX 11.2 Causes of Thyrotoxicosis Differentiated by Radioiodine Uptake

Thyrotoxicosis with a normal or elevated neck radioiodine uptake
- Graves' disease
- Thyroid adenoma
- Trophoblastic disease
- TSH-producing pituitary adenomas
- Resistance to thyroid hormone

Thyrotoxicosis associated with near-absent neck radioiodine uptake
- Painless thyroiditis
- Amiodarone-induced thyroiditis
- Subacute thyroiditis
- Iatrogenic thyrotoxicosis
- Factitious ingestion of thyroid hormone
- Struma ovarii
- Acute thyroiditis
- Extensive metastases from thyroid cancer

- Cooling blankets and cool environment
- Magnesium salts to reduce the severity and incidence of cardiac arrhythmias
- Correction of all electrolyte derangements

Inhibition of Thyroid Hormone Synthesis

- Propylthiouracil (PTU)—up to 1000 mg initially as a loading dose, then 250 mg orally or via nasogastric tube every 4 hours. It may take 6 to 8 weeks to achieve a full euthyroid state; PTU also inhibits peripheral conversion of T_4 to T_3.
- Methimazole—this is the preferred agent today. Twenty to 30 mg orally or via nasogastric tube every 4 to 6 hours. Achieves a euthyroid state more quickly than PTU and has a lower incidence of agranulocytosis, hepatitis, and vasculitis.

TABLE 11.2 Results of Thyroid Function Studies in Patients with Thyroid Disorders

	DISORDER	
Test	**Hyperthyroid**	**Hypothyroid**
TSH	Low	High
Total T_4	High	Low
Total T_3	High	Low
Reverse T_3	High	Low to normal
Free T_4	High	Low
T_3 resin uptake*	High	Low

*Approximates serum hormone binding by thyroxine-binding globulin (normal range is 33%–48%).
T3, Triiodothyronine; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone.

Iodide Therapy

Iodide inhibits thyroid hormone synthesis (called the Wolff-Chaikoff effect). However, one should delay iodide therapy for at least 4 hours after beginning PTU or methimazole therapy.

- Sodium iodide—1 g intravenously every 8 hours.
- Potassium iodide (SSKI, a saturated solution of potassium iodide), such as Lugol solution—10 drops orally every 6 hours. Lugol solution was once widely administered for 7 to 10 days before elective thyroidectomy in an effort to reduce vascularity of the gland.
- Iopanoic acid—0.5 to 1.0 g/day (also blocks peripheral conversion of T_4 to T_3).

Inhibition of Peripheral B-Adrenergic Activity

- β-Blockers, which also block peripheral conversion of T_4 to T_3:
  - Propranolol—0.5 to 1.0 mg/min intravenously, up to a total dose of 2 to 10 mg; repeat every 3 to 4 hours. After initial control with IV drug, treat with 20 to 40 mg orally every 6 hours; occasionally, a patient may require up to 2 g/day orally owing to the variability of hepatic metabolism in thyrotoxic individuals.
  - Esmolol—IV bolus with 0.5 to 0.75 mg/kg, followed by IV infusion with 50 μg/kg per minute. If effect is inadequate after 5 minutes, repeat IV bolus and increase IV infusion to 100 μg/kg per minute; it may even be necessary to increase the infusion to 300 μg/kg per minute.
  - Titrate β-blockade to achieve a heart rate of 80 to 90 beats per minute.
  - If the patient has a history of reactive airway disease, use caution and a short-acting cardioselective agent such as esmolol, atenolol, or metoprolol.
- If β-blockers are contraindicated, other sympatholytic drugs (e.g., reserpine, a depleter of catecholamines, or guanethidine, an inhibitor of catecholamine release) may be useful as second-line agents.

Inhibition of Peripheral Conversion of T_4 to T_3

- PTU or methimazole (see dosages given earlier)
- β-Blockade (see dosages given earlier)
- Hydrocortisone 300 mg load, then 100 mg intravenously every 8 hours, or dexamethasone 2 mg intravenously or orally every 6 hours

Intracellular Calcium Regulation

Dantrolene in doses of 1 mg/kg (equivalent to that used for malignant hyperthermia) has been reported in anecdotal cases; however, its utility and efficacy in the setting of thyroid storm are not well defined.

Removal of Circulating Thyroid Hormone

- Therapeutic plasma exchange (patients will need several treatments because only 20% of circulating T_4 is removed each session and even less T_3 is removed than with T_4)
- Charcoal hemoperfusion

PREVENTION

Prevention of complications in patients with hyperthyroidism (especially thyroid storm) relies on recognition of the stigmata of undiagnosed hyperthyroidism during the preoperative evaluation. In addition, anesthesiologists must anticipate potential airway difficulties during tracheal intubation, which occurs in 6% of patients anesthetized for thyroid surgery (see Fig. 11.1). Mortality rate with thyroid storm may be as high as 20%; therefore improved survival relies on early, aggressive therapy. In addition, definitive therapy requires treatment of any associated disorders, such as infection or diabetic ketoacidosis.

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12 Hypothyroidism: Myxedema Coma

Monica I. Lupei • Richard C. Prielipp

Case Synopsis

A 53-year-old woman with a long history of hypothyroidism and tobacco abuse presents to the emergency department with generalized weakness, lethargy, mild shortness of breath, edema of her lower extremities, constipation, and slow speech. She admits to stopping her thyroid replacement 2 years ago. Her current medication list includes only Flonase and Metamucil. Her physical examination is significant for hypothermia, lethargy, bradylalia, dry mucosa, brittle and coarse hair, distant heart tones, bradycardia, decreased breath sounds bilaterally, a distended but nontender abdomen, and bilateral lower extremity nonpitting edema. The laboratory results are notable for mild anemia (hemoglobin 9.4 g/dL), leukocytosis (white blood cell count 17.2 × 10^9/L), and hypokalemia (3.1 mM). The patient is profoundly hypothyroid with a thyroid-stimulating hormone (TSH) level of 120 mU/L (normal value 0.4–4.0 mU/L) and free T_4 of 0.08 ng/dL (normal value 0.46–0.76 ng/dL). Chest, abdomen, and pelvic computed tomography images reveal a large pericardial effusion, small right pleural effusion, and marked ascites. The endocrinology consultant immediately starts the patient on intravenous (IV) levothyroxine, liothyronine, and hydrocortisone. The patient also requires a dopamine infusion secondary to persistent bradycardia and hemodynamic instability.

Because there were mild signs of early tamponade, a needle pericardiocentesis was completed, followed 3 days later by a pericardial window for the large recurrent pericardial effusion. The induction of anesthesia for the pericardial window was performed using a combination of glycopyrrolate 0.4 mg, hydrocortisone 100 mg, etomidate 20 mg, fentanyl 50 μg, and succinylcholine 120 mg. The initial intubation attempt was unsuccessful with a 7.5 endotracheal tube (ETT), probably due to the airway edema and mucosal swelling. Therefore a 6.5 ETT was passed into the trachea. An appropriate depth of anesthesia was achieved with only 0.4 minimum alveolar concentration (MAC) isoflurane, low-dose fentanyl, and intermittent cisatracurium. Her anesthetic course was significant for hypothermia and bradycardia. Thus the patient also required a total of 50 mg of IV ephedrine to maintain an appropriate heart rate. The trachea was extubated at the end of the procedure after a prolonged emergence. Levothyroxine was continued throughout her hospitalization, and hydrocortisone was gradually tapered over 2 weeks. The pericardial drain was maintained for 3 days during her intensive care unit stay. The patient was discharged from the hospital to a long-term care facility 14 days after admission.

PROBLEM ANALYSIS

Definition and Physiology

Hypothyroidism is a common disease characterized by hypoactive thyroid function with decreased production and secretion of thyroid hormones. Myxedema is a life-threatening form of hypothyroidism manifested by decreased level of consciousness, leading to stupor or coma. Myxedema coma develops in chronic hypothyroid or untreated hypothyroid patients who face a secondary insult (infection, trauma, surgery, cold exposure, or even certain medications).

The thyroid gland normally secretes 80% thyroxine (T_4) and 20% triiodothyronine (T_3), the most active form of the thyroid hormones. T_4 and T_3 of thyroidal origin are synthesized by iodination and coupling of tyrosyl and thyroglobulin, and subsequently stored in the colloidal space. The majority of T_3 (80%) is actually synthesized by extrathyroidal conversion in organs such as the liver, kidney, and brain by deiodination of T_4. Some of the circulating T_4 is also converted to the inactive reverse-T_3 (rT_3). T_3 and T_4 are bound to serum proteins (thyroxin-binding globulin and transthyretin) in the plasma; *only free T_3 and T_4 are available for uptake* in the target tissues.

The thyroid-stimulating hormone (TSH) or thyrotropin is a pituitary hormone that stimulates biosynthesis and release of T_4 and T_3. The TSH secretion is regulated by T_3 and T_4 levels via a negative feedback mechanism. Hydrocortisone also inhibits the secretion of TSH. The TSH secretion is pulsatile, with the highest TSH level in the late evening. The thyrotropin-releasing hormone (TRH) is produced by the hypothalamus and stimulates the release of TSH.

The systemic activity of thyroid hormone is mediated via the nucleic receptors at the cellular level of many target tissues. Thyroid hormone also has an important role in neural and somatic development during fetal life and infancy. Thyroid hormone actions target almost all tissues and have important effects during adult life. They increase the basic metabolic rate; regulate protein, fat, and carbohydrate metabolism; stimulate bone growth; potentiate neural maturation; and increase sensitivity to catecholamine. The clinical effects include increased cardiac output and heart rate, ventilation rate, elevated basal metabolic rate, stimulated brain development and cognitive function, and increased global catabolism.

Recognition

Clinical Signs and Diagnosis

The clinical manifestations of hypothyroidism are nonspecific depending on the severity and the age of onset. Common symptoms include fatigue and weakness, weight gain, cognitive dysfunction, depression, dyspnea on exertion, cold intolerance, hoarseness, myalgia, dry skin, hair loss, constipation, infertility, and menstrual irregularities. Laboratory changes may reveal macrocytic anemia, hyponatremia, hypoglycemia, hyperlipidemia, and increased creatine kinase. Pericardial fluid, pleural effusion, and anasarca may become evident. The physical examination commonly reveals goiter, slow speech, delayed relaxation of tendon reflexes, bradycardia, diastolic hypertension, depressed spontaneous ventilation, and upper airway edema and possible obstruction. Other findings include severely attenuated response to hypoxemia and hypercarbia, depressed inotropy and chronotropy, increased vascular resistance, and intravascular volume depletion. The electrocardiogram may reveal sinus bradycardia, small-voltage QRS complexes, prolonged Q-T intervals, isoelectric T-wave changes, or even supraventricular tachycardia.

If hypothyroidism is suspected, the first test to be performed is TSH. If the TSH level is increased, the TSH test is repeated along with T_4. High TSH and low free T_4 characterize primary hypothyroidism (Table 12.1). Serum concentrations of thyroid peroxidase antibodies are elevated in patients with chronic autoimmune hypothyroidism. If TSH is high with a normal level of free T_4, the diagnosis is subclinical hypothyroidism. Therapy for such situations requires expert consultation to avoid complications. A TSH-secreting pituitary adenoma may also manifest with increased TSH and normal or high free T_4.

Central hypothyroidism is a consequence of low TSH either due to low pituitary secretion of TSH (secondary hypothyroidism) or decreased TRH secretion from the hypothalamus (tertiary hypothyroidism) (see Table 12.1). TSH is normal or low and T_4 is low in central hypothyroidism. Resistance to TSH manifests by increased TSH and normal free T_4 and T_3 (euthyroid) or low T_4 and T_3 (hypothyroid). Nonthyroidal illness characterized by low TSH and low free T_3 and T_4 may be present during critical care illness, including post–cardiopulmonary bypass patients, or even during extreme fasting (see Table 12.1).

TABLE 12.1 Laboratory Diagnosis of Hypothyroid States

Assessment	TSH	Free T_4	Free T_3
Primary hypothyroidism	High	Low	Low
Subclinical hypothyroidism	High	Normal	Normal
Central hypothyroidism	Low or normal	Low or normal	Low or normal
Nonthyroidal illness	Low	Low	Low
Resistance to thyroid hormones	High	Low or normal	Low or normal

TSH, Thyroid-stimulating hormone.

Etiology and Prevalence

Thyroid disease is second only to diabetes as the most common endocrine disorder. A large U.S. survey study found hypothyroidism in 4.6% of patients without known disease (0.3% overt illness with diagnosis and 4.3% subclinical). Hypothyroidism is 5 to 8 times more common in females, and is also more frequent in the elderly. The most common cause of primary hypothyroidism is Hashimoto's chronic autoimmune thyroiditis. This disease is characterized by gradual loss of thyroid function and is more common in elderly women. Autoimmune hypothyroidism is the most common cause of hypothyroidism in children.

The prevalence of overt hypothyroidism in pregnancy is similar with the general population, but if untreated is associated with increased maternal and fetal complications such as miscarriage, preterm labor, intrauterine growth restriction, gestational hypertension, placental abruption, and postpartum hemorrhage.

Both iodine deficiency and excess can result in hypothyroidism. Iodine deficiency is the most common cause of hypothyroidism with goiter worldwide. The World Health Organization estimates a total global goiter prevalence worldwide of 15.8%, examining data from 1993 to 2003.

The etiology of hypothyroidism can also be iatrogenic. Total or partial thyroidectomy, radioiodine treatment for hyperthyroidism, and external radiation therapy for malignancy are well-known causes of hypothyroidism. Hypothyroidism can be secondary to medication used to treat nonthyroidal conditions: lithium, amiodarone, iron, cholestyramine, interferon-α, and tyrosine kinase inhibitors (Table 12.2). Clinicians must also be cautious about certain medications that interfere with or alter standard thyroid tests in known euthyroid patients (Table 12.3). Other rare causes of hypothyroidism include infiltrative diseases: fibrous thyroiditis, hemochromatosis, scleroderma, leukemia, and sarcoidosis. Hypothyroidism can be transient as a result of painless lymphocytic thyroiditis, postpartum thyroiditis, or partial thyroidectomy, or following withdrawal of treatment with thyroid hormone in euthyroid patients.

Secondary hypothyroidism can be caused by hypopituitarism, most commonly pituitary macroadenoma. Other causes of secondary hypothyroidism include postpartum pituitary necrosis (Sheehan syndrome), trauma, and other tumors such as craniopharyngioma. Any disease that affects the hypothalamus or impedes the hypothalamopituitary blood flow can cause tertiary hypopituitarism. Hypothalamic damage can result from trauma, tumors, cerebrovascular accident, or infiltrative disorders.

Resistance to thyroid hormones is a rare inherited disorder (usually autosomal dominant) and sometimes sporadic, manifested by short stature, deficient bone maturation, and intellectual disabilities.

TABLE 12.2 Drugs That Affect Thyroid Function in Patients Prescribed Levothyroxine

Mechanism of Drug Interaction	Inhibits Levothyroxine Absorption	Increases Hepatic Metabolism	Decreases Hepatic Metabolism	Inhibits 5-Deiodinase	Increases Thyroxine-Binding Globulin
Drugs	Iron Calcium Aluminum hydroxide Colestyramine Sucralfate Raloxifene (Evista)	Phenobarbital Phenytoin Carbamazepine Rifampin	Metformin	Propylthiouracil Methimazole Propranolol Glucocorticoids Iodide	Estrogen Tamoxifen Methadone Fluorouracil

Modified from Haugen BR: Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab* 23(6):793-800, 2009.

Hypothyroidism and Anesthesia Complications

The most common anesthesia complication or manifestation of hypothyroidism in the perioperative period is "delayed emergence." However, delayed emergence after anesthesia is broadly defined and encompasses an expansive differential diagnosis. There are case reports in the literature of delayed emergence after anesthesia of patients with preoperatively optimized hypothyroidism or subclinical hypothyroidism most likely related to hypothermia and impaired drug metabolism. A patient in myxedema coma presented for emergent laparotomy for small bowel occlusion and underwent the surgery under epidural anesthesia. The patient received levothyroxine intraoperatively with gradual improvement of her mental status. There is a case report of delayed emergence after anesthesia for two different surgeries for the same patient who was on sunitinib (tyrosine kinase inhibitor) and subsequently developed myxedema coma perioperatively. The patient's intraoperative course was complicated by hypothermia, bradycardia, prolonged neuromuscular blockade, and, of course, delayed recovery from anesthesia. Another case report describes a patient with unknown hypothyroidism who suffered a cardiac arrest postoperatively after an uneventful anesthetic for hip replacement. The patient was resuscitated successfully, diagnosed with myxedema coma, and treated with thyroid hormones, with good recovery and outcome. Surgery and anesthesia can be the critical additional stress that precipitates myxedema coma—illustrated by a patient with known hypothyroidism who underwent partial mandibulectomy, glossectomy, and neck dissection for squamous cell carcinoma of the tongue. Last, there is a case report of a patient with an incidental finding of elevated creatine kinase who had delayed awakening after anesthesia. The patient was subsequently diagnosed and treated for significant hypothyroidism. And a final caution—there are reports of airway obstruction in the postoperative period in patients with known hypothyroidism.

MANAGEMENT AND PREVENTION

Most patients with mild and treated hypothyroidism can undergo surgery without significant increase of risks. Stable hypothyroid patients should continue their replacement therapy with levothyroxine (synthetic T_4) perioperatively.

Myxedema coma is a medical emergency with a high mortality rate (80%) if untreated. Thus IV therapy should begin even while awaiting confirmatory laboratory and other test results. The adequate treatment for myxedema coma in the perioperative period is paramount and the first 24 hours of therapy are critical. Expert consultation is recommended. Additional caveats of treatment include the following:

- A combination of synthetic T_3 (liothyronine) and T_4 (levothyroxine) should be considered; however, the superiority of this combination therapy remains uncertain.
- IV therapy is favored over oral administration because the gastrointestinal absorption may be impaired.
- A loading dose of levothyroxine 200 to 400 μg (some recommend doses as high as 500–800 μg) is given intravenously in 30 minutes, followed by 1.6 μg/kg (50–100 μg) daily; the lower dose is recommended in older patient with cardiac disease at risks for cardiac complications such as myocardial infraction or arrhythmia.
- Liothyronine may be administered simultaneously in a dose of 5 to 20 μg followed by 2.5 to 10 μg every 8 hours.
- Continuation of T_3 is recommended until there is clinical improvement or the patient is stable.
- Very high doses of thyroid hormones (T_4 >500 μg and T_3 >75 μg) may be considered, but have been associated with complications such as arrhythmias and other adverse outcomes.
- After obtaining a random cortisol level, concomitant corticosteroids should be administered for presumed adrenal insufficiency: hydrocortisone 100 mg every 8 hours.
- Volume resuscitation with dextrose and saline should be instituted. Check for possible presence of severe hyponatremia ([Na] <120 mEq/L).
- Vasopressors might be administered if the fluid replacement therapy does not restore hemodynamic stability.
- Mechanical ventilation might be necessary for severe hypoventilation or the inability to protect the airway.
- Passive rewarming is preferred because active warming can aggravate the vasodilation and shock.
- Empiric antibiotic therapy is recommended after appropriate cultures because infection might be the precipitating factor of the myxedema coma.
- Positive signs of resolution of myxedema symptoms should be seen within 24 hours of treatment.

TABLE 12.3 Euthyroid Patients With Altered Thyroid Function Tests Due to Concomitant Medication Administration

Test Abnormality	TSH Decreased Below Normal	Increased TSH (but <10 U/L)	Increased Free T_4	Decreased Free T_4
Drugs	Glucocorticoids Dexamethasone Hydrocortisone Dopamine Levodopa	Amiodarone Metoclopramide Iodinated contrast media	Furosemide Nonsteroidal antiinflammatories (especially aspirin)	Carbamazepine Phenytoin

TSH, Thyroid-stimulating hormone.

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13 Mechanical Assist Devices

Michelle Capdeville

Case Synopsis

A 58-year-old man with past medical history significant for poorly controlled hypertension, diabetes, and an active 30 pack-year smoking history presented to the operating room (OR) in cardiogenic shock following a failed emergency percutaneous coronary intervention (PCI). An intraaortic balloon pump (IABP) was emergently placed via the right femoral artery, and he was intubated before OR transfer for ongoing hemodynamic instability and pulmonary edema. In the OR he became increasingly unstable and was "crashed" on cardiopulmonary bypass (CPB) where he underwent three-vessel coronary artery bypass grafting. During attempted separation from CPB with IABP and high-dose inotropic support, the transesophageal echocardiogram (TEE) showed akinesis of the anterior and lateral walls with an estimated left ventricular ejection fraction of 15% to 20%.

PROBLEM ANALYSIS

Definition

Mechanical circulatory assist devices are used to support the failing heart. A variety of devices are available for both long- and short-term support, as well as univentricular or biventricular support. The simplest and most commonly used of these is the intraaortic balloon pump (IABP), which operates by the principle of counterpulsation and was introduced clinically in 1967. In simple terms, the IABP consists of a catheter-mounted polyurethane balloon that is generally placed percutaneously into the descending thoracic aorta, with the catheter tip just distal to the left subclavian artery. Balloon inflation is timed to the cardiac cycle with the net effect being *diastolic augmentation of coronary perfusion* and *systolic afterload reduction.* The overall result is an improvement in the balance between myocardial oxygen supply and demand. Unlike ventricular assist devices (VADs), the IABP does not provide "active" circulatory support, and requires some degree of native cardiac function. General IABP components include the IABP catheter with introducer sheath, a console, a trigger source, a gas source (helium), and a slave cable (for use with intraoperative monitors). The console displays the electrocardiogram (ECG), central aortic pressure waveform, balloon inflation trace, and augmentation. Important controls include trigger selection, start/standby, alarms, and automatic/semiautomatic/manual modes.

More complex VADs used for short- and long-term support include nonpulsatile centrifugal and axial flow pumps. Centrifugal pumps include extracorporeal membrane oxygenation (ECMO), the TandemHeart PLVAD (Cardiac Assist Technologies Inc., Pittsburgh, PA), and the HeartWare HVAD (HeartWare International, Inc., Miami Lakes, FL); axial flow pumps include the Impella (ABIOMED, Inc., Danvers, MA) and the HeartMate II (Thoratec Corporation, Pleasanton, CA).

General indications for VAD support can be divided into four broad categories: (1) bridge to transplant, (2) bridge to recovery, (3) bridge to decision, and (4) destination therapy. A "bridge to candidacy" category has also been described. A general description of these devices is provided in Table 13.1. Indications for ECMO are unique in that there are two configurations: veno-arterial (V-A) and veno-veno (V-V). V-A ECMO is used for cardiac failure, and V-V ECMO is used to support respiratory failure.

In simple terms, a VAD diverts blood from the left side of the heart to the systemic circulation (LVAD), or from the right side of the heart to the pulmonary circuit (RVAD), thereby bypassing the failing ventricular chamber. With LVAD support, blood is diverted from the left side of the heart (left atrium [LA] or left ventricle [LV]) to a pump that propels or ejects blood into the systemic circulation via an outflow cannula or graft (typically anastomosed to the ascending aorta for long-term support)—if the majority of support is derived from the pump, the aortic valve will remain closed; an RVAD will divert blood from the right atrium (RA) or right ventricle (RV) to the pulmonary artery (PA).

It is important to understand the nomenclature used when describing VADs. "Inflow" refers to the flow of blood directly *into* the pump, whereas "outflow" refers to propulsion of blood *out* of the pump and systemically. This is different from cardiopulmonary bypass, where systemic flow from the pump is into the aorta, femoral artery, or axillary artery (inflow), and flow to the pump is from the venous cannula (outflow) into a reservoir.

Recognition

Intraaortic Balloon Pump

The IABP is used both in the critical care setting and in the operating room. Placement is generally percutaneous via the femoral artery; however, alternate sites, including the axillary artery and aorta, have been used when femoral access was of poor quality. Proper positioning can be verified using chest radiography, fluoroscopy, or TEE. Indications and contraindications for IABP use are outlined in Box 13.1.

The IABP catheter has two lumens: one to the balloon, where helium gas is rapidly shuttled back and forth as the balloon inflates and deflates; and a second lumen that allows insertion of the catheter over a long guidewire and subsequent monitoring of central aortic pressure. Proper positioning of the catheter tip 1 to 2 cm distal to the

TABLE 13.1 General Overview of Commonly Used Short-Term and Long-Term Ventricular Assist Devices

	Pump Type	Type of Support	Flows/Pump Speed	Cannulation	Indications	General Description
Short Term						
ECMO	Centrifugal	R,L	Flows generated will depend on cannula size; 0–4,000 rpm; up to 7 L/min	V-A ECMO inflow: femoral artery, axillary artery, aorta (central); outflow: femoral vein/IVC, SVC, right atrium. V-V ECMO: femoral vein–femoral vein; femoral vein–SVC, or V-V ECMO: Avalon catheter (dual lumen; IVC, RA)	Cardiac support (V-A ECMO); respiratory support (V-V ECMO)	Extracorporeal centrifugal pump consists of impellers or rotating cones set in a clear plastic housing that is electromagnetically coupled with a motor. Rotary motion draws blood from pump head to a return cannula. Continuous veno-veno hemofiltration possible.
Impella	Microaxial	R,L	Impella LP 2.5, up to 2.5 L/min (maximum rotational speed 50,000 rpm); Impella LP 5.0, up to 5 L/min (maximum rotational speed 33,000 rpm); Impella RD 5.0, up to 5 L/min	9-Fr catheter in femoral artery (LVAD); Impella LP 5.0 requires cutdown; Impella RD 5.0 requires sternotomy for insertion into RA	LV support in cardiogenic shock; can serve as a bridge to recovery or as a bridge to a longer-term device; RV support in cases of postcardiotomy RV failure	Miniaturized axial flow pump. Impella LP 2.5 most useful for high-risk PCI; LP 5.0 better when increased cardiac support required, as in cardiogenic shock.
TandemHeart	Centrifugal	L	Up to 5 L/min; 3000–7500 rpm	21-Fr femoral venous transseptal cannula; 12–19-Fr femoral arterial cannula; can be placed percutaneously or at time of cardiac surgery	LV support in cardiogenic shock; can serve as a bridge to recovery or as a bridge to a longer-term device	Transseptal LA catheter has 14 side-holes to optimize drainage. Provides 80%–90% unloading of LV and physiologic pressures (90 mm Hg). Six-blade impeller is magnetically driven and is cooled and lubricated by a fluid infusion system.
Long Term						
HeartMate II	Axial	L	Up to 10 L/min flow possible; speed range 6000–15,000 rpm (clinical range 8600–9800 rpm)	Ventricular apex (inflow) and ascending aorta (outflow) made of woven Dacron and requires preclotting	Bridge to transplant; bridge to recovery; bridge to candidacy; destination therapy	Rotor sits in titanium pump housing; rotor is only moving part; motor in pump housing creates spinning magnetic field that spins rotor.
HeartWare HVAD	Centrifugal	L	Up to 10 L/min flow possible; 1800–4000 rpm (clinical operating range 2400–3200 rpm; lower ranges used for weaning from CPB)	Ventricular apex (inflow cannula); ascending aorta (outflow)	Bridge to transplant; bridge to recovery; awaiting approval for destination therapy	Miniaturized centrifugal pump sits in pericardial space. Inflow cannula integral to pump; impeller suspended by magnetic and hydrodynamic forces, and draws blood through pump; frictionless rotation at 1800–2400 rpm.

IVC, inferior vena cava; *L,* left; *PCI,* percutaneous coronary intervention; *R,* right; *RA,* right atrium; *SVC,* superior vena cava; *V-A,* veno-arterial; *VAD,* ventricular assist device; *V-V,* veno-veno.

left subclavian artery is important to prevent occlusion of major vessels (i.e., cerebral, renal, mesenteric).

Coronary blood flow depends on a number of factors, including perfusion pressure, myocardial extravascular intramural coronary compression, myocardial metabolic rate, and neurohumoral factors. Keeping in mind that coronary blood flow is equal to diastolic blood pressure minus left ventricular end diastolic pressure (CBF = DBP – LVEDP), and that the majority of left coronary blood flow occurs in diastole (right coronary flow occurs in both systole and diastole), it becomes easy to understand how balloon counterpulsation enhances blood supply to the heart. Rapid balloon deflation before systole displaces blood from the aorta, leading to reduced aortic pressure, improved forward ejection, decreased myocardial oxygen consumption (MVO_2), decreased wall stress, and improved myocardial performance. Balloon inflation at the time of aortic valve closure increases coronary perfusion, leading to improved contractility, decreased filling pressures, and overall improved diastolic performance.

Ventricular Assist Device

Short-Term Devices

The Impella consists of a miniaturized microaxial flow pump mounted at the tip of a catheter that is placed either percutaneously (Impella 2.5) or by cutdown (Impella 5.0) via the femoral artery and advanced retrograde up the descending thoracic aorta and into the left ventricular outflow tract (LVOT). With activation, blood is continuously propelled from the LVOT into the aortic root/ascending aorta. The Impella RD is a miniaturized RVAD that is inserted via median sternotomy (generally at the time of heart surgery to support postcardiotomy RV failure). The inflow cannula is implanted directly into the right atrium, and the outflow resides in the main PA. Flows up to 5 L/min can be generated.

The TandemHeart diverts blood from the left atrium (via a transseptal puncture and femoral venous access) to a small centrifugal pump, which in turn propels blood systemically to the aorta via a femoral arterial cannula. It can be inserted percutaneously or surgically while on CPB.

BOX 13.1 Indications and Contraindications for IABP Support

Indications

Postinfarct cardiogenic shock
Postinfarct mechanical complications (VSD, ruptured papillary muscle)
Ischemic arrhythmias
Intractable angina
High-risk cardiac catheterization/PCI
Major emergency (noncardiac) surgery in presence of severe CAD/ischemia
RV failure with pulmonary hypertension
Hypodynamic septic shock
Augmentation of thrombolysis with high risk for vessel reocclusion
Myocardial contusion
Failure to wean from cardiopulmonary bypass

Contraindications

Aortic insufficiency
Severe atherosclerotic disease (femoral, aortoiliac)
Aortic dissection
Aortic aneurysm
Infection at insertion site
Irreversible cardiac disease in a nontransplant candidate
"Do not resuscitate" status
Aortic, iliofemoral stents/grafts

CAD, Coronary artery disease; *PCI,* percutaneous coronary intervention; *VSD,* ventricular septal defect.

Long-Term Devices

After the landmark publication of the REMATCH study (Randomized Evaluation of Mechanical Assistance in the Treatment of Chronic Heart Failure) in 2001, long-term support of the failing heart with a mechanical circulatory assist device became a reality. The evolution of long-term VADs from the original first-generation volume displacement pulsatile devices (HeartMate I, Novacor LVAS, formerly World Heart Corporation, now a division of HeartWare; Thoratec paracorporeal PVAD) to second-generation (HeartMate II; DeBakey Micromed—MicroMed Technology, Houston TX; Jarvik 2000—Jarvik Heart Inc., New York, NY) and third-generation (HeartWare, HeartMate III) nonpulsatile devices has resulted in pumps with smaller components, thinner drivelines, fewer moving parts, less friction and heat generation, and more quiet operation. These latter pumps could also be implanted in smaller patients. First-generation devices were plagued with mechanical failures, thromboembolism, and infectious complications associated with larger drivelines, valves, and other moving parts. Despite these early problems, the REMATCH study was able to demonstrate superior outcomes and quality-of-life measures in transplant-ineligible patients supported with the HeartMate I compared with maximal medical therapy. When data from the REMATCH study were extrapolated and compared with outcomes from the HeartMate II Destination Therapy Trial, the newer-generation pump showed even better outcomes and fewer complications, most notably a reduction in mechanical failures and driveline-associated infections. Currently, roughly 25% of patients awaiting cardiac transplantation are supported with a VAD. Indications and contraindications are highlighted in Box 13.2.

Important parameters found on the console of the HeartMate II and HeartWare HVAD include pump speed (rpm), pulsatility (determined by how much native cardiac function contributes to cardiac output as reflected by aortic valve opening), power consumption (Watts), and estimated cardiac output (L/min). These parameters are each dependent on the patient's condition and provide information about pump function. Changes in baseline values are more important than absolute numbers. Pump speed should be set to maintain a degree of pulsatility, with goals being no interventricular septal shift,

BOX 13.2 Indications and Contraindications for VAD Support

Indications

Bridge to Transplant

May improve outcomes in status 1A patients who are medically managed and at greater risk of death or long waiting times for donor organ.

Bridge to Recovery

Some patients with nonischemic cardiomyopathy may recover myocardial function (i.e., "reverse remodeling") and undergo successful LVAD explant.

Bridge to Decision

Short-term VAD support with ECMO, Impella, or TandemHeart may allow sufficient recovery of failing organs, allowing for a greater window of time to determine feasibility of long-term device therapy.

Bridge to Candidacy

LVAD support may reduce PVR sufficiently in previously deemed noncandidates for heart transplant to make them transplant eligible; in heart-lung transplant candidates, reductions in PVR may change transplant eligibility status to heart only.

Destination Therapy

Transplant-ineligible candidates who are eligible for HeartMate II LVAD for lifelong mechanical support; suitable in end-stage heart failure patients who opt for device therapy in lieu of transplant.

Contraindications

Absolute

- Irreversible end-organ damage
- Ongoing coagulopathy
- Poor neurologic status
- Sepsis
- Substance abuse
- Social issues
- Noncompliance

Relative

- Mechanical AVR
- Active malignancy
- Morbid obesity

AVR, aortic valve replacement; *PVR,* pulmonary vascular resistance.

LV decompression, adequate cardiac index, and intermittent aortic valve opening.

The HeartMate II has been the most successful of the second-generation pumps (Fig. 13.1). It was approved as a bridge to transplant in April 2008 and for destination therapy in January 2010. The HeartMate II consists of a single rotor within a titanium housing. The inflow cannula is located at the left ventricular apex and is joined to the pump, which is placed in a preperitoneal pocket. An outflow cannula exits the pump and is anastomosed to the ascending aorta. As the rotor spins, blood is continuously drawn from the LV apex and propelled into the ascending aorta. A tunneled percutaneous driveline joins the pump to the controller (device control and power supply). Pump performance is determined by rotor speed and the pressure gradient across the pump (i.e., flow and pressure are inversely related).

Introduced clinically in 2006, the HeartWare HVAD is an intrapericardially placed pump where the inflow cannula is integral with a small continuous-flow centrifugal pump, and outflow is via a conduit anastomosed to the ascending aorta (Fig. 13.2). A thin flexible driveline is connected to the pump and exits the skin, where it connects to an external controller and power source (console or portable battery pack). The pump has a single moving part and no mechanical bearings. The rotating impeller is suspended within the pump housing by a combination of hydrodynamic and magnetic forces, resulting in frictionless motion. The pump console displays a flow waveform where

Fig. 13.1 HeartMate II (second-generation) axial flow LVAD in situ. Note apical inflow cannula at left ventricular apex and outflow graft anastomosed to ascending aorta. (Image courtesy of Thoratec Corporation, Pleasanton, CA.)

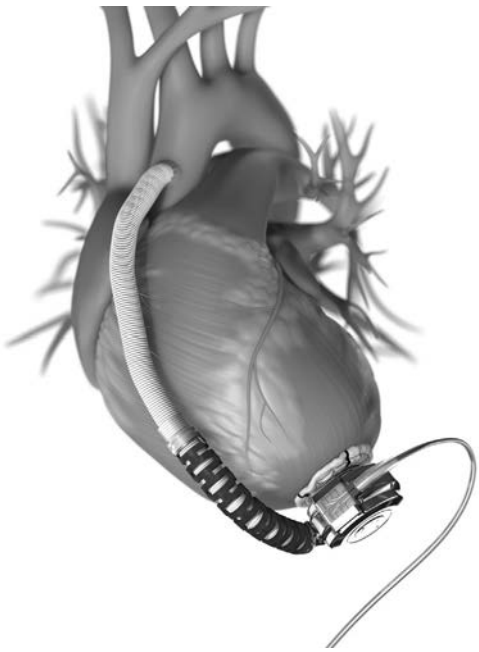


Fig. 13.2 HeartWare HVAD (third-generation) centrifugal flow LVAD in situ. Note intrapericardial pump with integral inflow cannula. Outflow is to ascending aorta. (Image courtesy of HeartWare International, Inc., Miami Lakes FL.)

pulsatility represents the difference between the minimum and maximum of the waveform (pulsatility should be greater than 2 L/min); the waveform trough should be greater than 2 L/min. This device is Food and Drug Administration (FDA) approved as a bridge to transplant and is nearing approval for destination therapy.

Risk Assessment

Intraaortic Balloon Pump

Today's balloon pump catheters are smaller than the earlier versions, which has reduced the incidence of complications, most notably vascular injuries (aortic dissection, pseudoaneurysm, aortic perforation). These injuries were particularly problematic in patients with smaller body surface areas, especially during the time period when catheter size options were more limited. Other reported complications have included distal or proximal embolization of plaque material, mechanical obstruction, limb ischemia, infection, balloon leakage or rupture, paraplegia, neurologic injury, lymphocele, catheter malposition, thrombocytopenia, bleeding, and improper balloon/catheter sizing. Current technology has improved the risk profile of IABP therapy, and sophisticated computer algorithms have improved on the safety of this treatment modality.

Ventricular Assist Device

Risk assessment is important in determining which patients will benefit from VAD therapy. INTERMACS (Interagency Registry for Mechanical Assisted Circulatory Support) is an elective registry that collects data on recipients of long-term FDA-approved mechanical circulatory support devices in the United States. This registry has identified important patient characteristics and defined appropriate timelines for the initiation of mechanical support (Table 13.2). Other risk scores have been used to assess mortality risk after VAD implantation and risk of right ventricular failure.

Short-Term VADs

Short-term VADS have been useful in the immediate stabilization of patients with postinfarct cardiogenic shock, allowing for appropriate treatment, whether it be interventional or surgical. These devices allow for appropriate assessment of a patient who may or may not be a long-term VAD or transplant candidate so that resources can be allocated appropriately. In situations where myocardial stunning has occurred, these devices can allow the heart to be "rested" as it recovers from an ischemic insult.

Long-Term VADs

The long-term effects of nonphysiologic, nonpulsatile flow have resulted in some events not seen in earlier pulsatile pumps, most notably gastrointestinal bleeding from arteriovenous malformations (AVMs). Interestingly, angiodysplasias seen in the small bowel of patients with aortic stenosis (Heyde syndrome) and which resolve following valve replacement suggest a similar mechanism in patients with axial flow pumps. Exposure of blood elements to high shear stress, as seen in patients with aortic stenosis and those supported with axial flow pumps, can lead to an acquired form of von Willebrand disease that resolves with removal of the primary source. HeartMate II patients have been shown to be lacking in the large von Willebrand factor multimers, with normalization of this hematologic abnormality after device explant.

Some patients have developed new aortic insufficiency as a result of commissural fusion of the aortic valve leaflets during VAD support. This phenomenon has been described in both native and bioprosthetic aortic valves. If aortic insufficiency becomes significant, it may result in blood flowing retrograde back into the left ventricle and into the pump, leading to a circuit of wasted flow and overall reduced forward cardiac output.

TABLE 13.2 INTERMACS (Interagency Registry for Mechanical Assisted Circulatory Support) Risk Stratification for VAD Implantation Based on Seven Clinical Profiles

Profile #	Description	Definition	Time to MCS
1	Crashing and burning	Critical cardiogenic shock	Within hours
2	Progressive decline	Inotrope dependence with continuing deterioration	Within a few days
3	Stable but inotrope dependent	Clinically stable on mild-moderate doses of intravenous inotropes (includes stable patients on temporary circulatory support without inotropes)	Within a few weeks
4	Recurrent advanced heart failure	"Recurrent" rather than "refractory" decompensation	Within weeks to months
5	Exertion intolerant	Comfortable at rest	Variable
6	Exertion limited	Able to do some mild activity; fatigued within a few minutes of any meaningful physical exertion	Variable
7	Advanced NYHA III	Clinically stable with a reasonable level of comfortable activity, despite nonrecent history of previous decompensation	Not a candidate for MCS

MCS, mechanical circulatory support; *NYHA*, New York Heart Association.
Data from Kirklin JK, Naftel DC, Pagani FD, et al: The seventh INTERMACS annual report: 15,000 implants and counting. *J Heart Lung Transplant* 34(12):1495-1504, 2015.

Hemolysis is generally an infrequent consequence of axial flow unless it is associated with pump thrombosis. Hemolysis should be suspected when pump power output increases and lactate dehydrogenase levels are elevated.

Though the reported incidence has been variably low, VAD support has led to myocardial recovery (i.e., reverse remodeling) in a limited number of patients with idiopathic cardiomyopathy, allowing for device explant in certain individuals. Predictors of myocardial recovery in this population, however, have been elusive because there are no reliable biomarkers. Pharmacologic interventions during mechanical support have been attempted with the goal of initiating reverse remodeling, reversing pathologic hypertrophy, and restoring cellular metabolic processes. Pump removal was possible in a significant number of these patients in a small pilot study.

With both the HeartMate II and HeartWare HVAD, high negative pressures can be generated at the pump inlet, which can in turn lead to ventricular collapse (also referred to as "suction events"). With the HeartWare HVAD, pump speeds above 3200 rpm increase this risk. Suction events can occur with hypovolemia, right ventricular failure, vasoplegia, tamponade, and elevated pulmonary vascular resistance. Suction detection can be seen echocardiographically and by observing the pump flow waveform on the HeartWare console, which typically shows flow below the baseline. It is important to understand that pump speed is set by the operator, unlike first-generation LVADs where a fill-to-empty mode allowed the pump to eject once it reached a threshold volume. Nonpulsatile pumps are continuous-flow devices, and rotational speed does not change with physiologic needs. Because these pumps are preload and afterload dependent, close attention must be paid to volume status and hemodynamic parameters, particularly in the dynamic OR environment immediately after implant.

Implications

Intraaortic Balloon Pump

Balloon counterpulsation has many unique applications, but its greatest use has been in coronary intensive care units (CICUs) and cardiac ORs. In the cardiac OR, when pharmacologic support is inadequate to support cardiac output during separation from CPB, balloon counterpulsation can improve myocardial function and facilitate weaning.

The net physiologic effects of balloon counterpulsation include decreased afterload, increased coronary blood flow, decreased stroke work, decreased heart rate, decreased wall tension, decreased systemic vascular resistance, decreased LVEDP, decreased pulmonary capillary wedge pressure (PCWP), and overall increased cardiac performance.

Ventricular Assist Device

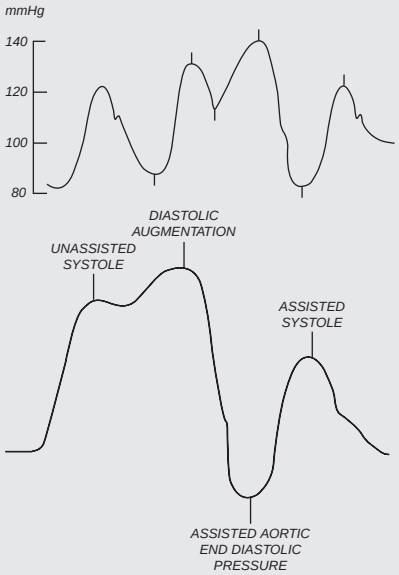
The role of VAD therapy in the management of end-stage heart failure and cardiogenic shock has grown tremendously in the last 2 decades. Indications have broadened and include the following:

- *Bridge to transplant:* According to the latest INTERMACS report, 30% of VAD recipients were listed for heart transplant at the time of device implant. Early institution of VAD therapy has been recommended when long waiting times are expected for a suitable donor, or in cases where blood type and size compatibility are an issue.
- *Bridge to recovery:* As stated previously, a relatively small number of patients with idiopathic cardiomyopathy will have sufficient myocardial recovery to be weaned from their device.
- *Bridge to decision:* In patients with multisystem organ failure and refractory cardiogenic shock, it is more prudent to place a short-term device such as the Impella, TandemHeart, or ECMO because these patients have significantly worse outcomes when they have not been optimized before implant of a long-term device.
- *Bridge to candidacy:* Registry patients receiving a VAD with the possibility of being subsequently listed for transplant numbered 23%. In patients who are ineligible for heart transplant because of pulmonary hypertension, VAD support has resulted in a reduction of pulmonary vascular resistance (PVR), allowing subsequent transplant. Along similar lines a candidate for heart-lung transplant supported with a VAD may undergo reversal of pulmonary hypertension with change in transplant candidacy status to heart transplant alone.
- *Destination therapy (DT):* The proportion of VAD implants for DT in 2014 was approximately 46%. The limited number of donor hearts has made DT a viable option for many patients. In some instances, patients have opted in favor of DT over bridge to transplant because of significantly improved symptoms and quality of life, and because they preferred to avoid another major surgical procedure with the associated risks of immune suppression.

The implications of the role of DT are far reaching as the number of heart transplants performed annually in the United States has plateaued at approximately 2300. The INTERMACS database includes more than 15,000 VAD patients, and the total number of implants annually is approximately 2500. Survival figures at 1 and 2 years with continuous-flow pumps have been excellent at 80% and 70%, respectively.

Importantly, a significant number of patients will go on to require noncardiac surgery while supported with a VAD, including endoscopy for gastrointestinal bleeding (20% incidence), laparotomy, neurosurgery, dental procedures, and so on. This latter point highlights the importance of being knowledgeable about VAD technology, as general

TABLE 13.3 Timing Problems With IABP Support

IABP Pressure Trace	Troubleshooting	Consequences
	**Normal trace:** Inflation occurs at onset of diastole (dicrotic notch-aortic valve closed); sharp "V" noted with augmentation; deflation occurs at end diastole; on the ECG, inflation occurs around the peak of the T wave (end systole) and deflation at the P-R interval (end diastole)	Increased coronary perfusion in diastole, reduced aortic end diastolic pressures, reduced afterload, reduced myocardial O_2 consumption, decreased cardiac work and increased CO
	Early inflation: Inflation occurs before aortic valve closes; diastolic augmentation wave occurs in systole when left ventricle is still ejecting	Can lead to increases in LVEDV, LVEDP, and PCWP; increased afterload and LV wall stress; increased MVO_2; decreased LV ejection; premature aortic valve closure may occur potentially causing aortic insufficiency

anesthesiologists will provide care for a significant number of these patients. In many centers, general anesthesiologists provide the majority of care for patients undergoing routine elective surgical procedures, in conjunction with a multidisciplinary team that includes a cardiac surgeon, a heart failure cardiologist, a VAD specialist/technician, a perfusionist, and appropriately trained nursing staff. More complex cases are generally relegated to a cardiothoracic anesthesiologist.

MANAGEMENT AND PREVENTION

Intraaortic Balloon Pump

A proper understanding of the principles of counterpulsation is needed in the management of patients supported with the IABP. Positioning must be verified before initiating counterpulsation. As mentioned previously, this can be done by chest radiography, with fluoroscopy, or with TEE. Balloon inflation and deflation will give the arterial trace a characteristic appearance. The balloon inflates at the dicrotic notch, creating a sharp "V" between the systolic and diastolic augmentation portions of the trace. Balloon deflation at end diastole results in a lower aortic end diastolic pressure compared with the unassisted trace, as well as a lower assisted systolic pressure. Normal and improperly timed IABP traces are illustrated in Table 13.3.

The trigger for IABP inflation refers to the signal used to identify the start of the next cardiac cycle, and can include the electrocardiogram, the central aortic pressure trace, A-pacing, AV/V-pacing, and an internal mode. Current systems have trigger and timing algorithms that can respond to changes in cardiac rhythm and automatically evaluate and select the optimal trigger source and ECG lead. The ratio of counterpulsation can be set at 1:1, 1:2, or 1:3. The latter two ratios are generally used for weaning from support. The IABP should never be left idle unless the patient is fully heparinized (as during CPB); otherwise the catheter could thrombose with potentially devastating consequences from embolization.

With the IABP in situ patients should be monitored for ischemic complications from the femoral access sheath (limb ischemia, infection), vascular injury (dissection, pseudoaneurysm), malpositioning (daily chest x-ray), bleeding, and heparin-induced thrombocytopenia (unless the patient has a heparin allergy and is receiving bivalrudin). Improvements in insertion techniques and the availability of smaller catheters and introducer sheaths (earlier catheter sizes ranged from 10.5–12 Fr) have led to a significant decrease in the incidence of vascular complications—a linear 7.5-Fr catheter is available for use in smaller patients. Current balloon sizes range from 25 to 50 mL.

Once the appropriate interventions have been made to reverse the cause of the patient's cardiac insufficiency, IABP therapy can be weaned and terminated.

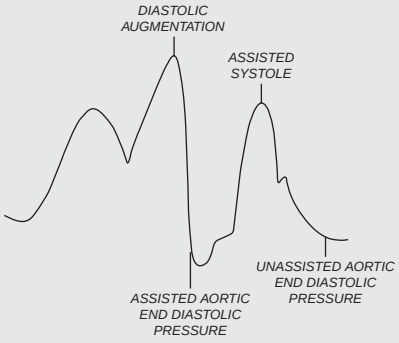
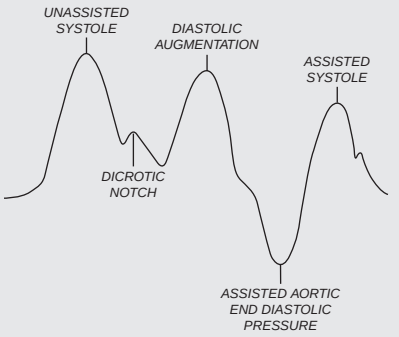
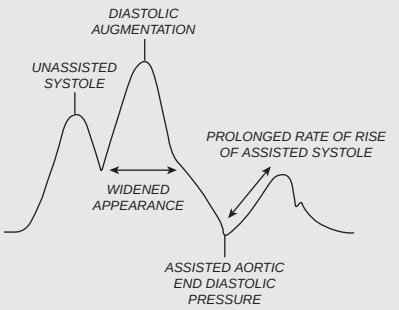
Ventricular Assist Device

As previously mentioned, perioperative management of VAD patients requires a multidisciplinary team approach. Echocardiography is indispensable in the real-time management of VAD patients, both intraoperatively (where inflow cannula position and outflow graft blood flow can be assessed, interventricular septum position verified as midline, and hemodynamics and volume status optimized) and postoperatively (where pump speed can be set to an appropriate level and ramped speed tests can be conducted).

A ramped speed test allows the determination of safe operating pump speed by examining low- and high-end ranges. Gradual reduction in speed until aortic valve opening occurs with each beat and the patient shows no echocardiographic evidence of heart failure is performed to determine the low-end range. For high-end range determination, pump speed is gradually increased until the aortic valve remains closed, the left ventricular end diastolic dimension decreases, and the pulse pressure is 10 to 15 mm Hg. Generally set pump speeds occur somewhere between the low- and high-end speeds established from the ramp test.

Echocardiography also allows for troubleshooting in the immediate postoperative period and thereafter. A number of problems can occur both early and late following LVAD implantation, including hypovolemia, tamponade, right ventricular failure, arrhythmias, hypoxemia, pulmonary embolism, and specific device-related problems (e.g., pump thrombosis, inflow cannula malposition, kinking of outflow cannula).

TABLE 13.3 Timing Problems With IABP Support—cont'd

IABP Pressure Trace	Troubleshooting	Consequences
	**Early deflation:** Deflation occurs prematurely in diastole leading to sharp drop after peak of augmentation	Diastolic augmentation of coronary perfusion becomes suboptimal; sharp drop in diastolic waveform can lead to retrograde blood flow (coronary, carotid); afterload reduction not optimized; increased MVO_2; assisted systolic pressure may increase
	**Late inflation:** Inflation occurs well after closure of aortic valve; diastolic augmentation upstroke occurs after dicrotic notch ("W"-shaped trace)	Diastolic augmentation of coronary perfusion is not maximized
	**Late deflation:** prolonged rate of rise of assisted systolic pressure; widened diastolic augmentation trace	No afterload reduction (LV ejects against greater afterload); increased MVO_2; increased wall strain

Pressure trace images courtesy of Maquet Cardiovascular, LLC, Wayne, NJ.

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For further general and technical information about the IABP, refer to the Maquet Cardiovascular (formerly DataScope) website where a number of educational materials can be downloaded: http://ca.maquet.com/clinician-information/educational-materials/.

14 Myasthenic Disorders

Mohamed Naguib

Case Synopsis

A 22-year-old woman, 154 cm tall and weighing 44.2 kg, presents with a 4-month history of myasthenia gravis and mild generalized weakness (Myasthenia Gravis Foundation of America's class IIA). The diagnosis is confirmed by the patient's rapid improvement after the administration of intravenous edrophonium chloride and by the presence of antibodies to acetylcholine receptors (12.3 nmol/L; reference value <0.25 nmol/L). Nerve conductions and electromyography studies were normal, but the repetitive stimulation of a nerve demonstrated decrements of the muscle action potential. Magnetic resonance imaging identified an abnormal thymus gland. The patient is scheduled for transcervical-sternal thymectomy. Preoperatively, she took pyridostigmine 60 mg orally three times a day and had plasmapheresis. Results of her preoperative pulmonary function tests were as follows: forced vital capacity (FVC), 2.79 L/second (79% of predicted); maximum expiratory flow at 50% of FVC, 3.2 L/second (68% of predicted); and forced midexpiratory flow between 25% and 75% of FVC, 3.03 L/second (77% of predicted). Anesthesia was induced with fentanyl and propofol and maintained with a thoracic epidural block supplemented with propofol and 70% nitrous oxide in oxygen. Tracheal intubation was performed under topical laryngotracheal anesthesia (4 mL 4% lidocaine). No neuromuscular blockers were used. She required mechanical ventilation for 12 hours postoperatively.

PROBLEM ANALYSIS

Definition

The plasticity of the neuromuscular transmission is dependent on a coordinated mechanism involving (1) synthesis, storage, and release of acetylcholine from the presynaptic motor nerve endings at the neuromuscular junction; (2) binding of acetylcholine to nicotinic receptors on the postsynaptic region of the muscle membrane, with consequent generation of the action potential; and (3) rapid hydrolysis of acetylcholine by acetylcholinesterase enzyme present in the synaptic cleft.

Autoimmune or genetic defects at the presynaptic region, synaptic basal lamina, or postsynaptic structure of the neuromuscular junction can compromise the safety margin of neuromuscular transmission. This can result in a diverse array of myasthenic disorders (Fig. 14.1). Fluctuating muscle weakness and fatigability are the main characteristics of myasthenic disorders (*mys,* meaning "muscle"; *aesthenia,* meaning "weakness"). Myasthenic disorders affect the motor system only. Sensory and autonomic functions are not impaired. The exception is Lambert-Eaton syndrome, a myasthenic syndrome in which a significant minority of patients have autonomic dysfunction. Myasthenic disorders can be classified into three main categories: myasthenia gravis, congenital myasthenic syndromes, and Lambert-Eaton myasthenic syndrome (Tables 14.1 and 14.2).

Recognition, Risk Assessment, and Implications

Myasthenia Gravis

Myasthenia gravis (MG) is the most common myasthenic disorder characterized by muscle weakness and fatigue. MG is a B-cell–mediated autoimmune disease with an incidence of 0.25 to 0.5 per 100,000 per year and a prevalence of 5 per 100,000. In adults, women are affected more often than men (3:2). In the elderly, the incidence is greater in men than women. Antibodies against the α-subunit of nicotinic acetylcholine receptors are present in approximately 80% to 85% of patients with MG. This antibody response is T-cell dependent because regulatory T cells (Tregs) and CD4+ T cells recognize acetylcholine receptor epitopes in the context of major histocompatibility complex class II molecules and exert a helper function on B cells to produce antibodies. In the remaining 15% to 20% of patients (called seronegative patients), nicotinic acetylcholine receptor antibodies are not detectable. The majority of these seronegative patients have antibodies against the muscle-specific receptor tyrosine kinase (MUSK), lipoprotein-related protein 4 (LRP4), or agrin; these antibodies are not present in seropositive patients. Muscle-specific kinase mediates the agrin-induced clustering of nicotinic acetylcholine receptors during synapse formation and development and is also expressed at the mature neuromuscular junction.

The loss of postsynaptic nicotinic acetylcholine receptors decreases postsynaptic excitation in response to acetylcholine release resulting in fatigable muscle weakness. In an attempt to maintain synaptic plasticity, substantially more acetylcholine is released than at the normal neuromuscular junction in an attempt to compensate for the decrease in postsynaptic acetylcholine receptors in MG; apparently, however, this compensatory homeostatic mechanism would not be sufficient to restore or maintain the normal neuromuscular function.

Triggers for the immune response in MG are not known. Thymic lymphoid follicular hyperplasia with germinal centers that produce antibodies to nicotinic acetylcholine receptors is present in approximately 70% of MG patients. A small percentage of MG patients develop autoantibodies as part of a paraneoplastic syndrome (12% of MG patients have thymoma). It is believed that antibodies to nicotinic acetylcholine receptors are produced in other locations, because thymectomy does not

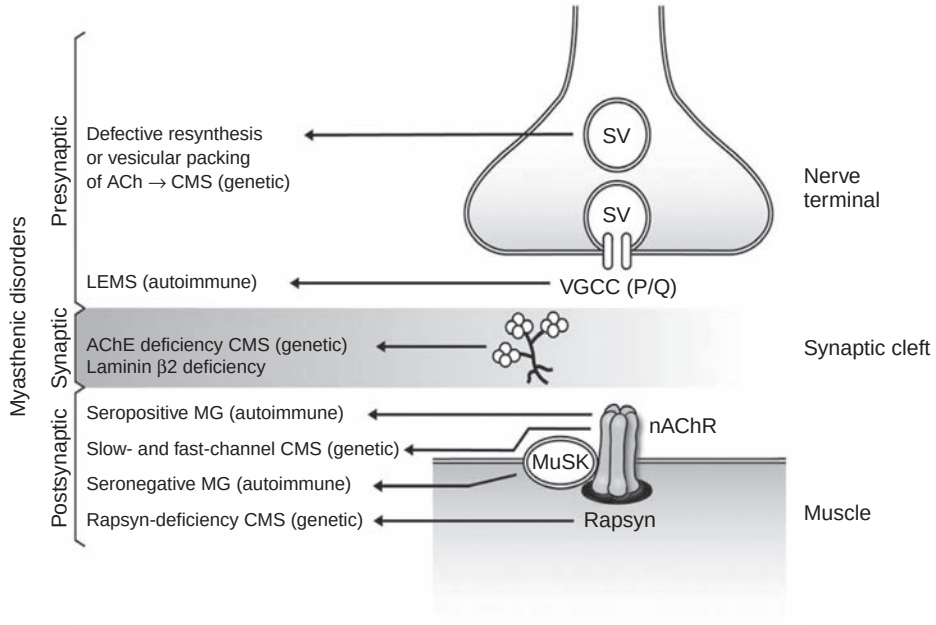

Fig. 14.1 Myasthenic disorders. *ACh,* acetylcholinesterase; *CMS,* congenital myasthenic syndrome; *LEMS,* Lambert-Eaton myasthenic syndrome; *MG,* myasthenia gravis; *MuSK,* muscle-specific kinase; *nAChR,* nicotinic acetylcholine receptor; *SV,* synaptic vesicle; *VGCC (P/Q),* voltage-gated calcium channel (P/Q type).

TABLE 14.1 Myasthenic Disorders

Site	Disorder	Type	Cause	Morphology	Clinical Features	Management
Presynaptic	Lambert-Eaton myasthenic syndrome	Autoimmune	Antibodies target voltage-gated calcium (Ca^{2+}) channels at motor nerve terminal and possibly another presynaptic component (synaptotagmin), leading to reduction in ACh release	Normal ACh contents and NMJ architecture	Approximately 60% of patients have paraneoplastic response, often in association with small cell lung carcinoma Weakness and fatigability	With malignancy, successful treatment can lead to marked improvement in symptoms 3,4-Diaminopyridine blocks prejunctional potassium (K) channels to (1) prevent K efflux, (2) increase action potential duration, (3) prolong activation of voltage-gated Ca^{2+} channels, and (4) increase intracellular Ca^{2+} stores and ACh release Pyridostigmine potentiates response to 3,4-diaminopyridine Often, plasmapheresis or IV immunoglobulin provides transient improvement
	Choline acetyltransferase deficiency	Genetic	Choline acetyltransferase mutations cause insufficient ACh resynthesis	Number of nAChRs and end-plate structure are normal	Autosomal recessive inheritance Characteristic apneic attacks along with myasthenic symptoms	AChE inhibitors
Synaptic	AChE deficiency	Genetic	Mutations in the gene encoding the collagenic tail subunit of the enzyme anchoring AChE in the synaptic cleft decrease the expression or the catalytic efficacy of the enzyme	Absent or reduced AChE activity (by histochemical staining) Secondary loss of nAChR and postsynaptic region degeneration	Autosomal recessive disease with variable phenotypic expression Moderately severe, generalized weakness and scoliosis with restrictive lung disease are common	Due to deficiency of AChE enzyme, patients do not benefit from anticholinesterase therapy

TABLE 14.1 Myasthenic Disorders—cont'd

Site	Disorder	Type	Cause	Morphology	Clinical Features	Management
	Laminin β_2 deficiency	Genetic	Mutations in the gene encoding laminin β_2 subunit	Immature hypoplastic nerve terminals, which remain encased by cytoplasmic processes of the Schwann cell Moderate simplification of postsynaptic folds and intact expression of the endplate acetylcholinesterase	Autosomal recessive inheritance	Ephedrine and albuterol (but not pyridostigimine) appear to improve neuromuscular transmission via an unknown mechanism
Postsynaptic	Myasthenia gravis: seropositive or seronegative	Autoimmune	Antibodies to nAChRs Antibodies to MuSK	End-plate regions have simplified architecture with smaller folds and marked reduction in nAChR (approximately 30% of that in normal NMJ)	Age at onset of myasthenic symptoms is earlier in MuSK antibody–positive patients Neck muscles are commonly involved in MuSK antibody–positive patients, and limb muscles in MuSK antibody–negative patients	Preoperative optimization by plasmapheresis and continued pyridostigmine therapy Patients are extremely sensitive to NDMRs Response to SCh and mivacurium depends on butyrylcholinesterase activity, which is expected to decrease after plasmapheresis or pyridostigmine
	Reduced expression of nAChR or rapsyn deficiency	Genetic	Mutations in nAChR or in rapsyn decrease expression of nAChRs	Changes in end-plate regions are similar to those seen with autoimmune MG	Autosomal recessive inheritance Patients exhibit myasthenic symptoms from birth or infancy Facial malformations are common in rapsyn deficiency	Response to anticholinesterase is incomplete Combined therapy with 3,4-diaminopyridine (which increases ACh release) is beneficial
	Slow-channel congenital myasthenic syndromes	Genetic	Kinetic defects and/or gain-of-function mutations in nAChR cause lengthy nAChR opening and excessive Ca^{2+} influx with postsynaptic degeneration	Postsynaptic degeneration with loss of nAChRs; AChE is normal	Usually dominant inheritance Selective weakness in cervical, scapular, and finger extensor muscles; variable weakness in other muscles	Open channel blockers (quinidine, fluoxetine) normalize slow-channel mutant opening durations No response to AChE medications Avoid SCh because it can worsen excitotoxicity
	Fast-channel congenital myasthenic syndromes	Genetic	Mutations in nAChR markedly reduce binding affinities, resulting in rapid ACh dissociation from binding sites, reducing the rate of channel opening, and increasing its closure rate	NMJ structure normal; density of nAChRs normal or decreased	Autosomal recessive inheritance Moderate symptoms from birth to infancy Partial response to AChE inhibitors	Combination treatment with 3,4-diaminopyridine and AChE

ACh, Acetylcholine; *AChE,* acetylcholinesterase; *MG,* myasthenia gravis; *MuSK,* muscle-specific kinase; *nAChR,* nicotinic acetylcholine receptor; *NDMR,* nondepolarizing muscle relaxant; *NMJ,* neuromuscular junction; *SCh,* succinylcholine.

TABLE 14.2 Differential Diagnosis of Myasthenic Disorders

	Myasthenia Gravis	Lambert-Eaton Myasthenic Syndrome	Congenital Myasthenic Syndromes
Cause	Autoantibodies targeting nAChRs or MuSK	Autoantibodies targeting presynaptic voltage-gated (P/Q) calcium (Ca^{2+}) channels or synaptotagmin	Genetic mutations of presynaptic, synaptic, or postsynaptic proteins Dominant or recessive inheritance (no antibodies against nAChRs, MuSK, or P/Q type Ca^{2+} channels)
Associated conditions	Thymic lymphoid follicular hyperplasia present in 70% of MG patients Thymoma present in 12% of MG patients (paraneoplastic autoimmune response) Associated autoimmune conditions include thyrotoxicosis, systemic lupus erythematosus, rheumatoid arthritis, and pernicious anemia	60% of LEMS patients have paraneoplastic autoimmune response Small cell lung carcinomas express voltage-sensitive Ca^{2+} channels; antitumor antibodies to these channels cross-react with prejunctional voltage-gated Ca^{2+} channels at the NMJ to impair ACh release	

TABLE 14.2 Differential Diagnosis of Myasthenic Disorders—cont'd

	Myasthenia Gravis	Lambert-Eaton Myasthenic Syndrome	Congenital Myasthenic Syndromes
Target location	Postsynaptic	Presynaptic	Presynaptic, synaptic, or postsynaptic component of NMJ
Dysautonomias	Absent	Present in approximately 30% of patients (dry mouth, impotence)	Absent
Improvement in muscle strength	After rest	After exercise	After rest
Antibody transfer	From myasthenic mother to fetus, causing neonatal MG Injecting healthy animals with MG IgG causes signs of MG	IgG from LEMS patients can block Ca^{2+} channels, inhibiting muscle contraction	Antibodies are not present
Electromyography (response to 30–50 Hz stimulation)	Fade	Facilitation	Fade
Effect of plasmapheresis	Transient	Transient	No effect
Anticholinesterases	Effective in managing symptoms	Minimal therapeutic value	Minimal therapeutic value
Response to 3,4-diaminopyridine	No effect	Significant improvement in symptoms	Effective in fast-channel congenital myasthenic syndromes
Response to succinylcholine	Resistant	Sensitive	Variable, not recommended due to potential hyperkalemic response in slow-channel mutations
Response to nondepolarizing neuromuscular blockers	Sensitive	Sensitive	Sensitive

ACh, Acetylcholine; *IgG,* immunoglobulin G; *LEMS,* Lambert-Eaton myasthenic syndrome; *MG,* myasthenia gravis; *MuSK,* muscle-specific kinase; *nAChR,* nicotinic acetylcholine receptor; *NMJ,* neuromuscular junction.

cure MG and does not protect against the occurrence of MG. There is also some evidence that antibodies generated in response to microbial antigens may constitute a trigger for MG in some patients. The antirheumatic drug D-penicillamine can induce a reversible form of MG.

MG can occur at any age. Extraocular and bulbar muscles are initially affected in a large majority of patients, resulting in ptosis, diplopia, dysphagia, and respiratory failure. As the disease progresses, neck and limb-girdle muscle weakness becomes apparent. In the rat model of MG, there is also evidence that diaphragmatic function is impaired. The clinical features of seropositive and seronegative patients are very similar. Neonatal transient MG occurs in infants of myasthenic mothers. Placental transfer of anti-AChR antibody or immunocytes results in transient impairment of neuromuscular transmission in the neonate in about 10% to 25% of neonates born to mothers with MG.

Osserman and Genkins proposed the following clinical classification of MG: class I (ocular signs and symptoms only), class II (mild generalized weakness), class III (moderate generalized weakness with or without bulbar involvement), and class IV (severe generalized weakness with or without bulbar involvement). However, the Osserman classification has several limitations. For instance, the descriptive terminology is vague, and it is difficult to have clear distinctions between groups. A task force of the Myasthenia Gravis Foundation of America (MGFA) developed a new classification system that provides better distinction between classes (Box 14.1).

Myasthenia gravis is a clinical diagnosis. Exercise-induced weakness usually gives strong clues to the diagnosis. Tests can be supportive but may be negative. Improvement in strength after intravenous injection of edrophonium (Tensilon) helps confirm the diagnosis of MG. After a test dose of 1 to 2 mg, a total dose of 10 mg is administered intravenously. A positive response is expected within 5 minutes. It should be noted that the effect of edrophonium test is nonspecific and can be seen in other neuromuscular diseases. Antibodies against the nicotinic acetylcholine receptor are usually detected in serum. Electrophysiologic testing may be used to directly evaluate muscle function aiming at eliciting a decremental response of the compound muscle action potential to repetitive stimulation of a motor nerve. Computed tomography scans or magnetic resonance imaging may identify an abnormal thymus gland or detect the presence of thymoma.

BOX 14.1 Myasthenia Gravis Foundation of America Classification System

Class I
Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II
Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
- **IIa:** Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
- **IIb:** Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III
Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
- **IIIa:** Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
- **IIIb:** Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV
Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
- **IVa:** Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
- **IVb:** Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both. The use of a feeding tube without tracheal intubation.

Class V
Defined as tracheal intubation, with or without mechanical ventilation, except when employed during routine postoperative management.

There is no specific therapy for MG. Anticholinesterases (such as pyridostigmine and neostigmine) are used to treat symptoms by preventing the degradation of acetylcholine in the synaptic cleft. Side effects include excessive cholinergic stimulation, such as increased airway secretions, increased bowel motility, bradycardia, or even worsening of weakness, simulating a myasthenic crisis. Immunosuppressant agents may help improve muscle strength by suppressing the

production of autoantibodies, but have many potential adverse effects associated with their use. Several Cochrane reviews found support for the use of corticosteroids but only limited evidence that cyclosporine, cyclophosphamide, and azathioprine improve MG.

Plasmapheresis and intravenous immunoglobulin (IVIG) are effective in myasthenic crisis and for the preoperative optimization of the patient's condition. Plasmapheresis is associated with a risk of hypotension or bleeding from the use of anticoagulation. Limited evidence from randomized, controlled trials does not show any difference in efficacy between corticosteroids and either azathioprine or IVIG.

Nonspecific immunosuppression with steroids and immunosuppressants and plasmapheresis are often combined with thymectomy. Thymectomy is the standard treatment for young patients and for those with thymoma. Thymectomy improves symptoms, remission rate, and clinical course of MG in patients without thymoma and has been shown to be associated with remission in up to 50% of cases.

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (CMSs) are a rare group of heterogeneous disorders that are caused not by autoantibodies but by inherited mutations in the synaptic vesicles, acetylcholinesterase, or nicotinic acetylcholine receptors. This results in either an increase (gain of function) or decrease (loss of function) in the magnitude of response to acetylcholine. The most frequent type of postsynaptic CMS is the slow-channel syndrome. The inheritance of CMS is either autosomal dominant or recessive. In contrast to neonatal MG, caused by passive transfer of antibodies to the fetus from a myasthenic mother, the mothers of infants with CMS do not have myasthenia. The onset of CMS usually occurs before 2 years of age. In contrast to autoimmune MG, immunosuppression and plasmapheresis are not effective in the management of CMS because antibodies play no role in its pathogenesis.

In patients with MG and CMS, electromyography is characterized by decremental responses on repetitive stimulation and block with single-fiber recordings. However, patients with a slow-channel CMS can also show characteristic repetitive discharges in response to a single supramaximal stimulus, the so-called double response.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is an acquired disorder resulting from autoantibodies targeting the presynaptic P/Q voltage-gated calcium channels and possibly another presynaptic component (synaptotagmin), leading to a reduction in acetylcholine release. Synaptotagmin is an exocytotic calcium sensor and plays an important role in synaptic vesicle fusion and the fast release of acetylcholine. Anti-P/Q-type voltage-gated calcium channel antibodies are detected in 85% of patients with LEMS (seropositive). A fraction of seronegative LEMS patients have antisynaptotagmin antibodies in their sera. In approximately 60% of LEMS patients, the syndrome is a paraneoplastic disorder, most often associated with small cell carcinoma of the lung. In patients without malignancy, LEMS is an autoimmune disorder. LEMS is characterized by proximal muscle weakness in the lower and upper extremities, fatigability, and autonomic dysfunction. Involvement of bulbar or respiratory muscles is uncommon in LEMS patients.

In patients with LEMS, electromyography typically shows low-amplitude compound muscle action potentials, associated with fade at slow rates of stimulation (2 Hz). Facilitation of response is seen after brief exercise or at high rates of repetitive stimulation (30–50 Hz).

MANAGEMENT AND PREVENTION

Thymectomy is an elective procedure and should be performed after optimization of the patient's condition. Preoperative assessment and preparation of MG patients should include the following: (1) review of the patient's neurologic history and a neurologic examination; (2) preoperative drug therapy (e.g., pyridostigmine and immunosuppressant drugs); (3) evaluation of bulbar symptoms or signs, such as dysphagia, dysarthria, or oropharyngeal weakness (because patients with bulbar involvement are at increased risk for postoperative respiratory complications); (4) search for the presence of other autoimmune diseases, such as diabetes mellitus, thyroid disease, systemic lupus erythematosus, or rheumatoid arthritis; (5) evaluation of pulmonary function tests, which should include flow-volume loops to help predict the need for postoperative mechanical ventilation; and (6) optimization of the patient's condition by preoperative plasmapheresis or high-dose IVIG. Pyridostigmine therapy should be continued preoperatively.

Myasthenic patients are generally resistant to succinylcholine owing to the decreased number of nicotinic acetylcholine receptors. However, butyrylcholinesterase (plasma cholinesterase) activity may be decreased in myasthenic patients by preoperative plasmapheresis or the administration of pyridostigmine, and this may result in the potentiation of succinylcholine. In the final analysis, the interplay between these factors (resistance to succinylcholine versus reduction in butyrylcholinesterase activity) should be considered when administering succinylcholine (or mivacurium) to patients with MG. Succinylcholine should be avoided in patients with slow-channel CMS because it can worsen excitotoxicity.

Patients with MG are extremely sensitive to nondepolarizing neuromuscular blockers due to the significant loss of postsynaptic nicotinic acetylcholine receptors. Nevertheless, nondepolarizing neuromuscular blockers are not contraindicated in these patients. With careful titration and with adequate monitoring of neuromuscular function, nondepolarizing agents have been safely used in myasthenic patients undergoing thymectomy. Long-acting neuromuscular blocking drugs should be avoided in these patients. Intermediate-acting drugs are better alternatives. Approximately one-fifth the ED_{95} of an intermediate-acting neuromuscular blocker should be given as a test dose. This helps estimate the patient's drug requirement as guided by a quantitative neuromuscular monitoring device. Myasthenic patients typically exhibit marked variations in their sensitivities to nondepolarizing neuromuscular blockers.

In myasthenic patients, reversal of residual block after surgery may be ineffective because acetylcholinesterase inhibition already exists as a result of chronic pyridostigmine therapy. Therefore it is advisable to allow spontaneous recovery from relaxation postoperatively, while continuing supportive mechanical ventilation.

Different anesthetic techniques have been used in myasthenic patients. Although surgical relaxation can be provided using only a potent inhaled anesthetic without neuromuscular blockers, this technique may be associated with a prolonged recovery from anesthesia due to the effects of inhalational anesthetics on neuromuscular transmission. Therefore it may be safer to use a small dose of an intermediate nondepolarizing neuromuscular blocker to facilitate tracheal intubation than to use deep inhalation anesthesia. Total intravenous anesthesia with a propofol-opioid infusion is a suitable alternative to a volatile anesthetic technique.

A thoracic epidural anesthetic in combination with balanced general anesthesia provides excellent analgesia both intraoperatively and following transsternal thymectomy. Regional anesthesia has also been used successfully to provide labor analgesia in parturients with MG. However, local anesthetics are known to potentiate neuromuscular blocking

drugs, and the metabolism of ester local anesthetics may be impaired if butyrylcholinesterase activity is reduced due to pyridostigmine therapy.

Patients with LEMS are sensitive to depolarizing and nondepolarizing neuromuscular blockers. In patients with LEMS, neostigmine is an ineffective antagonist for residual neuromuscular block. Oral 3,4-diaminopyridine should be continued after surgery.

All myasthenic patients should be closely monitored for neuromuscular weakness postoperatively in the surgical intensive care unit. The differential diagnosis of postoperative weakness in myasthenic patients should include the residual effects of neuromuscular blockers or anesthetic drugs, drugs that interfere with neuromuscular transmission (e.g., aminoglycoside antibiotics, phenytoin, β-blockers, quinidine, and lithium), and myasthenic or cholinergic crisis.

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15 Patient Confidentiality

Gail A. Van Norman

Case Synopsis

A physician's husband has undergone partial nephrectomy at her hospital for a suspicious lesion in his left kidney. The surgery was complicated by fever and acute renal failure. While on call one evening, curious to see how her friend's husband is doing, an anesthesiologist accesses the patient's electronic medical record. In the course of reading about the patient's progress, the anesthesiologist comes across a notation that the patient has tested positive for the human immunodeficiency virus (HIV) and has asked that his wife not be told because he is "not ready yet to disclose it to her." The anesthesiologist wants to inform her friend of the husband's positive HIV test.

PROBLEM ANALYSIS

Definition

Patient confidentiality is a cornerstone of medical professionalism. It is an ethical duty explicitly addressed by the various versions of the Hippocratic Oath, in which the duty to maintain confidentiality is not confined to mere health matters, but also encompasses "whatever, in the course of my practice I may see or hear (even when not invited), whatever I may happen to obtain knowledge of." In other words, the physician's duty to keep patient confidences includes anything the physician might learn in the course of patient care. Despite this foundational duty, however, physicians are often unaware of what constitutes a breach of confidentiality. In a study of over 500 Swiss physicians who were presented seven scenarios demonstrating "important" or "severe" breaches of patient confidentiality, many had difficulty recognizing instances in which such breaches occurred. Physicians were more likely to correctly identify such violations if they had been in practice longer than 20 years, had experienced some ethics education, and were of female gender. In another study, 71% of physicians felt they should disclose a patient's positive HIV status to surgical colleagues, even if the patient had asked them not to.

Confidentiality is vital to the maintenance of trust in the physician-patient relationship. That relationship necessarily involves the disclosure of sensitive information that might, if publicly disclosed, harm the patient through stigmatization, loss of community and employment, harm to primary relationships, and loss of other societal benefits. The willingness of patients to seek medical help and to be forthright in disclosing social and other information vital to the diagnosis and treatment of disease relies on the patient's trust that the physician will protect such disclosures completely. Three professions are often given common law protections with regard to confidentiality—attorneys, clergy, and physicians—due to special "social contracts" such professions hold and the critical nature of confidentiality in performing their duties.

The duty to keep secrets prohibits the physician from disclosing patient health care information to others without the patient's authorization, and it also more broadly encompasses a general respect for patient privacy. Ethical principles and law both require health care providers to actively take precautions to protect unauthorized access to such information. A provider must not leave patient records lying around in public places, or leave electronic records open and available on a public computer, for example. Even though health care information is often freely shared among all of the members of the patient's health care team, it is the duty of all team members to protect the information from others who do not have a legitimate reason for access. Furthermore, physicians do not have a right to access health information regarding persons with whom they do not have an established doctor-patient relationship except under very special circumstances.

In general, if the patient has not given explicit permission to disclose information, even to a spouse or other family member, the physician is not allowed to do so and it remains at the patient's discretion to disclose. There are a few exceptions to this rule.

Duty to Warn

If a spouse, family member, or any other third party is at specific personal risk of significant harm directly related to the patient's health information *or to any information disclosed to the physician in the course of the patient-doctor relationship,* the physician's duty of confidentiality may be waived. In some cases the law may even *require* the physician to violate confidentiality.

The classic case is that of *Tarasoff v. Regents of the University of California.* In 1969 a graduate student at Berkeley University, Prosinjit Podder, became obsessed with Ms. Tarasoff after they went on a couple of dates. When she rebuffed further contact with him, he became depressed and in the course of therapy confessed to his psychologist, Dr. Moore, that he intended to kill Ms. Tarasoff. Moore found these threats credible and alerted campus police, violating his patient's confidence in the process. Campus police believed that Podder was not an actual threat to Tarasoff and elected not to detain him. Neither Podder's doctor nor the police informed Tarasoff or her parents of Podder's threats, and Podder subsequently murdered her. Podder was convicted and eventually deported to India, his country of origin. The courts found in a later lawsuit brought by Tatiana's parents against the university that a duty to warn and/or protect existed and superseded the patient's (Podder's) right to confidentiality. In this case the court

TABLE 15.1 Laws Pertaining to Duty to Warn by State/District (2014)

Duty to warn/protect codified in state statute	AZ, CA, CO, ID, IN, KY, LA, MD, MA, MI, MN, MS, MO, MT, NE, NH, NJ, OH, OK, TN, UT, VA, WA
Duty to warn/protect supported by common law and legal precedent	AL, DE, GA, HI, IA, NC, PA, SC, SD, VT, WI
Legal "permission" for health care workers to breach confidentiality in the case of credible threat	AK; CT; Washington, DC; FL; IL; NY; OR; RI; TX; WV; WY
No legal guidance regarding to duty to warn/protect	AR, KS, ME, NV, NM, ND

found that Moore's violation of patient confidentiality *did not go far enough.* Merely reporting and/or investigating the threat was insufficient; the jury found that the specific threat should have been relayed to the (then) potential victim and her family so that she could take measures to protect herself.

As a result of the Tarasoff case, many states enacted legislation outlining a "duty to warn." As of 2014, 23 states had adopted mandatory "duty to warn" legislation concerning health care workers, 10 states had such duties present in common law and supported by precedent, and 11 states had a permissive duty (meaning there is no codification of a duty to warn, but legislation "permits" health care professionals to breach confidentiality in such cases). Only 6 states had no statutes regarding such a duty (Table 15.1).

Laws that require a duty to warn or protect present dilemmas to practitioners, who must assess whether the threat's risk level is high enough to establish this duty. Health care providers should be aware of the different thresholds by the state in which they practice. Is the victim specific and identifiable? Is the threat imminent? Is the threat not imminent, but nevertheless serious? Even in states that require a threat of imminent violence to create this duty to disclose, the law may interpret "imminent" in various ways, and include time frames that extend from days to months. Some legal experts have suggested that providers worry less about the imminence of a threat than a patient's demonstrated capacity to carry it out (e.g., does the patient have a history of carrying out such threats and possess the means to do so?). In our case scenario, the patient possesses the means to infect his spouse, for example, but proving that he presents an imminent threat, or that he would recklessly expose his wife to infection now that he has been informed of his HIV status, might be very difficult to prove. States without explicit legislation or legal precedent pose the greatest legal threat to providers, because provider protections in cases in which they breach confidentiality are not in place, and providers in those states face the threat of civil action no matter which way they choose to act.

Public Health and Benefit

The physician's duty of confidentiality may be specifically trumped by state laws that require disclosure of confidential information to appropriate public authorities. Examples include reporting certain communicable diseases to public health authorities, suspected child or elder abuse to various protective agencies, or gunshot wounds to the police. These exceptions are also generally extrapolated from duties of physicians to warn or protect innocent third parties from harm, as in the Tarasoff case.

Conversely, the patient's absolute right to confidentiality may be explicitly *reinforced* by state law in special cases, such as special rights of minors to confidentiality and to have access to health care treatment for certain specified conditions. In 45 states, minors have rights to undergo confidential treatment for addiction, mental illness, and general reproductive health issues (e.g., birth control). States that are exceptions are Alaska, Idaho, New Mexico, Utah, and Wyoming. In 38 states, minors can seek abortion without obtaining the permission of, or even notifying, their parents. These special circumstances generally rest in concerns that without such rights, minors would not seek health care that is vital to their well-being. In the case of pregnancies in minors, it has been shown that a significant concern is family shunning or even violence against the adolescent if pregnancy is disclosed.

Laws governing special exceptions to physician confidentiality rules are variable among the states, and physicians should always remain informed about current regulations relevant in the region where they practice. The National District Attorneys Association publishes a summary of medical treatment consent laws for minors in the 50 states, District of Columbia, and U.S. territories.

There are many challenges to keeping patient confidentiality in the daily practice of medicine. Institutions must protect the security and integrity of their records. The health care team is responsible for protecting the medical record from both intentional and unintentional, inappropriate intrusions, including the inappropriate use of unsecured e-mail for communication of private patient health information. In 1997 the Health Information Portability and Accountability Act (HIPAA) was passed, codifying strict health care information privacy provisions into federal law. HIPAA, for example, requires patient authorization for any disclosures not required for "treatment, payment or health care operations." Exceptions to the requirement for authorization include "public interest and benefit activities," such as disclosing lawfully required information to public health authorities or disclosure of serious threats to potential victims and to entities that have the power to mitigate/prevent the threat. In cases where there is disagreement between state law and HIPAA, HIPAA specifically provides that the federal law takes precedent.

Providers have implicit and explicit duties to prevent all breaches of confidentiality, intended and otherwise—from discussions of private patient information in public areas such as hallways and elevators where privacy cannot be guaranteed, to disclosures of private information to family members without the patient's permission.

Recognition

A good rule of thumb to determine whether a specific situation might represent an exception to the confidentiality rule is to ask, "Will some specific person or persons be at significant risk for real and serious imminent harm if this information is not disclosed?" If the answer to this question is no, it is unlikely that the duty can be ethically or legally violated. If the answer is that others are at risk of harm, but the risk is not imminent, professional rules of conduct suggest that the physician should try to convince the patient or his or her provider of the importance of disclosing the condition. Before intentional breach of confidentiality that runs counter to patient wishes, physicians may still be wise to consult with local legal expertise and/or the institutional ethics committee before proceeding. If others are at serious risk and the risk is imminent, appropriate local authorities and other parties (security personnel, police, etc.) should be contacted immediately.

Case Analysis

The case scenario describes two different types of breaches of confidentiality. The first occurred when the physician intentionally accessed the medical record of a person who was not her patient. The information she unexpectedly gained spurred her to want to commit a

second intentional breach of confidentiality and disclose the patient's HIV status to the patient's wife. Her justification was concern that the wife, her friend, may be at significant risk of HIV infection through exposure by her husband.

The first instance represented an unauthorized access of a patient record and is an example of clearly unethical (and illegal) conduct. Physicians are not granted the right to access medical records of any persons simply by virtue of the fact that they are physicians. No physician or health care worker should access the records of persons not under their care unless explicitly authorized for such a privilege, as in investigation of a sentinel event or quality assurance process. A physician who does so is guilty of the very same offense any common computer hacker would be who gained unauthorized access to an electronic record by other illegal means.

The second proposed breach of confidentiality relies on the justification that, irrespective of how it was obtained, the physician now possesses information about a serious risk of harm to the patient's wife by exposure to HIV through her husband. The question of whether such a secondary breach would be unethical is more complicated.

Does this physician have a "duty to warn"? The acceptability of breaking a patient's confidence depends on the details of each individual case. Relevant questions include whether the threat is real, the harm significant, and the threat of danger imminent. It would be hard to argue that the risk of HIV infection is insignificant and the harm of infection would not be great if it were to occur. But the imminence of the risk in this case seems remote: it is unlikely that spousal exposure will happen during the patient's hospital stay while he is recovering from serious complications following major surgery.

The scenario is further complicated by the fact that deciding to inform the patient's wife of her husband's HIV status will necessarily involve an admission on the part of the physician of unprofessional and unethical behavior in accessing the patient's record in the first place. Such an admission is likely to carry significant negative consequences for the physician, and may tend to bias her against disclosure even if a duty to warn exists. However, once an imminent threat of significant harm to a third party is known, the physician has a professional obligation to take action unless the patient can be convinced to discuss his HIV status with his wife on his own.

MANAGEMENT

When violation of patient confidentiality has occurred, whether deliberate or inadvertent, the patient should be informed of the violation and the steps that will be taken to prevent future occurrences. Root causes should be addressed, such as provider education and "holes" in the security of the patient record. Institutional and group practice policies should be in place and followed with regard to consequences for the physician's infractions involving patient privacy.

Whether or not the violation of confidentiality resulted from unethical provider behavior, in instances in which the confidential material reveals a real, substantial, and imminent risk of harm to third parties, it is the ethical obligation of the provider to pursue actions that protect the safety of third parties. They are obliged to do so even if this would place the provider at risk of consequences due to their own unethical behavior. In most states, this duty is also a legal requirement.

In the described case, the risk of harm may be real and substantial, but does not appear to be imminent. In that case, directly approaching the patient or the patient's primary physician to attempt to convince the patient to discuss his HIV status with his wife seems to be a reasonable first step. If the patient is adamant about not discussing his test results with his wife, local authorities such as the infection control board of the hospital or local public health authorities should be consulted regarding further actions and reporting requirements. The patient should then be fully informed of any actions the provider will take, and when.

PREVENTION

The problem of unauthorized access to a patient's record must be addressed individually, "culturally," and institutionally. All physicians should receive education during their orientation to a new practice environment about their professional obligation to respect and protect patient confidentiality. The education should include details about when it is appropriate to access medical records, when it is inappropriate to access records, and responsibilities of individuals to protect records from unauthorized access by others. Any local state variations in legal requirements should also be addressed.

The health care team should be imbued with an understanding of the role of patient confidentiality in promoting individual patient care and in fostering overall trust in the medical profession. Everyone should thoroughly understand legal requirements, including HIPAA regulations, regarding private patient information. The team should be reminded not to have public conversations that contain private patient information, even if they believe the information is not individually identifiable, because they might be in error in assuming so.

Practice groups should adopt policies and procedures for dealing with individuals who either inadvertently or deliberately cross professional boundaries with regard to this essential "social contract." A professional "culture" should be promoted in which casual conversations about patient care do not take place in public. Institutions should invest in patient record keeping systems that have adequate safeguards for sensitive patient information.

Institutional policies should address occasions when weaknesses in patient security are discovered and/or when individuals or employees break rules regarding confidentiality. Institutions and individuals can play important roles in developing and maintaining secure patient records. Current-day electronic record keepers are capable of setting up restricted access, alerting providers who access the chart to immediate special confidentiality concerns, and detecting inappropriate access by health care workers not involved in direct patient care.

SUMMARY

The duty of physician respect for patient privacy is a cornerstone of the doctor-patient relationship. This duty is of such importance that society affords physicians special privileges with regard to secret-keeping and only permits violation of patient confidentiality in special circumstances, such as when a third party may be in danger. The duty to protect patient privacy requires providers to actively protect patient information under most circumstances, and to avoid accessing information that is not necessary to patient care or that involves individuals with whom the provider does not have a specific patient-doctor relationship. Because rules and protections regarding patient confidentiality and provider "duties to warn and protect" vary from state to state, physicians should be familiar with local laws relevant to their practice.

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16 Patients With a Cardiovascular Implantable Electronic Device Undergoing Surgery

Peter M. Schulman • Marc A. Rozner

Case Synopsis

A 55-year-old man with a Medtronic Micra Leadless pacemaker (programmed VVIR) undergoes right total hip arthroplasty under general anesthesia. His past medical history is significant for atrial fibrillation and complete heart block. In the operating room the anesthesiologist intends to temporarily program the pacemaker to an asynchronous pacing mode (i.e., VOO) by applying a magnet. Before the start of surgery the nurse places the electrosurgery dispersive electrode (i.e., "bovie pad") on the patient's mid back. Initially the patient has a blood pressure of 155/80 mm Hg and a 100% ventricular paced heart rate of 70 beats per minute that does not appear to change after the magnet is applied. Several minutes into surgery and as soon as monopolar electrosurgery is used, the patient is asystolic.

PROBLEM ANALYSIS

Definition

Several million patients in the United States have an implantable pacemaker (PM) or implantable cardioverter-defibrillator (ICD), and hundreds of thousands of these cardiovascular implantable electronic devices (CIEDs) are implanted annually. The number of patients with a CIED will likely continue to increase because of population aging, new indications for these devices, and technologic advances. Consequently, anesthesia providers and other operative personnel should expect to routinely encounter CIED patients and care for them with increasing frequency.

Transvenous CIEDs consistent of a pulse generator that is typically implanted under the clavicle in a prepectoral pocket, and one to three leads inserted into the right atrium (RA), right ventricle (RV), and/or coronary sinus (CS). The device type (i.e., PM or ICD) and number and location of leads (RA, RV, CS) depends on the patient's underlying pathologic condition(s) and indications(s) for implant. Table 16.1 summarizes general indications for CIED implant.

Transvenous CIEDs virtually always have an RV lead and often also have an RA lead. When indicated, a CS lead is additionally implanted to pace the left ventricle for patients with heart failure and an intraventricular conduction delay. In select patients this treatment, termed *cardiac resynchronization therapy* (CRT) or *biventricular pacing,* improves cardiac output, heart failure symptoms, and mortality risk.

In addition to delivering high-voltage therapy (i.e., shocks and antitachycardia pacing [ATP]), transvenous ICDs are capable of performing all of the functions of a transvenous pacemaker. In 2012 a subcutaneous ICD (S-ICD) that uses a subcutaneous electrode instead of traditional transvenous (or epicardial) leads was granted Food and Drug Administration (FDA) approval. Compared with transvenous ICDs, this device has more limited functionality; it has no permanent antibradycardia pacing capability and cannot deliver ATP. In 2016 the first percutaneously implantable leadless pacemaker was FDA approved, and another leadless pacemaker is likely to be available in the United States soon. These devices are substantially smaller than a conventional pacemaker, but their only available pacing mode is VVI(R) (i.e., they cannot pace or sense the atrium).

Perioperative CIED management is complex and challenging. Issues include confusing nomenclature (see Table 16.2 for the pacemaker code), evolving technology (i.e., leadless pacemaker, subcutaneous ICD), distinct and proprietary features that are often not standardized among device types and manufacturers (including variable responses to magnet application), and published literature that is often outdated or sometimes even incorrect.

Additionally, electrical equipment such as monopolar electrosurgery (i.e., the "bovie") frequently used during surgery produce electromagnetic interference (EMI) that might adversely affect CIED function and lead to CIED damage and patient injury. Common problems include pacing inhibition (potentially causing profound bradycardia or asystole in the pacing dependent patient) and inappropriate high voltage therapy (including shocks and ATP) in the patient with an ICD.

Recognition

The case synopsis highlights three potential causes of CIED-related complications: (1) electromagnetic interference (EMI), (2) incorrect electrosurgery dispersive electrode positioning, and (3) improper magnet use.

Electromagnetic Interference

A CIED's normal performance can be disrupted by an electromagnetic field from an external source. Although there are many possible

TABLE 16.1 General Indications for CIED Implant

Device Type	Left Ventricular Ejection Fraction (%)	QRS Duration (msec)	Heart Failure Class	Atrioventricular Block	Sinoatrial Node Dysfunction
Transvenous PM	>35	Any	Any	Yes or no	Yes or no
Leadless PM	>35	Any	Any	Yes	No
Transvenous ICD	≤35[a]	Any	I, II, III	Yes or no	Yes or no
Subcutaneous ICD	≤35[a]	Any	I, II, III	No	No
Biventricular PM (CRT-P)	≤35[b]	≥150[c] or ≥120[d]	II, III, ambulatory IV[e]	Yes or no	Yes or no
Biventricular ICD (CRT-D)	≤35	≥150[c] or ≥120[d]	II, III, ambulatory IV[e]	Yes or no	Yes or no

[a]ICD sometimes indicated for secondary prevention even when left ventricular ejection fraction ≥35%.
[b]Most patients with left ventricular ejection fraction ≤35% receive an ICD.
[c]Class I recommendation.
[d]Class IIa recommendation.
[e]Class IV heart failure with no active acute coronary syndrome, no inotropes, and on guideline-directed medical therapy.
Modified from Schulman PM, Rozner MA, Sera V, et al: Patients with pacemaker or implantable cardioverter-defibrillator. *Med Clin North Am* 97(6):1051-1075, 2013.

TABLE 16.2 North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group (NASPE/BPEG) Generic PM Code (NBG) (revised 2002)

Position I	Position II	Position III	Position IV	Position V
Chambers paced	Chambers sensed	Response to sensing	Programmability	Multisite pacing
O = none	O = none	O = none	O = none	O = none
A = atrium	A = atrium	I = inhibited	R = rate modulation	A = atrium
V = ventricle	V = ventricle	T = triggered		V = ventricle
D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)

Modified 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* 25(2):260-264, 2002.

causes of EMI, in the operating room monopolar electrosurgery is the most common culprit (bipolar electrosurgery is very unlikely to cause EMI). The coagulation mode causes more EMI than non-blended cutting, and the risk of EMI is highest when electrosurgery is used in close proximity to the CIED (e.g., for a patient with a CIED implanted in the chest EMI is likely when monopolar electrosurgery is used superior to the patient's umbilicus).

The most frequent sequela of intraoperative EMI is ventricular oversensing (i.e., the device senses signals on the ventricular lead it should ignore) leading to (1) pacing inhibition and severe bradycardia or asystole in the pacing dependent patient, and/or (2) the delivery of inappropriate shock(s) or antitachycardia pacing by an ICD. Other less common consequences of intraoperative EMI include undesirable rapid pacing, activation of "power on reset" mode, and total device failure.

Electrosurgery Dispersive Electrode Positioning

The dispersive electrode of the electrosurgery unit (ESU) should be positioned so the current path from the ESU to the electrode is diverted away from the CIED pulse generator and leads (Fig. 16.1). Thus for a patient undergoing hip surgery (as in the case synopsis), the dispersive electrode should be placed on the patient's leg rather than patient's mid back.

Magnet Use

A magnet will often suspend the antitachycardia therapy of an ICD and will often cause a PM to pace asynchronously. Hence when EMI is likely during urgent or emergent surgery, magnet application is often the best strategy for suspending the antitachycardia therapy of an ICD or causing asynchronous pacing in the pacing-dependent PM patient. That said, magnet use might yield unpredictable and even untoward effects. Some CIEDs can be programmed to ignore a magnet, and in many instances the magnet response of an ICD cannot be confirmed. The asynchronous pacing rate produced by a magnet may not be optimal for some patients, and the pacing mode of an ICD can never be changed with a magnet. Furthermore, some newer CIEDs (such as the Medtronic Micra Leadless PM) have no magnet response. Thus whenever intraoperative magnet use is planned for elective surgery, the CIED's magnet response should be known and the magnet switch should be active. In addition, the patient should remain supine and the magnet should remain visible and accessible for the duration of the procedure.

Risk Assessment

CIEDs are generally very reliable; however, system malfunction or outright failure sometimes occurs, and might result from problems with the CIED system (i.e., pulse generator or leads) or external causes such as EMI.

An FDA database analysis provides insight into the general failure rate of these devices. Over a 12-year period per 1000 implants, 4.6 PMs and 20.7 ICDs were explanted for issues other than battery depletion, and out of 2.25 million PMs and 415,780 ICDs implanted, 30 PM and 31 ICD patients died as a direct result of device malfunction. A subsequent analysis of 459,000 transvenous ICD and 256,000 CRT-D implants between 2003 and 2007 uncovered 10,593 (2.3%) transvenous ICD and 1925 (0.8%) CRT-D failures.

Although data are limited, the presence of a CIED might increase perioperative morbidity and mortality, because perceived or actual device malfunction occurs with some regularity during surgical procedures. Although under routine circumstances outright device failure is rare, the exposure to EMI that frequently occurs in the operating room presumably places these patients at increased risk. Moreover, even perceived device malfunction ("pseudomalfunction") can cause patient injury or device damage.

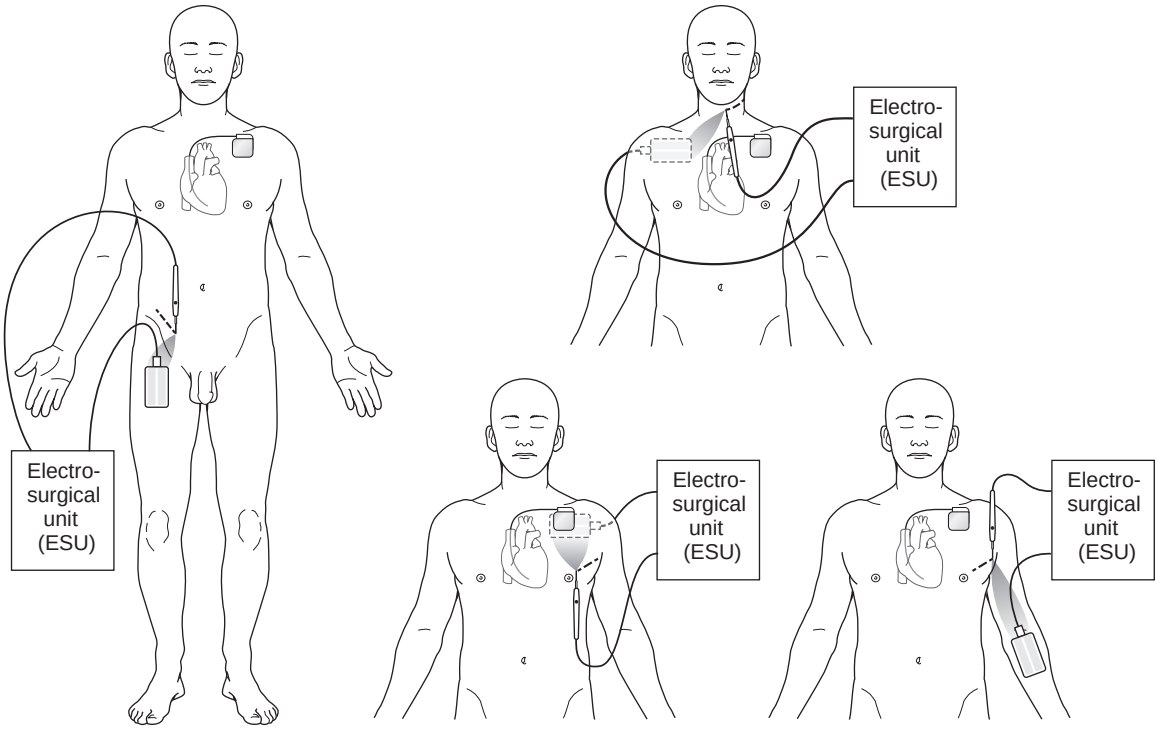

Fig. 16.1 Proper positioning of the electrosurgery dispersive electrode to divert electricity away from the CIED pulse generator and lead(s).

Pseudomalfunction results from multiple factors. Because all transvenous ICDs have antibradycardia pacing capabilities, and device terminology is often used "loosely" (i.e., "pacemaker/defibrillator"), ICDs are commonly mistaken for pacemakers and vice versa. All modern CIEDs have sophisticated features (rate sensors, algorithms to minimize right ventricular pacing, sleep modes, etc.) that when enabled might make the device behave unexpectedly. ICDs process and respond to EMI differently than PMs. Magnet behavior is not standardized among manufacturers or device types.

Implications

As suggested by numerous publications, the presence of a CIED might increase perioperative risk, but prospective data are lacking. CIEDs are complicated and the perioperative management of the CIED patient is complex. Most operative personnel including anesthesia providers and proceduralists are not CIED experts.

MANAGEMENT

To promote optimal care for surgical patients with CIEDs two important documents have been published: a Practice Advisory from the American Society of Anesthesiologists (ASA) and an Expert Consensus Statement from the Heart Rhythm Society (HRS). Anesthesia providers and other operative personnel should be familiar with these documents and closely adhere to their recommendations. A comprehensive review of all recommendations contained in these documents is beyond the scope of this chapter. However, many of the most important recommendations are summarized here.

Preoperative Recommendations

1. Identify the presence of a CIED.
2. Identify the manufacturer (e.g., Medtronic, Boston Scientific, St. Jude Medical, Biotronik, LivaNova) and device type (e.g., transvenous PM, leadless PM, biventricular PM, transvenous ICD, subcutaneous ICD, biventricular ICD).
3. Determine that the CIED is functioning properly (obtain records such as a copy of the most recent interrogation report and/or establish contact with the patient's CIED physician/clinic). Consider having the CIED interrogated by a competent practitioner shortly before the anesthetic (ASA). Alternatively, HRS recommends an interrogation within 6 months of scheduled surgery for an ICD, and within 1 year for a PM.
4. Determine the patient's underlying rate and rhythm and whether the patient is pacing dependent.
5. Determine how the CIED will respond when a magnet is applied.
6. Obtain a specific perioperative management plan from a CIED expert (HRS).

Intraoperative Recommendations

1. Program minute ventilation rate responsiveness off (if active).
2. Consider programming all rate enhancements off to prevent rhythm misinterpretation.
3. Consider increasing the pacing rate to optimize oxygen delivery to tissues.
4. If EMI is likely:
   a. For an ICD, disable high-voltage (antitachycardia) therapy.
   b. Consider asynchronous pacing for some pacing-dependent patients.

   Note: A magnet will *often* but not always cause a transvenous PM to pace asynchronously at a fixed rate. A magnet will *often* but not always suspend the high-voltage therapy of an ICD. A magnet will *never* change the pacing mode of an ICD.
5. Monitor cardiac rhythm/peripheral pulse with pulse oximeter plethysmogram or arterial waveform.
6. Consider disabling the artifact filter on the electrocardiogram monitor.

7. Whenever feasible, avoid use of monopolar electrosurgery (ESU). If monopolar ESU is planned, pure cut causes less EMI than blend or coagulation. Bipolar electrosurgery is very unlikely to cause EMI.
8. Position the ESU dispersive electrode to divert electricity away from the pulse generator and leads.
9. If monopolar electrosurgery causes problems such as ventricular oversensing, pacing quiescence, inappropriate tachycardia, or high-voltage therapy, immediately suspend monopolar electrosurgery use and consider CIED reprogramming, magnet application, and/or relocating the position of the electrosurgery dispersive electrode.

Postoperative Recommendations

1. Strongly consider interrogating the CIED to confirm proper function (especially if there was intraoperative hemodynamic instability or a concern for inappropriate CIED function).
2. Any CIED that underwent preoperative or intraoperative reprogramming should be reinterrogated and have its parameters appropriately restored (rate enhancements might need to be reinitiated, and optimum heart rate and pacing parameters often need to be determined and programmed).
3. The ICD patient must remain fully monitored (i.e., in the postanesthesia or intensive care unit) until high-voltage therapy is programmed back on.

PREVENTION

Take the following preventive measures:

- Before surgery, ensure that the CIED is functioning properly and obtain a perioperative management plan from a CIED expert.
- If EMI is likely, ICD antitachycardia therapy should be suspended and external defibrillation pads applied. Reprogramming to an asynchronous pacing mode should be considered for any pacing-dependent patient. In addition, some rate enhancements might require disabling, and for major surgery, other programming changes (e.g., increasing the lower rate limit) might be warranted.
- If magnet use is planned, magnet behavior should be known and confirmed.
- If monopolar electrosurgery use is planned, position the electrosurgery unit dispersive electrode to divert the current path away from the CIED.
- Postoperative CIED interrogation and/or programming changes are often needed.

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17 Patients With Seizure Disorder

R. Alexander Schlichter

Case Synopsis

A 33-year-old woman presents for a partial mastectomy and axillary lymph node biopsy. She has a history of seizure disorder well controlled on levetiracetam and mild asthma requiring occasional rescue with an albuterol inhaler. Her physical examination is normal.

PROBLEM ANALYSIS

Definition

Epilepsy is a type of neurologic disease that is caused by abnormal electrical activity in one (focal) or more (general) loci in the cerebral cortex. Its presentation depends on the location and severity of the seizure activity. The yearly incidence is estimated to be 0.5% to 2.3%, with up to 40% of patients developing intractable seizures (greater than one per month). Approximately 400,000 people in the United States have medically uncontrolled epilepsy. Two cases per 1000 patients per year result in sudden death. Various neurologic diseases are associated with epilepsy or the use of anticonvulsant drugs, such as migraines, depression, psychosis, mood or behavioral disorders, and chronic pain. The use of anticonvulsants for these conditions can influence how anesthesiologists treat these patients.

The type of seizures that a patient experiences (as well as the patient's allergies) can determine which treatment regimen is prescribed. Seizures can be classified as partial or general. Partial seizures occur in one hemisphere and can be subdivided as follows:

- Simple partial seizures: no change in mental status
- Complex partial seizures: change in mental status
- Partial seizure leading to generalized seizure

Generalized seizures occur globally in the cortexes that affect both hemispheres. They are associated with changes in mental status and can be subdivided as follows:

- Absence seizures
- Myoclonic seizures
- Tonic-clonic seizures
- Atonic seizures

Complex partial seizures are the most common form of epilepsy, accounting for approximately 25% of adult and 40% of pediatric epileptics. Tonic-clonic seizures, the second most common, account for about 25% of adult and 19% of pediatric epileptics.

The exact etiology of epilepsy is not completely understood. Seizures are associated with congenital diseases such as tuberous sclerosis, neurofibromatosis, multiple endocrine adenomatosis, and Jervell-Lange-Neilson syndrome. Pathologies associated with traumatic brain injury, stroke, brain tumor, and Alzheimer's disease are also associated with epilepsy.

Absence seizures are often triggered by stimuli such as bright or flashing lights and are thought to be caused by changes in communication between the thalamus and the frontal, visual, auditory, and somatosensory cortexes. This can lead to a dissociated state similar to non–rapid eye movement sleep in an otherwise awake patient. The success of treatment with valproic acid and ethosuximide suggests that γ-aminobutyric acid (GABA) receptors (valproic acid, benzodiazepines) and T-type calcium channels (ethosuximide) may be involved.

Other generalized seizures involve intense muscular activity (myoclonic, tonic-clonic) that are thought to be caused by frequent depolarization of sodium channels. Subsequently, a decrease in the number of voltage-stabilizing potassium channels has also been studied.

Partial seizures (simple and complex) may be caused by dysfunction of the GABA receptor leading to an increase of excitability and decreased inhibition of neurons affected.

Because of the limited contact with the patient in the perioperative arena, the anesthesiologist should consult with the medical providers managing the patient with epilepsy. The patient's evaluation should include the following:

- History of the diagnosis of the seizure disorder
- Possible etiologies of the seizure disorder
- Current and past managements of the seizure disorder
- Effectiveness of current pharmacologic regimen

The goal of the patient's management is to optimize the patient's ability to function. This includes the following:

- Minimizing the frequency and severity of epileptic attacks
- Surgical management of cerebral causes (masses, hydrocephalus, traumatic brain injury, stroke, bleeding, seizure foci)
- Balancing treatment regimens with side effects
- Compliance with therapeutic plan

In the absence of family history, a clear medical causality, and a negative electroencephalogram (EEG), a single epileptic episode (which may be a misdiagnosis) can lead to only expectant management. The chance of a recurrent seizure is about 25%; however, subsequent episodes increase the risk to 80%, and pharmacologic management is recommended. If an organic cause is diagnosed, the patient should be started on medication and invasive interventions may be indicated.

Parturients with epilepsy have an increased risk of the following:

- Passing on congenital abnormalities secondary to hereditary or pharmacologic causes
- Changes in pharmacokinetic effects of existing therapies due to physiologic changes of pregnancy
- Changes in therapy that may lead to subtherapeutic efficacy because of possible teratogenic effects of prepartum drug regimens
- Risk of preterm labor, preeclampsia, abruption, and intrauterine death

The pharmacologic regimen is determined by the patient's primary medical provider. The goals are as follows:

- Expectant management
- One medication
- Combination therapy (two or more medications)

The primary management should balance efficacy with side effects, optimizing the patient's ability to function, as well as ability to maintain compliance. If one regimen fails because of lack of efficacy or unacceptable side effects (including allergic reactions and pregnancy), the provider should look at one or more medications that work at alternative mechanisms of action.

If pharmacologic therapy fails to control epilepsy, interventional therapy may be considered. Vagal nerve stimulation (VNS), deep brain stimulation (DBS), or even a partial or total temporal lobectomy may be indicated, depending on the etiologies of the seizure disorder. VNS is referred to as a "pacemaker for the brain" according to the Epilepsy Foundation. DBS, originally advocated for treating Parkinson's disease, has shown promise in treating epilepsy in patients failing pharmacologic and VNS therapy. Ultimately, if seizure foci can be identified with functional magnetic resonance imaging (fMRI) or EEG mapping, partial or total temporal lobectomy may be considered.

A new therapy, MRI-guided laser interstitial thermal therapy, is being evaluated. The procedure involves stereotactic placement of fiberoptic fibers into the defined foci. Under MRI guidance the foci are ablated by heat generated by a laser. It is considerably less invasive than a craniotomy for lobectomy.

Recognition

Anesthesiologists caring for a patient with epilepsy should take into account the following:

- Frequency and sequelae of seizure activity
- Effectiveness of current treatment regimens
- Compliance with prescribed treatment regimens
- Triggers

Triggers include bright or flashing lights, noise, hunger, hypoglycemia, thirst, caffeine withdrawal, drug and substance intoxication or withdrawal, sleepiness, fatigue, stress, and anxiety. These triggers should be addressed in the perioperative period.

Risk Assessment

Patients with seizure disorders have a 20-fold increase in mortality risk, and this does not include other comorbidities that the patient may have. There are neurologic, cardiac, and pulmonary sequelae to epilepsy that can affect medical perioperative management of the patient. Nonperioperative effects such as impaired cognitive function from recurrent seizures, associated diseases (e.g., cerebral palsy), social isolation, stigma from the disease, and infantilization of a pediatric/adolescent patient can complicate the ability to obtain informed consent, obtain intravenous access, and ensure postoperative support. Patients on anticonvulsants often suffer from polypharmacy, including antidepressants, central-acting muscle relaxants, benzodiazepines, and pain medications.

Anticonvulsants can be sedating, which can effect induction of, maintenance of, and emergence from anesthesia. Many anticonvulsants induce cytochromes in hepatic metabolism, increasing the metabolism of aminosteroid nondepolarizing muscle relaxants (vecuronium, rocuronium). The binding drug sugammadex has decreased the incidence of overrelaxation to compensate, but its use is cautioned in women of childbearing age and patients with an allergy to sugammadex.

MANAGEMENT AND PREVENTION

Patients on an effective anticonvulsant regimen should continue the regimen up to the day of a procedure, including taking oral medications the day of the procedure with a sip of water. Patients not on therapy having supertentorial surgery can be given intravenous agents (levetiracetam, phenytoin) perioperatively. In the absence of enteral or parenteral medication delivery routes, rectal, intramuscular, or intranasal administration should be considered. Consultation with neurology and pharmacy is necessary to ensure that the bioavailability of the drug is appropriate.

The anesthesiologist involved in a patient having an active seizure should be prepared to intervene. The anesthesiologist can acquiesce the seizure with benzodiazepines, barbiturates, propofol, and/or inhaled ethers (isoflurane, sevoflurane, desflurane), depending on the location (operating room, intensive care unit, or ward) and availabilities of the drugs. The anesthesiologist should also be prepared to manage the airway emergently. This will require appropriate ventilation and airway equipment. The use of nondepolarizing muscle relaxants can reduce the risk of physical harm to a seizing patient in adjunct with other anesthetics. Finally, if the patient encounters hemodynamic abnormalities (extreme hypertension or shock), the anesthesiologist should be prepared to address these conditions with antihypertensives, anesthetics, or opioids for extreme hypertension; or pressors, inotropes, and intravenous fluid management for shock.

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18 Perioperative Management of Patients With Muscular Dystrophy

Katarzyna Luba

Case Synopsis

An 8-month-old boy undergoes myringotomy tube removal. Previous general anesthesia for tube placement was uneventful. Anesthesia is induced with intravenous thiopental and is maintained with nitrous oxide, halothane, and oxygen via a facemask. After removal of the myringotomy tube, the surgeon decides to perform an adenoidectomy. Airway obstruction at this time necessitates emergency intubation. After succinylcholine 2 mg/kg intravenously, an increase in masseter muscle tone is noted. The electrocardiogram (ECG) monitor shows a wide complex tachycardia progressing to bradycardia. End-tidal carbon dioxide (CO_2) of 40 to 50 mm Hg gradually decreases to 25 mm Hg. Arterial saturation decreases from 100% to 80%, then cannot be detected. Halothane is discontinued. Calcium chloride, epinephrine, and sodium bicarbonate are given intravenously. The ECG becomes increasingly dysmorphic, and pulses cannot be palpated. Chest compressions start. Venous blood analysis shows a pH of 7.13, CO_2 tension (Pco_2) is 73 mm Hg, and serum potassium level is over 10 mmol/L. Calcium, epinephrine, and bicarbonate are repeated. After 13 minutes of cardiopulmonary resuscitation, the ECG shows the return of a narrow complex tachycardia, and systolic blood pressure increases to 100 mm Hg. Twenty minutes after succinylcholine administration, a venous blood sample shows a pH of 7.30, Pco_2 of 49 mm Hg, and potassium of 7.1 mmol/L. A urinary catheter reveals red urine. The patient is transported to a pediatric intensive care unit. The creatine kinase (CK) level is 285,760 U/L. The patient is treated with vigorous intravenous hydration. He is discharged home in good condition. DNA studies show a deletion of the dystrophin gene, consistent with a diagnosis of Duchenne muscular dystrophy.

PROBLEM ANALYSIS

Definition

Muscular dystrophies are a clinically and genetically diverse group of hereditary disorders of the structure of striated muscle, characterized by progressive muscle weakness and wasting. The diagnosis of a muscular dystrophy is based on elevated serum CK, myopathic electromyogram features, and muscle biopsy. The morphologic changes common to all forms of muscular dystrophy present a random pattern of normal or hypertrophic muscle fibers, necrotic and necrotizing fibers, and interstitial accumulation of fatty and fibrous tissue. The latter changes result in the characteristic pseudohypertrophy of the calf muscles seen in Duchenne muscular dystrophy.

The previous classification of muscular dystrophies was based on patterns of inheritance and clinical features. A more recently proposed classification takes into account the type, localization, and function of defective proteins involved in the pathogenesis of different muscular dystrophies.

Plasma Membrane–Associated Proteins

Defective plasma membrane–associated proteins or the lack of such proteins causes the most common muscular dystrophies, including Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), the sarcoglycanopathies, and other forms of limb-girdle muscular dystrophy (LGMD).

Dystrophinopathies

The most common muscular dystrophies are X-linked recessive disorders caused by mutations of the dystrophin gene. Dystrophin is a large sarcolemmal protein essential for maintaining the integrity of the sarcolemma. The severe DMD form results from deficiency of dystrophin. The milder allelic form (BMD) is associated with a reduced amount of the truncated protein. The incidence of DMD is approximately 1 in 3500 live male births. A DMD or BMD phenotype may be expressed by a female patient with the dystrophin gene mutation and an X0 karyotype (Turner syndrome). Affected patients have delayed motor development, and when they start walking, they present with gait abnormalities. By the age of 5 years, muscle weakness is evident and calf pseudohypertrophy develops. Lumbar hyperlordosis and toe-walking result from progressive loss of muscle strength and tendon contractures. By age 12, most patients are confined to a wheelchair. Scoliosis, chest deformity, and diaphragmatic weakness lead to restrictive pulmonary disease by age 16 to 18. Respiratory failure, the most common cause of death, occurs in the third decade of life. Almost all patients have cardiomyopathy, but this rarely causes death. Intellectual impairment is common.

Compared with DMD, BMD has a later onset and a milder clinical course. Symptoms of proximal muscle weakness commonly start between ages 5 and 15, although the onset may be delayed until the

third or fourth decade of life. Patients generally ambulate beyond age 15. Calf enlargement occurs early and is prominent. Patients have a short life expectancy, but many live to their thirties or forties. Mental retardation is milder than in DMD. In patients with mild or subclinical BMD, dilated cardiomyopathy may be the presenting feature of the disease. Most BMD patients die of complications of cardiomyopathy.

Sarcoglycanopathies

These disorders are caused by mutations of genes encoding four transmembrane glycoproteins of the sarcoglycan complex. Mutations of any of the four sarcoglycan genes (alpha, beta, gamma, and delta) result in LGMD 2D, 2E, 2C, and 2F. Males and females are similarly affected. Proximal leg muscle weakness generally appears in the second or third decade but may be delayed. Upper limb involvement with scapular winging develops. Diaphragmatic weakness with respiratory insufficiency, cardiomyopathy, congestive heart failure (CHF), and arrhythmias may develop. Intellectual function is normal.

Caveolin Deficiency

This is a rare form of autosomal dominant muscular dystrophy. LGMD 1C is caused by deficient caveolin, a ubiquitous plasma membrane protein.

Extracellular Matrix Proteins

Deficiencies in extracellular matrix proteins result in congenital muscular dystrophies (CMDs), a group of autosomal recessive disorders that become symptomatic at birth or in infancy. They are diagnosed by hypotonia and a dystrophic muscle biopsy. The most severe form is merosin-deficient CMD. The maximal functional ability of a child with CMD is sitting unsupported. Cardiomyopathy may be present.

Proteins With Enzymatic Activity

Mutations in Genes Encoding Glycosyltransferases

These mutations are a recently identified mechanism for CMDs. The gene encoding the fukutin-related protein (FKRP—a glycosyltransferase) is mutated in a severe form of muscular dystrophy, CMD type 1C, as well as a mild form, LGMD 2I. Central nervous system involvement is present in the severe form, with cerebellar cysts, seizures, and developmental delay. Mild cardiomyopathy also may be present.

Protein Kinases

Heterozygosity for a trinucleotide repeat ([CTG]n) expansion mutation in the 3′ untranslated region of a protein kinase gene on chromosome 19 is the cause of myotonic dystrophy, the most common adult form of muscular dystrophy. This has a prevalence of 1 in 8000. Myotonic dystrophy is an autosomal dominant disorder characterized by myotonia, slowly progressive muscle weakness and wasting, frontal baldness, cataracts, and insulin resistance secondary to aberrant insulin receptor expression.

Other Muscle Proteins

Sarcomeric Proteins

Mutations in the titin gene, encoding a giant sarcomeric protein, underlie an autosomal dominant form of congenital dilated cardiomyopathy. Recently mutations of the same gene have been found in patients with isolated tibial muscular dystrophy.

Nuclear Proteins

Defects in two nuclear proteins are responsible for two distinct forms of Emery-Dreifuss muscular dystrophy (EDMD). X-linked EDMD is due to mutations in the gene encoding the nuclear protein emerin. Autosomal dominant EDMD results from mutations in the lamin A/C gene, encoding a protein of the nuclear lamina. Mutations in this gene also lead to a form of dominant proximal LGMD 1B and dilated cardiomyopathy. Skeletal muscle involvement in EDMD is usually mild and slowly progressive. Cardiac involvement is the predominant feature of the disease.

Cardiomyopathy in Muscular Dystrophies

Cardiac involvement is a universal feature of muscular dystrophies. The severity of cardiac involvement may determine the long-term prognosis for persons with any type of muscular dystrophy.

In DMD and BMD, lacking or faulty dystrophin has been demonstrated in both skeletal and cardiac muscle. Heart failure is often the cause of death, alone or in association with respiratory failure. Myocardial damage is initially subclinical but can be recognized through minor ECG and echocardiographic changes. Myocardial involvement progresses to a clinically evident stage of hypertrophy; arrhythmias, characterized by conduction defects (atrioventricular block, bundle branch block) or severe supraventricular or ventricular arrhythmias; and, eventually, dilated cardiomyopathy due to widespread myocardial fibrosis. Heart failure is the most common cause of death in patients with BMD. Female carriers of DMD and BMD have a 10% incidence of age-progressive cardiomyopathy. Patients with severe forms of muscular dystrophy rarely are candidates for heart transplant given the poor long-term prognosis of the disease. The use of destination left ventricle assist device in DMD patients with end-stage dilated cardiomyopathy has recently been described.

Sarcoglycanopathies (LGMD 2C, 2D, 2E, 2F) may have associated dilated cardiomyopathy. This results from disrupted sarcoglycan complexes in both skeletal and cardiac muscle.

LGMD due to mutations in the FKRP gene (LGMD 2I) may be associated with myocardial fibrosis, leading to dilated cardiomyopathy and repolarization abnormalities.

In myotonic dystrophies, cardiac conduction defects are a major cause of sudden death. The incidence of complete atrioventricular block among these patients is higher than in the general population. A prolonged His-ventricular conduction interval puts these patients at risk of paroxysmal atrioventricular block and justifies early pacemaker implantation. In congenital (neonatal) myotonic dystrophy, abnormal myocardial relaxation results in left ventricular diastolic dysfunction.

Severe cardiac involvement is common in EDMD. Both X-linked and autosomal dominant forms involve the risk of bradyarrhythmias (often requiring pacemaker implantation) and atrial fibrillation or flutter. Atrial fibrillation often precedes atrial standstill and may be the cause of embolic stroke at a young age. Prophylactic anticoagulation is recommended in EDMD patients with atrial arrhythmias or standstill. Finally, left ventricular failure is rare but may be severe.

Recognition

Patients with muscular dystrophy usually present for muscle biopsy, tendon contracture release, correction of kyphoscoliosis, or pacemaker implantation. Pediatric or young adult patients with undiagnosed muscular dystrophy may present for procedures unrelated to the disease.

All patients with muscular dystrophy should be suspected of having respiratory and cardiac dysfunction. Pulmonary function tests should be performed in all patients with muscle weakness because of the high incidence of restrictive lung disease secondary to diaphragmatic weakness and scoliosis. In asymptomatic patients with a diagnosis of muscular dystrophy, the specific type of dystrophy and the risk of cardiac involvement determine the need for further cardiac workup.

Intraoperative CHF may present as tachycardia and hypotension unresponsive to intravenous fluids. Physical signs of CHF include jugular vein distention, pulmonary rales, and dyspnea in a spontaneously breathing patient. Severe CHF may result in acute pulmonary edema. Diagnosis may be confirmed by transesophageal echocardiogram or by hemodynamic measurements with a pulmonary artery catheter. Typically, pulmonary artery occlusion pressure is elevated (>18 mm Hg), cardiac index is low (<2.2 L/min/m^2 body surface area), and systemic vascular resistance is high (>1200 dynes/sec/cm^{-5}).

In children with undiagnosed DMD, succinylcholine has been reported to induce hyperkalemic cardiac arrest. On the basis of these reports, the Food and Drug Administration recommended against the use of succinylcholine for nonemergent intubation in all children.

Exposure of patients with DMD and BMD to volatile anesthetics, halothane, isoflurane, and sevoflurane may result in hyperthermia, muscle rigidity, massive rhabdomyolysis, and hyperkalemia. Hyperkalemic cardiac arrest has been reported as the first manifestation of occult DMD in young patients undergoing general anesthesia without the use of succinylcholine. This clinical picture mimics malignant hyperthermia (MH) and it has long been believed to be true MH. However, dystrophinopathies (DMD and BMD) and MH are genetically distinct entities: dystrophinopathies result from an X chromosome mutation, whereas MH is caused by a mutation of the gene encoding the ryanodine receptor (RYR), located on chromosome 19.

Risk Assessment

All patients with muscular dystrophy are at risk for cardiomyopathy or conduction disorders. Signs and symptoms of myocardial dysfunction at the time of preoperative evaluation may be overt or masked by confinement to a wheelchair. Therefore all patients with muscular dystrophy should have their cardiac function evaluated preoperatively. ECG abnormalities (sinus tachycardia or bradycardia, short P-R interval, signs of left ventricular hypertrophy, conduction defects) are common. However, the best correlation between severe cardiac involvement and mortality is the degree of left ventricular echocardiographic dysfunction. Guidelines for the assessment of cardiac involvement in patients with DMD and BMD advise that those with DMD have an echocardiogram and ECG at the time of diagnosis, every 2 years up to age 10, and annually thereafter. BMD patients should have an echocardiogram and ECG at the time of diagnosis and then every 5 years. The same recommendations apply to patients with other forms of muscular dystrophy. Additional echocardiograms or ECGs should be obtained before surgery or when clinically indicated.

Patients with EDMD should have an ECG and echocardiogram at the time of diagnosis and annually thereafter. They should also be monitored annually for arrhythmias with a Holter monitor. An implanted pacemaker is justified for symptomatic patients or for asymptomatic patients whose ECG shows sinus node or atrioventricular node dysfunction. In autosomal dominant EDMD, sudden death is a possibility. Therefore an internal cardioverter-defibrillator should be considered whenever antibradycardia pacing is indicated. When atrial fibrillation or atrial standstill is diagnosed, systemic anticoagulation is indicated.

Intracardiac conduction should be evaluated in all adult myotonic dystrophy patients. Patients are selected to undergo cardiac electrophysiologic investigation based on the results of signal-averaged ECGs.

In patients with DMD, a steady decrease in vital capacity (VC) follows progressive muscle weakness and the development of scoliosis. Once VC falls below 20% of predicted values, ventilatory failure is inevitable, and 73% of patients die of respiratory failure. Obstructive sleep apnea (OSA) is common, leading to chronic hypoxemia and right ventricular failure. Preoperative pulmonary function tests and sleep studies are indicated to assess the severity of restrictive pulmonary disease and OSA.

Implications

Patients with muscular dystrophies are at an increased risk of perioperative CHF, arrhythmias, and respiratory failure. If the VC is less than 30% of predicted, the patient will likely require prolonged postoperative ventilatory support. OSA and weak pharyngeal muscles increase the risk for early postoperative airway obstruction and hypoxia. Outpatient general anesthesia is not advised, owing to the risk of delayed respiratory depression. Also, delayed gastric emptying increases the risk of aspiration.

Succinylcholine can cause hyperkalemic cardiac arrest; therefore its use is contraindicated. Nondepolarizing muscle relaxants (NDMRs) may have prolonged effects, and their reversal with neostigmine is unpredictable. Volatile anesthetics may trigger an MH-like reaction (muscle rigidity, rhabdomyolysis, hyperkalemia, and hyperthermia) in patients with Duchenne or Becker dystrophy.

In patients with myotonic dystrophy, hypothermia, shivering, succinylcholine, neostigmine, and direct muscle stimulation may precipitate a myotonic crisis, characterized by prolonged contracture of the skeletal muscles.

For these reasons, regional or local anesthesia, when suitable, is preferred for all patients with muscular dystrophy. Finally, patients with DMD previously treated with glucocorticoid steroids require supplemental perioperative steroids.

MANAGEMENT

The need to minimize the use of volatile agents and muscle relaxants favors the use of regional anesthesia or total intravenous general anesthesia. Agents used for the latter include propofol, ketamine, dexmedetomidine, and opioids. Short-acting opioids (remifentanil, sufentanil) may be preferable to reduce the risk of postoperative respiratory depression. Premedication with benzodiazepines and opioids may cause respiratory depression, airway obstruction, and delayed emergence from anesthesia and should be avoided.

Airway management should take into account the increased risk of aspiration. Premedication with an H_2-blocker and metoclopramide is advised. Modified rapid-sequence endotracheal intubation with the use of an NDMR should be considered if endotracheal intubation is necessary.

The choice of neuromuscular blocking agents is limited by contraindications to succinylcholine and increased sensitivity to NDMRs. Short-acting NDMRs (e.g., cisatracurium) should be used, and their dose should be titrated to the train-of-four response. Even with the use of short-acting NDMRs, delayed recovery has been reported in children with DMD. Reversal of NDMRs with neostigmine has been reported without adverse events. However, as mentioned earlier, reversal with neostigmine may be unpredictable.

The management of intraoperative CHF depends on hemodynamic stability. Diuresis and positive end-expiratory pressure may be sufficient. If hypotension develops, an inotrope (dobutamine or milrinone) should be used, and an arterial line placed. An arterial line is advised for all major surgery in patients with muscular dystrophy. Further management is guided by transesophageal echocardiography or pulmonary artery catheter measurements. If preload is adequate, inotropy and afterload reduction may help increase cardiac output and tissue perfusion.

In patients with myotonic dystrophy, anesthetic goals should include avoidance of the triggers of myotonic contractures. Severe

contractures may result in jaw and chest rigidity, impeding efforts to intubate and ventilate. Contractures do not respond to NDMRs; they may respond to intravenous quinidine, infiltration of the muscle with local anesthetic, and rewarming.

MH-like reaction to inhalational anesthetics is a life-threatening event. Management requires immediate discontinuation of the triggering agent; administration of 100% oxygen; active cooling; treatment of associated arrhythmias, hyperkalemia, and acidosis; and continued CPR as appropriate. Hyperkalemia above 5.5 mmol/L should be treated with intravenous sodium bicarbonate, calcium chloride, 50% dextrose, insulin, and hyperventilation. To prevent acute renal failure secondary to rhabdomyolysis, patients should be treated with aggressive intravenous hydration and mannitol.

The use of dantrolene in MH-like episodes triggered by volatile anesthetics in patients with DMD or BMD, although practiced, is controversial. In true MH, dantrolene works by binding to a ryanodine receptor isoform, RYR 1, and inhibiting excessive release of calcium from sarcoplasmic reticulum. Inhalational anesthesia-induced rhabdomyolysis (AIR) seems to result from the breakdown of sarcolemma and release of myocyte contents into the bloodstream, so dantrolene may not be helpful in AIR.

Patients with impaired respiratory function require admission to the intensive care unit for prolonged ventilatory support after extensive surgical procedures under general anesthesia.

PREVENTION

Prevention of perioperative complications in patients with muscular dystrophy requires thorough evaluation of the surgical risk. Surgery for the correction of scoliosis in patients with DMD should be performed before pulmonary function declines to a degree precluding a safe anesthetic and postoperative course. Knowledge of the severity of myocardial involvement is necessary to prevent perioperative exacerbation of CHF or life-threatening arrhythmias. The preoperative evaluation should include a recent ECG, echocardiogram, and electrophysiologic testing if indicated by the results of signal-averaged ECGs. In the presence of severe cardiomyopathy and respiratory dysfunction, invasive hemodynamic monitoring and postoperative critical care management should be an integral part of perioperative management of patients undergoing major surgical procedures. Outpatient surgery in this patient population is discouraged because the risk of delayed respiratory complications warrants overnight monitoring after general anesthesia of any duration.

Aspiration risk should be minimized by premedication with H_2-blockers and metoclopramide and by the use of an appropriate intubation technique. Succinylcholine should never be used. Inhalational anesthetics should be avoided because of their potential to trigger massive rhabdomyolysis and life-threatening hyperkalemia. The use of regional or local anesthesia, whenever feasible, may help avoid respiratory, cardiac, and metabolic complications of general anesthesia in patients with muscular dystrophy.

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19 Porphyrias

Mohamed Ehab Ramadan • Mashhood Salahuddin • Hamdy Awad

Case Synopsis

A 36-year-old woman with a history of intermittent abdominal pain was scheduled for elective laparoscopic cholecystectomy. Anesthesia and surgery were uneventful. On the first postoperative day, the patient was noted to be restless and was complaining of severe abdominal pain and vomiting. Her vital signs were heart rate 124 beats per minute, blood pressure 184/102 mm Hg, temperature 37.5° C, and respiratory rate 20 breaths per minute. The nurse informs the on-call resident that the patient's urine is dark. During the resident's assessment, the patient starts to shake in an attack of generalized seizure after which she is transferred to the surgical intensive care unit for further assessment and management.

PROBLEM ANALYSIS

Definition

Porphyria is a rare inherited metabolic disorder that results from mutation in any of the genes coding for the eight enzymes involved in heme biosynthesis. Partial deficiency in any of these enzymes can lead to accumulation of porphyrins and their precursors in the tissues, leading to neurovisceral and/or cutaneous manifestations.

Patients with porphyria can be misdiagnosed, and latent carriers of the disease may remain asymptomatic. The disease is transmitted most often by an autosomal dominant path. Everyone inherits two copies of the heme synthetic enzyme genes. Mutation of one allele, which results in a 50% reduction in enzyme activity, may be completely asymptomatic until the stresses on the heme synthetic system (as noted in the case synopsis) provoke an acute problem.

Recognition

The first and rate-limiting step in heme biosynthesis pathway is the conversion of glycine and succinyl coenzyme A to δ-aminolevulinic acid (ALA) by δ-aminolevulinic acid synthase (ALAS), which is negatively regulated by heme (Fig. 19.1). Acute porphyrias are precipitated by the induction of ALAS to increase heme synthesis, but because of the enzyme defects, porphyrins and their precursors build up in the tissues. Although the exact underlying mechanism for neuropathy is still unclear, the suggested two mechanisms are accumulated porphyrins causing neurotoxicity or the disturbed heme metabolism affecting neuronal function.

Classification of Porphyria

Several classifications have been proposed for porphyria:

1. Depending on the organs in which porphyrins and their precursors accumulate, they are classified into *hepatic* and *erythropoietic* (bone marrow).
2. Depending on their clinical presentation, they are classified as follows:
   a. Acute porphyrias: ALA dehydratase (ALAD) porphyria, acute intermittent porphyria (AIP), hereditary coproporphyria (HC), and variegate porphyria (VP) (see Fig. 19.1).
   b. Nonacute porphyrias: congenital erythropoietic porphyria (CEP), porphyria cutanea tarda (PCT), and erythropoietic protoporphyria (EP).

Of the acute porphyrias, ALAD porphyria and AIP predominantly present with neurovisceral manifestations. The nonacute porphyrias predominantly present with cutaneous manifestations (e.g., photosensitivity, skin fragility, and bullae). HC and VP can present with acute neurovisceral as well as cutaneous manifestations. Among all types, acute porphyrias are considered of most interest to anesthesiologists.

Clinical Presentation

Clinical manifestations of acute porphyria start with behavioral changes and psychiatric abnormalities that proceed to sensorimotor and autonomic neuropathy:

- Restlessness, anxiety, insomnia, depression
- Pain: severe poorly localized abdominal pain, pain in the back and the extremities
- Autonomic neuropathy: sweating, tachycardia, arrhythmias, hypertension, urinary retention, nausea, vomiting, and constipation (less commonly diarrhea)
- Motor neuropathy: proximal muscle weakness rather than distal weakness, bulbar and respiratory paralysis
- Sensory loss: numbness and paresthesia
- Confusion, hallucinations, convulsions from hyponatremia due to either syndrome of inappropriate antidiuretic hormone or repeated vomiting
- Dark reddish urine
- Death: common causes are cardiac arrest and pneumonia from prolonged mechanical ventilation

Diagnosis of acute porphyria requires a high index of suspicion in any patient with unexplained acute abdominal pain, confusion, and neuropathy. Acute attacks can be fatal if misdiagnosed and left untreated. Once acute porphyria is suspected, urine should be checked for detection of elevated levels of porphobilinogen (PBG)

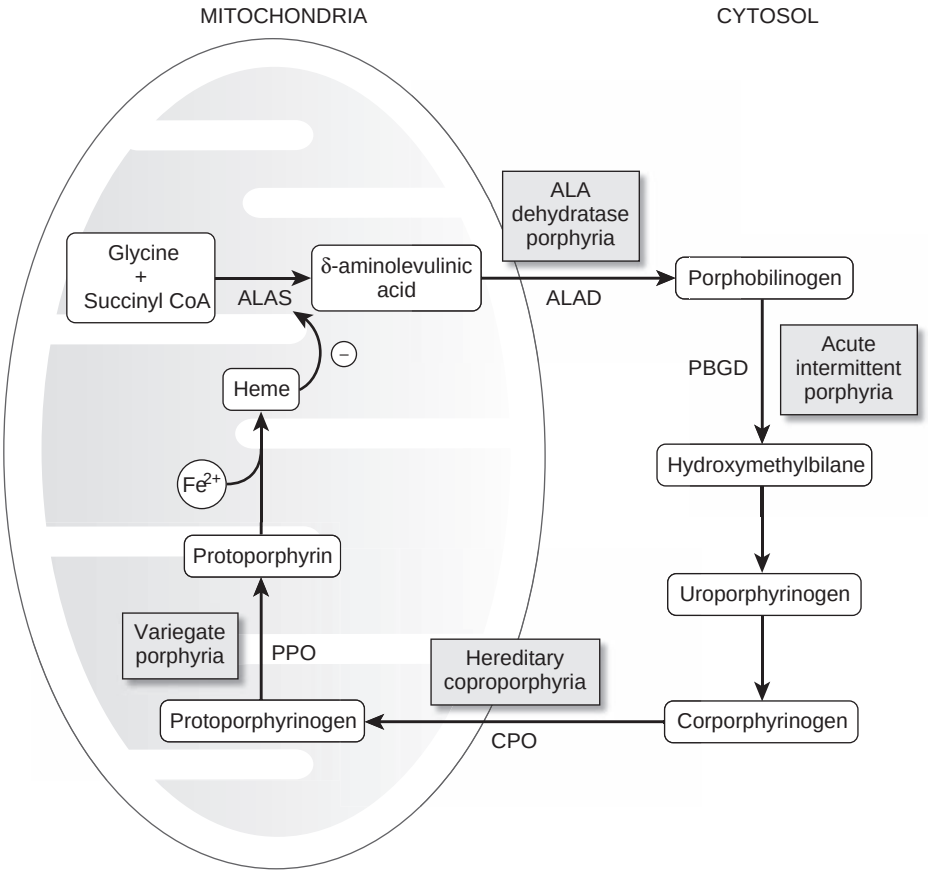

Fig. 19.1 Simplified diagram of the metabolic pathways for heme biosynthesis.Types of acute porphyrias: deficiency of δ-aminolevulinic acid dehydratase (ALAD) causes ALAD porphyria, deficiency of porphobilinogen deaminase (PBGD) causes acute intermittent porphyria, deficiency of corporphyrinogen oxidase (CPO) causes hereditary coproporphyria, and deficiency of protoporphyrinogen oxidase (PPO) causes variegate porphyria. *ALAS,* δ-aminolevulinic acid synthase; *CoA,* coenzyme A; F^{2+}, ferrous iron.

and/or ALA. PBG levels can be as high as 10 times the upper normal level. Measurement of ALA is not essential for the diagnosis but can be helpful for differentiation of AIP from ALAD porphyria. Fecal levels of porphyrins can help differentiate HC and VP from other types of acute porphyria. In addition, erythrocytes may also show reduced activity of PBG deaminase enzyme; however, 5% of porphyria patients may not express enzyme defect in their red blood cells. DNA tests can also detect the specific gene mutations and determine the type of porphyria. Enzyme activity assays and DNA testing are not necessary for the diagnosis of an acute attack, but are helpful in the diagnosis of uncertain cases and in screening of family members of newly discovered cases.

Several investigations can be done to aid in the diagnosis of associated complications (e.g., electrocardiogram for detection of arrhythmias, magnetic resonance imaging of the brain showing reversible white matter densities resembling posterior reversible encephalopathy in blind patients).

Risk Assessment

There are fewer than 200,000 cases of porphyria in the United States. Worldwide prevalence of porphyria is around 0.5 to 10 per 100,000 with predominance in females around their third to fourth decades of life. However, ALAD porphyria is extremely rare with very few reported cases. In AIP, over 400 gene mutations for PGB deaminase have been identified, yet only 10% to 20% of the carriers develop clinical manifestations.

Different risk factors that can precipitate an acute attack have been identified. Induction of heme-containing hepatic enzyme cytochrome P-450 by drugs (e.g., barbiturates, griseofulvin, and sulfonamides), hormones (estrogen, progesterone), smoking, and alcohol use stresses the defective heme synthesis pathway, leading to accumulation of porphyrins. In addition, fasting and fever may induce heme oxygenase (enzyme that degrades heme to biliverdin), leading to depletion of the heme stores, which in turn increases ALAS activity. Psychological stress is another risk factor that can trigger an acute crisis (Box 19.1).

Implications

Known cases of porphyria should have a thorough preoperative assessment with documentation of their neurologic status. A preoperative

BOX 19.1 Conditions That May Precipitate Acute Porphyrias

- Induction of hepatic enzyme cytochrome P-450:
  - Drugs (barbiturates, griseofulvin, and sulfonamides)
  - Hormones (estrogen and progesterone)
  - Smoking
  - Alcohol
- Induction of heme oxygenase enzyme:
  - Fasting
  - Fever
- Psychological stress

anesthetic plan should aim at avoiding triggers of an acute attack. During general anesthesia, barbiturates, etomidate, and ketamine are not good choices as induction agents, but propofol, midazolam, succinyl choline, all nondepolarizing muscle relaxants, and opioids can be safely used. All inhalational anesthetics are also considered safe for maintenance of anesthesia.

The choice of the anesthesia type is also important. Regional anesthesia is not generally contraindicated, but is better avoided during an acute attack to prevent worsening of sensorimotor neuropathy. Lidocaine, bupivacaine tetracaine, prilocaine, and mepivacaine are considered safe local anesthetic drugs. A list of safe/unsafe drug is available in Table 19.1. A more comprehensive drug list is available on the American Porphyria Foundation website (http://www.porphyriafoundation.com/) and the European Porphyria Network website (http://porphyria.eu/).

TABLE 19.1 Drugs Relevant to Anesthesia That May Produce Acute Porphyrias

Use/Safety[a]	Drugs
Do not use (unsafe)	Intravenous anesthetics: barbiturates, etomidate, ketamine Inhalational anesthetics: enflurane Others supportive drugs: pentazocine, hydralazine, calcium channel blockers, chlordiazepoxide, ketorolac, sulfonamides
Use (safe)	Intravenous anesthetics: propofol Inhalational anesthetics: isoflurane, sevoflurane, desflurane, halothane, and nitrous oxide Benzodiazepines: diazepam, midazolam Analgesics or antagonists: narcotics, aspirin, acetaminophen, naloxone Muscle relaxants and reversal agents: succinylcholine, nondepolarizing muscle relaxants, glycopyrrolate, neostigmine Local anesthetics: lidocaine, bupivacaine, tetracaine, prilocaine, and mepivacaine Other supportive drugs: cimetidine, ranitidine, ondansetron, sodium nitroprusside, metoclopramide, clonidine, angiotensin-converting enzyme inhibitors, β-blockers, droperidol, phenothiazines, atropine, corticosteroids, phenylephrine, dexmedetomidine, ephedrine

[a]Data from the American Porphyria Foundation (http://www.porphyriafoundation.com/, Spring 2011) and the safe drug list from the European Porphyria Network (http://porphyria.eu/, revised April 2015).

MANAGEMENT

Management of patients with porphyria is based on avoiding the triggers of an acute crisis. In those patients who develop an acute attack, the following measures are suggested:

- Remove the precipitating factor.
- Administer analgesics for pain control: paracetamol or opioid analgesics (e.g., morphine). Some patients may develop chronic pain requiring prolonged pain management.
- Increase caloric intake, either oral in patients tolerating oral intake or intravenous infusion (dextrose 300–500 g/day).
- Symptomatic treatment:
  - Tachycardia and hypertension: propranolol
  - Nausea and vomiting: chlorpromazine or prochlorperazine
  - Constipation: lactulose
  - Seizures: correction of hyponatremia with fluids restriction in mild cases or hypertonic saline (3%) infusion in severe cases, gabapentin for prolonged control
- Hematin or heme arginate: If the preceding general measures fail to control the acute attack in 2 to 3 days or in severe cases (e.g., convulsions), intravenous hematin or heme arginate can be infused to replenish the heme stores and inhibit ALAS enzyme activity. Side effects of hematin include thrombophlebitis and coagulopathy. It is recommended that hematin be reconstituted with albumin and that it be infused in a large vein at a dose of 3 to 4 mg/kg over 30 minutes once daily for 4 days. Heme arginate is another preparation, but is only available outside the United States.

PREVENTION

Every attempt should be made to avoid triggers of an acute attack during the perioperative period:

- Avoid prolonged fasting, administer intravenous dextrose (300–500 g/day).
- Preoperative sedation is important to avoid psychological stress.
- Identify and avoid the use of unsafe drugs during the perioperative period (e.g., avoid diclofenac as an analgesic and metoclopramide as an antiemetic).
- Porphyria patients should be closely monitored for delayed onset of an acute attack and are not considered candidates for same-day surgery. Daily repeated detailed neurologic examinations should be done for early detection of neuropathy. Electrolytes should also be checked to avoid hyponatremia and precipitation of convulsions.
- Avoid infections and development of fever.

Family members of newly diagnosed cases of porphyria should be screened for latent porphyria and those who carry the disease should be educated about it.

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Preanesthetic Evaluation: False-Positive Tests

20

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Case Synopsis

A 25-year-old male athlete presents for repair of the anterior cruciate ligament of his knee. He is currently not on any medications. He has a negative personal and family history of abnormal clotting or bleeding or easy bruising. Multiple tests, including prothrombin time and partial thromboplastin time (PTT), are ordered. The PTT results are reported as above normal. The surgery is postponed, and an extensive hematology workup is performed. The final report concludes "normal variant, no coagulation defect."

PROBLEM ANALYSIS

Definition

A test is useful only to the extent that clinicians (and patients) can understand the implications of a positive or negative result. Few, if any, tests always correctly identify the presence or absence of disease in all patients. Clinicians can decide what to do with a "positive" or "negative" test result only when they have a clear knowledge of the test's characteristics and its statistical predictive value when applied to a specific patient population. Such "medical decision analysis" directly affects the clinical care of patients.

Some tests provide a qualitative binary positive or negative result. Most test results, however, are quantitative and define a range of "normal" values around a central mean. Therefore members of any population will have an "abnormal" test result but do not actually have a disease. This means that a test result may be misleading owing to natural variability in the general population.

The test can give an incorrect result due to (1) inaccuracy, (2) imprecision, or (3) incorrect performance. The *accuracy* of a test is the difference between the mean value of test results and the true result, as measured by a gold-standard test. The *precision* of a test is the reproducibility of results between instruments or persons performing the test. An *incorrectly performed* test may completely invalidate any result.

Accuracy

Test accuracy can be described in several ways. The *sensitivity* of a test measures the proportion of individuals who have a disease and are correctly identified as being positive for that disease, based on the test. *Specificity* measures the proportion of individuals who do not have a disease and are identified as being disease free, based on the test. False-positive results are more likely with tests that have a high sensitivity, low specificity, or both. Sensitivity and specificity are characteristics of the test and do not change with the prevalence (frequency) of disease in the population. In other words, a test's sensitivity and specificity do not affect the probability of a patient having a disease.

Predictive Value

The *predictive value* of tests, in contrast, depends on the prevalence of a disease in a population of patients. The predictive value of a positive test indicates the proportion of those with a positive test who actually have the disease. Often, the predictive value of tests is expressed as the probability, or odds, that a condition is present.

Likelihood ratios express the amount that the odds change when the results of the test are available (Table 20.1). In this respect, an important concept is Bayes' theorem, which "relates the probability of an item (e.g., a patient) being a member of a particular group (e.g., clinical class), given the presence of an attribute (e.g., an abnormal test result), to the probability of known group members having the attribute and the probability of obtaining a group member when picking at random an item from the universe of items." It allows the calculation of changes in the probability of disease as new information (e.g., test results) becomes available. The "posttest" probability of having the disease in question can be estimated with the Fagan nomogram, as shown in Fig. 20.1. A web-interactive Fagan nomogram can be accessed at http://araw.mede.uic.edu/cgi-bin/testcalc.pl. There are also several desktop computer as well as mobile apps available for smartphones and tablets to calculate Bayesian analysis. A "two-step" Fagan nomogram, which simplifies estimation by adding lines for diagnostic sensitivity and specificity, can be accessed at http://www.adelaide.edu.au/vetsci/research/pub_pop/2step-nomogram/.

Recognition

A positive test result may not actually be true if the test was performed incorrectly. Alternatively, assuming that a test is performed correctly, non–gold-standard tests may falsely indicate that a patient has a disease when he or she does not. Finally, because of population variability, even a patient with a positive gold-standard test (outside the "normal" range) could be clinically normal.

Risk Assessment

If we assume that tests are being performed correctly and that their precision is high, then the accuracy of the test and the prevalence of the disease are the main factors that determine whether a test result will be "correct." Patients who undergo multiple tests are likely to have at least one that is falsely positive. This is true especially if the tested patient population has a low prevalence of the condition. This scenario often occurs when asymptomatic patients undergo a large number of preoperative screening tests.

TABLE 20.1 Accuracy and Predictive Value of Tests

	TARGET DISORDER, BASED ON GOLD-STANDARD TEST		
Diagnostic Test Results	**Present**	**Absent**	**Number of Patients With This Test Result**
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	

1. a/(a + c) = Sensitivity. The number of patients with a positive test who *have* a disease divided by *all* patients who have the disease. A test with high sensitivity will rarely miss patients who actually have the disease.
2. d/(b + d) = Specificity. The number of patients who have a negative test and do *not have* the disease divided by the number of patients who do not have the disease. A test with high specificity will rarely identify patients as having a disease when they really do not.
3. a/(a + b) = Positive predictive value, or posttest probability of having the target disorder among patients with positive test results.
4. d/(c + d) = Negative predictive value, or posttest probability of not having the target disorder among patients with negative test results.
5. c/(c + d) = Posttest probability of having the target disorder for patients with negative test results.
6. (a + c)/(a + b + c + d) = Prevalence or pretest probability of having the target disorder.
7. Sensitivity/(1 − Specificity) = Likelihood ratio (of having the target disorder) for a positive test result = [a/(a + c)]/[b/(b + d)].
8. (1 − Sensitivity)/Specificity = Likelihood ratio (of having the target disorder) for a negative test result = [c/(a + c)]/[d/(b + d)].
9. Posttest probability of the target disorder (expressed as odds) = Pretest probability of target disorder (expressed as odds) × Likelihood ratio for the test result.
10. Odds = Probability/[1 − Probability].
11. a = True Positive test (TP), b = False Positive test (FP), c = False Negative test (FN), d = True Normal test (TN).

Adapted from Sackett DL: A primer on the precision and accuracy of the clinical examination. *JAMA* 267(19):2638-2644, 1992.

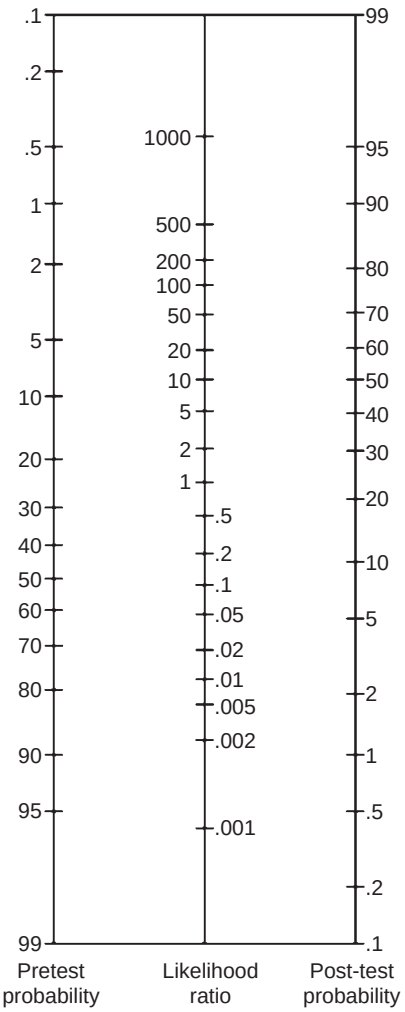

Fig. 20.1 Draw a line from the pretest probability through the likelihood ratio to determine the posttest probability. (Adapted from Fagan TJ: Nomogram for Bayes theorem [letter]. *N Engl J Med* 293[5]:257, 1975.)

Implications

In the preoperative setting, false-positive results of a test may lead to confusion over patient care or a diagnosis. A likely outcome of a false-positive test is the delay or cancellation of surgery. Physicians often repeat the test, hoping that the first result was due to an improperly performed test. Other tests to corroborate the diagnosis may be performed. However, both these options unnecessarily add to costs and wasted time. Further, if the additional test is invasive, it adds to the risk of physical harm to the patient. Yet if elective surgery is not delayed and the test was not falsely positive, the providers run the risk of professional or medicolegal scrutiny, unless they can justify proceeding with the surgery. Any unnecessary alteration in perioperative management may add cost and risk to the patient's care. Finally, a false-positive result, such as for hepatitis C or human immunodeficiency virus, may cause unnecessary psychological stress for the patient, as well as for providers.

MANAGEMENT

The decision to accept a positive test result as "true" must depend on knowledge of the test's characteristics and its performance pitfalls. The decision also depends on knowledge of the incidence of the tested condition in the patient population in question. Every test result should be examined to determine whether it fits the overall picture of the patient's condition. If it does not, and if there are no corroborative findings, further investigation may be required before accepting the result as actually true. In many cases, a lone finding should be suspect unless it is known that the specificity of the test is high, the incidence of the condition is high, or both.

PREVENTION

Clearly, the best way to minimize the chances of a false-positive test result is to avoid unnecessary testing. Overuse of preoperative testing is common among providers, and tests should be judiciously ordered based on each individual patient. Patient age, personal and family medical history, patient symptoms and signs, and type of surgery can dictate indications for testing. Appropriate guidelines should take

into account available scientific studies, as well as local and national expert medical opinion. If tests are needed, selection of tests with a high specificity can also reduce the number of false-positive results. The use of Bayesian tools can improve clinical understanding that the value of testing is not the same in all patient populations. In spite of the complexity of such evaluations and the need for subjective value judgments, the use of cost-benefit and risk-benefit analysis may also help decide whether a test should be performed at all. Furthermore, appropriate testing should only include tests that may potentially alter perioperative management of patients.

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21 Preanesthetic Evaluation: Inadequate or Missing Test Result

Jeffrey W. Lee • Scott R. Springman

Case Synopsis 1

A 64-year-old man with low activity tolerance, a history of hypertension, obesity, and vague episodes of epigastric discomfort is scheduled for elective open partial colectomy. No preoperative electrocardiogram is obtained. The patient subsequently sustains a perioperative myocardial infarction secondary to undiagnosed coronary artery disease.

Case Synopsis 2

A 73-year-old woman who is taking several diuretic medications is scheduled for elective hip arthroplasty. An outside provider obtained a chemistry and electrolyte panel and faxed the results to your surgeon's office. On the day of surgery the results are not available. A discussion ensues about the need to obtain a repeat test. The test is finally found and the plasma sodium is 124 mEq/L. Surgery is postponed.

PROBLEM ANALYSIS

Definition

Effective preoperative test selection may be enhanced by knowing how outcomes are affected by the performance or omission of testing. The following are four important unwanted outcomes:

1. Misinterpretation of test significance by providers or patients
2. Adverse medical events from incorrect actions as a result of a test, or failing to act on test results
3. Increased cost of care from the test, retesting, or subsequent follow-up tests or procedures
4. Litigation for any reason related to the above

Simply knowing the result of a preoperative test cannot ensure a good outcome. Moreover, the accuracy and usefulness of a test depend greatly on its sensitivity and specificity, combined with the frequency of the condition in the population. In addition, considering the pretest probability of disease for that particular patient will add greatly to the utility of testing.

Recognition

Tests may not be used for clinical care if they are not performed, not reviewed, or not available. A more difficult question is whether a specific test was actually indicated, if performed. Hindsight may not be adequate to determine actual preoperative need. Only well-structured clinical studies and logical analysis can provide direction for clinicians who wish to provide evidence-based care.

Risk Assessment

Patients are at risk for adverse outcomes when tests are not done owing to an oversight, inadequate history and physical examination, inadequate guidelines, or inappropriate emphasis on cost reduction. Process failures also occur when tests are done but the results are unavailable or lost or when providers fail to review the results before an anesthetic is administered. Depending on a patient's medical history and physical status, the lack of appropriate preoperative testing may place the patient at a higher risk of an adverse outcome. However, healthy patients undergoing routine surgery do not need a battery of preoperative tests, and perhaps none at all.

Implications

If a test is mandated by policy but is not done, the patient's outcome may or may not be affected. For example, if a patient has a slightly elevated serum calcium level or is slightly anemic, for most operations, adverse perioperative outcomes are unlikely.

However, if a patient has severe, unrecognized coronary disease and sustains a perioperative myocardial infarction, there will definitely be more medical care required, greater time spent in the hospital, increased costs, and possible long-term disability or risk of death. Further, emotional, professional, economic, and medicolegal risks for the providers will be increased.

Not factored into this discussion, but important, is how abnormalities discovered preoperatively could lead to primary or specialty care that improves long-term health.

MANAGEMENT

If a test is found to be missing before an anesthetic is begun and the surgery is elective, the anesthesiologist and the surgeon must determine whether internal or external policies absolutely mandate the test. If so, the test should be obtained, or the providers must justify in the medical record why they were willing to proceed with anesthesia or surgery without the test results. Of course, for emergent or urgent procedures, physicians should always weigh the expected benefits of a test against the risks of delay.

If the test is discovered to be missing after anesthesia or surgery has commenced, the providers must determine whether obtaining the test result at this point will make any difference or whether the procedure should be terminated (this is fortunately a rare occurrence). Tests may, of course, be obtained during the provision of an anesthetic and serve the same purpose as a preoperative test, if only needed for postoperative care. This is not true, however, if a preoperative test would have changed the decision to proceed with the procedure or if the test would have substantially affected the initial anesthetic plan. An example of this might be the finding of an elevated prothrombin time before the administration of a neuraxial anesthetic.

If a test is discovered to be missing after surgery, is there a need to obtain the test? It may actually be wise to do so if postoperative or long-term medical management would be altered by the results.

PREVENTION

Value-Based Medical Care

If the absence of a test leads to an adverse outcome, the system should be reexamined to prevent future omissions. Caution should be used, however, in ascribing causality. Bad outcomes do not necessarily mean that more defensive testing is indicated. We must consider whether testing really would have made a difference in the outcome. In addition, short-term and long-term benefits versus the potential harmful effects of testing should be considered. This is consistent with the concept of value-based anesthesia care. Complex cost-benefit analysis may be needed; time has actual value in medicine, and a seemingly more costly process may be less expensive in the long run versus a less costly but lengthier process.

Evidence-Based Medical Care

Ideally, all tests should be ordered using the principle of evidence-based medical care. Many articles have been written about preoperative assessment, but few cite sufficient rigorous evidence to offer definitive answers for all our patient populations. Recently an updated American Society of Anesthesiologists task force report again found that there were insufficient scientific outcome studies to support a specific scheme for preoperative testing other than sound medical practice based largely on a careful history and physical examination.

Focused Preoperative Testing

A good use of the history and physical examination is to focus preoperative testing. However, it is important to note that many symptoms or signs may be highly sensitive but are not highly specific indicators of problems. Interobserver variability is often high. In addition, the value of the medical history depends on the adequacy of the past medical record and on the patient's reliability and communication skills. Taking a good history or ordering tests may not predict poor outcomes for some conditions, especially bleeding. Other tests are associated with poorer outcomes, such as hyponatremia.

The American Society of Anesthesiologists Preoperative Evaluation guideline states the following:

Preoperative tests, as a component of the preanesthesia evaluation, may be indicated for various purposes, including but not limited to (1) discovery or identification of a disease or disorder that may affect perioperative anesthetic care; (2) verification or assessment of an already known disease, disorder, medical or alternative therapy that may affect perioperative anesthetic care; and (3) formulation of specific plans and alternatives for perioperative anesthetic care.

Nonselective Versus Selective Testing

Most schemes for preoperative testing distinguish between nonselective and selective testing. The former requires that every patient be tested or screened, even if asymptomatic. Although this approach was commonly used in the past, few recommend it today. Selective testing requires that certain criteria be used to determine the need for testing.

- *Patient factors.* These include, but are not limited to, symptoms, age, past medical history, gender, and physical findings. Other factors, such as the ability to obtain a reliable history or perform an adequate examination, should also be considered.
- *Type of surgery.* Baseline values may be required because the surgery itself will cause anatomic or physiologic derangements.

Nonetheless, some surgeries are so low risk that cardiac or other (nonsurgical) complications are rare. Eye surgery has been touted as a procedure that does not benefit from most testing, as long as the patient's condition is stable. Some have called for the elimination of testing before most outpatient surgery. With the trend toward scheduling patients with more comorbidities for more complex outpatient surgery, only using the designation of outpatient surgery to eliminate testing may not be appropriate.

Higher-complexity procedures that have a more profound impact on patient physiology may need baseline tests to follow perioperative changes. However, these should be ordered sparingly and with careful reasoning.

Practice Guidelines

The Institute of Medicine defines *clinical practice guidelines* as follows: "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options." Guidelines should ideally be based on good-quality studies and should follow principles similar to the American College of Cardiology methods. However, lacking rigorous outcome studies, criteria are often based on local and national expert opinion and experience. Policies or guidelines need to be constantly updated to be credible, and local consensus is an absolute necessity. Guidelines may be locally empiric or more complex and derived from widespread consensus. Examples of general guides include the 2016 NICE guidelines and the National Clearing House Perioperative Guidelines. The American College of Cardiology/American Heart Association 2014 guideline update can help determine the need for cardiac testing based on criteria that rely heavily on the history and physical examination. In the future there may be increasing use of screening biomarkers, such as B-type natriuretic peptide (BNP) or high-sensitivity troponin assays to stratify perioperative cardiac risk.

Many guides simply recommend testing "as indicated by history and examination." However, such nondirective guidelines may result in either more or fewer tests than needed, especially if nonanesthesia providers are responsible for ordering the tests. Guidelines may decrease inappropriate testing, but a recent survey found that

BOX 21.1 "Choosing Wisely" Initiative, American Society of Anesthesiologists

1. Do not obtain baseline laboratory studies in patients without significant systemic disease (ASA I or II) undergoing low-risk surgery—specifically complete blood count, basic or comprehensive metabolic panel, or coagulation studies when blood loss (or fluid shifts) is expected to be minimal.
2. Do not obtain baseline diagnostic cardiac testing (transthoracic/esophageal echocardiography) or cardiac stress testing in asymptomatic stable patients with known cardiac disease (e.g., coronary artery disease, valvular disease) undergoing low- or moderate-risk noncardiac surgery.

Adapted from American Society of Anesthesiologists: Five things physicians and patients should question. Choosing Wisely Initiative. October 2013. Retrieved from http://www.choosingwisely.org/societies/american-society-of-anesthesiologists/. Accessed May 9, 2016.

clinicians often go outside recommendations to reassure patients or themselves.

Importantly, there are good reasons to omit nonindicated tests. Even if the tests were to cost nothing, they can do harm by leading to further testing, inappropriately altering case management, giving the anesthesiologist and surgeon a false sense of security, and even distracting them from more important issues. Performing tests when there is no plan to review them before surgery is medically useless and legally dangerous.

The 2012 American Society of Anesthesiologists Preoperative Evaluation guideline recommends testing based on patient and procedure factors, rather than asymptomatic screening. To quote the guide regarding the case study mentioned earlier: "In asymptomatic or nonselected patients, coagulation abnormalities (i.e., bleeding time, prothrombin time, partial prothrombin time, or platelet count) were reported in 0.06%–21.2% of patients and led to cancellations or changes in management in 0.0%–4.0% of cases with abnormal findings (Category B2 evidence)." Although we cannot be sure how often reported changes in management affected outcomes in published studies on coagulation testing, it would seem that it should be uncommon to order coagulation tests without a specific indication or need.

Recent efforts to reduce unnecessary medical interventions include the "Choosing Wisely" initiative, with many professional societies participating. Two pertinent statements from the American Society of Anesthesiologists are included in Box 21.1.

Simply put, practice guidelines are excellent points of reference to start. However, patient comorbidities and self-reported history, information in the patient's medical chart, and the type and extent of the procedure must be factored into the decision-making process.

Preanesthetic Evaluation Clinics, Computerized Preoperative Assessment Systems, and Perioperative Surgical Homes

A preanesthetic evaluation clinic can provide a systematic, logical, cost-effective, and streamlined approach to preoperative testing and preparation. Over time, many have evolved beyond the simple "Every patient comes to the clinic" workflow. Useful tools that can enhance the collection of patient data and reduce the number of unnecessary or missed preoperative visits include a well-structured paper or computerized preoperative assessment system, as well as a telephone interview. Furthermore, an electronic medical record employing integrated decision support may substantially improve both the quality and accessibility of preoperative evaluation and testing. Standardized criteria are more uniformly applied with computerized support. The value of those standardized criteria are only as good as the logic that humans impart. After a preoperative clinic assessment and structured testing, the anesthesiologist's review of a patient's evaluation may then be more timely, convenient, complete, and useful.

As large medical data sets become available to analyze for patient outcomes and risk assessment, predictive analytics will become more useful in preoperative testing. Analytics work well in population-based models but they do not predict individual patient risk very well. This is one of the reasons many feel that guidelines and computerized analysis will not take the place of physicians in general (and perioperative) medical care.

Reviewing current testing guidelines and gaining local consensus about the indications for testing, the timing of testing, who orders tests, and who reviews test results is a key step in optimizing a preoperative evaluation process. Anesthesiologists participating in perioperative care, as part of a Perioperative Surgical Home, can have a substantial effect on preoperative testing and preparation.

Ultimately, what Asher wrote in 1954 is still true. Clinicians should always ask themselves these questions:

1. Why do I order this test?
2. What am I going to look for in the result?
3. If I find it, will it affect my diagnosis?
4. How will this affect my management of the case?
5. Will this ultimately benefit my patient?

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22 Preoperative Cardiac Intervention

Lee A. Fleisher

Case Synopsis

A 65-year-old man is admitted for a colon resection for a nonobstructing cancer. He had a myocardial infarction 4 months ago with placement of a drug-eluting stent. He has been asymptomatic since the stent placement. The patient is currently taking clopidogrel and aspirin, as well as atenolol for his hypertension. Surgery is scheduled for 7 days from now.

The anesthetic management of a patient who presents with a drug-eluting stent is a major challenge for the anesthesiologist, the surgeon, and the cardiologist. Soon after the introduction of percutaneous coronary interventions with coronary stents, there began to appear in the literature a series of case reports of stent thrombosis. The key question for a patient with a prior coronary stent placement is the optimal timing of surgery and management of the antiplatelet agents. Specifically, should the agents be continued or held, given the risks of stent thrombosis versus the risks of increased bleeding in the perioperative period? Acute thrombosis of a coronary stent has been known to lead to myocardial infarction and potentially death.

PROBLEM ANALYSIS

When patients present for surgery who have had a prior drug-eluting stent placed, a key decision preoperatively is when the surgery should be performed (i.e., how long to delay after stent placement) and the management of antiplatelet therapy. In 2016 the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines published a "focused update" on the duration of dual antiplatelet therapy in patients with coronary artery disease. There are no randomized trials of the optimal perioperative strategy including bridging therapy and therefore the recommendations were based on both randomized trials from the nonoperative setting and cohort studies of surgical patients. A second factor is the changes in antiplatelet management based on the generation of drug-eluting stent. The newer stents need shorter therapy because of the lower thrombotic tendency. The key question is the balance of bleeding risk from surgery performed on dual antiplatelet therapy versus thrombotic risk and the development of a myocardial infarction given the time from stent placement and reendothelialization and the use of different antiplatelet agents. The interventional cardiologists may take the anatomy of the stent placement into the calculus to decide on optimal treatment.

Definition

In a patient with a history of coronary stent placement undergoing noncardiac surgery, it is critical to determine (1) the indication for the coronary stent, (2) the type of coronary stent (first or second generation), (3) current antiplatelet therapy, and (4) the urgency of surgery.

Recognition

Although the preoperative preparation of the patient with a coronary stent has been the primary focus, the intraoperative detection and treatment of a stent thrombosis is also critical. Intraoperative or postoperative coronary stent thrombosis presents similar to other myocardial infarctions in the perioperative period but may more likely manifest as ST-segment elevation as opposed to depression. The extent of myocardium at risk from a stent thrombosis may be extensive and therefore may manifest as hemodynamic changes and may result in heart failure.

MANAGEMENT

Evidence

Several reports suggest that drug-eluting stents may represent an additional risk over a prolonged period (up to 12 months) compared with those with coronary disease and no recent stent placement, particularly if the use of antiplatelet agents is discontinued. Schouten's group retrospectively evaluated 192 patients who underwent noncardiac surgery after successful percutaneous coronary intervention (PCI) for unstable coronary artery disease within 2 years of the procedure. Drug-eluting stents accounted for 52% of the stents placed. Of the 192 patients, 30 underwent surgery before the recommended discontinuation of dual antiplatelet therapy for the particular stent (30 days for bare-metal stents and up to 6 months for sirolimus-eluting stents). In patients in whom antiplatelet therapy was stopped before the required time for use of clopidogrel (early-surgery group), the incidence of death or nonfatal myocardial infarction (MI) was 30.7% compared with 0% in patients who continued antiplatelet therapy. The elevated risk for stent thrombosis and cardiovascular events, however, seems to abate over time. In the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry of 4637 consecutive patients, 4.4% underwent major noncardiac surgery in the ensuing year. They reported a relative 27-fold increased rate of cardiovascular events in the week following surgery versus any other

week after stent implantation, but the absolute rate was only 1.9%. Wijeysundera and colleagues evaluated 8116 patients who underwent noncardiac surgery in Ontario, Canada, and found that 34% had a coronary stent implanted within the 2 years before surgery. Drug-eluting stents represented a third of the stents placed. Patients with bare-metal stents implanted less than 45 days before surgery had a 6.7% cardiovascular event rate, which dropped to 2.6% with a stent implanted 45 to 180 days before surgery. Subjects with a drug-eluting stent had a 20.2% cardiovascular event rate in the first 45 days after stent implantation, and the rate became similar to that in subjects without stenting when the stent was implanted more than 180 days before surgery. Bangalore and colleagues studied the impact of drug-eluting stents (DESs) compared with bare-metal stents (BMSs) placed preoperatively in 8415 patients in Massachusetts. In this cohort, the death, MI, and bleeding event rate was 8.6% in the first 30 days after PCI, dropping to 5.2% when surgery was performed more than 90 days after coronary revascularization. Using propensity matching to compare the BMS and DES populations, the death and MI rate was higher in the BMS cohort. In a Scotland-wide retrospective cohort analysis, perioperative death and ischemic cardiac events were much more common within the first 6 weeks after stent implantation than after 6 weeks, 42.4% versus 12.8%, respectively. Forty-five percent of the revascularizations in this cohort were performed for an acute coronary syndrome, increasing the baseline risk of the cohort. The event rate was higher in patients who underwent revascularization because of acute coronary syndromes within 6 weeks, in whom it reached 65%. In contrast to other reports, no temporal differences were noted between the BMS and DES groups. Data from more recent large observational studies suggest that the time frame of increased risk of stent thrombosis is on the order of 6 months, irrespective of stent type (BMS or DES). In a large cohort of patients from the Veterans Health Administration hospitals, the increased risk of surgery for the 6 months after stent placement was most pronounced in those patients in whom the indication for PCI was an MI. In nonsurgical patients with stable coronary artery disease or low-risk acute coronary syndromes treated with zotarolimus-eluting stents, 3 months of dual antiplatelet therapy demonstrated no difference in cardiac outcomes compared with 12 months of therapy. In contrast, dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

Guidelines for Perioperative Management

The recommendations as of 2016 are shown in Table 22.1. Surgery can safely be performed at 6 months after stent placement and can be considered at 3 months after stent placement if the risk of delaying surgery is greater than the risk of stent thrombosis. Ideally, dual antiplatelet therapy should be continued for at least 6 months and then aspirin can be continued. Timing of noncardiac surgery is illustrated in Fig. 22.1. A robust discussion among the surgeon, anesthesiologists, and cardiologists is the optimal strategy but is not always possible.

Management of a Stent Thrombosis

The optimal treatment of stent thrombosis includes the risk of bleeding related to any of the treatments that include antithrombotics. If a stent thrombosis is the presumed diagnosis, the patient should be transported urgently to the catheterization laboratory for angiography and attempted opening of the thrombosed stent.

TABLE 22.1 Recommendations for Perioperative Management–Timing of Elective Noncardiac Surgery in Patients Treated With PCI and DAPT

Category of Recommendation	Recommendations
I	Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation.
I	In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of $P2Y_{12}$ inhibitor therapy, it is recommended that aspirin be continued if possible and the $P2Y_{12}$ platelet receptor inhibitor be restarted as soon as possible after surgery.
IIa	When noncardiac surgery is required in patients currently taking a $P2Y_{12}$ inhibitor, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful.
IIb	Elective noncardiac surgery after DES implantation in patients for whom $P2Y_{12}$ inhibitor therapy will need to be discontinued may be considered after 3 months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis.
III: Harm	Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively.

BMS, bare-metal stent; *DAPT,* dual antiplatelet therapy; *DES,* drug-eluting stent; *PCI,* percutaneous coronary intervention.
Adapted from Levine GN, Bates ER, Bittl JA, et al: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 68(10):1082-1115, 2016.

PREVENTION

Intravenous administration of a short-acting glycoprotein IIb/IIIa inhibitor has been proposed as a bridge to surgery in patients on dual antiplatelet treatment. In a retrospective cohort study of 515 patients, low-molecular-weight heparin bridging in patients with coronary stents undergoing surgery resulted in worse ischemic outcomes at 30 days, and a significant risk of bleeding. In another small retrospective consecutive cohort study, perioperative bridge therapy using tirofiban was associated with reduced 30-day major adverse cardiac events (MACE) rate, particularly when surgery was performed within 60 days after stent implantation. At the current time, bridge therapy with heparin is not recommended because of increased risk and a lack of efficacy. With respect to the short-acting glycoprotein IIb/IIIa inhibitors, the data are insufficient to make a recommendation.

It is this author's recommendations that the glycoprotein IIb/IIIa inhibitor be discontinued for only 5 days because of the risk of rebound hyperthrombotic tendency around 7 to 10 days. If there is no plan for restarting dual antiplatelet therapy, surgery should be delayed for approximately 2 weeks based on expert opinion.

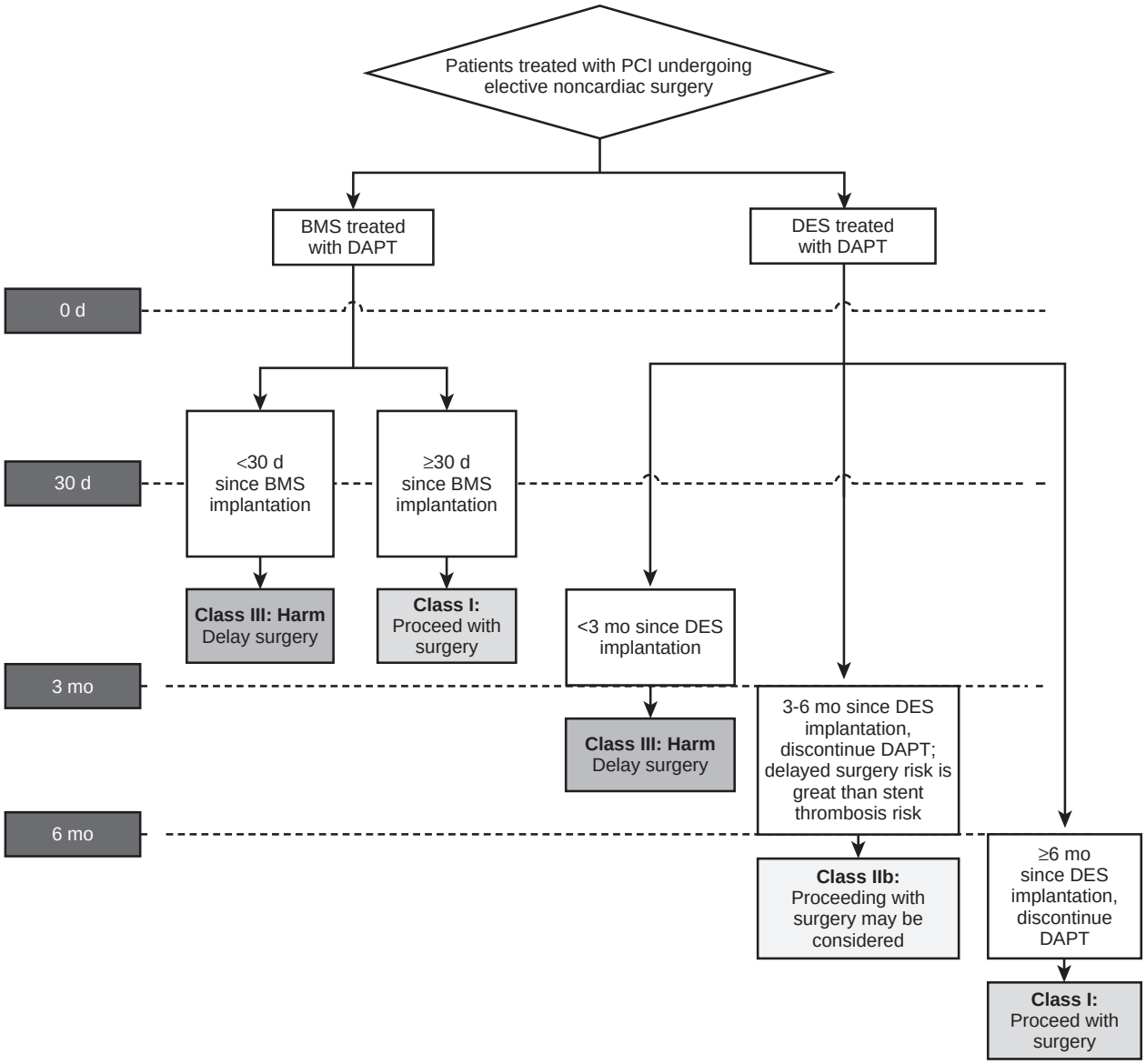

Fig. 22.1 Treatment algorithm for the timing of elective noncardiac surgery in patients with coronary stents. *Gray shading* corresponds to classes of recommendation. *BMS,* Bare metal stent; *DAPT,* dual antiplatelet therapy; *DES,* drug-eluting stent; *PCI,* percutaneous coronary intervention. (From Levine GN, Bates ER, Bittl JA, et al: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 68[10]:1082-1115, 2016.)

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Sarcoidosis

23

Barry A. Harrison • Martin L. De Ruyter

Case Synopsis

A 50-year-old African American woman with known pulmonary sarcoidosis, stage III, is to undergo a thoracotomy for resection of a right upper lobe aspergilloma. Chronically, she has a hoarse voice, dyspnea at rest, and swollen ankles. She is receiving corticosteroids and ambulatory oxygen therapy at a rate of 2 L/min. She complains of palpitations and fainting spells.

PROBLEM ANALYSIS

Definition

Sarcoidosis is a systemic granulomatous disease, and although described 140 years ago, its etiology is still unknown. A complex interaction of genetic, environmental, and/or infectious antigens triggers a type 1 T-lymphocyte response that is characterized by chronic inflammation, monocyte recruitment, and granuloma formation. Pathology consists of noncaseating granulomas that are discrete and compact. Granulomas are composed of mononuclear phagocytes, such as epithelioid cells and multinucleated giant cells and lymphocytes. The central cells are surrounded by fibroblasts and mast cells (Fig. 23.1).

Recognition

Clinical Features

- Sarcoidosis occurs mainly between the ages of 20 and 40 years, with prevalence in the United States of approximately 20 per 100,000. It has a slightly greater female-to-male ratio, and an African American–to–Caucasian ratio of 15:1.
- Sarcoidosis may present acutely, subacutely, or insidiously. Between 30% and 60% of cases are asymptomatic and incidentally detected through an abnormal chest radiograph. Constitutional symptoms may occur and consist of fever, fatigue, anorexia, cough, dyspnea, and vague retrosternal discomfort. Syndromes including erythema nodosum, anterior uveitis, arthritis, parotid enlargement, and facial nerve palsy are associated with acute sarcoidosis. In patients with an insidious presentation, respiratory symptoms usually predominate.
- No specific infectious agent has been defined as an etiologic antigen. However, exposure to combustible wood products has been implicated. Interestingly, an increased incidence of a sarcoid-like granulomatous disease has been documented in the firefighters who participated in the rescue effort following the World Trade Towers 9/11 terrorist attack.
- Diagnosis requires relevant clinical features and a tissue biopsy demonstrating noncaseating granulomas.
- Degree and variability of disease activity together with the organ involved determine the variation in clinical presentation. These factors contribute to the delay in diagnosis seen observed in sarcoid patients.
- Beryllium and hypersensitivity pneumonitis should be excluded before the diagnosis of sarcoidosis.
- Death from sarcoidosis results usually from progressive pulmonary, cardiac, or neurologic involvement. Over the past 20 years the sarcoid mortality rate has increased by 3% per year.

Pulmonary Presentation

In up to 95% cases of sarcoidosis the lung is involved.

Upper airway. Although laryngeal sarcoid may be an isolated finding, it is usually associated with systemic manifestations. Occurring in up to 5% of patients with sarcoidosis, symptoms and signs of laryngeal sarcoidosis include dysphagia, hoarseness, throat pain, dyspnea, and stridor.

Granulomas or nodules involving the supraglottic larynx or the entire larynx often are found (Fig. 23.2). Airway obstruction can occur and a tracheostomy may become necessary in some cases. Recurrent laryngeal nerve involvement can result in unilateral vocal cord paralysis.

Lower airway. Enlarged intrathoracic lymph nodes can compress large airways, potentially causing tracheal and bronchial stenosis, airflow obstruction, and pulmonary atelectasis.

Pulmonary parenchyma. The lung and intrathoracic lymph nodes are involved in 90% of cases. Approximately 50% of patients develop permanent pulmonary abnormalities, with 5% to 15% developing pulmonary fibrosis. Chronic hypoxemic respiratory failure and cor pulmonale may result from pulmonary sarcoidosis.

Chest radiographic and laboratory findings. Ninety percent of patients with sarcoidosis have an abnormal chest radiograph at some time. Three classic chest radiographic patterns have been described, with increasing stages correlating with an increased frequency of dyspnea (Table 23.1). An increase in the serum concentrations of angiotensin-converting enzyme (sACE), an enzyme secreted by sarcoid granulomas, can assist in making the diagnosis. Unfortunately other chronic inflammatory conditions are associated with increased sACE. Recent findings demonstrate that sACE has not been consistently correlating with disease activity or treatment response.

Computed tomography (CT). High-resolution computed tomography (HRCT) is helpful if the chest radiograph is equivocal and in up to 75% of cases a diagnosis can be made. HRCT can be used to diagnose small, well-defined nodes and peribronchial interstitial thickening, whereas conventional CT is better for the evaluation of diffuse parenchymal sarcoidosis (Fig. 23.3).

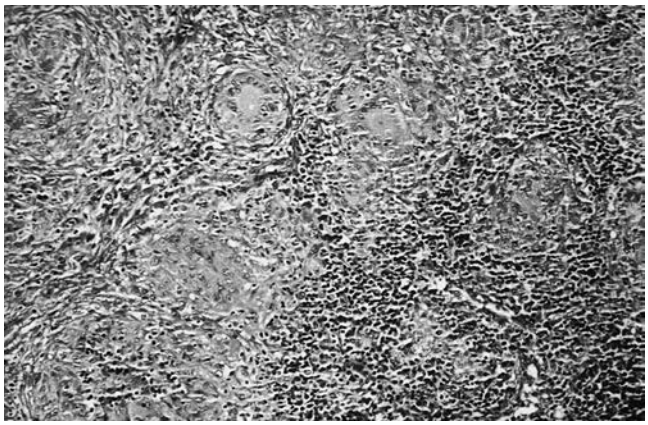

Fig. 23.1 Sarcoid granulomas in lung tissue. (Photomicrograph courtesy of Dr. Thomas A. Gaffey, Department of Pathology, Mayo Clinic and Foundation, Rochester, MN.)

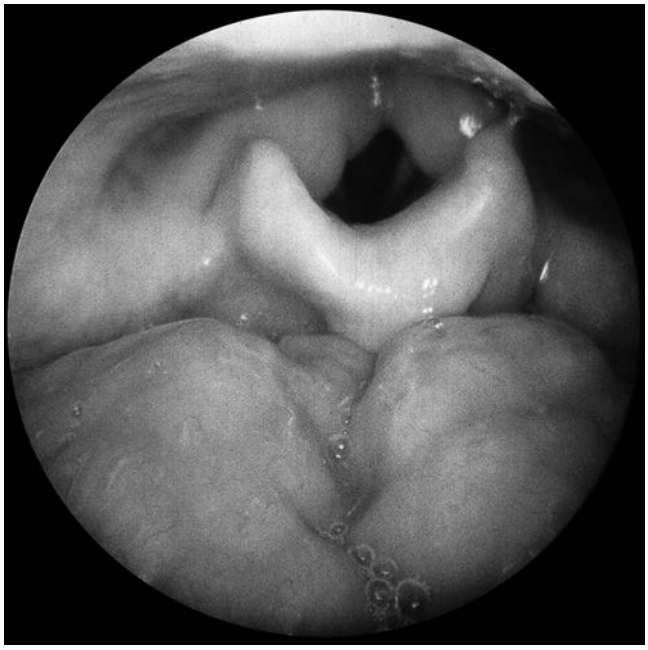

Fig. 23.2 Granulomas involving the supraglottic region. (From Neel HB, McDonald TJ: Laryngeal sarcoidosis. *Ann Otol Rhinol Laryngol* 91:361, 1982.)

TABLE 23.1 Three Classic Chest Radiograph Patterns in Sarcoidosis

Chest Radiograph Pattern	Radiographic Findings	Incidence of ACE Elevation (%)
Stage I	Hilar and mediastinal abnormality without pulmonary parenchymal abnormality	67
Stage II	Hilar and mediastinal abnormality associated with pulmonary parenchymal abnormality	88
Stage III	Diffuse pulmonary disease without node enlargement	95

ACE, Angiotensin-converting enzyme.

Transbronchial biopsy. Transbronchial biopsy is diagnostic in 90% of cases. The yield is excellent even if interstitial infiltrates are not detectable on chest radiography.

Bronchoalveolar lavage. Lavage may be helpful, especially if the lymphocyte population is analyzed; a lavage with greater than 15% lymphocytosis has a diagnostic sensitivity of 90%. A CD4/CD8 ratio greater than 3.5 has a specificity of 94%.

Cardiac Presentation

Clinically overt cardiac involvement occurs in about 5% of patients with sarcoidosis, usually without evidence of disease elsewhere. Cardiac involvement may be manifested by cardiac arrhythmias (ventricular more frequently than supraventricular), conduction disorders, cardiomyopathy, pericarditis, wall motion abnormalities, or cardiac arrest. Electrocardiography, echocardiography, and, in select patients, cardiac catheterization with myocardial biopsy may be helpful in evaluating patients with cardiac findings. Myocardial sarcoidosis may be difficult to diagnose in the absence of systemic manifestations. Myocardial biopsy may be falsely negative due to sampling bias. Cor pulmonale may result from pulmonary parenchymal disease. Sudden death is associated with cardiac sarcoid; however, with progress in antiarrhythmic drugs, cardiac pacemakers, and automatic implantable defibrillators, congestive heart failure associated with myocardial sarcoid is now a more frequent cause of death from cardiac sarcoid.

Pulmonary Hypertension Presentation

Pulmonary hypertension associated with sarcoidosis has an incidence of 5% to 15%. The most frequent association is precapillary hypertension. Causes include lung fibrosis obliterating pulmonary vascular bed, adenopathy compressing pulmonary vasculature, a granulomatous arteritis, pulmonary venoocclusive disease, and hypoxic pulmonary vasoconstriction. Sarcoid-associated left ventricular dysfunction is also a cause of sarcoid pulmonary hypertension. This subgroup has a better outcome compared with other causes of sarcoid-associated pulmonary hypertension. Because of the multiple etiologies of sarcoid-associated pulmonary hypertension, it is classified as World Health Organization Group 5.

Multisystem Presentation

In patients with sarcoidosis, greater than 40% have disease extending beyond the cardiopulmonary system. As such, this disease will have implications for the anesthesiologist (Table 23.2).

Risk Assessment

Risk assessment is dependent on the severity and extent of organ systems affected by sarcoidosis.

Pulmonary Function Testing

Pulmonary spirometry, lung volumes, and diffusing capacity of carbon monoxide ($DLCO_2$) are initial pulmonary function tests applicable in evaluating the patient for pulmonary sarcoid. As elastic resistance of the lungs is increased, the patient with sarcoidosis adapts to minimize the work of breathing by taking rapid, shallow breaths. The most common findings are reductions in lung volume and a decrease in $DLCO_2$ (Fig. 23.4). Expiratory flow rates also may be decreased, suggesting airflow obstruction and reduced lung compliance. Arterial hypoxemia with exercise occurs frequently; however, arterial hypoxemia at rest

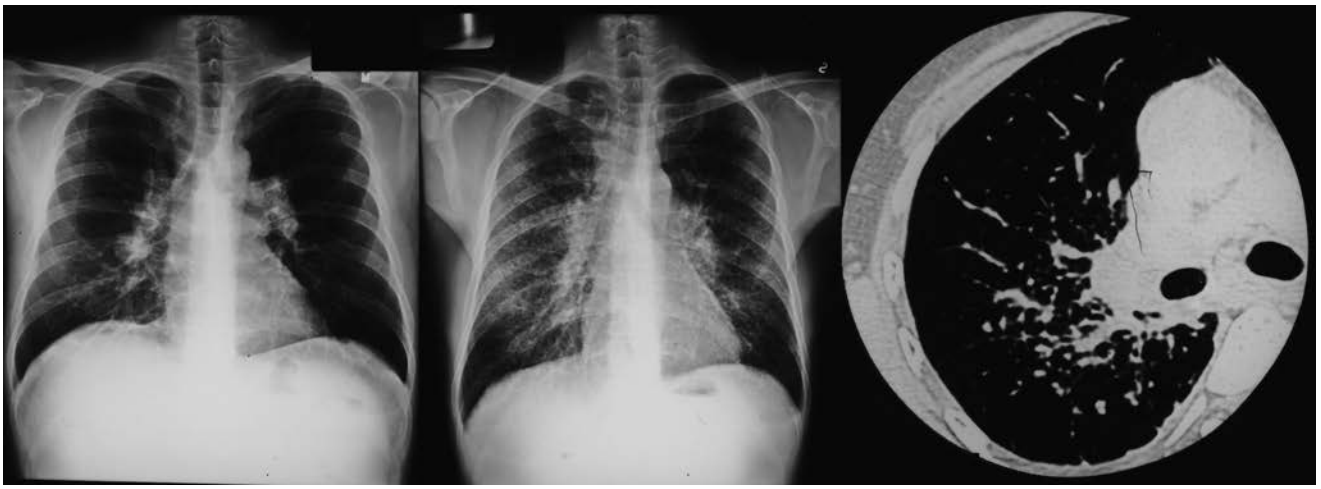

Fig. 23.3 Left, Bilateral hilar lymphadenopathy (stage I). Middle, Bilateral hilar lymphadenopathy and interstitial infiltrates (stage II). Right, High-resolution chest computed tomographic scan showing extensive nodular interstitial process. (Radiograph courtesy of Department of Radiology, Mayo Clinic and Foundation, Rochester, MN.)

TABLE 23.2 Multisystem Involvement of Sarcoidosis

Organ System (Incidence of Involvement)	Manifestations	Anesthetic Implications
Nervous (5%)	Peripheral neuropathies, central nervous system symptoms: meningitis, encephalitis, epilepsy, cranial nerve disturbances	Caution with muscle relaxants
Musculoskeletal (5%)	Arthritis of peripheral joints: ankles, knees, wrists, hands; ankylosis of temporomandibular joints	Examine airway
Renal (1%–2%)	Hypercalcinuria with or without hypercalcemia, nephrocalcinosis, nephrolithiasis	Altered drug excretion
Hepatic (20%–30%)	Hepatomegaly, abnormal liver function tests	Altered drug metabolism
Hematopoietic (15%)	Anemia, thrombocytopenia, neutropenia, eosinophilia, splenomegaly	Check complete blood count
Eye (25%)	Uveitis, conjunctival nodules, keratoconjunctivitis sicca	Standard eye precautions
Skin (25%)	Erythema nodosum, plaques, subcutaneous nodules	Lesions may be tender and painful
Endocrine	Posterior pituitary: diabetes insipidus, hypercalcemia	Monitor serum Ca^{2+}, Na^{+}, and urine output

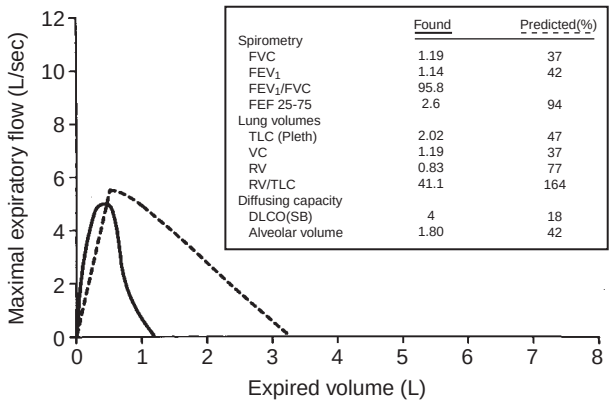

Fig. 23.4 Expiratory flow volume loop, spirometry, lung volumes, and diffusing capacity found in pulmonary sarcoidosis. (Data from Pulmonary Function Laboratory, Mayo Clinic and Foundation, Rochester, MN.)

indicates severe disease. Although sarcoid lung pathology is caused by fibrosis and granuloma formations, pulmonary function testing may reflect disease extent but not necessarily disease activity. Pulmonary function testing, however, may provide objective data when following a patient's response to therapy.

Cardiopulmonary exercise testing, such as the 6-minute walk test, has been used to asses the functional status and evaluate dyspnea in sarcoid patients with normal pulmonary function tests and echocardiography.

Cardiac Assessment

Electrocardiography, 24-hour electrocardiography monitoring, echocardiography, and cardiac catheterization with myocardial biopsy may be helpful in the evaluation of cardiac sarcoidosis. Thallium-201 myocardial imaging may demonstrate segmental defects consistent with granulomas or fibrous scars. Magnetic resonance imaging has also been used to identify areas of myocardium affected by sarcoidosis and to guide myocardial biopsy.

Pulmonary Hypertension and Right-Sided Heart Dysfunction

Pulmonary hypertension is often overlooked and thus undiagnosed. Unexplained dyspnea, a subperformance on the 6-minute walk (less than 150 meters), and associated oxygen desaturation all suggest that an echocardiogram is indicated. Echocardiographic pulmonary artery systolic pressure greater than 30 mm Hg has a significant correlation with that obtained by direct measurement via cardiac catheterization. Tricuspid regurgitation and tricuspid annular plane systolic excursion are indicators of right ventricular dysfunction.

Implications

Patients with sarcoidosis undergo procedures for biopsy and diagnosis that may require anesthesia. These procedures range from fiberoptic bronchoscopy with transbronchial biopsy, scalene node biopsy,

mediastinoscopy for hilar lymph node biopsy, and lung biopsy either by video-assisted thoracoscopy or thoracotomy. Many patients with sarcoidosis require anesthesia due to complication of therapy, for example, a perforated duodenal ulcer secondary to corticosteroid therapy. Sarcoid patients routinely require anesthesia for comorbid conditions. In the case synopsis the patient has developed an aspergilloma fungus ball in a lung cavity secondary to cystic destruction of lung tissue due to sarcoidosis. Progressive pulmonary sarcoid with chronic hypoxemia respiratory failure and right-sided heart failure and/or progressive cardiac sarcoid cause problems with anesthesia and increase risk.

MANAGEMENT

Approximately 30% to 50% of cases remit spontaneously over a 3-year period. Over the next 5 to 10 years, 30% show disease progression and the remaining 20% remain stable. Thus not all patients with sarcoidosis require specific therapy, especially patients with stage I radiographic pattern. The percentage of sarcoid patients requiring systemic therapy ranges from 20% to 80%.

Pharmacologic Treatment

Corticosteroids

Treatment for sarcoidosis is indicated for progressive symptomatic disease. Clear-cut examples include cardiac, neurologic sarcoidosis and hypercalcemia secondary to sarcoid. Pulmonary sarcoid with respiratory symptoms associated with progressive loss of lung function also requires treatment.

A systematic evidence-based review of corticosteroids in sarcoidosis found that they improved radiographic assessment (stage II and stage III radiographic patterns) and performance with pulmonary function testing. However, there is a lack of data supporting that corticosteroids significantly affect long-term disease progression. Typically, clinicians conduct a 3-month trial of corticosteroid before reevaluating the patient's treatment regimen. Inhaled corticosteroids have been tried as well; however, an insufficient number of clinical trials have been conducted to date to determine efficacy.

Antimetabolites—Corticosteroid Sparing

Antimetabolites are used in sarcoidosis to control disease progression, especially if corticosteroids have failed or in effort by the clinician to decrease the patient's corticosteroid exposure. Methotrexate, azathioprine, leflunomide, and mycophenolate mofetil have all been used; the most frequently used agent is methotrexate. It may take up to 6 months of use to properly assess a patient's response. Unfortunately these medications are associated with significant toxicities, which may limit their use.

Anti–Tumor Necrosis Factor–α Biologicals

If organ and/or life-threatening sarcoid disease develops despite corticosteroid or antimetabolite therapy, anti–tumor necrosis factor–α (anti–TNF-α) treatment is considered. Two agents that have shown benefit are infliximab and adalimumab. Other anti-TNF–αagents (etanercept and golimumab) have not demonstrated efficacy against sarcoidosis.

Pulmonary Hypertension

Prostacyclin, endothelial receptor antagonists, phosphodiesterase inhibitor, and combinations have all been tried in care reports, series, and occasional prospective case series. Generalizations from these studies suggest the hemodynamics are improved; however, the 6-minute walk and oxygen saturation may not be increased. An explanation for this observation is either that the treatment period of pulmonary vasodilators was limited or that the pulmonary sarcoid was severe, limiting the response to pulmonary vasodilators.

Chronic Hypoxemia, Respiratory Failure, and Cor Pulmonale

Long-standing progressive pulmonary sarcoidosis may give rise to chronic hypoxemic respiratory failure and cor pulmonale. *Cor pulmonale* is defined as pulmonary arterial hypertension resulting from diseases affecting the structure and/or function of the lungs; pulmonary arterial hypertension results in right ventricular enlargement (hypertrophy and/or dilation) and may lead over time to right-sided heart failure. The treatment of both conditions first and foremost is the titration of continuous oxygen to increase arterial oxygen saturation to above 90%. If right-sided heart failure is present, diuresis, usually furosemide, should be initiated. Excessive fluid loss is dangerous because it may decrease right ventricular preload. Digitalis use is controversial because the potential for digitalis toxicity is high even at low serum concentrations when hypoxemia, alkalosis-induced hypokalemia, and cor pulmonale are present.

Lung and Cardiac Transplantation

Lung transplantation is indicated in patients with end-stage sarcoidosis lung disease where there has been a failure to respond to aggressive medical therapy. Pulmonary hypertension is an important factor in deciding the need for lung transplantation. Bilateral lung transplantation is preferred over single lung transplantation. Lung transplant surgery is complicated by adhesions, aspergilloma, and previous lung surgery. Recurrence of sarcoid granulomas within the lung allografts occurs in a majority of patients but rarely causes clinical symptoms. The survival rates for single- or double-lung transplantation are 70% at 2 years. Cardiac transplantation has been used in end-stage sarcoid cardiac disease refractory to medical therapy.

Anesthesia

Preoperative

Because sarcoidosis is a multisystem disease, all systems must be evaluated for possible sarcoid involvement during preoperative assessment; however, the pulmonary and cardiac system must be given high priority. Focusing on the pulmonary system, exercise capacity, oxygen amount and duration, and intercurrent infection all need to be assessed, especially if recent deterioration has occurred. Equal focus is the cardiac system, especially the presence of malignant cardiac arrhythmias or deterioration in left and right ventricular function. Symptoms and signs of upper airway involvement with sarcoidosis must be specifically addressed before intubation. The use of corticosteroids and the potential for adrenal gland insufficiency must be evaluated and preoperative corticosteroids used where applicable.

Operative

Monitored Anesthesia Care

Usually considered a "safe" selection if chronic hypoxemic respiratory failure and right-sided heart failure are present, hypoxia, hypercapnia, and acidosis must all be avoided as these act to increase pulmonary artery pressure, further exacerbating right-sided heart failure. Oxygen saturation greater than 92% and arterial carbon dioxide between 35 and 45 mm Hg should be maintained. Due to advanced pulmonary lung disease with its associated increased dead space, end-tidal carbon dioxide will not accurately reflect arterial carbon dioxide.

General Anesthesia

The anesthetic aims are to maintain oxygen saturation greater than 92%, arterial carbon dioxide 35 to 45 mm Hg, and pH between 7.35 and 7.45, as well as maintaining systemic arterial pressure while minimizing pulmonary arterial pressure and optimizing intravascular fluid administration (avoiding exacerbating left- and right-sided heart failure). To achieve these aims, monitoring of central venous pressure and pulmonary artery pressure needs to be considered. Invasive arterial pressure monitoring is important, and strong consideration should be given to central venous and pulmonary artery pressure monitoring. A pulmonary artery catheter or transesophageal echocardiography can achieve these aims. Both these monitors will aid intravascular fluid assessment and administration. One anesthetic agent to consider avoiding is ketamine because it increases pulmonary artery pressure.

Mechanical ventilation is a major focus on proper anesthetic delivery. The aim of mechanical ventilation in patients with advanced pulmonary sarcoidosis is to avoid further lung injury. This is particularly important if the patient is undergoing thoracic surgery. With mechanical ventilation it is vital to limit inspiratory plateau pressure to less than 30 cm H_2O, especially in the setting of pulmonary fibrosis. This can be achieved by setting the mechanical ventilatory tidal volume to between 4 and 8 mL/kg (patient's ideal body weight) and observing the pressure. Alternatively, the ventilator can be set to pressure-controlled ventilation with the pressure set at 30 cm H_2O. In both settings, noting the resultant tidal volume and measured end-tidal CO_2 are important and parameters should be adjusted to ensure adequate ventilation. In patients with pulmonary fibrosis, positive end-expiratory pressure may need to be increased to levels greater than 10 cm H_2O to provide adequate oxygenation. To achieve these mechanical ventilatory aims, neuromuscular blockade is often required.

Regional Anesthesia

The use of regional anesthesia has potential advantages especially if the surgical site is below the level of the umbilicus. In surgical sites above the umbilicus, high central neural axis blockade may interfere with intercostal muscle function and exacerbate respiratory failure. In patients with advanced lung disease accessory muscle function is an important component of ventilatory function. Excessive intravascular fluid administration, due to hypotension associated with sympathetic blockade, may exacerbate right-sided heart failure. Blood pressure is maintained with vasopressors to ensure perfusion of the right side of the heart.

Postoperative Care

With sarcoidosis-induced pulmonary hypertension, chronic hypoxemic respiratory failure, and right-sided heart failure, careful consideration must be given to postoperative analgesia. Systemic opioid administration may depress ventilation and precipitate hypoxemia. Thus consideration should be given to a central neural axis technique with the use of local anesthetic agents, opioids, or both. Many advocate the use of local anesthetics via peripheral nerve block and continuous catheter infusions to optimize analgesia, reducing the need for opioids and thus limiting respiratory side effects. It is recommended to titrate inspired supplemental oxygen to maintain oxygen saturation greater than 92% with the aim to minimize the deleterious effects of pulmonary hypertension if present. Patients on chronic steroids will need coverage and tapering in the postoperative period, but are also at risk for peptic ulcer disease and require gastrointestinal bleeding prophylaxis.

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24

Sepsis, Systemic Inflammatory Response Syndrome, and Multiple Organ Dysfunction Syndrome

Jesse M. Raiten • Jacob T. Gutsche

Case Synopsis

A 35-year-old man sustains a gunshot wound to the abdomen. He is taken emergently to the operating room where he is found to have a perforated colon with stool and pus in the abdomen. He undergoes a partial colectomy and colostomy. Throughout the surgery he becomes progressively more tachycardic and hypotensive requiring large-volume resuscitation and the initiation of vasopressors and invasive hemodynamic monitoring. At the completion of the surgery he is transported to the intensive care unit for further management.

PROBLEM ANALYSIS

Definition and Recognition

The systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ dysfunction syndrome (MODS) are conditions that may arise in patients throughout the perioperative period. They are defined by the presence of specific signs and symptoms (Boxes 24.1 and 24.2). Advances in medical care and improved therapies for patients suffering from complex medical and surgical conditions, along with a desire to facilitate categorization and comparison of patients with multiple medical morbidities, have helped the definitions of SIRS, sepsis, and MODS evolve to their current states.

SIRS criteria are general enough that some anxious preoperative patients, and virtually all postoperative patients, may meet the criteria. Its development may therefore fail to trigger a heightened level of concern for the clinician in the perioperative period. However, SIRS criteria often herald the development of the more troublesome condition of sepsis, and the considerable morbidity and mortality that it carries. As the difference between SIRS and sepsis hinges merely on the presence of infection, many patients presenting for surgery meet the criteria for sepsis. The proinflammatory nature of surgery has the potential to further progress a patient into the category of septic shock.

MODS is a dynamic process characterized by the progressive failure of multiple organ systems and may be precipitated by sepsis, trauma, or other processes. MODS is commonly observed in patients in the intensive care unit (ICU) and may be encountered in the perioperative setting when an ICU patient requires surgical intervention.

Risk Assessment and Implications

Although the physiologic parameters that define SIRS are common and may represent a heightened stress response, sepsis is a highly pathologic condition. Surgery and acute illness have a profound effect on metabolic and immunologic function and may increase a patient's risk for developing sepsis and MODS. The body's ability to extract and utilize oxygen is impaired in sepsis, and lactate production is increased. Endocrine abnormalities become prominent, including a reduction in vasopressin production and resistance to other hormones, including insulin and catecholamines.

Each year millions of patients experience surgical site infections, and surgical patients account for 30% of patients with sepsis. Risk factors for perioperative sepsis include the elderly population, male sex, and African American race. Early identification of patients at risk for developing sepsis and MODS may facilitate early intervention and proper triage of patients to an intensive care environment. Early and aggressive treatment of sepsis has been shown to reduce morbidity and improve survival. Anesthesiologists are in a unique and favorable position to initiate therapy for patients with SIRS and sepsis, including securing central venous access and invasive monitors, providing volume resuscitation, and administering antibiotics. For patients with MODS, diagnostic interventions such as echocardiography may be performed in the operating room or ICU, and supportive treatment initiated or continued under an anesthesiologist's care.

BOX 24.1 Criteria for Systemic Inflammatory Response Syndrome

Fever or hypothermia (core temperature >38° C or <36° C)
White blood cell count >12,000 or <4000, or >10% bands
Heart rate >90 beats/min or >2 standard deviations above normal for age
Tachypnea (respiratory rate >20 breaths/min)

BOX 24.2 Consensus Definitions of Sepsis and Septic Shock

Sepsis: SIRS in the presence of infection
Severe sepsis: Sepsis with the presence of dysfunction in at least one organ system
Septic shock: Sepsis with persistent hypotension despite administration of intravenous fluids

SIRS, Systemic inflammatory response syndrome.

MANAGEMENT AND PREVENTION

There is no simple cure for SIRS, sepsis, or MODS. They are complex physiologic processes that require a multimodal approach to manage and limit their progression. Without one specific target to focus on, management is based on a combination of *source control, supportive care, and prevention of further complications.* The Surviving Sepsis Campaign is an international organization dedicated to advancing the care of patients with sepsis and septic shock, and novel therapies for sepsis remain a strong area of research.

Source Control

The inflammatory process that defines SIRS may be initiated by any number of insults to the body—infection, trauma, metabolic abnormality, or disease process. The patient's history, physical examination, and laboratory or diagnostic studies are useful to identify infectious causes of continuing inflammation. Source control is a hallmark of management. Early identification and treatment of the underlying condition may prevent progression of inflammation and/or the development of sepsis or MODS. In some situations, such as surgical debridement of an infection, achieving source control may transiently worsen a patient's clinical condition as the patient's body reacts to the additional stress of surgery.

Supportive Care

Supportive care may be divided into different categories.

1. Fluid and Blood Product Administration

SIRS and sepsis are characterized by systemic capillary leak, and volume resuscitation is a cornerstone of management. The benchmark study "Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock" by Rivers and colleagues aimed to achieve a central venous pressure of 8 to 12 mm Hg as part of an effort to optimize the patient's central venous oxygen saturation and hemodynamics. The Surviving Sepsis Campaign recommends administration of 30 mL/kg of crystalloid for hypotension or an elevated lactate. Patient responsiveness to volume administration may be assessed by improvements in hemodynamics, monitoring pulse pressure variation, and metabolic markers such as trends in lactate levels. Restoration of adequate blood pressure is usually defined as a mean arterial pressure of 60 to 65 mm Hg.

Although studies of crystalloid versus colloid administration are difficult to compare because of a heterogeneous patient mix, duration of fluid administration, and bias risks, resuscitation with balanced crystalloids or albumin, compared with other fluids, may be associated with reduced mortality. Red blood cell transfusion triggers have been widely studied in numerous patient populations, and most studies suggest that a hemoglobin of 7.0 g/dL is sufficient for critically ill patients who are not actively bleeding. The Surviving Sepsis Campaign recommends a transfusion trigger of 7.0 g/dL with a target hemoglobin of 7.0 to 9.0 g/dL in adults, assuming there is no active myocardial ischemia, severe hypoxemia, or active hemorrhage.

2. Vasopressors and Inotropic Support

In patients with sepsis or septic shock, fluid resuscitation may be inadequate to restore organ perfusion. Hypotension in the setting of sepsis is often multifactorial—hypovolemia, vasodilation, and myocardial dysfunction may all contribute. Although sepsis-induced myocardial dysfunction may occur in up to 40% of cases of sepsis, vasodilation is a hallmark of sepsis physiology and often necessitates the use of vasopressors. Dopamine has historically been used for patients with hypotension and sepsis, but current recommendations call for norepinephrine as the first-line drug. Norepinephrine, with both α- and β-receptor activity, reduces vasodilation and enhances cardiac contractility.

If a second agent is needed, the Surviving Sepsis Guidelines recommend epinephrine. Endogenous vasopressin levels in septic shock may be reduced relative to a patient's increased needs, a condition known as a "relative vasopressin deficiency," and low-dose vasopressin infusion may be added to norepinephrine if needed. In settings of severely reduced cardiac contractility, inotropic agents such as dobutamine may be used, although their β-receptor activity may worsen vasodilation.

3. Mechanical Ventilation

Sepsis-induced respiratory failure is common. Increased metabolic demands from the respiratory muscles combined with limited energy supplies and production create an imbalance and may precipitate respiratory failure and the need for mechanical ventilation. Acute lung injury and acute respiratory distress syndrome (ARDS) are common in patients with sepsis, and respiratory failure is often part of MODS. Respiratory support in patients with sepsis-induced respiratory failure parallel the guidelines for patients with ARDS. The Surviving Sepsis Campaign recommends that clinicians use a tidal volume of 6 mL/kg of predicted body weight and that plateau pressures be maintained less than 30 cm H_2O. Such a lung protective strategy of ventilation has been shown to improve outcomes. The use of positive end-expiratory pressure (PEEP) is encouraged to maintain alveolar recruitment, with the supplemental use of recruitment maneuvers in patients with refractory hypoxemia. The head of the bed should be maintained between 30 and 45 degrees (a strategy that may not be possible intraoperatively) to reduce the risk of pulmonary aspiration.

4. Antibiotics

SIRS often progresses to sepsis when active infection is identified. Early administration of antibiotics is a cornerstone of treating sepsis. Mortality risk increases with delay in antibiotic administration, and the Surviving Sepsis Guidelines recommend that antibiotics be started within 1 hour of the diagnosis of severe sepsis or septic shock. Although antibiotics are usually administered at the beginning of surgery, the choice of antibiotic should be carefully considered in a

patient with SIRS or sepsis. A detailed history and physical examination can suggest the source of infection, and antibiotics can be tailored appropriately. In many cases patients will already be receiving appropriate antibiotics before they undergo surgery.

5. Endocrine Support

Sepsis may be characterized by suboptimal cortisol production and relative adrenal insufficiency. In the past, adrenal responsiveness was assessed via the ACTH stimulation test; however, this is no longer recommended. Numerous studies have investigated the use of steroid administration for patients with sepsis and septic shock, with often conflicting results. Based on the available data, most sources agree that patients with sepsis in the absence of shock should not receive steroid supplementation. In patients with refractory septic shock (hypotension failing to respond to fluid resuscitation and vasopressor support), stress steroids are indicated. Hydrocortisone is usually administered in divided doses for a total of 200 to 300 mg per day. There is no consensus on the duration of steroids or whether a taper is necessary.

As discussed, a relative vasopressin deficiency exists in the pituitary gland during sepsis. Vasopressin is most active in controlling tone in the splanchnic circulation, and a major component of sepsis-associated vasodilation arises in this bed. Infusion of replacement vasopressin (0.01–0.04 U/min) restores normotension and may help wean the patient from other vasoactive substances.

6. Renal Replacement and Acid-Base Support

Acidemia is common in patients with sepsis and MODS and is often multifactorial in etiology. Sepsis-induced renal failure may contribute to acidosis, and organ hypoperfusion may cause lactic acidosis that may only improve with correction of the underlying process. Renal replacement therapy (RRT) may be indicated for a variety of reasons in patients with sepsis and MODS, including acidosis, electrolyte abnormalities, volume overload, and uremia. Both continuous RRT and intermittent hemodialysis are reasonable, although continuous RRT may be better tolerated in patients with unstable hemodynamics. Acidosis may be transiently corrected with the administration of sodium bicarbonate, although this is not recommended except in cases of severe acidemia that is refractory to vasopressors.

7. Glucose Control

The systemic inflammatory and stress response from SIRS and sepsis causes hyperglycemia. Although it is generally accepted that hyperglycemia in sepsis should be treated, the target glucose level is less well defined. Tight glucose control (80–100 mg/dL) leads to an increased risk of hypoglycemia, and many practitioners and protocols target a serum glucose less than 150 mg/dL. The Surviving Sepsis Campaign recommends a target of less than 180 mg/dL. Given the rapid changes in patients' metabolic status, frequent glucose monitoring is prudent, and insulin administered by infusion allows for easier adjustment of doses.

Prevention of Further Complications

The myriad complications that stem from sepsis and MODS span across virtually every organ system (Table 24.1). The classic teaching that "an ounce of prevention is worth a pound of cure" strongly applies to our management of patients with SIRS and developing sepsis. Early source control, aggressive volume resuscitation, initiation of antibiotics, and hemodynamic support can decrease morbidity and mortality. When early intervention and source control involve operative intervention, anesthesiologists are well positioned to ensure optimal care for patients with SIRS, sepsis, or MODS.

TABLE 24.1 Criteria for Organ Dysfunction

	SEVERITY OF DYSFUNCTION	
Body System	**Mild**	**Severe**
Pulmonary	Hypoxia or hypercarbia requiring assisted ventilation for ≥3–5 days	ARDS requiring PEEP ≥10 cm H_2O and Fio_2 ≥0.5
Hepatic	Bilirubin ≥2–3 mg/dL; prothrombin time or other liver function tests ≥2 times normal	Jaundice with bilirubin ≥8–10 mg/dL
Renal	Oliguria (<500 mL/day) or increasing creatinine (≥2–3 mg/dL)	Need for dialysis
Gastrointestinal	Intolerance of gastric feeding >5 days	Stress ulceration with need for transfusion; acalculous cholecystitis
Hematologic	Partial thromboplastin time ≥125% of normal, platelets <50,000–80,000	Disseminated intravascular coagulation
Central nervous system	Confusion	Coma
Peripheral nervous system	Mild sensory neuropathy	Combined motor and sensory deficit
Cardiovascular	Decreased ejection fraction, persistent capillary leak	Hypodynamic state not responsive to vasopressors

ARDS, Acute respiratory distress syndrome; *Fio_2*, fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure.

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Steroids

25

Nancy B. Greilich • Philip E. Greilich

Case Synopsis

A 55-year-old man with severe chronic obstructive airway disease and steroid dependence is taken to the operating room emergently for an acute abdomen due to a perforated colonic diverticulum. The patient has been maintained on 10 mg of prednisone per day for the past year. Intraoperatively, he demonstrates hemodynamic instability requiring large-volume fluid resuscitation and the use of vasopressors. Postoperatively, he is transferred to the intensive care unit, where he remains intubated and hemodynamically unstable.

PROBLEM ANALYSIS

Definition

Steroids are the mainstay of therapy for a variety of disorders requiring immune suppression. These include dermatologic, pulmonary, and autoimmune disease as well as prevention of rejection in organ transplantation. It is also the primary replacement therapy for those with inadequate cortisol production due to a pituitary or adrenal etiology. In the perioperative setting the incidence of acute adrenal insufficiency is estimated to be between 0.01% and 0.1%. The most likely trigger of an Addisonian crisis in this circumstance is insufficient cortisol levels to meet the increased glucocorticoid demands of trauma, infection, and surgical stress. Following surgery, peak plasma cortisol concentrations are achieved 4 to 5 hours postoperatively and may remain elevated for 48 to 72 hours, especially after major procedures. In a normal stress response, minor surgery induces less than 50 mg of cortisol production during the first 24 hours whereas major surgery produces 75 to 100 mg of cortisol in the same period. With maximal stress (e.g., septic shock or major trauma), the adrenals may produce as much as 300 to 500 mg of cortisol per day.

Adrenal insufficiency is classified as primary, secondary, or tertiary, based on the anatomic level of impairment within the hypothalamic-pituitary-adrenal (HPA) axis. With primary adrenal insufficiency, the abnormality is in the adrenal gland. More than 90% of the adrenal gland must be destroyed before symptoms of glucocorticoid and mineralocorticoid deficiency are evident. The most common cause of primary adrenal insufficiency in the United States is autoimmune in nature. In secondary adrenal insufficiency, the abnormality is at the level of the pituitary gland. Such patients show symptoms of glucocorticoid deficiency but usually have intact mineralocorticoid function given the additional influence of angiotensin II on aldosterone secretion. Tertiary adrenal insufficiency is the most prevalent type in the perioperative setting and is caused by suppression of the HPA axis by chronic exogenous steroid use. This is the result of increased plasma cortisol levels secondary to glucocorticoid administration and its negative feedback effect on the hypothalamus. The reduction in corticotropin-releasing hormone reduces pituitary adrenocorticotropic hormone (ACTH) secretion and hence production of endogenous glucocorticoids (and to a lesser degree mineralocorticoids) by the adrenals. The return of functionality to the HPA axis is variable both clinically and biochemically.

In addition to the potential risk of impairment of the HPA axis, chronic steroid ingestion can create a host of other clinical problems in the perioperative period. Friable skin can present a problem with difficult intravenous access and skin breakdown. These patients are also at increased risk for infection, making aseptic technique particularly important. Last, they may have occult gastrointestinal bleeding or ulcer disease that is unrecognized.

Recognition

The clinical presentation of an Addisonian crisis varies from mild, nonspecific constitutional symptoms to the presence of profound shock unresponsive to vasopressor therapy. In the perioperative period, clinicians should maintain a high index of suspicion when caring for patients chronically taking or recently discontinuing steroid therapy. Mild symptoms of adrenal insufficiency include nausea, vomiting, anorexia, fatigue, and abdominal pain. Mineralocorticoid deficiency infrequently accompanies an Addisonian crisis, yet when it occurs it can present with hyponatremia, hyperkalemia, and metabolic acidosis. With severe adrenal insufficiency, arterial hypotension with postural accentuation is common. Such hypotension may be refractory to fluid and vasopressor therapy given glucocorticoids' profound effect on vasomotor sensitivity to catecholamines. This clinical presentation is highly unlikely in patients who have received their usual daily dose of steroids, especially if they are not experiencing high levels of physiologic stress.

Risk Assessment

The following are important risk factors for the development of adrenal insufficiency in the perioperative period:

- Daily dose of steroids (>20 mg/day of prednisone or equivalent)
- Duration of steroid therapy (>3 weeks)
- Suppression of the HPA axis based on serum testing (cortisol level, ACTH stimulation test)
- High degree of physiologic stress (surgery, trauma, burns, infection)
- Primary or secondary adrenal insufficiency requiring steroid replacement therapy

It has been shown that the total daily dose of steroids determines the responsiveness of the HPA axis to stress. LaRochelle and colleagues demonstrated that when the total daily dose of prednisone was 5 mg or less, there was a normal response to the ACTH stimulation test. With doses greater than 5 mg/day, responses to the ACTH test can vary widely. Others have suggested that doses equivalent to 20 mg/day of prednisone may also leave the HPA axis unsuppressed if administration is limited to less than 3 weeks and discontinued for greater than 14 days. For those receiving higher doses of steroid therapy (>20 mg prednisone) and/or for a longer duration (>3 weeks), the HPA axis should be considered impaired for up to 6 months after therapy has been discontinued. When in doubt, a two-tiered approach is recommended. If time permits, morning cortisol can be tested with the patient withdrawn from steroids for 24 hours. If the cortisol level is less than 5 μg/dL, the axis is impaired and supplemental steroid dosing is needed based on the anticipated degree of surgical stress. A morning cortisol of greater than 10 μg/dL connotes an intact HPA axis, and no additional dosing is needed except the patient's chronic dosing. A result between 5 and 10 μg/dL is indeterminate and requires that an ACTH simulation test be performed, if feasible, to determine whether the HPA axis has returned to normal.

In the case of surgical patients with concomitant major trauma, burns, or sepsis, random serum cortisol levels can be used to determine whether the physiologic response to major surgery and critical illness is adequate. A review by Marik and Zaloga supports judicious use of supplemental steroids in these critically ill patients using a 25 μg/dL serum cortisol level as a cutoff for treatment. When the random serum cortisol level is found to be low, particularly in patients with sepsis, stress doses of steroids are often administered in the intensive care unit setting.

Implications

Addisonian crisis secondary to inadequate steroid supplementation is rare, but vigilance by the anesthesiologist for subtle signs of adrenal insufficiency is important to avoid complications. The cumulative daily dose, the duration of chronic steroid therapy, and the nature of surgery are important factors for predicting the integrity and responsiveness of the HPA axis. A preoperative Cushingoid appearance is indicative of excessive steroid use and should be an alert for probable HPA axis suppression. Recent exposure to etomidate use as an induction agent also puts the patient at higher risk for HPA axis suppression and should be considered when postoperative hypotension is unresponsive to conventional treatments. The anesthesiologist should consider avoiding etomidate administration in those patients at higher risk for HPA axis abnormalities because of its known ability to inhibit steroid synthesis. Topical and inhaled steroids generally present little risk of adrenal insufficiency, but higher doses over prolonged periods of time require special attention (e.g., >2 g/day topically of superpotent agents), as do three or more intraarticular or epidural steroid injections within 3 months of surgery.

Surgical patients with accompanying septic shock, major trauma, or burns represent a special group. Work by Annane studying septic shock patients has shown improved clinical outcomes when treating with supraphysiologic doses of steroids. Given the potential risk of high-dose steroids (hyperglycemia, hypertension, fluid retention, increased infection risk), dosing should be based on measured random cortisol levels. Finally, patients with primary or secondary adrenal insufficiency are also at high risk for perioperative exacerbation due to their inability to increase cortisol secretion in times of physiologic stress. Therefore it is prudent that they receive supplemental dosing in addition to their chronic therapy.

MANAGEMENT

The most recent Cochrane systematic review concluded that there is insufficient evidence to support empiric treatment of potential adrenal suppression perioperatively. It does support, however, the continuation of chronic daily dosing in patients already on steroids. Endocrinologists go one step further and recommend judicious use of supplemental steroids in selected high-risk patients (major surgery, septic shock). *A standard dose for all patients should be avoided.* Instead, dosing of perioperative supplemental steroids should be based on the patient's history of steroid use in combination with the degree of anticipated surgical stress (see Tables 25.1 and 25.2 for details).

For those actively being treated, continuation of the prescribed morning dose before surgery is the first step. Supplemental doses should be based on total daily dose, duration of therapy, severity of perioperative stressors, and concomitant use of antiemetic doses (4–8 mg) of dexamethasone. Although some data suggest that a minimum of 2 months is sufficient time for the resumption of normal cortisol production, it is prudent to assume that HPA axis function may be impaired for up to 6 months. Although the ACTH stimulation test is useful for determining the integrity of the HPA axis, it is impractical and unnecessary to perform the test in all patients. Those taking less than 5 mg/day of prednisone or its equivalent can be assumed to have an intact HPA axis and do not require supplemental doses of steroids; however, it is important to continue their chronic daily dosing as treatment for the underlying disease.

TABLE 25.1 Supplemental Steroid Dosing ("Stress Dose") Guidelines

Daily Dose of Prednisone	Duration of Treatment	Degree of Surgical Stress	Perioperative Management[a]
<5mg	Any	Not applicable	Normal HPA axis; give daily dose if still on steroids.
5-20 mg	<3 weeks		
5-20 mg	>3 weeks, but stopped within 14 days		
5-20 mg	>3 weeks, but not stopped within 14 days	If HPA axis untested, follow recommendations for higher (>20 mg/day) chronic steroid dosing	If status of HPA axis is unknown, consider axis testing; otherwise, base supplement on degree of surgical stress. Give daily dose if on steroids.
>20 mg	Any	Minor (e.g., hernia repair)	Give daily dose only.
		Moderate (e.g., joint replacement)	Daily dose plus 50 mg IV preop, then 75 mg IV hydrocortisone over 24 hours, and then resume daily dosing.
		Major (e.g., Whipple)	Daily dose plus 100 mg IV hydrocortisone preoperative, then 150 mg over 24 hours. Taper dose by 50% until is daily dose achieved.

HPA, Hypothalamic-pituitary-adrenal.
[a]Concomitant antiemetic doses (4–8 mg) of dexamethasone may reduce or eliminate the need for additional hydrocortisone on the day of surgery. See Table 25.2 for equivalence dose.

TABLE 25.2 Steroid Comparisons: Relative Glucocorticoid and Mineralocorticoid Potencies and Duration of Action

Steroid	Glucocorticoid Potency	Mineralocorticoid Potency	Duration of Action (hr)
Hydrocortisone[a]	1	1	8–10
Prednisone	4	0.8	18–36
Prednisolone	4	0.8	12–36
Methylprednisolone	5	0.5	18–36
Dexamethasone	25–30	0	36–54
Fludrocortisone	10	120	18–36

[a]Identical to cortisol.

With minor surgery (e.g., local anesthesia, inguinal herniorrhaphy, laparoscopic), provision of the normal daily steroid dose on the morning of surgery should be adequate. Equivalent dosing would be provided postoperatively if return to oral therapy were not feasible. With moderately stressful surgery (e.g., total joint, partial colectomy), supplemental doses of 75 to 125 mg/day of intravenous (IV) hydrocortisone should be administered in addition to the usual morning dose on the day of surgery. Supplemental hydrocortisone can be provided as a continuous infusion or divided into doses every 8 hours. In the absence of the signs and symptoms of septic shock, supplemental steroids should be weaned within 24 hours and chronic oral steroid dose reinstituted immediately. With major surgical stress (e.g., coronary artery bypass graft, Whipple, esophagectomy), supplemental doses of 150 to 250 mg of IV hydrocortisone should be administered in addition to the usual morning dose on the day of surgery. Continuous infusion or every-8-hour dosing can be used for the first 24 hours following surgery and then reduced by 50% every day until equivalent preoperative dosing is achieved. Supplemental dosing of hydrocortisone should be continued or increased (100 mg intravenously every 8 hours or 10 mg/h) if patients become critically ill and/or have signs and symptoms of septic shock refractory to fluid and vasopressor therapy. Ideally, a random serum cortisol should be drawn before treatment to document the presence of adrenal insufficiency (cortisol <25 μg/dL).

Taking current clinical anesthesia practice into account, it is worth noting that the intraoperative use of dexamethasone as an antiemetic agent likely requires adjustment in the supplemental steroid dosing regimen. Since the mid-1990s, dexamethasone has been used frequently in patients with a higher risk for postoperative nausea and vomiting (frequently in conjunction with other synergistic agents). The 4- to 8-mg dose is equivalent to 100 to 200 mg of glucocorticoid potency. If administered intraoperatively, this degree of steroid supplementation should eliminate the risk of adrenal insufficiency in the first 24 hours for most surgical procedures.

PREVENTION

The following steps are useful for preventing acute adrenal insufficiency and side effects of excessive (supraphysiologic) glucocorticoid administration:

- Identify patients who are at risk of developing adrenal insufficiency.
- Pursue testing of the HPA axis in patients at risk for adrenal sufficiency.
- If testing is not feasible, be vigilant for subtle signs of acute adrenal insufficiency and have a low threshold for treating patients.
- Tailor perioperative dosing based on history of steroid use and degree of surgical stress.
- Consider use of high-dose steroids in patients with septic shock given the evidence of improved outcomes in this patient subgroup.
- Reduce or eliminate the dose of supplemental hydrocortisone on the day of surgery when concomitant dexamethasone is administered as a prophylactic antiemetic.

ACKNOWLEDGMENT

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26 The Jehovah's Witness Patient

Gail A. Van Norman

Case Scenario

Mrs. R, a 45-year-old woman, was admitted to the hospital pregnant with her fourth child. She was delivered of her daughter the next day but suffered hemorrhagic complications related to placenta accreta. Because of her religious beliefs, Mrs. R had refused blood transfusion. Nevertheless, when Mrs. R had lost approximately 80% of her blood volume, physicians first sought legal counsel and then after a delay administered 2 units of blood—the only blood available in the operating room. Mrs. R died approximately 2½ hours after her daughter's birth. Her family sued the doctors for medical malpractice, and a Supreme Court jury in New York awarded the plaintiffs $1.25 million in damages.

PROBLEM ANALYSIS

Definition

The doctrine of the Jehovah's Witness church regarding blood transfusions is based on the denomination's interpretation of Biblical passages prohibiting the ingestion of blood:

> *Genesis 9:3—Every moving thing that liveth shall be meat for you; even as the green herb have I given you all things. But flesh with the life thereof, which is the blood thereof, shall ye not eat.*
>
> *Leviticus 17:10–16— … I will set my face against the soul that eateth any manner of blood, and will cut him off from among his people. … no soul of you shall eat blood, neither shall any stranger that sojourneth among you eat blood. … Ye shall eat the blood of no manner of flesh; for the life of all flesh is the blood thereof; whosoever eateth it shall be cut off.*
>
> *Acts 15:28–29— … that ye abstain from things sacrificed to idols, and from blood, and from things strangled, and from fornication; from which if ye keep yourselves, it shall be well with you. Fare ye well.*

As a result of 20th-century interpretations of this passage, many Jehovah's Witnesses refuse blood transfusions under any circumstances, even if such a transfusion would be lifesaving. This may present significant ethical difficulties for some anesthesiologists and surgeons, who are more focused on the present, physical well-being of the patient rather than on the hereafter.

Ethical Implications

In Western medical ethics, respect for patient autonomy holds a predominant place governing physician actions. Before the 20th century, physicians relied on a paternalistic ethical framework, in which the physician, and not the patient, determined what constituted the patient's "best interests," and the determination of best interest generally rested in decisions favoring preservation of life. Throughout the 20th century, however, cultural changes as well as legal precedents shifted the weight of decision making from the physician to the patient. The emphasis of ethical medical care was not "preservation of life," per se, but rather preservation of quality of life. Thus patient consent for care, and in particular *informed consent,* became the cornerstone of both ethical and legal values in medical practice.

Respecting autonomous patient wishes also serves the second principle in medical ethics—that of beneficence, or "doing good." By respecting the wishes of Jehovah's Witness patients, the physician demonstrates respect for their spiritual beliefs and their prioritization of a goal of a good spiritual life after death. Furthermore, the physician avoids participating in harm to the patient's spiritual well-being.

What if respecting the patient's beliefs would cause a physician to violate his or her own moral principles? Can physicians become "conscientious objectors"? Physicians can and do sometimes argue that it is against their personal moral beliefs to not administer available lifesaving therapy if it is available, and that refusal of blood transfusions (and other common lifesaving medical therapies such as cardiopulmonary resuscitation) violates the physician's moral "rights." However, physicians have a special "social contract" with their patients—one that affords the physician significant societal privilege in return for putting the interests of a competent patient above their own interests, and the moral rights of patients above their own.

Physicians are generally aware of these obligations to patients, and do have the choice to not enter medical practice or to avoid specialty areas of medical practice in which their own moral principles will be violated. In addition, they are often able to avoid specific patient relationships that might violate personal ethics. But allowing individual physician ethics to routinely supersede general principles of medical ethics would challenge the very integrity of medical philosophy within the medical profession as a whole. A physician is not allowed to proceed without informed consent, for example, just because he or she does not believe it is an important principle. *Society* has placed top priority on the rights of consent and refusal, and physicians serve a facilitating role in society. Many anesthesia practices have policies recognizing that strongly held personal moral beliefs may be anticipated and conflicts avoided with foresight and planning. To the degree that options can be offered to the practitioner in a timeframe that still allows appropriate patient care, physicians may ethically remove themselves from patient care in favor of another practitioner who does not have personal moral objections. Thus practices often allow for some practitioners to "opt out" of abortion procedures, for example. Unfortunately, time does not always offer such options, and the

physician is obligated to provide care that is broadly morally required in ethical medical care, rather than force their individual moral beliefs on their patients.

Legal Considerations

Federal law and legal precedents support the rights of competent patients to refuse lifesaving transfusions, although there are some exceptions. The landmark case of *Schloendorff v. Society of New York Hospital* in 1914 determined that "every person of adult years and sound mind has a right to determine what shall be done to his own body." These rights are based in constitutional guarantees of privacy and noninterference.

The cases of Karen Ann Quinlan and Nancy Cruzan involved comatose patients whose surrogate decision makers wanted to discontinue life-sustaining treatments. The New Jersey State Supreme Court and the U.S. Supreme Court, respectively, found that rights grounded in the 14th amendment of the constitution allowed patients to refuse such therapies. The U.S. Congress passed the Patient Self-Determination Act of 1990 and established in federal law the rights of patients to refuse any medical therapy (see Box 7.1 in Chapter 7), including life-sustaining therapy. The more recent case involving Terri Schiavo, a woman in a persistent vegetative state whose husband wanted to discontinue tube feedings, demonstrated the durability of this constitutional right.

Recognition

Clinical situations evolve quickly and can require rapid decision making. Providers should be familiar with basic situations and appropriate responses before such scenarios arise.

Adult Competent Patients

If an adult patient with decision-making capacity is informed of the relevant risks and refuses certain aspects of medical care, both ethical principles and legal precedents weigh heavily in their favor, even if their life is at stake.

Adult Incompetent Patients

Respect for patient autonomy acknowledges that competent patients may declare decisions they have made about potential future health care issues that might arise when they are incompetent and/or unable to express their wishes. Living wills, do-not-resuscitate decisions, transfusion refusals, and organ donation constitute advance directives that are ethically and legally recognized as the patient's own voice. Surrogate decision makers may make decisions for incompetent patients under many circumstances, and many states have established legal hierarchies describing who can make and express such decisions on behalf of the patient (Box 26.1).

Pregnant Patients

Ethical principles establish ethical and legal authority of the decisions of pregnant women, particularly early in pregnancy when decisions that affect the life of the fetus, up to and including abortion, are generally respected. As pregnancy advances and the possibility of independent survival of the fetus becomes more likely, the weight of maternal decisions may be lessened, and courts have been inconsistent in whether a mother's health care decision would necessarily prevail over fetal interests. When maternal-fetal conflicts arise during pregnancy and labor, the more advanced the woman's pregnancy is, the more likely she might be legally compelled to defer to fetal interests. However, this is not a given, as illustrated in the findings of the case of Darlene Brown. Brown underwent surgery when she was 34{3/7} weeks pregnant. She expressed that, as a Jehovah's Witness, she would refuse blood transfusion. When unexpected, severe blood loss ensued, her physicians sought and obtained a court order to transfuse her, citing, in addition to her own risks, the risks that nontransfusion posed to her undelivered fetus. She later delivered a healthy baby boy. Brown then filed an appeal in Illinois courts of the prior ruling, in order, as the court stated, to establish for future guidance of public officials whether it was rightful for doctors to override her autonomous wishes to refuse blood transfusion. The court found in her favor, stating the following:

> *The liberty of the [pregnant] woman is at stake in a sense unique to the human condition and so unique to the law ... [the woman's] suffering is too intimate and personal for the State to insist, without more, upon its own vision of the woman's r*ole, however domi*nant that vision has been in the course of our history and our culture. The destiny of the woman must be shaped to a large extent on her own conception of her spiritual imperatives and her place in society.*

BOX 26.1 Example Hierarchy for Surrogate Decision Making*

- Durable Power of Attorney for Health Care Decisions
- Conservator or guardian having authority to make health care decisions
- Spouse or domestic partner
- Adult son or daughter, or adult children as a group if unanimous
- Custodial parent or parents if unanimous
- Adult siblings if unanimous
- Adult grandchildren if unanimous
- Other available adult relative with closest degree of kinship to the patient

*Hierarchy may vary somewhat from state to state.

Minor Patients

Due to cognitive and emotional immaturity, minor patients are not automatically assumed to be competent until age 18. At that time, competence to make medical decisions is assumed unless circumstances otherwise suggest the patient is incompetent. In some cases, minors may be able to legally challenge this rule, and are awarded the rights to make medical decisions due to their individual cognitive and emotional capabilities. In addition, many states recognize special circumstances in which the law awards minors the right to make medical decisions and seek medical care without parental knowledge or consent. Common situations include issues of reproductive health, treatment for addiction, and treatment for mental health disorders. Laws vary from state to state, and practitioners should be familiar with their own local regulations. Further information with regard to minors' rights can be found in Chapter 15.

In most "normal" situations, medical decision making for children is done by surrogate decision makers on the principle of what is in the child's "best interests" rather than based on the child's wishes. Such decisions generally fall to parents, because in most cases there is no reason to question whether anyone is better qualified to understand what that would be than the parents. When parents decide to refuse lifesaving care for a minor child, however, such as in the case of transfusion decisions for the children of Jehovah's Witnesses, ethical principles suggest that the decision should at least be reexamined from a "best interest" perspective. Courts are more likely to intervene and countermand parental decisions in such cases.

Emergency Situations

Competent patients do not automatically lose their constitutional rights in emergency situations, and if they refuse medical interventions, these wishes should ethically and legally be honored. However, medical emergencies are fraught with conditions that can impair a patient's competence to make decisions—head injury, intoxication, shock, and so on. Patients document advance directives, such as living wills and transfusion decisions, anticipating precisely circumstances in which they may not be in a condition to express their wishes. Advance directives should be followed in such cases. In situations where a patient is not competent and the patient's wishes are unknown, the physician may have to proceed with what he or she believes is in the best interest of the patient.

Informed Consent and the Jehovah's Witness Patient

Whenever a patient is refusing blood transfusions, it is especially important to ensure that the patient is fully informed of the risks and benefits of this decision. Full risk disclosure includes the risk of not only death but of other health consequences that may occur if blood transfusion is not done during critical blood loss. Such issues include risks of stroke, major adverse cardiac events, kidney failure, and other relevant consequences. If the patient is pregnant, potential fetal loss or injury should be included in the discussion. In the case of Jehovah's Witness patients, other information should also be reviewed. In the case of solid organ transplantation, patients should be informed that there are some blood cells in solid organs. Blood conservation techniques should be discussed, including hemodilution. Blood salvage techniques such as cell-saver technology should be described, and patients should be asked to indicate which if any blood components they might accept.

Coercion

It is common for members of the Jehovah's Witness church community, as well as family members, to accompany a Jehovah's Witness patient requiring medical treatment, both to support their loved one and to reinforce tenets about blood transfusion. Although rare, some health care providers have experienced cases in which the decision a Jehovah's Witness patient expresses in private is different from the one that the patient expressed in front of his or her family and community. These interactions serve to remind us that all patients should be offered an opportunity to express their wishes regarding health care in an environment that is free of potential coercive influences. This might be done once family and church members have been sent to the surgical waiting room. The intent of a private discussion should not be to convince the patient to accept blood transfusion, which would be coercive, but rather to ensure that the patient's true wishes are known. Any decisions that the patient makes in private about blood transfusion should be held in strict confidence.

MANAGEMENT

Details of our case scenario are taken from an actual lawsuit that demonstrates some of the subtleties of the dilemmas regarding transfusion refusals, and indeed pertinent to almost any advance directive that expresses a patient's refusal of lifesaving treatments.

In this case we do not have a maternal-fetal conflict with regard to the transfusion. If the mother had required transfusion to survive long enough to deliver the child, or if a transfusion of the mother was needed primarily to save the life of the fetus, refusal by the mother would create both an ethical and legal dilemma because it would place the autonomous rights of the mother in conflict with the principle of beneficence to another potential human being, the fetus. How this conflict might be resolved ethically and legally depends on many factors: the likelihood that the harm to the mother (transfusion) would benefit the child, for example. If the likelihood is remote, it is much more difficult to argue that the mother's rights should be violated. On the other hand, if the likelihood is quite high, then other ethical questions arise regarding whether the intrinsic value of life should outweigh respect for autonomy. In general, the courts do not treat fetuses as "minors" and are much less willing to intervene than in the case of a born child. In our case, the child has been delivered, and maternal life alone is at stake.

Ethical principles of respect for patient autonomy dictate that the mother's refusal should be honored. The question of whether the mother should be forced to undergo a transfusion so as not to leave her child motherless has been vacated by the courts in decisions that point out that we do not require parents in general to not engage in activities that are only dangerous to themselves and risk their lives in other ways (e.g., skydiving, scuba diving, rock climbing) simply because they have children.

In our case, the physicians decided to violate this ethical principle, arguing a principle of beneficence (ignoring that the patient's concept of beneficence is different from theirs). In the United States this definition of beneficence would generally not supersede respect for autonomy, ethically or legally. An even greater problem arose when, once the physicians made this decision, they failed to act in a manner consistent with standards of care. Transfusion came too little, too late—in part because the physicians were waiting for an attorney to absolve them of potential liability before proceeding. In other words, the physicians proceeded in a manner to preserve themselves from future harm rather than in a manner to prevent harm to the patient. Because of their approach, transfusion had little chance to succeed in the goal of saving the patient, although it was virtually guaranteed to cause profound spiritual harm.

It is unclear whether the physicians in this case had opportunities to prepare in advance for the possibility of life-threatening blood loss in a patient who was refusing transfusion. Once a patient who refuses transfusion is identified as being at risk for severe hemorrhage, consideration should be given to the use of special techniques to limit blood loss, such as hemodilution and intraoperative blood salvage. If elective surgery is planned, consideration should be given to hematocrit-boosting therapies ahead of planned surgery, such as treatment with erythropoietin and iron supplements. Unfortunately, sudden blood loss may occur in surgeries in which significant blood loss is not expected.

When a physician decides to violate the wishes of an autonomous patient, it is hard to argue that they are justified in doing so if they do not practice in such a way that meet minimal medical standards of care. In such circumstances, the patient is doubly harmed: Not only is the patient's autonomy disregarded, but the patient suffers the consequences of substandard care. Although it is not the intention of this chapter to suggest that it is *ever* truly justified to violate a competent patient's wishes, it nevertheless should be obvious that such an ethical violation should only be accompanied by excellent technical medical care.

Whenever possible, if physicians feel that their personal morals will not allow them to follow primary medical ethical principles, such as respect for patient autonomy, they should withdraw from care of the patient in favor of a physician who is not conflicted. These principles are expressed in the Ethical Guidelines for the Anesthesia Care of Patients With Do-Not-Resuscitate Orders or Other Directives That Limit Treatment, first published by the American Society of Anesthesiologists Committee in 1993 (Box 26.2).

BOX 26.2 Summary of the American Society of Anesthesiologists' Ethical Guidelines for the Anesthesia Care of Patients With Do-Not-Resuscitate Orders or Other Directives That Limit Treatment

Policies automatically suspending DNR orders or other orders that limit treatment may not sufficiently address a patient's right to self-determination. Such policies should be reviewed and revised.

Directives limiting resuscitation procedures should be reviewed with the patient or designated surrogate and, when necessary, modified to reflect the patient's wishes.

Clarifications/modifications of the patient's advance directives should be documented in the patient's medical record.

Plans for postoperative care should include plans to restore the patient's previous directives.

Discussions and documentation should include whether there are any exceptions to the injunctions against resuscitation for specific complications.

Concurrence by the patient's primary physician, the surgeon/proceduralist, and the anesthesiologist is desirable.

In case of conflicts:

- When an anesthesiologist finds the patient's or surgeon's/proceduralist's decisions regarding limits of interventions to be irreconcilable with the anesthesiologist's own moral views, he or she should withdraw in a nonjudgmental fashion, providing for timely care.
- If the patient's or surgeon's/proceduralist's limitation of intervention decisions is incompatible with acceptable standards of care, ethical practice, or institutional policy, the anesthesiologist should express this concern and present it to the appropriate institutional body.

DNR, Do not resuscitate.

PREVENTION

Jehovah's Witness patients, indeed *all patients,* have both legal and moral rights to refuse medical treatments, even if the treatment would be lifesaving. Appropriate ethical management of Jehovah's Witness patients undergoing surgery and anesthesia involves responsibilities of individual physicians, clinical practices, and health care institutions.

The individual physician has responsibilities to provide medical care to patients in accordance with their autonomous wishes. Autonomous decisions can only occur in the setting of appropriate information about risks and benefits, and physicians should engage in honest, noncoercive conversations with patients about these issues, including intraoperative techniques to reduce blood and intraoperative blood salvage techniques. When elective surgery that entails significant blood loss is contemplated in a patient who refuses blood transfusions, consideration should be given to advance medical preparation of the patient, even delaying surgery so that administration of erythropoietin or other measures can be undertaken.

Physicians who self-identify as morally unable to follow a patient's directive regarding blood administration should excuse themselves from cases in which such a decision may arise and refer the patient to providers who are not conflicted by the patient's decision.

Group practices should be prepared to accept that some members may have moral objections to certain medical practices, and have policies and practices in place that address this issue, including when and how one provider should seek to transfer patient care to another.

Institutional policies should clearly address appropriate procedures when autonomous patients refuse lifesaving medical treatments. Special circumstances such as blood refusal by a pregnant patient, or refusal of parents to allow transfusion of a child, should be clearly outlined.

Further Reading

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27 Unstable Cervical Spine: Atlantoaxial Subluxation

Suneeta Gollapudy • Lois A. Connolly

Case Synopsis

A 79-year-old man presents with C1 and odontoid fractures sustained in a fall down stairs while he was intoxicated. He was found at the bottom of the stairs 2 days after the injury. In addition to alcoholism, the patient has a history of hypertension and smokes one to two packs of cigarettes per day. The patient is not oriented to time, place, or person and has inappropriate verbal responses, but there is no apparent neurologic deficit.

PROBLEM ANALYSIS

Definition

Cervical spine stability is defined as the ability of the spine to maintain relationships between vertebrae during physiologic loading, so as not to damage contained neural structures. Cervical spine instability occurs when physiologic loading causes patterns of vertebral displacement that jeopardize the cervical spinal cord. The muscles of the neck, along with ligamentous structures, intervertebral disks, and osseous articulations, all play a role in cervical spine stability. Upper cervical spine stability may be affected by trauma, congenital disorders, and inflammatory diseases, all of which may result in atlantoaxial instability (Box 27.1).

Traumatic Cervical Spine Instability

The cervical spinal cord is particularly prone to injury because of spinal flexibility and the mass of the head. The spinal cord is injured when the ligaments, muscles, and osseous structures fail to dissipate the energy of impact. Transmission of this energy results in microhemorrhage in the spinal cord central gray matter and loss of neurotransmission in the surrounding white matter. A biochemical cascade that destabilizes the neurologic axon membrane and promotes vasospasm creates a secondary injury pattern after the initial insult. Also, primary cervical spinal cord injury leads to altered autonomic tone, loss of autoregulation, depressed cardiovascular function, and hypotension.

A traumatic atlantoaxial dislocation (atlantodental interval of >3 mm in adults older than 18 and >5 mm in children) occurs with forced displacement of the neck such as those sustained during tackling in football or rugby and often is associated with head injuries. If atlantoaxial dislocation or a type II odontoid fracture (fracture occurs at the base of the odontoid between the transverse ligament and the body of C2) occurs, there is a very high likelihood of ligamentous injury. The transverse ligament normally allows no more than 3 mm of anteroposterior translation between the odontoid and the anterior arch of the atlas. If disruption of this ligament occurs, displacement of the odontoid reduces the space available for the spinal cord (Fig. 27.1). In the normal spine, the space available for the spinal cord is about 20 mm. Cord compression does not occur when the space is greater than 18 mm, but it does occur if it is less than 14 mm.

Congenital Cervical Spine Instability

Congenital or chromosomal anomalies may contribute to cervical spine instability, mostly atlantoaxial instability by means of either odontoid hypoplasia or laxity of the transverse ligaments. The stabilizing action of the odontoid during extension is lost with odontoid hypoplasia, and subluxation of the atlas occurs on the axis anteriorly, reducing the space available for the spinal cord. Laxity of the transverse ligament is present in 14% to 22% of patients with trisomy 21. Excessive laxity of other joints correlates with the presence of atlantoaxial instability. Other congenital conditions with skeletal dysplasia, such as Goldenhar syndrome, spondyloepiphyseal dysplasia, and Morquio (mucopolysaccharidosis type IV) syndrome, are high at risk for atlantoaxial instability.

Inflammatory Cervical Spine Instability

Cervical spine involvement is common in inflammatory arthropathies such as rheumatoid arthritis (RA) and ankylosing spondylitis. The pathophysiology of RA involves pannus formation, with subsequent destruction of cartilage and subchondral bone, along with ligamentous laxity and instability. Atlantoaxial subluxation occurs in about 25% of patients with RA. It occurs more frequently in men, in those with disease of long duration, in patients with subcutaneous nodules or seropositive disease, and in those receiving steroid therapy. Vertical subluxation of the odontoid process through the foramen magnum may also occur in patients with RA.

Epidemiology

- Cervical spine injuries occur in 1.5% to 7.7% of all major trauma cases.
- The peak distribution of injury is at the C4–C6 levels.

BOX 27.1 Conditions Associated With Atlantoaxial Subluxation

Congenital
Down syndrome
Odontoid anomalies
Mucopolysaccharidoses

Acquired
Rheumatoid arthritis
Juvenile rheumatoid arthritis
Ankylosing spondylitis
Psoriatic arthritis
Enteropathic arthritis
- Crohn's disease
- Ulcerative colitis

Reiter's syndrome
Trauma
- Odontoid fracture
- Ligamentous disruption

From Crosby ET, Lui A: The adult cervical spine: implications for airway management. *Can J Anaesth* 37(1):77-93, 1990.

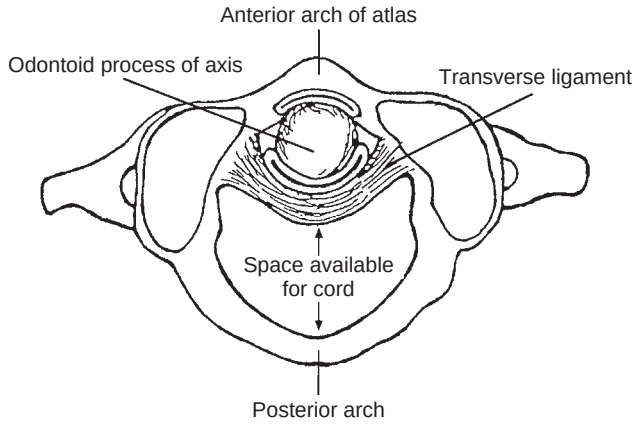

Fig. 27.1 Atlantoaxial articulation—view from above. (From Crosby ET, Lui A: The adult cervical spine: implications for airway management. *Can J Anaesth* 37[1]:77-93, 1990.)

- The most common age of injury is 19 years. Nearly a quarter of all injuries occur between ages 17 and 22 years (24.3%), nearly half of all injuries occur between ages 16 and 30 (48.9%), and 10.7% of all injuries occur at age 60 or older. The average age at injury has increased from 29 years during the 1970s to 42 years currently. Males account for approximately 80% of new spinal cord injury (SCI) cases.
- Most cervical spine injuries result from motor vehicle accidents (MVAs; 42%–56%), falls (19%–30%), or gunshots and sports-related activities (6%–7%).
- MVAs and sports-related activities account for the majority of cervical spine injuries in younger patients, whereas falls account for most cervical spine injuries in older patients.
- Young children are less susceptible to cervical spine injury because they weigh less and have more cartilage than adults do; vulnerability increases with age.
- Cervical spine injuries in children younger than 2 years are exclusively C1–C2 injuries, because facet joints at this level are more horizontal and the ligaments more lax.
- Diseases of the respiratory system are the leading cause of death (67.4% of these are cases of pneumonia). The second leading cause of death is infective and parasitic diseases. These are usually cases of septicemia (89.2%) and are usually associated with decubitus ulcers, urinary tract infections, or respiratory infections.
- The cumulative 10-, 20-, 30-, and 40-year survival rates for patients with SCI are 81.71%, 68.05%, 52.99%, and 37.44%, respectively.

Recognition

History and Physical Examination

Recognition of a cervical spine injury begins with the history. High-risk causes (e.g., motor vehicle accident, fall, long-standing RA) or known chromosomal abnormalities may alert the clinician to the presence of an unstable cervical spine. For example, a patient with RA may complain of clicking on neck flexion and pain and stiffness of the neck. An alert trauma patient may complain of neck pain or tenderness. An alert patient without neck pain or neurologic deficit does not require further cervical spine evaluation, immobilization, or special precautions during airway manipulation. If the patient is not fully alert, complains of neck pain, has neurologic deficits, or has other painful injuries, cervical spine precautions should be maintained.

Vertebral injury can occur without cord damage because the spinal canal is widest in the cervical region. Neurologic deficits are present in 46% of patients and are more frequent with injuries involving C5–C7. A thorough neurologic examination should enable classification and identification of the level of the spinal cord lesion.

Autonomic instability may occur acutely and is termed *spinal shock*. With spinal shock, loss of sympathetic tone leads to generalized hemodynamic instability characterized by bradycardia, peripheral arterial and venous vasodilation, hypotension, and arrhythmia.

Respiratory compromise may occur acutely due to loss of intercostal muscle innervation or, with high cervical lesions, due to phrenic nerve loss. In normal individuals, expansion of the rib cage accounts for 60% of resting tidal volume. Therefore alveolar ventilation and the ability to cough are decreased with loss of intercostal muscle innervation, even if phrenic nerve function remains intact. Thus acute cervical cord injury may cause hypoxia, atelectasis, and respiratory failure. The possibility of aspiration pneumonitis may compound the situation. In addition, neurogenic pulmonary edema may be associated with SCI due to massive sympathetic discharge associated with trauma.

Vertebral artery injuries can occur with cervical spine injuries. If unrecognized or untreated, the incidence of mortality due to cerebrovascular ischemia is as high as 30%. The vertebral artery is most susceptible to injury at the point of entrance into the transverse foramen at C6. The second most common site is at C1–C2. Despite diagnosis and anticoagulation therapy, 5.8% become clinically symptomatic and 2.9% die due to cerebrovascular ischemia.

Radiographic Evaluation

The National Emergency X-radiography Use Study (NEXUS) Low Risk (NLR) criteria and the Canadian C-Spine Rule (CCR) were designed to identify patients who do not need diagnostic imaging to exclude a significant cervical spine injury. Cervical spine (CS) radiographs are indicated unless the patient meets the following five characteristics:

1. Alert
2. Not intoxicated
3. No posterior cervical tenderness
4. No neurologic changes
5. No distracting injuries such as crush, burn, large lacerations, or significant fractures.

The CCR has a sensitivity of 99.4% (NLR 90.7%) in detecting injury and poses three questions:

1. Does the patient have any high-risk injury (age >65, mechanism of injury is dangerous such as MVA, fall, bicycle accident)?
2. Are there any low-risk factors present that would allow a safe assessment of range of motion to be obtained? Low-risk factors are simple rear-end collisions, ability to sit upright, ambulation, delayed onset of neck pain, or absence of cervical tenderness.
3. Is the patient able to actively rotate neck 45 degrees to the right and the left?

If the patient has active rotation with low-risk factors and the absence of any high-risk factors, the physician can safely clear the cervical spine without radiographic imaging.

Plain radiography typically includes three views: anteroposterior, lateral, and odontoid. Plain radiography has been mostly replaced by computed tomography (CT) imaging because the false-negative rate is higher than that with CT. Emergency departments routinely rely on CT imaging to evaluate patients for injury. CT is best for detecting boney abnormalities. The most appropriate method for clearing the cervical spine in patients with altered mental status remains controversial. The Eastern Association for the Surgery of Trauma's 2009 Practice Management Guidelines for Identification of Cervical Spine Injuries following Trauma notes that significant changes in practice have occurred since the first cervical spine injury guidelines were released in 1998. Now CT has replaced the three-view radiographic as the primary screening tool in the trauma patient who requires imaging. In the obtunded patient, flexion/extension dynamic bedside fluoroscopy adds no useful information, is inadequate, and may be dangerous. For the obtunded patient with a negative CT of the cervical spine, magnetic resonance imaging (MRI) may be obtained to further define ligamentous injury. If MRI is negative, immobilization of the CS can be discontinued. Controversy exists because the incidence of a ligamentous injury with a negative CT scan is very low. Hogan in 2005 studied 366 patients with a negative CT for CS injury. MRI imaging was also negative in 96.7%. Ligamentous injury was detected in 1.1% of these patients. Most often a spinal cord injury is associated with radiographic findings such as fractures, ligamentous injuries, or subluxations; however about 3.3% of adult patients with spinal cord injury without radiographic abnormality (SCIWORA) had spinal cord injury detected on MRI. So, at present, there is no definitive recommendation on the need for MRI after a negative CT of the CS. Additional MRI screening cares significant risk for the obtunded trauma patient and is expensive. Additionally, collar complications such as collar-related rash, skin breakdown, and pressure-related injuries; increase in intracranial pressure; higher incidence of ventilator days and intensive care length of stay; higher incidence of delirium; difficult central venous access; and delay in tracheostomy are possible when collars are left on for more than 72 hours. These issues need to be weighed against the small but potential possibility of a missed CS injury.

A diagnostic algorithm for the evaluation of a patient with possible cervical spine injury is shown in Fig. 27.2.

In chronic medical conditions associated with the possibility of atlantoaxial subluxation (e.g., RA, Down syndrome), lateral cervical spine films are obtained in neutral, flexed, and extended positions (Fig. 27.3). Evidence of both anterior and vertical subluxation should be sought, and the space available for the spinal cord should be measured. In patients with RA, the anteroposterior view may be examined for the presence of laryngeal deviation.

Risk Assessment

Preoperative assessment in a patient with a known unstable cervical spine should include the following:

- Evaluation of the cervical spine radiographically
- Determination of the adequacy of respiration (blood gas analysis or spirometry)
- Examination for evidence of spinal shock (blood pressure, heart rate, arrhythmia, electrocardiographic changes, need for vasopressors)
- Evaluation of the injury's effect on the central nervous system (neurologic evaluation, evidence of closed cranial trauma)
- Examination of associated injuries (chest radiograph or CT and electrocardiogram to rule out chest injuries)
- Determination of hemoglobin, electrolyte levels, coagulation status, and creatinine level
- Assessment of temperature balance

Implications

As discussed, multiple organs are affected by acute spinal cord trauma. Spinal shock requires invasive arterial monitoring, central venous access, and titration of vasopressors to ensure adequate perfusion pressure. If neurogenic pulmonary edema exists, further monitoring with a pulmonary artery catheter or transthoracic/transesophageal echocardiogram may be warranted. Acute spinal cord injuries have been treated with high-dose methylprednisolone. Based on the National Acute Spinal Cord Injury Study (NASCIS) II, infusion of 30 mg/kg was given within the first 8 hours or an infusion of 5.4 mg/kg/h for 24 hours if started less than 8 hours after injury. NASCIS III evaluated an infusion of 5.4 mg/kg/h for 48 hours and found no benefit. However, the most recent guidelines from the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) have now reclassified methylprednisolone as an OPTION, not a REQUIREMENT. Based on the downgrade, observed lack of efficacy of methylprednisolone, and complications of such therapy (e.g., an increased rate of wound infection and a greater risk of gastrointestinal hemorrhage), most level I trauma centers have abandoned its use altogether. Initial immobilization, with supervised reduction and realignment, is achieved with skeletal traction. Cervical immobilization is paramount and must be maintained during airway manipulation.

MANAGEMENT

Intraoperative Concerns

The primary intraoperative concerns are as follows:

- Monitoring
- Airway management
- Positioning
- Cardiopulmonary management
- Administration of anesthetic drugs (succinylcholine)
- Fluid management, glucose administration
- Postoperative vision loss

Intraoperative management requires tracheal intubation. The urgency of airway intervention is probably the most important factor in planning for airway management. Other factors include patient cooperation, assessment of the airway, and risk to the cord with neck movement. Endotracheal intubation in the presence of cervical spine instability adds the risk of spinal cord injury. The concern is that, at an unstable cervical segment, the forces of conventional direct laryngoscopy may result in abnormally great (pathologic) motion of the unstable segment and result in cervical cord compression and injury. Direct laryngoscopy requires atlanto-occipitoaxial extension and mild inferior rotation of C3–C5, although there is minimal movement below C3. Accordingly,

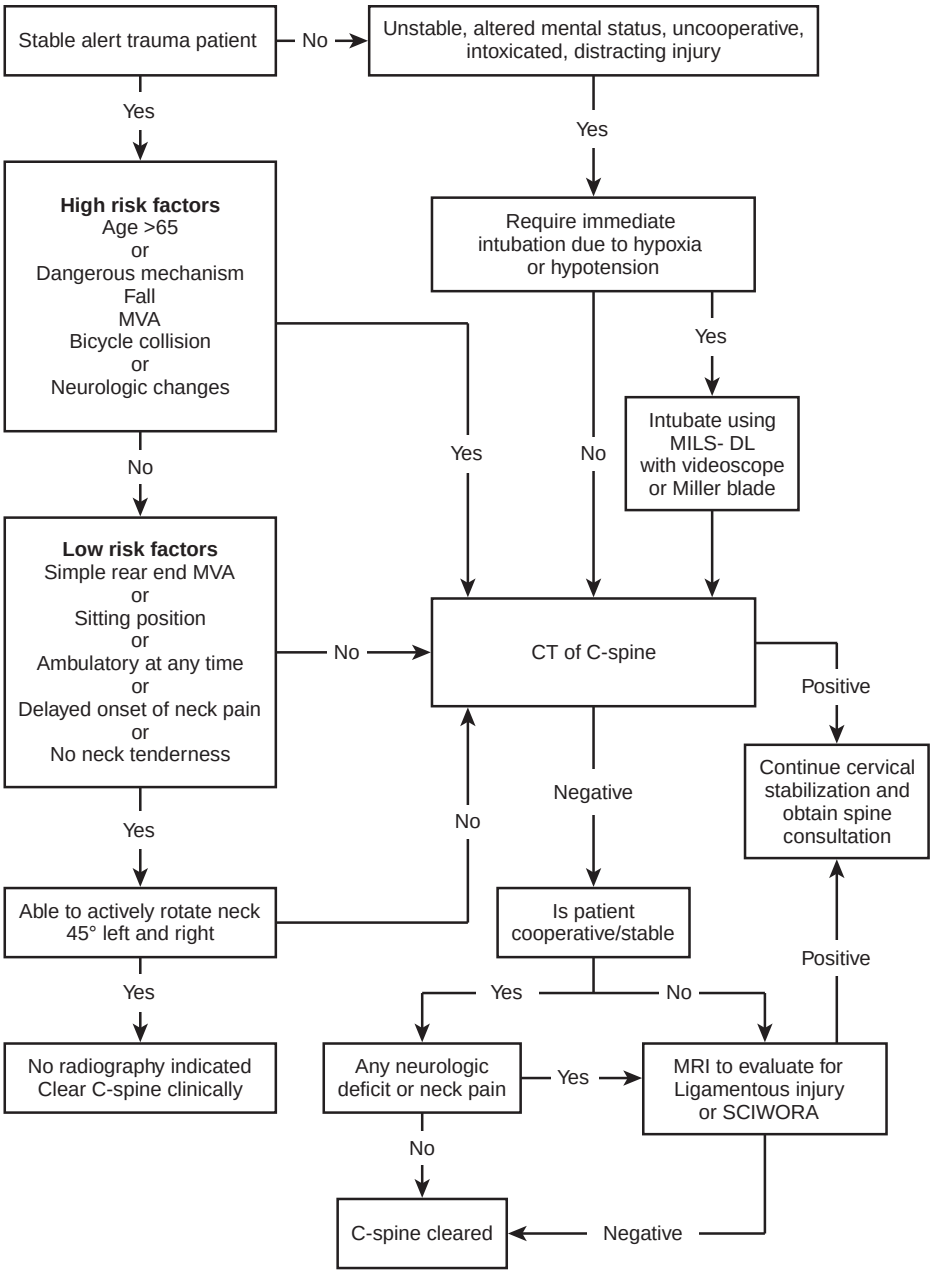

Fig. 27.2 Algorithm for evaluation of cervical spine injury. *C-spine,* Cervical spine; *CT,* computed tomography; *DL,* direct laryngoscopy; *MILS,* manual in-line stabilization; *MRI,* magnetic resonance imaging; *MVA,* motor vehicle accident; *SCIWORA,* spinal cord injury without radiologic abnormality.

unstable C1–C2 injuries are most likely to cause neurologic damage. Manual in-line traction reduces atlanto-occipital extension during intubation, and several published series detail the use of direct laryngoscopy with in-line traction without evidence of neurologic deterioration.

The use of a Miller-type blade results in less movement (i.e., axial distraction) than the use of curved (e.g., Macintosh) blades. Preintubation techniques, such as jaw-thrust and chin-lift maneuvers, cause the most motion and narrowing of the space available for the cord; therefore great care must be taken when performing these maneuvers. Failed intubation is a danger, however, and the laryngoscopist's view may be hindered by the stabilization. Direct laryngoscopy with in-line stabilization is most useful when it is vital to gain rapid control of the airway (e.g., patients with respiratory failure, hemodynamic instability, increased intracranial pressure). The newer videoscopes have gained popularity as an alternative to direct laryngoscopy. Glidescope, Airtraq, and CMAC have been used. There is 50% less movement at C2–C5 compared with direct laryngoscopy with manual inline stabilization (MILS) with glidescope. Lighted stylet is also another alternative to direct laryngoscopy. C-spine movement is 57% less than direct laryngoscopy (Table 27.1).

Awake tracheal intubation is probably the ideal way to secure the airway in a patient with an unstable cervical spine, although it may be inappropriate if rapid intubation is necessary. Use of the fiberoptic scope allows intubation under direct vision, but it may be difficult if the patient has pharyngeal bleeding or is uncooperative. Other awake techniques include blind nasal intubation or retrograde intubation over a wire.

Use of a laryngeal mask airway is not advised because it can exert a great deal of pressure against the cervical vertebrae, but is part of the

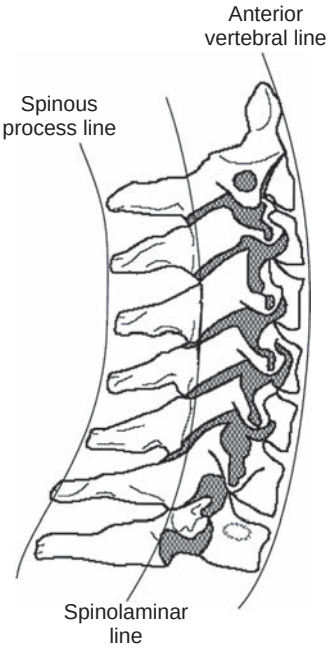

Fig. 27.3 Lateral cervical spine.

TABLE 27.1 Airway Management Techniques and Effects on the Cervical Spine

Manual in-line stabilization	Eliminates distraction and diminished angulation but increased subluxation
Mask ventilation	Significant anterior posterior translation displacement with maximal flexion and extension of head
Oral/nasopharyngeal	≈2 mm widening disk space at level of injury
Chin lift/jaw thrust	>5 mm widening disk space at level of injury
Cricoid pressure	Single handed cricoid pressure causes vertical displacement of neck ≈5 mm but no spine movement
Laryngoscopy	Extension at occipitoatlantal and C1–C2 articulations, C2–C5 displaced minimally, sniffing position: flexing lower neck on the chest and extending the head on the upper neck; 3–4 mm widening disk space at level of injury
Glidescope	Overall spine movement reduced 50% at C2–C5 compared with curved blade
Light wand	57% less motion on all the segments
Laryngeal mask airway	May produce posterior displacement of upper cervical spine; for insertion: C5 and superior segments flexed <2 degrees; during intubation: C4 and superior segments flexed <3 degrees; little movement above C3.

failed or difficult intubation algorithm. Indeed, it may produce posterior displacement of the cervical spine (C2–C6) and possible rupture of the posterior longitudinal ligament. Cricothyrotomy or tracheotomy may be considered if attempts at placing an endotracheal tube by other means are unsuccessful. Placement of a reinforced endotracheal tube could be considered, as it reduces risks of kinking during positioning.

Once tracheal intubation is achieved in a conscious patient, positioning for surgery requires that continuous cervical spine stability be maintained. Often, the patient is positioned awake, so that any neurologic deterioration can be identified immediately.

Systemic hypotension is common secondary to either hemorrhage due to associated injuries or neurogenic shock as a result of autonomic instability. The AANS published recommendations for the hemodynamic goals for a SCI patient. Hypotension (systolic blood pressure <90 mm Hg) should be avoided if possible, and maintenance of mean arterial blood pressure at 85 to 90 mm Hg for the first 7 days following acute SCI to improve spinal cord perfusion is recommended. Initially crystalloid is given intravenously in response to mean arterial pressure (MAP) below 85 mm Hg. Colloid is administered if the hematocrit is low (blood) or as a volume expander (albumin). If the patient's volume status is optimal but the MAP remains below threshold, the AANS recommends the use of pressors, typically (although not exclusively) a βa-agonist (Dopamine) before the addition of an α-agonist (Neosynephrine), to elevate the MAP.

Respiratory insufficiency and pulmonary dysfunction are common after traumatic cervical spine injury. Severely injured patients may demonstrate marked reductions in vital capacity and are more prone to hypoxemia, which can worsen cord ischemia. Hence, careful monitoring with frequent arterial blood gas analysis is essential, and good clinical judgment is required regarding extubation at the end of surgery.

In addition to securing the airway and correct patient positioning, choice of anesthetic agents is paramount. Beyond the first 24 hours after injury, succinylcholine may cause hyperkalemia. In denervated muscle, motor end plates proliferate, and succinylcholine produces an exaggerated depolarizing response with a large release of potassium. This acute increase in potassium may lead to arrhythmia, cardiac arrest, and death.

Anesthetic drugs are chosen based on preserved spinal cord perfusion and autoregulation and neuroprotective effects. If somatosensory evoked potential monitoring is done intraoperatively, anesthetic drugs may affect the latency or amplitude of evoked potentials. Hypotension and hypothermia may also affect somatosensory evoked potential monitoring. A drug regimen based on intravenous anesthetic, opiates, and nondepolarizing muscle relaxants, with minimal use of potent inhalational agents, appears most advantageous. If motor evoked potentials (MEPs) are also done, total intravenous anesthetics should be used. Volatile anesthetics have been repeatedly shown to decrease cortical amplitude in a dose-dependent fashion, and nitrous oxide has been shown to reduce the cortical amplitude more than the inhaled anesthetic. Propofol has been shown to preserve cortical waveform amplitude and latency even with escalating doses. In clinically relevant doses, dexmedetomidine as an adjunct to total intravenous anesthesia does not seem to alter evoked potentials (EPs) and therefore can be safely used.

Fluid management should balance the need to maintain intravascular volume to ensure adequate perfusion with the avoidance of interstitial edema. Use of goal-directed fluid management algorithms assists in minimizing positive fluid balance. Avoidance of hypotonic and glucose-containing solutions is important because they may exacerbate cord edema. Worsening neurologic outcomes have been demonstrated with transient spinal cord ischemia and exposure to modest elevations in plasma glucose concentrations.

Postoperative visual loss is rare and infrequent in cervical spine surgeries, but should be discussed with patients in prone position. Risk factors include length of surgery, estimated blood loss, administration of noncolloid fluids, anemia, and prolonged hypotension.

Postoperative Concerns

Extubation relies on the level of the neurologic lesion and the absence of associated injuries to the head and chest. Weaning criteria used for other patients, which include a maximum inspiratory force of –20 cm H_2O, a vital capacity of 1000 mL, and a Pao_2/Fio_2 ratio greater than 250, may not be appropriate for a quadriplegic patient. The decision to extubate the patient at the end of surgery or leave the patient intubated should be a collective decision between the surgeons and the anesthesiologists. It has been theorized that anterior cervical soft-tissue trauma and the dependent position of the prone patient result in upper airway edema and potential respiratory embarrassment. Epstein and colleagues developed a protocol in which patients undergoing anterior and posterior cervical spine surgeries were left intubated overnight and

extubated on the first postoperative day after fiberoptic assessment of the reactive tracheal swelling. Kwon and colleagues suggest that airway edema is the final pathologic pathway that ultimately leads to airway compromise and postoperative respiratory embarrassment. They also indicated the use of overnight intubation to prevent any untoward respiratory emergencies. Assessment of readiness for extubation by the cuff leak test form a safe and effective postoperative protocol for airway management in these patients. They suggest that long operative times, large volumes of crystalloid and blood administration, and blood loss are related to delayed extubation. The cuff leak test is performed by deflating the endotracheal tube cuff, plugging the end of the tube with a finger, and demonstrating whether an awake patient can move air around the outside of the endotracheal tube. If air moves on inspiration and expiration, the airway is considered patent. If the surgical approach includes the anterior neck, a cuff leak test around the endotracheal tube is helpful to rule out edema or airway compression from a neck hematoma. Both the recurrent laryngeal nerve and branches of the vagus may be damaged during neck dissection (more common on the right side than the left), leading to vocal cord paralysis and stridor on extubation, as well as dysphagia.

PREVENTION

Prevention of neurologic deterioration with an unstable cervical spine requires the following:

- Recognition of cervical spine injury and stabilization of the cervical spine during airway maneuvers and positioning
- Preservation of spinal cord perfusion by optimizing MAP
- Minimization of spinal cord edema by careful attention to fluid management
- Prompt treatment of respiratory compromise to prevent hypoxia and further neurologic deterioration
- Neuroprotection

The quest to improve final neurologic outcome in patients with SCI has led to targeting the secondary mechanisms of injury processes such as ischemia, axonal degeneration, and inflammation. Despite many human trials evaluating the efficacy of potential neuroprotective therapies, none has shown conclusive benefit in preserving or improving spinal cord function. Neuroprotective agents evaluated include methylprednisolone, neuroganglioside GM-1, gacyclidine (aspartate receptor antagonist), tirilazad (free radical scavenger), and naloxone. Efficacy has never been demonstrated, and many of these modalities carry severe side effects. Additionally, there is no evidence for the use of hypothermia.

In summary, the unstable cervical spine requires prompt recognition, evaluation of neurologic deficits, and evaluation and treatment of systemic effects, as well as meticulous airway management to ensure optimal outcome from the cervical spine injury.

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28 Upper Respiratory Tract Infection

Harshad Gurnaney • Arjunan Ganesh

Case Synopsis

A 4-year-old girl with a history of recent upper respiratory tract infections (URIs) and symptoms of clear rhinorrhea and occasional nonproductive cough and a history of low-grade fever 3 days ago presents for a tonsillectomy and adenoidectomy under general anesthesia. She has a history of frequent URIs and has had four episodes in the last 3 months. Laryngospasm occurs during inhalation induction of anesthesia with sevoflurane.

PROBLEM ANALYSIS

Definition

Conflicting information is available regarding the outcome of children with active URIs who undergo anesthesia for elective surgical procedures. Some studies suggest that children with URIs are at increased risk for perioperative respiratory complications. Others indicate that these children have no increased risk (Table 28.1). Increased mortality has not been demonstrated in any controlled study. Study design limitations that clinicians need to understand when drawing conclusions regarding the risk-to-benefit ratio of anesthetizing these children include retrospective study data acquisition for these case-control studies, absence of well-defined criteria for URI between studies, heterogeneous group of children with regard to age, type of surgery, anesthetic technique included in the cohort, nonuniform definition and reporting of adverse patient occurrences between studies, and selection bias based on the cancellation practice of each anesthesiologist. Retrospective data indicate that children with a recent URI (during the previous 2 to 6 weeks) have an increased risk of pulmonary complications compared with either those without or with an active URI. The clinical importance of these potential complications will further influence the decision to cancel or proceed. Does an increased incidence of laryngospasm, for example, lead to increased morbidity, or can this complication be identified and treated without harm by anesthesiologists? A recent prospective study suggested that although children with acute and recent URIs have a greater risk for respiratory complications, most of those children might undergo elective procedures without significant increase in adverse anesthetic outcomes. The study was, however, nonrandomized, and the decision to proceed was left to the discretion of the attending anesthesiologist taking care of the patient. The common reasons for cancellation were severe URI, presence of lower respiratory tract infection, and bacterial infection. A prospective cohort study found that among pediatric patients receiving a general anesthesia with an laryngeal mask airway for an elective surgical procedure, presence of a recent URI was associated with increased odds of developing a perioperative respiratory complication (odds ratio: 1.8; confidence interval: 1.3–2.6).

Recognition

At least two of the following signs and symptoms must exist for a child to have a URI: (1) sore or scratchy throat, (2) sneezing, (3) rhinorrhea, (4) congestion, (5) malaise, (6) nonproductive cough, (7) fever less than 38.5° C, and (8) laryngitis. Combination of items 1 and 5, 2 and 3, 3 and 6, and 4 and 6 requires the presence of at least one additional symptom to meet the criteria for a URI. Children with higher fever and constitutional symptoms and/or signs of lower respiratory tract involvement do not have a simple URI in the sense that their ailment extends beyond localized involvement of the upper respiratory tract.

Risk Assessment

Children suffer five to eight URIs per year (higher incidence in children in day care and whose parents smoke). Out of all pediatric surgical candidates, 6% present for anesthesia and surgery with an active URI. Pulmonary changes may last 4 to 7 weeks after resolution of symptoms. Phase of URI (onset, active, resolution, etc.) may influence risk. In addition, the type of surgery, age of the child, anesthetic plan (intubation), and coexisting medical conditions should be considered in assessing risk.

Implications

Potential respiratory complications secondary to either secretions and/or irritable airway are laryngospasm (other risk factors for laryngospasm are young age, airway surgery, inexperienced anesthetist); bronchospasm (intubated patients only); postextubation stridor; and perioperative arterial oxygen desaturation.

The cost associated with these complications includes prolonged day-surgery stay, unexpected admission of an outpatient, unexpected intensive care unit admission, and potential for medicolegal issues secondary to these complications. The cost associated with cancellation include additional preoperative appointment and repeated testing (if needed), lost revenue from inefficient utilization of operating room due to short-notice cancellation, and inconvenience to patient and family with potential for lost income to family.

TABLE 28.1 Incidence of Respiratory Complications in Children With URIs Undergoing General Anesthesia

	FREQUENCY (%) (URI STATUS)					
Outcome Measure	**Active**	**Recent**	**None**	***N***	**Intubated**	**Study Design**
Airway obstruction*	1.6	5.3	1.6	3585	Most	R
Laryngospasm	1.3	2.4	1.2	489	None	P
Bronchospasm	13.3		0.6	402	Half	P
Croup	3.8		0.7	22,159	Some	P
Hypoxemia	32	25	10	130	None	P
Hypoxemia	40		16	402	Half	P
Hypoxemia	20		0	50	Most	P

*Includes laryngospasm and bronchospasm.
P, Prospective; *R*, retrospective; *URI*, upper respiratory infection.

MANAGEMENT

Be aware of potential complications. All patients are not the same, and when making a decision as to whether to proceed, the practitioner should take into consideration the age of the child; the frequency of URIs (both as an individual and compared with age-matched controls); type and urgency of surgery, as well as whether the procedure may alleviate or reduce the frequency of chronic nasal congestion or recurrent ear infections; the child's other medical problems; the anesthesiologist's skill and experience; parental understanding of risks associated with the anesthetic in the setting of a recent/current URI; and other issues (e.g., availability of surgeon, designated or autologous blood that would expire).

If a decision is made to proceed, a detailed documentation should be recorded in the chart regarding the risks having been discussed with the surgeon and the family and that everyone is in agreement about the increased risks and is willing to proceed with the surgery. Then formulate an anesthetic plan that gives consideration to incorporate the following: (1) administration of an anticholinergic agent preoperatively (atropine, ipratropium nebulization); (2) use of bronchodilators for bronchospasm; (3) use of a smaller endotracheal tube, laryngeal mask airway, or anesthesia with a mask; (4) use of a smaller endotracheal tube, laryngeal mask airway, or anesthesia with a mask; and (5) monitoring of arterial blood oxygen saturation (Spo_2) postoperatively and administration of supplemental oxygen when appropriate.

PREVENTION

Many preschool and early school-age children have or are recovering from a URI at any given time. It is impossible to postpone surgery for all children with a URI until 4 to 6 weeks after resolution of symptoms. Such a strategy would result in many children having a narrow or no window for surgical intervention. Sound clinical judgment, discussion with the patient's family and the surgeon, documented informed consent, and experience of the anesthesiologist are important in deciding to proceed with each case.

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29 Abdominal Aortic Aneurysm Repair

Christopher J. O'Connor • Anthony de la Cruz

Case Synopsis

A 74-year-old man with chronic stable angina, hypertension, and a previous myocardial infarction is undergoing an endovascular aneurysm repair (EVAR) of an infrarenal para-anastomotic aortic aneurysm under general anesthesia. Previous dipyridamole thallium testing revealed a large, fixed myocardial defect with no evidence of reversible disease. It has been 4 months since his prior open abdominal aortic aneurysm (AAA) repair in which his postoperative recovery involved a 1-week stay in the intensive care unit (ICU) and treatment for acute kidney injury (AKI). During deployment of the endovascular graft, there is mild hypertension that resolves quickly after balloon deflation. A total of 2 L of Plasmalyte was given during the case. The patient is successfully extubated at the end of the procedure and transported to the ICU.

PROBLEM ANALYSIS

Definition

EVAR is becoming a common approach for the treatment of both primary and reoperative AAAs (Fig. 29.1). The anesthetic considerations for EVARs are quite different than for open AAA repairs. Understanding aspects of each technique will help develop an appropriate anesthetic plan when determining monitoring choices, anesthetic technique, and the anticipated intraoperative and perioperative complications.

Open surgical repair (OSR) of an AAA involves clamping of the infrarenal aorta. The surgical dissection leading up to aortic occlusion, the occlusion of the aorta itself, and the pathophysiologic events following release of the aortic clamp are associated with varying degrees of hemodynamic instability. Hypotension during the extensive surgical exposure is relatively common, although it is usually transient and well tolerated. Myocardial ischemia is sometimes encountered in patients with known or previously undiagnosed coronary artery disease (CAD) and may be accompanied by increased pulmonary capillary wedge pressure, reduced cardiac output, and transesophageal echocardiogram (TEE) evidence of regional wall abnormalities. During aortic occlusion hypertension and left ventricular (LV) dysfunction may occur. Table 29.1 compares the hemodynamic changes associated with aortic occlusion at different levels of the aorta. Hypotension after release of the aortic cross-clamp is a common and expected event.

Recognition

Appropriate monitoring for the planned procedure that is tailored to the patient's comorbidities facilitates recognition of these hemodynamic events. For OSRs direct arterial and central venous pressure monitoring are commonly employed, whereas pulmonary artery catheters and TEE may be considered in patients with severe CAD or LV dysfunction to further assess preload, ventricular function, and indicators of myocardial ischemia. Hypovolemia is diagnosed by a significant decrease in pulmonary capillary wedge pressure, pulmonary artery end-diastolic pressure, or LV end-diastolic area on TEE. Myocardial ischemia typically manifests as ST-segment changes in conjunction with new regional wall motion abnormalities on TEE.

Anticipation of these intraoperative hemodynamic changes during OSR is facilitated by a clear understanding of the pathophysiologic changes that occur during different stages of the procedure and that relate directly to clamping of the infrarenal aorta. Hypotension during surgical exposure of the aneurysm may be secondary to prostacyclin release from bowel eventration and mesenteric traction, causing profound vasodilation, tachycardia, and facial flushing. Although this so-called *mesenteric traction syndrome* is a transient event, it usually requires treatment with a vasopressor such as phenylephrine. The concomitant use of epidural anesthesia may contribute to hypotension by reducing systemic vascular resistance (SVR) and LV preload.

Mild hypertension (HTN) is relatively common during infrarenal placement of the aortic cross-clamp and is generally attributed to a sudden increase to aortic impedance and an increase in afterload. In contrast, if the aortic cross-clamp is placed on the supraceliac aorta, HTN is more pronounced and may be due to diversion of blood flow from the splanchnic bed to the central circulation leading to an increase in venous return and possibly cardiac output. However, an infraceliac cross-clamp may not create blood volume redistribution even though HTN occurs.

Importantly, however, the absence of HTN or the development of hypotension during the period of aortic cross-clamping should trigger an immediate assessment of LV function, intravascular volume, and surgical blood loss. Hypotension from hypovolemia is often due to unrecognized blood loss and third-space fluid losses before and during aortic cross clamping. Also, if myocardial ischemia develops, LV dysfunction may further diminish cardiac output, thereby compounding the adverse effects of hypovolemia and vasodilation.

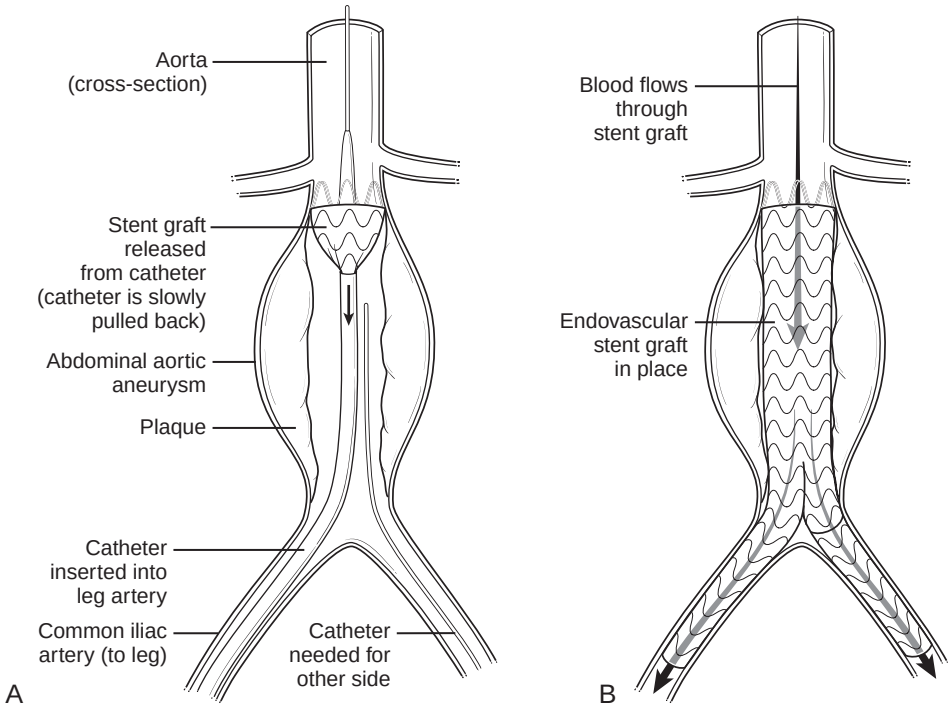

Fig. 29.1 Placement of a stent graft in an aortic aneurysm. A, A catheter is inserted into an artery in the groin (upper thigh). The catheter is threaded to the abdominal aorta, and the stent graft is released from the catheter. **B,** The stent graft allows blood to flow through the aneurysm. (Redrawn from National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Department of Health and Human Services [DHHS]: How is an aneurysm treated? 2011. Available at https://www.nhlbi.nih.gov/health/health-topics/topics/arm/treatment. Accessed January 26, 2016.)

TABLE 29.1 Percentage Change in Cardiovascular Variables on Initiation of Aortic Occlusion during Supraceliac Versus Infrarenal Aortic Aneurysm Surgery

	LEVEL OF AORTIC OCCLUSION		
Variable	**Supraceliac**	**Suprarenal-Infraceliac**	**Infrarenal**
Mean arterial blood pressure	+54	+5*	+2*
Pulmonary capillary wedge pressure	+38	+10*	0*
End-diastolic area	+28	+2*	+9*
End-systolic area	+69	+10*	+11*
Ejection fraction	−38	−10*	−8*
Patients with wall motion abnormalities	+92	+33	0
New myocardial infarction	+8	0	0

*Statistically different ($P < .05$) from group undergoing supraceliac aortic occlusion.
From Roizen MF, Beaupre PN, Alpert RA, et al: Monitoring with two-dimensional trans esophageal echocardiography: comparison of myocardial function in patients undergoing supraceliac, suprarenal-infraceliac, or infrarenal aortic occlusion. *J Vasc Surg* 1:300-305, 1984.

Hypotension after the release of the aortic cross-clamp is a common and expected event. It is attributed to a decrease in SVR and central hypovolemia. Ischemic vasodilation develops in the lower extremities during the period of occlusion, and with reperfusion of these vascular beds, ischemic metabolites and humoral factors are released into the systemic circulation, causing a decrease in SVR. In addition, pooling of blood in these dilated venous and arterial vessels contributes to reduced venous return and central hypovolemia. The degree of hypotension encountered depends on the level and duration of aortic occlusion, speed of clamp removal, intravascular volume status before aortic clamp release, and persistent effects of anesthetics and pharmacologic vasodilators. Severe hypotension can be largely avoided with appropriate fluid loading and replacement of blood losses before unclamping the aorta, as well as gradual release of the aortic clamp. The pathophysiology of hypotension resulting from cross-clamp release is depicted in Fig. 29.2.

In contrast to OSRs, EVARs are rarely associated with significant intraoperative hemodynamic changes. The use of percutaneous vascular access devices instead of open abdominal surgical exposure and only a transient, if any, occlusion of the aortic lumen are significant advantages of EVAR versus OSR. The hemodynamic derangements and their sequelae are infrequently encountered during balloon occlusion of the aorta with EVARs. Therefore it is common for monitoring and intravenous (IV) access choices to be deescalated for EVAR compared with OSRs, such that a single large-bore IV and an intraarterial catheter are all that are required. Further, the typical anesthetic is either a "light" general anesthetic (GA) using small doses of a short-acting opiate such as fentanyl (or an infusion of remifentanil) and a volatile anesthetic. Extubation is routine if a general anesthetic has been employed.

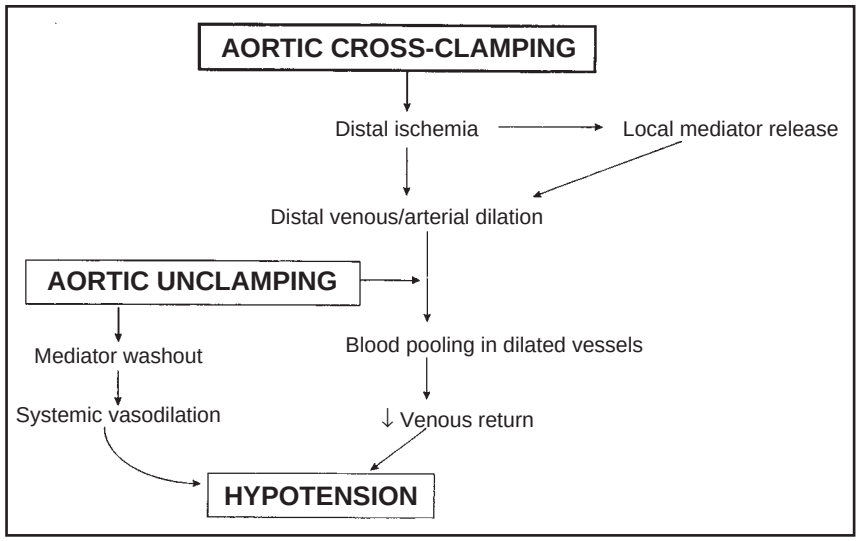

Fig. 29.2 Cause of hypotension after aortic unclamping.

TABLE 29.2 Comparison of Complication Rates: Endovascular Repair of Abdominal Aortic Aneurysms Versus Open Surgical Repair

Complication	Endovascular Aneurysm Repair (EVAR)	Open Surgical Repair	Odds Ratio (EVAR)
30-year mortality rate (%)	1.4	4.2	0.33
4-year mortality rate (%)	37.3	37.8	Not significant
Fatal stroke (%)	.02	.03	Not significant
Cardiac death (%)	.08	.07	Not significant
Pulmonary complications (%)	.03	.08	.36
Renal complications (%)	.02	.01	Not significant

From Paravastu SC, Jayarajasingam R, Cottam R, et al: Endovascular repair of abdominal aortic aneurysm. *Cochrane Database Syst Rev* 1:CD004178, 2014.

The following should be considered when considering local/regional (L/R) with monitored anesthesia care (MAC) versus GA for patients undergoing EVAR:

- L/R anesthesia has been demonstrated to be successful in 75% of patients undergoing EVAR.
- L/R anesthesia for EVAR is associated with less perioperative pulmonary and cardiac complications than GA.
- Regional anesthesia is associated with decreased blood transfusion compared with GA.
- L/R anesthesia is associated with a shorter operative time and decreases in ICU stay, hospital stay, and overall cost compared with GA.
- The surgeon may prefer that ventilation be held during deployment of the aortic stent, which may preclude use of L/R with MAC.

Risk Assessment

Immediate EVAR complications include surgical complications such as incision-site hematomas, limb ischemia, arterial occlusions, femoral pseudoaneurysms, vascular rupture (e.g., iliac arteries), and stent migration. However, overall immediate outcomes of EVAR are more favorable compared with OSR. EVAR is associated with a significantly lower risk of morbidity and mortality compared with OSR. Despite using IV contrast during EVAR, the incidence of AKI remains lower in EVAR versus OSR. Moreover, reduced blood loss, a reduction in blood transfusions, and reduced ICU and hospital stays are common with EVAR versus OSR. However, long-term outcome differences remain controversial, as all-cause mortality and major morbidity after 1 year have only recently been shown to be less with EVAR compared with OSR. In general, 30-day mortality risk is less with EVAR, but there is no difference in overall mortality rate between the two approaches at 4 years (Table 29.2).

Implications

The current trend is to treat AAAs with endovascular interventions. However, not all patients qualify for EVAR due to anatomic reasons. Further studies may reexplore the open surgical technique for some patient populations, and thus the anesthetic management of open surgical repair of AAAs remains relevant, as does the emergent repair of ruptured AAAs.

When hypotension develops, aggressive evaluation of the intravascular volume and degree of blood loss is the first diagnostic maneuver, because hypovolemia is the most likely cause. Evidence of myocardial ischemia should be assessed with ST-segment analysis, TEE, or both. It is treated by providing adequate coronary perfusion pressure, possibly intravenous nitroglycerin, and β-blockers when there is associated tachycardia. Maintenance of β-blockade throughout the perioperative period is essential for patients at risk for postoperative cardiac morbidity due to CAD.

Management of hypotension depends on its relation to aortic occlusion:

- *Hypotension before aortic occlusion:* Consider the effects of epidural anesthesia, mesenteric traction, or preoperative hypovolemia.
- *Hypotension during aortic occlusion:* Consider severe hypovolemia. Aggressive volume resuscitation with blood and crystalloid solutions is indicated before release of the aortic cross-clamp to increase central venous pressure or pulmonary capillary wedge pressure by 10% to 20% above baseline levels.
- *Hypotension after release of the aortic cross-clamp:* Administration of all anesthetic agents and vasodilators should be temporarily discontinued as appropriate. Vasopressors such as norepinephrine, vasopressin, or phenylephrine should be available to counteract the

accompanying vasodilation and preload reduction. Blood must be available in case hemorrhage is severe, and cell-saver systems for intraoperative blood salvage are strongly recommended.

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30 Adenotonsillectomy

Lynne R. Ferrari

Case Synopsis

An obese 3-year-old boy (body mass index 30) with obstructive sleep apnea (apnea hypopnea index 10) presents for tonsillectomy and adenoidectomy. In the postanesthesia care unit, his respiratory rate is 10 breaths per minute with significant respiratory pauses, and his heart rate is 140 beats per minute. A small amount of blood is noted in the oropharynx, and he has bilateral rales on auscultation. Oxygen saturation by pulse oximetry is 86%.

PROBLEM ANALYSIS

Definition

Tonsillectomy, with or without adenoidectomy, is one of the most frequently performed surgical procedures in the United States, with more than 700,000 cases completed per year. Many patients have medical comorbidities that must be optimized preoperatively, and the potential for perioperative complications must be thoroughly understood. The vast majority of children do well after surgery; however, complications can be serious and at times life threatening. The risk of death after tonsillectomy in all patients is 1:10,000. The proper selection of patients and attention to anesthetic risk and technique can reduce this risk and complications related to the following factors:

- Bleeding
- Young age
- Postoperative pulmonary edema
- Postoperative pain
- Obstructive sleep apnea

Recognition

Bleeding

Postoperative hemorrhage occurs in 0.1% to 8.1% of patients. In 75% of cases, bleeding occurs within 6 hours of surgery and is usually the result of surgical technique; in the remaining 25%, it can occur as late as the eighth postoperative day and is related to sloughing of the postoperative eschar. Most bleeding is noted by blood-stained sputum or the vomiting of "coffee grounds" material.

Young Age

In the past, all children were admitted to the hospital postoperatively after tonsillectomy for management of vomiting, dehydration, bleeding, pain, and apnea. The advent of cost containment, along with a trend toward ambulatory surgery, has changed this practice. Recent guidelines suggest that only children age 3 years or younger are routinely admitted to the hospital after tonsillectomy, in addition to those who have severe obstructive sleep apnea syndrome (OSAS) (apnea-hypopnea index of 10 or more obstructive events per hour), oxygen saturation nadir less than 80%, or both.

Pulmonary Edema

Pulmonary edema may present as frothy pink fluid in the endotracheal tube, decreased oxygen saturation, wheezing, dyspnea, or increased respiratory rate after tracheal extubation. The differential diagnosis of postobstruction pulmonary edema includes aspiration of gastric contents, respiratory distress syndrome, congestive heart failure, volume overload, and anaphylaxis. A chest radiograph illustrating diffuse, usually bilateral, interstitial pulmonary infiltrates, combined with an appropriate clinical history, confirms the diagnosis.

Postoperative Pain

Pain is minimal after adenoidectomy but often severe after tonsillectomy. The combined effects of irritant blood in the stomach, interference with the gag reflex caused by edema, and stimulation of receptors in the chemoreceptor trigger zone contribute to postoperative vomiting, which can occur in up to 70% of tonsillectomy patients who do not receive prophylactic antiemetic therapy.

Obstructive Sleep Apnea

Hypertrophied tonsils may obstruct the upper airway during sleep, causing OSAS in approximately 3% to 12% of children. The highest incidence is in children younger than 5 years of age. The definitive diagnosis of OSAS is confirmed by polysomnography, which is a graphic record of respiratory activity during natural sleep; however, it is not feasible to test every child suspected of OSAS and sleep-disordered breathing. For this reason many authors have attempted to design a pediatric preoperative questionnaire to facilitate the diagnosis of OSAS in the same way the STOP-BANG questionnaire has been validated in the adult population. A positive sleep study is an indication for tonsillectomy, especially if related systemic abnormalities are present. The clinical presentation of OSAS is quite varied. Some patients have significant limitations, whereas others are minimally affected (Box 30.1).

Risk Analysis

Bleeding

The tonsillar fossa, nasopharynx, or both are the sites for 67%, 27%, or 6% of postoperative bleeding, respectively.

BOX 30.1 Clinical Presentation of Obstructive Sleep Apnea

Young age (<6 years old)
Snoring during sleep
Failure to thrive
Recurrent respiratory tract infections
Craniofacial dysmorphism
Cardiac arrhythmias
Apnea during sleep
Somnolence while awake
Developmental delay
Obesity
Behavioral difficulty
Cor pulmonale

Young Age

Age younger than 3 years is the most significant risk factor for the development of respiratory compromise after adenotonsillectomy. *Respiratory compromise* is defined as oxygen saturation less than 90%, with an obstructive breathing pattern or acute respiratory distress requiring intervention.

Pulmonary Edema

Factors that increase venous return and preload in either ventricle, or those that reduce the ability of the pulmonary lymphatic system to acutely remove large amounts of fluid, increase the risk of postobstruction pulmonary edema. Postoperative laryngospasm and breathing against a closed glottis cause negative transpulmonary pressures, leading to an increased hydrostatic gradient and subsequent pulmonary edema.

Postoperative Pain and Vomiting

Significant differences in the degree of postoperative pain are related to the surgical technique of tonsil removal. Increased pain medication requirements, otalgia, and irritability have been observed in patients undergoing tonsillectomy with electrocautery and laser excision compared with sharp dissection. Tonsillotomy, or partial tonsillectomy, is being increasingly used as an alternative therapy due to evidence suggesting lower rates of postsurgical hemorrhage and decreased pain compared with tonsillectomy. Vomiting is multifactorial and may be due in part to the stimulation of vagal mediators in the hypopharynx, as well as systemic serotonin release.

Obstructive Sleep Apnea

The degree of tonsillar hypertrophy does not correlate with the severity of upper airway obstruction in patients with OSAS. Children with only slightly enlarged tonsils may have severe OSAS, whereas those with very enlarged tonsils may not have OSAS at all. The risk for OSAS increases with changes in the nasopharyngeal airway and obesity. Children with OSAS have a narrowed aperture of the nasopharyngeal airway, so posterior displacement of the tongue causes hypopharyngeal obstruction. Up to 60% of children affected with OSAS are obese, and it has been suggested that there is a need to develop a specific OSAS screening questionnaire for obese children. Fatty infiltration of the neck, along with relaxation of the pharyngeal muscles, compounds obstruction, because the collapsing force of negative inspiratory pressure exceeds the expanding force of pharyngeal muscular contraction. These children are at risk for respiratory related adverse events, as well as being more sensitive to the respiratory depressant effects of opioids.

Implications

Bleeding

Posttonsillectomy bleeding may be controlled by the application of topical agents to promote coagulation. However, most episodes require surgical exploration and treatment. Large volumes of blood may be swallowed but not appreciated by the patient, parents, or surgeon. Therefore all posttonsillectomy patients with tonsillar hemorrhage are considered to have a full stomach, and appropriate anesthetic precautions must be taken. Because the amount of swallowed blood is usually underappreciated, examination for orthostatic hypotension as a measure of intravascular volume adequacy is required.

Young Age

Children younger than 3 years are at increased risk for inadequate oral intake and subsequent dehydration immediately following surgery. They are also at increased risk for postoperative respiratory compromise.

Pulmonary Edema

Pulmonary edema can occur when airway obstruction is relieved by tonsillectomy. It has been suggested that increased negative inspiratory pressure consequent to airway obstruction increases venous return and pulmonary blood volume (Fig. 30.1). Peak negative inspiratory intrapleural pressure, which is normally 2.5 to 10 cm H_2O, increases to 30 cm H_2O with airway obstruction. A negative transpulmonary pressure gradient of this magnitude can disrupt the integrity of the pulmonary capillary walls. Concurrently, increased pulmonary blood flow and hydrostatic pressure facilitate transudation of fluid into the alveolar space. To counteract this, positive intrapleural and alveolar pressure is generated during exhalation (similar to the expiratory grunt or Valsalva maneuver). This reduces pulmonary venous return and blood volume. Relief of airway obstruction after tonsillectomy reduces airway pressure, but it also increases venous return and pulmonary hydrostatic pressure. This can lead to hyperemia and ultimately pulmonary edema. Bear in mind that the counterbalancing effect of the expiratory grunt to limit pulmonary venous return is lost with relief of airway obstruction.

Postoperative Pain and Vomiting

Uncontrolled pain, swallowed blood, and poor oral intake contribute to nausea and vomiting after tonsillectomy. Dehydration occurs in 1% of patients and can be prevented by intravenous hydration to restore intravascular volume. Hospital admission for rehydration with intravenous fluids is warranted.

Obstructive Sleep Apnea

Central neurologic dysfunction contributes to a worsening of cardiopulmonary function in many children with OSAS. Persistent hypercapnia, hypoxemia, and right ventricular dysfunction contribute to arrhythmias and cor pulmonale. Pulmonary artery pressure increases progressively, perhaps because vascular reactivity is increased with OSAS.

MANAGEMENT

Bleeding

Bleeding is controlled with pharyngeal packs, topical agents, or both. If this approach fails, patients are returned to the operating room for

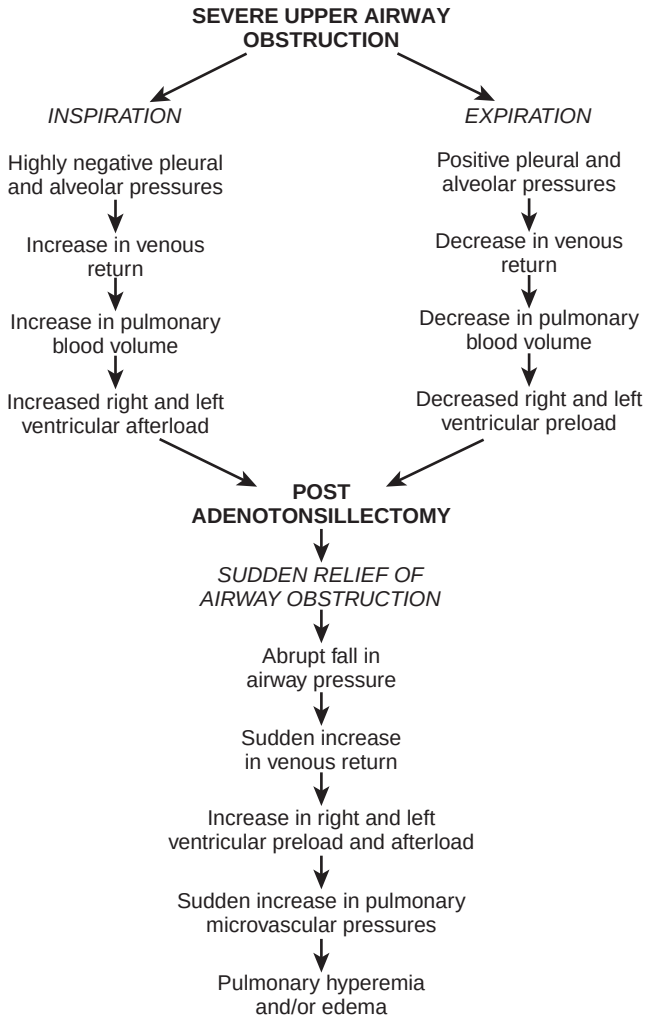

Fig. 30.1 Physiologic changes leading to pulmonary edema after treatment for upper airway obstruction. (Adapted from Galvis AG, Stool SE, Bluestone CD: Pulmonary edema following relief of acute upper airway obstruction. *Ann Otol Rhinol Laryngol* 89[2 Pt 1]:124-128, 1980.)

exploration and surgical hemostasis. Both intravenous and inhalational anesthetic techniques are appropriate, but patients should be responsive at the end of surgery and should be extubated awake. A rapid-sequence induction, accompanied by cricoid pressure and a styletted endotracheal tube, is suggested. Finally, surgical procedures for control of bleeding are usually quite brief, so anesthesia should be planned accordingly.

Young Age

In the absence of evidence of posttonsillectomy complications, otherwise healthy children older than 3 years can be discharged home after 4 hours of observation.

Pulmonary Edema

Treatment is supportive: maintain a patent airway and administer oxygen and diuretics if needed. Tracheal intubation and mechanical ventilation with positive end-expiratory pressure may be required in severe cases. Resolution is usually rapid, sometimes within hours of surgery. Many cases resolve without treatment within 24 hours.

Postoperative Pain

Intraoperative administration of corticosteroids may reduce edema formation and subsequent patient discomfort. Infiltration of the peritonsillar space with a local anesthetic and epinephrine can reduce intraoperative blood loss and provide immediate and protracted postoperative pain relief. One explanation for the latter may be that neural blockade prevents nociceptive impulses from entering the central nervous system during and immediately after surgery, thus suppressing the formation of a sustained hyperexcitable state, which facilitates pain perception. Local anesthetic and epinephrine infiltration is not without danger, however; intravascular (especially intraarterial) injection can be lethal. Small, repeated doses of narcotic are effective for pain relief. Because of the presence of an inherited genetic ability to convert codeine into a life-threatening amount of morphine in some children, the use of oral codeine for treatment of posttonsillectomy pain is contraindicated. Up to 16% of postoperative morbidity and mortality is related to opioid use. Recent studies of nonsteroidal antiinflammatory agents have demonstrated that their effects on platelet function did not result in an increase in postoperative bleeding. Ketorolac is the exception, and medications other than ketorolac may be safely administered for postoperative pain management. Antiemetic agents including ondansetron and steroids, gastric decompression with an orogastric tube (a nasogastric tube is contraindicated after adenoidectomy), and adequate pain control are indicated in the control of posttonsillectomy vomiting.

Obstructive Sleep Apnea

Before extubation after tonsillectomy, patients with OSAS should be breathing spontaneously and able to protect their airway. Sedatives and analgesics should be titrated very carefully because the need for analgesia and the risk of respiratory depression must be balanced. Residual central nervous system dysfunction, hypercarbia, and hypoxemia may persist after tonsillectomy, despite relief of airway obstruction. For this reason, children with OSAS should be hospitalized for apnea monitoring postoperatively (Box 30.2). Most OSAS patients have normal carbon dioxide tension (P_{CO_2}) levels and are extubated after anesthesia; however, patients with severe OSAS (i.e., cor pulmonale, resting P_{CO_2} greater than 50 mm Hg) should remain intubated and be mechanically ventilated until P_{CO_2} has normalized. They are then extubated and observed carefully.

PREVENTION

Bleeding

Prevention of vomiting by routine intraoperative intravenous administration of dexamethasone 0.5 mg/kg will decrease the risk of posttonsillectomy bleeding. Mild bleeding may be treated with topical application of silver nitrate; however, some children will require surgical reexploration to achieve hemostasis. Before anesthetic induction, a tilt test is performed to assess orthostatic changes due to hemorrhage, intravenous access is established, volume replacement is begun, hematocrit is measured, and a blood sample is sent for type and crossmatch. Assorted laryngoscope blades, handles, and endotracheal tubes should be on hand, and at least two suction apparatuses should be available in case the suction tube becomes plugged with blood clots during attempted airway visualization.

BOX 30.2 Criteria for Hospital Admission of Patients After Adenotonsillectomy

Patients must be admitted if they meet any of the following criteria of the American Academy of Otolaryngology's Head and Neck Surgery–Pediatric Otolaryngology Committee:

- Abnormal coagulation values with or without a known bleeding disorder in the patient or family
- Evidence of an obstructive sleep disorder or apnea due to tonsil or adenoid hypertrophy
- Systemic disorders that put the patient at increased postoperative cardiopulmonary, metabolic, or general medical risk
- Presence of craniofacial or other airway abnormalities, including but not limited to the following:
  - Treacher Collins syndrome
  - Crouzon syndrome
  - Goldenhar syndrome
  - Pierre Robin anomaly
  - CHARGE association defects*
  - Achondroplasia
  - Down syndrome
- Isolated airway abnormality
  - Choanal atresia
  - Laryngotracheal stenosis
- Procedure performed for acute peritonsillar abscess
- Extended travel time, weather, or home social conditions that are not consistent with close observation, cooperation, and ability to return to the hospital quickly at the discretion of the attending physician

*CHARGE association defects consist of colobomatous malformation sequence (ranging from isolated iris coloboma to clinical anophthalmos), heart defects (e.g., tetralogy of Fallot, atrial or ventricular septal defects, patent ductus arteriosus), atresia of choanae, retarded growth and development or central nervous system anomalies, genital anomalies or hypogonadism (males), and ear anomalies or deafness.

Young Age

Postoperative morbidity after tonsillectomy is well documented in younger children; therefore the American Academy of Otolaryngology guidelines recommend overnight hospitalization for children younger than 3 years or those meeting other criteria (see Box 30.2).

Pulmonary Edema

There is no reliable method to predict which patients will experience postobstructive pulmonary edema after surgery. Moderate, continuous positive airway pressure during anesthesia allows time for circulatory adaptation to take place. This is similar to the approach to acute upper airway obstruction secondary to epiglottitis or laryngospasm. Postobstructive pulmonary edema is not common in children with long-standing airway obstruction, but unfortunately, it is unavoidable in some children after their tonsils are removed.

Postoperative Pain and Vomiting

Antiemetic agents, oral gastric decompression, adequate pain relief, and quiet emergence from anesthesia can help diminish the frequency of posttonsillectomy vomiting.

Obstructive Sleep Apnea

Digitalization and surgical removal of the tonsils and adenoids can reverse the progressive cardiovascular changes that occur in most patients with OSAS. The occurrence of OSAS in children is usually not preventable. Admission to the intensive care unit is recommended for children under age 3 years or those with an apnea hypopnea index greater than 10 by the American Academy of Otolaryngology Head and Neck Surgery and greater than 24 by the American Academy of Pediatrics. There have been many attempts at designing a preoperative questionnaire to identify those children who are at risk for OSAS postoperatively.

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31 Anesthesia for Electroconvulsive Therapy

Ross MacPherson

Case Synopsis

A 65-year-old man with a major depressive illness is scheduled to commence his first course of electroconvulsive therapy (ECT). Medical assessment before commencing treatment reveals he is otherwise well, apart from being hypertensive (serial readings in the order of 180/95). For management of his psychiatric condition he is currently taking tranylcypromine, lithium, and sodium valproate. Following anesthesia with thiopentone and suxamethonium and a period of hyperventilation, the stimulus is delivered. There was a significant motor seizure, evidenced by tonic-clonic movement of all limbs. The seizure is accompanied by a significant increase in heart rate. This falls rapidly as the seizure comes to an end. In the postanesthesia care unit, the blood pressure remains elevated for 15 minutes, slowly returning to pre-ECT levels. On emergence from anesthesia, the patient is confused and combative. Small doses of midazolam are given to help settle the patient. Eventually he wakes and is orientated to time and place. He has no memory of recent events.

When he presents for his next treatment he complains of severe widespread muscle pain.

PROBLEM ANALYSIS

This case demonstrates the main complications associated with ECT anesthesia: medication management, inadequate relaxation, hemodynamic changes, emergence agitation, and suxamethonium-induced myalgia.

Although anesthesia for electroconvulsive therapy (ECT) is usually a fairly straightforward process, there can still be significant complications associated with the procedure (Tables 31.1 and 31.2), the risk of which can be minimized with careful management. The initial treatment session is referred to as a "titration" session, during which a number of stimuli are usually applied with the aim of establishing the threshold for eliciting a seizure in an individual patient. Such sessions are usually slightly longer than standard treatment session and can be associated with a higher incidence of adverse effects in general. The anesthetist needs to be especially vigilant during the titration session. The patient may have a number of such sessions during a course of treatment as a result of either change in electrode placement or needing to reestablish a level of stimulation during a prolonged series of treatments.

TABLE 31.1 Complications During ECT Treatment

Complication	Management Options
Inadequate response to treatment or seizures of brief duration	Use lowest possible dose of induction agent, adding remifentanil if needed to reduce awareness. Ensure agents with anticonvulsant activity have been ceased.
Inadequate muscle relaxation	Increase dose of suxamethonium. Wait 90 seconds after injection. Use tendon hammer to check tendon reflexes.
Prolonged seizure	Use small dose of induction agent to terminate. Usually responds promptly.
Changes in pulse rate and blood pressure during treatment	Changes are usually transient and interventions have not been shown to confer any particular benefit.
Hypoxia during treatment	Ensure adequate oxygenation with hyperventilation before treatment. Minimize muscle activity (which increases oxygen consumption) during treatment.

TABLE 31.2 Complications Following Treatment

Complication	Management
Prolonged hypertension	Usually settles without treatment; otherwise glyceryl trinitrate, hydralazine, or metoprolol
Post-ECT agitation	Restrain as appropriate; midazolam or propofol as intravenous aliquots
Myalgia	No effective treatment; almost always settles after initial treatment
Nausea	Standard antiemetics

MANAGEMENT

Patient Selection

In previous years numerous publications have detailed extensive lists of conditions that, if present, are contraindications for the performance of ECT. The well-described increases in blood pressure and cerebral blood flow associated with ECT will make such a treatment a higher-risk undertaking in patients with conditions such as cerebral aneurysms and space-occupying brain lesions. However, despite these increased risks, ECT has been successfully undertaken in such patients and in those with other conditions such as abdominal aortic aneurysms or aortic stenosis.

In patients with preexisting cardiac conditions there is no evidence of increased risk, and intervention is not usually necessary. Patients with cardiac pacemakers can safely undergo ECT treatment without any specific intervention.

To help guide patient assessment before ECT a number of recent reviews have been published that provide useful information, although the majority of such advice is based on clinical logic rather than clinical trials data.

Conduct of Anesthesia

Following administration of an appropriate dose of induction agent and muscle relaxant, the patient needs to be adequately ventilated. Hyperventilation is a useful strategy in ECT, as it not only ensures optimal denitrogenation of the lungs but also has been shown to improve seizure quality.

Adequate pre-ECT oxygenation usually ensures that the procedure will proceed without precipitous falls in oxygen saturation, and patients can usually remain apneic for at least 2 minutes. However, morbidly obese patients, or patients who have a particularly vigorous motor seizure, may desaturate during the procedure. This is somewhat problematic, as trying to provide effective ventilation during the seizure can be difficult. If such is the case, there is little option but to wait for the seizure to end and then vigorously ventilate to restore oxygenation.

The cardiovascular charges during ECT have been well described. Immediately following the application of the stimulus, there may be a period of intense bradycardia, or even a brief period of asystole, which is seen more commonly in patients having bifrontal as opposed to bitemporal or unilateral treatment. This is followed by tachycardia and a further period of parasympathetic discharge and bradycardia. If blood pressure is being measured, there will be an accompanying rise in that parameter as well. During recovery, heart rate and blood pressure will again rise. The use of propofol rather than barbiturates ameliorates the cardiovascular responses to some degree. All these cardiac responses follow a usual pattern and are usually transient. Intervention is rarely required, and most authorities recommend against using any form of prophylaxis.

Myalgia associated with suxamethonium use is common and unrelated to either the dosage or the degree of fasciculations. It rarely requires any intervention. The patient can be reassured that it will diminish after the first or second treatment. Despite a range of interventions that have been suggested over the years, there appears to be little that can be done to ameliorate the problem.

Recovery Room Issues

Cardiovascular Challenges

Post-ECT hypertension is common, and systolic blood pressure can rise by 20% or more immediately postprocedure. However, rapid intervention is rarely necessary, as the reading will rapidly fall to pre-ECT levels. If hypertension does persist, rapidly acting agents with a short duration such as glyceryl trinitrate or esmolol are useful first-line drugs. For patients receiving antihypertensive medications, it is important to ascertain that these have been given. If the patient has preexisting hypertension, as outlined above, this usually needs some intervention.

Hypoxic Events

Following treatment, as soon as spontaneous ventilation returns, provided the airway remains patent, return of consciousness usually follows within 5 to 7 minutes. However, upper airway obstruction can still occur. Although routine use of Guedel airways is usually unnecessary, placing the patient in the lateral position after treatment is to be recommended. Recovery staff need to be alert to the onset of upper airway obstruction and hypoxia.

Emergence Agitation

Most patients emerge from ECT treatment uneventfully, occasionally accompanied by varying degrees of postictal confusion that requires little more than gentle reorientation.

Occasionally, however, patients will awake in a very confused state and may be physically violent and a risk to themselves and others. This can constitute a real emergency. Trying to predict which patients are more likely suffer this event is difficult, although some studies have suggested that it is more common in younger patients, those having unilateral ECT, those receiving lithium, and following the first (titration) treatment. There is no substitute for a securely fastened intravenous cannula in such circumstances.

Midazolam is the usual agent of choice in the emergency management of such patients, although some have suggested the use of a small dose of propofol at the conclusion of treatment; however, the incidence is low enough that treatment of the individual patient (should the need arise) with an appropriate dose of midazolam seems more appropriate.

PREVENTION

Most patients undertake ECT with few significant complications; therefore preventive strategies to reduce these are few. In the majority of cases, complications must be managed as they arise. However, there are some areas where preventive action can improve outcomes.

Preexisting Hypertension

Unmanaged or poorly managed hypertension, if identified, should be treated before commencing treatment if possible, because it can affect perioperative hemodynamic changes. Appropriate management before commencement of ECT will be rewarded by a smoother postoperative course.

Medication Management

Medications taken preoperatively should be continued. Importantly, there is no practical reason to cease monoamine oxidase inhibitor agents. Although there may be some theoretical reasons to do so, such an intervention can have an important negative impact on the patient, and at least one trial has shown that patients taking these medications are at no greater risk of adverse effects from anesthesia than the general population.

Some medications do, however, require particular attention. First, there has been increasing use of antiepileptic agents, used as "mood stabilizers" in some patients presenting for ECT. If at all possible, these agents should be discontinued before commencing on a course of therapy, but this may not always be practicable. A common alternative approach, omitting the evening dose of such agents, is unlikely to have any significant benefit, because of the moderate half-life of most of these agents.

The situation is similar with regard to benzodiazepines, especially long half-life agents that have significant anticonvulsant effects. Again, such agents need to be tapered and preferably discontinued before ECT if at all possible. The routine use of flumazenil as an alternative to cessation cannot be recommended as an alternative approach to cessation.

The situation with regard to lithium carbonate is unclear. Some suggest that it can be maintained during treatment, whereas others suggest cessation. Its use is thought to be associated with an increased risk of post-ECT agitation, which can be a significant problem in the recovery room. Although there is a theoretical interaction in that

lithium may prolong the activity of suxamethonium, this does not appear to be a problem in clinical terms.

Muscle Relaxation

Obviously adequate skeletal muscle relaxation is critical in reducing the risk of injury to the patient during ECT. It can be very difficult to achieve anesthesia to reduce the risk of damage to the patient during the induced seizure. Trying to achieve complete paralysis of skeletal muscle is difficult in all patients, especially in the young patient with a high muscle mass. In general, the safest strategy is to start at a high dose of suxamethonium, in the range of 75 to 100 mg, and adjust the dose as necessary. In some cases doses in excess of 100 mg are needed. After administration of the suxamethonium, maximal relaxation is usually achieved in about 90 seconds. Some authors have suggested that waiting 15 seconds after the cessation of fasciculations (if they appear) is also a useful guide.

Because of the ever present risk of damage to dentition, a detailed dental history is mandatory, noting the presence of caps and crowns. Occasionally, if the patient has particular problems, especially loose teeth or crowns, these may need treatment before commencement of ECT.

A mouth guard is always used to reduce the risk of dental damage and should be inserted personally by the anesthetist. A variety of different types are available but whatever form is used, it needs to be placed well back in the oral cavity abutting the molar teeth.

Prevention of Hemodynamic Changes

Apart from management of preexisting hypertension, there is little that can be done to ameliorate the expected hemodynamic changes associated with ECT treatment. Although some authorities have suggested the routine use of either anticholinergic, β-blocking drugs or other antihypertensive agents as a means of reducing increases in blood pressure and heart rate, definitive evidence that such interventions are of any benefit is lacking. Many authorities now favor an approach of treating where necessary in selected patients rather than preemptive intervention in all.

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Anesthetic Complications of Fetal Surgery: EXIT Procedures

32

Jagroop Mavi • Joseph Previte

Case Synopsis

A 28-year-old gravida II, para I woman at 36{2/7} weeks' gestation presents with a fetus prenatally diagnosed with a large cystic left lung mass. Ex utero intrapartum therapy is planned to establish an airway before delivery and possibly transition the fetus onto extracorporeal membrane oxygenation.

PROBLEM ANALYSIS

Definition

Fetal surgery encompasses many different procedures that can be divided into three broad categories: (1) minimally invasive surgery (fetoscopy), (2) midgestation or open fetal surgery, and (3) ex utero intrapartum therapy (EXIT). Fetoscopic, or minimally invasive, procedures (Table 32.1) involve manipulation of the placenta or umbilical cord through an endoscope, and only local or regional anesthesia is required. Open fetal surgical procedures (Table 32.2) require complete uterine relaxation, usually with high concentrations of volatile anesthetics in addition to regional anesthesia for control of postoperative pain. Both fetoscopy and open fetal surgeries are performed in midgestation to allow for fetal growth after the procedure.

In contrast, the EXIT procedure is used for neonates in which prenatal imaging suggests a low probability of survival with conventional treatments at birth. The procedure is usually deferred until as late in gestation as possible, based on both the maternal and fetal condition. The particular intervention performed in an EXIT procedure varies by indication (Table 32.3) and may involve securing an airway, resecting an intrathoracic mass, resecting a neck mass in a controlled setting, special circumstances with thoraco-omphalopagus conjoined twins, or inserting cannulas for extracorporeal membrane oxygenation (ECMO). The role of EXIT to ECMO is controversial, as it is difficult to assess the actual need for ECMO in the first few minutes of ventilation, especially while the fetus is still on placental support. In the case synopsis, the large lung mass puts the fetus at risk for perinatal asphyxia if it proves difficult or impossible to oxygenate and ventilate the lungs after conventional delivery. EXIT allows extended uteroplacental support while the airway is secured by direct laryngoscopy, rigid or fiberoptic bronchoscopy, and possible insertion of an ECMO cannula if required. With emphasis on techniques aimed to maximize uterine relaxation and maintain uteroplacental blood flow, it is now possible to maintain placental support for up to 180 minutes before delivery and separation from placental circulation.

TABLE 32.1 Indications for Minimally Invasive Fetoscopic Surgery

Disease	Procedure
Twin-twin transfusion syndrome	Laser photocoagulation of placental vessels
Twin reversed arterial perfusion	Coagulation of umbilical cord
Amniotic band syndrome	Division of amniotic bands

TABLE 32.2 Indications for Open Midgestation Fetal Surgery

Disease	Procedure
Myelomeningocele	Repair of neural canal defect
Sacrococcygeal teratoma	Resection or debulking of teratoma
Intrathoracic masses	Resection of mass
Congenital diaphragmatic hernia with low lung-to-head ratio	Tracheal occlusion

TABLE 32.3 Indications for Ex Utero Intrapartum Therapy (EXIT)

Disease	Procedure
Severe aortic stenosis or left lung hypoplasia	ECMO cannulation
Congenital diaphragmatic hernia	Removal of tracheal clip or balloon that was placed in utero ECMO cannulation
Congenital high upper airway obstruction syndrome	Tracheostomy
Giant cervical neck mass	Resection of mass
Severe pulmonary hypoplasia from intrathoracic mass (congenital pulmonary airway malformation or CPAM)	Resection of mass ECMO cannulation
Anticipated difficult intubation	Obtain surgical airway

CPAM, congenital pulmonary airway malformation; *ECMO*, extracorporeal membrane oxygenation.

TABLE 32.4 Physiologic Changes of Pregnancy

Organ System	Changes in Pregnancy	Risk during Anesthesia
Neurologic	Decreased MAC	More sensitive to anesthetics
	Engorged epidural plexus	More sensitive to neuraxial anesthetics
Respiratory	Upper airway edema	Potentially difficult mask ventilation and intubation
	Decreased functional residual capacity and increased minute ventilation	Faster desaturation with apnea
Cardiovascular	Inferior vena cava behind gravid uterus	Supine aortocaval compression
	Plasma volume increased more than red cell volume	Relative anemia of pregnancy; little or no change in blood pressure
	Increased cardiac output and reduced peripheral vascular resistance	More sensitive to anesthetics
Gastrointestinal	Reduced lower esophageal sphincter tone and increased intraabdominal pressure	Increased risk of aspiration
Hepatic	Decreased plasma proteins and albumin	Increased risk of pulmonary edema
	Reduced plasma cholinesterase	Prolonged succinylcholine effect

MAC, Minimum alveolar anesthetic concentration.

Recognition

Access to prenatal care is essential for prenatal diagnosis of fetal anomalies, and advances in ultrasound and magnetic resonance imaging have led to better delineation of structural anomalies and their potential impact on the fetus or newborn. Most fetal disease is initially detected by ultrasonography and abnormal findings prompt further testing. Optimal imaging techniques include high-resolution fetal sonography, three-dimensional fetal sonography, ultrafast fetal magnetic resonance imaging, and fetal echocardiography. An in-depth ultrasound examination is used to assess fetal weight and overall health. Estimated fetal weight is important to prepare accurate doses for fetal analgesia, muscle relaxation, and resuscitation drugs. Amniocentesis provides amniotic fluid for analysis, including karyotyping. Structural or functional cardiac defects can be identified using fetal echocardiography. Prenatal imaging of all fetal anomalies is used to visualize areas of involvement, determine the relationship to normal structures, and determine tracheal location. Serial radiographic examinations are also important to monitor the growth of masses, response to treatment medications, and the development of hydrops fetalis. Hydrops fetalis is a life-threatening condition that causes edema in two or more organ systems as a result of immune incompatibility, heart and lung problems, severe fetal anemia, or developmental defects. Care must be taken to assess placental location, as abnormal placentation such as placenta previa or evidence of subchorionic hemorrhage might increase the risk of intraoperative complications.

Although specific criteria for identifying a fetus that would benefit from an EXIT procedure vary by indication, some conditions have similar presentations. For example, cervical neck masses prevent the swallowing of amniotic fluid, resulting in polyhydramnios. Pulmonary amniotic fluid accumulation causes the lungs to appear large and echogenic. Chronic fetal disease from many causes can lead to hydrops fetalis, progressive ascites, pleural and cardiac effusions, and generalized edema that without intervention will ultimately lead to fetal demise.

Risk Assessment

Fetal Risk

The fetus is at risk for adverse events both during and after the EXIT procedure. During surgery, maintenance of normothermia is hampered by exposure of the fetus, whose thin skin is susceptible to evaporative fluid and heat loss. In a preterm fetus, the effects and duration of anesthetic agents are increased owing to immature organ function, incomplete myelination, and delayed elimination.

As a result of decreased fetal heart contractility, the fetus may not be able to compensate for hemodynamic changes. Changes in fetal heart rate, such as tachycardia with fetal incision or bradycardia from inadequate uteroplacental perfusion or umbilical cord compression, may be tolerated for only a brief period. Maternal hypoxia, increased systemic vascular resistance, or the negative inotropic effects of anesthetic agents may further compromise fetal cardiac function. Decreased cardiac preload from impaired venous return during surgical manipulation or blood loss can lead to fetal hypotension, bradycardia, shock, and cardiac arrest. Warm fetal blood products should be readily available to treat poor fetal cardiac function as a result of hypovolemia.

During an EXIT procedure, the fetus remains on the sterile field until division of the umbilical cord, limiting monitoring options to detect physiologic derangements. Hemodynamic data are obtained from a sterile fetal pulse oximeter (normal fetal oxygen saturation being in the range of 60%–70%) and intermittent fetal echocardiography. The use of fetal echocardiography helps identify early problems such as decreased filling, fetal bradycardia, decreased myocardial contractility, ductal constriction, and atrioventricular valve incompetence. Ideally, the surgeon places a fetal intravenous catheter, permitting the administration of inotropic medications, blood, and fluids by the anesthesiologist. If fetal intravenous access is not available, resuscitation is limited to intramuscular injections by the surgeon and maternal interventions by the anesthesiologist. The intramuscular mixture of atropine, fentanyl, and a nondepolarizing muscle relaxant is often administered as soon as the shoulder is exposed by the surgeon. Maintenance of maternal blood pressure and adequate oxygen (O_2) delivery is essential to fetal well-being, as is ensuring complete uterine atony and unobstructed umbilical cord blood flow.

The greatest risk to the fetus is fetal demise or severe disability from the underlying disease process. To be considered for EXIT, the fetus must have a dismal prognosis without intervention. With intervention, in addition to the risks already mentioned, there are risks specific to the disease process and its treatment. An adjacent operating room with a separate team of surgeons, anesthesiologists, and nurses is sometimes necessary to continue care of the neonate after delivery. Finally, depending on the timing of EXIT, the infant's condition may be further complicated by premature birth. From a fetal standpoint, EXIT procedures are normally well tolerated in terms of acid-base status, indicating a well-preserved uteroplacental perfusion despite the prolonged use of high concentrations of volatile agents.

Maternal Risk

The mother is also exposed to significant risk during an EXIT procedure. Like any parturient, she has experienced the physiologic changes of pregnancy and is subject to the associated risks of general anesthesia (Table 32.4). An edematous airway might make intubation difficult, and an increase in gastric reflux and the gravid uterus place the mother at increased risk for aspiration pneumonitis. The thrombophilic state of pregnancy combined with a prolonged surgical procedure places

the mother at risk for venous thromboembolic events, thus pneumatic compression boots are indicated until the patient is fully ambulatory. She is also at risk for amniotic fluid embolism during labor or intraabdominal surgery, and at risk for postoperative wound infection. Additional maternal risks unique to EXIT include the following:

- *Obligate cesarean section for all future deliveries.* EXIT generally requires a larger incision than standard cesarean delivery and the varying location of the hysterotomy location increases the risk of uterine rupture during subsequent labor and vaginal delivery.
- *Risks of invasive monitoring.* Because the welfare of the fetus depends on uteroplacental perfusion, which in turn is dependent on maternal blood pressure, continuous monitoring of maternal blood pressure during EXIT and open midgestation procedures is indicated.
- *Increased risk of blood loss requiring transfusion.* The profound uterine relaxation required to maintain uteroplacental support during EXIT in addition to maternal circulatory instability increases the risk of uterine atony after the third stage of labor. Even if uterine tone is reestablished expeditiously, the likelihood of transfusion of blood products is greater with an EXIT procedure than with routine cesarean delivery. Blood products should be readily available if needed.

Maternal patients recovering from an EXIT procedure have potential postoperative complications similar to a cesarean section, including wound dehiscence, infection, bleeding, and urinary retention.

Implications

Fetal surgery is proposed only after a thorough evaluation by a fetal therapeutics committee and a careful consideration of the risks and benefits for both the mother and the fetus. Because fetal surgery involves substantial risk, it is considered appropriate only when the fetus is "sick" and the mother is "healthy." Once a case is deemed appropriate for consideration of fetal intervention, a team meeting is held involving the mother, selected family members or friends, and the appropriate practitioners. A full explanation of the risks and benefits is presented by the pediatric surgeon, obstetrician, neonatologist, anesthesiologist, and other relevant medical specialists. Once the mother consents to proceed, the complexity of the procedure requires close coordination of personnel and operating room resources.

MANAGEMENT

Whereas cesarean delivery is performed under maternal regional or general anesthesia, with no anesthesia for the fetus, EXIT procedures require general anesthesia for both. The goals of anesthetic management of an EXIT procedure include the following:

- Anesthesia for the mother
- Anesthesia for the fetus
- Complete uterine relaxation to facilitate surgery and exposure
- Absence of contractions
- Preserved placental perfusion and gas exchange with hemodynamic stability
- Maintenance of uteroplacental perfusion until division of the umbilical cord

General endotracheal anesthesia for the mother with volatile anesthetics accomplishes these goals to some extent. Additional drugs are required to supplement each of the listed goals during the course of the procedure.

Preinduction

As for any pregnant patient requiring anesthesia, aspiration precautions include 8 hours of fasting, intravenous metoclopramide, and oral sodium bicitrate before induction. If postoperative maternal epidural analgesia is planned, the catheter is placed preoperatively, and a test dose is administered to confirm placement. Left uterine displacement is mandatory to prevent aortocaval compression and to maximize venous return and preserve an adequate maternal cardiac output.

A decision is made as to whether the procedure is suitable to be performed solely under epidural anesthesia, in which case the epidural is dosed with local anesthetic and a T4–T6 level is confirmed before incision.

Induction

After adequate preoxygenation, a rapid-sequence induction is performed, and the airway is secured with a cuffed endotracheal tube. A smaller-sized endotracheal tube is often used due to pregnancy-related changes to the oropharynx. Emergency airway equipment should always be immediately available. Following intubation, additional intravenous access is obtained, and intraarterial and bladder drainage catheters are inserted. Before surgical incision, muscle relaxation is achieved with nondepolarizing neuromuscular blocking drugs.

Start of Surgery

Ultrasonography is used just before surgical preparation to verify fetal well-being and identify the location of the placenta. Before uterine incision, complete uterine relaxation is induced using at least two minimum alveolar anesthetic concentrations (MAC) of volatile anesthetic, supplemented by incremental doses of nitroglycerin (100–200 μg in divided doses) followed by an infusion of 0.5 to 1 μg/kg/min, if needed. Benefits reported for nitroglycerin use include its high potency, easy titration, and short duration. Uterine tone is often determined by manual palpation by the surgeon. As the volatile anesthetic concentration is increased, nitrous oxide is discontinued, and 100% O_2 is administered to maximize O_2 delivery to the fetus. No comparative study exists to determine which halogenated agent provides the most uterine relaxation; therefore sevoflurane, desflurane, and isoflurane are all commonly used in current practice.

High doses of volatile anesthetics invariably decrease maternal systemic vascular resistance and cardiac output. Thus ephedrine and phenylephrine are titrated to maintain maternal systolic blood pressure within 20% of baseline. Reduced maternal blood pressure adversely affects the fetus, because uteroplacental perfusion is directly related to maternal blood pressure. Phenylephrine has been shown to be slightly more effective in raising maternal blood pressure and therefore supplementing uteroplacental perfusion. Some institutions have found a total intravenous anesthetic technique to be beneficial in terms of preserving hemodynamic stability during periods where uterine relaxation is not required.

Once the surgical site is confirmed, to minimize maternal bleeding a stapled hysterotomy is performed using a hemostatic uterine stapling device. The placenta is localized by ultrasound and a 5 cm margin from placental edge to hysterotomy incision is ensured to reduce the risk of placental abruption. Warm uterine irrigation is performed to prevent fetal hypothermia and to maintain uterine volume. Adequate uteroplacental blood flow is ensured by attention to complete uterine relaxation, maintenance of normal maternal blood pressure and oxygenation, and avoidance of kinking or compression of the umbilical cord.

To monitor the fetus, a sterile pulse oximeter probe is placed on an extremity and covered with foil to deflect ambient light. Supplemental fetal anesthesia is administered as either an intravenous or intramuscular "cocktail" consisting of a nondepolarizing muscle relaxant and a narcotic, with or without atropine. In the case of a cervical neck mass,

the fetal head and torso are delivered into the surgical field for direct laryngoscopy and potential tracheostomy. Intermittently, sterile fetal echocardiography can monitor cardiac function, ductal patency, and volume status.

Post-Exit Care

Once the procedure is complete, umbilical, arterial, and venous catheters can be placed by the Seldinger technique while the umbilical cord is still engorged from uteroplacental blood flow. Before the umbilical cord is divided, adequate chest rise and an appropriate increase in oxygen saturation are confirmed. Fetal O_2 saturation in utero is normally 55% to 65%. Ventilation with 100% O_2 should increase the hemoglobin O_2 saturation to 95% to 100%. When the umbilical cord is divided, the delivery time is recorded, and the baby is taken from the sterile field for evaluation and resuscitation. A brief physical examination, confirmation of bilateral breath sounds, and hemodynamic stability must be ensured soon after delivery. If additional immediate surgery is indicated, the infant is usually taken to an adjacent operating room, where a second team of anesthesiologists, surgeons, and nurses awaits.

After delivery of the placenta, volatile anesthetic concentrations are reduced, and intravenous Oxytocin 20 units/1000 mL of lactated Ringer's solution is administered to restore uterine tone. Provided the mother is hemodynamically stable, analgesia can be provided by dosing the epidural catheter. Intramuscular methylergonovine 0.2 mg and/or intramuscular carboprost tromethamine 250 μg may be required for cases of refractory uterine atony. As the hysterotomy and laparotomy incisions are closed, volume resuscitation is provided to the mother as indicated by vital signs and estimated blood loss. At the conclusion of surgery, muscle relaxants are reversed, and the mother is extubated when fully awake, followed by transport to the recovery area.

PREVENTION

Although it is impossible to prevent all adverse outcomes, proper preparation for the anesthetic can help minimize any associated risks. For EXIT procedures, anesthetic preparation must include consideration of two patients—the mother and the fetus. Continued, concise communication, including a preoperative debriefing among the specialist physicians and the nursing staff during the EXIT planning stages, can identify potential risks and problems and allow for the best possible care for both patients.

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Antepartum Hemorrhage

33

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Case Synopsis

A 30-year-old woman, gravida 3, para 2, presents at 28 weeks' gestation with vaginal bleeding. She has had a previous myomectomy and two previous cesarean deliveries. This is her first episode of bleeding in pregnancy. The estimated blood loss is about 200 mL. She is hemodynamically stable and her hematocrit is 30%. Ultrasonography reveals evidence of placenta accreta.

PROBLEM ANALYSIS

Definition

Antepartum hemorrhage is defined as bleeding from or in the genital tract before delivery. From 3% to 5% of all pregnancies are complicated by antepartum hemorrhage, and it remains a leading cause of maternal and perinatal morbidity and mortality worldwide.

Many reviews suggest that hemorrhage-related deaths may be avoided by improvements in care. Recommendations to improve care include (1) identification of women at high risk for hemorrhage, (2) improved recognition of the hemorrhage, and (3) timely management of the bleeding. Recognition of hemorrhage is challenging, as the physiology of pregnancy allows a pregnant women to lose more blood than a nonpregnant woman before showing signs or symptoms of hypovolemia. Furthermore, clinicians are poor at estimating blood loss. Multidisciplinary protocols have been developed to standardize the approach and management of hemorrhaging parturients.

Miscarriage, ectopic pregnancy, placenta previa, placental abruption, uterine rupture, and vasa previa are the most common causes of significant antepartum hemorrhage. The etiology of antepartum hemorrhage may vary with gestational age. Bleeding during early pregnancy (before 20 weeks' gestation) can result from abnormal embryo implantation (e.g., placenta previa, placenta accreta, placental abruption, or vasa previa), miscarriage, ectopic pregnancy, gestational trophoblastic disease, dysfunctional uterine bleeding, and benign and malignant tumors of the reproductive tract. Among pregnancies complicated by bleeding in the first trimester, less than 50% progress normally beyond 20 weeks' gestation; 10% to 15% are ectopic pregnancies, 0.2% are hydatidiform moles, and more than 30% result in miscarriage. The most common causes of bleeding beyond 20 weeks' gestation are placental abruption and placenta previa.

Placental Abruption

Placental abruption—also referred to as abruptio placentae or placental separation—is defined as the premature separation of a normally situated placenta from its attachment to the placental decidua basalis before the birth of the fetus. Such separation is thought to result from a rupture of placental arteries or veins. Placental abruption occurs in 0.5% to 1.8% of all pregnancies, with approximately 40% of cases occurring after the 37th week of gestation, 40% occurring between the 34th and 37th weeks, and less than 20% occurring before the 32nd week. In 20% to 35% of cases, the bleeding may be concealed (i.e., no vaginal bleeding occurs); therefore attention to signs and symptoms of hypovolemia is important for appropriate management.

Placenta Previa

Placenta previa is implantation of the placenta in the lower uterine segment. It is classified by the degree to which the cervical os is encroached on or covered (Fig. 33.1). As the lower uterine segment elongates during gestation, the amount of placental encroachment on the cervical os (and therefore the risk of bleeding) may lessen. Placenta previa occurs in up to 1% of third-trimester pregnancies.

Placenta Accreta

On occasion, the placenta can adhere to the implantation site with an absent decidua, an abnormality that produces an absence of the physiologic line of cleavage through the decidual layer. The placenta can also invade the myometrium (placenta increta) or can extend through the myometrium and adhere to surrounding structures (placenta percreta).

Vasa Previa

Although the umbilical cord typically is attached to the placenta, in about 1% and 9% of single and twin gestations, respectively, it attaches to the chorioamniotic membranes. Such atypical or velamentous insertion exposes the umbilical vessels to trauma or compression as they traverse between the amnion and chorion to reach the placenta. Vasa previa exists when the velamentous umbilical vessels present ahead of the fetus, placing the fetus at even greater risk with rupture of membranes. Fetal exsanguination and demise often result.

Uterine Rupture

Uterine rupture is defined as a defect in the uterine wall associated with fetal distress or maternal hemorrhage sufficient to require cesarean delivery or postpartum laparotomy. Rupture of the gravid uterus occurs in less than 1% of pregnancies, most often in patients with prior uterine trauma. Uterine scar dehiscence does not require surgical intervention. Although it is more common than true uterine rupture,

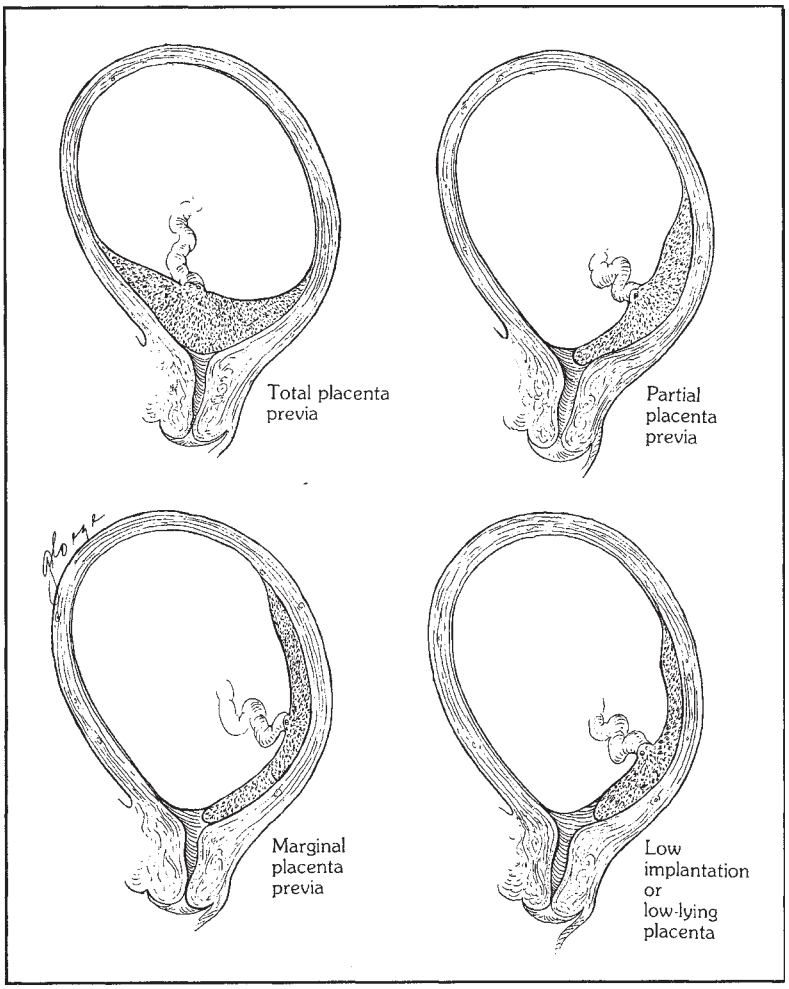

Fig. 33.1 Types of placenta previa. (From Ricci JM: Antepartum hemorrhage. In Hacker NF, Moore JG, editors: *Essentials of obstetrics and gynecology,* 2nd ed. Philadelphia, WB Saunders, 1992, p 156.)

most cases are asymptomatic and are not likely to cause maternal or fetal mortality. However, uterine scar dehiscence can result in significant morbidity, especially if it causes extension of the placenta laterally into major uterine vessels or there is abnormal placentation (placenta accreta, increta, or percreta). Cesarean scar rupture is more likely to occur if labor has been induced.

Miscarriage

Miscarriage (i.e., spontaneous abortion) is defined as the loss of a recognized pregnancy before 20 weeks' gestation. Miscarriages may be classified as threatened, inevitable, complete, incomplete, septic, recurrent, or missed. Between 15% and 20% of all clinically diagnosed pregnancies result in miscarriage, but the actual incidence may be higher depending on the definition of miscarriage used. Typically, the presentation includes a history of vaginal spotting or mild bleeding. When vaginal bleeding during the first 12 weeks of pregnancy is as heavy as normal menstrual blood loss, the pregnancy is rarely successful. Larger amounts of blood loss are observed with intrauterine fetal demise, especially at greater gestational ages.

Ectopic Pregnancy

Approximately 2% of pregnancies do not implant normally in the uterus, and the incidence appears to be increasing. Although ectopic pregnancies classically present as pelvic pain with intraperitoneal bleeding, they can also masquerade as a number of other entities, including appendicitis, ovarian cyst torsion, endometriosis, and pelvic inflammatory disease. Major blood loss with sudden death has been described. The risk of bleeding and the outcome correlate with the implantation site (e.g., isthmic or interstitial portion of the fallopian tube, ovary, cervix, abdomen) and the timing of diagnosis. Ectopic pregnancies may resolve spontaneously, be treated medically, or require laparoscopic or open surgery. Surgery is indicated in the presence of peritoneal signs, hemodynamic instability, or failed conservative management.

Unclassified Bleeding

Unclassified bleeding accounts for almost half of antepartum bleeding (vasa previa is sometimes included in this category). It usually occurs in late pregnancy, and its cause either is unknown or does not become apparent until later. This type of bleeding, though typically mild with spontaneous resolution, is associated with high perinatal mortality rate (3.5%–15.7%). This may be due to placental dysfunction and higher rates of preterm labor in patients with unclassified bleeding.

Recognition

Hemorrhage during pregnancy can be masked by the normal physiologic changes of pregnancy. As early as 6 to 8 weeks' gestation, there is a progressive increase in plasma volume, reaching near-maximal volume (4700–5200 mL) by 32 weeks. This volume, which represents a 45% increase over that in nonpregnant women, is further augmented with multiple gestations and appears to be correlated with fetal weight. Placental chorionic

TABLE 33.1 Assessment of Obstetric Hemorrhage

Shock Severity	Findings	Blood Loss (%)
None	None	15–20
Mild	Tachycardia (<100 bpm), mild hypotension, peripheral vasoconstriction	20–25
Moderate	Tachycardia (100–120 bpm), hypotension (SBP 80–100 mm Hg), restlessness, oliguria	25–35
Severe	Tachycardia (>120 bpm), hypotension (SBP <60 mm Hg), altered consciousness, anuria	>35

bpm, Beats per minute; *SBP,* systolic blood pressure.

TABLE 33.2 Characteristics of Early and Late Antepartum Hemorrhage Diagnoses

Diagnosis	Characteristics
Early Pregnancy (< 20 wk)	
Miscarriage	Vaginal bleeding (± pain) >8 wk after last menstrual period; slight tenderness to uterine examination; no adnexal mass
Ectopic pregnancy	Possibly, no vaginal bleeding; pain <8 wk after last menstrual period; unilateral tenderness; possibly shock and normal-sized uterus
Late Pregnancy (≥ 20 wk)	
Placenta previa	Painless vaginal bleeding (≤ 10% have painful abruption); malpresentation of fetus (35%); difficulty palpating the presenting fetal part
Placental abruption	Painful vaginal bleeding; uterine irritability or tetany; coagulopathy; fetal distress or demise
Uterine rupture	Vaginal bleeding (± pain); hypotension; cessation of labor; fetal distress
Vasa previa	Painless vaginal bleeding; fetal hemoglobin present in shed blood
Unclassified bleeding	Painless vaginal bleeding; mild bleeding (often resolves spontaneously); often >37 wk gestation

somatomammotropin, progesterone, erythropoietin, and prolactin act in concert to increase red cell mass by 250 to 450 mL at term, an increase of 20% to 30% over pregestational values. The disproportionate increase in plasma volume versus red cell mass accounts for relative hemodilution and the maximal decreases in hematocrit seen by the middle of the third trimester. The resulting decrease in blood viscosity is believed to improve intervillous perfusion, reducing the risk for thromboembolic events. It also serves to reduce red cell loss during delivery. The changes in hematocrit and blood volume help increase maternal cardiac output. The heart rate increases from the fifth week of gestation to a maximal increment of 15 to 20 beats per minute by 32 weeks. This is in response to the relative anemia, reduced vagal control, and increased sympathetic tone. Increased stroke volume, which is primarily responsible for the early increase in cardiac output, is related to increased myocardial muscle mass in the first trimester and end-diastolic volume in the second and early third trimesters. Overall, there is a 30% to 50% increase in cardiac output during pregnancy. Half the increase occurs during the first 8 weeks of gestation. The greatest increase is seen immediately postpartum. The resultant anemia, tachycardia, and decreased blood pressure seen in normal pregnancy mimic similar physiologic derangements seen in hemorrhage.

These physiologic alterations of pregnancy allow the pregnant patient to tolerate 1000 to 1500 mL of blood loss without major hemodynamic changes. However, because nearly 20% of cardiac output (600–700 mL of blood) flows through the placental intervillous spaces each minute, obstetric hemorrhage can rapidly result in severe signs of shock (Table 33.1). Also, owing to the potential for severe

TABLE 33.3 Risk Factors Associated With Antepartum Hemorrhage

Cause	Risk Factor
Early Pregnancy (<20 wk)	
Miscarriage	Previous miscarriage; increased maternal age; genetic aberrations; uterine abnormalities; endocrine abnormalities; infection; thrombophilic disorders; immune response abnormalities; tobacco, alcohol, drugs
Ectopic pregnancy	Endometriosis; infertility; infection; past tubal sterilization or reconstruction; intrauterine contraceptive device
Late Pregnancy (≥ 20 wk)	
Placenta previa	Increased parity or maternal age; prior placenta previa or cesarean delivery
Placental abruption	Trauma; ruptured membranes; cocaine, methadone, tobacco use; preeclampsia; fibroid uterus
Uterine rupture	Previous uterine surgery; trauma; history of intrauterine manipulations, including placental extraction, curettage, version, forceps use; grand multiparity; uterine anomaly; placenta percreta; tumor; fetal issues (e.g., macrosomia, malposition, anomaly); induced or augmented labor
Vasa previa	Multiple gestation; low-lying placenta; pregnancy after in vitro fertilization; velamentous umbilical cord insertion; bilobed and succenturiate placentas

blood loss with antepartum bleeding, the characteristics of the common causes of such bleeding should be reviewed to assist in early diagnosis and treatment (Table 33.2).

Risk Assessment

The risk for hemorrhage is affected by many factors, including the presence of any obstetric pathology, medical conditions, or fetal anomalies (Table 33.3). Early identification of risk factors for hemorrhage is important for mobilization of resources. Pretransfusion blood testing (i.e., sending a specimen to the blood bank, type and screen, type and crossmatch) should be performed based on the amount of blood lost, continuing bleeding, and the need for blood transfusion. Institutional protocols should also be activated for hemorrhaging patients, or if a patient has the potential for massive hemorrhage.

Implications

In addition to the risk of postpartum hemorrhage, antepartum hemorrhage may have important sequelae. These include coagulopathy, acute renal failure, pituitary necrosis, shock, and both maternal and fetal mortality. Perinatal morbidity and mortality are primarily the result of poor placental perfusion or preterm delivery.

Coagulopathy, which is initially dilutional from ongoing loss of blood components and rapid volume replacement, may be accompanied by disseminated intravascular coagulation (DIC). Although DIC is an ongoing concern with all cases of antepartum hemorrhage, it most commonly occurs with placental abruption (up to 20% of cases). Laboratory findings supporting the diagnosis of DIC are prolonged prothrombin time and partial thromboplastin time, hypofibrinogenemia, thrombocytopenia, and elevated fibrin degradation products. Although treatment for DIC is controversial, restoration of clotting factors, especially fibrinogen, is required. For a 70-kg adult, 4 g of fibrinogen is required to increase fibrinogen levels by 100 mg/dL. Fibrinogen is found in a 3- to 10-fold greater concentration in cryoprecipitate than in fresh frozen plasma. Fibrinogen levels in pregnancy are elevated to 400

mg/dL or greater. A fibrinogen level less than 200 mg/dL in the setting of continued significant bleeding is an indication for transfusion.

Acute renal failure, with or without associated DIC, occurs in about 10% of patients with severe antepartum hemorrhage. Acute renal failure is related to hypotension, renal ischemia, fibrin deposition, microvascular clotting, and myoglobinuria. It is most common with placental abruption and may be prevented by aggressive blood transfusion and volume resuscitation.

Ischemic pituitary necrosis (Sheehan syndrome) may accompany severe hemorrhage or even delivery without significant blood loss. Enlargement of the pituitary gland, small sella size, DIC, or autoimmunity may also contribute to Sheehan syndrome. Most commonly it presents as mild pituitary dysfunction, such as the failure to lactate or to resume menses. Acute hyponatremia and hypoglycemia may also accompany Sheehan syndrome.

MANAGEMENT

Hemodynamic Management

Although less than 1% of parturients require transfusion and are healthy and can tolerate a relative anemia while remaining asymptomatic, providers need to be aware that massive hemorrhage can happen quickly and need to be prepared for resuscitation. Underestimation of blood loss and inadequate volume resuscitation are common in patients with antepartum hemorrhage and likely contribute to associated maternal mortality. In one report, substandard care was considered a contributing factor in 79% of maternal deaths associated with antepartum hemorrhage.

Most institutions have protocols in place for management of obstetric hemorrhage. The National Partnership for Maternal Safety recently published a consensus bundle on obstetric hemorrhage emphasizing the importance of response with a stage-based obstetric hemorrhage emergency management plan with checklists on every obstetric unit. Consideration should be given to activation of resources, including blood bank, and other services (e.g., interventional radiology) as appropriate. Neonatology should be consulted based on the risk of delivery and the gestational age of the fetus.

Volume replacement is important for maintenance of tissue perfusion and oxygenation. Colloids and blood products should be administered early, if indicated, along with a request for assistance, placement of a second large intravenous line, and use of pressurized transfusion equipment. Hemodynamic monitoring with invasive blood pressure monitoring or transthoracic echocardiography may assist in assessing volume status and the need for inotropes or vasopressors. Central venous catheters or transesophageal echocardiography may be necessary in more extreme cases of hemorrhage.

There have been many studies looking at optimal transfusion strategies; however, to date, no randomized controlled trial has been performed on hemorrhaging obstetric patients. The American Association of Blood Banks recommends allowing symptomatology rather than hemoglobin levels dictate the need for blood component transfusion. There is now interest in the use of adjuvants, in addition to component therapy, to aid in the mediation of obstetric hemorrhage, including erythropoietin to boost red cell production, autologous blood donation, intraoperative salvage, acute normovolemic hemodilution, and antifibrinolytic therapy. Further study is needed to determine the utility of such therapies.

Anesthetic Management

Hemorrhaging parturients should be prepared for surgery simultaneously while optimizing hemodynamic status. Full replacement of blood loss before surgery is unrealistic, because the bleeding will continue until the cause is removed. Although regional anesthesia may be considered, other, more pressing concerns may rule in favor of general endotracheal anesthesia. These include the following:

- Hemodynamically unstable patient
- Ongoing, labor-intensive blood and volume resuscitation
- Possible loss of consciousness with an unprotected airway
- Concern for coagulopathy

Induction of general anesthesia may result in deleterious alterations in the patient's hemodynamics, and patients in shock should have vasopressors readily available before induction. Hypotension commonly occurs with induction and can prove very challenging in a patient who is already demonstrating hemodynamic instability. After left uterine displacement, preoxygenation, and rapid-sequence induction and intubation, exposure to volatile agents should be minimized, as they promote uterine relaxation. Instead, oxygen and nitrous oxide, benzodiazepines, and short-acting narcotics should be titrated, as tolerated. Urine output should be checked often, and the need for additional intravenous lines or invasive monitoring should be assessed frequently. After removal of the fetus and placenta, uterotonic agents (oxytocin, methylergonovine, 15-methyl prostaglandin F2α) should be administered as necessary. However, underlying uterine pathology may not permit restoration of normal uterine tone or cessation of bleeding. If so, a gravid hysterectomy may be required. The hysterectomy may be performed using neuraxial anesthesia if an epidural catheter was in place for delivery, remains functional, and the patient is cooperative. Otherwise, general anesthesia should be used.

PREVENTION

Prevention of complications related to severe antepartum hemorrhage requires a high index of suspicion based on the patient's history and symptoms, evaluation by ultrasonography or magnetic resonance imaging, and an expedited team response. Imaging, especially with color Doppler blood flow enhancement, has greatly improved the diagnosis of placenta previa, placental invasion of the uterine wall (placenta accreta, increta, percreta), and vasa previa and the maternal and fetal outcomes. Even so, there are limits to the diagnostic sensitivity and specificity of these imaging methods, as well as limited access in some places. Therefore a double setup may be required. This involves digital examination of the vaginal fornices in the operating room, with the patient prepared for emergent cesarean delivery. This is now done only for patients with active bleeding, known fetal well-being, and equivocal imaging studies. Alternatively, interventional radiologists can place balloon occlusion catheters in the uterine arteries of very high-risk parturients, permitting rapid control of bleeding should this become necessary.

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34 Anterior Mediastinal Mass

Devon Aganga • Randall P. Flick

Case Synopsis

An 8-year-old, previously healthy girl is admitted with respiratory distress, wheezing, and stridor. Her symptoms have been slowly progressive over 2 weeks and are associated with nocturnal fever and exercise intolerance. The chest radiograph demonstrates a widened mediastinum and a retrosternal mass (Fig. 34.1). A computed tomography (CT) scan of the chest confirms the presence of an anterior mediastinal mass (Fig. 34.2). A biopsy of the mass is scheduled.

PROBLEM ANALYSIS

Introduction

The anesthetic management of children and adults who present for tissue diagnosis or surgical resection of anterior mediastinal masses poses one of the greatest challenges we see in anesthesiology. This is because these patients can suffer life-threatening extrinsic compression of the airway, obstruction of cardiac output, or obstruction of venous return during the induction of anesthesia and at any point during the anesthetic. A seemingly asymptomatic patient may develop one of the aforementioned catastrophic events while under anesthesia. Despite better understanding of the pathophysiology and management of patients with anterior mediastinal masses, perioperative complications ranging from mild airway obstruction to complete cardiopulmonary collapse are estimated to occur in approximately 9% to 20% of anesthetic procedures. What is the safest way to go about anesthetizing these patients? How do we determine who is at greatest risk preoperatively? Are there ways to reduce a patient's risk while optimizing the ability to obtain a tissue diagnosis? These are some of the challenges posed by patients who present with anterior mediastinal masses.

Definition

The mediastinum is defined as that portion of the thorax between the medial aspects of the pleura, above the diaphragm and below the thoracic inlet. It is bound anteriorly by the sternum and posteriorly by the thoracic vertebrae. A line between the fourth thoracic vertebra and the sternal angle subdivides the mediastinal space into inferior and superior compartments. The inferior space is further subdivided by the pericardium into anterior, middle, and posterior regions. The anterior mediastinum lies between the sternum anteriorly and the pericardial sac. The middle mediastinum includes the pericardial sac and its contents, and the posterior mediastinum includes the space between the pericardial sac and the thoracic vertebrae. There are no fascial planes that separate these regions, so masses that originate in one compartment may cross over to another. Mediastinal masses can affect many intrathoracic structures. Most significant are those that compress the heart or major vessels within their respective compartments. Most commonly, they involve the anterior mediastinum and, to a lesser extent, the middle and posterior mediastinum. The location of a mediastinal mass, whether benign or malignant, is characteristic. It provides the clinician with clues to the origin of the mass and determines what physiologic effects it will have on surrounding mediastinal and other thoracic structures. The differential diagnosis for anterior mediastinal masses include the *terrible **T**'s: **T**errible lymphoma, **T**hymoma, **T**eratoma,* and ***T**hyroid tumor.* The most commonly reported of these in children are malignant lymphomas, accounting for as many as 45% of anterior mediastinal masses. In adults, thymomas and lymphomas have been reported to account for more than 50% of anterior mediastinal masses. Other potential pathology of anterior mediastinal masses include metastases, intrathoracic goiter, neuroblastoma, thymic cysts, bronchogenic cysts, and pericardial cysts.

Recognition

Adult patients with anterior mediastinal masses present with a variety of signs and symptoms. Most, however, are either asymptomatic or have minimal to moderate symptoms, including cough, dyspnea on exertion, chest pain, fatigue, and vocal cord paralysis. Severe symptoms in a minority of adults include orthopnea, stridor, cyanosis, jugular vein distention, or superior vena cava syndrome. Children may present for medical evaluation of seemingly benign respiratory ailments such as persistent colds, wheezing, cough, or stridor, but a chest radiograph clues the medical provider to a more sinister etiology. Regardless of the presentation, a tissue biopsy is crucial in establishing an accurate diagnosis to guide definitive treatment. This is especially true in children where there is significant variation in chemotherapeutic regimens depending on the tissue diagnosis.

Risk Assessment

A thorough preoperative evaluation of the patient with an anterior mediastinal mass is essential for safe provision of anesthesia. Typical laboratory evaluations performed include a complete blood count, blood smear, electrolytes, uric acid, lactate dehydrogenase, and flow cytometry, to name a few. Patients may also undergo a variety of diagnostic procedures, including lumbar puncture, bone marrow aspirate, CT, transthoracic echocardiography, and pulmonary function testing. These patients come to the attention of the anesthesiologist for care during surgical procedures that include cervical lymph node biopsy, Chamberlain procedure (mediastinal node biopsy), bone marrow

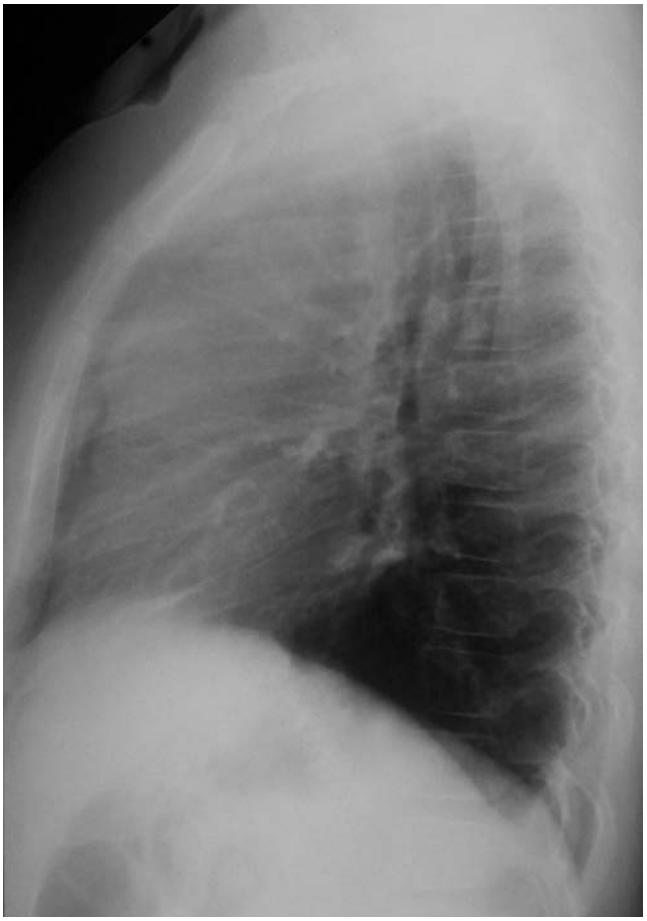

Fig. 34.1 Lateral chest film of an 8-year-old girl later determined to have lymphoma. A large mass is seen in the anterior mediastinum. Treatment was initiated before biopsy.

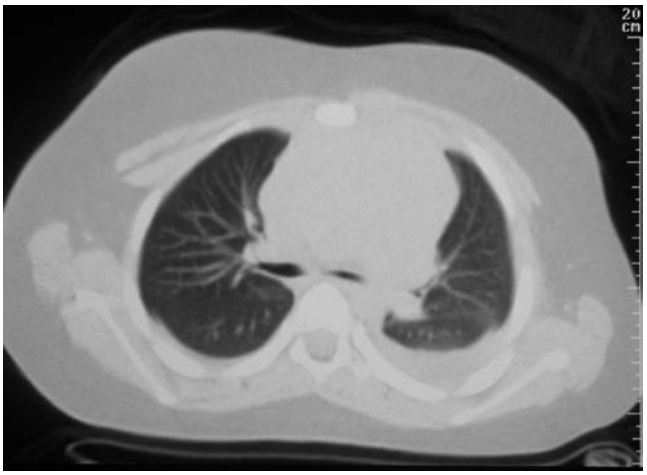

Fig. 34.2 Chest computed tomography scan revealing near-complete compression of the distal trachea and main-stem bronchi by a large anterior mediastinal mass. The mass measured approximately 7 × 7 cm and involved not only the trachea but also the great vessels and pericardium.

biopsy, central line placement for chemotherapy, and (less commonly) tumor resection. Anesthetic considerations for patients presenting with an anterior mediastinal mass will vary depending on the individual anatomy, symptoms, age of the patient, and proposed surgical procedure. Although there are general principles for safe provision of anesthesia, there is a definite need to individualize management for each presenting patient. All patients should have a targeted history and physical examination, a chest x-ray, and CT scan as part of their preoperative evaluation. The presence of orthopnea, cough when positioned supine, stridor, wheezing, facial engorgement, or upper body edema should alert the anesthesiologist to the possibility of increased perioperative risk. It should be noted that the absence of clinical signs does not preclude the potential for life-threatening complications. Of particular importance, the anesthesiologist should determine whether there is a positional component to the symptoms and establish those positions in which the patient is least symptomatic.

A CT scan will show the extent of the mass, presence and degree of airway compression, and invasion and/or compression of other surrounding structures. Magnetic resonance imaging is not routinely obtained and in small children would require the need for sedation or general anesthesia to procure. In patients with concern for cardiovascular involvement of an anterior mediastinal mass, an echocardiogram can be used to evaluate for cardiac function; tumor infiltration of the pericardial and myocardial tissue; compression of the superior vena cava, pulmonary arteries, right atrium, and right ventricle; and presence of pericardial effusion, and to assess for tamponade physiology. Pulmonary function tests (PFTs) in the upright and supine positions have been advocated by some authors in the workup of anterior mediastinal masses in children and adults. Flexible bronchoscopy with airway topicalization is another useful tool to assess for dynamic airway obstruction.

Peak expiratory flow rates have been used to assess for dynamic airway collapse. The shape of the flow-volume loop may give clues to the site of airway obstruction (intrathoracic versus extrathoracic) and indicate whether the obstruction is fixed or variable. It has been reported in literature that a supine peak expiratory flow rate less than 50% of predicted or PFTs with a mixed restrictive and obstructive pattern correlated with an increased rate of preoperative respiratory complications. More recent literature questions the need for PFTs and suggests that PFTs are rarely useful in the preoperative evaluation of patients with anterior mediastinal masses. One such study found that flow-volume loops had a poor correlation to the presence of symptoms or to the degree of airway compression found on a CT scan.

Aggregating the clinical signs and symptoms with the results of diagnostic studies can help identify those patients who are at high risk for preoperative complications. Predictors of cardiopulmonary compromise under general anesthesia include the following:

- The presence of severe preoperative symptoms, especially orthopnea
- Patients with superior vena caval obstruction
- Evidence of pulmonary artery outflow obstruction
- Ventricular dysfunction
- Presence of pericardial effusion/tamponade physiology
- Tracheal compression with greater than 50% reduction in cross-sectional area on CT and/or carinal or bronchial compression
- Supine peak expiratory flow rate less than 50% of predicted
- Combined obstructive and restrictive pattern on pulmonary function testing

Careful consideration should be given to patients with any of these findings as to their suitability to safely undergo general anesthesia. The possibility of obtaining a tissue biopsy under local anesthesia with or without sedation should be strongly entertained. For those patients deemed to be at very high risk, consideration should be given to preoperative corticosteroid therapy and/or radiation therapy. Treatment can cause widespread tumor lysis and alleviate airway obstruction and cardiovascular symptoms, thus reducing the patient's anesthetic risk. The concern with this approach is that steroids and radiation may obscure the ability to later obtain a tissue diagnosis. However, a study

reported up to 95% successful tissue diagnosis rate in patients who were treated with a brief period of corticosteroids up to an absolute maximum of 5 days.

MANAGEMENT

A multidisciplinary approach to the management of patients with anterior mediastinal masses is ideal and may consist of specialists from oncology, anesthesiology, radiation oncology, radiology, and surgical specialties. After review of the patient's clinical data and imaging, as well as assessment of the patient's preoperative risk, determination as to how best to make a tissue diagnosis needs to be made. The anesthetic choices come down to the following:

- General anesthesia (inhalation and/or intravenous)
- Local anesthesia only
- Local anesthesia with provision of sedation

Older and more cooperative children thought to be at high risk of cardiopulmonary compromise can have their masses biopsied under local anesthesia with or without sedation. Fine-needle aspiration has been reported to be sufficient to make an accurate diagnosis in more than 80% of cases. In young children, even if peripheral sites such as cervical lymph nodes and bone marrow are being biopsied, it is hard to provide ideal surgical conditions (immobility) without provision of general anesthesia.

It is key to understand the balance of pressures that act on anterior mediastinal tumors. In essence, in the supine position, the effect of gravity pulling down on the mediastinal mass is counterbalanced by the effect of negative intrathoracic pressure generated from the recoil of the rib cage and the lungs. The negative intrathoracic pressure is the sum of both anatomic (intercostal and other muscle tone) and physiologic (respiratory) forces. In the supine position, the diaphragm is in a more cephalad position, intrathoracic pressure is less negative, and the effect of gravity causes the mass to exert more pressure on structures behind it, namely the airway, the right side of the heart, and the major vessels. Therefore any maneuvers that make the intrathoracic pressure less negative can further exacerbate the physiologic effects of an anterior mediastinal mass. Such maneuvers include the administration of general anesthesia and cessation of spontaneous ventilation. Both anesthetic agents and neuromuscular blocking drugs lead to a reduction in muscle tone, which will shift the balance of forces on the mediastinal mass in the favor of gravity.

During general anesthesia, maintaining spontaneous ventilation throughout the procedure or until the airway is definitively secured is the safest approach. This can be achieved by securing the airway using airway topicalization with local anesthesia and fiberoptic intubation, or with either inhalation induction or careful titration of intravenous anesthetic infusions. There are several case reports of the use of varying combinations of ketamine, propofol, remifentanil, and dexmedetomidine infusions for this purpose. Use of general anesthesia with mask induction and maintenance of spontaneous ventilation via a mask airway have also been reported in the pediatric anesthesia literature. It is probably safest to establish intravenous access before the induction of anesthesia. Premedication is best avoided in children who are clinically symptomatic or are high risk based on diagnostic imaging. In patients with superior vena cava syndrome, intravenous access is best established in the lower extremities.

Keeping the head of the bed elevated will reduce the cephalad displacement of the diaphragm. The patient can be placed in the sitting or lateral decubitus position to help maintain airway potency and reduce cardiovascular compression. The multidisciplinary team before the initiation of anesthesia should make contingency plans to manage any cardiorespiratory collapse during the procedure. The surgical team, anesthesia team, and operating room staff should be well versed with this plan. If airway obstruction were to ensue, the patient's condition may improve with positioning in the prone, reverse Trendelenburg, or lateral decubitus position (or in the position the patient described as being most comfortable preoperatively). Obstruction of the trachea may be alleviated by advancement of an endotracheal tube beyond the point of obstruction. In the case of severe airway obstruction, or if the location of the obstruction is distal, insertion of a rigid bronchoscope may improve the situation. As such, a rigid bronchoscope and experienced personnel should be immediately available during the entire procedure. Life-threatening cardiovascular compression or airway obstruction unresponsive to rigid bronchoscopy may require the surgeon lifting the sternum (placing a finger under the sternal notch and the xiphoid and lifting) or an emergent sternotomy to lift the mass. Some authors have discussed having cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) available in the event of cardiovascular collapse. Support of pediatric and adult patients with mediastinal masses with ECMO has been described and institution of ECMO in awake adults has been reported. Recent studies, however, question the usefulness of the approach of having ECMO or cardiopulmonary bypass on "standby," making the case that in the event of cardiopulmonary collapse, by the time ECMO is successfully instituted, the patient would likely have suffered severe hypoxic ischemic neurologic injury.

Postoperatively, patients thought to be high risk should be monitored in an intensive care unit. Extubation should be performed when the patient is fully awake and in a head-up position. Patients with significant airway obstruction may manifest respiratory difficulties in the postoperative period. This should the treated with repositioning, and if the patient is at risk for imminent respiratory failure, he or she will require reintubation.

PREVENTION

Prevention of acute airway compromise in patients with symptomatic mediastinal masses is best achieved by avoiding general anesthesia or deep sedation. Instead, biopsies should be performed with local anesthesia if possible. Alternatively, radiation or corticosteroid therapy could be administered to reduce the size of the mass before general anesthesia for tissue biopsy. Although debates are ongoing, it appears that the ability to make a molecular diagnosis has greatly improved, even after radiation or a brief course of corticosteroid therapy. For the patient in whom general anesthesia is mandatory, the anesthesiologist must proceed with extreme vigilance and caution.

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35 Anticoagulants and Peripheral Nerve Block

Christina M. Spofford

Case Synopsis

A 70-year-old man with a history of valvular heart disease, peripheral vascular disease, and diabetes mellitus is scheduled to undergo a below-the-knee amputation. The patient has been receiving daily anticoagulation with warfarin since his aortic valve replacement 5 years ago. Five days before surgery, the patient's warfarin was discontinued by his primary care physician, at which time he began therapeutic anticoagulation bridging therapy with low-molecular-weight heparin (LMWH). The patient's last injection of LMWH was 24 hours ago. The orthopedic surgeon intends to reinitiate anticoagulation with LMWH 12 hours after surgery. During the preanesthetic interview, the patient requests peripheral nerve catheters for extended postoperative analgesia.

PROBLEM ANALYSIS

Definition

The use of peripheral nerve blocks (PNBs) for perioperative anesthesia and analgesia has increased dramatically. Reasons for the increased use of PNBs include not only the potential benefits (Box 35.1) but also the avoidance of complications that may accompany general anesthesia and/or central neuraxial techniques. These include concerns about postoperative nausea and vomiting, respiratory depression from parenteral opioids, hemodynamic instability resulting from sympathetic block, and delayed discharge after outpatient surgery.

However, the use of PNBs is associated with its own unique set of concerns and complications. In particular, hemorrhagic complications have been reported with greater frequency as changes in clinical practice occur (e.g., more aggressive perioperative anticoagulation, new regional techniques, and new anticoagulants). Although hemorrhagic complications are quite rare, they can be among the most devastating complications of PNB and have been reported with a variety of PNBs.

Recognition

In general, localized bruising and tenderness are common following PNB, with reported frequencies ranging from 8% to 23%. True hemorrhagic complications appear to be much less common. For example, the reported frequency of hematoma formation after brachial plexus block ranges from 0.2% to 3%. Most hematomas are small, unrecognized, and clinically inconsequential. However, there have been reports of more severe hemorrhagic complications, as well as significant neurologic impairment after hematoma formation. Recognition of bleeding complications relies on astute clinical vigilance throughout the perioperative period; this is especially important in patients receiving perioperative anticoagulation. Significant hypotension, localized pain or tenderness, severe ecchymosis, unexplained anemia, or the development of neurologic deficits may signal underlying hemorrhage or a compressive hematoma. Imaging may be required for confirmation and to determine the location and extent of injury.

BOX 35.1 Potential Benefits of Peripheral Nerve Block

- Superior postoperative analgesia
- Improved rehabilitative efforts (owing to analgesia)
- Decreased perioperative nausea and vomiting
- Faster emergence and recovery
- Earlier mobilization (unilateral blockade)
- Faster outpatient discharge
- Improved blood flow to affected extremity
- Benefits extended with continuous catheter techniques

Risk Assessment

There are no reports on the frequency or severity of hemorrhagic complications with PNB in patients receiving anticoagulants. Reports of direct vascular injury after PNB are limited to case reports. Such complications have occurred in patients with normal hemostasis and in those receiving anticoagulation therapy. Neurologic compromise from bleeding is usually transient and self-limited. Thus in contrast to central neuraxial bleeding, bleeding into a more compliant peripheral nerve site seems unlikely to be associated with irreversible, permanent nerve injury.

The majority of severe hemorrhagic complications after PNB have been associated with either posterior lumbar plexus (i.e., psoas compartment; see Chapter 175) or lumbar sympathetic blocks. In all instances, patients received anticoagulants before, during, or after PNB. Irreversible platelet aggregation inhibitors (e.g., ticlopidine, clopidogrel) are also implicated as contributing to hemorrhagic complications in patients with PNB. Severe hemorrhage requiring transfusion, but not permanent neurologic injury, may be the most serious complication of PNB in anticoagulated patients. Severe hemorrhage and subsequent injury is most likely if the PNB is performed at concealed, noncompliant sites (e.g., psoas compartment). Further, such occult bleeding may go unrecognized for several hours to days.

Implications

Perioperative anticoagulation for the prevention of venous thromboembolism can result in significant morbidity, mortality, and resource allocation. Knowledge of specific clinical risk factors for

thromboembolism (Box 35.2) is the basis for the proper use of perioperative anticoagulation treatment or prophylaxis. These risk factors are present alone or in combination in a high proportion of hospitalized patients. Consequently, many patients who present for elective or emergency surgery are, or will be, receiving medications that alter normal hemostasis. All clinicians should be aware of this, especially when performing regional anesthesia.

BOX 35.2 Clinical Risk Factors for Venous Thromboembolism

- Increased age
- Prolonged immobility (paresis)
- Prior stroke or paralysis
- Previous venous thromboembolism
- Cancer (active or occult) and cancer therapies
- Major surgery
  - Abdominal surgery
  - Pelvic surgery
  - Lower extremity surgery
- Trauma, especially lower extremity injury
- Obesity
- Varicose veins and other flow obstructions (tumor, arterial abnormality)
- Cardiac dysfunction
- Indwelling central venous catheter
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy, postpartum period, estrogen use, and estrogen receptor modulators
- Erythropoiesis-stimulating agents
- Paroxysmal nocturnal hemoglobinuria
- Thrombophilia (acquired or inherited)

Adapted from Geerts WH, Bergqvist D, Pineo GF, et al: Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 133(6 Suppl):381S-453S, 2008.

MANAGEMENT

Patients receiving anticoagulants may be at the greatest risk of hemorrhagic complications after PNB. Therefore astute clinical vigilance is mandatory. If such a complication is suspected, immediate clinical evaluation should occur, including the following:

- Focused review of the patient's perioperative history
  - Past medical history
  - Preoperative coagulation status
  - Preoperative and perioperative medications (e.g., hemostasis-altering drugs, herbals)
  - Surgical course, including intraoperative and postoperative blood loss
  - Immediate postoperative course
- Consideration of the patient's chief complaint
  - Pain (location, duration, nature)
  - Neurologic deficits (sensory or motor, onset, duration, fluctuation)
  - Orthostatic symptoms
  - Fatigue, syncope, lightheadedness, postural hypotension
- Physical examination (including a detailed neurologic assessment)
- Laboratory investigation (complete blood count, coagulation profile, electrolytes)
- Radiographic imaging for definitive diagnosis (computed tomography, magnetic resonance imaging, ultrasonography)

TABLE 35.1 American Society of Regional Anesthesia and Pain Medicine Guidelines for Central Neuraxial Anesthesia in Patients Receiving Thromboprophylaxis

Anticoagulant	Recommendation
Antiplatelet medications	No contraindication with NSAIDs Discontinue ticlopidine for 14 days Discontinue clopidogrel for 7 days Discontinue glycoprotein IIb/IIIa inhibitors 8–48 hr in advance
Unfractionated subcutaneous heparin	No contraindication with <10,000 U daily Consider delaying heparin until after block if technical difficulty is anticipated
Unfractionated intravenous heparin	Heparinize 1 hr after neuraxial technique Remove catheter(s) 2–4 hr after last heparin dose No mandatory delay if traumatic needle placement
Low-molecular-weight heparin (LMWH)	Preoperative dosing: • Needle placement should occur at least 10–12 hr after last LMWH dose (prophylactic dosages) or at least 24 hr after higher doses (treatment dosages) Postoperative twice-daily dosing: • LMWH 24 hr after surgery, regardless of technique • Remove neuraxial catheter(s) 2 hr before first LMWH dose Postoperative once-daily dosing: • LMWH 6–8 hr after surgery • Give second postoperative dose no sooner than 24 hr after first dose • Indwelling catheter(s) can be safely maintained • Remove catheter(s) 10–12 hr after last dose of LMWH and 2 hr before subsequent dosing
Warfarin	Document normal INR before neuraxial technique Remove catheter(s) when INR ≤1.5 (within initiation of therapy)
Fondaparinux	Single injection with atraumatic needle placement Avoid indwelling catheters
Direct thrombin inhibitors	Insufficient data to make a recommendation Avoidance of neuraxial techniques and indwelling catheters
Thrombolytics	Absolute contraindication
Herbal therapy	No evidence of mandatory discontinuation before neuraxial techniques Be mindful of potential drug interactions

INR, International normalized ratio; *NSAID*, nonsteroidal antiinflammatory drug.
Data from Horlocker TT, Wedel DJ, Rowlingson JC, et al: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (third edition). *Reg Anesth Pain Med* 35(1):64-101, 2010.

Surgical decompression with hematoma evacuation may be necessary if (1) the hematoma continues to expand, (2) there is progressive neurologic deterioration, (3) neural dysfunction does not improve despite hematoma resolution, or (4) there is evidence of airway, vascular, or lymphatic obstruction. In select cases, when these criteria are not satisfied, observation and conservative management may be appropriate. However, prompt assessment and appropriate intervention are critical in all patients to prevent hemorrhagic catastrophes and irreversible neurologic impairment.

PREVENTION

Development of a central neuraxial hematoma due to bleeding into a fixed and noncompressible site is clearly the most significant and potentially devastating hemorrhagic complication of regional anesthesia. In an effort to reduce this risk, the American Society of Regional Anesthesia and Pain Medicine developed evidence-based guidelines for central neuraxial anesthesia and analgesia in anticoagulated patients (Table 35.1). Because the risk of such complications in anticoagulated patients undergoing PNB is not clearly defined, one approach might be to apply these guidelines to all patients receiving regional anesthesia, including PNB. However, this might be overly cautious. Instead, it might be more prudent to consider the compressibility of the PNB needle insertion site, the ultrasonographic view of the nerve target(s), the vascular structures at risk, and the overall risk-benefit for the particular patient. This is especially true if the PNB will be performed in a region where an expanding hematoma could compress the airway (e.g., deep cervical plexus, interscalene, or "plumb-bob" supraclavicular block) or might not become apparent for several hours to days in a noncompressible site (e.g., psoas compartment with a lumbar plexus block). Regardless, good communication among all clinicians involved in the perioperative care of any patient receiving drugs that affect hemostasis is critical to provide optimal patient care and to reduce the risk of serious hemorrhagic complications.

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Anticoagulation Initiation and Reversal for Cardiac Surgery

36

Peter Tassani-Prell

Case Synopsis

An 81-year-old woman with dyspnea at rest due to aortic stenosis (valve area 0.4 cm^2, mean gradient 50 mm Hg) presents for aortic valve replacement. Past medical history is significant for a recent pulmonary embolism, for which she received intravenous heparin therapy. At the time of operation, antithrombin III (AT-III) levels are low and the activated partial thromboplastin time is elevated. After heparinization (375 U/kg), the activated clotting time (ACT) increases to 325 seconds. An additional 125 U/kg heparin and 2000 units of AT-III concentrate are given. Thereafter the ACT increases to 866 seconds, and cardiopulmonary bypass (CPB) is commenced without further complications.

PROBLEM ANALYSIS

Definition

Unfractionated heparin is a heterogeneous mixture of sulfated oligosaccharides with molecular weights ranging from 5000 to 50,000 daltons. The anticoagulant activity of heparin is initiated via binding to AT-III, which results in a conformational change that increases its inactivation of thrombin and factors Xa and IXa. Thus in the setting of low AT-III activity, the clinical effect of heparin is reduced.

Recognition, Risk Assessment, and Implications

There is wide individual variability in the clinical anticoagulant response to a single dose of heparin. This necessitates evaluation with on-site or laboratory coagulation testing. Owing to the extreme importance of ensuring sufficient anticoagulation before initiating CPB, on-site testing is preferred. A number of options are available to clinically assess heparin-induced anticoagulation.

The activated partial thromboplastin time is sensitive to low plasma heparin concentrations (0.1–1.0 U/mL). However, with the high doses of heparin required for the initiation of CPB, values exceed this method's detection limit.

The ACT assesses the clinical anticoagulation effect of the large doses of heparin (200–400 U/kg) required for the initiation of CPB. In their historical study from 1975 Bull and colleagues found out that an ACT of 300 seconds was enough in 50 patients. The authors added a 60% safety margin (180 seconds), which gives the number of 480 seconds. Since then, for 40 years ACT values above 480 seconds have been considered safe worldwide for anticoagulation during routine CPB. Even so, ACT values may be misleading because they can be prolonged by factors other than heparin, such as hypothermia, hemodilution, and thrombocytopenia. Further, clinical investigations have shown that ACT values correlate poorly with plasma heparin concentrations in patients during mild hypothermic CPB. However, methods using the heparin concentration as "gold standard" instead of ACT measurements have not been shown to be superior, while being much more complicated and expensive. The problem with false high values using celite activated ACT tubes in the presence of aprotinin is—after withdrawal of the drug (aprotinin) from the market—no longer of importance.

Heparin resistance results in an unanticipated small increase in ACT values after initial and subsequent heparin dosing. Approximately 1 in 2000 patients has a heterozygotic deficiency (40%–70% activity) of AT-III and is thus predisposed to developing deep vein thrombosis and pulmonary embolism. Significant reductions in AT-III levels may also occur secondary to AT-III consumption during heparin therapy. Other causes of heparin resistance include left ventricular clot, use of oral contraceptives, and thrombocytosis. These entities may be due to reduced plasma concentrations of heparin caused by its increased binding to plasma proteins and endothelium.

Heparin may cause thrombocytopenia via immune-mediated and non–immune-mediated mechanisms. There are two types of heparin-induced thrombocytopenia (HIT) that can result from heparin use. Type I is non–immune mediated, and type II is immune mediated. For standardization, the term *non–heparin immune-associated thrombocytopenia* is recommended for type I HIT. This is a benign condition, with no heparin-dependent antibodies present. The term *heparin-induced thrombocytopenia* is recommended for type II HIT, in which heparin-dependent antibodies are detectable and produce thrombocytopenia.

MANAGEMENT

Three different aspects of anticoagulation during cardiac surgery with CPB are discussed: routine management using anticoagulation with heparin and neutralization with protamine, management of AT-III deficiency (as in the case synopsis), and HIT.

For the initiation of CPB, the heparin dose is based on body weight (300–400 U/kg). It is essential to obtain an ACT of at least 480 seconds

TABLE 36.1 Pretest Scoring System for HIT: The Four *T*'s

Four *T*'s	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20[a]	Platelet count fall 30%–50% or platelet nadir 10–19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5–10 or platelet fall ≤1 day (prior heparin exposure within 30 days)[b]	Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts); onset after day 10[c]; or fall ≤1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis[d]; acute systemic reaction post–intravenous unfractionated heparin (UFH) bolus	Progressive or recurrent thrombosis[e]; non-necrotizing (erythematous) skin lesions[d]; suspected thrombosis (not proven)[f]	None
Other causes for thrombocytopenia	None apparent	Possible[g]	Definite[g]

[a]Greifswald, Germany (GW): platelet count fall >50% or nadir 20–100; Hamilton, Canada (but not GW): platelet count fall >50% directly resulting from surgery counts as 1, rather than 2, point.
[b]GW: onset from days 5–14 (rather than days 5–10); platelet fall within 1 day (heparin exposure within 100 days).
[c]GW: onset after day 14.
[d]Skin lesions at heparin injection sites.
[e]Progression refers to objectively documented increase in thrombus size (usually, extension of deep-vein thrombosis by ultrasonography); recurrence refers to newly formed thromboembolus in previously affected region (usually, new perfusion defects in a patient with previous pulmonary embolism).
[f]In GW, "suspected thrombosis (not proven)" was not included as a criterion.
[g]Determination of whether the presence of another apparent cause of thrombocytopenia was "possible" or "definite" was at the discretion of the investigator.
From Lo GK: Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 4(4):759-765, 2006.

before initiating CPB. Determining the ACT before initiating CPB allows one to detect inadequate heparin dosing or AT-III deficiency. It is also recommended that the heparin injection be given via a central venous line after aspirating blood to ensure vascular delivery. Subsequent heparin can be dosed empirically during CPB (e.g., 5000–10,000 U/h, one-third the initial dose every hour). It is, however, strongly recommended to measure the ACT every 30 minutes when on bypass. If the ACT is less than 480 seconds, an additional dose (see earlier discussion) should be given. Hypothermia and hemodilution prolong ACT values independent of heparin concentration. Thus basing subsequent heparin doses on ACT values may lead to inadequate inhibition of thrombin activity and subclinical thrombosis, fibrinolysis, and depletion of coagulation factors and platelets. Maintenance of patient-specific heparin concentrations during CPB may result in more accurate heparin dosing, more complete thrombin inhibition, and reduced postoperative bleeding and blood product use.

With suspected heparin resistance, one must first confirm that the heparin was indeed given intravenously, followed by the administration of additional heparin from another vial or lot to exclude lot-specific reduced heparin activity. If the ACT values still remain below those expected, despite large doses of heparin, AT-III concentrates should be given, with an initial dose of at least 2000 U. Because of the danger of AT-III deficiency (thrombosis during CPB), the routine clinical practice in most centers is to confirm adequate AT-III levels in patients before any operation is performed requiring extracorporeal circulation.

Non–heparin immune-associated thrombocytopenia (type I HIT) implies absent heparin-dependent antibodies. This entity is probably caused by direct nonimmune platelet activation by heparin. Type I HIT is usually associated with larger doses of heparin. In contrast, type II HIT can occur with any heparin dose. Further, type I HIT occurs earlier in the clinical treatment course (usually within 4 days) in 30% of patients receiving intravenous heparin therapy. The induced platelet abnormality is usually mild and reversible, even with continued heparin administration. Type I HIT is self-limited and usually causes no important complications (e.g., thrombosis). Heparin therapy is continued despite low platelet counts. The clinical importance of type I HIT lies in the necessity to differentiate it from the more serious type II HIT.

Type II HIT (or heparin-induced thrombocytopenia with thrombosis [HITT] syndrome) is an immune-mediated reaction to heparin that is often underdiagnosed and may lead to venous and arterial thrombosis. Type II HIT exists as three distinct entities: (1) latent (antibodies without thrombocytopenia), (2) HIT (antibodies with thrombocytopenia), and (3) HITT (antibodies with thrombocytopenia and thrombosis).

Type II HIT is potentially more dangerous than type I HIT because it can be associated with thromboembolic complications (absent in type I). About 0.5% to 3% of patients given heparin develop type II HIT and moderate thrombocytopenia. In some, this leads to venous or arterial thrombosis. Thrombosis frequently leads to disastrous clinical sequelae, including loss of limbs and even death. The basis for this severe adverse drug reaction is production of an immunoglobulin G antibody that reacts with heparin and platelet factor 4 antigenic complexes. The diagnosis of type II HIT is made with the "four *T*'s"—thrombocytopenia, timing of platelet count fall, thrombosis or other sequelae, and other causes for thrombocytopenia (Table 36.1). This score is not only a laboratory diagnosis but uses clinical patient factors. In up to 20% of the patients there are antibodies to immobilized heparin–platelet factor 4 antigenic complexes detectable. This does not alone lead to the diagnosis HIT. The heparin-induced platelet aggregation test (HIPA) assay is the gold standard to make the diagnosis.

For patients with type II HIT who will be exposed to CPB, treatment generally includes either the use of alternative anticoagulants or combined treatment with platelet function inhibitors and heparin. The author recommends the following alternatives:

- *Bivalirudin.* This is a direct thrombin inhibitor and an analog of the peptide fragment hirugen derived from hirudin. Bivalirudin is recommended over other nonheparin anticoagulation drugs, as there are some clinical studies published using bivalirudin.
- *Tirofiban.* A more recent approach in patients with a history of HIT is to selectively block platelet aggregation using monoclonal antibodies directed toward glycoprotein IIb/IIIa (GP IIb/IIIa) or to use a specific GP IIb/IIIa inhibitor (e.g., tirofiban). An 80% block of GP IIb/IIIa receptors and suppressed platelet aggregation (<20%) permit the use of unfractionated heparin and CPB in the usual way. After CPB, as usual, unfractionated heparin is neutralized with protamine.
- *Plasma exchange.* There are some case reports and small series published using plasma exchange before operation using CPB and then regular heparin-protamin management.

The author favors the use of tirofiban and one single dose of heparin during CPB and (of course) regular reversal with protamine. After operation no more heparin should be used, as development of antibodies is likely to occur. In practice we use a bolus of 10 μg/kg

tirofiban about 15 minutes before heparin, followed by an infusion of 0.15 μg/kg/min until 1 hour before the predicted end of CPB.

In patients with a history of HIT but no detectable antibodies, heparin is currently the safest approach to the high-dose anticoagulation required for CPB. However, before and after surgery, alternative anticoagulants should be used.

After approximately 2 to 12 months, most patients with a history of type II HIT no longer have laboratory evidence of heparin-induced platelet aggregation. If so, heparin use is likely acceptable. However, caution is advised with regard to further heparin exposure during the postoperative period (e.g., heparin flushes, cardiac catheterization).

Heparin reversal after CPB is usually accomplished with protamine, a protein derived from salmon sperm. The appropriate dosage is controversial. Most cardiac anesthesiologists use 1.0 to 1.3 mg/100 U of previously administered heparin. Commercial systems for whole blood, circulating heparin assays, may allow exact titration of the required amount of protamine; however, despite their theoretical advantage, a fixed dose based on the amount of heparin used is more conventional. Additional protamine may be given about 30 minutes after heparin reversal. Protamine has a high number of positively charged arginine residues that form stable complexes with negatively charged heparin and are eliminated via the reticuloendothelial system.

Protamine has been associated with significant clinical complications, consisting of three major types of adverse responses:

- Type I is the most common, consisting of hypotension from too rapid administration of protamine. It is likely related to the release of histamine, and hypotension can be associated with a marked decrease in systemic vascular resistance.
- Type II is anaphylaxis and can be mediated by immunoglobulins. It occurs more frequently in patients with a history of fish allergy. Subsequent release of histamine and leukotrienes results in systemic and pulmonary capillary leakage.
- Type III is associated with the formation of heparin-protamine complexes. Pulmonary macrophages activate complement and leukocyte aggregation, causing the release of free radicals and activation of the arachidonic acid pathway, which leads to the formation of thromboxane. This causes intense pulmonary vasoconstriction, pulmonary hypertension, and reduced left atrial pressure. The net result is right heart chamber dilation and heart failure. Fortunately, type III responses are very uncommon.

PREVENTION

The appearance of heparin resistance can delay surgery and disrupt the operating room schedule. Consequently, some clinicians advise preoperative AT-III level screening for all patients having cardiac surgery requiring CPB. Determination of the heparin dose-response curve can also alert clinicians to heparin resistance before CPB. This allows advance planning for subsequent heparin dosing. If possible, surgery is delayed in patients with type II HIT until antibody titers are absent. New drugs, such as bivalirudin, may be useful alternatives to heparin in such patients.

To eliminate protamine reactions, antihistamines can be used. Also, protamine should be given slowly, preferably via a peripheral vein after substantial dilution. Some surgeons inject it into the aortic root to bypass the lungs during its initial distribution. Although heparin-bonded CPB circuitry may allow lower doses of intravenous heparin, this technology remains unproved.

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37 Arteriovenous Malformation: Normal Perfusion Pressure Breakthrough

Jason A. Ellis • Shailendra Joshi

Case Synopsis

A healthy, 41-year-old man presented to his primary care physician with a 3-month history of right-sided temporal-occipital headaches. He was initially treated conservatively with oral analgesics and subsequently an occipital nerve block without significant improvement. Magnetic resonance imaging (MRI) was eventually obtained demonstrating the presence of a 2 × 3 cm arteriovenous malformation (AVM) located in the right temporal lobe (Fig. 37.1). After neurosurgical consultation, a catheter cerebral angiogram was obtained confirming the presence of a Spetzler-Martin Grade III AVM (Table 37.1). The AVM was fed by middle cerebral artery and posterior cerebral artery branches and had drainage by both superficial Sylvian veins and the vein of Labbé to the transverse-sigmoid sinus junction.

Treatment options including radiosurgery, embolization, surgical resection, and conservative management were discussed with the patient. He was counseled that radiosurgery would not diminish the risk of hemorrhage during the 2- to 3-year delay to treatment effect. Furthermore, although the cure rate after radiosurgery is good (70%–80%), it was not guaranteed. He was told that embolization alone could not cure the AVM but would be an excellent adjunct before surgical resection. He was also told that the prognosis for headache resolution was good once the AVM was cured. The patient elected to undergo staged preoperative embolization followed by craniotomy for resection of the AVM.

The patient was electively brought to the neuroendovascular suite where his baseline blood pressure after arterial line placement was 130/70 mm Hg. General endotracheal anesthesia was induced. The femoral artery was cannulated and embolization of the AVM commenced with the use of *N*-butyl cyanoacrylate (NBCA) glue. Near the end of the uneventful procedure, it was noted that significant contrast extravasation was present adjacent to the AVM (see Fig. 37.1). His systolic blood pressure suddenly became elevated to 170 mm Hg. DynaCT rotational angiography confirmed the presence of a large hemorrhage with mass effect adjacent to the AVM. The patient was immediately taken to the operating room where hemicraniectomy as well as intracerebral hemorrhage (ICH) evacuation and AVM resection were performed. Postoperative catheter cerebral angiogram demonstrated no residual arteriovenous shunting.

The patient was taken to the neurologic intensive care unit (ICU) where he was slowly woken up and his systolic blood pressure was maintained between 90 and 120 mm Hg using a nicardipine infusion. He was extubated the following morning and noted to have a mild left-sided hemiparesis and superior quadrantanopsia. The patient was eventually discharged to an acute rehabilitation facility and made a full recovery.

PROBLEM ANALYSIS

Normal perfusion pressure breakthrough (NPPB) theory was originally proposed by Spetzler and coworkers in 1978 to account for postoperative brain edema and hemorrhage in AVM patients. Although the theory was originally applied only to patients after AVM resection, it may also be applied to patients who have had extensive AVM embolization performed during a single session. The sudden obliteration of large arteriovenous shunts during embolization bears similarity to surgical resection in the acute setting. The proposed pathophysiology of NPPB is as follows: High blood flow through the arteriovenous fistula creates a region of chronic cerebral hypotension in the neighboring vascular territories. Chronic cerebral hypotension leads to a state of near-maximal vasodilation and vasoparalysis that impairs the vessels' ability to constrict or even dilate effectively. Excision of the low-resistance AVM shunt restores perfusion in the formerly hypotensive regions of brain. However, owing to the inability of these beds to effectively vasoconstrict, normalization of cerebral perfusion pressure results in cerebral hyperemia ("luxury perfusion") with the consequence of cerebral edema formation and ICH. NPPB may share certain pathophysiologic features with the cerebral hyperperfusion syndrome classically observed after carotid endarterectomy.

Alternative mechanisms for unexplained brain hemorrhage or swelling have been suggested, including the following: (1) unrecognized technical

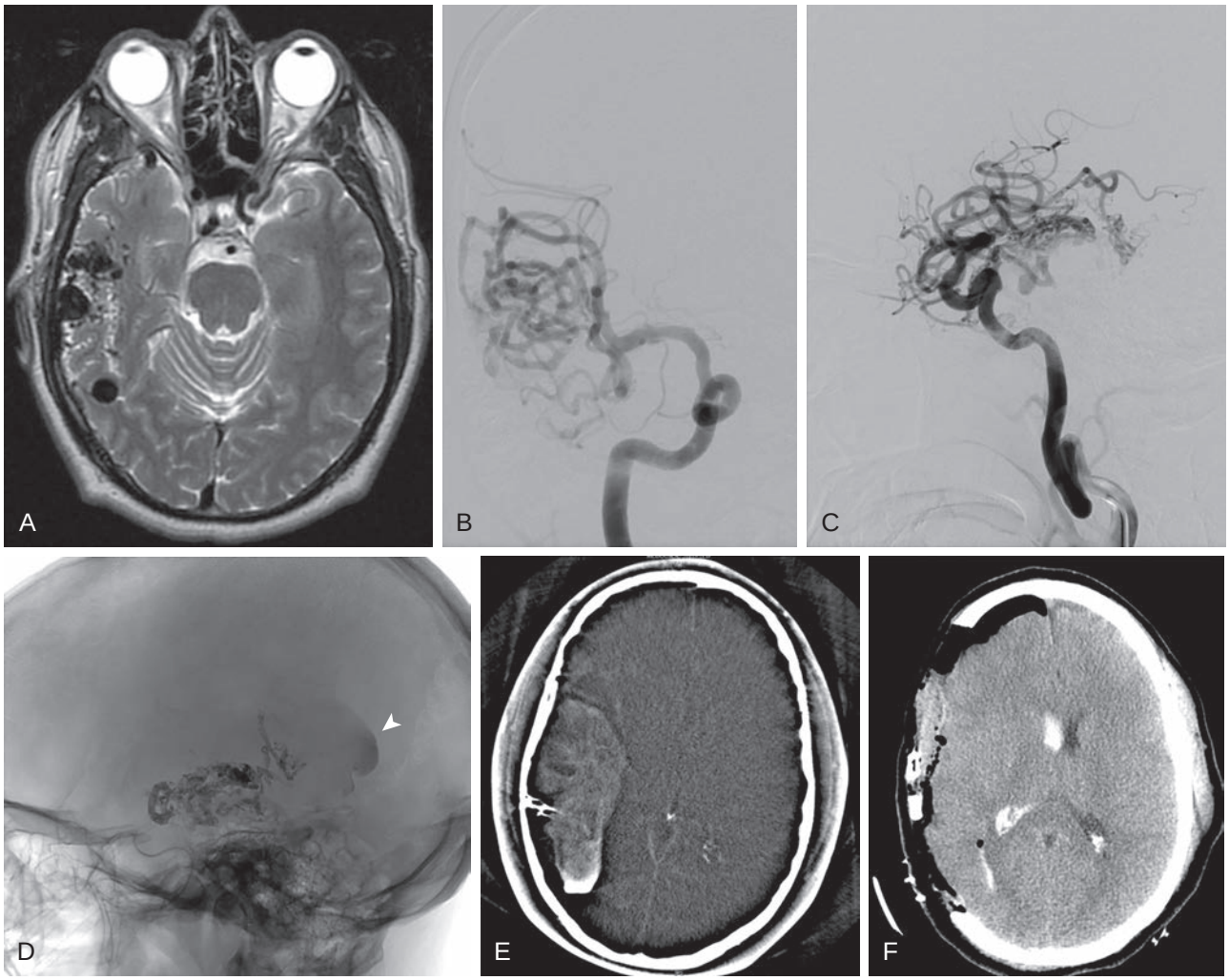

Fig. 37.1 Hemorrhage after AVM embolization. Axial T2 MRI shows prominent flow voids within the right temporal lobe consistent with the presence of an AVM **(A).** Internal carotid arteriogram in anteroposterior **(B)** and lateral **(C)** projections shows the intricate arterial network of the AVM nidus fed by branches of the middle cerebral artery. Intranidal NBCA glue is clearly visualized on postembolization lateral skull x-ray **(D).** Extravasated blood is also seen posterior to the glue cast in the temporal-occipital region *(arrowhead).* DynaCT rotational fluoroscopy indicates the presence of a large hemorrhage, which may be due to NPPB phenomena immediately after embolization **(E).** Postoperative noncontrast head CT shows excellent decompression after hemicraniectomy, ICH evacuation, and AVM resection **(F).**

TABLE 37.1 Spetzler-Martin Grading Scale

	Points
Size	
Less than 3 cm	1
3–6 cm	2
Greater than 6 cm	3
Location	
Not eloquent	0
Eloquent	1
Venous Drainage	
Superficial	0
Deep	1

complications at the time of surgery; (2) vascular disturbances due to abnormal autonomic activity resulting in the release of vasoactive peptides from innervated cerebral vessels; (3) hemorrhage from a structurally deficient capillary vessel bed adjacent to the AVM, perhaps secondary to overexpression of angiogenic factors such as vascular endothelial growth factor or angiopoietin-2; and (4) venous occlusion after resection of the AVM. Indeed, venous occlusion is central to the most commonly cited alternative to NPPB theory, namely occlusive hyperemia theory as proposed by Al-Rodhan and colleagues in 1993 (Table 37.2).

MANAGEMENT

NPPB is a diagnosis of exclusion rendered after more common causes of cerebral edema and hemorrhage have been ruled out. The possibility of residual AVM should be entertained and excluded with catheter angiography if not previously done immediately after resection as we recommend. Causes of postoperative cerebral edema and/or hemorrhage, including hypoxia, hyponatremia, systemic hypertension, coagulopathy, qualitative platelet defect, inadequate surgical hemostasis, and mechanical manipulation, should be considered and corrected where possible. Treatment of cerebral edema/hemorrhage requires careful management of fluid and electrolyte imbalances, judicious use of osmotic and loop diuretics, and attention to cerebral perfusion pressure. Severe symptomatic swelling

may necessitate mechanical ventilation, hypothermia, and/or barbiturate coma. Intracranial pressure monitoring and electroencephalography (EEG) are useful adjuncts if deep sedation is instituted.

If surgical decompression is not required, aggressive supportive care in a neurologic ICU setting is important for achieving satisfactory clinical results (Fig. 37.2). We have had good success using a strategy that aims for normotension, normonatremia, normocapnia, normothermia, and normoglycemia. With regard to blood pressure parameters, an initial systolic goal between 90 and 140 mm Hg is reasonable. In select high-risk cases, mild systemic hypotension may minimize the chances of hyperemia, edema, and ICH progression. However, such a maneuver may jeopardize brain regions that depend on collateral pathways for the maintenance of perfusion.

Persistent symptoms such as obtundation, paresis, or cranial nerve dysfunction may require bolus hyperosmotic therapy with mannitol or hypertonic saline (typically 2%, 3%, or 23%) for a goal serum sodium greater than 140 mEq/L. Glucocorticoid therapy (4–10 mg of dexamethasone IV every 6 hours) may improve vasogenic edema with the proviso that glycemic control is maintained with an insulin infusion as needed.

TABLE 37.2 Theories of Postoperative Brain Edema and Hemorrhage

	Key Features
Normal perfusion pressure breakthrough	• Loss of autoregulation in arteries/arterioles of surrounding brain • Diversion of high blood flow to chronically dilated perinidal vessels
Occlusive hyperemia	• Obstruction of venous outflow from surrounding brain • Stagnation of blood flow in perinidal vessels
Other	• Residual AVM • Surgical trauma • Inadequate hemostasis • Coagulopathy • Ischemia/stroke

AVM, Arteriovenous malformation.

PREVENTION

It has been suggested that staged embolization before surgical resection may reduce the likelihood of NPPB. Staged embolization presumably permits perinidal vessels to gradually adapt to increased perfusion pressure by unclear mechanisms. Indeed, since the institution of such a protocol for all large AVMs we have rarely observed this complication. Maintenance of normotension with a systolic blood pressure of less than 140 mm Hg throughout surgery and perioperatively, smooth extubation with avoidance of Valsalva, and adequate postoperative analgesia are important preventive strategies as well.

ACKNOWLEDGMENT

We are indebted to the late William L. Young, M.D., who contributed not only to the previous edition of this chapter but also greatly to the fields of cerebrovascular physiology and neuroanesthesia. In Bill's honor, we have retained relevant portions of this chapter from the second edition.

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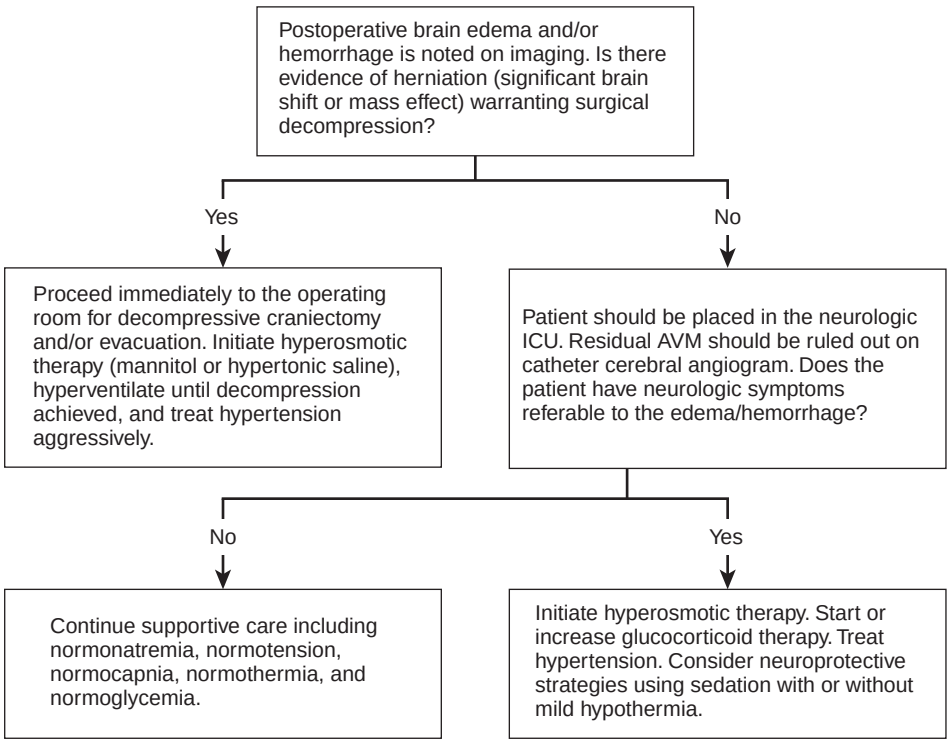

Fig. 37.2 Treatment algorithm.

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38 Bleeding After Cardiac Surgery

Klaus Martin • Peter Tassani-Prell

Case Synopsis

A 73-year-old man presents with a history of aortic stenosis, coronary artery disease, peripheral vascular disease, dyspnea at rest, and chronic renal failure (creatinine level 1.6 mg/dL). Myocardial function is moderately reduced (left ventricular ejection fraction is 35%). Combined aortic valve replacement and coronary artery bypass graft surgery is performed. Total cardiopulmonary bypass (CPB) time is 142 minutes. Postoperative bleeding as measured by chest tube output was 2200 mL in the first 24 hours, which is significantly elevated.

PROBLEM ANALYSIS

Definition

Excessive bleeding after cardiac surgery is basically divided into two categories: surgical and nonsurgical. Surgical bleeding can originate from multiple locations—most frequently, vascular anastomoses, cannulation sites, mammary harvesting sites, sternal wires, or atrial and ventricular access sites. Therefore minimizing surgical bleeding requires adequate surgical technique. Nonsurgical bleeding refers to coagulopathy, which recently was categorized as hemodilution, activation, and consumption. For appropriate therapy, all these conditions require specific knowledge about pathophysiologic circumstances that might appear during cardiac surgery.

Recognition

Before reversal of heparinization by an adequate amount of protamine is started, a critical inspection of the surgical field for major vascular bleeding should be performed. To distinguish between surgical and nonsurgical bleeding, it is of utmost importance that surgical suture lines are tight and macroscopic bleeding is avoided by sophisticated surgical hemostasis. If there is ongoing bleeding after protamine administration without a visible vascular leakage, it is up to the anesthesiologist to look for and correct any hemostatic disturbances. Postoperatively, mediastinal chest tube drainage is monitored hourly. As a rough rule of thumb, drainage should not exceed 100 to 125 mL/h for the first 4 postoperative hours, 250 mL for any hour during this period, or 50 to 75 mL/h for the subsequent 24 hours.

Life-threatening hypotension from postoperative bleeding can result from cardiac tamponade or hypovolemia. Nonsurgical hemostatic bleeding should be determined, and appropriate laboratory analysis should be initiated early to obtain results in the operating room (OR) before the patient is transferred to the intensive care unit. Timely detection of particular hemostatic deficiencies ensures specific therapy instead of nonspecific transfusion ("shotgun therapy") of multiple types of blood products and coagulation therapies.

Risk Assessment

Risk factors for postoperative bleeding include the following:

- Patient related:
  - Advanced age
  - Chronic steroid use
  - Female gender
  - Chronic liver insufficiency
  - Hematologic/hemostatic disease
  - Preoperative treatment with anticoagulant drugs
- Procedure related:
  - Prolonged duration of CPB
  - Repeat cardiac procedures
  - Combined procedures (e.g., bypass grafting and valve surgery)
  - Low body temperature after surgery
  - Increased cell salvage usage
  - Unexpected surgical difficulties
  - Intraaortic balloon counterpulsation
  - Internal mammary artery harvesting

Individual screening of patient-related risk factors in the preoperative period is essential to identify patients at increased risk for postoperative bleeding. In addition to medical history, a standardized questionnaire with regard to clinical hemostatic irregularities must be completed and carefully evaluated.

Drugs that affect the coagulation system or platelet function are commonly used in patients scheduled for cardiac surgery. Glycoprotein IIb/IIIa inhibitors, such as abciximab, eptifibatide, and tirofiban, are increasingly used as adjuncts to heparin or aspirin therapy in patients with acute coronary syndromes or in those having preoperative percutaneous coronary interventions. They may even be used for secondary long-term antithrombotic prophylaxis. It is also likely that patients requiring emergent cardiac surgery will have received anticoagulation therapy, specifically antiplatelet therapy, in the catheterization laboratory before transferal to the OR. When in doubt, additional laboratory analysis for specific coagulation disorders may be indicated.

In contrast, procedure-related risk factors are only partially predictable in the preoperative period. Some of the most affecting issues such as duration of CPB, intraaortic balloon counterpulsation, and increased cell salvage can arise during surgery. The same also applies for unexpected surgical difficulties. Whatever the risk factor, the anesthesiologist must determine the hematologic cause of the disorder for a specific treatment.

Implications

The major difference of cardiac surgery compared with other surgical disciplines is the use of the heart-lung machine. This extracorporeal circulation offers the surgeon the opportunity to separate the heart from the blood circuit and maintain the perfusion of the body. However, this procedure requires a temporary iatrogenic inhibition of the coagulation system to avoid clotting in the extracorporeal circuit. This inhibition is almost always performed with a large intravenous dose of heparin. Additionally, use of CPB has multiple implications on the pathogenesis of coagulopathy such as transient activation of platelets, hemodilution, hypothermia, and heparin and protamine.

Mechanical Stress and Contact Activation

When connected to the CPB circuit, the patient's blood becomes exposed to the artificial surface of the CPB tubes. This contact leads to an activation of the coagulation, fibrinolytic, and inflammatory cascades. Additionally, blood is pumped through the system by a roller pump. This mechanical squeezing means stress to all corpuscular cells in the bloodstream and leads to potentially detrimental damage. Consequently, platelet function is affected, which is considered to be a major contributor to postoperative bleeding. Additionally, the use of pericardial suction devices during surgery damages blood cells and returns activators of coagulation to the CPB system via the venous reservoir. Some of these effects on the hemostatic system have been proposed to be reduced by the use of closed reservoirs, coated CPB circuits, and retransfusion of the suctioned blood after processing in a cell saver.

Hemodilution

Crystalloid CPB priming and cardioplegic solutions lead to a more or less significant dilution of the patient's blood. The concentration of erythrocytes, platelets, and coagulation factors is reduced depending on the patient's intravascular volume and the volume of the CPB and cardioplegia. Improvements in the miniaturization of the CPB components for adult patients led to a reduction of the priming volume from well above 2 L in the 1990s to almost 1 L in the 2010s. With that downsizing, the amount of clinical hemodilution and its effect on hemostasis could be reduced significantly. Therefore hemodilution is rarely the sole cause of postoperative bleeding because coagulation factor concentrations of 25% to 30% and platelet counts of 50,000 to 100,000/μL can be tolerated without excessive bleeding if platelet function is normal. Because miniaturization of the CPB circuit is limited by technical issues, the smallest patients, children and newborns, are affected by the largest amount of hemodilution, as much as 200% or more, depending on the individual volume ratio. Nonetheless, progressive evolution led to first clinical reports demonstrating transfusion-free cardiac surgical procedures.

Hypothermia

Hypothermia may result in impaired platelet function and reduced function of temperature-dependent coagulation factors. Also, laboratory coagulation system assessment is uniformly done at 37° C. Therefore misleading results may appear when analyzing cold blood samples obtained during hypothermic CPB. Cooling to more tepid temperatures (mild hypothermia) has been proposed to reduce the activation of inflammatory cascades and lessen coagulation disturbances.

Cell Salvage Systems

Because coagulation factors and platelets are removed during routine red blood cell salvage, retransfused products from cell salvage devices are almost free of these plasmatic components. Additionally, it should be mentioned that direct reinfusion of shed mediastinal blood from postoperative chest tube drainage is not a suitable alternative because it is not recommended as a means of blood conservation and may cause harm (Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists [STS/SCA] guidelines, 2008).

Heparin and Protamine

Heparin is the most commonly used anticoagulant that is administered before the patient is connected to the CPB system and extracorporeal circulation is started. After discontinuation from bypass, the anticoagulatory effect is reversed by administration of protamine. Knowing that not only heparin but also protamine has an anticoagulatory effect, the importance of an appropriate dosage is clear. The heparin-protamine complex itself partially suppresses platelet function, which is measureable with a platelet function analyzer. Despite initial adequate neutralization with protamine, heparin rebound can occur 2 to 6 hours afterward, leading to inhibition of platelet function.

MANAGEMENT

Treatment of postoperative bleeding can be challenging because of its complex and multifactorial origin. Excessive mediastinal tube drainage requires urgent surgical reexploration in the OR to stop probable surgical bleeding, especially when accompanied by hemodynamic instability. However, reexploration is associated with a significantly increased risk for the patient, namely increased perioperative morbidity and mortality. Therefore the indication for surgical reexploration is of critical importance. Hence, in less seriously bleeding patients, such a decision should not solely be based on the amount of chest tube drainage. This is especially important because different surgical procedures have a different risk of bleeding. For example, a primary mitral valve repair with just one atrial access suture line besides the CPB connection sites has a much smaller risk of bleeding than an aortic aneurysm repair or a CABG surgery under ongoing antiplatelet medication with two mammary artery harvesting sites. In the past, when there were no clinical measurements fast enough to monitor the coagulatory system in an appropriate time, physicians had to treat their patients according to their local empirical standard and availability of hemostatic medications. These standards also depended on the availability and speed of laboratory tests and therefore had a large variability. Recent technical improvements in point-of-care (POC) devices offer the opportunity of rapid bedside testing of different aspects of the hemostatic system and subsequently a goal-directed therapy of specific disturbances. In the meantime, several transfusion and coagulation management algorithms have been published. Depending on their local circumstances and capabilities, every institution must create its own algorithm. In general, such structured proceedings seem to be effective in reducing bleeding, transfusion requirements, and hospital costs and improving patient outcomes.

Heparin and Protamine

As mentioned, the first step in recovering a normal coagulation after CPB discontinuation is the complete reversal of heparinization with an appropriate dosage of protamine. Most institutions prefer an empirical calculation of the protamine needed for this issue. Interestingly, there is a broad interinstitutional difference for such calculations. As far as we know, the range starts at approximately 70% and goes up to 125% of the total heparin dosage.

There are several options for the verification of adequate heparin reversal. A return to baseline values in the activated clotting time (ACT) measurement is commonly interpreted as complete heparin neutralization. But one has to keep in mind that the ACT measurement is not as accurate as expected. Even when ACT has returned to baseline, heparin plasma concentrations can be as high as 0.2 U/mL. A more evidence-based approach would be to measure the heparin concentration at the end of CPB and then calculate the protamine dosage according to the estimated blood volume. A relatively simple device to measure heparin in clinically relevant concentrations is the Hepcon HMS system. Heparin concentration is quantified by titration of protamine and measurement of clotting time. With knowledge of the patient's height and weight, the system calculates blood volume and the resulting protamine dosage. Completeness of reversal or residual heparin can be documented. Another sensitive, but only qualitative, test for residual heparinization is thromboelastography (i.e., ROTEM). If clot formation time in the INTEM is significantly higher than in the HEPTEM, residual heparinization is probable. Third, the activated partial thromboplastin time is sensitive and well quantifiable, but heparin concentrations cannot be calculated. Direct measurement of heparin concentrations is possible, but this parameter is not a comprehensive offer in most clinical laboratories, especially in emergency situations.

Platelets

Primary hemostasis describes the adhesion of platelets on the damaged endothelium where they degranulate. They change their shape, which increases their ability to create a stable plug, the primary platelet plug. This physiologic reaction on damaged vessels requires the presence of an adequate quantity of platelets having a sufficient quality. In the clinical setting, both aspects should be monitored: platelet count and platelet function. When there is ongoing bleeding, at least 50,000/μL, and preferably 100,000/μL, should be maintained to keep the hemostatic capability adequate for a physiologic hemostasis. Platelet count can easily be measured in the clinical laboratory, but it does not reflect platelet function. The assessment of platelet function can indirectly be performed by global hemostatic analyses such as thromboelastometry, or more specifically by light transmission aggregometry or whole blood aggregometry (i.e., MULTIPLATE). These devices are especially important in patients who may need antiplatelet treatment or when there was a long CPB duration with suspected damage to the platelets. When platelet count is acceptable and platelet function only slightly decreased, a first attempt with the administration of desmopressin acetate (DDAVP), a synthetic analog of antidiuretic hormone, can be attempted. DDAVP is thought to augment platelet function by the release of factor VIII and von Willebrand factor from endothelial cells. Other studies, however, indicate that DDAVP may have direct beneficial effects on platelets, such as increased expression of the adhesive receptor (glycoprotein Ib). The usual dose of DDAVP is 0.3 to 0.4 μg/kg, given continuously over 30 minutes. The principal adverse effect is hypotension.

With either low platelet count or significantly decreased platelet function, the only causative therapy is transfusion of platelet concentrates. There is an ongoing debate whether multiple-donor pooled or single-donor apheresis products are preferred. Both preparations are available, but they are used in variable proportions. According to the appropriate dosage, there is a therapeutic dilemma; on one hand, the dosage should be large enough for a sufficient primary hemostasis, but on the other hand, platelets bear the highest risk for transmission of infections and bacterial contamination. Additionally, availability of these blood components is usually limited and costs are high.

Coagulation Factor Deficiencies

Recently several investigations showed an association between postoperative bleeding and specific hemostatic disturbances such as low platelet count, low fibrinogen levels, or other diminished factors. With regard to the developed POC devices, many clinicians attempted a goal-directed therapy in order to rapidly correct specific hemostatic disturbances. This led to an increase in single-factor or component usage. Fibrinogen, prothrombin complex, and even activated factor VII were investigated in many trials. Several trials showed a significant association between fibrinogen or other factor deficiencies and postoperative bleeding. Interventional studies mostly demonstrate a beneficial effect of factor transfusion on hemostasis. Therefore clinical strategies increasingly favor such goal-directed strategies, while plasma transfusions are significantly reduced.

Antifibrinolytic Prophylaxis and Therapy

The fibrinolytic system is known to be up-regulated during CPB owing to the activation of multiple physiologic systems. This results in clot dissolution, coagulation factor consumption, and platelet dysfunction. Many clinical studies indicate that the prophylactic administration of antifibrinolytic drugs reduces blood loss and the number of transfusions in patients after cardiac surgery, particularly reoperations. Until 2007, aprotinin was the most commonly used antifibrinolytic medication throughout the world. After the publication of Mangano and the premature termination of the BART Trial, serious concerns about its clinical safety arose. The manufacturer immediately stopped distribution, which still holds in most countries. (Health Canada in 2011 and the European Medicines Agency in 2012 allowed the reintroduction of the drug under specific circumstances and safety precautions.) Alternative medications that are thought to be safer and equally effective are the two lysine analogs, tranexamic acid and aminocaproic acid. Availability of these medications varies between countries, but tranexamic acid seems to be favored in most institutions. Although there is a wide range in dosage and application, a suggested protocol for tranexamic acid might be administration of an initial loading dose after heparin administration of 10 mg/kg with a maintenance dose of 1 mg/kg/h, or alternatively, a repetition dose of 5 mg/kg every 2 hours until chest closure. Because efficacy of aminocaproic acid is only about one-tenth that of tranexamic acid, the equipotent dosage must be 10 times higher: loading dose 100 mg/kg, maintenance dose 10 mg/kg/h, and repetition dose 50 mg/kg every 2 hours.

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39 Cardiomyopathies

Mallik G. Reddy • B. Craig Weldon

Case Synopsis

A 3-year-old boy presents for inguinal hernia repair. His past medical history is unremarkable except for an upper respiratory infection 3 weeks ago that was characterized by a low-grade fever, thin rhinorrhea, and a mild cough that resolved last week. His physical examination and vital signs are normal. On anesthetic induction with nitrous oxide, oxygen, and sevoflurane his heart rate increases to 180 beats per minute, the electrocardiogram (ECG) QRS complex is noted to be wide, the pulse oximeter plethysmograph flattens, and no femoral pulse can be palpated. Full cardiopulmonary resuscitation is performed but proves unsuccessful. Autopsy reveals a dilated left ventricle and evidence of myocardial inflammation consistent with viral myocarditis.

PROBLEM ANALYSIS

Definition

The World Health Organization defines cardiomyopathies (CMs) as myocardial diseases associated with cardiac dysfunction. Primary CMs are classified by the dominant pathophysiology:

- Dilated cardiomyopathy (DCM)
- Hypertrophic cardiomyopathy (HCM)
- Restrictive cardiomyopathy (RCM)
- Arrythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/CM)
- Left ventricular hypertrabeculation/noncompaction (LVHT/NC)

Secondary CM may result from a number of different etiologies:

- Ischemia
- Valvular
- Hypertensive
- Inflammatory
- Metabolic
- Peripartum
- Toxin exposure
- Vitamin deficiency
- Certain neuromuscular disorders

Recognition

Unfortunately, many children with CM are asymptomatic or have mild symptoms of heart failure, making recognition of their condition very difficult in the preoperative period. There may be a history of decreased exercise tolerance, cough, breathlessness, syncope, chest pain, or poor feeding. A child with these symptoms or a condition known to be associated with CM should prompt a careful examination looking for signs of heart failure, an ECG, and possibly consultation with a pediatric cardiologist. An echocardiogram will usually establish a definitive diagnosis of which pathophysiologic category of CM is present. A family history of sudden cardiac death (SCD) may be the only indicator of potential CM in an otherwise healthy-appearing child or adolescent.

Dilated cardiomyopathy (DCM) is characterized by left ventricular chamber dilation and impaired systolic function involving the left ventricle (LV), right ventricle (RV), or both. DCM may be due to inflammatory (viral or immunologic), idiopathic, or genetic processes. A familial form of CM has been associated with SCD. DCM can result from toxin exposure or, in young children, be associated with a treatable congenital heart disease such as anomalous left coronary artery or critical aortic coarctation. In children diagnosed with CM the 5-year mortality rate has been reported to be 35% to 70%. Echocardiography usually demonstrates dilated, poorly contractile ventricles, biatrial enlargement, and atrioventricular (AV) valve regurgitation.

Hypertrophic cardiomyopathy (HCM) may involve the LV, RV, or both and is often asymmetric. Ventricular volume may be normal or reduced and is characterized by diastolic dysfunction, with preserved systolic function. The ECG may be normal or show ventricular hypertrophy, and echocardiography is diagnostic. HCM is most commonly a genetic or idiopathic disease but may also be associated with malformation syndromes, various neuromuscular disorders, and inborn errors of metabolism (e.g., glycogen storage disease type II or Pompe syndrome). Patients with idiopathic HCM may be asymptomatic or present with exertional dyspnea, chest pain, and syncope. The ECG shows a progressive pattern, from septal hypertrophy to generalized left ventricular hypertrophy. Typically these patients develop dynamic LV outflow tract obstruction, which may be the cause of some of the symptomatology. However, there is a subset of patients with focal hypertrophy that encases a coronary artery (i.e., myocardial bridge) who are subject to exertional myocardial ischemia and ventricular arrhythmias. This makes HCM the most common cause of SCD in children and young athletes.

Restrictive cardiomyopathy (RCM) is a rare form of CM characterized by restricted left or right (or both) ventricular filling due to reduced ventricular diastolic compliance. RCM may be idiopathic, or it can be associated with endomyocardial fibrosis or the hypereosinophilic syndrome. There may be normal or near-normal systolic function in the early stages of the disease that deteriorates over time. Elevated LV end-diastolic pressure leads to an insidious, relentless increase in pulmonary vascular resistance followed by cor pulmonale and death. The echocardiogram is characterized by small ventricular volumes with large, dilated atria.

Arrhythmogenic right ventricular cardiomyopathy (ARVCM) is characterized by fibrofatty replacement of right or left ventricular (or both) myocardium. ARVCM is a genetic cardiac disease with autosomal dominant inheritance and incomplete penetrance. Patients with ARVCM often present with dyspnea, fatigue, hepatomegaly, and ascites, but SCD may be the initial manifestation of the disease in an otherwise

asymptomatic patient. Fifty percent of these patients have abnormal ECGs that may show impaired AV conduction. A definitive diagnosis is made with myocardial biopsy, but ARVCM is suggested by the combination of ventricular arrhythmias (most often sustained ventricular tachycardia) with a left bundle branch block configuration. Wall motion abnormalities in the free wall of the RV are seen on echocardiography. The echocardiogram may also show atrial dilation associated with near-normal ventricular dimensions and AV valve regurgitation.

Left ventricular hypertrabeculation/noncompaction (LVHT/NC) is a rare disorder often associated with neuromuscular diseases including muscular dystrophies, myopathies, mitochondrial diseases, and others. These patients often present with signs of heart failure, arrhythmias, and ECG abnormalities. There is decreased LV function on echocardiography, but the diagnosis may require magnetic resonance imaging. The natural course of disease is dictated by any underlying neuromuscular disorder, as well as the severity of myocardial dysfunction.

Risk Assessment

DCM is the most common form of CM in children and it has an equal prevalence in males and females. HCM usually does not present before adolescence, but morbidity and mortality are greatest in patients diagnosed at younger ages. Premature death is commonly due to ventricular fibrillation. RCM is uncommon in children but, when present, is often an end-stage finding after myocarditis or with an infiltrative myocardial disease. ARVCM is uncommon but accounts for a high percentage of sudden cardiac deaths in children and adolescents. The prevalence in females is threefold greater than in males. LVHT/NC should be considered in the following neuromuscular disorders: Duchenne and Becker muscular dystrophy, myotonic dystrophy, Charco-Marie-Tooth disease, Friedreich ataxia, Barth syndrome, mitochondriopathy, dystrobrevinopathy, glycogenosis, myoadenylate-deaminase deficiency, and zaspopathy.

Implications

In DCM, cardiac output is maintained by sympathetically mediated tachycardia and ventricular chamber dilation with increased stroke volume. However, this leads to increased myocardial wall tension and oxygen utilization. In HCM, there is ventricular inflow obstruction secondary to diastolic dysfunction. Approximately 25% of patients also have dynamic obstruction of the left ventricular outflow tract. The systolic volume of the LV, the force of left ventricular contraction, and the transmural pressure gradient distending the outflow tract determine the severity of the obstruction. With RCM, the ejection fraction is maintained early in the process. However, as ventricular fibrosis progresses, left ventricular end-diastolic pressure increases, resulting in pulmonary hypertension and decreased stroke volume and cardiac output. With ARVCM, contractility is normal initially, but the onset of ventricular arrhythmias coincides with a slow deterioration of right ventricular function. Eventually, ventricular tachyarrhythmias (ventricular tachycardia or fibrillation) become resistant to antiarrhythmic therapy. LVHT/NC presents with variable degrees of myocardial dysfunction and has been associated with ventricular chamber thrombus formation. Underlying neuromuscular disorders can further complicate the anesthetic management of these patients.

MANAGEMENT

The perioperative management of children with known CM requires an understanding of normal cardiovascular physiology and an appreciation of the particular pathophysiology associated with the patient's CM. Maintenance of cardiac output is the primary objective through the management of preload, contractility, afterload, and heart rate. As illustrated by the case synopsis, induction of anesthesia may cause myocardial depression or loss of systemic vascular tone, leading to abrupt circulatory collapse and, possibly, malignant arrhythmias and cardiac arrest.

The myopathic ventricle requires at least normal to increased preload to maintain adequate stroke volume. However, intravenous volume loading may upset a delicate balance between sufficient preload and that which will dilate the ventricle and increase its end-diastolic pressure. The latter reduces endocardial perfusion, leading to a decrease rather than an increase in stroke volume. Invasive monitoring helps assess hemodynamic responses to intravenous fluid challenges, as well as intermittent positive-pressure ventilation. Patients who have been fluid restricted preoperatively are most susceptible to severe hypotension in response to intermittent positive-pressure ventilation.

Once preload has been optimized contractility should be addressed. Except for patients with HCM, children with CM have compromised contractility and limited myocardial functional reserve. Anesthetic agents should be administered with this in mind. Inotropes (e.g., dopamine, dobutamine, epinephrine) or inodilators (e.g., milrinone) may be required perioperatively to maintain cardiac output. Augmented contractility improves stroke volume, but at the cost of increased myocardial oxygen consumption.

Increased afterload, due to increased systemic or pulmonary vascular resistance, impedes the contraction of the LV and/or RV. Intramyocardial wall stress (a major determinant of afterload) increases directly with ventricular diameter according to Laplace's principle. Thus at the same level of arterial pressure, afterload encountered by an enlarged ventricle is higher than that for a ventricle of normal size.

Children with end-stage CM may have pulmonary hypertension. Every effort should be made to avoid increases in pulmonary vascular resistance. This is done by minimizing mean airway pressures, maintaining normocapnea or mild hypocapnia, providing permissive metabolic alkalosis, and giving exogenous pulmonary vasodilator agents (e.g., nitric oxide, prostaglandins).

Finally, a reduction in stroke volume often results in a sympathetically mediated increase in heart rate to compensate for the decrease in cardiac output. Maintenance of sinus or atrial-origin rhythms (e.g., wandering atrial pacemaker), and the associated atrial contribution to ventricular filling, is critical. Loss of sinoatrial rhythm with nonatrial, lower pacemaker escape rhythms (e.g., atrioventricular junctional or idioventricular rhythms or tachycardia) leads to inadequate diastolic filling and lower end-diastolic volumes. This aggravates any preexisting diastolic dysfunction.

Management objectives for the specific CM subtypes are found in Table 39.1.

PREVENTION

To avoid a catastrophic reduction in cardiac output during anesthesia and surgery in pediatric patients with CM the condition must first be recognized. As stated, this is often not possible and the first indication of trouble comes on induction of anesthesia. Foreknowledge of a patient's underlying CM allows for thorough preparation of the patient for elective or less urgent surgery and helps reduce the risk of perioperative deterioration. Extensive discussion with the child's cardiologist, surgeon, and parents is mandatory.

When more urgent surgery is required, it may not be possible to optimize the patient's medical condition before his or her arrival in the

TABLE 39.1 Pathophysiology and Anesthetic Management Goals for Cardiomyopathies

Subtype	Pathophysiology	Anesthetic Management Goals
Dilated (DCM)	↓ Ventricular contractility	Preload—normal
	↓ Cardiac output	HR—normal to ↑
	CHF	Afterload—normal to ↓
		Contractility—↑
		Inodilators preferred
Hypertrophic (HCM)	Dynamic LV outflow tract obstruction	Preload—normal to ↑
	Normal contractility	HR—↓
	↓↓ Stroke volume	Afterload—normal to ↑
	↓ Ventricular lisotropy	(phenylephrine recommended for ↓ BP/myocardial ischemia)
Restrictive (RCM)	↓ Ventricular lisotropy	Preload—normal
	Gradual ↓ in contractility	HR—normal to ↑
	Pulmonary hypertension	Afterload—normal
		Contractility—↑
		Avoid ↑ PVR
Arrythmogenic RV dysplasia (ARVD/CM)	Fibrofatty infiltration of RV	Preload—normal
	RV failure	HR—normal sinus rhythm
	Fatal perioperative ventricular arrhythmias	Pacer defibrillator pads in OR
		Afterload—avoid ↑ or ↓
		Contractility—normal
LV hypertrabeculation/noncompaction (LVHT/NC)	Variable myocardial dysfunction	Preload—normal to ↑
	Arrhythmias	HR—normal
	Associated neuromuscular disorders	Afterload—normal to ↓
	Possible ventricular thrombi	Contractility—normal
		Avoid negative inotropes

BP, Blood pressure; *CHF,* congestive heart failure; *HR,* heart rate; *LV,* left ventricle; *OR,* operating room; *PVR,* pulmonary vascular resistance; *RV,* right ventricle.

operating room. If so, the cardiologist should be immediately available for consultation with the anesthesia team. In general, preoperative preparation should follow the management objectives outlined earlier.

Further Reading

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Cardioversion

40

Johnny J. Kenth • Andrew F. Smith

Case Synopsis

An 88-year-old woman with a background of hypertension, angina, and mild asthma presented to the emergency department (ED) with a 10-day history of abdominal pain, nausea and vomiting, and reduced oral intake. She was initially being treated for acute dehydration secondary to gastroenteritis. On further questioning, she had a significant history of ischemic heart disease (IHD) limiting exercise tolerance, having suffered from a previous myocardial infarction in the right coronary territory, for which she underwent emergency (primary) percutaneous coronary intervention. On examination, the airway was patent, respiratory rate was labored at 30 breaths per minute, arterial saturations were 92% on 5 L of oxygen via facial mask, heart rate (HR) was irregularly irregular at 137 beats per minute, and blood pressure (BP) was 94/45 mm Hg. The laboratory results demonstrated a serum potassium of 3.1 mEq/L, blood urea nitrogen 33 mg/dL, creatinine 310 mmol/L, magnesium 0.57 mmol/L, and phosphate 0.38 mmol/L. The 12-lead electrocardiogram (ECG) showed new-onset atrial fibrillation (AF) with a rapid ventricular response, and Q waves and ST depression in leads 2, 3, and aVF. Following initial resuscitation, she was found to have a small bowel obstruction on abdominal computed tomography and was booked for urgent surgical intervention. Her HR was now 160 beats per minute and her BP was 60/35 mm Hg despite fluid therapy. To facilitate emergent direct current (DC) cardioversion within the ED, the anesthesiologist induced general anesthesia, and the patient was successfully cardioverted to sinus rhythm (SR) after the third shock at 150 J. Invasive monitoring was then instituted, and she was transferred to the operating room for urgent surgical intervention.

PROBLEM ANALYSIS

Definition

Cardioversion can be electrical or chemical therapy and is used to restore SR in a variety of contexts. DC cardioversion is exploited in three major situations: first, as the modality of choice for the management of tachyarrhythmias in unstable patients with hemodynamic instability; second, when pharmacologic therapy has failed, is contraindicated, or is not tolerated; and third, in an elective capacity in patients with dysrhythmias that have failed to be managed by pharmacologic therapy.

DC cardioversion involves the application of electrical energy synchronized to the QRS phase of the cardiac cycle. Electrical energy is applied across the thorax, stimulating the myocardium, simultaneously exciting cardiac myocytes, inducing rhythmic ventricular contraction. The concurrent activation and contraction of ventricular myocytes subsequently causes the myocardium to enter an effective refractory period, abating reentrant circuitry propagation. The rationale for failure of successful DC cardioversion by electrophysiologic evidence has been abstracted as two paradigms, the first being due to the critical mass theory and the second being the upper limit vulnerability theory. The former is based on the premise that a critical myocardial mass is required to generate and propagate an arrhythmia. Consequently, if all available myocytes are refractory and thus inaccessible to promulgate arrhythmogenic foci, this results in terminating the arrhythmia. The second theory is based on the premise that subtherapeutic defibrillations are unable to render a critical number of myocytes refractory, causing certain myocytes to become refractory while paradoxically stimulating other myocytes during a vulnerable phase in the cardiac cycle, culminating in arrhythmogenic reentrant circuits.

The usage and procedural conduct of DC cardioversion contrasts to defibrillation (DF). DF is not synchronized to a specific phase of the cardiac cycle, and it is used in emergent contexts such as pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF). DC cardioversion can be used for a multitude of tachyarrhythmias, whether they arise from the atria, the atrioventricular (AV) node (together forming the supraventricular tachycardia [SVT]), or the ventricles. SVTs include circuit reentrant propagation; examples include atrial fibrillation and atrial flutter. Arrhythmias of ventricular origin (ventricular tachyarrhythmias) include VT and VF.

A defibrillator is a device that stores electrical charge and releases a predefined quanta of energy in a controlled and coordinated manner according to a predetermined and preset amount, and it is conventionally measured in joules, the SI unit for energy. The electrical current is discharged via defibrillation pads or paddles. Optimum pad positioning includes the anterolateral (anteroapical) position or the anteroposterior position. The anterolateral position is where one pad is placed under the right clavicle on the right sternal margin at the second intercostal level. The second pad is placed at the second intercostal level, over the cardiac apex. In the anteroposterior position, the anterior pad is placed over the left sternal margin overlying the cardiac apex, and the posterior pad is placed distally, between the scapulae. Modern defibrillators use conductive pads that improve electrical current delivery by reducing thoracic impedance. Some studies have suggested that the paddles may be associated with a higher incidence of successful cardioversion to SR.

Successful outcome in DC cardioversion can be broadly divided into patient-related factors and equipment-related factors.

Patient-related factors include the following:

- Thoracic impedance: energy level, electrode skin interference, distance, polarity, phase of ventilation, intrinsic myocardial properties, and overall ability to conduct electricity

- Type of arrhythmia
- Duration of arrhythmia
- Electrolyte imbalances (i.e., potassium, magnesium, and phosphate)
- Toxins and proarrythmogenic drugs (chronotropes, bathmotropes, and dromotropes)
- Concomitant chronic diseases
- Presence of implantable cardiac devices

Equipment-related factors include the following:

- Electrode: type, size, position
- Paddles versus adhesive pads
- Total energy used and duration
- Waveform: monophasic versus biphasic

An important distinction between defibrillation paddles and pads is that in the former, the operator must apply the paddles onto the patient's thorax with a force of approximately 110 Newtons (25 pounds). Pads, on the other hand, do not require the operator to remain in contact with the chest during defibrillation, thereby improving safety. Pads also provide additional functionality such as the ability to undertake transcutaneous pacing.

Recognition

Acute issues presented within the case scenario include the following:

- Elderly
- Acute AF with a rapid ventricular response in context of IHD
- Severe dehydration
- Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypophosphatemia
- Significant hemodynamic instability
- Shortness of breath (SOB) with supplementary oxygen
- Acute kidney injury

The case synopsis demonstrates that the patient has an unstable tachyarrhythmia compounded by dehydration and electrolyte imbalances. The juxtaposition of the acute physiologic derangement against the substantial history of cardiovascular complications (IHD, previous myocardial infarctions with the need for coronary stents, and diastolic dysfunction) leads to an oxygen demand versus supply imbalance. This imbalance culminates into AF with rapid ventricular response, reducing diastolic filling and further compounding the oxygen demand versus supply disparity.

The advanced cardiovascular life support (ACLS) and the advanced life support (ALS) guidelines both recommend DC cardioversion for the management of tachyarrhythmia for the treatment of unstable tachyarrhythmia in hemodynamically unstable patients.

Adverse features of an unstable rhythm include the following:

- Myocardial insufficiency, ischemia (chest pain, SOB, sympathetic stimulation)
- Cardiac failure (fatigue, SOB, orthopnea, peripheral and/or pulmonary edema)
- End-organ hypoperfusion (cardiac [ischemia, failure], renal [reduced urine output])
- Cerebral hypoperfusion (altered mental status, decreased consciousness, syncope)

DC cardioversion may also be recommended as the treatment modality of choice in preference to pharmacologic agents, even in stable patients, as they prevent untoward and proarrhythmogenic effects (see Chapter 161). This is particularly important in patients who may have structural heart disease or have a diseased myocardium, such as previous myocardial infarction, acute ischemia, and presence of heart failure (e.g., a reduced ejection fraction less than 35%). In these contexts, the side effects of drugs may indeed outweigh the benefits.

The main contraindications for cardioversion include the lack of operational experience and technical expertise, the presence of multiform atrial (ectopic) tachycardia, and dysrhythmias due to enhanced automaticity (i.e., digitalis toxicity). Pregnancy and the presence of an implantable device are not absolute contraindications; however, certain precautionary measures should be undertaken. These include using the lowest feasible energy, placing the DF pads at least 12 cm away from the implantable device, and if possible having the device switched off or reprogrammed to a nonsensing mode.

Risk Assessment

When faced with a patient with an arrhythmia, it is paramount to adopt a structured and protocolized approach to an unwell patient, using an airway (A), breathing (B), circulation (C), and disability (D; ABCD) paradigm. Furthermore, it is also important to undertake the simultaneous correction of any life-threatening conditions while undertaking the initial assessment. Using this approach may attenuate end-organ damage by restoring tissue and organ reperfusion. It is also important to emphasize that emergency cardioversion in unstable patients is time critical and requires prompt action.

In stable patients, arrhythmias do not require emergency correction, and recent evidence favors rate over rhythm control. If cardioversion is indicated, this should only be undertaken after anticoagulation, which can be organized in an elective capacity (discussed later).

Implications

The elective management of cardioversion in stable patients is both a safe and common procedure. In contrast, an emergency situation presents multiple challenges, in terms of patient-, equipment-, and location-related factors:

Patient-related factors:

- Emergency cases
- Deranged physiology
- Preexisting myocardial disease
- Concomitant chronic diseases
- Oxygen demand versus supply imbalance

Equipment- and location-related factors:

- Remote site
- Unfamiliarity and limitation of available equipment
- Limited availability of anesthetic and resuscitation drugs
- Availability of the minimum standards of monitoring
- Presence of a trained assistant

The advent of improved techniques, drugs, and training has sanctioned the safer delivery of cardioversion. Cardioversion that adopts biphasic waveform significantly reduces the amount of energy required for successful cardioversion. Biphasic cardioversion and DF delivers energy in two (opposing) vectorial planes, by alternating the polarity and thus electrical axis, contrasting to the unidirectional monopolar waveform. The former requires appreciably greater energy: 360 J versus 200 J for DF. Cardioversion involves the delivery of electrical current to stimulate the myocardium, triggering rigorous muscular contractions that can result in pain and discomfort. To mitigate these, anesthesia or sedation is required. Stable patients undergo elective cardioversion in a day surgery setting, providing they are hemodynamically stable and similarly fulfill the usual requirement for undergoing day surgery. Despite cardioversion having a long history of safe provision, especially in the elective environment, it is still fraught with several (potentially lethal) complications. These include the following:

Airway and breathing:

- Pulmonary aspiration of gastric contents, especially in patients who are nonfasted or have gastric stasis

TABLE 40.1 The ASA Classification of Sedation

	CATEGORY OF SEDATION			
	Minimum/Anxiolysis	**Moderate/Conscious Sedation**	**Deep Sedation**	**General Anesthesia**
Airway	Unaffected	Maintained, no intervention required	Intervention may be required	Intervention often required
Breathing Spontaneous ventilation	Unaffected/maintained	Adequate, supplementary oxygen only, no need for IPPV	May be inadequate	Often inadequate
Cardiovascular function	Unaffected/maintained	Usually maintained	Usually maintained	May be impaired
Neurologic function/responsiveness	Normal response to verbal stimuli	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable even to painful stimulus

ASA, American Society of Anesthesiologists; *IPPV*, intermittent positive-pressure ventilation.

- Failed intubation
- Difficulty in bag-valve-mask (BVM) ventilation
- Loss of airway

Cardiovascular system:

- Failure to cardiovert to SR
- Hypotension and myocardial instability, compounded by anesthetic agents
- Bradycardias, particularly with concurrent AF
- Progression to a ventricular dysrhythmia
- Cardiac arrest: pulseless VT, VF, asystole, pulseless electrical activity

Neurologic system:

- Venous thromboembolic events: cerebrovascular accident (CVA), transient ischemic attack (TIA)
- Altered consciousness, confound under general anesthesia

Musculoskeletal system:

- Long bone and vertebral fractures, especially in patients with osteoarthritis, mineral deficiency, and metabolic bone disorders (1.5-fold increased risk)
- Myopathic pain

MANAGEMENT

Patients requiring cardioversion range from stable cases, undertaken on an elective day surgery list, to emergent situations in unstable patients, potentially in unfamiliar surroundings. Sedations can be conceptualized as a continuum, ranging from an awake, alert, and conscious patient, anxiolysis, progressing to moderate (conscious) sedation, deep sedation, and finally general anesthesia (see Table 40.1 for the American Society of Anesthesiologists [ASA] classification of sedation). All practitioners administering sedation targeting a certain depth are required to have the capacity to manage inadvertent deeper level of sedation, including interventions to preserve the patient's physiologic milieu.

Sedation for cardioversion has evolved from the use of long-acting pharmacologic agents with numerous side effects, including apnea, drowsiness, hangover, and hypotension, to newer agents with a more favorable side-effect profile. These ultrashort-acting agents allow rapid onset and offset, abating hangover, while facilitating deeper planes of sedation. The caveat is that the clinician must be trained and experienced to manage any potential complications, including the inadvertent induction of general anesthesia.

The selection of the sedative agent will depend on the duration, depth, discomfort, and pain. Clinicians should also be mindful of the wide interpersonal variability of different agents and their potential adverse effects. A Cochrane systematic review undertaken by the chapter authors ascertained that there was no evidence for the superiority of one agent over another. The authors recommend clinician experience, use of short-acting agents, and the importance of maintaining hemodynamic stability. Despite the variations in practice being contextualized to clinical experience, national guidance, and local cultures and customs, the review highlighted the fallacy for stoical usage of any particular agent without prudence of its ramifications; emphasizing the paramount in successfully managing complications fashioned successful outcomes (Table 40.2).

Despite the majority of studies investigating anesthesia or sedation for cardioversion involving intravenous agents, nitrous oxide and/or the volatile inhalation anesthetic agents may also be used. Nitrous oxide has been associated with poorer outcomes in patients with IHD and also inhibits cobalamin and methionine synthesis after prolonged and repeated exposure.

Whenever cardioversion is undertaken, irrespective of the context, a thorough preoperative assessment should be undertaken, including history, examination, and assessment of relevant investigations. The ASA advocates that when sedation or anesthesia is undertaken, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) minimum monitoring standards be mandated. These include continuous ECG (minimum three leads), noninvasive blood pressure, Spo_2, ability to monitor Fio_2, and waveform capnography. In addition, a self-inflate bag, Mapleson C breathing circuit, spare oxygen cylinders, and an assortment of airway devices, including endotracheal tubes, supraglottic airway devices (SADs), and availability to undertake rescue techniques (such as emergency cricothyroidotomy) should be immediately available. As per the ASA and the UK Medical Royal College safe sedation standards, individuals administering sedation should be competent to do so, including managing any potential complications. Moreover, the individual operating the defibrillator should be distinct from the person administering the sedation, who would also be responsible for monitoring the patient. The airway can be safely managed with a BVM with or without an oropharyngeal airway (such as the Guedel airway) or an SAD, as appropriate. In the emergent setting, or when there is a risk of aspiration of gastric contents, endotracheal intubation is obligatory.

The complications of cardioversion have been addressed previously. Specifically, hypotension can be treated with judicious boluses of intravenous fluid such as lactated Ringer's solution; however, vasopressive and inotropic drugs may be required, especially in cardiovascularly unstable patients. Acute neurologic sequelae (CVA, TIA) and musculoskeletal injuries (vertebral fractures) can be managed by a combination of generic supportive measures, specific imaging, and specialist consultation as required. A high index of suspicion is prudent, and the presence of any new signs and symptoms should alert the clinician to the risk of these potentially deracinating complications.

Emergent Cardioversion for Unstable Tachyarrhythmias

In contrast to elective cardioversion, emergency cardioversion can present with a number of challenges. These include patient factors,

TABLE 40.2 Commonly Used Agents for Cardioversion, Suggested Doses, and the Common Advantages and Disadvantages

Name of Agent	Suggested Dose	Advantages	Disadvantages
Propofol Hypnotic, propyl phenol	Bolus 0.5–2 mg/kg TCI C_{ET} 1.5–3 μg/mL	Rapid onset/offset Safe in renal and hepatic failure Allows easy titration of sedation Achieve very deep levels of sedation/general anesthesia Antiemetic properties	Negative inotropic, dromotropic, chronotropic ↓ HR, ↓ SVR, ↓ CI Severe CV instability and hypotension in unstable patients ↑ incidence of apnea Pain on injection[a] Involuntary muscle movements [nonepileptogenic][b]
Thiopental Thiobarbiturate	2–5 mg/kg	Rapid onset, in one arm; brain circulation[b] Less ↓ SVR and CI than propofol Classical component of RSI	Hangover: slower clearance Less titratable Can cause ↓ HR, ↓ SVR, ↓ CI Histaminergic; unsafe in porphyria Apnea, does not obtund the laryngeal reflexes
Midazolam Benzodiazepine	0.5–2 mg increments, up to 10 mg	Long history of safety and familiarity (i.e., by nonanesthesiologists) CV stable Maintains MV[c] Less likely to yield deeper planes of sedation	Significant interpersonal variability Long terminal $T_{½}$ (up to 6 hours) Significantly longer offset/hangover in renal/hepatic impairment Active metabolites
Etomidate	50–100 μ/kg	Rapid onset, one arm; brain circulation Maintains SVR and CI Most CV stable hypnotic Especially useful in shocked patients	Concerns regarding inhibition of steroidogenesis Apnea Myoclonic jerks[d] Emetogenic Slower offset/hangover
Ketamine	0.5–2 mg/kg IV 2–4 mg/kg IM	CV stable Analgesic properties Maintains MV[c]	Hallucinations and emergent phenomenon ↑ Sympathetic tone, ↑ MVO_2 (caution in IHD) Emetogenic Drug of abuse
Remifentanil	0.05–0.20 μg/kg/min TCI C_{ET} 1.5–3 μg/mL	Rapid onset/offset Context insensitive Allows deeper planes of sedation Works synergistically with propofol Potent analgesic	Modest ↓ HR, ↓ SVR, ↓ CI, exaggerated in shocked states Less CV stable than alfentanil ↓ RR, ↓MV; cause chest-wall rigidity Pharmacoeconomics: only available in ampules, resulting in excess cost Analgesia rapidly offsets
Alfentanil	5–20 μg/kg 0.02–0.7 μg/kg/min	Fastest onset of all opiates Rapid offset due to redistribution More CV stable than other opiates Economical	Clearance slower than remifentanil; clinically insignificant for very short procedures Respiratory effects as above Marginally longer analgesic effects
Fentanyl	0.5–1 μg/kg	CV stability Potent analgesia	Far longer acting than the other opiates mentioned; can lead to longer drug hangover Respiratory effects as above

CI, Cardiac index; *CV,* cardiovascular; C_{ET}, effect site concentration; *MV,* minute ventilation; MVO_2, myocardial oxygen consumption; *RR,* respiratory rate; *RSI,* rapid sequence induction; *SVR,* systemic vascular resistance; *TCI,* target-controlled infusion.

[a]Pain on injection can be decreased by the preinjection of lidocaine (up to 50 mg) and avoiding using a small vein. Doses greater than 100 mg of may affect the threshold of cardioversion by proxy of their actions as a membrane stabilizer, by inhibiting sodium influx.

[b]Time taken for the drug to travel from the injection site (e.g., the arm) to the effect site (i.e., the brain).

[c]Midazolam and ketamine both maintain spontaneous breathing and MV, significantly reducing the risk of respiratory depression.

[d]Myoclonic movement (e.g., by etomidate) may interfere in the ECG readings and therefore affect the sensing of synchronized cardioversion, by missensing, and risk discharging the defibrillator during a vulnerable phase of the cardiac cycle.

such as underlying disease process, hemodynamic instability, and cardiovascular instability; and anesthetic factors, including the cardiodepressant, hypotensive, and proarrhythmogenic effects of anesthetic agents. Remote site anesthesia, unfamiliarity, and unavailability of equipment pose further considerations and highlight the hazards in administering anesthesia for cardioversion in emergent contexts.

Both the ACLS and ALS guidelines recommend cardioversion for unstable rhythms. They advocate the management of unstable patients adopting the ABCDE approach, with simultaneous assessment and resuscitation. As stated, the safe provision of anesthesia for cardioversion requires the AAGBI minimum standards for monitoring, presence of a trained assistant, availability of resuscitation drugs, and appropriate equipment. Furthermore, the DF should have been confirmed, tested, and deemed to be functioning appropriately. In certain contexts, it may be preferable to stabilize patients by transferring them to a safe and more familiar environment such as the operating room. However, the transfer of unstable patients can result in deleterious outcomes, and the benefits must outweigh the risks.

It is imperative to determine whether the patient is stable or unstable within the initial assessment. Clinicians can then interrogate whether the rhythm is sinus, the QRS complex is wide or narrow complex (greater than 120 msec), and the ventricular rhythm is regular or irregular. The rationale in defining the specific rhythm present is that the different arrhythmias require different energy for cardioversion.

Specific cardioversion energy doses include the following:

- Narrow regular: 50 to 100 J biphasic
- Narrow irregular: 120 to 200 J biphasic or 200 J monophasic
- Wide regular: 100 J
- Wide irregular: 200 J biphasic or 360 J monophasic (nonsynchronized)

When titrating energy doses for cardioversion, the lowest possible energy should be used, as there is a positive correlation between the cumulative energy used with risk of myocardial dysfunction. Following DC cardioversion, drug therapy may be required to prevent the recurrence or deterioration of a tachyarrhythmia. Amiodarone 150 mg can be administered as a loading dose over 15 to 30 minutes,

followed by a maintenance infusion of 900 mg over 23 hours. The drug management of arrhythmia is discussed in further detail in Chapters 133 and 161.

Children, especially neonates and infants, have a higher HR than do adults, and rely on this to maintain cardiac output. Although rare, DC cardioversion may be required in children with tachyarrhythmias, which are often SVT in origin. Expert help should be sought early, as these cases are often complex and can present serious risks and complications to the child. Like adults, the generic ABCD paradigm (as described earlier) must be used. The energy levels for cardioversion in children commence with 0.5 to 2 J/kg, with 4 J/kg used for DF in pulseless VT/VF. VT is rare in children, especially in the absence of structural heart disease, aberrant conduction pathways, channelopathies, severe physiologic abnormalities, or poisoning. In hemodynamically stable patients, a loading dose of amiodarone can be used, at 5 mg/kg over 30 minutes, followed by maintenance infusions of 15 mg/kg/day.

The anesthetic drugs used for children will depend on clinician experience and preference, but must also be contextualized to the child's acute physiologic status. Ketamine has a favorable side-effect profile in children, and it is cardiovascularly stable, nonvagolytic, and can be used in subhypnotic doses for sedation. It has minimal respiratory depressant effects and has analgesic properties. Similar to adults, if the patient is not fasted or at risk of pulmonary aspiration, endotracheal intubation is obligatory; otherwise, BVM can be used. A precalculated dose of atropine should be immediately available, as transient bradycardias can rapidly deteriorate.

Cardioversion for Atrial Fibrillation

The axioms for management of patients in AF include the following:

1. Rate control
2. Reinstatement and preservation of SR
3. Avoidance of thromboembolic events, especially in patients with additional risk factors

Cardioversion is frequently used in patients with AF in the context of both stable and unstable patients. The duration of AF over 48 hours is a relative contraindication for cardioversion, as there is an unacceptable thromboembolic risk. Oral anticoagulants are therefore commenced for a minimum of 3 to 4 weeks, and transesophageal echocardiography is undertaken to dismiss the presence of an intraatrial thrombus. Novel oral anticoagulants have emerged to supplant vitamin-K antagonists (VKAs) such as warfarin. These can be categorized into factor Xa inhibitors and direct thrombin (factor II) inhibitors. Although these newer agents may offer certain advantages over VKAs, they lack familiarity, and specific tests to assess the degree of clotting inhibition (both quantitative and qualitative) are not universally available.

From systematic reviews of randomized control trials, the success rate for cardioversion has been quoted to be up to 90%. The probability of successful cardioversion, and for the maintenance of normal SR (in the absence of structural heart disease or after an acute coronary syndrome [ACS]), is positively correlated with duration. Long-standing chronic AF has a significantly lower incidence of successful cardioversion than AF with relatively more recent onset. Adjuvant pharmacologic therapy (before or after cardioversion) can help maintain SR and has proven to be beneficial in patients after cardiac surgery as a preventive measure.

In addition to the generic complications of cardioversion, in the context of AF, bradycardias are far more prevalent and problematic. Patients at particular risk include those with sick sinus syndrome, post-ACS (especially if the sinoatrial node branches of the right coronary artery were occluded), channelopathies, or the presence of pathologic reentry circuits. VF is a potential fatal complication of cardioversion and is often attributed to the indecorous execution of unsynchronized shocks, especially during the vulnerable part of the cardiac cycle, R-on-T phenomenon. This can be minimized by synchronizing the shock to the R wave on the dominant lead. Transient ST changes such as ST elevation may occur after cardioversion; these are often attributed to coronary artery spasm and may resolve. Continual and evolving ST changes, ongoing chest pain, and biochemical evidence of myocardial necrosis, such as raised troponin, should alert the clinician to the presence of a potential ACS.

PREVENTION

Many of the preventive measures that help minimize risk when administering anesthesia for cardioversion have been addressed. In elective patients, or those with stable hemodynamic parameters, standardized fasting regimens ascribed to all patients must be followed. This includes 6 hours for solid foods, including drinks with particulate matter, and 2 hours for clear fluids. Premedications include metoclopramide, ranitidine, and sodium citrate (30 mL of 0.3 M), because these help reduce gastric pH and volume, reducing the risk of pulmonary aspiration of gastric contents. In emergencies, where prescribed fasting may be overridden, this regimen can still be used to help reduce the risk of pulmonary aspiration.

In elective patients where no airway device is used, a bite guard can be used to prevent laceration and injury to the lips, tongue, and gums. Newer supraglottic airway devices such as the Igel have a bite guard built into their outer casing, along with a gastric suctioning port, thereby being ideal for elective cases. In emergency cases, endotracheal intubation is mandated in nonfasted patients, with the judicious titration of agents with minimum cardiodepressant effects. Before cardioversion, if the patient becomes apneic, ventilation should be assisted with a BVM to prevent respiratory acidosis, as this lowers the threshold to potentiate arrhythmias. Although seldom used, a short-acting muscle relaxant can reduce the risk of sustaining fractures or dislocations.

In closing, anesthesia for cardioversion is a common and safe procedure. A thorough preoperative assessment, with emphasis on resuscitation and stabilization in unstable patients, will help prevent potential compilations.

ACKNOWLEDGMENT

The authors wish to thank Dr. M. Franckowiak and Dr. N. D. Nader for their contribution to the previous edition of this chapter.

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Carotid Endarterectomy

41

Mark D. Stoneham

Case Synopsis

An 82-year-old woman with a significant past medical history of hypertension and coronary artery disease undergoes carotid endarterectomy (CEA) under regional anesthesia. She experienced an episode of dysphasia and transient weakness affecting her left side 3 days previously. Investigations revealed an 80% stenosis of the right internal carotid artery. Her blood pressure is 180/95 mm Hg before surgery. Surgery proceeds uneventfully, although she remains hypertensive throughout. In the postanesthesia care unit postoperatively, the patient's blood pressure is 200/100 mm Hg, and she becomes agitated and develops a frontal headache. Intravenous labetalol, 50 mg in divided doses, and intravenous hydralazine, 20 mg, are administered, causing her blood pressure to drop precipitously. Her conscious level deteriorates and she develops dysphasia and lateralizing signs suggestive of ischemic stroke. She undergoes computed tomography of the head, which reveals appearances consistent with cerebral infarction. Unfortunately her condition deteriorates and she dies the following day.

PROBLEM ANALYSIS

Definition

The aim of CEA is to decrease the subsequent risk of stroke in patients with significant carotid stenosis, but the benefits are only realized if perioperative morbidity and mortality are low. Patients undergoing CEA are at increased risk of complications because of cardiovascular comorbidities (Box 41.1). Arterial pressure may be difficult to control, yet perioperative hemodynamic instability can directly or indirectly influence morbidity and mortality.

CEA is unique in that one of the principal components of the physiologic control mechanisms of arterial pressure—the baroreceptors in the carotid sinus—are involved in the disease process itself, and may be affected by the surgical procedure, concurrent drug therapy, and the effects of anesthesia. Patients who have suffered recent transient ischemic attack (TIA) or stroke have altered baroreceptor sensitivity and are at increased risk of hemodynamic instability. Many patients presenting for CEA have essential hypertension, with others being diagnosed as hypertensive following their presenting TIA or stroke and have therefore recently been commenced on antihypertensive treatment. This latter phenomenon is made worse by the recent trend to operate on patients within days of their presenting neurologic event.

Thus blood pressure management during CEA involves "walking a tightrope" between two extremes. On the one hand, blood pressure must be maintained high enough to maintain cerebral perfusion, particularly during the carotid cross-clamp period when the ipsilateral cerebral cortex is relying on collateral flow around the circle of Willis. On the other hand, blood pressure must not be so high that hypertensive complications such as myocardial ischemia, hyperperfusion syndrome, or hemorrhagic stroke develop. This can be difficult to manage, which helps explain why perioperative stroke and mortality rate for CEA remain relatively high.

The choice of anesthesia for CEA does affect the intraoperative and postoperative hemodynamic profile. Patients undergoing CEA under regional anesthesia tend toward hypertension during the period of cross-clamping, and hypotension after restoration of cerebral blood flow and into the postoperative period. In contrast, the usual pattern under general anesthesia is of relative intraoperative hypotension and postoperative hypertension.

Recognition

Perfusion of the brain is at risk throughout carotid surgery. Before internal carotid artery cross-clamping, perfusion of the ipsilateral cerebral cortex through a narrow carotid stenosis may be dependent on maintenance of a relatively high blood pressure. During cross-clamping, perfusion of the ipsilateral cerebral cortex is reduced and reliant on collateral flow around the circle of Willis. Once the cross-clamp is released after removal of the stenosis, perfusion of both sides may be affected by fluctuations in arterial pressure. The cerebral vasculature is also affected by the type of anesthesia used. Cerebral autoregulation and baroreceptor function are both affected considerably more by general anesthesia compared with regional anesthetic techniques. Arterial carbon dioxide levels also have significant influence on cerebral vasodilation and vasoconstriction.

Close arterial pressure control is therefore vital throughout the operation, coupled with some method of assessing cerebral perfusion while the carotid is cross-clamped. The choice of which monitoring

BOX 41.1 CEA Postoperative Problems

- Hemodynamic instability
  - Hypertension
  - Hypotension
  - Myocardial infarction
- Wound hematoma
- Glossopharyngeal edema with airway compromise
- Cranial nerve damage
- Neurologic dysfunction
  - Acute graft thrombosis (may require reexploration)
  - Minor focal deficits
  - Watershed ischemia
  - Hyperperfusion syndrome leading to subarachnoid hemorrhage

technique to use may be affected by the surgeon's decision whether or not to use a carotid shunt (a method of bypassing the carotid cross-clamp and thereby maintain ipsilateral perfusion during carotid cross-clamping). Whereas some surgeons elect to place a shunt in all patients, others never use a shunt, relying instead on speed of surgery to minimize cerebral ischemia. However, a third group of vascular surgeons use intraoperative monitors of cerebral perfusion and ischemia to guide them as to whether to place a shunt. Shunting is not without risk; vessel wall disruption, dislodgment of atheromatous plaque with thromboembolism, shunt kinking, or air embolism can all occur, as well as brisk arterial hemorrhage if the shunt is accidentally dislodged.

Methods used to assess the need for a shunt include: neurologic assessment of awake patients (under local or regional anesthesia, such as cervical plexus block); transcranial Doppler; electroencephalogram (EEG), somatosensory evoked potentials (SEPs); measurement of distal cerebral artery stump pressures (i.e., pressure created by backflow from the contralateral carotid artery across the circle of Willis); or direct measurement of cerebral blood flow with xenon (Table 41.1). The sensitivity of any technique for detecting perioperative ischemia is limited, because most strokes occur postoperatively and are likely caused by thromboembolic phenomena.

Postoperatively patients are monitored in the postanesthesia care unit (PACU) for a period of several hours with continuous arterial pressure monitoring and frequent neurologic monitoring. A protocol for the management of arterial pressure and prescription of appropriate vasoactive drugs may be used to control hemodynamic stability in the PACU (Box 41.2).

TABLE 41.1 Monitors of Cerebral Ischemia During Carotid Endarterectomy

Regional Anesthesia	
Central nervous system examination of the awake patient	The "gold standard." Assessment of contralateral grip strength, speech, and cerebration at regular intervals during the cross-clamp period.
General Anesthesia	
Electroencephalogram (EEG)	EEG represents cortical electrical activity, which decreases with cerebral ischemia. Disadvantages of EEG monitoring include the inability to monitor deep brain structures, the presence of false-negative findings due to preexisting or fluctuating neurologic deficits, and the influence of general anesthesia on EEG patterns.
Somatosensory evoked potentials (SEPs)	SEPs can monitor deeper brain structures. SEPs are a result of electrical impulses that originate peripherally and travel through first- and second-order neurons to synapse in the brainstem. Subsequently, these impulses are transmitted to the somatosensory cortex. As with EEG monitoring, false-negatives may result if anesthetics produce SEP changes that mimic cerebral hypoxia.
Internal carotid artery stump pressure	Now largely historical. The presence of a palpable pulse or a mean stump pressure greater than 60 mm Hg suggests sufficient backflow to prevent ischemia.
Xenon-133 washout	Intravenous or intracarotid administration of radioactive xenon or krypton. This method is specialized, expensive, and largely a research tool.
Transcranial Doppler ultrasonography (TCD)	TCD measures the velocity of blood flow in the middle cerebral artery. It can be used to detect acute thrombotic occlusion or embolization during or after carotid surgery, or to identify patients at risk for developing a postoperative hyperperfusion syndrome.
Near-infrared spectroscopy (rSO_2)	Noninvasive assessment of cortical oxygen saturation using a sensor on the forehead. A decrease in rSO_2 of <20% from preclamp to early cross-clamp value has a high negative predictive value. However, it has a high false-positive rate.

Risk Assessment

All patients undergoing CEA are, by definition, arteriopaths and at risk of cardiovascular and cerebrovascular complications. Important risk factors for carotid disease include advanced age, hypertension, tobacco abuse, and a history of diabetes mellitus. Because these patients are at high risk for stroke but are more likely to die of myocardial infarction, the preoperative risk assessment, workup, and timing of surgery can be challenging and controversial.

Cardiac risk assessment can include exercise or dobutamine stress testing or cardiopulmonary exercise testing to determine the need for preoperative coronary revascularization (e.g., coronary artery bypass grafting or percutaneous coronary transluminal angioplasty). However, the benefits of coronary revascularization must be balanced against the risk of stroke due to delay, or placement on cardiopulmonary bypass during coronary artery bypass grafting. There are no clear guidelines for anesthesiologists managing patients with advanced carotid and coronary artery disease, and the decision to pursue an invasive intervention is generally based on the patient's clinical history, stability of symptoms, and institutional and personal preference.

Implications

The overall mortality and stroke rate of CEA in the largest study ever completed (GALA trial) was 4.5%. The best centers consistently report stroke/death rates of approximately 1% to 2%. Risk factors for stroke or death following CEA include female sex, congestive heart failure, peripheral vascular disease, low surgeon case volume, and occlusion of the contralateral internal carotid artery.

MANAGEMENT AND PREVENTION

It is important to get a feel for the patient's "normal" blood pressure—from the outpatient clinic, from the preoperative assessment clinic, and from the values obtained preoperatively on admission before surgery.

As a general rule, many anesthetists and surgeons aim for a systolic pressure of around 160 mm Hg or less before elective CEA. Antihypertensive therapy (including β-blockers but excluding angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) should be continued up to the morning of surgery, and restarted immediately after surgery. However, the introduction of β-blockers, particularly metoprolol, immediately before surgery has been associated with an increased risk of hypotensive stroke. Statins have been shown to improve outcome after CEA and are recommended to be given to all patients. Assessment of the risk-benefit of continuation of antihypertensive and antiplatelet medication is recommended for each individual patient.

Traditional anesthetic teaching for vascular surgery suggests maintaining systolic arterial pressure at plus or minus 20% from the preoperative baseline value. However, concern about "watershed" stroke during the period of carotid cross-clamping, together with some clinical evidence from patients undergoing awake CEA whose developing neurologic deficits were reversed by elevation of blood pressure to "normal" values, has revised these limits in patients undergoing CEA to between normal and 20% above baseline.

Slightly different considerations apply during the preoperative, intraoperative, and postoperative periods. Preoperatively it is important to control and maintain blood pressure but avoid excessive decreases in cerebral perfusion distal to a carotid stenosis. Intraoperative goals are to maintain cerebral perfusion pressure and collateral

BOX 41.2 Protocol for the Management of Blood Pressure Following CEA

(1). Patient in PACU: Systolic Pressure >170 mm Hg

General Points

- Does the patient have urinary retention or is he or she in pain?
- Has the patient received his or her normal antihypertensive medication today?
- Patient should remain in the PACU while any vasoactive infusion is running and for >2 hours following cessation of the infusion.

First-Line Agent: Labetalol

100 mg labetalol in 20 mL of 0.9% saline (i.e., 5 mg/mL^{-1}). Give 10 mg (2 mL) boluses *slowly* every 2 minutes up to 100 mg (i.e., 20 mL given over 20 minutes).
If blood pressure (BP) remains elevated after 20 minutes, move to second-line agent.
If BP decreases and does not rebound, continue regular BP observations.
If BP decreases initially but increases again, start infusion at 50–100 mg/h^{-1}, titrating dose to BP.

Second-Line Agent: Hydralazine

10 mg hydralazine in 10 mL of 0.9% sodium chloride (i.e., 1 mg/mL^{-1}).
Give 2 mg (2 mL) boluses *slowly* every 5 minutes up to 10 mg (i.e., 10 mL given over 25 minutes).
If BP remains elevated after 25 minutes, move to third-line agent.
If BP decreases and does not rebound, continue regular BP observations.
If BP decreases initially but increases again, move to third-line agent.

Third-Line Agent: Glyceryl Trinitrate (GTN)

50 mg GTN in 50 mL 0.9% sodium chloride (i.e., 1 mg/mL^{-1}).
Start infusion at 5 mL/h^{-1} (5 mg/h^{-1}), increasing rate to 12 mL/h^{-1} (12 mg/h^{-1}), titrated to BP.

(2). Patient Is on the Surgical Ward: Systolic BP >170 mm Hg, but *NO* Headache/Neurology

Three scenarios:

(1) Patient is not normally on antihypertensive therapy
(2) Patient is normally on antihypertensive therapy
(3) Patient cannot swallow tablets

(2.1) Patient Is *NOT* Normally on Antihypertensive Therapy

First-Line Agent: Nifedipine Retard

10 mg, repeated after 1 hour if no change in BP.
Do *NOT* use crushed nifedipine capsules.
If no reduction in BP, move to second-line agent.

Second-Line Agent: Bisoprolol

5 mg. If either contraindicated or no effect, move to third-line agent.

Third-Line Agent: Ramipril

5 mg, repeated at 3 hours if necessary.
Contact hypertension specialists for clinical review.

(2.2) Patient *IS* Normally on Antihypertensive Therapy

First-Line Agent:

Check whether the patient has received normal antihypertensive medication. If not, administer this.

Second-Line Agent:

Contact hypertension specialists for clinical review.
A = ACE inhibitor, B = β-blocker, C = calcium channel blocker, D = diuretic:
If patient is on A, add in C (nifedipine LA 10 mg).
If patient is on C, add in A (ramipril 5 mg).
If patient is on D, add in A (ramipril 5 mg).
If patient is on A + C, add in D (bendrofluazide 2.5 mg).
If patient is on A + D, add in C (nifedipine LA 10 mg).
If patient is on A + C + D, add in B (bisoprolol 5 mg).

(2.3) Patient Cannot Swallow Tablets

Pass nasogastric tube and administer appropriate medicines in liquid form as prescribed above.

(3). Patient Is on the Surgical Ward: Systolic BP >170 mm Hg + Headache/Seizure or Central Nervous System (CNS) Deficit

Treatment should start **IMMEDIATELY** on the ward using noninvasive monitoring.
Use first-line, second-line, and third-line protocol as in (1) above.

- Antihypertensive protocol is the same as used in recovery.
- On-call surgical resident must do the following:
  - Contact consultant vascular surgeon to inform her or him of high BP associated with seizure/headache or onset of CNS deficit.
  - Contact ICU to arrange urgent transfer for invasive BP monitoring.
  - Consider administration of steroids (e.g., dexamethasone IV, 8 mg).

flow during a period when cerebral pressure autoregulation may be impaired by the effects of anesthesia. Baroreflexes are impaired by the direct effects of surgery, but cerebral blood flow may be impaired by carotid clamping or surgery itself. Postoperatively, cerebral circulation distal to the surgical site is increased compared with preoperative values in the presence of impaired autoregulation and baroreflexes.

The principal goals of intraoperative management are to protect the brain and protect the heart, but these two goals may be conflicting. For example, increasing blood pressure to augment cerebral blood flow can increase afterload or myocardial contractility, thereby increasing the oxygen demand of the heart.

Under general anesthesia, manipulation of arterial carbon dioxide tension ($Paco_2$) affects cerebral blood flow. Although permissive hypercapnia dilates cerebral vessels in nonischemic areas of the brain, it may be detrimental if blood flow is diverted from already maximally dilated cerebral arteries perfusing ischemic areas. Conversely, hypocapnia may constrict vessels in adequately perfused, nonischemic areas of the brain to reroute blood to ischemic areas, thereby causing inverse steal. Because neither of these responses is predictable, most experts recommend maintenance of normocarbia.

Monitoring during carotid endarterectomy includes standard monitoring for general or regional anesthesia: temperature probe, blood pressure cuff, pulse oximeter, and end-tidal carbon dioxide. An intraarterial catheter is placed for beat-to-beat blood pressure monitoring for earlier detection and treatment of changes in blood pressure. Leads II and V5 of the electrocardiogram should be monitored for ST-T segment changes due to the high incidence of myocardial ischemia after carotid reperfusion.

The development of new neurologic signs postoperatively requires immediate assessment and investigation, including Doppler assessment of carotid flow and imaging of the brain. Immediate return to the operating room may be required.

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42 Chronic Nonsteroidal Antiinflammatory Drug Use

Arthur Kitt • Celeste M. Lombardi

Case Synopsis

A 60-year-old man with a history of osteoarthritis has been taking naproxen for the past 3 years without complications or side effects. He experienced sudden severe nausea and vomited frank blood. He was taken to the emergency department and underwent an urgent upper gastrointestinal (GI) endoscopy, which revealed a bleeding gastric ulcer.

PROBLEM ANALYSIS

Definition

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used drugs that act by inhibiting cyclooxygenase and the formation of prostaglandins. Prostaglandins are derived from arachidonic acid, formed by phospholipase A_2 acting on cell membrane phospholipids (Fig. 42.1). NSAIDs are among the most commonly used drugs worldwide and are usually well tolerated. However, like all medications, NSAIDs are not without side effects. They are known to cause the following:

- GI toxicity, leading to the formation of peptic ulcers
- Unwanted antiplatelet effects (nonselective inhibitors of cyclooxygenase)
- Potential for increased thrombogenicity (selective cyclooxygenase-2 [COX-2] inhibitors)
- Renal toxicity, with potential alterations of potassium and fluid balance, decreased renal function, nephrotic syndrome with interstitial nephritis, papillary necrosis, and rhabdomyolysis
- Anaphylactic and anaphylactoid reactions in select patients

Recognition

Gastrointestinal Effects

NSAID use is the second most important cause of peptic ulcers after *Helicobacter pylori* infection. The primary mechanism of ulcer formation is from suppression of gastric prostaglandins, although decreases in nitric oxide and calcitonin gene-related peptide may also be involved. This leads to decreases in epithelial mucus, bicarbonate secretion, and mucosal resistance to injury. NSAIDs also reduce gastric mucosal blood flow, with subsequent damage to the vascular endothelium (an early effect of NSAID administration) in conjunction with an enhanced adherence of neutrophils to the vascular endothelium. The neutrophil adherence causes endothelial injury by release of oxygen-derived free radicals.

Thrombogenic Effects

Thromboxane A_2 is a major product of COX-1 metabolism in platelets (see Fig. 42.1). It causes platelet aggregation, vasoconstriction, and smooth muscle proliferation. In patients with peripheral vascular disease, increased thromboxane production is associated with increased risk of major vascular events. Aspirin is a potent inhibitor of platelet cyclooxygenase (COX-1), which blocks thromboxane production for the life of the platelet. With other NSAIDs, this process lasts 24 hours or less. This effect underlies aspirin's ability to reduce the incidence of cardiovascular death, myocardial infarction, and stroke in high-risk patients. However, high doses or toxic doses of aspirin can inhibit vitamin K–dependent coagulation factors, leading to an increase in prothrombin time and international normalized ratio.

In contrast, prostacyclin is a product of COX-2 metabolism in vascular endothelium. This is postulated from the finding that pharmacologic inhibition of COX-2 leads to the inhibition of prostacyclin formation. Prostacyclin inhibits platelet aggregation and smooth muscle proliferation and causes vasodilation. Nabumetone, etodolac, and nonacetylated salicylates (relatively COX-2–selective NSAIDs) inhibit COX-2–mediated prostacyclin biosynthesis and seem to have little or no effect on platelet aggregation. Other NSAIDs block COX-1 thromboxane biosynthesis and COX-2 prostacyclin production with less selectivity (Table 42.1; Fig. 42.2).

Renal Effects

Up to 5% of patients on regular NSAID therapy develop one or more nephrotoxic side effects, including fluid and electrolyte abnormalities, acute renal failure, and nephrotic syndrome (Box 42.1). The mechanism of action of these side effects is inhibition of the production of prostaglandins I_2, E_2, and D_2 by blocking of the COX-1 isoenzyme. This reduces renal perfusion by causing acute renal artery vasoconstriction, medullary ischemia, and, in some cases, acute renal failure. NSAIDs also decrease the efficacy of antihypertensive medications because they require intact renal prostaglandin function. The exceptions are calcium channel blockers and angiotensin II receptor antagonists, which are not influenced by renal prostaglandins. Various NSAIDs have different effects on blood pressure, depending on their capacity to inhibit renal vasodilatory prostaglandins. Sulindac, for instance, may be a weaker inhibitor of renal prostaglandins and thus exert less effect on blood pressure in hypertensive individuals. Blood pressure needs to be closely monitored in patients who are started on NSAID therapy and take antihypertensive medication, especially those 55 years and older.

Fluid and electrolyte disturbances are common NSAID-associated renal side effects. They occur as a result of inhibition of prostaglandin formation in the thick ascending limb of the loop of Henle and the

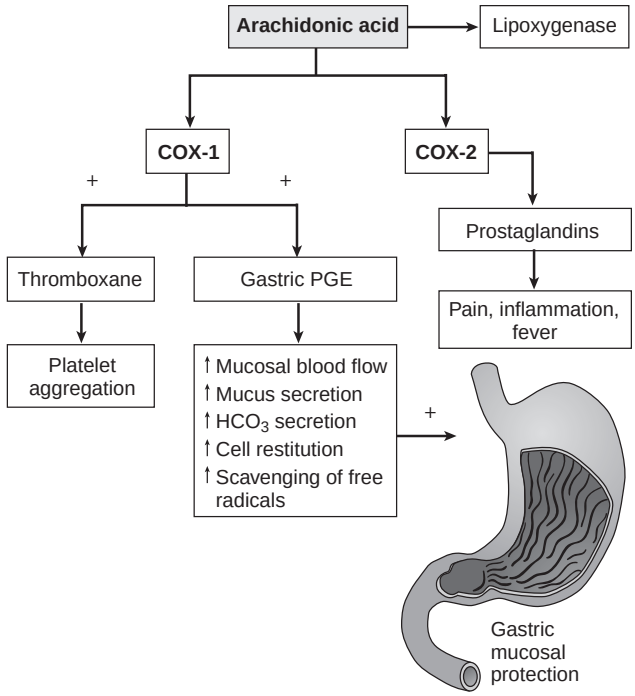

Fig. 42.1 Biosynthesis of prostaglandins from arachidonic acid via the cyclooxygenase (COX-1 and COX-2) pathways. Arachidonic acid, the immediate precursor of prostaglandins, is derived from membrane phospholipids in reactions catalyzed by the two COX isoenzymes. The gene for COX-1 (the "housekeeping" enzyme) is expressed constitutively and maintains organ homeostasis, including integrity of the gastric mucosa. The gene for COX-2 (the "inflammatory" enzyme) is inducible. Thromboxane derived via COX-1 causes platelet aggregation or the listed gastric mucosal protective effects. In contrast, prostaglandins such as prostacyclin (PGI_2) derived via COX-2 are mediators of pain, inflammation, and fever. *PGE,* Prostaglandin E. (Adapted from Wolfe MM: Therapy and prevention of NSAID-related gastrointestinal disorders. In Wolfe MM, editor: *Therapy of digestive disorders: a companion to Sleisenger and Fordtran gastrointestinal diseases.* Philadelphia, WB Saunders, 2000, pp 96-112.)

TABLE 42.1 Inhibition of Prostacyclin and Thromboxane Biosynthesis and Risk of Thrombosis

Drug	Prostacyclin	Thromboxane	Thrombosis Risk
Low-dose aspirin	±	⇊	↓
Conventional	↓	↓	Unclear
COX-2–specific inhibitors	↓	±	Unclear

COX, cyclooxygenase.
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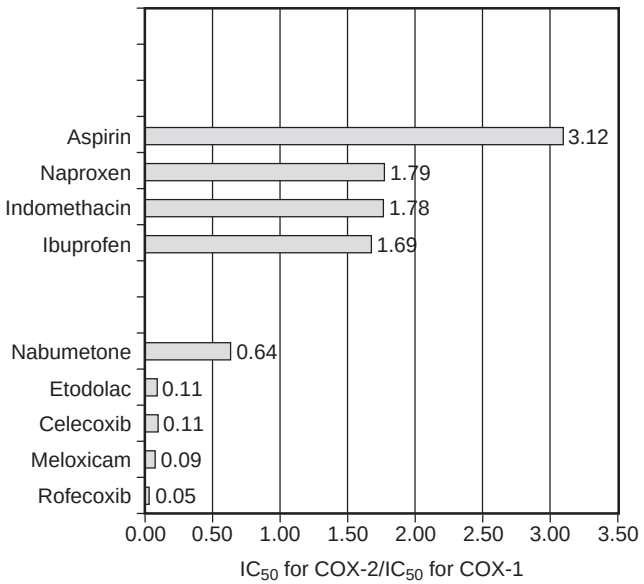

Fig. 42.2 Selectivity of COX-2 inhibitors. Comparison of in vivo inhibitory concentration (IC_{50}) ratios (COX-2/COX-1) of selective and nonselective nonsteroidal antiinflammatory drugs. A lower ratio indicates an increased degree of selectivity for COX-2. (Adapted from Feldman M, McMahon AT: Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional anti-inflammatory drugs, with less gastrointestinal toxicity? *Ann Intern Med* 132:134-143, 2000.)

distal renal tubule, leading to hypotonic sodium and water retention. With the inhibition of the cyclooxygenase pathway, there is a theoretical increase in leukotriene formation via the 5-lipoxygenase pathway, leading to increased capillary permeability and edema formation. This is often seen in patients who develop congestive heart failure.

Hyperkalemia is a rare but serious complication of chronic NSAID therapy. This can occur as a result of inhibition of prostaglandin-mediated renin release. This, in turn, leads to decreased aldosterone formation and decreased secretion of potassium in the distal renal tubules.

The development of nephrotic syndrome with interstitial nephritis is rare and is not clearly understood. It is theorized that the preferential formation of leukotrienes and inhibition of prostaglandins increase vascular permeability, leading to nephrotic-range proteinuria and interstitial nephritis.

Renal papillary necrosis is also rare and is thought to occur in cases of NSAID overdose in severely dehydrated patients. The combination of prostaglandin inhibition and high intrapapillary doses of NSAIDs, which may be cytotoxic themselves, leads to papillary necrosis. This is unlikely to occur with conventional doses of NSAIDs.

Anaphylactic and Anaphylactoid Reactions

A small number of patients experience allergic and pseudoallergic reactions to aspirin and NSAIDs. Some reactions are caused by the similar pharmacologic properties of traditional NSAIDs, which inhibit both COX-1 and COX-2. Prostaglandin E_2 formation is blocked by the inhibition of COX-1, leading to a relative increase in leukotriene formation and histamine release from mast cells. Such a pseudoallergic reaction occurs after the first exposure to the NSAID, which makes prior sensitization impossible. Aspirin and other NSAIDs that are more specific for COX-1 than COX-2 (see Fig. 42.2) can induce rhinorrhea, bronchospasm, and laryngospasm in patients with a prior history of sinusitis and asthma. Cross-sensitivity of aspirin and other relatively COX-1–specific NSAIDs with newer COX-2–selective antagonists does not occur. This is further evidence that COX-1 inhibition is the inciting event in aspirin-induced respiratory symptoms.

Some patients display a true allergy to a specific NSAID, with prior exposure leading to the formation of immunoglobulin E (IgE) antibodies. On subsequent exposure, they experience symptoms, including urticaria, angioedema, and anaphylaxis. Assays for specific drug haptens have not been developed, and IgE antibodies are rarely found in the blood of these patients. Therefore the term *anaphylactoid* has been used to describe such reactions. These reactions are caused by a specific NSAID, and patients are able to take other NSAIDs without difficulty.

BOX 42.1 Renal Syndromes Related to Therapy With Conventional Nonsteroidal Antiinflammatory Drugs

Fluid and electrolyte abnormalities
Acute renal failure
Hemodynamic compromise
Nephrotic syndrome (minimal-change glomerulopathy, interstitial nephritis)
Acute papillary necrosis (typically, single drug cause)
Other systemic interactions
Hypernatremia
Water retention
Hyperkalemia
Membranous glomerulopathy
Chronic papillary necrosis (typically, multidrug causes)
Chronic heart failure
Hypertension (treated)

Risk Assessment and Implications

Gastrointestinal Injury

Dyspepsia is not a reliable means of assessing GI mucosal damage. Ten percent to 20% of patients on NSAID therapy complain of dyspepsia, yet 50% of endoscopic findings show normal GI mucosa. Most patients do not complain of GI symptoms until they develop a life-threatening upper GI bleed. Risk factors for the development of ulcers include advanced age (older than 65 years), renal or hepatic impairment, prior history of ulcers, smoking, alcohol use, concomitant use of oral corticosteroids or anticoagulants, high doses of NSAIDs, and prolonged duration of therapy.

Since recognition of the two isoforms of cyclooxygenase, the COX-1 enzyme has been identified as the one responsible for the formation of gastric prostaglandin E_1, and nonselective NSAIDs have been implicated in a higher risk of GI complications. It is important to understand the relative selectivity of the NSAIDs for COX isoforms, because this may influence the decision of which drug to choose for a patient. For example, etodolac, meloxicam, and nabumetone have a relatively higher affinity for COX-2 than for COX-1 (see Fig. 42.2) and have a safer profile with respect to GI toxicity.

The Celecoxib Long-Term Arthritis Safety Study (CLASS) was a 6-month randomized, double-blind, controlled trial comparing the GI toxicity of celecoxib (400 mg twice a day) with that of more traditional NSAIDs (diclofenac 75 mg twice a day; ibuprofen 800 mg three times a day). The primary end point was ulcer-related complications (gastric perforation, gastric outlet syndrome, GI bleeding), and the secondary end point was symptomatic ulcers. Although there appeared to be a difference in symptomatic and complicated ulcers, this was not statistically significant. Two confounding factors in the study were the supratherapeutic doses of celecoxib used and the inclusion of 21% of patients on low-dose aspirin for cardiovascular prophylaxis. Aspirin is known to increase the risk of upper GI hemorrhage. The ulcer complication rate among the nonaspirin users who took celecoxib was similar to that of the general population, but because there was no placebo group, it was difficult to assess the risk of ulcers with celecoxib. However, we were able to ascertain that patients tolerate celecoxib better than diclofenac and ibuprofen, with less decline in hematocrit, a reduced incidence of dyspepsia, and fewer required endoscopies.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) was a 12-month trial performed to compare the GI toxicity of rofecoxib (Vioxx)[1] 50 mg daily to the more traditional NSAID naproxen 500 mg twice a day. The primary end point was confirmed clinical upper GI events, including symptomatic gastroduodenal ulcers, perforation, or obstruction or upper GI bleeding. The secondary end point was complicated GI events causing severe patient compromise. Results showed a statistically significant reduction in GI events with rofecoxib compared with naproxen. The reduced incidence of GI toxicity with rofecoxib was even present in patients with risk factors for GI events, including advanced age, corticosteroid use, prior history of GI perforation or obstruction, and *H. pylori* infection. This was the first study to demonstrate a definitive benefit with the use of a selective COX-2 inhibitor. Since then, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, which, compared the rates of upper gastrointestinal events among patients taking etoricoxib and diclofenac, showed a lower rate of uncomplicated gastrointestinal events among those taking etoricoxib (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.45–0.74). This was the case for patients taking concomitant aspirin and proton pump inhibitors. Uncomplicated gastrointestinal events included evidence of uncomplicated bleeding, as well as gastric and esophageal ulcer formation. However, there was no difference in the rate of complicated gastrointestinal events between the etoricoxib and diclofenac groups.

Thrombogenicity

COX-2–selective antagonists preferentially block the formation of prostacyclin, with little effect on thromboxane production. Thus there is a theoretical concern about an increased risk of thrombosis.[2] This may be especially true among elderly patients, who are at higher risk of atherosclerotic disease.

In the Adenoma Prevention with Celecoxib (APC) study, celecoxib at 200 mg and 400 mg twice daily was shown to be associated with an increased rate of cardiovascular events compared with that of placebo. Seven of 679 patients in the placebo group (1.0%) had myocardial infarction, stroke, or heart failure, whereas 16 of 685 patients receiving 200 mg of celecoxib twice daily (2.3%; 95% CI 0.9–5.5) and 23 of 671 patients receiving 400 mg of celecoxib twice daily (3.4%; 95% CI 1.4–7.8) had myocardial infarction, stroke, or heart failure. In the MEDAL study, diclofenac appeared to be related to a 1.3% annual risk of cardiovascular event per year, and the selective COX-2 inhibitor etoricoxib was associated with a 1.46% annual risk—not a statistically significant difference. In 2015 the Food and Drug Administration (FDA) strengthened label warnings on all nonaspirin NSAIDs stating that these medications are known to increase the risk of heart attack and stroke.

Renal Injury

Patients with the greatest risk of developing renal insufficiency due to the inhibition of renal prostaglandins are the elderly and those with renal or liver disease, hypertension, some degree of cardiovascular compromise, congestive heart failure, or hypovolemia. It has been noted that COX-2 is also produced in the kidney, so both nonselective and selective inhibition of COX-2 can lead to edema formation.

Celecoxib has been evaluated for its ability to impair renal function—specifically, nephrotic syndrome, interstitial nephritis, increased

[1] Rofecoxib (Vioxx) was voluntarily withdrawn from the market by its manufacturer (Merck) on September 30, 2004, owing to an increased risk of coronary events.

[2] See footnote 1 and Topol EJ: Failing the public health—rofecoxib, Merck, and the FDA. *N Engl J Med* 351:1707-1709, 2004; and Fitzgerald GA: Coxibs and cardiovascular disease. *N Engl J Med* 351:1709-1711, 2004.

serum creatinine levels, and papillary necrosis. Celecoxib seems to cause less renal impairment compared with nonselective COX inhibitors, but this has not been tested rigorously. Therefore, at least for now, selective COX-2 inhibitors must be used with caution in patients with preexisting renal disease, just as with traditional NSAIDs.

Allergic Reactions

There have been rare reported cases of aseptic meningitis in patients with arthritis who were treated for months with specific NSAIDs. In these cases, the aseptic meningitis is thought to be an immune reaction to the NSAID. IgG and immune complexes have been found in the cerebrospinal fluid of patients with aseptic meningitis. This has not been reported with aspirin. There have also been rare reports of cough, fever, pulmonary infiltrates, and eosinophilia after exposure to multiple NSAIDs, except aspirin. Such allergic alveolitis or hypersensitivity pneumonitis is also thought to be mediated by an immune reaction, because interstitial lymphocytes and eosinophils were found in lung biopsies taken from these patients. This could be either an IgE-mediated reaction or delayed hypersensitivity.

MANAGEMENT

Gastrointestinal Toxicity

About 15,000 people die each year as a result of major GI complications from NSAIDs, including hemorrhage, perforation, and obstruction. NSAID-induced ulcers heal spontaneously, but slowly, once the NSAID is discontinued; antisecretory therapy accelerates ulcer healing. Although H_2-antagonists are inexpensive, proton pump inhibitors are generally preferred. They cause more rapid ulcer healing and early symptomatic relief. If patients continue to take NSAIDs while on ulcer therapy with an H_2-antagonist (e.g., ranitidine 150 mg twice a day) or a proton pump inhibitor (e.g., omeprazole 20 mg daily), there is a high rate of ulcer recurrence. Surgery is reserved for patients who present with severe GI hemorrhage or perforation. NSAIDs should be avoided in patients who are taking antiplatelet agents (e.g., clopidogrel) or anticoagulant medications, as this has been shown to further increase bleeding risks.

Allergic Reactions

Aspirin desensitization has been successfully undertaken, with patients receiving aspirin 650 mg twice a day for up to 2 weeks. Urine leukotrienes have been followed, with a significant decrease noted after desensitization. Such desensitization may be especially beneficial for older patients with cardiovascular disease who need to be on long-term aspirin therapy.

PREVENTION

Peptic Ulcers

Misoprostol, a prostaglandin E_1 analog, decreases the risk of gastric and duodenal ulcers. H_2-antagonists and proton pump inhibitors are used to reduce the incidence of duodenal ulcers and gastric ulcers, respectively. For patients at high risk of developing GI complications, a selective COX-2 antagonist is preferred. Studies have also shown that topical NSAIDs, such as diclofenac, has been associated with decreased risk of peptic ulcers in patients of all ages.

Thrombogenicity

If patients are taking traditional NSAIDs and COX-2–selective antagonists, those at risk for cardiovascular events should be on low-dose aspirin. Because the traditional NSAIDs and aspirin inhibit COX-1, there may be competitive antagonism. There is also the added risk of upper GI bleeding. Thus for patients taking aspirin, an H_2-antagonist may be the better choice for GI prophylaxis. Omeprazole increases aspirin's rate of absorption. It may rapidly increase salicylate levels, with potential toxic effects.

Renal Toxicity

In general, patients with a serum creatinine level of 2.5 mg/dL or higher should not be started on conventional NSAID therapy. Those on antihypertensive therapy need to have their blood pressure closely monitored during the initiation of NSAID therapy. A recent study also showed that NSAID therapy is more likely to cause chronic kidney disease in patients with hypertension than in the general population. Patients at risk of developing congestive heart failure should also be closely monitored while on NSAID therapy.

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43 Complications After Pneumonectomy

Harleena Gulati • Eric Jacobsohn

Case Synopsis

A 72-year-old man is scheduled for a right-sided pneumonectomy for non–small-cell lung cancer. He has a past medical history of long-standing smoking, diabetes mellitus, and hypertension. He has a remote history of non–Q-wave myocardial infarction with a coronary artery stent placed in his left anterior descending artery. He had a nuclear medicine stress test performed 1 year previously that was negative for myocardial ischemia. His medications include aspirin, simvastatin, and metoprolol.

His surgical course is uncomplicated and includes a combined general anesthetic–thoracic epidural technique with a standard posterolateral chest incision. There is minimal blood loss, and he receives limited intraoperative and postoperative fluid. The chest tube is removed on postoperative day 1. On postoperative day 3, the patient has increasing dyspnea, and a chest radiograph shows that the left lung has diffuse bilateral pulmonary infiltrates, in keeping with pulmonary edema. Because of progressive respiratory distress, he is intubated, and mechanical ventilation is commenced. The patient's oxygen saturation remains between 90% and 94% on 100% oxygen, 10 cm H_2O positive end-expiratory pressure, and optimal ventilator settings. A pulmonary artery catheter is judiciously inserted, and appropriate placement is confirmed by chest radiograph. The cardiac output and wedge pressure are low, there is moderate pulmonary artery hypertension and a transpulmonary gradient, and the right atrial pressure is elevated. A transesophageal echocardiogram shows mild right ventricular and right atrial dilation, with no demonstrable intracardiac shunt. A diagnostic bronchoalveolar lavage is performed and is negative for inflammatory cells or organisms (subsequent cultures are negative). A diagnosis of postpneumonectomy pulmonary edema, complicated by right ventricular dysfunction, is made. Supportive therapy includes diuresis, lung-protective ventilatory support, low-dose dobutamine, steroids, and inhaled prostacyclin (for increased pulmonary artery pressure and refractory hypoxemia). On postoperative day 5, hemodynamically unstable atrial fibrillation develops, and the patient is cardioverted. An amiodarone infusion is commenced. The patient's troponin level increases to 1.1 ng/mL. He is fully heparinized, and β-blockade is intensified. After 14 days of supportive therapy, including an early tracheostomy, he is successfully weaned from mechanical ventilation. After discharge from the intensive care unit, an angiogram shows stable coronary artery disease.

PROBLEM ANALYSIS

Definition and Recognition

Pneumonectomy is one of the surgical curative options for non–small-cell lung cancer. It is most frequently performed for bronchogenic carcinoma involving the hilum, and is part of a multimodal treatment approach combined with chemotherapy and radiotherapy. It is rarely performed for inflammatory lung disease, traumatic lung injury, congenital lung disease, and irreversible atelectatic conditions. If pneumonectomy is considered for a centrally located lesion, a parenchymal-sparing sleeve lobectomy may have some benefit. Although it is technically a more complex operation, there may be some advantages such as preserved pulmonary function, avoidance of postpneumonectomy complications, and improved patient quality of life.

Extrapleural pneumonectomy (EPP) is typically done for local control of malignant pleural mesothelioma. In addition to a pneumonectomy, an EPP operation requires an en bloc resection of lung, pleura, pericardium, and diaphragm.

Pneumonectomy is a major operation that results in changes in anatomy and cardiopulmonary physiology. Potentially serious and sometimes life-threatening postpneumonectomy pulmonary, cardiovascular, or other complications are relatively frequent. These are summarized in Box 43.1.

Risk Assessment

Many postoperative complications can be minimized by appropriate patient selection. A thorough assessment of the patient's respiratory mechanics (forced expiratory volume over 1 second [FEV_1]), cardiopulmonary reserve (maximum oxygen uptake [VO_2 max]), and lung parenchymal function (diffusing capacity of the lung for carbon monoxide [DLCO] and arterial blood gas analysis) is required (Fig. 43.1). Predicted postoperative DLCO is the strongest predictor of increased operative mortality and respiratory morbidity. Evaluation of and optimal therapy for any coexisting diseases or conditions, including obesity, cigarette smoking, reversible lung disease, and coronary artery disease, is also important.

Mortality

Right-sided pneumonectomy is associated with a greater mortality rate compared with left-sided pneumonectomy (10%–12% vs. 1%–3.5%). The indication for pneumonectomy may affect outcome; for example, pneumonectomy for lung cancer has a mortality rate of 3% to 4%, whereas that performed for benign disease may be as high as 26%. Emergent pneumonectomy in cases of trauma or massive hemoptysis is associated with mortality rates greater than 30%. Also, pneumonectomy performed by thoracic surgeons has a lower mortality than that performed by general surgeons. Associated lung disease, history of coronary artery disease, history of congestive heart failure, hypertension, atrial fibrillation, cerebrovascular accident, cigarette smoking, and a 10% or greater weight loss over the 6-month period before surgery all contribute to higher mortality risk.

BOX 43.1 Complications After Pneumonectomy

Pulmonary
Hypoxemia
Postoperative respiratory failure
Pneumonia
Acute lung injury
Chronic pulmonary debility or deficiency
Postpneumonectomy pulmonary edema
Postpneumonectomy syndrome
Bronchopleural fistula
Pulmonary embolism
Empyema
Esophagopleural fistula
Hemothorax
Chylothorax
Contralateral pneumothorax
Pneumomediastinum
Mediastinal infection (mediastinitis)
Vocal cord paralysis
Atelectasis

Cardiovascular
Supraventricular tachyarrhythmias
Sustained ventricular tachycardia/fibrillation
Nonsustained ventricular tachycardia
Bradyarrhythmias
Myocardial infarction
Intracardiac shunt
Cardiac tamponade or herniation
Pneumopericardium

Miscellaneous
Postpneumonectomy paralysis
Postpneumonectomy scoliosis
Difficulty interpreting pulmonary artery catheter data
Wound infection
Deep vein thrombosis
Renal failure

Postoperative Pulmonary and Cardiac Function

Multiple studies have looked at postoperative changes in pulmonary and cardiac function after pneumonectomy. These are summarized in Box 43.2.

Postpneumonectomy pulmonary function predictably decreases, but changes are less than anticipated for the amount of tissue resected. FEV_1, DLCO, and forced vital capacity (FVC) usually decrease by less than 50%. FEV_1 continues to decrease by 3% to 4% annually. Arterial oxygen saturation, Po_2, and Pco_2 do not change in patients who have a relatively healthy remaining lung. Patients with adequate remaining lung function have been shown to tolerate further major surgeries.

Postpneumonectomy cardiovascular function changes, but with conflicting reports depending on the study. Some studies show that right ventricular ejection fraction decreases with an increase in right ventricular end diastolic volume postoperatively; however, this is inconsistent.

MANAGEMENT AND PREVENTION

Complications occurring after pneumonectomy may be pulmonary, cardiac, or unrelated to either of these systems.

Pulmonary Complications

Postoperative Respiratory Failure

Proper patient selection and the identification and treatment of reversible disorders involving the heart and lungs have greatly reduced postoperative respiratory failure. The following factors may also reduce the incidence of perioperative respiratory complications associated with pneumonectomy:

- Surgery performed by a certified thoracic surgeon in a medical center that does a large volume of pulmonary surgeries
- Appropriate perioperative use of pulmonary rehabilitation, bronchodilators, steroids, and antibiotics
- Smoking cessation before surgery
- Effective postoperative physical therapy and incentive spirometry
- Good postoperative pain control (e.g., thoracic epidural analgesia)

Chronic Pulmonary Insufficiency

This condition is largely preventable by appropriate patient selection and preoperative assessment of lung function.

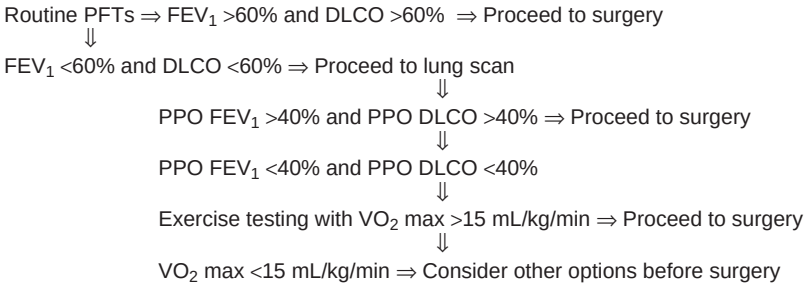

Fig. 43.1 Algorithm for the preoperative pulmonary assessment of pneumonectomy patients. *DLCO,* Diffusing capacity of the lung for carbon monoxide; *FEV_1,* forced expiratory volume over 1 second; *PFT,* pulmonary function test; *PPO,* predicted postoperative; *VO_2* max, maximum oxygen uptake.

Postpneumonectomy Pulmonary Edema

This syndrome develops in up to 5% of patients undergoing pneumonectomy, with a greater incidence in right-sided surgery. Mortality rate exceeds 50%. Postpneumonectomy pulmonary edema results in hypoxemic respiratory failure, with chest radiograph findings of diffuse infiltrates resembling those of acute respiratory distress syndrome. It usually occurs within 72 hours of surgery. Its pathogenesis is multifactorial and not entirely clear, including the following:

- Excessive fluid administration or use of fresh frozen plasma
- Hyperinflation injury during one-lung ventilation
- Coexisting pulmonary hypertension
- Impaired lymphatic drainage due to surgical dissection of hilar lymph nodes
- Occult pulmonary aspiration

There are no specific methods for managing or preventing postpneumonectomy pulmonary edema. Likely beneficial measures include avoidance of hypervolemia and excessive diuresis, lung-protective ventilatory support, and inhaled pulmonary artery vasodilators if pneumonectomy is associated with refractory hypoxemia or elevated pulmonary artery pressures. Steroid therapy remains controversial. Patients with this condition may also benefit from early tracheostomy.

Postpneumonectomy Syndrome

This syndrome is the result of extrinsic compression of the distal trachea and main-stem bronchus, caused by a mediastinal shift toward the side of pneumonectomy and hyperinflation of the remaining lung. It occurs about 6 months after surgery, is more common in patients having pneumonectomy during childhood, and is usually a complication of right pneumonectomy. Treatment involves repositioning the mediastinum and filling the empty thorax with a nonabsorbable material.

Pneumonia

The incidence of postoperative pneumonia is 2% to 40% depending on the population studied. It has been associated with higher rates of reintubation, prolonged length of stay, and increased mortality rate (up to 19%). First- and second-generation cephalosporins are recommended antibiotic prophylaxis.

BOX 43.2 Postpneumonectomy Pulmonary and Cardiac Changes

Pulmonary
Decreased lung volumes (<50%)
Decreased FEV_1 and FVC (<50%)
Annual decrease in FEV_1 by 3–4 mL/yr
Decreased DLCO (<50%)
Decreased lung compliance
Increased airway resistance
Increased or decreased deadspace
Little or no change in P_{O_2} and P_{CO_2}

Cardiovascular
Decrease in right ventricular ejection fraction
Increase in right ventricular end-diastolic volume
Transient increase in pulmonary systolic pressures
Increase in right atrial pressures

DLCO, Diffusing capacity of the lung for carbon monoxide; *FEV_1,* forced expiratory volume over 1 second; *FVC,* forced vital capacity.

Bronchopleural Fistula

The incidence of bronchopleural fistula ranges from 1.5% to 4.5%; it is associated with 30% to 80% mortality and is more common after right pneumonectomy. It often presents 1 to 2 weeks after pneumonectomy as fever, productive cough, hemoptysis, and subcutaneous emphysema. Other associations include large bronchial stump size, incomplete tumor resection, concurrent radiation or chemotherapy, and poor wound healing (e.g., debilitated patients, steroid therapy). Treatment includes antibiotics, longer-term drainage of the pleural space, and repair of any air leaks with muscle flap procedures when appropriate.

Acute Respiratory Distress Syndrome

The incidence of acute respiratory distress syndrome in lung resection cases is 1% to 3%.

Pulmonary Embolism

Most pulmonary emboli arise from the deep veins of the legs. Rarely, they can arise from the pulmonary artery stump or the tumor itself. This complication can be devastating for patients with an already reduced pulmonary vascular reserve. Proper prophylaxis for perioperative deep venous thrombosis is critical. Management includes anticoagulation, but emergent embolectomy may be required immediately postoperatively. In patients further removed from surgery, intravenous thrombolytics should be considered. In those presenting with significant deep venous thrombosis and no pulmonary embolism, retrievable inferior vena cava filter placement may be indicated.

Other Pulmonary Complications

Other complications include empyema, chylothorax and acute hemothorax, esophagopleural fistula, contralateral pneumothorax, and vocal cord paralysis. Management may require surgery (incision and drainage, fistula closure, mediastinal repositioning, and filling of the empty thorax with nonabsorbable material). For partial or complete vocal cord paralysis, consultation with an otolaryngologist is recommended.

Cardiac Complications

Arrhythmia

Atrial tachyarrhythmias (see Chapter 161), especially atrial flutter or fibrillation, are common after thoracic surgical procedures and occur in about 20% of cases. Eighty percent occur within the first 72 hours after surgery. Risk factors for such arrhythmias include age older than 60 years, right pneumonectomy, intrapericardial pneumonectomy, preexisting coronary artery disease, and chronic hypertension. Primary prophylaxis for atrial tachyarrhythmias after pneumonectomy is a β-blocker—either a primary β-blocker or sotalol, which is a β-blocker but also has class III antiarrhythmic activity (see Chapter 161). Amiodarone may also be effective, and there is growing evidence of the role in atrial fibrillation prophylaxis postpneumonectomy or thoracotomy. Pulmonary toxicity can occur with short-term or more commonly with chronic amiodarone administration. Hemodynamically unstable atrial flutter or fibrillation requires immediate direct-current cardioversion, with further management and prevention according to established (advanced cardiovascular life support) guidelines (see Chapter 161).

Myocardial Infarction

Perioperative myocardial infarction (MI) occurs in 1% to 5% of patients after thoracic surgery. Prophylactic perioperative β-blockers should reduce the incidence of acute MI and other cardiac events after thoracic surgery. Preoperative risk stratification for patients having pneumonectomy should follow the new American Heart Association–American College of Cardiology guidelines, which classify pneumonectomy as an elevated risk surgical procedure (intermediate risk category has been removed). The patient described in the case synopsis had been revascularized and was physically active. He also had a negative stress test a year before the planned pneumonectomy, making further preoperative testing unnecessary. All patients receiving chronic β-blocker therapy should continue these drugs. Patients with known coronary artery disease or peripheral vascular disease, and those with two or more risk factors for coronary disease (age older than 65 years, treated or untreated hypertension, diabetes mellitus, hypercholesterolemia, current or recent MI [≤6 months]), should receive perioperative β-blockers.

Routine withdrawal of aspirin therapy before major surgery in patients with coronary artery disease or peripheral vascular disease is probably contraindicated. However, the decision whether to cease such therapy must be individualized. Patients with coronary artery disease on chronic aspirin therapy may develop an aspirin withdrawal syndrome leading to acute MI. Factors such as the severity of cardiovascular and cerebrovascular disease and the presence and age of any stents must also be considered. The risk of withdrawing aspirin must be weighed against the risk of possible increased bleeding.

There is accumulating evidence that statin therapy may be protective in the perioperative period in patients with cardiovascular disease. This is likely related to the drugs' pleiotropic effects. Patients taking statins should not have their therapy interrupted in the perioperative period.

Intracardiac Shunting

A patent foramen ovale may be present in 30% of the population. This can cause significant right-to-left shunting and severe hypoxemia if right-sided heart pressure becomes elevated. This could occur due to poor patient selection, increased preoperative pulmonary artery pressures, pulmonary embolism, pneumonia, pneumothorax, postpneumonectomy pulmonary edema, or pulmonary aspiration. Treatment for the underlying cause of increased right atrial pressure is critical. This includes optimizing right ventricular function and reducing pulmonary artery pressures, if elevated. Measures include inhaled pulmonary artery vasodilators, such as prostacyclin or nitric oxide. Percutaneous closure of the shunt may have to be done in some patients.

Cardiac Herniation

Herniation of the heart through a defect in the pericardium can occur at any time after the surgical procedure. In addition to herniation through a pericardial defect, the heart or mediastinal contents may herniate into the pleural space if a chest tube is inadvertently placed on suction. Hence, many surgeons believe that routine chest tubes, even for short periods, are contraindicated after pneumonectomy. Cardiac herniation presents as sudden-onset hypotension and shock, cyanosis, chest pain, and symptoms of the superior vena cava syndrome. Emergent reopening of the thoracotomy is required to immediately reposition the heart. Suturing the edges of the pericardium to the myocardium or placing a prosthetic patch over the pericardial defect during surgery can prevent this complication. If it is caused by inadvertent chest tube suctioning, this must be stopped immediately. Repositioning the patient with the pneumonectomy side up may also be helpful.

Complications Unrelated to the Cardiopulmonary System

Only a few of the more common and difficult to manage complications unrelated to the heart and lungs are discussed here.

Postpneumonectomy Spinal Cord Ischemia and Paralysis

This is a rare complication caused by intraoperative injury of the intercostal arteries to the thoracolumbar region of the spinal cord, leading to an anterior spinal artery syndrome. Treatment options are limited and largely unproved. They include maintaining a high spinal cord perfusion pressure and use of cerebrospinal fluid drainage.

Postpneumonectomy Scoliosis

Scoliosis is estimated to affect 90% of patients undergoing pneumonectomy. This complication is due to shrinkage of the thoracic cage after surgery. Associated symptoms are usually mild and mostly inconsequential.

Difficulty Interpreting Pulmonary Artery Catheter Data

A pulmonary artery catheter or central venous access is not routinely required for pneumonectomy. However, if a pulmonary artery catheter is used during thoracic surgery, it is important to note that data derived from the catheter may vary, depending on which lung or segment it floats to (e.g., dependent or nondependent zone), whether one-lung ventilation is used, and when the readings are made. Depending on the clinical circumstances, a pulmonary artery catheter has the potential to provide misleading data. If placed in the postoperative period, caution must be exercised when floating and inflating the balloon in the newly sutured or stapled pulmonary artery. Further, one should consider floating the pulmonary artery catheter under fluoroscopy or echocardiographic guidance.

Other Complications

Other complications after pneumonectomy involve primarily the gastrointestinal system and include motility disorders and gastric volvulus. Optimal management may be medical or surgical; if necessary, appropriate consultation should be sought as soon as these complications become apparent.

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Complications of Adrenal Surgery

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Rajeshwari Subramaniam

Case Synopsis 1

Pheochromocytoma
A 38-year-old woman presents in the surgical outpatient department with recurrent attacks of palpitations, headache, diaphoresis, occasional right-sided abdominal pain over the last year, and a neck swelling for the last 2 months. On examination she is severely hypertensive (220/130 mm Hg); a 3-cm thyroid nodule is present in the front of the neck. An ultrasound of the abdomen reveals a right-sided suprarenal mass. She is admitted for further evaluation, optimization, and surgical excision of the suprarenal mass.

Case Synopsis 2

Cushing Syndrome
A 45-year-old man presents in the endocrinology outpatient department with a history of progressive proximal muscle weakness, low back pain, and generalized edema for 6 weeks. Investigations reveal bilateral adrenal hyperplasia, elevated cortisol and adrenocorticotropic hormone (ACTH) levels, hypokalemia, and metabolic alkalosis. His condition deteriorates rapidly during hospitalization, and he is scheduled for emergent adrenalectomy.

Case Synopsis 3

Conn Syndrome
A 56-year-old male patient with gallstone disease is found to have asymptomatic hypokalemia ($[K^+]$ 2.0). He is also a hypertensive on treatment. Computed tomography evaluation shows a left adrenal neoplasm measuring 2.7 × 2.4 cm, and he is admitted for diagnosis and possible laparoscopic adrenalectomy combined with cholecystectomy.

PROBLEM ANALYSIS

Definition

Disorders of the adrenal gland can be broadly grouped into those arising from the cortex (producing cortisol and/or mineralocorticoid and/or androgen excess) and those arising from the medulla (producing an excess of catecholamines and their metabolites). Cortex-related disorders are Cushing and Conn syndromes. Cushing syndrome is usually associated with bilateral hyperplasia; Conn syndrome (primary hyperaldosteronism) is usually caused by a single adenoma. Adrenal hyperplasia resulting from pituitary ACTH production is termed *Cushing disease* and is associated with hyperpigmentation. *Cushing syndrome* resulting from other sources of ACTH (ectopic ACTH) is accompanied by bilateral adrenal hyperplasia and symptoms of severe cortisol excess. Pheochromocytomas are tumors derived from the neural crest and can arise anywhere in the sympathetic chain and the adrenal medulla. Traditionally, those arising in the adrenal medulla are termed *pheochromocytomas* and the others are termed *paragangliomas.* These not only secrete epinephrine, norepinephrine, and dopamine, but elaborate their metabolites metanephrine and normetanephrine through intratumoral catecholamine-O-methyltransferase (COMT). Norepinephrine is methylated by phenylethanolamine-N-methyltransferase (PNMT) to epinephrine. The majority of pheochromocytomas are unilateral. Bilateral tumors are associated with congenital syndromes and found mainly in children. Extraadrenal pheochromocytomas (paragangliomas) rarely produce epinephrine and may be multiple or malignant, and are also associated with genetic mutations in the succinyl dehydrogenase (SDH) gene subunits. Up to 25% of apparently sporadic pheochromocytomas may be genetic or familial. Germ-line mutations have been found in five genes (RET proto-oncogene responsible for the MEN syndrome, VHL gene, NF1 gene, SDH subunits D and B) in patients with pheochromocytoma.

A significant proportion (10%–30%) of pheochromocytomas may present as "incidentaloma." These patients may be totally asymptomatic, but experience severe blood pressure (BP) and heart rate fluctuations during surgery.

Adrenal malignancies are associated with signs and symptoms of androgen excess, along with cortisol/mineralocorticoid excess and pressure effects of the tumor.

Significant secondary hypertension is a frequent finding in almost all adrenal tumors, regardless of the cause. Excess cortisol/mineralocorticoid production also results in metabolic disorders such as hyperglycemia, hypokalemia, and metabolic alkalosis.

Recognition

Pheochromocytoma

The combination of hypertension with the clinical triad of headache, palpitations, and diaphoresis is strongly suggestive of pheochromocytoma. Hypertension may be sustained or episodic. Pheochromocytomas can present as a variety of hypertensive, cardiac, neurologic, or metabolic crisis and require a high index of suspicion for their diagnosis. Demonstration of catecholamine excess forms the first step in diagnosing pheochromocytoma. Plasma-free metanephrines are associated with the highest sensitivity for detection of pheochromocytoma and their absence reliably excludes the condition. Good correlation has been found between tumor size, location, and plasma metanephrine concentrations. If increase in plasma metanephrine is greater than 15% of combined metanephrine and normetanephrine, the tumor is likely to have an adrenal location. Anatomic location of the tumor is by magnetic resonance imaging and functional localization by MIBG/DOTANOC-PET scans.

Cushing Syndrome

The cortex elaborates glucocorticoids and mineralocorticoids, which govern a variety of metabolic processes including glucose homeostasis and Na^+/K^+ balance. Cushing syndrome may be due to primary adrenal hyperplasia or result from stimulation from an ectopic source of ACTH. Adrenal hyperplasia secondary to excess ACTH from a pituitary microadenoma results in Cushing disease. An ectopic ACTH-producing tumor results in adrenal hyperplasia, hyperpigmentation, and features of cortisol excess.

Clinical features of Cushing syndrome, usually prominent, are truncal obesity, thin skin, easy bruising, abdominal striae, proximal muscle weakness, hypertension, and hyperglycemia. Although clinically obvious, the diagnosis needs to be confirmed by high concentrations of serum cortisol. Identification of Cushing disease requires the dexamethasone suppression test and the corticotropin-releasing hormone test. The former causes ACTH to fall to very low concentrations in the absence of an ACTH-producing tumor. The latter should cause a marked increase in ACTH release with primary pituitary disease, but not in patients with adrenal tumors or ectopic ACTH production.

Conn Syndrome

Primary hyperaldosteronism (Conn syndrome) is associated with hypokalemia, metabolic alkalosis, hypernatremia, severe hypertension, muscle weakness, polyuria, and thirst, and is usually caused by solitary adenoma. Renal dysfunction may occur secondary to hypertension. The diagnosis is confirmed by high serum aldosterone and low plasma renin concentrations. Conn syndrome accounts for 0.5% to 3% of all cases of secondary hypertension.

Adrenal Cancer

Adrenal malignancies are associated with overproduction of sex hormones, cortisol, and aldosterone. Clinical findings including virilizing effects of androgens, signs and symptoms of Cushing syndrome, and aldosterone excess (hypokalemia and hypertension). Diagnosis is usually made by radiologic studies.

The definitive treatment of adrenal cortical and medullary tumors remains adrenalectomy, after initial medical treatment to provide symptom control and metabolic optimization.

TABLE 44.1 Perioperative Complications of Adrenal Surgery

PREOPERATIVE ISSUES		
Pheochromocytoma	**Cushing Syndrome**	**Conn Syndrome**
Hypertension Cardiac involvement Vasoconstriction	Hypertension Hyperglycemia Metabolic alkalosis Hypokalemia Difficult airway, vascular access Osteopenia Immunosuppression	Hypertension Hypokalemia

INTRAOPERATIVE COMPLICATIONS	
Related to Disease	**Related to Surgical Access/ Technique**
Hemodynamic instability: hypertension/hypotension/pulmonary edema/congestive heart failure	Pneumoperitoneum-related hemodynamic changes
Arrhythmias	Vascular injury and hemorrhage
Hypokalemia	Solid organ injury
Metabolic alkalosis	Diaphragmatic injury, pneumothorax
Glucose homeostasis	Bowel injury

POSTOPERATIVE COMPLICATIONS	
Related to Removal of the Adrenal(s)	**Consequent to Surgical Procedure**
Hypotension Hypoglycemia Hyperkalemia Steroid/mineralocorticoid dependence	Pulmonary complications Deep venous thrombosis Wound infections

Risk Assessment and Implications

Adrenalectomy as a procedure is at high risk of adverse events. Perioperative mortality rates after bilateral adrenalectomy for Cushing syndrome may reach 5% to 10%. The implications of adrenalectomy are related to the individual adrenal lesion, its etiology, and the surgical procedure (Table 44.1) (see later discussion).

Pheochromocytoma: Perioperative Implications

Preoperative Problems and Preparation

Preoperatively, most patients present with severe hypertension, which needs evaluation and control. Cardiovascular involvement includes myocardial ischemia, arrhythmias, or congestive failure (catecholamine cardiomyopathy). Severe vasoconstriction may be seen due to circulating catecholamines, evidenced by pallor and high hematocrit values. Selective α-blockers are the first line of treatment and result not only in control of BP but also in symptom control. Phenoxybenzamine has now been replaced by doxazosin and prazosin. Calcium channel blockers and clonidine may be added if escalating α-blocker dosage does not result in satisfactory BP control. β-blockers may be subsequently added for heart rate and arrhythmia control. Preoperatively, an electrocardiogram, BP, and heart rate record and echocardiography are strongly recommended. Hyperglycemia is frequent and may mandate therapy with insulin. α-Receptor–mediated insulin inhibition predominates over β-insulin–releasing actions causing glucose intolerance in pheochromocytoma.

Intraoperative Hypertension

The majority of significant hypertensive episodes in pheochromocytoma manifest at induction, during events causing sympathetic stimulation (e.g., laryngoscopy, endotracheal intubation, and orogastric or nasogastric tube insertion). Use of drugs that are vagolytic, result in catecholamine secretion, release histamine, or cause dopamine receptor blockade can induce hypertension. These include ketamine, morphine in large doses, atropine, pancuronium, droperidol, metoclopramide, halothane, and desflurane. Vigorous surgical scrubbing, positioning, or surgical incisions in the presence of inadequate analgesia may also result in severe rises in BP. Hypertension in these instances is due to the release of excess catecholamine stores in the sympathetic nerve endings and is responsive to appropriate treatment (e.g., increasing depth of anesthesia). In contrast, pneumoperitoneum, direct manipulation, or squeezing of the gland during surgery can result in hypertensive crises that are far more severe and dramatic, necessitating use of multiple vasodilators for control. High plasma norepinephrine concentration, large tumor size, profound (>10 mm Hg) postural BP fall after α-blockade, mean arterial pressure above 100 mm Hg, and symptomatic high BP have all been seen to correlate with severe intraoperative hemodynamic instability. Intraoperative stability has been observed to be better with doxazosin. Familial pheochromocytomas tend to have more severe hypertension.

Consequences of Severe Intraoperative Hypertension

Uncontrolled or severe intraoperative hypertension can result in myocardial ischemia, pulmonary edema, or congestive cardiac failure. It may rarely progress to multisystem failure, requiring dialysis and ventilator support. Rhabdomyolysis consequent to severe intraoperative hypertension and vasoconstriction occurring at the onset of pneumoperitoneum has been reported. Intraoperative catecholamine crisis has been reported to result in mydriasis and pulmonary edema.

Management of Intraoperative Hypertension

Phentolamine (10–20 mg), sodium nitroprusside (0.01% solution titrated to effect), nitroglycerin (1–2 μ/kg/min), and magnesium sulfate (30–50 mg/kg bolus, 1–2 g/h infusion) have been used to treat intraoperative hypertension. Magnesium sulfate has multiple beneficial effects: it inhibits catecholamine release, blocks the action of catecholamines on adrenoceptors, and is an antiarrhythmic. It has also been shown to be of value in Takotsubo cardiomyopathy, often associated with pheochromocytoma. Nicardipine (5–10 mg/h) and fenoldopam (0.2 mg/kg/min) have been used in resistant cases. Urapidil infusion (10–15 mg/h) has been successfully used to preempt hemodynamic crises during laparoscopic pheochromocytoma excision. More recently, dexmedetomidine (0.3–0.7 μg/kg/h) has been found to be useful for intraoperative hemodynamic management.

Arrhythmias

Supraventricular arrhythmias are common during tumor manipulation. Occasionally ventricular ectopy or arrhythmia may occur. Esmolol in boluses of 0.5 mg/kg is suitable for supraventricular arrhythmias and lidocaine 1 mg/kg for ventricular arrhythmias; for patients with impaired cardiac contractility, amiodarone may be suitable. Labetalol (10–20 mg bolus) may also be useful for pheochromocytomas that predominantly secrete epinephrine.

Hypotension

Persistent hypotension is the most frequent cause of extended recovery room or intensive care stay after adrenalectomy for pheochromocytoma. Postoperative hypotension has been attributed to various causes, including down-regulation of α-adrenergic receptors, residual effects of long-acting α-blockers or intraoperatively administered vasodilators, contralateral adrenal suppression, or hypovolemia. Rarely, hypertension may persist for 1 to 3 days after surgery. The majority of patients become normotensive within 10 days of surgery. Tumor size greater than 60 mm, urinary epinephrine levels greater than 200 mg/day, and urinary norepinephrine levels greater than 600 mg/day are independent predictors of prolonged hypotension requiring postoperative catecholamine support. Postoperative hypotension has been observed more frequently with doxazosin use compared with phenoxybenzamine. An increased blood volume may not protect against hypotension. The drug of choice is norepinephrine titrated to effect (usually 4–20 μg/min). Other drugs are phenylephrine (10–100 μg boluses, or infusion), ephedrine boluses (5–10 mg), and, rarely, epinephrine (1–10 μg/min). Refractory hypotension may necessitate use of vasopressin (0.1–0.4 U/min), with its attendant risk of myocardial ischemia.

Hypoglycemia

Postoperative hypoglycemia is not infrequent after excision of pheochromocytoma and may present insidiously. It is probably caused by excessive rebound secretion of insulin. Onset of drowsiness or stupor after a brief period of wakefulness or delayed recovery postoperatively usually suggests hypoglycemia. The rarity of this condition underscores the importance of regular blood glucose monitoring.

Conn Syndrome: Perioperative Implications

Hypokalemia and hypernatremia are constant findings in Conn syndrome (primary hyperaldosteronism). Severe metabolic alkalosis is also a frequent finding, and care should be taken to avoid hyperventilation. Hypokalemia may be refractory to potassium replacement and spironolactone therapy. Hypokalemia and alkalosis can potentiate and prolong the actions of neuromuscular-blocking drugs. Hypokalemia increases myocardial excitability and risk of intraoperative dysrhythmia and can be worsened by hyperventilation and sevoflurane-induced polyuria. Intraoperative manipulation of the adrenal gland can produce brisk catecholamine release, and often refractory hypertension, in patients with Conn syndrome, who also should have invasive monitoring in place. Frequent arterial blood gas estimations can guide ventilator therapy.

Hypotension may also occur after adrenalectomy for hyperaldosteronism (Conn syndrome) and is corrected by the administration of fludrocortisone. Postoperative hyperkalemia occurs in 5% of patients undergoing adrenalectomy for Conn syndrome. This condition is usually accompanied by postural hypotension and the etiology is thought to be due to suppression of the mineralocorticoid activity of the contralateral gland. It responds dramatically to mineralocorticoid supplementation.

Cushing Syndrome: Perioperative Implications

These patients often have a difficult airway due to central obesity, "buffalo" hump, and preexisting hypoxemia. Severe metabolic alkalosis frequently leads to compensatory respiratory depression and acidosis, atelectasis, and hypoxemia. Intraoperative ventilatory difficulties may occur due to poor lung compliance, worsening the existing hypercarbia and hypoxemia. Hypokalemia occurs due to the weak mineralocorticoid action of cortisol. Nearly 80% patients with Cushing syndrome have diabetes mellitus, and control of hyperglycemia is important in the perioperative period. Increased blood glucose level is associated with increased mortality, higher rates of infection, and longer hospitalization. The guidelines of the American Association of Clinical Endocrinologists and the American Diabetes Association have recommended target values of 140 to 180 mg/dL for the intensive care unit and 100 to 180 mg/dL in the perioperative period. Susceptibility to fractures and easy bruisability mandates extreme care during positioning of these patients. Vascular

cannulation and central line insertion may be particularly challenging. A large recent series analyzing more than 300 patients reported that steroid replacement is routinely required in patients with Cushing syndrome undergoing adrenalectomy and should be started preoperatively.

Rarely, features of hypercortisolism may be refractory to medical treatment and become life threatening, leading to uncontrolled anasarca, metabolic alkalosis, and hypokalemia, warranting emergent adrenalectomy.

Surgical Complications Associated With Adrenal Surgery

Since Gagner's publication in 1992, laparoscopic adrenalectomy has established itself as the standard of care for adrenalectomy, and the open approach is reserved for tumors larger than 10 cm or adrenal malignancy. Open adrenalectomy has been seen to result in a higher incidence of pneumonia, unplanned intubation, unsuccessful ventilator weaning, systemic sepsis, cardiac arrest, renal insufficiency, wound infections, and high 30-day morbidity. The laparoscopic route has the advantages of high-quality resolution and magnification, good hemostasis, reduced hemodynamic fluctuations and blood loss, less postoperative pain, better cosmesis, and earlier ambulation and recovery.

Pneumoperitoneum and Hemodynamic Changes

Earlier studies on laparoscopic pheochromocytoma excision reported severe hypertensive response to CO_2 insufflation. However, subsequent publications demonstrated that the laparoscopic approach actually resulted in lesser hemodynamic perturbations due to the magnified surgical field, micromanipulation, and "dissection of the patient away from the tumor." Intraabdominal pressures less than 10 mm Hg are associated with lesser catecholamine release and hemodynamic changes. However, severe hypertension and pulmonary edema refractory to vasodilators after the onset of pneumoperitoneum have been reported to lead to conversion to open surgery.

Vascular Injury and Hemorrhage

Vascular injuries are the most common surgical complication of laparoscopic adrenalectomy, commonly involving the inferior vena cava/right adrenal vein. The incidence ranges from 0.7% to 5.4%. Transfusion requirements in laparoscopic adrenal surgery, which may be used as surrogate for blood loss, have been reported to be as high as 10%. The pressure of the pneumoperitoneum prevents bleeding from smaller veins, which can become manifest as hematoma or hemodynamic instability postoperatively.

Bowel Injury

A majority of bowel injuries during adrenalectomy are discovered late (>72 hours) when peritonitis develops and are associated with high mortality rates.

Liver, Splenic, and Pancreatic Injuries

These organs are vulnerable on the respective sides (i.e., the liver during right adrenalectomy and the spleen and pancreas on the left).

Pleural and Diaphragmatic Injuries

The high intraabdominal pressure during pneumoperitoneum facilitates entry of gas into the pleural cavity through small diaphragmatic lesions accidentally made by cautery or sharp instruments. An incidence of 0.6% has been reported for laparoscopic renal surgery; no corresponding figures for adrenalectomy are available.

Increase in airway pressure is the first sign of pleural breach to alert the anesthesiologist, accompanied by increase in end-tidal carbon dioxide and a gradual fall in Spo_2 and hypotension. These changes may normally accompany high intraabdominal pressures, or may be confused with endobronchial tube migration secondary to pneumoperitoneum, so the diagnosis may be delayed. A high index of suspicion for this possibility is essential for timely diagnosis. The loss of negative pressure in the pleural cavity causes the diaphragm to billow into the abdominal cavity every time pressure is released ("floppy diaphragm" sign). Small diaphragmatic rents may be sutured endoscopically; for large pneumothoraces, an intercostal drain is placed for 24 to 48 hours.

Major Surgical Complications Resulting From Laparoscopic Adrenalectomy

A series of rare but high-grade and potentially life-threatening complications of laparoscopic adrenalectomy, which were attributed to surgeon inexperience or occurring outside of major referral centers, have recently been reported. These included complete transection of the porta hepatis, ligation of the hepatic artery, ligation of the ureter, ligation of the renal artery, and resection of the normal adrenal instead of a polar renal cell carcinoma. In the first two instances hepatic failure necessitated liver transplant. The third and fourth patients had loss of renal function ultimately requiring nephrectomy.

Postoperative Steroid Replacement

Serious infections and increased length of hospital stay are more frequent in patients receiving steroids.

Postoperative Pulmonary Complications After Adrenalectomy

Postoperative pulmonary complications such as atelectasis and pneumonia may occur in up to 85% of patients with Cushing syndrome undergoing open adrenalectomy. The advent of laparoscopic surgery in patients with Cushing syndrome has dramatically reduced the incidence of pulmonary complications.

Venous Thromboembolism in Cushing Syndrome

Cushing syndrome patients undergoing adrenalectomy have a significantly high incidence of pulmonary thromboembolism, which could be due to glucocorticoid-induced hypercoagulability, as well as surgery and obesity. It appears that patients with Cushing syndrome have a procoagulative phenotype due to cortisol-associated changes in hemostatic and fibrinolytic markers, leading to increased incidence of venous thromboembolism mandating some form of thromboprophylaxis.

In conclusion, many of the complications occurring perioperatively in patients undergoing adrenalectomy are a consequence of the primary disease. Focused preoperative assessment and optimization, use of invasive monitoring, and aggressive intraoperative hemodynamic and metabolic control can minimize the incidence. Surgical complications can be minor or catastrophic, and can be reduced by ensuring that these procedures are carried out in high-volume referral centers by surgeons with adequate experience.

Further Reading

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45 Complications of Carcinoid Tumors

Kerri M. Wahl

Case Synopsis

A 55-year-old man is scheduled for emergency exploratory laparotomy for small bowel obstruction. Anesthesia is induced with intravenous (IV) fentanyl, lidocaine, propofol, and succinylcholine and maintained with sevoflurane in an air-oxygen mixture with vecuronium. During the surgery the patient becomes profoundly hypotensive. His blood pressure does not respond to boluses of IV fluid, ephedrine, and epinephrine. The patient's face and neck appear flushed.

PROBLEM ANALYSIS

Definition

Carcinoid tumors are neuroendocrine tumors that arise from the gastrointestinal (GI) tract (67.5% are midgut carcinoids: ileum, appendix, rectum, pancreas) or an extra-GI primary such as lung or bronchi (25.3% are foregut carcinoids). Primary midgut carcinoid tumors metastasize to the liver or regional lymph nodes and may present with bowel obstruction. They may be nonsecreting or may be associated with flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction. Tumors synthesize, store, and release up to 40 bioactive mediators, the most prominent being serotonin, 5-hydroxytryptophan, histamine, bradykinin, tachykinins, and prostaglandins. The liver usually inactivates mediators secreted into the portal circulation. As such, carcinoid syndrome results from the direct release of vasoactive amines, polypeptides, proteins, and prostaglandins into the systemic circulation. This may occur with extensive liver metastasis of GI tumors, primary hepatic carcinoid tumors, and primary tumors without portal venous drainage (bronchial, ovarian, retroperitoneal). In carcinoid tumor cells, 70% of tryptophan is converted into serotonin, which is then metabolized in the liver, lungs, and brain by monoamine oxidases to 5-HIAA (5-hydroxyindoleacetic acid) and excreted in the urine. Serotonin uptake and storage also occurs in platelets. Urinary serotonin is usually either normal or slightly increased.

The incidence of carcinoid tumors is between 1.2 and 2.1 in 100,000 persons per year, with autopsy incidental findings as high as 8%. The highest incidence is seen in African American males, 4.5 per 100,000. Between 75% and 80% of patients with carcinoid syndrome have small bowel tumors. Patients with small bowel carcinoids tend to present in the fifth and sixth decades, most often with mass effects from the tumor (e.g., abdominal pain or obstruction). The majority of small bowel carcinoids have metastases at presentation and approximately 5% have the carcinoid syndrome. The 5-year overall survival rate is 80%, which decreases to 20% with distant metastasis.

A life-threatening carcinoid "crisis" is an acute exacerbation of the carcinoid syndrome. It results in profound flushing, hypotension or extreme changes in blood pressure, stupor, diarrhea, confusion, bronchospasm, arrhythmias, and hyperthermia. Such crises can be triggered by tumor palpitation, induction of anesthesia and tracheal intubation, inadequate analgesia, surgical stress, drug-induced mediator release, chemotherapy, and hepatic arterial embolization.

Recognition

Carcinoid syndrome is relatively uncommon, affecting approximately 10% of patients with carcinoid tumors. The diagnosis of carcinoid syndrome is usually suspected by the clinical features and confirmed by identification of the focal primary lesion, localization of metastatic lesions, and detection of increased urinary excretion of the byproduct of serotonin metabolism, 5-hydroxyindoleacetic acid (5-HIAA). A positive result for 5-HIAA has a 73% sensitivity and a 100% specificity for carcinoid tumor. Serum chromagraffin A is a glycoprotein secreted with other hormones by neuroendocrine tumors and is 95% specific and almost 80% sensitive for carcinoid tumors. Diagnosis of a neuroendocrine tumor is confirmed with immunohistochemical markers. Natriuretic peptides (NT-proBNP) can be used as a simple marker for the diagnosis of carcinoid heart disease, which can then be confirmed by two-dimensional echocardiography. Metastatic disease is most commonly diagnosed using abdominal computed tomography with contrast. Deposits appear as isodense, hypervascular lesions. Somatostatin receptor scintigraphy using indium-111–labeled octreotide is also useful.

Clinical features of carcinoid syndrome include the following:

- Episodic cutaneous vasomotor flushing, telangiectasia, cyanosis
- Hypotension/hypertension
- Diarrhea and cramping
- Bronchospasm
- Carcinoid valvular heart disease

There is significant patient variability with regard to the type and severity of symptoms. Bradykinin and histamine may play a prominent role in hypotension and sporadic flushing, which is the hallmark of carcinoid syndrome. A mild burning sensation and reddish color may suddenly appear on the face, neck, and chest that lasts for 30 seconds to 30 minutes. As the disease progresses, flushing lasts longer, and may become more diffuse and cyanotic, with the appearance of telangiectasia in the face. These symptoms may be accompanied by severe hypotension and tachycardia. Triggers include certain foods (e.g., avocados, fruits, nuts, melons), coffee and alcohol, defecation, emotional events, mechanical stimulation, and anesthesia. Flushing may also be accompanied by sweating, wheezing, and shortness of breath.

Serotonin causes secretory diarrhea and abdominal cramping. Other symptoms include bronchoconstriction, hypertension, and

bowel ischemia. Serotonin also stimulates fibroblast growth and fibrogenesis leading to peritoneal and cardiac valvular fibrosis. Carcinoid heart disease is characterized by plaque-like deposits of fibrous tissue composed of smooth muscle cells, myofibroblasts, and an overlying endothelial cell layer. These deposits occur most commonly on the endocardium of valvular cusps and leaflets, the cardiac chambers, and occasionally on the intima of the pulmonary arteries or aorta. These changes cause severe tricuspid regurgitation (TR), pulmonary valve abnormalities, and right-sided endocardial disease. The valves and endocardium of the right side of the heart are most often affected because inactivation of humoral substances by the lung protects the left heart. Left-sided heart disease is uncommon and generally associated with bronchial carcinoid or right-to-left intracardiac shunting. Carcinoid heart disease, which eventually occurs in over 50% of patients with carcinoid syndrome, is a major cause of morbidity and mortality. Echocardiography is the standard for detection and quantitation of TR. Elevation of biomarkers chromogranin-A and NT-proBNP (N-terminal probrain natriuretic peptide) are associated with the severity of TR and overall mortality.

Differential diagnosis of severe refractory hypotension may include the following:

- Serotonin-induced carcinoid crisis
- Angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors taken preoperatively
- Anaphylaxis/allergic reactions
- Sepsis with or without shock
- Unrecognized volume depletion or blood-volume deficit from bleeding
- Cirrhosis with portal hypertension and low systemic vascular resistance
- Adrenal insufficiency
- Etomidate, large IV dose of propofol, wrong drug
- Mechanical caval compression
- Air/embolic embolism to the right ventricle
- Carcinoid heart failure, coronary ischemia, arrhythmia
- Biochemical environment: hyponatremia, hyperkalemia, metabolic/respiratory acidosis

The most common treatment approach for perioperative hypotension is to verify the blood pressure, check Spo_2 (oxygen saturation), reduce the depth of anesthesia, and administer IV fluids and a bolus dose of pressor drug (phenylephrine, ephedrine, epinephrine, or vasopressin). For hypotension resistant to the initial resuscitation efforts, a review of the patient's medical history and surgical technique; patient assessment for flushing, rash, hives, or bronchospasm; and verifying that the IV is patent are necessary. Usually, the most likely diagnosis will determine subsequent interventions that may include a pressor infusion, colloid, blood transfusion, steroids, or cardiac evaluation with transesophageal echocardiography (TEE). Carcinoid crisis presenting as refractory hypotension is a diagnosis of exclusion. For patients with known or suspected carcinoid tumors, the most appropriate treatment for severe intraoperative hypotension would be vasopressin, octreotide bolus/infusion, and fluids.

Risk Assessment

Carcinoid tumors occur relatively frequently, but are only rarely symptomatic. Without treatment, the median duration of survival with malignant carcinoid syndrome ranges from 12 to 38 months from the onset of symptoms. The estimated 5-year survival for localized disease is 75% to 93%. With cardiac involvement and symptomatic right-sided heart failure (New York Heart Association class III or IV), the prognosis is poor, with a median survival of less than 1 year. Patients with carcinoid heart disease have much higher (twofold to fourfold) values for serum and plasma serotonin, platelet serotonin, and urine 5-HIAA than those without cardiac involvement. Levels of CgA and NT-proBNP are also associated with overall mortality. Survival at 5 years is 81% in patients with normal CgA levels, 44% in those with elevated CgA but normal NT-proBNP levels, and 16% in those with elevations in both CgA and NT-proBNP.

Implications

Anesthesia can precipitate carcinoid crisis in patients with carcinoid syndrome. As has been described, this syndrome is characterized by flushing, extreme changes in blood pressure, bronchoconstriction, arrhythmias, and confusion or stupor, which can be fatal. Preoperative assessment should include history and physical and evaluation for volume depletion, malnutrition, anemia, and electrolyte imbalance due to secretory diarrhea. Carcinoid heart disease occurs in over 50% of patients with carcinoid syndrome. As such, cardiac evaluation should include a baseline echocardiogram, electrocardiogram, and chest x-ray, especially when NT-proBNP is elevated.

Octreotide acetate (Sandostatin) has simplified the perioperative management of patients with carcinoid tumor and is widely considered the standard treatment for carcinoid symptoms and crises. Control of carcinoid symptoms with an octreotide analog should be a goal before surgery, and meticulous perioperative care is required. Large doses of somatostatin are often necessary in the perioperative and postoperative periods. Octreotide is a synthetic octapeptide analog of somatostatin with an elimination half-life of about 1.5 hours following subcutaneous administration. Octreotide-LAR (monthly injection) may prevent the release of bioactive amines by binding to the sstr-2 subtype of somatostatin G protein–coupled receptors. Octreotide acetate exerts pharmacologic actions similar to the natural hormone somatostatin, but it is an even more potent inhibitor of growth hormone, glucagon, and insulin. Similar to somatostatin, it also suppresses luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. Octreotide has widespread effects including QT prolongation, bradycardia, conduction defects, abdominal cramps, nausea, and vomiting. Symptoms are relieved in more than 80% of patients, although the average response lasts only 18 months. Insulin release in response to hyperglycemia is inhibited as well, which can complicate glucose management in obese patients or non–insulin-dependent diabetics. Unfortunately, octreotide does not prevent or delay cardiac valve disease.

MANAGEMENT

Anesthetic management of patients with carcinoid tumors requires the following:

- Octreotide IV to treat perioperative carcinoid crises (50 μg bolus IV before induction, 100 μg/h IV infusion during surgery; may start continuous infusion 12 hours before surgery and continue postop for 48 hours; may increase as needed to 500 μg/h, e.g., before manipulation of liver metastases).
- Invasive monitoring: arterial line and possible central venous pressure/TEE; large bore IV access; fluid warmers.
- Anesthetic considerations for moderate/severe TR, or right-sided heart failure identified on preoperative echocardiogram.
- Avoid epinephrine, ephedrine, norepinephrine, or calcium, which may provoke release of mediators from the tumor.
- Cautious use of small doses of phenylephrine.
- Treat hypotension with IV octreotide bolus, fluids, and vasopressin.

Stop surgical manipulation of the tumor. Decrease depth of anesthesia. If hypotension is refractory to IV bolus and infusion of octreotide, consider aprotinin (kallikrein inhibitor).

- Bronchospasm: β-agonists may cause intense, prolonged vasodilation. Treat with octreotide, antihistamines, and nebulized ipratropium.
- Partial liver resection/liver transplantation may be associated with large blood loss due to the vascularity of the lesion and high venous pressures (hepatic vein pressures) from TR/PR or right-sided heart disease.
- Consider pretreatment with steroids, H_1 or H_2 antagonists, and 5-HT2 antagonist.
- Intraoperative crisis: flushing, sustained hypotension, bronchospasm, acidosis, and ventricular tachycardia.
- Avoid mediator release caused by stress, induction, intubation, histamine-releasing drugs, hypotension, hypothermia, sympathomimetic drugs, and tumor manipulation.
- Enhanced recovery after surgery protocol ideal with general anesthesia/thoracic epidural/remifentanil infusion.
- Avoid drugs that cause QT prolongation.
- Postoperative care: monitor for symptoms of mediator release, octreotide infusion (undetected metastases may still secrete peptides) for up to 48 hours; fluids and electrolytes, acute pain management; intensive care unit setting.

There is the potential for unpredictable, uncontrolled hormone release precipitated by hemodynamic variation, anesthetic, or surgical stimulus. This may result in hypotensive or hypertensive crises and hemodynamic collapse, which is unresponsive to conventional inotrope and pressor therapy. Continuous blood pressure monitoring is highly desirable, because blood pressure changes may be abrupt. In the event of severe hypotension that is unresponsive to IV fluids, patients with known carcinoid tumors should receive octreotide IV boluses as first-line therapy, followed by a continuous infusion. Vasopressin bolus/infusion would be second-line therapy. If hypotension continues, stop surgical manipulation of the tumor, decrease the depth of anesthesia, and consider aprotinin. Sympathomimetics are often administered but may actually worsen the hypotension, because α-adrenergic stimulation can cause further peptide release from the tumor. Norepinephrine has been shown to activate kallikrein in the tumor and lead to synthesis and release of bradykinin, paradoxically worsening vasodilation and hypotension. Phenylephrine or other adrenergic agonists may trigger further peptide release as well.

Serotonin accentuates the vascular response to catecholamines by stimulating the release and inhibiting the reuptake of norepinephrine. It may also directly stimulate postjunctional α_1-receptors. The resulting hypertension is amenable to standard treatment, such as increasing the depth of anesthesia or administering agents such as labetalol, nicardipine, or nitroprusside. Katanserin (2.5–5 mg IV bolus with IV infusion at 5 mg/h) has also been used. It blocks 5-HT, α_1-receptors, and H_1-receptors.

Therapeutic options for patients with carcinoid tumors include somatostatin analogs to reduce hormone secretion and symptoms; resection of the primary tumor; and excision or ablative therapy for metastases (e.g., radiofrequency ablation, cryotherapy, arterial chemoembolization). In selected cases, liver transplantation may be a treatment option. Other therapeutic options include m-iodobenzylguanidine (MIBG) preparations, interferon-α, and chemotherapy. Cardiac valve replacement surgery is feasible with carcinoid valvular heart disease but is associated with significant morbidity and mortality rates.

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Complications of Laparoscopic Surgery

46

Katarzyna Luba

Case Synopsis

A 75-year-old man with dyslipidemia and hypertension is scheduled for elective laparoscopic repair of hiatal hernia. He has been on nothing-by-mouth (NPO; from the Latin, *nil per os*) status for 12 hours except for his antihypertensive medications (losartan and hydrochlorothiazide). During induction of general anesthesia, his systolic blood pressure drops to 85 mm Hg. The patient receives a 500-mL bolus of lactated Ringer's solution and an intravenous bolus of 100 μg of phenylephrine, and his blood pressure stabilizes. The anesthesiologist places an arterial line and advises the surgeon that he may proceed with the operation. After peritoneal insufflation with carbon dioxide (CO_2), the patient is placed in an extreme reverse Trendelenburg (head-up) position. The blood pressure suddenly drops below 60 mm Hg, and then the arterial line waveform becomes flat and there is no palpable carotid pulse. Breath sounds are present bilaterally and equal. The electrocardiogram (ECG) tracing initially shows normal sinus rhythm but rapidly progresses to sinus bradycardia with ST segment depression. Blood pressure and ECG return to normal after intravenous administration of 1 mg of epinephrine and 1000 mL of crystalloid solution, immediate deflation of the abdomen, and placing the patient in Trendelenburg (head-down) position. However, the anesthesiologist and the surgeon decide to cancel the case and submit the patient to a thorough cardiac workup to rule out a coronary event.

PROBLEM ANALYSIS

Definition

Although a laparoscopic technique is minimally invasive with regard to wound healing time, postoperative pain, length of hospital stay, and patient satisfaction with cosmetic effects, it significantly interferes with normal physiology. Physiologic changes during laparoscopy result from the combined effects of abdominal insufflation, Trendelenburg (head-down) or reverse Trendelenburg (head-up) position, systemic absorption of carbon dioxide (CO_2) used to produce pneumoperitoneum, and the cardiovascular effects of general anesthesia. Administering safe anesthesia for laparoscopic surgery requires the anesthesiologist's awareness of side effects and complications inherent in the laparoscopic technique.

Increased intraabdominal pressure caused by insufflation results in caval compression, reduced venous return, increased systemic and pulmonary vascular resistance, and an increase in left ventricular wall tension. Cardiac output decreases, mainly at the beginning of peritoneal insufflation. A decrease in left ventricular end-diastolic volume has been demonstrated by transesophageal echocardiography (TEE). However, cardiac filling pressures rise due to an increase in intrathoracic pressure during abdominal insufflation. The effects of abdominal insufflation on venous return and cardiac output are somewhat mitigated by the Trendelenburg position, but may be greatly exacerbated by the reverse Trendelenburg position, especially when combined with hypovolemia and vasodilation.

Pneumoperitoneum is accompanied by an acute neurohormonal response. Catecholamine and vasopressin release and the renin-angiotensin-aldosterone axis are activated and contribute to an increase in systemic vascular resistance. Renal blood flow, glomerular filtration rate, and urine output decrease during abdominal insufflation.

Ventilatory effects of pneumoperitoneum include reduced lung compliance, decreased functional residual capacity, and increased ventilation-perfusion mismatch. The Trendelenburg position favors the development of atelectasis. Reduced alveolar ventilation and CO_2 absorption from the peritoneal cavity result in respiratory acidosis. Increased $Paco_2$ and the Trendelenburg position increase cerebral blood flow and intracranial pressure, as well as intraocular pressure, but the extent and clinical significance of these effects are currently unknown.

Arrhythmias occurring during laparoscopy have multiple causes. Tachyarrhythmias (sinus arrhythmias, atrial and supraventricular ectopic beats and tachycardias, ventricular ectopic beats, ventricular tachycardia or fibrillation) most frequently occur early during insufflation when hemodynamic disturbances are most intense. They also may be an early sign of venous gas embolism. Tachyarrhythmias occurring during established pneumoperitoneum may be due to hypercarbia and related catecholamine surge. Bradyarrhythmias (sinus bradycardia, wandering atrial pacemaker, junctional rhythm, atrioventricular heart block, asystole) are likely vagally mediated and secondary to a rapid increase in intraabdominal pressure, or due to severe respiratory acidosis. Pulseless electrical activity may develop in a setting of extreme hypotension, for example, when a combination of increased intraabdominal pressure and reverse Trendelenburg position critically interfere with venous return.

Incorrect placement of the insufflating needle (Veress needle) may result in extraperitoneal insufflation of CO_2. The incidence of subcutaneous emphysema in laparoscopic procedures is between 0.4% and 2%. Insufflation of CO_2 may extend into the mediastinum and pericardium. Pneumopericardium may produce a clinical picture of pericardial tamponade. Pressurized gas also may dissect into the pleural space, either via natural peritoneal-pleural communications or after

an accidental injury of the diaphragm, resulting in pneumothorax. Finally, inadvertent intravascular placement of the Veress needle during insufflation results in intravascular gas embolism. Minor vascular gas embolism can be detected by TEE in up to two-thirds of all patients undergoing laparoscopic cholecystectomy. CO_2 is quickly absorbed and readily expired by the lungs, so the consequences of gas embolism with CO_2 may be less severe. The lethal embolic dose of CO_2 is five times greater than that estimated for air. However, an unrealized intravascular insufflation will result in a massive gas embolism that is usually lethal.

Placement of an abdominal trocar may result in an accidental bowel perforation or a solid organ or vascular injury, resulting in a severe hemorrhage that may initially go unnoticed. Control of hemorrhage during laparoscopy is difficult and usually requires emergency conversion to an open procedure. Decompression of the stomach with a gastric tube placed before abdominal insufflation is believed to decrease the risk of gastric perforation by the Veress needle or a trocar.

Rhabdomyolysis is a rare complication of prolonged surgery in the extreme Trendelenburg position. This complication probably results from a combination of decreased arterial perfusion of the elevated lower limbs, venous compression by leg supports, and impairment of femoral venous drainage by increased intraabdominal pressure.

The introduction of robotic surgery in 1999 has added another layer of complexity to the anesthetic management of laparoscopic procedures. The robot is bulky and it commands most of the operating room space. Its arms are rigid, so any patient movement during the procedure may result in a serious injury. Once the robot is docked in place, access to the patient in general, and to the airway in particular, is severely restricted, and adjusting the patient's position on the operating table is no longer possible; therefore risk of position-related injuries and accidental loss of airway is increased. Robotic gynecologic and urologic procedures require an extreme Trendelenburg position and very high insufflation pressures, so hemodynamic and respiratory challenges of anesthetic management are exacerbated. Prolonged extreme Trendelenburg position may result in significant facial and upper airway edema. The incidence of corneal abrasion in robotic surgery appears to be higher.

Postoperative nausea and vomiting occur in 40% to 70% of patients after laparoscopy. Postoperative pain due to diaphragmatic irritation is usually localized to shoulder, neck, or upper abdomen.

Recognition

Vigilance and awareness of the potential complications of laparoscopic surgery and of their temporal relation to surgical maneuvers may help the anesthesiologist promptly recognize and manage those often serious and occasionally life-threatening events.

An acute decrease in chest compliance and hemodynamic instability may accompany abdominal insufflation and placing the patient in the Trendelenburg position at the beginning of the procedure. Reverse Trendelenburg positioning and an increase in abdominal insufflation pressure may cause additional hemodynamic instability at any time during laparoscopy. Close monitoring of hemodynamic parameters and ventilatory mechanics, with rapid response to any dynamic changes, is the essence of anesthetic management during these maneuvers.

Sudden hypotension may result from a combination of hypovolemia and high-pressure abdominal insufflation, especially in the reverse Trendelenburg position. Other possible causes, such as hemorrhage, bradycardia, and tension pneumothorax, just to mention a few, must be taken into consideration.

Peak inspiratory pressure (PIP) typically increases during and after abdominal insufflation. A gradual increase during insufflation is expected because of limited diaphragmatic excursion and reduced lung compliance. A sudden increase, however, should raise the suspicion for pneumothorax, which may be caused by diaphragmatic injury and communication between the pleural cavity and the insufflated peritoneal cavity, or by barotrauma of the lung. Differential diagnosis should include endotracheal tube (ETT) obstruction or main-stem migration. Lung auscultation, attempt at manual ventilation, passing a suction catheter down the ETT, fiberoptic tracheobronchoscopy, and analysis of the $ETCO_2$ waveform are all useful in rapidly establishing the cause of acutely increased PIP.

Capnography is one of the most useful monitors during laparoscopy. It may provide early warning signs of impending catastrophic events. A sudden partial decrease in $ETCO_2$ may be seen in low cardiac output or main-stem migration of the ETT, but also may mean venous air embolism, pulmonary embolism, or cardiac arrest. Complete sudden disappearance of the capnography waveform usually indicates circuit disconnection, obstruction of sampling tubing, obstruction of the airway, or extubation.

Invasive blood pressure monitoring is rarely necessary during laparoscopic procedures. It is, however, very helpful in patients with preexisting severe myocardial or valvular dysfunction or respiratory pathology. It helps with diagnosis and management of significant physiologic disturbances. It also is indicated in extremely obese patients in whom noninvasive monitoring of blood pressure may not be possible after positioning for laparoscopy, for example, with both arms tucked in. Transesophageal echocardiography is valuable for emergency diagnosis of different causes of severe hemodynamic instability, such as hypovolemia, myocardial ischemia, ventricular dysfunction, venous gas embolism, or pulmonary embolism.

Risk Assessment

There are few conditions that may be considered an absolute contraindication to laparoscopy because the risk to the patient is prohibitive or because laparoscopy is technically not feasible. Relative contraindications are more common, including conditions in which laparoscopy may be technically challenging and risky, or undesirable because of physiologic limitations posed by the patient's comorbidities.

Pneumoperitoneum may lead to cardiac arrest in a patient with preexisting severe hemodynamic compromise, for example, shock, severe aortic stenosis, advanced heart failure, or pericardial effusion. Severe restrictive pulmonary disease, such as extreme scoliosis or previous pneumonectomy, or severe interstitial lung disease with diffusion defects, should also preclude consideration of the laparoscopic technique. In those patients, atelectasis and increased intrapulmonary shunting with pneumoperitoneum may lead to life-threatening hypoxemia. In addition, restricted lung volume does not allow hyperventilation to compensate for CO_2 absorption during pneumoperitoneum. Extreme hypercapnia may result, leading to postoperative ventilatory failure and the inability to extubate the patient. Forced expiratory volume less than 70% and diffusion capacity less than 80% are predictive of more severe hypercapnia during laparoscopy. Moreover, hypoxia and hypercapnia will exacerbate pulmonary hypertension and right ventricular dysfunction, present in many patients with chronic restrictive or interstitial pulmonary disease. Patients with bullous emphysema or severe obstructive pulmonary disease are at increased risk of barotrauma and pneumothorax during laparoscopy.

Laparoscopy may not be feasible in patients with severely increased intraabdominal pressure—caused, for example, by an extensive, space-occupying tumor, abdominal compartment syndrome, or massive ascites. Other technical challenges to laparoscopy include pregnancy, bowel distention, coagulopathy, abdominal wall infection, and previous extensive abdominal surgery.

Pneumoperitoneum and Trendelenburg positioning are relatively contraindicated in conditions with increased intracranial pressure (brain tumor, hydrocephalus, ventriculoperitoneal shunt) and extreme obesity. Abdominal insufflation, especially in conjunction with the reverse Trendelenburg position, will be poorly tolerated by patients with uncorrected hypovolemia, congestive heart failure, or aortic stenosis. Coexisting coronary artery disease places those patients at an increased risk for intraoperative coronary events. Patients with cerebrovascular disease including carotid or vertebral artery stenosis are at risk for perioperative ischemic stroke during protracted hypotensive episodes.

Major complications of laparoscopic surgery are predominantly due to cardiac events and vascular injury. Mortality rate with laparoscopy is estimated at 0.13%. Cardiac complications account for 25% of laparoscopy-related deaths.

Implications

Laparoscopy has become the gold standard for several surgical procedures (e.g., cholecystectomy or gastric bypass). Laparoscopic surgery is commonly performed in outpatient surgical facilities. Robotically assisted laparoscopic surgical technique, since its introduction in 1999, has gained popularity as a method of choice for several urologic and gynecologic procedures. Owing to the popularity and convenience of laparoscopic approach and a growing collective surgical experience with the technique, some formerly "absolute" contraindications to laparoscopy are no longer considered an obstacle to its use. Consequently, patients at an increased risk for complications inherent in laparoscopic surgery have become a common challenge in contemporary anesthesia practice. The anesthesiologist therefore must be prepared to properly select, screen, and counsel patients considering a laparoscopic procedure. The anesthesiologist and surgeon must be thoroughly familiar with the profound perturbations of normal physiology that take place during laparoscopy and be able to diagnose and manage any complications resulting from these changes.

MANAGEMENT AND PREVENTION

High intraabdominal pressure is the chief reason for hypotension during laparoscopy. It impedes venous return and may cause vagally mediated reflex bradycardia by stretching the peritoneum during insufflation. Effects of pneumoperitoneum on venous return may be mitigated by gradual, rather than rapid, insufflation. Administrating intravenous fluids before laparoscopy may correct preexisting hypovolemia and prevent severe hypotension. Instructing patients to hold their antihypertensive medications, such as diuretics or angiotensin-converting enzyme inhibitors, on the day of surgery may decrease the incidence of refractory hypotension during laparoscopy. Intravenous fluids should also be used to augment venous return when hypotension develops after insufflation. Bradycardia should be treated with anticholinergic agents—glycopyrrolate or atropine. Epinephrine should be used to treat extreme bradycardia and hypotension if cardiac arrest is impending. Reducing the degree of reverse Trendelenburg positioning improves venous return. Intraabdominal pressure should be reduced to 10 to 15 mm Hg, or temporarily completely released in a situation of severe hemodynamic compromise. If fluid administration and reducing abdominal insufflation pressure and the degree of reverse Trendelenburg position fail to improve the patient's tolerance of pneumoperitoneum, laparoscopic technique may need to be abandoned.

Intraabdominal pressure above 15 mm Hg decreases preload and increases systemic vascular resistance and afterload. The net hemodynamic effect may be hypertension, even as the cardiac output falls, especially if the patient is in the Trendelenburg position. Aggressive treatment of hypertension may unmask decreased venous return and cardiac output and result in hemodynamic instability. Nicardipine, a rapidly reversible arterial dilator, may be the best choice to treat hypertension in this setting.

Tachycardia and hypertension during laparoscopy are a manifestation of sympathetic stimulation in response to progressive hypercapnia resulting from absorption of carbon dioxide from peritoneal cavity. Increase in arterial partial pressure of carbon dioxide and end-tidal CO_2 can be controlled by adjusting respiratory rate to increase minute ventilation. Increasing minute ventilation by about 20% is usually sufficient to maintain normocapnia. Hypercapnia may be difficult to correct when there is a large extraperitoneal reservoir of CO_2, such as subcutaneous emphysema or pneumomediastinum. In such situations, hypercapnia may persist for several hours after laparoscopy has been completed.

Tension pneumothorax is a life-threatening emergency. If it is strongly suspected on the basis of the clinical picture, immediate decompression may prevent rapid escalation of cardiopulmonary instability to the point of cardiac arrest. Emergency decompression is performed by placing a large-bore, at least 2-inch–long intravenous catheter in the midclavicular line at the level of the second intercostal space. It is crucial to rapidly recognize a bilateral pneumothorax and perform bilateral decompression. The catheter (or catheters) should remain in place connected to a water seal system. Concurrently, abdominal insufflation should be immediately stopped and released. The thoracocentesis catheter should be left in place until positive pressure ventilation is discontinued. Chest tube placement is rarely needed, as CO_2 gets quickly absorbed from the pleural cavity. Serial postoperative chest radiographs are mandatory.

Suspicion of venous gas embolism should prompt emergency management without delay.

Abdominal insufflation should be stopped immediately, the pneumoperitoneum released, and the patient placed in a simultaneous steep Trendelenburg position and right-side-up position. This places the right ventricular outflow tract in a dependent position with relation to the right atrium and may help release the gas bubble locking the right ventricle outflow. Ventilation with 100% oxygen should be started, and nitrous oxide, if used, should be immediately discontinued. Venous gas embolism frequently causes supraventricular tachyarrhythmia, so using Neo-Synephrine as a first-line agent to manage resulting hypotension may be helpful. Epinephrine and vasopressin are used if hemodynamic instability becomes more severe. Placement of a multiorifice central venous catheter into the right atrium and aspiration of gas bubbles should be attempted. If cardiac arrest occurs, chest compressions and cardiopulmonary resuscitation may be ineffective without aspiration of the gas embolus from the right side of the heart. A patent foramen ovale (PFO) is present in about 25% of the adult population, so the possibility of paradoxic emboli to cerebral or coronary arteries through a PFO must be kept in mind. The patient should be evaluated for neurologic defects and myocardial ischemia after surviving a venous gas embolism event.

Deep venous thrombosis (DVT) may occur during long laparoscopic procedures and may be further complicated by pulmonary embolism (PE). Bariatric and cancer patients are at an increased risk for DVT. Routine prevention consists of administering subcutaneous heparin immediately before the procedure and applying sequential compression devices to the lower extremities. Over 50% of bariatric surgeons use preoperative placement of inferior vena cava (IVC) filters as PE prevention in high-risk patients. The efficacy of prophylactic IVC filters before gastric bypass surgery has not been established.

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Complications of Lithotripsy 47

Jerome F. O'Hara Jr.

Case Synopsis

A 78-year-old woman with a history of severe coronary artery disease underwent extracorporeal shock wave lithotripsy with general anesthesia. Ten minutes after placement in the water bath, the patient's heart rate increased from 78 to 138 beats per minute, and pink frothy fluid was noted in the endotracheal tube. The patient was removed from the water bath, and an immediate chest radiograph revealed congestive heart failure.

PROBLEM ANALYSIS

Definition

Extracorporeal shock wave lithotripsy (ESWL) is accomplished by the transmission of shock waves through the patient's body to pulverize urinary calculi. Unlike second-generation lithotriptors, first-generation units require that the patient be immersed in a water bath (Fig. 47.1). In addition to anesthetic risks, this unique environment exposes patients to potential complications from water immersion and the release of energy by the shock waves.

During ESWL a mechanically generated shock wave passes through water as a single pressure impulse. On reaching the patient, the wave passes through the patient's tissues en route to the "target zone," which is defined as the area that contains the calculus (Fig. 47.2). Fluoroscopy is used to confirm that the urinary calculi remain in the target zone. When the shock wave encounters a different density, such as the urinary calculus, it releases energy to fragment the calculus into sand-like particles, which is the desired therapeutic effect. However, damage to other tissues or implanted mechanical devices can occur. To prevent cardiac arrhythmias, the lithotriptor can be synchronized to trigger the shock wave during the refractory period of the patient's cardiac cycle. In certain patients, hydrostatic pressure created by immersion can significantly compromise cardiovascular and pulmonary function.

Recognition

Undesirable effects of the shock wave energy include the following:

- Cardiovascular instability from atrial or ventricular arrhythmias
- Potential damage to and malfunction of a pacemaker or implantable cardioverter-defibrillator
- Hypotension from perirenal or intraabdominal bleeding
- Skin petechiae and painful ecchymoses, especially in thin patients
- Patient discomfort and movement from inadequate analgesia

Undesirable effects during immersion lithotripsy include the following:

- Nerve and musculoskeletal injury from pressure points associated with use of the hoist chair
- Hyperthermia or hypothermia caused by the temperature of the water bath

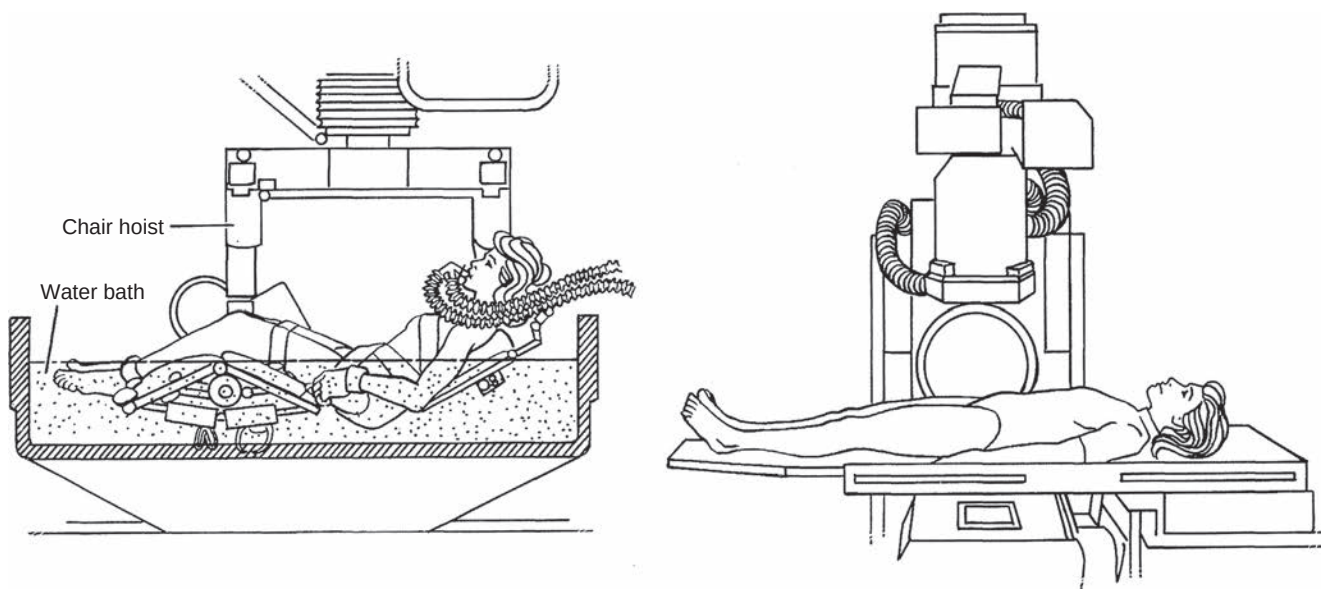

Fig. 47.1 First-generation lithotriptor, with the patient in a chair hoist, immersed in the water bath *(left).* Newer, second-generation lithotriptor *(right).*

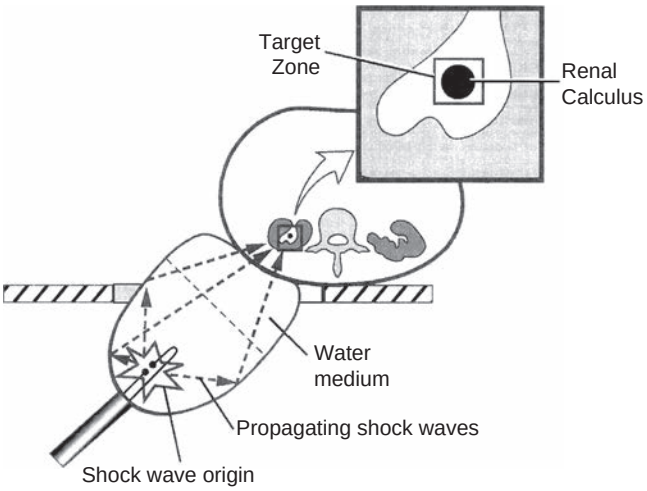

Fig. 47.2 Illustration of how the shock wave is generated and then delivered to the renal calculi.

TABLE 47.1 Cardiopulmonary Changes on Immersion during Lithotripsy

System	Variable	Direction of Change
Cardiovascular	Central blood volume	Increased
	Central venous pressure	Increased
	Pulmonary artery pressure	Increased
Respiratory	Pulmonary blood flow	Increased
	Vital capacity	Decreased
	Functional residual capacity	Decreased
	Tidal volume	Decreased
	Respiratory rate	Increased

Modified from Malhotra V: Anesthesia and the renal and genitourinary systems. In Miller RD, editor: *Anesthesia*. New York, Churchill Livingstone, 1994, p 1961.

- Relative inaccessibility of the patient's airway
- Cardiovascular and pulmonary changes (Table 47.1)

Risk Assessment

If the shock wave is misdirected or encounters tissue other than the urinary calculi, energy may be released and injure the patient. Such injuries include the following:

- Pulmonary contusion and hemoptysis, especially in children, because the lung base and kidney are in close proximity
- Neurologic damage if air is introduced into the epidural space during administration of epidural anesthesia
- Possible damage to and rupture of a calcified aortic or renal artery aneurysm

Cardiovascular and pulmonary changes associated with water immersion can lead to serious complications in some patients. For example, acute congestive heart failure can occur in patients with severe ventricular dysfunction. Patients with significant chronic obstructive pulmonary disease may not be able to maintain adequate ventilation under regional anesthesia. Absolute and relative contraindications to ESWL are listed in Box 47.1.

Implications

To avoid complications that can arise during ESWL, the anesthesiologist must understand the physics of shock wave generation and delivery to the patient. Certain risks need to be considered during the preoperative evaluation of a patient who requires an anesthetic for this elective procedure.

BOX 47.1 Contraindications to Extracorporeal Shock Wave Lithotripsy

Absolute Contraindications
Obstruction distal to renal calculi
Bleeding disorder or anticoagulation
Pregnancy

Relative Contraindications
Large calcified aortic or renal artery aneurysm
Untreated urinary tract infection
Pacemaker or implantable cardioverter-defibrillator
Morbid obesity

MANAGEMENT

The choice of anesthesia depends on the type of lithotriptor and the anesthesiologist's preference. High-energy shock waves (>18 kV) usually require general or regional anesthesia, whereas low-energy shock waves (<18 kV) often require only intravenous sedation.

The advantage of general anesthesia is the ability to secure the airway with endotracheal intubation and to deliver smaller, more consistent tidal volumes. Small, consistent volumes minimize the displacement of renal or ureteral calculi, ensuring that they remain within the target zone. Regional anesthesia allows the patient to participate in positioning within the chair hoist and permits easier patient transport if an additional urologic procedure is needed at a different location. A T4–T6 sensory block is required with spinal or epidural anesthesia. Potential disadvantages of regional anesthesia include the following:

- Time required to establish anesthesia
- Altered respiratory dynamics
- Potential for inadequate sensory block
- Inability to redose after a single-dose injection

Regardless of the anesthetic used, recovery from ESWL involves mainly recovery from the effects of anesthesia. Thus ESWL should be approached as an outpatient procedure. Patients with cardiopulmonary disease need to be identified and their increased risk of immersion-related complications understood. Although invasive monitoring may be required for a patient who has substantial cardiopulmonary compromise, controlling the speed and depth of immersion is equally important. To prevent crush, pressure, brachial plexus, or neck injuries during anesthesia, proper positioning and padding are required, especially if a water bath is used.

Certain patients scheduled for ESWL require the following specific considerations:

- Pediatric patients usually receive general anesthesia so that their movements can be controlled during the procedure. Styrofoam padding is used to protect the lower lung fields from the shock waves.
- Paraplegic patients require anesthesia because of the risk of autonomic hyperreflexia.
- Morbidly obese patients can exceed the mechanical capacity of the lithotriptor to support or properly position them. This must be evaluated before the induction of anesthesia.
- Patients with cardiac rhythm management devices (CRMDs)—that is, pacemakers or internal cardioverter-defibrillators (see Chapter 16)—can safely undergo ESWL, but changes in programmed parameters may occur. The following steps should be taken:

- It is advisable to turn off the programmed adaptive-rate response in patients with CRMDs.
- An internal cardioverter-defibrillator must be deactivated and shielded with Styrofoam to protect it from the shock waves, and the device should be interrogated after the procedure. This applies to pacemakers as well.
- The indication for the CRMD must be known so that the team is prepared to treat arrhythmias, especially if some CRMD therapies (e.g., tachyarrhythmias) have been turned off. If so, temporary pacing capability and an external cardioverter-defibrillator must be available.
- Preprocedure and postprocedure pulse generator functions must be confirmed when treating a patient who has an implantable CRMD.

PREVENTION

The anesthesiologist must identify patients at risk for ESWL-related complications and vigilantly monitor the patient's position and hemodynamic changes during ESWL, especially during water bath immersion and on the initiation of shock wave therapy. It is advisable to establish and rehearse a plan of action for gaining airway access or treating cardiac arrest in patients who are immersed. An emergency protocol to facilitate the transfer of a patient with cardiac instability from a freestanding or mobile ESWL unit to a critical care setting should also be in place.

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48 Complications of Massive Transfusion

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Case Synopsis

A 50-year-old man presents to the emergency department after falling from the roof of his house. He is tachycardic (heart rate of 120 beats per minute) and normotensive (blood pressure of 130/88 mm Hg), with a grossly distended abdomen on arrival. His Glasgow Coma Scale score is 15, and computed tomography suggests intraabdominal bleeding. The decision for emergency laparotomy is made and, on opening of the abdomen, the blood pressure falls to 60/30 mm Hg. He requires 6 units of red cells before hemostasis is achieved 1 hour later.

PROBLEM ANALYSIS

Definition

No universal agreement exists on the definition of the term *massive transfusion.* It seeks to quantify the blood and blood products that are used during the management of major hemorrhage. Some of the definitions include the following:

- Replacement for blood loss of more than 150 mL/min
- Replacement of 5 units or more in 3 hours
- More than 10 units of red blood cells replaced over 24 hours
- Total blood volume replaced over 24 hours
- Half of total blood volume replaced over 4 hours

Recognition

Massive transfusion and related complications are the result of therapy for acute blood loss, which necessitates rapid replacement of intravascular volume with crystalloid, non–red blood cell (RBC) colloids, blood, and blood products. The most common circumstance leading to massive transfusion is major trauma. Other situations include the following:

- Gastrointestinal bleeding
- Major obstetric hemorrhage
- Major vascular surgery/injury
- Cardiac surgery
- Hepatic surgery/injury
- Craniofacial surgery
- Radical oncologic surgery
- Orthopedic/spinal reconstructive procedures

It has been noted that the incidence of massive transfusion is on the decline, as early recognition and aggressive management of hemorrhage and the associated coagulopathy have resulted in the use of less blood products.

Circumstances that enhance and may contribute to the development of transfusion-related complications include the following:

- Use of anticoagulants
- Clotting factor deficiencies (hereditary, dilutional, or acquired; consumption of clotting factors; extracorporeal membrane oxygenation and circulatory assist devices)
- Hypothermia
- Use of a cell-saver or autotransfusion device

Loss of up to 30% of the blood volume is usually well tolerated in children and young adults. Signs of hypovolemia may be subtle and include a small to moderate increase in heart rate and decrease in pulse pressure.

Risk Assessment

Any patient who requires acute, massive intravascular volume replacement is at risk for complications related to massive transfusion. Infants and neonates appear to be at increased risk owing to the immaturity of their native coagulation systems. The following complications are likely to occur:

- Coagulopathy
- Hypothermia
- Acidosis
- Hypokalemia or hyperkalemia
- Hypocalcemia

A more complete list of generally recognized complications is provided in Box 48.1.

Implications

Patient outcome depends on early recognition, the rate and severity of blood loss, and timely intervention. Neonates and infants have laboratory values that are outside the adult reference ranges for the integrity of coagulation (especially prothrombin time [PT] and partial thromboplastin time [PTT]). As such, normal laboratory values for adults do not measure neonatal hemostatic competence, and comparisons must be made with caution.

MANAGEMENT

Management goals are to maintain the quantitative and qualitative integrity of intravascular volume. Oxygen-carrying capacity and

BOX 48.1 Complications of Massive Blood Transfusion

Early
Dilutional coagulopathy
Acid-base derangement
Hypothermia
Hyperkalemia/hypokalemia
Increased citrate load (hypocalcemia)
Transfusion-associated circulatory overload (TACO)
Hemolytic transfusion reactions
Febrile nonhemolytic reactions
Transfusion-related acute lung injury (TRALI)
Allergic reactions
Bacterial sepsis
Microembolization or microaggregate formation leading to acute respiratory distress syndrome

Late
Transfusion-related diseases (bacterial and viral)
Delayed hemolytic reactions
Change in red blood cell deformability
Graft-versus-host disease
Transfusion-related iron overload
Transfusion-related immunomodulation

hemostasis are of primary importance. In the face of massive volume loss, these goals can be met only by transfusing whole blood or components of fractionated whole blood. The components commonly used and their dosage are detailed in Table 48.1.

The administration of large volumes of red cells or components can lead to the complications listed in Box 48.1.

Dilutional Coagulopathy

The most common complication of massive transfusion is dilutional coagulopathy. Dilution of hemostatic blood elements occurs from substances used for volume expansion (crystalloid, albumin), transfused blood, and blood products. Continuous dilution of remaining platelets and clotting factors results in impaired hemostasis. Dilutional coagulopathy can be prevented by the early use of fresh frozen plasma (FFP).

Consumptive Coagulopathy

Hemostatic failure can occur without significant dilution. This can occur via hyperfibrinolysis, activation of anticoagulant pathways, or platelet dysfunction. With the exception of thrombocytopenia (platelet counts <100,000/mm^3), the existence of a coagulopathy can rarely be documented in a timely fashion. Therefore platelets and FFP must be administered during a massive transfusion without waiting for a documented coagulopathy to develop. Although no differentiation is made between infants and adults, some recommended transfusion protocols include the following:

- Administration of 0.3 U/kg platelets to achieve a platelet count of more than 50,000 mm^3 (or 100,000 if actively bleeding)
- Administration of 4 U of FFP for every 6 U of packed RBCs transfused

Indications for component replacement and the positive and negative attributes of specific component therapy are listed in Table 48.2. Infants and neonates have lower plasma clotting factor concentrations than adults do, so dilutional coagulopathy develops more quickly. Therefore the threshold for replacement of coagulation factors in infants is lower.

Metabolic Derangement

Acid-base alterations may occur simply from the blood collection and preservation process. The pH of freshly collected blood added to citrate phosphate dextrose solution decreases to 7.0; over the next 21 days of storage, it decreases to 6.84. The majority of this decrease is due to an increase in the partial pressure of carbon dioxide, because storage containers do not permit its egress.

The correction of acidosis using sodium bicarbonate is not recommended (unless used as a temporizing measure in severe acidosis). The mainstay of therapy is fluid resuscitation and improvement of tissue perfusion.

TABLE 48.1 Dosage of Common Blood Components in Major Hemorrhage

Blood Component	Dosage in Major Hemorrhage
Red blood cells	Aim to maintain hemoglobin at >80 g/L (10 g/L in patients with cardiovascular disease)
Fresh frozen plasma	15 mL/kg
Cryoprecipitate	5–10 mL/kg (max. 300 mL)
Platelets	1 adult bag
Factor concentrates	Use after consultation with hematology

Hypothermia

Hypothermia commonly occurs with massive transfusion and can be a cause of coagulation dysfunction. The trauma literature supports a 100% mortality rate if a patient's core temperature falls below 32° C, regardless of the severity of injury. Large volumes of unwarmed crystalloid, non–RBC-containing colloids, blood, and blood products can produce cardiac arrest. This can be prevented by the warming of fluids before infusion and patient temperature monitoring.

Hyperkalemia

Hyperkalemia can develop with the rapid transfusion of stored RBCs. The potassium concentration in stored blood increases over time as cells lyse. Although patients with normal renal function rarely display hyperkalemia or its hemodynamic consequences, neonates and infants with immature renal function, or patients with renal dysfunction, should receive washed RBCs. Occasionally, seeming paradoxic delayed hypokalemia may be seen after the transfusion of stored RBCs ceases.

Hypocalcemia/Hypomagnesemia

Hypocalcemia, or functional hypocalcemia, occurs after the rapid administration of blood stored with citrate. The citrate chelates the calcium and other covalent cations, such as magnesium. Hypotension can result from overly rapid transfusion, especially of platelet concentrates or FFP. Correction should be limited to those with signs of hypocalcemia or citrate toxicity (tetany, hypotension, prolonged QT interval, decreased myocardial contractility, narrow pulse pressures). Magnesium levels should be checked and supplementation given if required.

Pulmonary Dysfunction, Multiple Organ Failure, and Systemic Inflammatory Response Syndrome

Injury to the lungs and other organs can occur because of the following:

- Microaggregate formation and increased permeability in the pulmonary vasculature
- Release of inflammatory mediators giving rise to systemic inflammatory response syndrome
- Immune reactions involving the human leukocyte antigen system

TABLE 48.2 Indications for Component Replacement and Anticipated Hemostatic Attributes

Product	Indication	Advantages	Disadvantages
Packed RBCs	Hypovolemia associated with RBC loss	Readily available (autologous, homologous, cell-saver blood); more efficient than blood substitutes; maintains or ↑ O_2 transport capacity and BV	Dilutional coagulopathy; hemolytic reaction; infection; rare blood types may be unavailable
Fresh whole blood	Anemia; hypovolemia with anemia; massive transfusion (neonates)	Less donor exposure, especially neonates; platelets and clotting factors functional; maintains or ↑ O_2 transport capacity and BV	Limited availability; hemolytic transfusion reaction
Fresh frozen plasma	Coagulopathy	Replaces all protein clotting factors at presumed normal adult concentrations; available universally in frozen state	Timing of administration; infection; concentration of specific factors may be inadequate in some cases (e.g., fibrinogen); availability (minimum of 30 min to thaw)
Cryoprecipitate	Coagulopathy; factor VIII deficiency	High concentrations of fibrinogen and factor VIII	Pooled product; risk of infection; timing of administration; availability (not stored in all blood banks)
Platelets	Platelet dysfunction; thrombocytopenia	Increases platelet count: 1 U increases platelet count by 20–40 × 10^9/L	Hypotension; single donor vs. multiple donors; infection; brief functional half-life

BV, Blood volume; *RBCs,* red blood cells.

It can be difficult to distinguish between transfusion-related lung injury (TRALI), which usually occurs within 6 hours of transfusion, and transfusion-associated circulatory overload (TACO). Cardiac output monitoring and B natriuretic peptide may be helpful.

Infection

The risk of infection escalates with massive transfusions, either by the transmission of infectious agents or by the depression of immune responses. Although the risk for transmission of human immunodeficiency virus (HIV), viral hepatitis, West Nile virus, and cytomegalovirus is low, each donor exposure increases a patient's likelihood of contracting a potentially fatal disease. Rarely, bacterial contamination of a blood product may occur.

Hemolysis

Hemolysis, usually due to an ABO incompatibility, can be catastrophic. The most common cause is administrative error. Antibodies found in the Kell, Kidd, and Lewis systems also may precipitate a hemolytic response. Therefore whenever possible, a complete type and crossmatch should be carried out before administering any blood products.

Thrombosis

Standard venous thromboprophylaxis should be commenced as soon as possible after hemostasis, as patients develop a prothrombotic state following massive hemorrhage.

Other Therapies and Interventions to Limit the Need for Transfusion

Autotransfusion and Cell-Saver Devices

The use of blood salvage devices to return lost RBCs has become commonplace. Processing washes the salvaged blood and returns concentrated RBCs suspended in normal saline. Although these devices reduce the need to administer homologous RBCs, they contribute to the dilution of all hemostatic elements. Thus when transfusion approaches or surpasses 1.5 blood volumes, laboratory assessment of hemostasis is essential, regardless of the replacement strategy used.

Fresh Whole Blood

Not all patients are optimally managed by component therapy for massive volume loss. However, the use of fresh whole blood is impractical for emergencies and is difficult to provide logistically. Additionally, nucleic acid testing of donated blood for HIV may not be accomplished in less than 48 hours, making fresh whole blood less safe than banked blood. Despite its theoretic advantage in massive transfusion, this technique has not been studied outside the infant cardiac surgery population.

Recombinant Factor VIIa

Recombinant factor VIIa has been used to treat microvascular bleeding when replacement therapy has been judged adequate but the bleeding continues. Originally developed to treat hemophilia, recombinant factor VIIa promotes hemostasis at the site of injury by interacting with tissue factor. It has been incorporated into trauma management protocols, although controlled clinical trials for this application are currently lacking and controversy still exists about its use. It should therefore be used as a lifesaving intervention only and protocols for its use should be put in place. Recombinant factor VIIa has a short half-life and requires redosing (90 U/kg) every 2 hours until bleeding is controlled. Other drugs, such as aprotinin, were reported in the cardiac and orthopedic surgical literature as adjuncts to reduce blood loss and transfusion requirements, but are no longer in common use. Colleagues reported that in the absence of thrombocytopenia, PT and PTT values in adult surgical patients may be increased to 1.5 times control values without clinical evidence of increased or unusual blood loss.

Tranexamic Acid

Tranexamic acid is a plasminogen activator; its use is supported by the CRASH-2 trial. Dosing is 1 g intravenously stat followed by 1 g over 8 hours as an intravenous infusion. It is contraindicated in patients who have intracranial bleeding.

Prothrombin Complex Concentrate

Prothrombin complex concentrate is pooled from human plasma. It contains factors II, VII, IX, and X, as well as protein C and protein S, and is licensed to urgent reversal of warfarin. Dosing is 25 to 50 IU/kg.

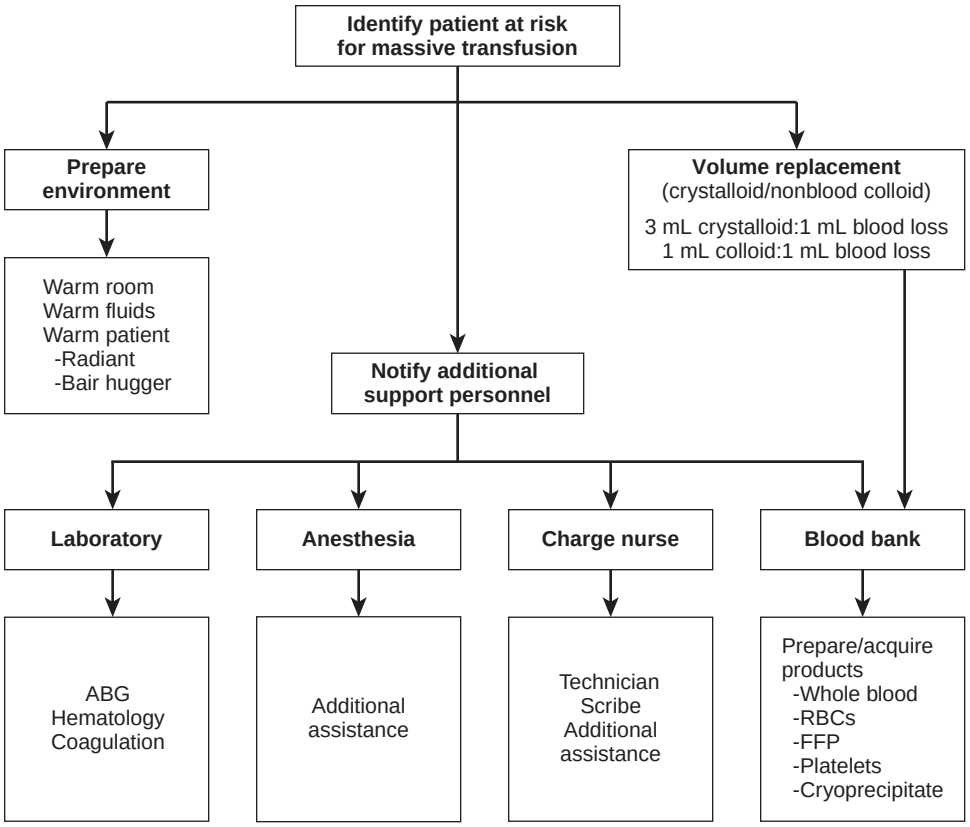

Fig. 48.1 Algorithm for the management of massive transfusion. *ABG,* Arterial blood gas; *FFP,* fresh frozen plasma; *RBC,* red blood cell.

Aprotinin

Aprotinin is a serine protease inhibitor and is used to reduce blood loss associated with increased fibrinolysis. However, there have been serious safety concerns. It is now only used for myocardial revascularization.

PREVENTION

Successful management of patients with massive hemorrhagic volume loss requires the following:

- Use of preventive measures in elective procedures where blood loss is expected:
  - Correction of preexisting coagulopathy preoperatively (or as soon as possible in an emergency)
  - Preoperative use of erythropoietin and intravenous or oral iron in patients with iron deficiency anemia
  - Early control of bleeding (tourniquet, pressure, surgery)
  - Intraoperative use of cell salvage and tranexamic acid
- Blood bank support (hematologist and technicians)
- Laboratory support
- Appropriate personnel (porters, runners, etc.)
- Patient warming and temperature monitoring: warming of all intravenous and surgical irrigation fluids and use of external warming devices
- Monitoring for acute transfusion reactions
- Ensuring that the correct blood or blood product is administered to the correct patient using manual or electronic patient identification systems

The prevention of complications requires the immediate availability of blood bank resources, appropriate administration equipment, and rapid laboratory turnaround time. Careful recording and reporting of the quantity, type, and time of all fluid infused (including crystalloid, colloid, and blood products), along with communication of anticipated needs to the blood bank, are critical. Additional personnel are essential to track multiple details, facilitate communication, and transport specimens and supplies.

The implementation of major hemorrhage protocols in most hospitals has improved the speed of availability of appropriate blood products, as well as the functionality of teams involved. All staff members are briefed on their expected role. Major hemorrhage drills allow staff to develop familiarity with the process in anticipation of an event (Fig. 48.1).

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49 Complications of Radical Urologic Surgery

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Case Synopsis

A 44-year-old man with treated hypertension and an extensive smoking history presents with malaise, weight loss, and painless hematuria. Computed tomography (CT) reveals a right-sided renal tumor with thrombus extending into the right renal vein and minimal extension into the inferior vena cava (IVC). He is listed for angioembolization of the kidney, radical nephrectomy, cavotomy, and IVC repair. On admission he is found to be dyspneic and in sinus tachycardia. His arterial blood gas (ABG) values are as follows:
pH: 7.47
Po_2: 9.2 kPa (69 torr)
Pco_2: 3.9 kPa (29.25 torr)
HCO_3: 22
Base excess (BE): −1.0

A CT pulmonary angiogram (CTPA) reveals multiple subsegmental pulmonary emboli. An intravenous heparin infusion is administered but stopped 4 hours before surgery. Conduct of anesthesia is uneventful until the surgeon mobilizes the renal vein and blood fills the surgical field. Invasive blood pressure is measured at 78/48 mm Hg, heart rate is 120 beats per minute, and pulse-oximetry saturations are 89% with a poor pulsatile waveform.

PROBLEM ANALYSIS

The tension exemplified in the case synopsis between bleeding risk and venous-thromboembolism risk is commonly problematic in the perioperative management of patients undergoing radical urologic surgery.

Definition

The term *radical* is typically used when describing surgery intended to remove malignant as opposed to benign pathology. It is expected that adjacent anatomic structures also affected by the cancerous organ are also removed. It should be noted that these surgeries are increasingly being performed by laparoscopic approach and as such the complications expected will differ in incidence and nature.

Radical Cystectomy

In females, radical cystectomy involves the removal of the bladder, pelvic lymph nodes, lower ureters, urethra, and anterior vaginal wall. The uterus, fallopian tubes, and ovaries may sometimes be removed. An ileal conduit may be performed as part of the procedure. In males, this is usually termed a *cystoprostatectomy* as structures removed are the bladder, prostate, pelvic lymph nodes, lower ureters, vas deferens, and seminal vesicles. It is typically performed for invasive transitional cell carcinoma of the bladder.

Radical Nephrectomy

The affected kidney is removed along with the whole of the surrounding Gerota fascia, perinephric fat, ipsilateral adrenal gland, and surrounding lymphatics. The vast majority (approximately 90%) of solid renal masses are renal cell carcinomas (RCCs) with the remainder being mainly transitional cell carcinoma or Wilms' tumor in children.

Radical Prostatectomy

In contrast with transurethral resection of the prostate (TURP; see Chapter 52), the entire prostate, seminal vesicles, ejaculatory ducts, and a portion of the bladder neck are removed. Approximately 90% of prostate cancers are adenocarcinomas.

Laparoscopic Radical Urologic Surgery

Increasingly, all of the aforementioned procedures may be performed via open or laparoscopic approach. Laparoscopic procedural complications are discussed in detail in Chapter 46. As with all major surgery, careful attention should be paid to patient positioning, avoidance of nerve injury, and prevention of pressure sores. A considered approach to mechanical ventilation is required, given the impact of surgical technique on intrathoracic pressures. A compromise may have to be made between allowing good surgical access and ideal ventilatory parameters. For example, in the lateral decubitus position for nephrectomy, insufflation of gas into the peritoneum for laparoscopy and requirement for steep Trendelenburg position will affect respiratory mechanics. Addressing this with high inspiratory pressures may cause barotrauma, hence acceptance of intraoperative respiratory acidosis may be a reasonable approach.

Recognition

The case synopsis alludes to two of the major complications of radical urologic surgery—venous thromboembolism (VTE) and major hemorrhage.

Venous Thromboembolism

Patient risk factors include malignancy, advancing age, and a smoking history. In addition to general risk factors, there are specific concerns

TABLE 49.1 Novick Classification of Cavoatrial Tumor Extension in Patients With RCC

Level 1	Thrombus into IVC but <2 cm above renal vein
Level 2	Thrombus below the intrahepatic vena cava
Level 3	Thrombus involves the intrahepatic vena cava but below the diaphragm
Level 4	Thrombus involves the right atrium

IVC, Inferior vena cava; *RCC,* renal cell carcinoma.

TABLE 49.2 Signs and Symptoms of Venous Thromboembolism

Signs	Symptoms
Tachypnea (70%)	Dyspnea (73%)
Tachycardia (30%)	Chest pain (66%)
Crepitations (51%)	Cough (37%)
Low-grade fever	Apprehension
	Sweating

surrounding extension of tumor and thrombus into the renal veins, iliac veins, IVC, and right atrium. The Novick classification of cavoatrial disease extension in RCC describes how far the tumor or thrombus has extended beyond the renal vein. It is unclear how directly this classification relates to prognosis or likelihood of pulmonary embolus. Approximately 4% to 10% of all RCCs have extension into the IVC at presentation (Table 49.1).

The rate of VTE in open urologic surgery has been reported as between 0.2% and 5%. Similar rates of between 0.3% and 4.8% have been reported for laparoscopic urologic surgery.

Presentation of VTE varies from asymptomatic cases to dyspnea, pleuritic chest pain, calf pain and swelling, cough and hemoptysis, and acute cardiovascular collapse. The latter group can be termed *submassive* or *massive* pulmonary embolism (PE) depending on degree of cardiovascular compromise. The investigation of such patients should include 12-lead electrocardiogram, chest radiograph, locally approved cardiac enzyme assay, and an ABG, in addition to a screening blood panel. An echocardiogram and CTPA may then be indicated (Table 49.2).

Intraoperatively, sudden PE may result in tachycardia, reduced blood pressure, and breath-to-breath reduction in end-tidal carbon dioxide ($ETCO_2$). Intraoperative imaging by transesophageal echocardiography (considered routine in some centers) may confirm PE in real time.

Hemorrhage

Given the anatomic relations of the structures resected, the majority of bleeding in radical urologic procedures is venous in origin.

Santorini plexus (shown in Fig. 49.1), dorsal to the prostate, is vulnerable during radical resection of the gland.

Resection of pelvic lymph nodes can incur bleeding from the hypogastric veins, and retroperitoneal lymph node resection can prompt extensive hemorrhage from the IVC or surrounding veins.

Bleeding has been reported as accounting for 40% of all complications in laparoscopic urologic surgery. Average volume of blood loss from open radical prostatectomy is given as approximately 500 to 1000 mL, even in high-volume, experienced centers. Clinical vigilance during procedures is required, and assessment of volume status is key. Routine monitoring may show tachycardia and hypotension bearing in mind the possible influence of other drugs (e.g., β-blockers, remifentanil). ABG analysis may show an acute drop in hemoglobin or raised serum lactate, particularly if large volumes of intravenous fluids have been administered, further exacerbated by an existing preoperative anemia.

Noninvasive cardiac output monitoring devices are increasingly used during major uro-oncologic surgery. Such monitors use patient *fluid responsiveness* or specific dynamic measurements such as *stroke volume variation* to detect early hypovolemia that may be secondary to occult hemorrhage.

Air Embolus

It should be noted that where pelvic veins are open, the risk of air embolism is present. This risk is pronounced when the Trendelenburg position is used. It is recognized similarly to a VTE to the pulmonary circulation. Large air emboli may cause complete obstruction to the right ventricular outflow tract and cause profound cardiovascular compromise, arrhythmia, and cardiac arrest.

Urosepsis

In patients with obstructive characteristics to their urologic disease, low-grade bacterial infections may become clinically significant when the urinary system is manipulated intraoperatively. Pyrexia, tachycardia, hypercapnia, and hypotension may be evident.

Acute Kidney Injury

Although it is unlikely that an acute kidney injury (AKI) develops during all but the most prolonged and complex of surgeries, its likelihood can be considered perioperatively. Prerenal and renal obstructive causes are likely to be relevant in urologic patients, although perioperative critical illness, anemia, and perioperative cardiovascular complications may also adversely affect renal function. Urinary output monitoring should be carried out intraoperatively where possible and preoperative parameters for kidney function taken into account when anesthesia and postoperative care are conducted. The Acute Kidney Injury Network (AKIN) criteria for the identification of AKI are listed in Table 49.3.

Risk Assessment

The population in whom radical urologic surgery is required has a mean age of 60 years. The radical prostatectomy group may be relatively free of comorbid disease due to the use of radiotherapy as an alternative treatment option in those considered high risk for surgery. Radical cystectomy and nephrectomy is offered to a wider cohort of patients because treatment (curative) options are fewer.

General Considerations

Major surgery prompts an appropriate assessment of the patient that will consider the complexity of surgery, comorbidity of patient, urgency, and life expectancy with surgery or conservative treatment. Given the radical nature of the surgery, this may include an assessment of cardiopulmonary capacity. Assessment for surgery is reviewed by a multidisciplinary team to ensure good patient selection and allow for medical preoperative optimization. In general, open surgery for removal of larger tumors carries more risk than laparoscopic procedures for smaller masses. Age and preoperative renal function are important determinants of outcome after nephrectomy. Younger patients with greater life expectancy may have the option of nephron-sparing surgery depending on the site of the tumor (e.g., partial nephrectomy for lower pole tumor). These are more complex to perform but ultimately give a better result with respect to preservation of renal function.

Hemorrhage

Surgical factors predisposing to increased risk of hemorrhage include previous history of surgery (e.g., TURP or multiple prostatic biopsies) or radiotherapy rendering the surrounding tissues more friable or adherent.

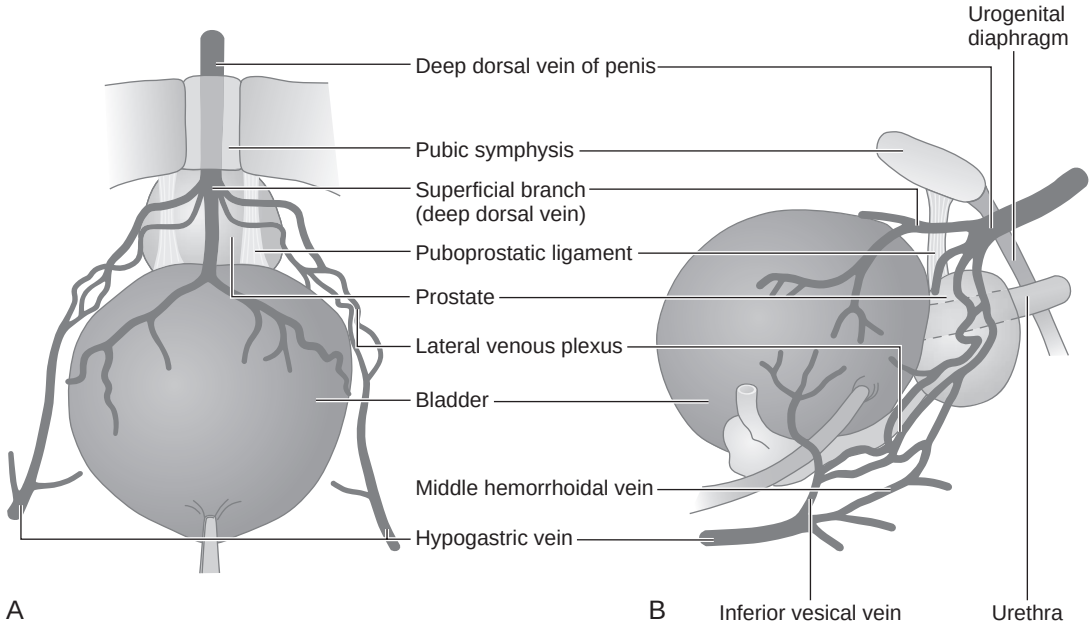

Fig. 49.1 The prostatic vein drains into Santorini plexus, which receives blood from the penis, prostate, bladder, and seminal vesicles. This plexus also communicates with the pubic, pudendal, deep epigastric, obturator, and hemorrhoidal veins. (From Reiner WG, Walsh PC: An anatomical approach to the surgical management of the dorsal vein and Santorini plexus during radical retropubic surgery. *J Urol* 121[2]:198-200, 1979.)

TABLE 49.3 AKIN Classification/Staging System for Acute Kidney Injury

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine ≥0.3 mg/dL (≥26.4 μmol/L) or increase to ≥150%–200% (1.5–2×) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2	Increase in serum creatinine to >200%–300% (>2–3×) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3	Increase in serum creatinine to >300% (>3×) from baseline (or serum creatinine ≥4.0 mg/dL [≥354 μmol/L] with an acute increase of at least 0.5 mg/dL [44 μmol/L])	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

AKIN, Acute Kidney Injury Network.

Surgical access may be more challenging because of tumor position, and this should be identified with thorough review of preoperative imaging.

Venous Thromboembolism

All patients with cancer are deemed to be at high risk for VTE. The risk assessment should therefore take into account further factors such as Novick classification and the balance of bleeding versus VTE risk with each drug therapy proposed.

Implications

Radical urologic surgery is often carried out in the elderly and carries with it a risk of major hemorrhage, VTE, or air embolus, as well as the more generic risks of major surgery. General risks include nerve injury from improper positioning, postoperative surgical infections, and respiratory complications such as infection or pneumothorax. Poor assessment, prevention, recognition, and management of these risks poses a significant threat.

Reported mortality and morbidity rates vary. One large study of 11,010 men undergoing radical prostatectomy showed overall mortality rates of 0.5%. The same study showed 20.4% of patients encountered one or more complications within 30 days of surgery. With techniques improving and more treatments being offered, more high-risk populations may be offered radical urologic surgery in the future.

MANAGEMENT

Venous Thromboembolism

Patients who present with PE should be anticoagulated perioperatively with consideration of the most appropriate therapies, taking into account timing of surgery and preexisting renal function (e.g., intravenous unfractionated heparin or appropriate doses of low-molecular-weight heparin). Anticoagulation bridging therapy needs to be agreed and discussed with the surgical team because this may affect the use and management of neuroaxial anesthesia (e.g., epidural).

In complex cases such as those with RCC and extension into the IVC, some centers insert a balloon filled with saline and contrast agent into the IVC under fluoroscopic control in order to capture thrombus dislodged during manipulation of the tumor. Intraoperative imaging with transesophageal echocardiography is useful under these circumstances. In some instances, the decision to prepare for cardiopulmonary bypass may be made if embolization is highly likely given the position of the thrombus.

Hemorrhage

Management should center on meticulous surgical technique, assessment, and response to cardiovascular parameters in the form of fluid and blood product resuscitation. Plans for blood loss management should be discussed before the case beginning with estimation of blood loss and crossmatching as appropriate. If major hemorrhage is encountered, the major hemorrhage protocol should be activated. Point-of-care testing for hemoglobin, platelet count, and dynamic measurement of clotting ability (such as thromboelastography) are beneficial in guiding perioperative decision making.

Guidelines exist that support the use of tranexamic acid in patients with predicted blood loss greater than 500 mL as a strategy to limit

autologous blood transfusion. In addition, cell salvage should also be considered in such cases with concerns about malignancy and cell salvage now resolved. It should be remembered, however, that if bowel is to be manipulated (e.g., in the forming of ileal conduit), cell salvage should be discontinued at this point to limit contamination. In patients with large RCCs with extension into the IVC, angioembolization of the kidney before *knife to skin* is useful in reducing blood loss at the time of nephrectomy.

Air Embolism

If large volumes of air gain entry to the circulation cardiovascular collapse is likely. Supportive measures such as maximal inspired oxygen concentration must be instituted immediately. Likewise, if arrest occurs, cardiopulmonary resuscitation must be instituted. To allow the entrained embolized air to escape from the pulmonary outflow tract the patient must be placed head-down in the left lateral position. It may then be possible to aspirate the air from the right side of the heart if a central line is in situ. To prevent further air being embolized, sterile fluid may be used to flood the surgical field.

Urosepsis

Intraoperative management is largely supportive and with appropriate use of antimicrobials. Cardiovascular support with vasopressor or inotrope therapy may be indicated while surgical source control is carried out. Postoperative critical care may be required for patients in whom sepsis has been encountered.

PREVENTION

Acute Kidney Injury

Identification of patient features associated with increased risk of perioperative AKI allows a preemptive approach to management. A large, prospective U.S. study identified nine risk factors for patients presenting for general surgery. Patients with six or more of these factors had a 10% incidence of AKI.

- Age greater than 56 years
- Male sex
- Active congestive cardiac failure
- Presence of ascites
- Hypertension
- Emergency surgery
- Intraperitoneal surgery
- Preoperative creatinine greater than 107 μmol/L
- Diabetes mellitus (oral hypoglycemic agent or insulin controlled)

In addition to these factors, avoidance of or mitigating for the presence of nephrotoxic agents is a reasonable approach. Radiopaque contrast is nephrotoxic. The least toxic variant available in the lowest possible dose should be used. Potentially nephrotoxic drugs should be stopped if possible preoperatively (e.g., angiotensin-converting enzyme inhibitors and nonsteroidal antiinflammatory drugs). Consideration may be given to preoperative fluid administration and intraoperative *N*-acetylcysteine as preemptive measures in intermediate- or high-risk cases.

Intraoperatively, a balance must be struck between mitigating prerenal factors with intravenous fluid therapy and overloading patients to the detriment of other systems. For example, pulmonary edema may be encountered with overzealous fluid administration, particularly in those with cardiac failure. In addition, steep Trendelenburg positioning and liberal use of fluids may result in postoperative cerebral edema.

Postoperatively, daily renal blood profile and careful fluid balance will aid management of such patients.

Urosepsis

Surgical site infections (SSIs) and urosepsis are significant risks in radical urologic surgery. SSIs almost double the direct costs of hospitalization and render the patient more likely to need a critical care stay. Benefit from surgical antimicrobial prophylaxis may be determined by evaluation of patient factors, surgical factors, and the potential morbidity of infection.

Consideration should be given to administering prophylactic antibiotics within 60 minutes of *knife to skin,* as per local guidelines and in addition to scrupulous sterile surgical technique. This should be as a single dose in most instances or at most be discontinued within 24 hours of surgery without clinical suspicion of ongoing infection. Dosing should take into account renal function. Major blood loss would necessitate additional doses of antibiotic therapy.

Hemorrhage

The prevention of major hemorrhage in these procedures shares much in common with other major surgeries. As such, the results of ongoing clinical trials into the use of preoperative optimization of hemoglobin levels with intravenous iron preparations may inform practice. Use of such agents should be considered on a case-by-case basis.

Avoidance of venous congestion, high intrathoracic pressures, and hypercapnia may help minimize venous bleeding. The use of hypervolemic dilution to reduce the hematocrit may be inappropriate given the venous congestion it may cause. Careful attention should be paid to avoidance of hypothermia and its coagulopathic effects.

Regional anesthesia techniques may be employed to reduce surgical blood loss if these are otherwise appropriate.

Venous Thromboembolism

An individualized plan to prevent VTE should be made for each patient presenting for radical urologic surgery. Most will be high risk and may have VTE already as outlined earlier. The choice of treatment to discourage clot formation should be made with the specifics of the patient and timing of surgery borne in mind.

Surgical interventions to prevent clot migration such as use of saline-filled balloons or cardiopulmonary bypass must be planned preoperatively.

ACKNOWLEDGMENT

The authors wish to thank Dr. Terri G. Monk for his contribution to the previous edition of this chapter.

Further Reading

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Complications of Spinal Surgery

50

Jason D. Walls • Diana Ayubcha

Case Synopsis

A 78-year-old man with morbid obesity (body mass index [BMI] 43), chronic atrial fibrillation on dabigatran (discontinued 5 days prior), and metastatic renal cell carcinoma to T8 is undergoing corpectomy and multilevel instrumented fusion using propofol-based total intravenous anesthesia (TIVA) with intraoperative somatosensory evoked potentials (SSEPs) and transcranial motor evoked potentials (tcMEPs). Intraoperatively, major blood loss ensues requiring massive transfusion of all blood components. SSEPs and tcMEPs decrease globally, but improve to baseline with correction of acute anemia and hypotension. Surgery proceeds for a total of 7 hours. The patient is extubated the following morning in the intensive care unit (ICU). On awakening, the patient notes acute bilateral vision loss.

PROBLEM ANALYSIS

Nerve injury

Definition

Nerve injury following spine surgery appears to be a rare event, but can result in permanent and disabling outcomes. From stabilization of traumatic injuries to the delicate removal of tumors, indications for spinal surgery vary and can lead to different patterns of postoperative neural injury, compromising the spinal cord, individual nerve roots, or even terminal nerves of the brachial plexus. Postoperative complications can range from mild sensory changes to more serious central cord syndrome, Brown-Sequard syndrome, and quadriplegia.

Recognition

Without intraoperative monitoring, nerve injury during spine surgery cannot be identified until the patient is awake after anesthesia. This is often too late for corrective measures. However, intraoperative neurophysiologic monitoring (IONM) allows for real-time assessment and detection of impending neural injury. IONM alerts the surgeon when neural structures are at risk and allows for corrective actions. Overall, IONM attempts to improve the overall safety of spine surgery and limit major, debilitating nerve injury.

IONM consists of various modalities to monitor spinal cord integrity, including SSEPs, tcMEPs, and electromyography (EMG). More specifically, SSEPs allow for the continuous monitoring of the ascending dorsal column–medial lemniscus sensory pathway after the stimulation of a peripheral nerve. However, SSEPs do not monitor the anterior portion of the spinal cord, specifically the corticospinal tracts. To monitor these motor pathways, tcMEPs are intermittently checked at critical moments during the procedure by sending an electrical stimulus through the scalp to stimulate distal muscles groups of the upper and lower extremities. For a more comprehensive survey of spinal cord integrity, tcMEPs can be combined with continuous SSEPs to monitor both the anterior and posterior portions of the spinal cord. Finally, EMG, either spontaneous (free-run) or triggered, allows for more accurate monitoring during surgery around nerve roots and during pedicle screw placement. Although tcMEP can monitor motor function during nerve root surgery, significant overlap in muscle groups does not allow for the isolation of specific nerve roots that can be achieved using EMG.

Although IONM allows for the real-time assessment of neural integrity with the goal of improved safety, standardized recommendations for clinical use do not exist due to a lack of high-quality studies and randomized controlled trials. The use of IONM is common in complex spine surgery, but its overall use is not uniform throughout the spectrum of spine surgery. Although the debate remains about the overall cost/benefit analysis of IONM improving clinical outcomes, this monitoring modality does provide intraoperative feedback of neural integrity in an effort to decrease the incidence of debilitating postoperative nerve injury.

Risk Assessment

Of the varied etiologies of perioperative spinal cord injury, surgical trauma appears to pose the greatest risk for postoperative nerve injury. Mechanisms of injury include direct nerve trauma, compression, traction, insertion of hardware, and major spine geometric changes seen during scoliosis surgery. In addition, other perioperative factors can contribute to neural injury, including improper patient positioning, shoulder taping, hypotension, blood loss, and airway manipulation.

Of great importance is the patient presenting with known cervical spine instability or myelopathy. In this situation, extreme caution must be taken during airway manipulation to prevent pathologic motion of the cervical spine. However, most postoperative injuries to the cervical spine appear to occur in the absence of instability, and instead occur in the patient with cervical spine disease ranging from anatomic abnormalities to inflammatory processes (Table 50.1). These conditions either lower the threshold for cervical spine injury or make airway management more challenging, increasing the risk of intraoperative cervical cord injury. A thorough assessment of these conditions should be ascertained and appropriate imaging studies (i.e., flexion/extension

TABLE 50.1 Conditions With Increased Risk of Postoperative Cervical Spine Injury

Congenital anomalies	Achondroplasia, Down syndrome, Klippel-Feil syndrome, neurofibromatosis 1, Chiari malformation, Morquio syndrome, congenital cervical canal stenosis
Degenerative changes	Cervical spondylosis, disc herniation, destructive spondyloarthropathy
Inflammatory diseases	Rheumatoid arthritis, ankylosing spondylitis
Infectious diseases	Grisel syndrome

TABLE 50.2 Effects of Common Anesthetics on IONM During Spine Surgery

Drug Name	Drug Class	Effect on SSEPs	Effect on MEPs
Propofol	GABA agonist	↓	↓
Etomidate	GABA agonist	↑↑	–
Midazolam	Benzodiazepine	↓	–
Ketamine	NMDA antagonist	↑	–/↓
Fentanyl	Opioid	–/↓	↓
Remifentanil	Opioid	–/↓	–/↓
Sufentanil	Opioid	–/↓	↓
Dexmedetomidine	α_2-Agonist	–/↓	–/↓
Isoflurane	Inhalational	↓↓	↓↓↓
Sevoflurance	Inhalational	↓↓	↓↓
Desflurane	Inhalational	↓↓	↓↓
N_2O	Inhalational	↓↓	↓↓

GABA, γ-Aminobutyric acid; *IONM,* intraoperative neurophysiologic monitoring; *MEPs,* motor evoked potentials; *NMDA, N*-methyl-D-aspartate; *SSEPs,* somatosensory evoked potentials.
Adapted from Rabai F, Sessions R, Seubert CN: Neurophysiological monitoring and spinal cord integrity. *Best Pract Res Clin Anaesthesiol* 30(1):53-68, 2016.

films, computed tomography scan) reviewed before proceeding with spine surgery. Identifying at-risk patients in the preoperative period allows for the implementation of advanced monitoring and airway techniques in an effort to limit and prevent devastating neural injury.

In addition to spinal cord injury, certain conditions increase the risk of perioperative peripheral nerve injury, including diabetes mellitus, renal disease, hypothyroidism, alcohol abuse, vitamin deficiencies, and malnutrition. When choosing the appropriate intraoperative position for these patients, one must consider the risks of peripheral nerve injury versus the benefits of adequate surgical exposure.

Implications

Prevention of perioperative nerve injury during spine surgery influences many aspects of anesthesia practice, including airway management, IONM, and anesthetic choice. Airway management of cervical spine instability, regardless of etiology, requires careful preparation and advanced equipment. These patients are at high risk for perioperative spinal cord injury, and airway manipulation must limit pathologic cervical motion that can lead to critical cord compression. Although there are no definitive standards for the safest approach to successful tracheal intubation, awake fiberoptic intubation remains the safest method. In patients deemed to have a stable cervical spine in the setting of significant pathology, advanced airway techniques should be used based on physical examination findings and pertinent imaging studies. Studies have shown that in patients with critical cervical stenosis there is an increased susceptibility to injury from even minimal neck extension.

When using IONM, the specific type of anesthesia must be carefully planned. Nearly all medications used in current practice interfere with IONM (Table 50.2). Both SSEPs and MEPs are polysynaptic signaling pathways that rely on stable homeostasis for proper function. SSEPs are more robust than tcMEPs, and if used as a sole monitoring technique, a standard balanced general anesthetic with potent volatile agents (approximately 50% minimum alveolar concentration [MAC]) and muscle relaxation can be instituted. When using tcMEPs, TIVA without neuromuscular blockade appears to be the best approach. Both volatile anesthetics and TIVA can be safely used with EMG monitoring, but neuromuscular blocking drugs must be avoided. With all IONM techniques, a stable, background anesthetic should be achieved before critical surgical maneuvers.

Hemorrhage

Definition

Significant blood loss can be a major complication of certain spinal procedures. Inadequate surgical hemostasis can lead to either intraoperative or postoperative hemorrhage, despite apparent hemostasis. Hemorrhage can lead to serious and fatal complications such as spinal cord ischemia.

Specific to spine surgery, bone decortication and epidural venous bleeding are the primary causes of intraoperative hemorrhage, with the greatest risk occurring during corpectomy, multilevel spinal instrumentation, and fusion surgery. Along with inadequate surgical hemostasis, coagulopathy and uncontrolled hypertension are two additional etiologies of hemorrhage in the setting of spine surgery.

Perioperative coagulopathy has many etiologies, including hypothermia, low levels of plasma clotting factors, thrombocytopenia, breakdowns in enzymatic systems that ensure proper coagulation and platelet function, or hyperfibrinolysis.

Recognition

Hemorrhage results in a decrease in circulating volume that activates neural reflexes increasing the sympathetic outflow to the heart and other organs. This response is made evident in the perioperative setting by tachycardia, hypotension, vasoconstriction, and redistribution of blood flow away from nonvital organs. In addition to vigilantly monitoring the patient's vital signs and physical examination for these perturbations, it is extremely important to maintain an open line of communication with the surgical team to anticipate and treat impending blood loss.

Risk Assessment

A thorough preoperative assessment including history, physical examination, and laboratory tests (if warranted) can reveal potential risk factors for perioperative hemorrhage or coagulopathy. Patients should be questioned about known bleeding disorders, easy bruising, abnormal bleeding (epistaxis), medications (clopidogrel, aspirin, warfarin, non–vitamin K antagonist oral anticoagulants, and heparin), and nutritional deficiencies. Other possible risk factors include previous spine surgery, increased daily alcohol consumption, high BMI, prior nonsteroidal antiinflammatory drug use, and advanced age.

Based on the patient's history, preoperative laboratory tests including a platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio may be warranted. Bleeding time, activated clotting time, fibrinogen level, and thromboelastogram are often unnecessary. In patients with complex hereditary bleeding disorders, a hematology consultation may be warranted to assist in perioperative coagulation management.

Implications

Hemorrhage can lead to serious and fatal complications, including spinal cord ischemia. In patients with a history of spinal cord injury,

autoregulation of spinal cord blood flow is impaired, increasing the risk of ischemia. Additionally, external compression from vertebral displacement or surgical retraction can further decrease spinal blood flow. Hypotension, a result of hemorrhage, has been associated with worse neurologic outcomes after traumatic spinal cord injury.

Perioperative Visual Loss

Definition

Perioperative visual loss (POVL) is a rare but devastating complication. Although the estimated incidence is only 0.03% to 0.2% following spine surgery, POVL after prone spine surgery has the highest reported frequency of all surgeries, accounting for more than half of all reported cases. In patients undergoing prone spine surgery, POVL has three distinct mechanisms of injury: central retinal artery occlusion (CRAO), ischemic optic neuropathy (ION), and cortical blindness. By far the most common etiology after spine surgery is ION, followed by CRAO. These two conditions will be discussed further.

CRAO causes postoperative blindness secondary to direct, external pressure on either eye, often related to improper head positioning. External compression of the eye increases intraocular pressure that decreases central retinal artery blood flow and alters oxygen delivery to the entire retina. Other rare causes of CRAO include emboli and arterial thrombosis.

ION consists of two types of injury, depending on the anatomic site of optic nerve injury. Anterior ION (AION) and posterior ION (PION) occur anterior and posterior to the lamina cribrosa, respectively. The etiology of ION is multifactorial and not completely understood. Overall, PION appears to be more common than AION after prone spine surgery.

Recognition

Typically, CRAO presents as new-onset unilateral vision loss in the immediate postoperative period. Physical examination reveals an absent pupillary light reflex. On funduscopic examination, the retina appears whitened and ischemic with a cherry-red spot at the macula. Similarly, ION manifests in the immediate postoperative period but typically presents as bilateral painless vision loss. AION varies in presentation and can have a delayed onset of several days. Physical examination will reveal an afferent pupillary defect or absent light reflex. In AION, funduscopic examination initially reveals optic disc edema with blurring of disc margin with possible peripapillary splinter hemorrhages progressing to optic disc pallor after several weeks. In PION, initial funduscopic examination is normal but will progress to optic disc pallor and is indistinguishable from AION after several weeks.

Risk Assessment

The risk of POVL from CRAO is directly proportional to the use of any device that potentially places pressure on the eyes. For this reason, the horseshoe headrest and eye goggles should be avoided in the prone position.

Although the specific etiology of ION is not clearly defined and is most likely multifactorial, six independent factors increase the risk of developing this rare complication (Box 50.1). However, ION has been reported in the absence of these findings, highlighting the incomplete understanding of its mechanism of injury. The prone position and absolute nadir of intraoperative hemoglobin and hypotension do not appear to independently increase the risk of ION.

BOX 50.1 Independent Risk Factors for Ischemic Optic Neuropathy After Spine Surgery

- Male sex
- Obesity
- Use of the Wilson frame
- Longer anesthetic/surgical durations
- High estimated blood loss
- Decreased ratio of colloid versus nonblood fluids for resuscitation

Implications

POVL, from either ION or CRAO, has a very poor prognosis, with minimal to no return of vision and no effective treatment options. Because POVL has an increased risk following major spine surgery, this devastating complication should be discussed with the patient during the informed consent process.

Airway Compromise

Definition

Airway compromise after spine surgery includes conditions that demand emergency reintubation or tracheostomy. Recent reports suggest that airway complications can occur in up to 5% of anterior cervical spine procedures, with reintubation being required in roughly 1% of all cases. The etiology of airway compromise after spine surgery is multifactorial and includes edema of the laryngopharyngeal or prevertebral soft tissue, postoperative neck hematoma, cerebrospinal fluid (CSF) leak, abscess formation, construct dislodgement, and even recurrent laryngeal nerve injury. Additionally, traumatic intubation can lead to edema, bleeding, or tracheal injury that can potentially lead to airway obstruction. The off-label use of bone morphogenic protein during cervical spine fusion can lead to delayed airway edema through an intense inflammatory response. Although the etiology is varied, airway compromise following spine surgery must be recognized and treated to avoid airway obstruction, hypoxia, and ultimately irreversible brain ischemia.

Recognition

Patients with postoperative airway compromise can present with a range of symptoms including tachypnea, dyspnea, stridor, agitation, or cyanosis. The onset of airway symptoms following cervical spine surgery can indicate the causative etiology. Airway obstruction from laryngopharyngeal edema typically presents 12 to 72 hours postoperatively. Early airway compromise, within the first 12 hours postoperatively, is suggestive of wound hematoma. Delayed compromise can be seen with abscess, CSF leak, and hardware failure.

In a patient suspected of airway compromise, a focused physical examination must be performed with a check of vitals signs, including pulse oximetry. Assessment of head and neck anatomy should include evaluation of oral and tongue edema, as well as neck hematoma. Swift recognition of airway compromise and implementation of corrective measures are paramount to safely avoiding postoperative hypoxia.

Risk Assessment

Following cervical spine surgery, recent reviews have highlighted patient, surgical, and anesthesia factors that increase the risk of postoperative airway compromise (Table 50.3). When comparing all factors, intraoperative surgical factors appear to be the most significant contributor to postoperative airway compromise.

TABLE 50.3 Risk Factors for Airway Compromise After Cervical Spine Surgery

Patient	Surgical	Anesthetic
Morbid obesity	>3 vertebral bodies	Multiple intubation attempts
Obstructive sleep apnea	C2–C4 levels	Poor glottis view with laryngoscopy
Pulmonary disease	Blood loss >300 mL	
Cervical myelopathy	Operative time >5 hours	
Prior anterior cervical surgery	Anterior/posterior surgery	

Adapted from Palumbo MA, Aidlen JP, Daniels AH, et al: Airway compromise due to laryngopharyngeal edema after anterior cervical spine surgery. *J Clin Anesth* 25(1):66-72, 2013.

Implications

The risk of postoperative airway compromise should be considered before the extubation of any patient following cervical spine surgery. Patient and surgical risk factors should be assessed, as well as any known history of difficult airway. If there is a reasonable concern for postextubation airway obstruction, the patient should remain intubated and be transported to the ICU for postoperative management. No specific guidelines or randomized controlled trials exist that establish the optimal time to safely perform tracheal extubation. Current practice allows the patient to stay intubated overnight. However, understanding that laryngopharyngeal edema can occur up to 72 hours postoperatively may warrant a delay in extubation until after this period in high-risk patients.

MANAGEMENT

Nerve Injury

Preoperative communication among the surgical, anesthesia, and neuromonitoring teams is the first step in preventing major, debilitating postoperative nerve injury. Patient positioning, IONM, and type of anesthesia should be agreed on before spine surgery. Diseases that pose a threat to spinal cord integrity must be identified and advanced technology used to limit potential neural injury. Until future research details the best and safest method of endotracheal intubation for patients with either cervical instability or stable, chronic cervical disease, a conservative approach using fiberoptic intubation to minimize cervical motion is recommended. Even preintubation maneuvers including chin lift and jaw thrust can cause cervical motion and must be cautiously used when necessary. In emergency situations, rapid sequence induction with manual in-line stabilization and video laryngoscopy appears to be best approach.

Intraoperatively, homeostasis should be achieved through stable hemodynamics, avoidance of hypotension, resuscitation during blood loss, and continued surveillance of patient positioning. Intraarterial blood pressure (IABP) monitoring should be considered when large-volume resuscitation is expected, for rapid correction of hypotension, or for inducing relative hypertension when clinically indicated. In the setting of changes in IONM signals, reversible causes must be identified, including hypothermia, hypotension, use of potent volatile agents, and technical issues with monitoring electrodes, as well as reversing high-risk surgical maneuvers.

Hemorrhage

Perioperative hemorrhage or coagulopathy requires immediate and rapid intervention. Treatment is focused on using the appropriate medications and blood products to correct any reversible causes of coagulopathy. When coagulopathy requires blood derivatives for correction, treatment options include fresh frozen plasma, platelets, cryoprecipitate, nonactivated prothrombin complex concentrate, or recombinant factor VIIa. If bleeding is related to a qualitative platelet dysfunction, desmopressin can be administered. All fluids and blood products should be warmed before administration. Additionally, active patient warming should be implemented with warm air blankets or hot lights to further prevent hypothermia.

Induced hypotension is another technique available to reduce blood loss and transfusion requirements during elective spine surgery. The use of this method is based on clinical judgment, assessing the risk versus benefit to the patient based on preexisting comorbidities and the specific type of spine surgery. Nicardipine, an arterioselective vasodilator, has gained favor over sodium nitroprusside and nitroglycerin for this specific use. Although animal models suggest that nitroglycerin is best for preserving spinal cord blood flow during hypotension, this has not yet been confirmed in humans. However, hypotension has been associated with worse neurologic outcomes after traumatic spinal cord injury, and extreme caution should be used in this patient population, as well as those with significant spinal cord compression.

Intraoperative autologous blood salvage is another useful tool for hemorrhage management. Blood lost from the patient is salvaged, washed or filtered, and autotransfused as needed. However, fibrinolysis and disseminated intravascular coagulation may occur with filtration-type autotransfusion. The removal of soluble products by cell-washing systems can also induce coagulopathy through the loss of coagulation factors and platelets. Previously, purulent infection and malignancy were relative contraindications, but with the use of advanced filtration and washing systems, autologous blood salvage is possible.

Perioperative Visual Loss

Currently there are no effective treatment options available for POVL. Although not evidence based, recommendations with limited success include correction of severe anemia, maintaining a normal baseline blood pressure, head elevation to decrease periorbital edema, mannitol, high-dose steroids, and hyperbaric oxygen. Until future research provides successful therapeutic options, the best treatment of POVL is prevention. When POVL is suspected, urgent ophthalmology consultation should be obtained.

Airway Compromise

Airway compromise following spine surgery can progress from mild symptomatology to an emergency situation requiring immediate reintubation. From airway edema and a limited neck motion secondary to recent surgical fusion, to known difficult airway from preexisting cervical spine disease, intubation can be challenging. Often, advanced airway equipment including video laryngoscopy should be considered to improve first attempt intubation success. Fiberoptic intubation remains the safest technique in this potentially difficult airway situation.

Additionally, surgical airway equipment should be available to perform an emergent tracheostomy if unable to secure the airway, using both standard and advanced anesthesia techniques. If the airway obstruction is caused by a neck hematoma, the surgical wound should be reopened, allowing for hematoma evacuation, followed by securing the airway. Ultimately, quick decision making and open communication will allow for the most rapid use of available equipment to safely rescue the patient from postoperative airway obstruction.

PREVENTION

Nerve Injury

Even with careful planning, appropriate monitoring, and anesthesia management deemed the standard of care, nerve injury after spine surgery can still occur. However, with careful vigilance during the perioperative period, preventable injury can be identified and controlled. Preoperatively, a detailed history of pertinent conditions related to spinal cord disease might alert the team of at-risk patients. Intraoperatively, conservative and careful airway management using fiberoptic technology could limit pathologic cervical motion. During critical surgical interventions, providing a stable anesthetic will allow for appropriate IONM and smooth hemodynamics. Above all, communication among the surgical, anesthesia, and neuromonitoring teams allows for an open dialogue and provides the safest and most coordinated patient care during spine surgery.

Hemorrhage

As discussed previously, a thorough preoperative patient assessment can reveal potential risk factors for hemorrhage during spine surgery, and appropriate steps should be taken to prepare for significant blood loss. Adequate large-bore intravenous access must be obtained before surgery, including possible central venous access. IABP monitoring can be useful during large-volume transfusions and for frequent laboratory checks to monitor the patient's coagulation profile. A current type and crossmatch are necessary to ensure the availability of appropriate blood products.

Perioperative Visual Loss

Prevention is the mainstay of treatment for POVL after spine surgery. In high-risk patients or those undergoing extensive spinal surgeries, exact preventive measures have not been firmly established. Maintaining an elevated mean arterial pressure, lowering colloid transfusion thresholds, altering intraocular pressure, and using antiplatelet agents and steroids have not been proven in the literature to affect outcomes. Current recommendations for intraoperative management include increasing the percentage of colloid versus nonblood fluids used for large-volume resuscitation, maintenance of a normal blood pressure, serial hemoglobin checks, appropriate use of vasoactive drugs, avoidance of the head-down position, and consideration of staging for complex spine procedures. To prevent CRAO, vigilance and frequent eyes checks at least every 20 minutes may limit eye compression and retinal ischemia.

Airway Compromise

No proven formula or evidence-based guidelines exist to quantify the risk of airway compromise following spine surgery. A high level of suspicion based on known clinical risk factors should guide preventive measures for postoperative airway obstruction. In high-risk patients, extubation should be delayed and the patient should remain intubated in the ICU. No consensus guidelines exist detailing the appropriate length of time the patient should remain intubated, and clinical expertise should guide the decision for extubation. In high-risk patients, a cuff-leak test may provide usual information before extubation. Recent reports show that the absence of a cuff leak could be a harbinger for airway obstruction following extubation. However, the presence of a leak has a low predictive value of airway compromise after extubation. The use of corticosteroids does not appear to prevent airway edema after spine surgery. Ultimately, clinical expertise, known patient risk factors, and the potential for a difficult airway must guide the decision to extubate the patient following spine surgery.

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51 Complications of Thyroid Surgery

Senthil Nadarajan • Kavitha Kuntumalla

Case Synopsis 1

A 55-year-old woman with a 5-year history of swelling in the front of the neck presented for subtotal thyroidectomy. She has a history of palpitations on minimal exertion. She gives a history of shortness of breath on lying supine and prefers to sleep on her side. She also has an altered voice. A prominent thyroid gland is palpated on physical examination. The chest radiograph demonstrates moderate displacement of the trachea to the right from the midline. Indirect laryngoscopy revealed bilateral normal vocal cord function.

Case Synopsis 2

The same patient underwent uneventful subtotal thyroidectomy for multinodular goiter. The patient complains of difficulty in breathing 3 hours after surgery. On examination the patient is slightly restless, and mild inspiratory stridor is noted. Pulse oximetry reveals an arterial oxygen saturation of 94% on 2 L/min of nasal O_2 and other vital signs are stable.

PROBLEM ANALYSIS: CASE SYNOPSIS 1

Thyroid surgery may range from lobectomy to total thyroidectomy (Table 51.1). Solitary thyroid nodule may be removed by lobectomy or hemithyroidectomy. The most common cause of hyperthyroidism is Graves disease. Toxic adenoma and toxic multinodular goiter (MNG) are other causes of hyperthyroidism. Surgical management of Graves disease involves near-total thyroidectomy. However, aggressive thyroid malignancy may require extensive neck dissection in addition to total thyroidectomy.

Preoperative Assessment

Adequate preoperative assessment with optimal preparation of the patient minimizes the postoperative complications of thyroidectomy. Preoperative assessment involves history, examination, thyroid function tests, imaging, and evaluation of vocal cord function (Table 51.2). Preoperatively it is important to ensure euthyroid status. Graves disease is a common cause of hyperthyroidism, followed by MNG and toxic adenomas.

Elevated calcitonin levels may suggest medullary carcinoma of thyroid. Medullary carcinoma of thyroid gland is rare and may be associated with multiple endocrine neoplasia type 2 (MEN 2). The presence of pheochromocytoma should be excluded in all patients with MEN 2A or MEN 2B syndrome.

Recognition and Preparation of the Hyperthyroid Patient

Hyperthyroid patients may present with sudden weight loss, palpitations, fine tremors, and an enlarged thyroid gland. Correct diagnosis of the etiology of hyperthyroidism must be made before therapy is commenced. Hyperthyroid patients are at risk of developing thyroid storm perioperatively, so adequate preoperative treatment of hyperthyroidism is important. In the surgical management of hyperthyroidism, methimazole is the initial antithyroid agent used except in pregnant patients where propylthiouracil is preferred. In addition, β-blockers may be used, to control symptoms until euthyroid status is achieved. Inorganic iodine may be given for up to 10 days before surgery to decrease the vascularity of the thyroid gland in patients with Graves disease. Patients should have their thyroid function assessed at 4-week intervals. Neutrophil count should be monitored, as methimazole can cause agranulocytosis. Methimazole can be discontinued on the day of surgery.

Risk Assessment

Airway

A comprehensive airway assessment must be performed. The size and duration of goiter or thyroid enlargement should be ascertained. Stridor, if present, may indicate narrowing of the airway due to a large goiter. Long-standing goiters have the potential to cause tracheomalacia postoperatively, although this is rare.

A rapid increase in the size of the swelling suggests malignancy. Aggressive thyroid malignancy has the potential to invade the recurrent laryngeal nerve. Therefore, in any patient with hoarseness of voice, it is important to ascertain the function of the vocal cords by fiberoptic laryngoscopy or indirect laryngoscopy.

It is important to assess for retrosternal extension of the goiter. Retrosternal goiters may cause lower airway compression. Surgical access may be difficult through the neck, and rarely sternal split may be required. This has implications for airway management. Shortness of breath or choking sensation on lying supine and a preference to lie on the lateral position may indicate tracheal compression by the retrosternal goiter.

TABLE 51.1 Types of Thyroid Surgery

Thyroid Disease	Type of Surgery	Potential for Complication
Small solitary nodule	Hemithyroidectomy	Low risk of injury to laryngeal nerves
Solitary toxic adenoma	Ipsilateral lobectomy	Hyperthyroidism
Retrosternal goiter	Subtotal thyroidectomy	Risk of severe bleeding, airway obstruction May require a sternotomy approach
Graves disease	Total thyroidectomy	Hyperthyroid crisis
Aggressive malignancy	Total thyroidectomy with neck dissection	Injury to the laryngeal nerves May require tracheostomy
Thyroglossal duct cyst excision	Sistrunk procedure	Inadvertent damage to thyroid cartilage causing severe airway obstruction

TABLE 51.2 Preoperative Assessment

History	To assess airway compromise (dyspnea on lying supine) To assess symptoms of hyperthyroidism/hypothyroidism Medication history including antiplatelet agents/anticoagulants Remember: association of pheochromocytoma with medullary carcinoma of thyroid
Examination	For retrosternal extension of goiter Look for SVC obstruction—facial plethora—Pemberton sign
Blood tests	Full blood count (methimazole may cause agranulocytosis) Blood grouping and typing Thyroid function tests
Imaging	Chest x-ray—tracheal deviation CT scan—anatomic level and extent of tracheal narrowing
Nasendoscopy	Assessment of vocal cord function
ECG (e.g., in AF)	Assess rhythm, presence of LVH, ischemic changes
Lung function tests Flow-volume loop	In extrathoracic airway obstruction (goiter) the inspiratory airflow is reduced This distinguishes local pressure effects caused by the goiter from underlying asthma

AF, Atrial fibrillation; *CT,* computed tomography; *ECG,* electrocardiogram; *LVH,* left ventricular hypertrophy; *SVC,* superior vena cava.

Superior vena cava (SVC) obstruction is a rare complication of retrosternal extension of goiter. Facial plethora and venous engorgement on raising both arms indicates SVC obstruction (Pemberton sign). Imaging, especially computed tomography, helps determine the site and extent of airway compression, which may be useful in choosing the appropriately sized tracheal tube.

Extension of the neck is a requirement for positioning during thyroid surgery. However, if there is any limitation in neck movement preoperatively, take care during positioning.

MANAGEMENT

Airway

General anesthesia and endotracheal intubation with a reinforced tube are the preferred option. The following considerations must be taken into account. Neural integrity monitor is frequently used to monitor the proximity of recurrent laryngeal nerve during surgery. This requires the use of an electromyogram (EMG) tracheal tube. This tube has a large external diameter. This might pose a challenge during intubation of the large goiters with airway compression. Videolaryngoscopes improve laryngeal visualization, and a preformed curved stylet facilitates the careful placement of the EMG tracheal tube under vision.

Awake fiberoptic intubation under careful topical anesthesia may be considered, for example in patients with limited neck movement, provided there is no significant tracheal narrowing. Fiberoptic intubation may be dangerous in a compromised narrow airway and is best avoided.

Opinion is divided among experts on the management of obstructed airway. In patients with subglottic airway obstruction, insertion of the tracheal tube may not be possible. In such situations, a rigid bronchoscope inserted by the surgeon is a useful technique in providing ventilation and should be a backup plan. Also, it is important to note that tracheostomy and cricothyroid access may be difficult in the presence of large goiters. It is important to discuss the management plan with the surgeon. In patients with severe mediastinal compression, femoral venous cannulation and cardiopulmonary bypass as standby may be the safest option.

PREVENTION

Intraoperative Complications

Bleeding is an important complication in vascular thyroids such as Graves disease and in patients with retrosternal goiters. Head-up positioning, the use of tapes instead of ties to secure the tracheal tube, and controlled hypotension reduce the potential for bleeding. Using a remifentanil infusion–based technique decreases the need for neuromuscular blockade and facilitates recurrent laryngeal nerve monitoring by the surgeon. Careful neck positioning and support to avoid hyperextension prevents injury and neck pain. Abrasions may occur in patients with exophthalmos. Therefore eye protection with proper padding, after lubrication and taping of eyelids, is important. The use of dexamethasone reduces the risk of airway edema developing in the emergence phase. Inadvertent tracheal perforation during thyroidectomy is a very rare complication. It is important to avoid hyperinflation of the tracheal tube cuff. Performing a Valsalva maneuver toward the end of the procedure helps the surgeon to look for any air leaks or bleeding.

Perioperative Thyroid Crisis

This is rare and can occur intraoperatively or up to a few hours postoperatively. It has a high mortality rate if not diagnosed and managed promptly. Clinical diagnosis is the key for immediate management. Hyperthyroid patients who are not adequately treated are at risk. Sudden rise in temperature and significant tachycardia may be the first signs of thyroid crisis during thyroid surgery. Arrhythmias and heart failure may occur (Fig. 51.1).

The differentiation from malignant hyperpyrexia (MH) may be difficult, although muscle rigidity and rapid rise in end-tidal CO_2 are characteristic features of MH. Treatment involves supportive management and inhibition of synthesis, release, and peripheral action of thyroid hormone.

Emergence and Extubation

Smooth awake extubation in a spontaneously breathing patient is a safe approach. It is important to avoid coughing because this may increase the risk of bleeding and hematoma. After extensive surgery for malignancy involving neck dissection, airway compromise due to swelling and edema may occur. In such cases, before extubation, visualize the airway and observe for the presence of a leak around the tracheal tube cuff, after deflation of the cuff. Absence of leak may suggest tracheomalacia.

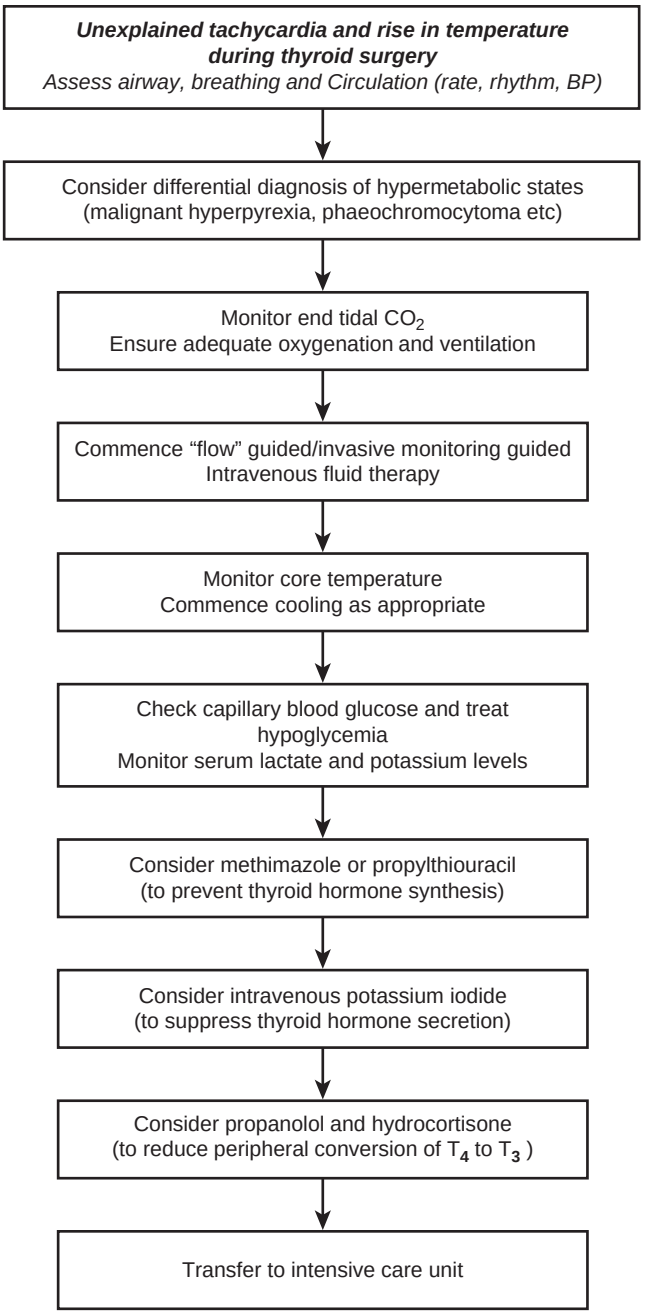

Fig. 51.1 Approach to the patient with hyperthyroid crisis.

If there is any concern of reintubation difficulty, defer extubation or consider extubation over an airway exchange catheter. This provides a channel for maintaining oxygenation and also facilitates railroading of the tracheal tube, should the patient require reintubation.

PROBLEM ANALYSIS: CASE SYNOPSIS 2

The causes of airway obstruction and stridor may be due to postthyroidectomy hematoma, laryngeal edema due to any cause, bilateral recurrent laryngeal nerve palsy, tracheomalacia, or laryngospasm due to hypocalcemia.

MANAGEMENT AND PREVENTION

Hematoma

Close monitoring for bleeding/hematoma is essential in the immediate postoperative period. Hematoma may occur in the early postoperative period, and some may progress to cause airway obstruction. Definitive treatment is the early evacuation of the hematoma. However, compartment syndrome caused by hematoma below the strap muscles can impair venous drainage, leading to laryngopharyngeal edema. This might make reintubation of the airway difficult.

Assess patency of the airway and adequacy of breathing. Sit the patient up and commence high-flow oxygen. Consider the removal of clips to release the neck hematoma by the bedside, if the patient is in extremis. Make urgent arrangements to transfer the patient to the operating room for exploration of hematoma. In addition, consider intravenous dexamethasone and nebulized epinephrine to reduce laryngeal edema. Anticipate difficult intubation, seek senior help, and have a range of equipment including videolaryngoscope and a small-diameter tracheal tube to secure the airway.

Recurrent Laryngeal Nerve Palsy

Recurrent laryngeal nerve (RLN) palsy occurs in 5% to 11% of patients following thyroidectomy and is the second most common early complication. Unilateral RLN injury produces abductor vocal cord paralysis. The affected vocal cord assumes a paramedian position. Patients often present with postoperative hoarse voice. RLN paralysis recovers in most cases.

Bilateral recurrent nerve paralysis occurs in less than 0.1% of patients following thyroidectomy. This causes adduction of the vocal cords during inspiration, leading to obstruction of the airway and aphonia. It is a rare complication of total thyroidectomy that requires emergency airway management.

Hypocalcemia

Transient hypocalcemia is the most frequent early complication of thyroidectomy, occurring in about 20% to 30%. Laryngospasm due to hypocalcemia causing stridor is rare. This may occur up to 48 hours postoperatively. Hypocalcemia occurs as a result of trauma or removal of the parathyroid gland. Diagnosis is by recognition of the symptoms of hypocalcemia such as tingling, numbness in the perioral area, or facial twitching progressing to carpopedal spasm. QT prolongation may occur on electrocardiogram. Continuous positive airway pressure is helpful in relieving airway obstruction. Intravenous calcium gluconate is titrated to the patient's symptoms and serum ionized calcium concentration. This is switched to oral calcium and vitamin D and continued for at least 10 days.

Other Complications

Inadvertent tracheal perforation is a very rare complication occurring during thyroidectomy. If it is not recognized intraoperatively, presentation may be delayed up to a week postoperatively. Tracheal wall injury or ischemia may very rarely result in delayed tracheal rupture. This may present as surgical emphysema or pneumomediastinum and require prompt management.

Complications of thyroid surgery for goiter removal are listed in Table 51.3.

TABLE 51.3 Complications of Thyroid Surgery

Intraoperative	Hyperthyroid crisis (Graves disease)
	Bleeding (retrosternal goiters)
	Corneal abrasion (especially with proptosis)
Complications presenting at extubation	Tracheomalacia (rare)
	Bilateral recurrent laryngeal nerve palsy (biphasic stridor)
Early complications	Hematoma (common)
	Laryngeal edema
	Transient hypocalcemia (20%–30%)
	Hypocalcemia causing laryngospasm (rare)
Late complications	Hypoparathyroidism 4%
	Hypothyroidism
	Infection
	Tracheal perforation (very rare)

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52 Complications of Transurethral Surgery

Anuj Malhotra • Vinod Malhotra

Case Synopsis

An otherwise healthy 70-year-old man undergoes combined transurethral resection of the prostate (TURP) and transurethral resection of a bladder tumor (TURBT) under spinal anesthesia with sedation. His blood pressure is 130/90 mm Hg, heart rate is 68 beats per minute, respirations are 16 breaths per minute, and hematocrit is 38%. Ninety minutes into surgery, the patient becomes restless. His blood pressure is 180/100 mm Hg and his heart rate is 40 beats per minute. The electrocardiogram (ECG) shows depressed T waves. Laboratory values are as follows: hematocrit 27%, sodium 123 mEq/L, potassium 3.0 mEq/L, and chloride 95 mEq/L.

PROBLEM ANALYSIS

Definition

TURP syndrome is a general term used to describe a wide range of neurologic and cardiopulmonary symptoms and signs caused by intravascular absorption of hypotonic bladder-irrigating fluids during transurethral procedures, especially TURP. In conscious or sedated patients, the sudden onset of restlessness should raise the suspicion for TURP syndrome. Hypertension is indicative of hypervolemia. Reflex bradycardia occurs in response to the increased blood pressure. T-wave depression on the ECG is caused by glycine in the irrigating fluid. Hyponatremia is yet another sign of hypotonic irrigant absorption (Table 52.1).

A reduced hematocrit is most likely due to a combination of blood loss and hemodilution. Bradycardia may also occur after bladder perforation. In this case bradycardia is an efferent vagal response to peritoneal stimulation secondary to any extravasated fluid. Abdominal or shoulder pain and hypotension usually accompany the bradycardia.

Recognition

The case synopsis illustrates three significant complications of transurethral surgery: (1) TURP syndrome, (2) severe hemorrhage, and (3) bladder perforation.

TURP Syndrome

TURP syndrome is a constellation of signs and symptoms that result from the following circumstances or conditions:

- Circulatory overload
- Water intoxication or hypo-osmolality
- Hyponatremia
- Glycine toxicity
- Ammonia toxicity
- Hemolysis
- Coagulopathy

These signs and symptoms may occur simultaneously (Table 52.2). The clinical presentation may be further complicated by bacteremia or septicemia, which causes chills, hypotension, and tachycardia.

Severe Hemorrhage

Severe hemorrhage is usually evident as surgical bleeding, although it is difficult to measure because blood is mixed with copious amounts of irrigating fluid. Occult internal bleeding may occur if bladder perforation has occurred. Clinical signs of excessive bleeding include hypotension and reflex tachycardia. However, tachycardia may not occur in the presence of age-related sinus node dysfunction or with the use of β-blockers or high spinal anesthesia.

Bladder Perforation

Bladder perforation is difficult to recognize during general anesthesia. Hypotension and bradycardia or tachycardia may occur, but these are nonspecific findings. An experienced surgeon, however, usually recognizes a bladder perforation immediately. With spinal anesthesia, the complaint of abdominal or shoulder pain is helpful in making the diagnosis.

Risk Assessment

Approximately 400,000 TURP procedures are performed annually in the United States. About 10% of men older than 65 years require TURP. The incidence increases to 20% to 30% for men older than 80 years. Patients undergoing TURP commonly have one or more of the following conditions or factors:

- Heart disease
- Hypertension
- Diabetes
- Chronic obstructive pulmonary disease
- History of smoking

Perioperative morbidity is related to associated disease, age, and sepsis. Morbidity is increased in African Americans and in patients to whom the following factors apply:

- Resection time longer than 90 minutes
- Prostate weighing more than 45 g
- Acute urinary retention
- Age greater than 80 years

The amount of absorbed irrigating fluid is influenced by the following factors:

TABLE 52.1 Hypotonic Irrigants Used for Transurethral Resection of the Prostate or a Bladder Tumor

Solution	Osmolality (mOsm/kg)
Water	0
Glucose, 2.5%	139
Sorbitol, 3.5%	165
Urea, 1%	167
Glycine, 1.2%	175
Cytal (sorbitol 2.7% and mannitol 0.54%)	178
Glycine, 1.5%	220
Mannitol, 5%	275

TABLE 52.2 Pathophysiology and Clinical Features of TURP Syndrome

Pathophysiology	Clinical Features
Fluid overload	Hypertension; bradycardia; arrhythmia; angina; pulmonary edema and hypoxemia; ventricular failure and hypotension
Water intoxication or hypo-osmolality	Confusion and restlessness; twitching or seizures; lethargy or coma; dilated, sluggish pupils; papilledema; low-voltage EEG; hemolysis
Hyponatremia	CNS changes as above; reduced inotropy; widened QRS complex; low-voltage ECG; T-wave inversion on ECG
Glycine toxicity	Nausea and vomiting; headache; transient blindness; loss of light and accommodation reflexes (blink reflex preserved); myocardial depression; ECG changes
Ammonia toxicity	Nausea and vomiting; CNS depression
Hemolysis	Anemia; acute renal failure; chills, clammy skin; chest tightness and bronchospasm; hyperkalemia resulting in malignant arrhythmias or bradyasystole
Coagulopathy	Severe bleeding; primary fibrinolysis; disseminated intravascular coagulation

CNS, Central nervous system; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *TURP*, transurethral resection of the prostate gland.

- Resection time
- Prostate gland size
- Hydrostatic pressure of the irrigating fluid
- Number and size of venous sinuses opened
- Whether the prostatic capsule is intact

Chronic inflammation, repeated instrumentation, and indwelling Foley catheters increase prostatic vascular congestion and predispose to increased bleeding and bacteremia during TURP. Prolonged resection of a large prostate allows for significant release of plasminogen activators from prostatic tissue into the bloodstream. This can cause primary fibrinolysis. Prostatic tissue and multiple microthrombi may also enter the circulation, leading to disseminated intravascular coagulation (DIC).

Bladder perforation occurs in up to 1% of TURBT. A higher likelihood of bladder perforation is expected if the bladder tumor is sessile versus pedunculated, is large and fragile, or infiltrates the bladder wall. A bladder wall that is chronically inflamed, previously irradiated, or thin and stretched is more prone to perforation. The likelihood of perforation is further increased if the tumor is difficult to access, bleeding obscures the surgeon's vision, the patient unexpectedly moves or coughs, or instrumentation is difficult or traumatic.

Implications

Overall mortality of TURP has steadily decreased with advances in technology and monitoring, from 2.5% in 1962 to 0.10% in 2003. Perioperative morbidity is more frequent and ranges from 7% to 20%. Most mortality and morbidity occur in patients who develop complications of TURP, including TURP syndrome, bladder perforation, or sepsis. In 15% of patients, transient bacteremia occurs. Of these, 6% to 7% develop septicemia, which is associated with significant mortality. Because the consequences of these complications are severe, aggressive management is required.

MANAGEMENT

TURP Syndrome

Immediate aggressive therapy is essential if the patient is to survive. The following measures are suggested:

- Terminate the surgery as soon as possible.
- Administer 20 mg of intravenous (IV) furosemide.
- Immediately obtain the following laboratory tests: hematocrit; serum electrolyte, creatinine, and glucose concentrations; serum osmolality (if available); arterial blood gas analyses; and 12-lead ECG.
- Continue or start the administration of normal saline. Hypertonic saline (3% or 5%) may be administered (at a rate less than 100 mL/h) if the serum sodium concentration is less than 100 mEq/L, severe central nervous system side effects of hyponatremia and hypo-osmolality are evident, or reduced inotropy results in cardiovascular collapse. Care should be taken to avoid too rapid or overcorrection of hyponatremia as this may lead to central pontine myelinolysis.
- Administer IV midazolam in 1-mg incremental doses to treat twitching or seizures; a barbiturate may be added if seizures persist.
- Auscultate chest and obtain chest radiographs to detect pulmonary edema. Intubate and mechanically ventilate the patient at the earliest evidence of pulmonary edema.
- Transfuse packed red blood cells as necessary.
- If bleeding continues, investigate for DIC or primary fibrinolysis. DIC is treated with crystalloids and blood products to achieve hemodynamic stability and normal coagulation. Primary fibrinolysis responds well to aminocaproic acid (Amicar) administered as an IV infusion of 3 to 5 g in the first hour, followed by continuous IV infusion at 1 g/h until the bleeding is controlled.
- Institute invasive monitoring and provide supportive therapy to maintain circulation and pulmonary function and to prevent renal failure.

Bladder Perforation

As soon as bladder perforation is detected, undertake the following measures:

- Stop surgery and achieve hemostasis.
- Treat hypotension with IV crystalloids, vasopressors, and inotropes.
- Obtain a hematocrit. Start blood transfusion if brisk bleeding continues. Occult blood loss into the intraperitoneal or retroperitoneal space may occur.
- Perform a cystourethrogram to locate the perforation.

For most perforations, suprapubic cystotomy, an indwelling Foley catheter, and (occasionally) ureteral stents are sufficient. In some instances, immediate exploratory laparotomy may be necessary to control bleeding and repair the perforation.

Septicemia

Chills and fever should be treated aggressively and immediately with IV antibiotics to cover urogenital flora. Cardiovascular support may be necessary.

PREVENTION

TURP Syndrome

Take the following preventive measures:

- Limit resection time to less than 1 hour.
- Keep the prostate capsule intact until the end of resection.
- Maintain irrigating fluid height less than 60 cm above the prostate gland.
- Measure serum electrolyte levels during and after the procedure.
- Use regional anesthesia and very light or no sedation to allow early detection of changes in the patient's mental status.

Bladder Perforation; Bacteremia and Septicemia

Avoid overdistention of the bladder, rough instrumentation, patient movement, and extensive prostate or bladder tumor resections at one sitting. Use broad-spectrum antibiotic prophylaxis for bacteremia and septicemia.

Monopolar TURP, Bipolar TURP, and Laser Prostatectomy

The conventional gold standard for TURP has been the monopolar resectoscope, which emits a cutting current that then passes locally through tissue and exits via a grounding pad. Accordingly, this technique requires use of a nonelectrolyte, hypo-osmolar irrigant to minimize dispersion of current and that, if absorbed, can lead to TURP syndrome. Bipolar TURP uses a continuous loop electrode to contain both the inflow and outflow of current within the resectoscope, allowing for the use of normal saline as irrigant. Meta-analyses have shown improved outcomes using this technique, as it avoids the complications of hyponatremia and hypo-osmolality that can occur with monopolar TURP. Volume overload can still occur, however, if excess normal saline is absorbed through open prostatic sinuses.

Holmium:yttrium-aluminum-garnet (Ho:YAG), photoselective high-powered potassium titanyl phosphate (KTP or Greenlight), and Greenlight High Performance System (HPS) are the three most common laser systems used in TURP. These techniques produce a thin coagulation zone that seals prostatic veins during treatment. Additionally, normal saline can be used as a bladder irrigant. The main advantages over conventional TURP include minimal blood loss (as little as 50 to 70 mL) and minimal fluid absorption, which should nearly eliminate these two major complications of TURP. It is advocated as the option of choice for anticoagulated patients and given the lower risk for TURP, some practitioners have deemphasized the use of regional anesthesia as a preferred technique. However, due to the thin treatment zone, procedures can take longer than with classic TURP and other complications are possible, including coagulation through the prostatic fossa and sloughing of prostatic debris in the postoperative period, which can lead to urinary obstruction and retention. Intraoperatively, protective eyewear should be worn, and a means of evacuating the smoke plume is required.

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Complications of Trauma Surgery

53

Maged Argalious

Case Synopsis

A 23-year-old man arrives in the emergency department with a gunshot wound to the right upper quadrant of the abdomen. He is combative and confused. His vital signs include systolic blood pressure, 70 mm Hg; heart rate, 119 beats per minute; and respiratory rate, 22 breaths per minute.

PROBLEM ANALYSIS

Definition

Trauma-related injury (TRI) is the leading cause of death in the United States for persons between 1 and 45 years old and is the fifth-leading cause of death overall. Because TRI affects primarily the young, it is the leading cause of years of life lost before age 75 years. The World Health Organization (WHO) estimates that TRI is the leading cause of mortality globally for both men and women between 15 and 45 years of age. Also, WHO estimates that by 2020, TRI will be the third-leading cause of death in all age groups.

TRI victims present unique challenges to the health care delivery system. They often have multiple injuries to multiple organ systems that necessitate resource-intensive care. Further, TRI can adversely interact with many chronic underlying medical conditions. The top four TRI causes are motor vehicle accidents (cars, trucks, motorcycles), falls, assaults, and pedestrians hit by vehicles.

Many trauma injuries are preventable. Alcohol or drug use was documented in 40% of car and truck crash injuries involving adults and in 38% of motorcycle crash injuries. Trauma is classified as either intentional (e.g., homicide) or accidental, as well as according to the mechanism of injury (e.g., penetrating versus blunt). Owing to improvements in trauma care, there has been a decline in trauma-related deaths in recent years.

Recognition

Evaluation of acute trauma victims has three key components: rapid overview, primary survey, and secondary survey. Resuscitation can be initiated at any time during this triage. Rapid overview takes only a few seconds and is used to determine whether the patient is stable, unstable, or dead. The primary survey involves the rapid evaluation of functions that are critical to survival. The ABCs of *airway* patency, *breathing,* and *circulation* are assessed, followed by a brief neurologic examination. Priority is then given to cervical spine injury or impending cerebral herniation. The rapid overview and the primary survey are also referred to as the "golden hour" because rapid intervention to identify and treat life-threatening injuries in the first 60 minutes can affect survival and outcomes of trauma patients. The secondary survey entails a systematic, comprehensive evaluation of each anatomic region and usually detects injuries that were overlooked initially. Three quarters of such previously undetected injuries are orthopedic. Based on the results of the secondary survey, patients are rushed immediately to the operating room for surgery, transferred to the radiology suite for further diagnostic studies, or reexamined and observed in an intensive care unit.

Knowledge of the patterns of injury associated with different mechanisms of trauma (i.e., clusters of injury) can help anticipate and identify injuries early. The presence of the worst possible injuries should be assumed until the diagnoses are either confirmed or excluded. Many trauma-related complications are diagnosed intraoperatively (Box 53.1).

Blunt trauma causes localized or widespread transfer of energy to the body. Depending on the site of impact and the amount of energy, this can cause visceral rupture or tissue disruption, including multiple fractures. Penetrating trauma is commonly limited to the track along which a bullet or sharp object has traveled.

Risk Assessment

Triage scoring systems are based on the physical examination and physiologic or mechanism-of-injury parameters. They have traditionally been used to determine patterns of patient referral to trauma centers. Survival is the major outcome variable. The revised trauma score (RTS) is a prospective scoring system that exists in two forms: one is designed for use as a triage tool, and the other is used to evaluate in-hospital patient outcomes. The RTS accurately predicts mortality following traumatic injury, but there is a lack of definitive evidence supporting its use as a primary triage tool in the field or as a predictor of functional outcome and quality of life. To determine the RTS, the Glasgow Coma Scale (GCS) score, systolic blood pressure, and respiratory rate are assigned coded values from 4 (normal) to 0. These are then added and weighted (Table 53.1). When summed, values can range from 0 to 7.84. Higher values indicate a better prognosis. Of the many trauma scoring systems, the RTS is the most popular worldwide.

Traumatic injuries and subsequent intraoperative complications depend on patterns of injury. Factors that affect these include age, gender, impact resistance and fixation of body parts, anatomic protection of organs, and mechanism of injury.

Patients at risk for cervical spine injury include conscious patients with neck pain or severe pain with distraction, 20% of unconscious patients with injuries above the clavicle, intoxicated patients, and those with neurologic signs or symptoms. Cervical spine injury is

BOX 53.1 Injuries and Potential Perioperative Complications in Trauma Victims

Central Nervous System
Cervical spine instability or injury and possible spinal cord injury
Closed head injury with increased intracranial pressure
Possible brainstem herniation due to increased intracranial pressure
Brain herniation through open skull fracture

Chest and Pulmonary
Endobronchial intubation
Tension pneumothorax or hemothorax
Pneumomediastinum
Rib fracture and possible flail chest
Pulmonary contusion
Bronchopleural fistula
Aspiration pneumonitis
Bronchospasm
Tracheobronchial plugging
Fat embolism with long bone (e.g., femur) fracture

Cardiovascular
Myocardial contusion or cardiac rupture
Pericardial tamponade or pneumopericardium
Aortic dissection or disruption
Disruption of pulmonary vasculature or vena cava
Hypotension: hypovolemic or neurogenic
Hypovolemic circulatory shock
Air embolism

Abdomen
Disruption or laceration of hollow viscera
Hepatic laceration
Splenic rupture

Coagulation
Coagulopathy, especially with massive blood transfusion
Disseminated intravascular coagulopathy
Primary fibrinolysis
Hemolytic transfusion reaction

Electrolyte or Other Imbalance
Hypocalcemia secondary to citrate toxicity
Hyperkalemia, hypomagnesemia
Acid-base imbalance

TABLE 53.1 Revised Trauma Scoring System

Glasgow Coma Scale Score	Systolic Blood Pressure (mm Hg)	Respiratory Rate (breaths/min)	Coded Value
13–15	>89	10–29	4
9–12	76–89	>29	3
6–8	50–75	6–9	2
4–5	1–49	1–5	1
3	0	0	0

Revised trauma score = $0.9368(GSC_c) + 0.7326(SBP_c) + 0.2908(RR_c)$, where GCS is Glasgow Coma Scale score, SBP is systolic blood pressure, RR is respiratory rate, and the subscript c denotes the coded value for the indicted parameter.
Adapted from Champion HR, Copes WS, Sacco WJ, et al: Improved predictions from a severity characterization of trauma (ASCOT) over Trauma and Injury Severity Score (TRISS): results of an independent evaluation. *J Trauma* 40:42-48, 1996.

uncommon with penetrating trauma that is remote from the neck. Spine films that visualize all seven cervical and the first thoracic vertebrae in the lateral, anteroposterior, and odontoid views are required before clearing the cervical spine. Even with normal cervical radiographs, the possibility of ligamentous injury can be ruled out only by computed tomography scanning.

Recognition of a potentially difficult airway, whether due to anatomic predisposition or the actual trauma, is one of the most important roles of the anesthesiologist. Intubation in a patient with an unstable cervical spine involves the potential for irreversible spinal cord injury.

The risk for pulmonary aspiration of the gastric contents is high in trauma victims. Gastric emptying virtually stops at the time of injury, and protective airway reflexes are impaired in obtunded or comatose victims. The greatest risk for aspiration in conscious patients occurs between the induction of anesthesia and endotracheal intubation. The mortality rate with pulmonary aspiration is 5%.

Fracture of the first or second ribs, flail chest, a widened mediastinum, massive hemothorax, and scapula fractures often correlate with pulmonary or vascular injury. In blunt trauma, rib fractures are the most common injury; hemothorax or pneumothorax is more common with penetrating injuries.

Resuscitation frequently requires massive transfusion of blood and blood components, as well as volume replacement with crystalloids and colloids. For massive uncontrolled traumatic hemorrhage, the priority is for immediate blood, blood component, and volume resuscitation, followed by definitive surgical control of hemorrhage from major vessels. However, transfusion and achieving hemostasis with blood component therapy entail significant risks. Normal saline has been associated with hyperchloremic metabolic acidosis, and the use of large volumes of hetastarch solution has been implicated in coagulopathy and renal insufficiency.

Implications

The risk of cervical spine injury and aspiration determines the method used to secure the airway. If time permits, aspiration prophylaxis includes metoclopramide, an H_2-antagonist, and sodium citrate to facilitate gastric emptying and reduce gastric pH. Most patients arrive in the operating room wearing a cervical spine collar because cervical spine injury has not been ruled out. Options for securing the airway include awake fiberoptic oral endotracheal intubation after topical oropharyngeal anesthesia in cooperative, spontaneously breathing patients. Awake nasal intubation is typically avoided because of the risk of brain injury from nasal instrumentation in the presence of preexisting basilar skull or cribriform plate fracture. However, it can be a viable option in patients with massive oral trauma. Alternatively, patients are intubated after intravenous (IV) rapid-sequence induction of anesthesia using direct laryngoscopy, videolaryngoscopy (e.g., Glidescope), or asleep fiberoptic technique. Before induction, the front portion of the cervical spine collar must be removed, and the cervical spine is stabilized with manual in-line traction. Then the patient is preoxygenated, with cricoid pressure applied during rapid-sequence induction and endotracheal intubation with a cuffed endotracheal tube performed using one of the aforementioned methods for intubation. Once the endotracheal tube cuff is inflated and adequate ventilation and oxygenation are confirmed, cricoid pressure can be released and the anterior portion of the cervical spine collar can be reattached. It is important to note that the efficacy of cricoid pressure in preventing gastric aspiration has been questioned, especially in the absence of evidence to support its use. The application of cricoid pressure is therefore no longer considered a class I recommendation, especially with studies documenting worsening of the laryngoscopic view in up to 30% of patients with application of cricoid pressure during intubation (also called Sellick maneuver).

Fluid resuscitation of patients with TRI should be considered in two phases:

- Early: during active ongoing hemorrhage
- Late: following control of hemorrhage

BOX 53.2 Indications for Endotracheal Intubation in Trauma-Related Injury

- Cardiac or respiratory arrest
- Airway obstruction or respiratory insufficiency
- Airway protection (e.g., head injury and Glasgow Coma Scale score <9)
- Need for deep sedation or analgesia up to and including general anesthesia
- Postresuscitation hypoxia or hypoventilation
- Delivery of 100% O_2 in victims of carbon monoxide poisoning
- Facilitation of diagnostic workup in uncooperative or intoxicated patient

Data from Mccunn M, Grissom TE, Dutton RP: Anesthesia for trauma. In Miller RD, editor: *Miller's anesthesia,* 8th ed. Philadelphia, Elsevier, 2015, pp 2423-2459.

Several studies have documented that during the early phase, a restrictive resuscitation regimen with a target systolic blood pressure below 100 mm Hg (mean arterial pressure [MAP] between 50 and 60 mm Hg) improves survival in patients with ongoing hemorrhage. This hypotensive resuscitation regimen aids in achieving spontaneous hemostasis and lessens the dilutional coagulopathy that large volumes of crystalloids can cause. Further reduction in MAP can result in end-organ hypoperfusion and is therefore not recommended.

In early "out-of-hospital" phase (e.g., battlefield trauma), the use of damage control resuscitation based on preestablished massive transfusion protocols that allow empiric administration of blood products to approximate whole blood (e.g., packed red blood cells–fresh frozen plasma–platelets in a 1:1:1 ratio) is commonly adopted.

If the early phase occurs in the "in-hospital" setting, protocol-driven goal-directed hemostatic resuscitation regimens that use blood products based on point-of-care viscoelastic monitoring (and limit the use of crystalloids) can be employed.

These "goal-directed regimens" can then be continued after the control of hemorrhage (late resuscitation) with the endpoint of normalizing cardiac output, blood pressure, coagulation profile, acid-base status, and core temperature and achieving the lowest accepted hematocrit threshold. The use of goal-directed regimens in the late resuscitation phase applies regardless of the type of early resuscitation method used (protocol or goal directed) because it aims to restore perfusion to all organ systems while continuing to support vital functions.

Placement of sufficient IV access above the diaphragm is crucial. A rapid IV infusion device allows rapid intravascular volume repletion with warmed IV fluids, blood, and blood products. The patient's volume status, hemodynamic stability, and presence of pulmonary complications (e.g., pneumothorax) determine which agents can be used for the induction and maintenance of general anesthesia. Central venous and direct arterial pressure monitoring are established after the airway is secured.

Once the arterial line is secured, an arterial blood sample is withdrawn and sent to determine the patient's oxygenation (Po_2), ventilation (Pco_2), pH, and hematocrit. Without prompt correction, hypovolemia and acidosis can lead to irreversible shock and death. Massive transfusion of blood and blood products may complicate trauma surgery. Complications include excessive or inadequate blood product replacement, dilutional coagulopathies, hypocalcemia from citrate toxicity, hypothermia, acid-base and electrolyte disturbances, and sepsis leading to multiorgan system failure.

In patients with documented cervical spine or lower spinal cord injury, high-dose IV bolus methylprednisolone (30 mg/kg) within 8 hours of injury, followed by an infusion (5.4 mg/kg per hour) for 24 hours, may improve neurologic recovery.

MANAGEMENT

Airway

Airway management must take into account the presence of cervical spine injury, full stomach, lack of patient cooperation, and anticipated difficult intubation. Use of direct laryngoscopy-assisted oral endotracheal intubation in a conscious patient requires topical anesthesia and possibly judicious use of IV sedation. Fiberoptic laryngoscopic or bronchoscopic techniques with topical anesthesia can also be used in awake or sedated patients, or the airway may be secured after IV rapid-sequence induction of general anesthesia using direct or video laryngoscopy or asleep fiberoptic intubation. Adequate preoxygenation before rapid-sequence induction increases the period of apnea that patients can withstand before O_2 desaturation ensues.

Box 53.2 lists common indications for endotracheal intubation in trauma patients. Indications for a surgical airway include failed intubation, an apneic patient with suspected cervical spine injury, facial trauma with suspected cervical spine injury, and severe facial and laryngeal trauma with altered anatomy.

Neck stabilization techniques may impair the laryngeal view, thereby increasing the potential for difficult intubation. The algorithm developed by the American Society of Anesthesiologists Task Force on Difficult Airway Management is applicable in the case of trauma (see Chapters 27 and 139). Devices such as the laryngeal mask airway can be used temporarily as a bridge for establishing airway patency while securing a surgical airway or to facilitate fiberoptic intubation.

Surgical options include cricothyrotomy, transtracheal jet ventilation, and tracheostomy. Cricothyrotomy takes less time to perform than tracheostomy and is therefore the preferred surgical approach. Because tracheostomy requires neck extension, it may exacerbate cervical spine injury. Tracheostomy is indicated in laryngeal trauma and with complete tracheal transection.

Breathing

Management of ventilation requires attention to oxygen saturation, end-tidal carbon dioxide concentration, and peak inspiratory pressures. If gastric aspiration occurs, treatment includes increasing the inspired oxygen concentration, adding positive end-expiratory pressure, and bronchoscopy with saline lavage for airway plugging. A pressure-limited ventilatory mode can reduce the risk of barotrauma. The treatment for pneumothorax is immediate needle decompression at the second intercostal space in the midclavicular line, followed by thoracostomy tube placement.

Circulation

Shock in trauma is due to hypovolemia until proved otherwise. Other causes, such as obstructive shock (due to tension pneumothorax) or neurogenic shock (due to spinal cord transection or spinal vasoparesis), must be excluded. Hemodynamic stabilization requires surgical bleeding control, restoration of circulating blood volume, correction of acidosis, and adequate oxygen transport (hematocrit). Vasopressors may be used to maintain blood pressure during volume restoration.

Crystalloid replacement may be sufficient with blood loss less than 30% of the total blood volume, but at that point, colloids are usually added. The need for blood products is based on estimated blood loss, vital signs, evidence of active bleeding, and serial hematocrit measurements. The trigger for blood transfusion has been lowered, so that hematocrits in the low to mid-20s are now acceptable.

It is rarely necessary to give type O, Rh-positive blood (Rh-negative blood for women of childbearing age), because type-specific blood should be available within 15 minutes. Typed and crossmatched blood (requiring 30 to 45 minutes) is used when available. The concept of delayed blood or blood product resuscitation ("permissible hypovolemia") until surgical bleeding is controlled is not a widely accepted practice.

Hypothermia

Trauma victims are often hypothermic on arrival in the operating room. Increasing the temperature in the operating room and the use of forced air warming devices, warmed IV fluids and blood products, humidified inspired gases, and low fresh gas flows helps keep core temperature at 36°C or higher. Hypothermia reduces cardiac output and drug metabolism and attenuates immune responses. Hypothermia can also aggravate vasoconstriction, myocardial ischemia, hypotension, bradycardia, arrhythmias, and coagulopathies. During rewarming, oxygen needs are increased.

Coagulopathy

Dilutional coagulopathies caused by component deficiencies (fibrinogen, platelets, coagulation factors), fibrinolysis, and disseminated intravascular coagulation are medical causes of bleeding in trauma patients, especially those who have sustained major vascular injuries as well. Routine screens for disseminated intravascular coagulation (prothrombin time, partial thromboplastin time, platelets, fibrinogen, D-dimers) or thromboelastography to assess clot formation and lysis can serve as guides for the correction of coagulopathies. Fresh frozen plasma is used to correct an abnormal prothrombin time. Cryoprecipitate is used if fibrinogen is less than 100 mg/dL. Platelets are used when there is active bleeding and the platelet count is less than 100,000/mm^3. ε-Aminocaproic acid, tranexamic acid, or aprotonin is used to treat primary fibrinolysis.

In patients with abdominal trauma, the use of recombinant activated factor VIIa (rFVIIa) administered goal-directedly guided by thromboelastography is more effective in correcting trauma-associated coagulopathy and decreasing the amount of blood product transfusion. Disseminated intravascular coagulation requires identification of the causative agent. Then clotting factors (fresh frozen plasma), platelet transfusions, and small IV doses of heparin (50 U/kg) are given.

PREVENTION

Primary Prevention

Public safety campaigns must emphasize the hazards of drinking and driving. Seatbelt and helmet laws must be enforced. Use of gun locks must be encouraged and gun control laws enforced. Motorcycle and driver safety courses and the use of child restraint seats can also reduce TRI and death.

Secondary Prevention

Vigilant and capable anesthesiologists, along with surgeons with expertise in trauma surgery, are key to the secondary prevention of complications related to trauma. However, the anesthesiology-surgery trauma team must work efficiently and in concert with emergency department physicians and staff, as well as operating room and intensive care unit staff. The hospital's radiology, laboratory medicine, and transfusion services must also be capable of providing the required ancillary support. Taken together, all these capabilities and their efficient deployment can facilitate the timely diagnosis and stabilization of trauma victims, thereby reducing the risk for secondary morbidity or mortality.

Further Reading

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Continuous Nerve Blocks: Perineural Local Anesthetic Infusion

54

W. Michael Bullock • Stuart A. Grant

Case Synopsis

A 62-year-old man undergoing ankle arthrodesis has adductor canal and popliteal-sciatic perineural catheters placed under ultrasound guidance. He initially received 0.5% ropivacaine for surgical anesthesia and then 0.2% ropivacaine infusion through both catheters for postoperative analgesia. In the recovery room he was pain free, but during the first postoperative night he complained of pain throughout his ankle. He was bolused 0.5% ropivacaine through both catheters with good pain relief. The next day, the worried surgeons contact you because of the profound motor block present in his lower extremity and because the physical therapist states that he fell during their session together that morning.

PROBLEM ANALYSIS

Definition

The case synopsis raises a discussion about side effects of local anesthetic versus potentially more serious complications of regional anesthesia for surgery. Regional anesthesia provides high-quality analgesia and minimizes opioid-related side effects. Although both opioid and surgical complications are much more prevalent than regional anesthetic complications, some do occur.

Numerous studies have shown that perineural local anesthetic infusions provide profound analgesia. Continuous techniques such as these have been used to provide both intraoperative anesthesia and postoperative analgesia. Certain complications are block specific, such as a pneumothorax with supraclavicular or infraclavicular blocks or epidural spread with a lumbar plexus block. This chapter does not discuss block-specific complications, but rather perioperative complications regarding continuous peripheral nerve blockade.

A variety of complications associated with peripheral nerve block, perineural catheter insertion, and surgery have been reported (Table 54.1). Early recognition of complications is essential in subsequent treatment. Recognition of problems potentially related to a nerve block begins with a focused history and physical examination. Review of the medical record for medications administered systemically or through peripheral nerve catheters can aid in narrowing the differential. Furthermore, surgical factors, including but not limited to patient positioning intraoperatively, surgical approach, and postoperative surgical dressings, may be causal factors.

Recognition

Problems with peripheral nerve catheters may present in a variety of ways based on the primary pathology. The clinical features of neurologic complications, including nerve injury, include the following:

- Prolonged motor block long after cessation of local anesthetic infusion
- Reduced touch or paresthesias that persist or worsen after cessation of infusion
- Pain that is neuropathic in nature
- Numbness and perception of a heavy or weak extremity
- Loss of proprioception

The clinical features of inadequate analgesia or ischemia include the following:

- Increasing or high patient-reported pain score without numbness
- Increasing or high patient-reported pain score with numbness
- Increased opioid requirements and opioid-related side effects

The clinical features of infectious complications include the following:

- Late onset of symptoms, 2 to 3 days after peripheral nerve catheter placement
- Tissue erythema and swelling at catheter insertion site
- Pain and tenderness at catheter insertion site
- Leukocytosis and fever

The clinical features of local anesthetic toxicity will not be discussed here as they are the focus of Chapter 103.

Risk Assessment

The incidence of complications following peripheral nerve block is low; benefit must be assessed against the risks of general anesthesia and central neuraxial techniques. Auroy and coworkers reported the incidence of serious complications related to regional anesthesia in a prospective study using data from 103,730 cases. They found that the incidence of cardiac arrest and neurologic injury related to regional anesthesia was low, more than 3 standard deviations less after regional procedures compared with spinal anesthesia. Although these data did not discriminate between single-injection and continuous peripheral nerve block, in general, peripheral nerve blocks were associated with fewer neurologic injuries and cardiac arrests when compared against central neuraxial techniques.

TABLE 54.1 List of Complications

Anesthetic Complications	Surgical Complications
Difficulty in placement or insertion of nerve block/catheter	Neuropathy secondary to intraoperative positioning
Pain during injection or infusion via the perineural catheter	Surgical injury: scalpel, retraction, or tourniquet
Prolonged action of motor block secondary to local anesthetic	Compression/ischemia: postoperative surgical dressings
Nerve injury caused by needle: neuropraxia, axonotmesis, neurotmesis	Compression: hematoma arising from surgical procedure
Nerve injury caused by local anesthetic or additives: direct toxicity or ischemia secondary	Compression: limb ischemia causing compartment syndrome or deep vein thrombosis
Nerve injury caused by catheter: damage or avulsion by insertion or removal	Compression: Tourniquet overinflation postsurgical pain
Compression from hematoma arising from catheter insertion	Transection of catheter
Migration of catheter in vessel	Postoperative surgical infection
Retained catheter fragments	
Inflammatory neuropathy	
Infection along catheter distribution	

Brull and colleagues in a publication reviewed 32 studies and estimated the rate of nerve complications at approximately 0.4% for neuraxial block and 0.3% for peripheral nerve blocks. However, they also noted that permanent neurologic injury was uncommon with regional anesthesia. Bergman and coworkers retrospectively examined the neurologic complications after 405 consecutive continuous axillary nerve block catheter procedures where they found no greater incidence of neurologic complications using continuous catheter techniques than using single injections. Borgeat and colleagues prospectively examined complications associated with interscalene block for shoulder surgery and found no differences between catheter techniques and single-injection blocks.

Leaving a catheter in situ entails the potential risk of infection and catheter migration into a vessel. This risk must be balanced against the benefit of superior analgesia compared with oral medications alone. In addition, although Cuvillon and coworkers were able to isolate bacterial colonization in 57% of 208 femoral nerve catheters, no clinically relevant infectious complications occurred. There was one case (0.1% incidence) of a serious infection (abscess), and superficial erythema was observed in 0.7% of the patients in Borgeat's series (cited earlier). Only superficial skin infections (5% incidence) were reported in the recent series by Boezaart and associates. Only one case report of migration into a vessel has been reported in the literature, so the incidence of that complication is unknown.

Following resolution of the primary block with long-acting amide local anesthetics, inadvertent catheter dislodgment or incorrect initial catheter positioning is the most common cause of pain. This can occur in up to 10% to 20% of patients and is by far the most common complication of continuous perineural nerve block. Additionally, patients with infusions of low concentrations of local anesthetics in a functional perineural catheter may suffer breakthrough pain. Use of patient-controlled bolus, in addition to the background basal infusion, can reduce the severity of breakthrough pain. As the case synopsis illustrates, the challenge for the clinician is to balance the risk of motor block or even local anesthetic toxicity against the patient's discomfort from inadequately controlled pain.

The cause of postoperative falls is multifactorial, encompassing lower extremity surgery, age, and obesity. Some controversy exists regarding the incidence of postoperative falls with patients receiving regional anesthesia. Wasserstein and colleagues and Ilfeld and colleagues identified continuous femoral nerve block as an independent risk factor for falls following total knee arthroplasty. Conversely, Memtsoudis and colleagues reviewed a national database of over 191,000 patients in more than 400 hospitals that did not show an association between regional anesthesia and inpatient falls. However, they were not able to discriminate between single-shot blocks and catheters. Care must be taken in patients with peripheral nerve catheters, and involvement of anesthesiologists in development of a hospital falls prevention program can help minimize risks.

Implications

Neurologic complications can result in weakness and chronic pain, with reduced functional capacity after surgery. Careful technique and patient selection are important factors in reducing these complications. Prolonged motor block produced by high local anesthetic concentrations may delay early ambulation, but has not been shown to affect long-term functional outcomes following arthroplasty. In fact, patients given either epidural or peripheral nerve catheters after knee arthroplasty have increased rates of recovery for the first 6 weeks after surgery compared with those on opioid analgesia regimens. Failed blocks result in pain and reduced patient satisfaction, many times leading to increased use of opioids and opioid-related side effects such as respiratory depression, pruritus, nausea, vomiting, and constipation. Infection can result in discomfort, limitation of activity, potential for infected hardware, and reoperation. Falls can increase morbidity, cause prolonged hospital length of stay, and may lead to reoperation.

MANAGEMENT

History and Physical

A focused anesthetic history and physical examination is key in determining the cause of or contributing factors to neurologic deficits after peripheral nerve block (Box 54.1). Infusion details should be checked initially, including rate and patient bolus function. The infusion should be stopped, and if appropriate, an adequate time given for the block to subside before subsequent neurologic examination. Pain should be assessed using the patient-reported analog scale.

Further Management

Management is directed by the findings of a careful history and focused neurologic examination. Early multimodal analgesia, including gabapentinoid and nonsteroidal antiinflammatory medications unless contraindicated, should be initiated for postoperative pain regardless of the etiology. The flowchart in Fig. 54.1 outlines management and suggested treatment modalities based on primary complication. As always, the anesthesiologist should have close patient follow-up throughout.

PREVENTION

Understanding the incidence of complications specific to the surgical procedure is essential. Patient-specific conditions, such as diabetes, chronic pain, or any other preexisting neurologic conditions such as Charcot-Marie-Tooth, are important to recognize and while formulating an anesthetic plan. Once all surgical and patient factors are taken into account, determination can be made as to whether regional anesthetic techniques are safe and appropriate.

BOX 54.1 Pertinent History and Physical

History

- What block technique was used?
- Was the technique difficult?
- Was the injection difficult (e.g., high pressure or "tight")?
- Was anything added to the local anesthetic (epinephrine, dexamethasone, etc.)?
- Did the patient have any anatomic variations or anomalies?
- Did the patient recover function after the initial block only to lose function after another intervention?
- Is the neurologic deficit unilateral?
- Is the neurologic deficit in the expected distribution of the nerve blocked?
- Does the patient have any prior neurologic deficits (e.g., preexisting paresthesias, radiculopathies, or neuropathies)?
- Does the patient have any other comorbidities such as neuromuscular disorders (Charcot-Marie-Tooth), diabetes, nutritional deficiencies (including previous weight loss surgeries), alcohol abuse, chemotherapy, chronic pain, or any other neuropathies?
- Is the patient taking any medications that can explain or contribute to the presentation?
- Were any surgical factors contributing to the deficits seen?
- Could anything postoperatively, including mechanical injury or physical therapy, be part of the problem?

Physical

- Assess overall mental status for delirium, dementia, or severe anxiety
- Motor testing in all four limbs to rule out prior bilateral (e.g., diabetes) or unilateral (e.g., stroke) deficits
- Sensory testing in all four limbs to rule out prior bilateral (e.g., diabetes) or unilateral (e.g., stroke) deficits
- Palpation of pulses in all four limbs to determine vascular supply to each extremity
- Inspection of the catheter site for proper catheter insertion depth or significant leaking
- Inspection of the catheter site for swelling, tenderness, or erythema
- Aspiration of catheter for heme
- Inspection of surgical dressings, including splints and casts, for appropriate pressure/tension

Neurologic Complications

Evidence regarding the prevention of neurologic perineural catheter complications is scant, but performing blocks in lightly sedated patients, minimizing injection pressure, and discontinuing injections immediately when pain is experienced probably reduce the likelihood of nerve injury. Safety with the use of blunt tip versus sharp needle is often debated in the literature, as is the use of nerve stimulation versus ultrasound guidance. If surgical nerve injury is possible and immediate postoperative nerve function needs to be assessed, a dry catheter can be placed and subsequently bolused for analgesia once nerve function is verified.

The likelihood of motor block can be reduced by using lower concentrations of drug in perineural local anesthetic infusions. Ropivacaine provides a better sensory versus differential motor blockade than bupivacaine. Carefully securing the catheter at time of insertion, use of bolus local anesthetic via the catheter for breakthrough pain, and use of a patient-controlled regional anesthesia catheter can help reduce the likelihood of postoperative pain.

Patient Complications

Patient selection and an appropriate preoperative discussion before surgery are important to prevent perioperative complications. A thorough history and physical examination can identify preexisting neurologic conditions or other potential detractors, many times accomplished by preoperative clinic appointments. For example, patients with delirium or dementia may not be good candidates for perineural catheters, and those with diabetic or other peripheral neuropathies may not benefit from nerve block. Patients with severe anxiety may need concurrent anxiolysis throughout admission and may exhibit higher pain scores if anxiety is not appropriately treated. Patients with chronic pain should be treated according to their home regimen to achieve baseline pain control and should have an early referral to the in-house pain service. Diabetics many times do not need additives to the local anesthetic, specifically epinephrine, as further neurovascular function may be compromised. Medications should be reviewed before surgery, specifically for anticoagulants or chemotherapeutics.

Anesthetic and Surgical Complications

Both anesthetic and surgical techniques should be carefully planned to avoid nerve damage. Some anesthesiologist argue that a combination of techniques, such as ultrasound guidance with nerve stimulation and injection pressure monitoring, is the least likely way to cause nerve damage from the block. Intraoperative patient positioning is important to avoid compression or stretch injuries and should be confirmed by both surgeon and anesthesiologist. Appropriately placed surgical dressings should not cause pressure that can manifest as pain despite nerve block. Compartment pressure monitoring in cases with high risk for compartment syndrome can prevent serious injury, even though no evidence suggests nerve blockade masks the ischemic pain experienced in compartment syndrome.

Infectious Complications

Infectious complications can be reduced by the use of appropriate skin preparations: chlorhexidine is more effective than iodine-based preparations in this regard. Care must be taken to ensure that the chlorhexidine has dried before needle insertion, both for antibiosis and because of the potential for neurotoxicity. Additionally, the choice of catheter insertion site is important. For example, a femoral nerve catheter placed in an obese patient with a large pannus is more likely to become infected. Best medical practice supports the use of prophylactic antibiotics whenever foreign material is being inserted, including nerve catheters. If the surgeon does not prescribe antibiotics for the patient, the anesthesiologist may want to consider prescribing them for prophylaxis of perineural catheter infection.

Fall Risk Complications

Despite an increased risk for falls, regional anesthesia is safe to perform in patients undergoing lower extremity surgery and subsequently engaging in physical therapy (Memtsoudis and colleagues). Ensuring the patient has a mobility aid, such as a walker, and help with ambulation by one or multiple people is important. Inpatients should have a falls risk protocol implemented, and outpatients should have appropriate facilities for movement with crutches, walker, or wheelchair. All patients should be closely monitored and instructed not to ambulate alone.

SUMMARY

Despite the potential for a variety of complications, perineural catheters are a safe and effective mode of analgesia when performed correctly and on an appropriate patient. They can provide superior analgesia, especially when used together with oral medications. Early recognition and effective management of any perioperative problems are essential in preventing further complications. Communication among the patient, anesthesiologist, and surgeon to develop an appropriate perioperative plan is the first, and most important, step in successful surgery.

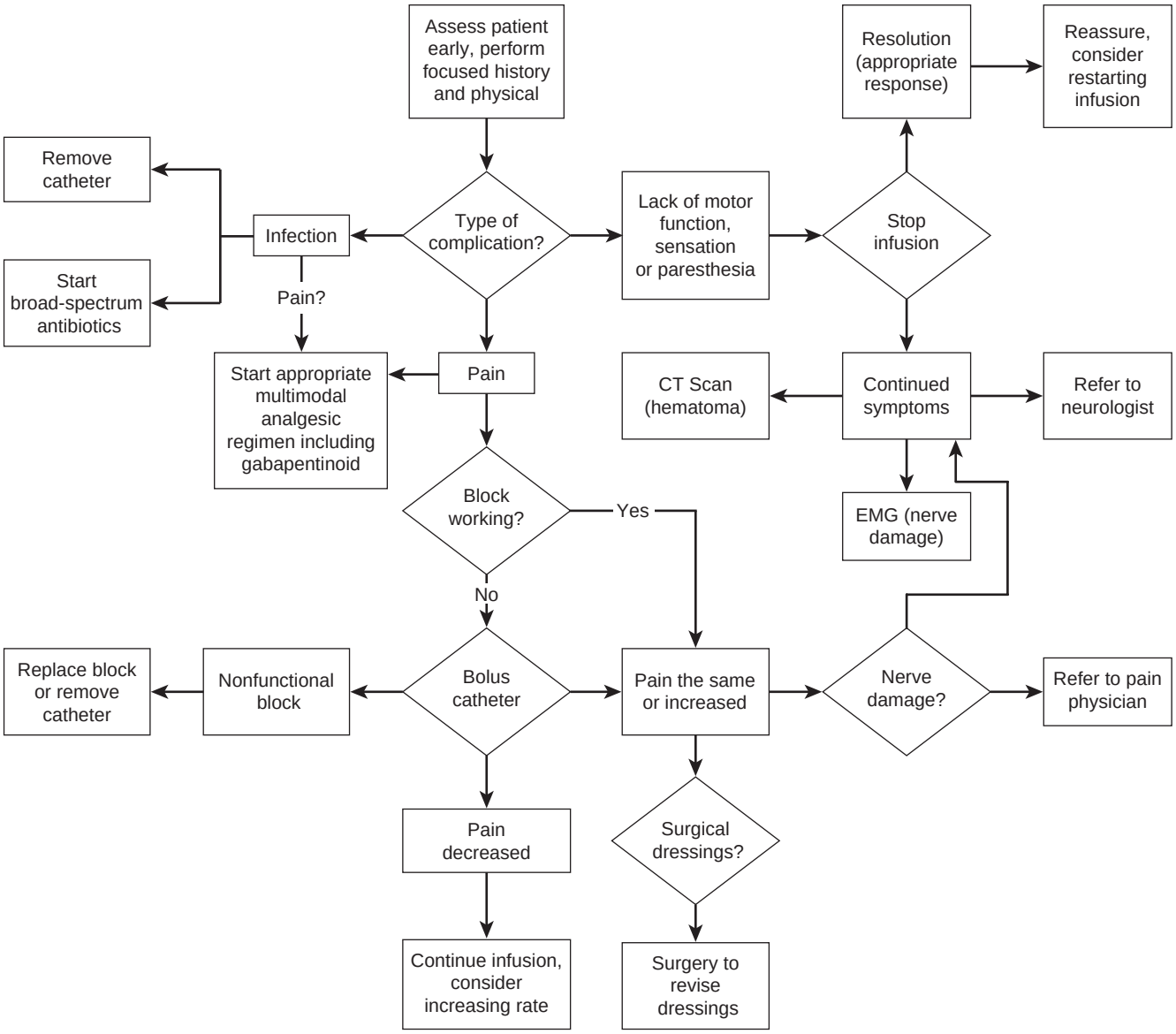

Fig. 54.1 Perioperative management of regional anesthesia and perineural catheter complications. *CT,* Computed tomography; *EMG,* electromyogram.

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55 Extremity Tourniquets

H. David Hardman • Cody Rowan • Jay Schoenherr

Case Synopsis

A 75-year-old woman is undergoing a revision of a left total knee arthroplasty under spinal anesthesia and intravenous sedation. She is morbidly obese, on chronic opioids for pain relief, and an insulin-dependent diabetic. A continuous adductor canal catheter is placed for postoperative pain control before the placement of a single-shot spinal anesthetic. A conventional rectangular thigh tourniquet is placed for surgical hemostasis. After limb exsanguination, the cuff pressure is set at 300 mm Hg. Surgery proceeds uneventfully, with a total tourniquet time of 2 hours. The spinal anesthetic resolves, and the adductor canal catheter is removed on postoperative day 2. Subsequently, she complains of numbness and weakness in her left leg.

PROBLEM ANALYSIS

Definition

Tourniquets are commonly used during surgery of the upper and lower extremities to minimize intraoperative blood loss. Tourniquet use has a very long history and a low (but not zero) incidence of complications. These may take many forms, ranging from localized and relatively minor skin tears to neurologic dysfunction (Box 55.1). Direct compression of neural, vascular, and muscular structures, as well as ischemia and reperfusion, contribute to the pathophysiology of tourniquet complications. Postoperative neurologic dysfunction after tourniquet use is a well-documented but infrequent phenomenon, and permanent defects are rare. Systemic effects may occur, which may reflect the direct effect of limb compression (e.g., pulmonary embolism) or systemic inflammation as a result of ischemia of underlying tissues.

Arterial tourniquets are widely used in upper and lower extremity surgery and in intravenous regional anesthesia. This practice continues because it is widely accepted that the benefit from minimizing surgical blood loss and creating a bloodless operative field exceeds the risk of tourniquet-related complications. It is important for anesthesiologists to be aware of the potential for tourniquet-related tissue injury, systemic effects of tourniquet inflation and deflation, and the possibly catastrophic events that could occur at these times.

BOX 55.1 Complications of Tourniquets

- Skin injury
- Muscle necrosis
- Nerve injury
- Limb ischemia
- Autotransfusion
- Hypertension
- Hypotension
- Hypercapnia
- Metabolic acidosis
- Reduced antibiotic penetration
- Right-sided heart failure
- Hypothermia
- Deep venous thrombosis
- Pulmonary embolism
- Systemic thromboembolism

It should be recognized that surgeons and anesthesiologists share any medicolegal liability for tourniquet-related complications. Documentation should include the location of the tourniquet, the use of padding and draping, and inflation pressure and duration. Tourniquet pressure relative to systemic blood pressure values, prolonged inflation, and total vascular occlusion times must be communicated to the surgical team and documented on the anesthesia record.

Local Injury

Pressure-related injuries to skin, muscles, nerves, and blood vessels depend on the pressure of tourniquet inflation and its duration. Injuries occur as a result of direct pressure, but axial stretching and shearing forces may also occur, especially at the edges of the tourniquet. The absence of arterial blood flow distal to the tourniquet causes ischemia, which leads to progressive acidosis, hypoxemia, and hypercarbia. The associated release of inflammatory mediators increases capillary permeability and causes tissue edema, which worsens ischemic injury, especially after reperfusion. Ultrastructural cellular changes are detectable after 30 minutes of ischemia but are reversible with ischemia lasting 2 hours or less. High-energy intracellular phosphate depletion occurs more gradually. However, injury to the Na^+,K^+-ATPase–dependent ion exchange pump causes extracellular potassium leak and intracellular edema. The sarcoplasmic reticulum loses glycogen, the mitochondria swell, and myelin degeneration occurs. Cellular necrosis ensues if ischemia is not corrected.

A list of tissue sites affected by local tourniquet pressure follows.

Skin

Trauma to the skin can be caused by pressure necrosis due to inadequate padding between the skin and tourniquet or friction burns due to movement of a poorly applied tourniquet. Obese patients with redundant upper extremity skin folds are at increased risk for skin injury. Skin preparation solutions may soak into the padding under the tourniquet, resulting in full-thickness chemical burns.

Muscle

Myocytes are very sensitive to compression and ischemia. Injury is more severe with lengthy tourniquet inflation or high pressure. Usually, injury is greatest beneath the tourniquet. Associated ischemia, edema, and microvascular congestion cause the post-tourniquet

TABLE 55.1 Characteristics of Nerve Injury

Neuropraxia	Myelin sheath damaged
	Axon remains intact
	Best prognosis
Axonotmesis	Myelin sheath and axon damaged
	Requires regeneration of nerve tissue
	Recovery may be incomplete
Neurotmesis	Complete destruction of nerve
	Requires surgical repair
	Poor prognosis

syndrome. This includes stiffness, pallor, and weakness (not paralysis), with subjective extremity numbness. Rhabdomyolysis may occur if the tourniquet is inflated for a prolonged period of time under high pressure. Compartment syndrome may occur after tourniquet deflation as a result of edema and reperfusion hyperemia.

Peripheral Nerves

Mechanical pressure compresses nerves directly beneath the tourniquet cuff, and shear forces at the proximal and distal edges of the cuff also cause nerve injury ranging from paresthesia to complete paralysis. Distal ischemia plays a lesser role. The contribution of tourniquet time to the development of nerve injury is unclear, and paralysis has been reported with as little as 30 minutes of tourniquet inflation. Lower extremity nerve injury usually involves the sciatic nerve. The upper extremity appears to be more commonly associated with tourniquet related nerve injury than the lower extremity, with radial nerve injury more frequently observed than either ulnar or median nerve injury. When tourniquet-related nerve injury occurs in the lower extremity, the sciatic nerve is the most likely to be affected.

Localized nerve injuries tend to be neuropraxic injuries, with structural damage limited to the myelin sheath surrounding individual axons, without injury to the axon itself. Neuropraxic injuries tend to be self-limiting, with an excellent prognosis for complete recovery within a period of several days to weeks. In contrast, axonotmetic injuries involve damage to the axon itself, resulting in loss of signaling function once electrical excitability is lost and depolarization can no longer occur. These injuries take longer to recover as the axon must regenerate along the connective tissue highway, and some injuries may not completely recover. Rarely, a permanent nerve deficit occurs (Table 55.1).

Vasculature

Arteries and veins, especially prosthetic grafts (e.g., arteriovenous fistulas, arterial bypass grafts), are susceptible to traumatic injury from mechanical compression. Although direct arterial injury is rare (0.03% to 0.14% incidence), fractured atherosclerotic plaque may cause localized thrombosis or embolize distally to cause ischemia. Although deep venous thrombosis (DVT) is a known and common complication of lower limb surgery, tourniquets bear no relation to deep venous stasis and thrombus formation. Rather, systemic hypercoagulability is due to catecholamine release and platelet aggregation caused by tourniquet-related or surgical pain. In contrast, active bleeding after tourniquet release may be aggravated by ischemia-caused tissue plasminogen activator release and fibrinolysis.

Systemic Effects

Systemic effects occur with tourniquet inflation and deflation. The intensity and duration of these derangements are directly proportional to the length of tourniquet inflation time and the size and number of tourniquet-isolated limbs. The following effects are observed.

Autotransfusion

Limb exsanguination and rapid tourniquet inflation shunt blood into the central circulation (autotransfusion) and increase systemic vascular resistance. As much as 800 mL of blood is autotransfused with the simultaneous inflation of bilateral thigh tourniquets. This causes a transient increase in central venous pressure and systolic blood pressure, which gradually returns to baseline. In patients with compromised left ventricular function, congestive heart failure due to circulatory overload and cardiac arrest has been reported.

Hypertension

Tourniquet-induced hypertension is common. Patients develop an increase in heart rate and systolic and diastolic blood pressures within 30 to 60 minutes of inflation, which persists until tourniquet deflation. This increase in mean arterial pressure has been attributed to (1) an acute increase in systemic vascular resistance with removal of a vascular bed; (2) limb exsanguination before tourniquet cuff inflation, which causes acute central blood volume expansion; and (3) pain associated with tourniquet compression and limb ischemia. The incidence of this constellation of vital signs is related to the type of anesthesia, and ranges from 2.5% of patients under brachial plexus anesthesia to 67% of patients under general anesthesia. A cutaneous mechanism is thought to be responsible, as demonstrated by the attenuation of tourniquet discomfort by topical eutectic mixture of local anesthetic agents (EMLA). A sympathetically mediated pathway may be unlikely given the lack of effectiveness of stellate ganglion block in reducing upper arm tourniquet discomfort in a limited size volunteer study. The leading hypothesis for the mechanism of tourniquet pain is the loss of inhibition of unmyelinated, slow-conducting C fibers. These fibers are usually inhibited by fast, myelinated A-delta fibers, which are blocked at the tourniquet site after approximately 30 minutes of tourniquet inflation and mechanical compression.

Hypotension

Tourniquet deflation results in reduced blood pressure and central venous pressure secondary to a shift of blood volume back into the extremity and postischemic reactive vasodilation. Also, with reperfusion, metabolites released from ischemic areas into the systemic circulation have the potential to cause myocardial depression and further reduce blood pressure. Hypotension is usually self-limited (≤15 minutes).

Hypercapnia

End-tidal carbon dioxide ($ETCO_2$) increases after tourniquet release owing to the efflux of hypercapnic venous blood from the ischemic limb into the systemic circulation. The peak $ETCO_2$ increase occurs within the first minute after deflation, and it returns to baseline approximately 10 to 13 minutes later. Spontaneously breathing patients compensate by increasing their respiratory rate. However, those with controlled ventilation require a transient increase in minute ventilation by 50% for about 5 minutes to maintain normocapnia. Hyperventilation can prevent the associated increase in cerebral blood volume and intracranial pressure that might otherwise be detrimental to a patient with intracranial hypertension.

Metabolic Acidosis

Elevated serum lactate and reduced pH are observed for approximately 30 minutes after reperfusion of the isolated extremity. The degree of change is proportional to the duration of tourniquet inflation.

Blood Oxygen Saturation

Arterial oxygen saturation usually remains normal. However, as large volumes of deoxygenated blood are returned to the central circulation

after tourniquet release, mixed venous oxygen saturation is transiently decreased.

Impaired Antibiotic Penetration

Intravenously administered antibiotics may not penetrate to the operative site if the tourniquet is inflated before or while the antibiotics are still being administered. An interval of 5 minutes between antibiotic administration and tourniquet inflation is probably adequate to allow antibiotic penetration.

Core Body Temperature

Most patients remain normothermic during tourniquet use. Tourniquet inflation above arterial pressure transiently increases core body temperature, and tourniquet deflation transiently decreases it. The decline in core body temperature due to the return of hypothermic venous blood from the previously occluded limb into the systemic circulation is usually 0.7°C or less.

Deep Venous Thrombosis, Pulmonary or Systemic Thromboembolism

These potentially devastating complications may occur with lower limb trauma and surgery, but rarely intraoperatively. Although studies with transesophageal echocardiography have shown up to a 70% incidence of right atrial embolization following tourniquet release, most emboli are small and are unlikely to cause major morbidity. However, this risk is increased in patients with hypercoagulable states and thrombus due to trauma or prolonged immobilization. In this setting, it is believed that thrombus becomes dislodged during limb exsanguination or with tourniquet inflation. Catastrophic events such as DVT or pulmonary or systemic thromboembolism are more likely to occur postoperatively during rehabilitation. Use of enoxaparin for DVT prophylaxis has dramatically reduced the incidence of fatal pulmonary embolism. However, given that pulmonary and cerebral emboli have been reported during both inflation and deflation of tourniquets, anesthesiologists should be especially vigilant during these times. Attention should be focused on the patient's neurologic status and any sudden, unexpected changes in arterial oxygen saturation and $ETCO_2$. Significant pulmonary emboli result in an acute reduction in $ETCO_2$, with tachycardia and hypotension, followed by hypoxemia and myocardial ischemia. Right ventricular dysfunction may also be observed (also see Chapters 65 and 142).

Recognition

Given the increased use of regional blocks for lower extremity surgery, which significantly reduces postoperative pain scores and permits earlier ambulation, how does one differentiate a nerve injury related to use of a tourniquet from one related to regional anesthesia?

Posttourniquet syndrome is the most common problem associated with tourniquet use. Mild weakness, diffuse subjective numbness, swelling, stiffness, and slight pallor of the affected limb usually develop several hours after tourniquet deflation. Furthermore, ischemic injury to muscle is distinguished from nerve injury by normal nerve conduction studies and the presence of elevated creatine kinase (MM) enzymes and myoglobinuria.

If the tourniquet has produced a compressive nerve injury, it may be difficult to distinguish this injury from one related to regional block, particularly when the tourniquet or the edge of the tourniquet overlaps the site of the peripheral nerve block. Tourniquet-related nerve injury can range from paresthesia to complete paralysis of the affected limb. Fortunately, localized tourniquet-related nerve injury is often neuropraxic, in which case the prognosis for full recovery is good, although axonometic injuries can also occur. In these cases, the prognosis for recovery depends on the extent of axonal damage and whether or not the neural connective tissue architecture remains intact (see Table 55.1).

BOX 55.2 Factors That May Increase the Risk of Tourniquet-Related Complications

Tourniquet Related
- Equipment not regularly serviced and inspected for pressure accuracy
- Bilateral tourniquet use
- Revisions, malignancies, or other surgeries requiring longer tourniquet times

Vascular and Metabolic
- Diabetes
- Peripheral vascular disease
- Obesity
- Raynaud disease
- Prosthetic vascular grafts

Coagulopathies
- Sickle cell disease and trait
- Preexisting coagulopathies
- Patients at increased risk for deep venous thrombosis

Other
- Peripheral neuropathy
- Prolonged immobilization before surgery
- Traumatized limb with extensive soft tissue injury
- Localized infection
- Latex allergy (must use latex-free tourniquets and tubing)

Brief neurologic assessment of the affected extremity should follow surgery and be compared with the preoperative examination. Evidence of severe motor and sensory deficits requires neurologic consultation and electrodiagnostic studies to determine the site and severity of the injury, as well as the prognosis for recovery. With regional anesthesia, there may be a delay in the diagnosis of nerve injury, especially if indwelling catheters are used for postoperative analgesia.

Acute compartment syndrome has been observed immediately after surgery or after a delay of several hours. Reactive hyperemia occurring after tourniquet deflation may result in swelling of the limb by as much as 10%, potentially exacerbating this complication, especially if tight dressings or casts are used. The limb is typically swollen, muscles are stiff, and pain is more severe than the physical findings would suggest. This diagnosis is confirmed when compartment pressure monitoring indicates elevated pressure. Neurologic dysfunction is also a common sequela.

Postoperative complex regional pain syndrome type I or II may present weeks or months after surgery. Burning pain and autonomic dysfunction develop, followed by dystrophic changes in the extremity.

Skin injuries are usually evident on tourniquet cuff removal. Ecchymoses, persistent erythema, bullae formation, or skin burns may be present.

Vascular insufficiency due to arterial injury should be suspected when cuff deflation does not result in reperfusion of all or part of the extremity.

Risk Assessment

The potential for a postoperative nerve injury (PNI) may influence the choice of anesthesia technique for anesthesiologists working in a higher-risk malpractice environment, when faced with treating patients at elevated risk for tourniquet-induced PNI. Factors that may increase the risk of complications with tourniquet use are listed in Box 55.2.

The safe upper limits for inflation time and pressure for arterial tourniquets are controversial. Nerves appear most susceptible to mechanical pressure and muscles to prolonged ischemia. Most clinicians recommend the shortest tourniquet inflation time possible, with a limit of 2 hours in healthy patients; for surgical procedures exceeding 2 hours, the tourniquet should be deflated every 2 hours to allow 10 minutes of limb reperfusion. Muscle injury, especially beneath the cuff, can occur even with short tourniquet times. Elderly trauma patients and those with peripheral vascular disease are most susceptible to muscle injury. Therefore the lowest pressure needed to produce arterial occlusion should be used. In a normotensive, average-size adult patient, an inflation pressure of 200 mm Hg should be adequate for the upper limb and 250 mm Hg for the lower limb. The tourniquet pressure should be maintained 50 to 150 mm Hg above the systolic pressure. Using conical pressure cuffs in lieu of conventional rectangular pressure cuffs will produce arterial occlusion at lower pressures and potentially attenuate pressure-related tissue damage.

Implications

Most tourniquet-related compressive nerve injuries are neuropraxic and will resolve completely within days to weeks after the injury. Treatment is palliative with physical therapy and neuropathic pain management. More serious injuries such as axonotmetic or neurotmetic injuries will have a variable recovery path, on a time period of months to years, and restoration of complete function may never occur, even with reconstructive neurosurgery entailing nerve grafts and nerve transfers. In the worst-case scenario, a concomitant complex regional pain syndrome (CRPS) may develop as well.

Weakness and swelling due to posttourniquet syndrome can interfere with rehabilitation and wound healing. Pressure-related skin injuries increase the risk of infection. Compartment syndromes pose a significant risk for ischemic necrosis and permanent contracture of the involved muscle groups. Unrecognized arterial insufficiency can lead to necrosis of soft tissue and bone.

In patients given regional anesthesia, tourniquet pain and associated hypertension may require deep sedation with propofol or ketamine or even general anesthesia. Opiates alone are usually ineffective. Hypotension with tourniquet deflation is expected and usually self-limited. If not, a fluid challenge and small doses of vasopressors are used until the hypotension resolves.

Massive pulmonary embolism causes hemodynamic instability, right ventricular strain, and cardiovascular collapse. Nonfatal embolism may result in hypoxemia due to ventilation-perfusion mismatching, myocardial infarction, or stroke due to paradoxic cerebral embolism with intracardiac shunts.

MANAGEMENT

Severe nerve injuries (significant motor weakness or paralysis of a limb) that do not resolve within 48 hours should be referred to a neurologist for assessment to rule out a treatable surgically related cause, such as compressive hematoma formation. Follow-up studies could include an ultrasound examination of the tourniquet and surgical site, along with magnetic resonance imaging (MRI). More detailed electrodiagnostic studies, such as nerve conduction studies (motor and sensory) and a needle electromyogram, can be obtained immediately after a nonresolving serious injury and then repeated at 1-month and 3-month intervals. Posttourniquet syndrome is managed with elevation of the extremity, monitoring of wound healing, physical therapy, and nonopiate analgesics. Pressure-related skin injuries are treated as needed. Bullae or chemical burns require burn care, although these injuries may be avoided by applying a nonpermeable plastic barrier drape over the distal end of the tourniquet cuff before preparing the skin. CRPS requires management by a comprehensive chronic pain management team, and early referral is essential. Compartment syndromes are a surgical emergency and require fasciotomy to decompress the affected muscle compartments.

Arterial insufficiency of an extremity requires surgical revascularization or thrombolytic therapy. Diagnosis of intraoperative pulmonary emboli is facilitated with transesophageal echocardiography. Therapy for pulmonary emboli is supportive and includes controlled ventilation, oxygen, pressor support, and cardiopulmonary resuscitation if needed. Systemic anticoagulation, thrombolytic therapy, surgical thrombectomy, or thrombus removal by interventional radiology may be necessary in some patients. Cerebral embolization is diagnosed with computed tomography or MRI scans, and therapy is directed by a neurosurgeon and/or interventional neurologist/radiologist for clot lysis, stenting, or evacuation.

PREVENTION

Catastrophic complications are minimized by judicious patient selection. During screening of patients at high risk for DVT (prolonged immobilization, hypercoagulable state), if a thrombus is detected, elective surgery should be postponed. However, screening all patients for right-to-left intracardiac shunts with contrast-enhanced transthoracic echocardiography is not cost-effective, and it is questionable whether the presence of a right-to-left intracardiac shunt would affect anesthetic or surgical management.

Safety factors in the use of pneumatic tourniquets for hemostasis during hand surgery were first described in 1951, and Bruner's 10 rules were subsequently revised by Braithwaite and Klenerman in 1996. Fortunately, most pneumatic tourniquet complications in extremity surgery are avoided by limiting maximum tourniquet pressure and tourniquet inflation time. Although there are no randomized, controlled, prospective clinical studies to provide us with evidence-based guidelines, there are sufficient animal studies and clinical data to make the following recommendations:

- Carefully select patients preoperatively.
- Use a wide, low-pressure tourniquet cuff.
- Inflate tourniquets to the lowest pressure needed to prevent bleeding.
- Limit tourniquet ischemia time to 2 hours or less.
- Set maximum tourniquet pressure settings as follows: arm tourniquets, 50 to 75 mm Hg above the baseline systolic pressure; leg tourniquets, 75 to 100 mm Hg above the baseline systolic pressure.
- Ensure adequate padding beneath the tourniquet.
- Use barrier techniques to prevent any skin preparation solutions from running underneath the tourniquet cuff.
- Alternate the use of two tourniquets when possible.
- Ensure tourniquet reliability with regular maintenance checks.

There are other simple things that we can do to reduce tourniquet-related injuries, without waiting for advances in research and technology. Using the following general guidelines may result in tourniquet cuff pressures 30% to 50% lower than those currently used in routine clinical practice:

- Use conical, tapered tourniquet cuffs instead of conventional rectangular cuffs. These can reduce limb occlusion pressure by as much as 23% compared with conventional cuffs. Also, they are more efficient at transmitting surface pressure to deep tissues because they more nearly conform to the shape of the extremity.
- Set tourniquet pressures by determining limb occlusion pressure with Doppler or portable ultrasonography. Then set tourniquet pressures 40 to 80 mm Hg above limb occlusion pressure.

- Subsystolic occlusion pressures can be generated with wider conical cuffs or with a cuff width–to–extremity circumference ratio greater than 0.5.

In the future, tourniquet-related injuries may be minimized and allowable tourniquet times extended with techniques such as ischemic preconditioning of skeletal muscle, more frequent reperfusion intervals, and combined regional hypothermia and ischemic preconditioning.

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Fetal Distress

56

James N. Bates

Case Synopsis

A 38-year-old, 120-kg primigravida with poorly controlled type 2 diabetes presents at 35 weeks' gestation with ruptured membranes and a temperature of 38.5°C. The decision is made to induce labor. During labor the obstetrician declares that the electronic fetal heart rate monitor indicates fetal distress (Fig. 56.1) and urgent cesarean delivery is required.

PROBLEM ANALYSIS

Definition

Fetal distress is an imprecise term that has been used progressively less in the medical record since the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion in 1998 that suggested replacing the term *fetal distress* with *nonreassuring fetal heart rate tracing*. Despite the ominous implications associated with the term *fetal distress,* it was frequently associated with delivery of an infant in good condition. In accordance with the ACOG recommendations, the medical record usually describes nonreassuring fetal heart rate (FHR) tracing with additional descriptions of the findings such as fetal bradycardia, repetitive late or variable decelerations, or loss of variability. Nonetheless, the term *fetal distress* is still often used when communicating patient condition and carries the implication of great urgency. When called to help with the treatment of fetal distress, part of the initial communication with the obstetrician should be to get clarification of the maternal and fetal condition and the true urgency of delivery because these will largely determine the anesthetic options.

Recognition

One of the great challenges to obstetricians managing patients in labor is deciding when the risk of injury to the mother or child is greater by continuing in labor than it would be by proceeding to an operative delivery. The obstetrician has a limited number of tools for assessing the condition of the fetus and predicting the future course of labor. Electronic FHR monitoring is the primary means of assessing fetal oxygenation because it is usually simple, continuous in real time, minimally invasive or noninvasive, and widely available. It is a monitor of the fetus' own measurement and response to oxygenation and perfusion, which makes it at the same time both richly informative and subject to many confounders. Factors that alter the fetal central nervous system and autonomic responses, such as drugs (e.g., opioids, anesthetics, sympathetic or parasympathetic modulators such as β-agonists or atropine), neurologic abnormalities (e.g., anencephaly), or conditions that alter the measured response such as fetal cardiac arrhythmias are examples of influences that will make interpretation of the FHR more complicated. On the other hand, decades of widespread use and interpretation have produced a large library of observed FHR patterns and associated fetal outcomes that make it the most useful and trusted primary monitor of fetal well-being in labor.

Other measures of fetal well-being, such as the presence or absence of meconium in the amniotic fluid; the FHR response to acoustic or scalp stimulation; measurement of plasma pH in a blood sample obtained from a fetal scalp; and umbilical artery Doppler velocimetry looking for evidence of reduced, absent, or reversed umbilical artery diastolic blood flow can all be used to add information about fetal status, but none has the utility or value of FHR monitoring.

FHR monitoring is based on the premise that increasing degrees of hypoxia or asphyxia produce characteristic changes in the FHR pattern. Regulation of the FHR involves mechanisms that are still incompletely understood. At its most basic level, input from baroreceptors and chemoreceptors for oxygen and carbon dioxide are processed through brainstem nuclei and centers in the hypothalamus and cerebral cortex to produce sympathetic, parasympathetic, and humoral signals that modulate heart rate.

Electronic FHR monitors record the FHR and uterine contractions. The baseline FHR and changes in the heart rate can be analyzed in relation to uterine contractions. The main features of the FHR pattern that are measured (Box 56.1) include baseline heart rate, heart rate variability, accelerations, and decelerations (three types: early, late, and variable). In 2008 a three-tier system for FHR tracing interpretation was introduced in the United States to standardize the overall interpretation and communication of FHR tracings (Box 56.2). Tracings are rated Category I (Normal), Category II (Indeterminate), or Category III (Abnormal) based on the features observed in the tracing and their prognostic value.

Risk Assessment

The incidence of a fetal crisis where without intervention fetal death or severe injury is likely, but with appropriate intervention fetal injury can be reduced or prevented, is hard to calculate. Analysis of a Canadian database found an intrapartum death rate of 0.67 per 1000 live births, with 0.09 per 1000 births deemed preventable (not severely preterm or anomalous). This may represent one estimate of the failure-to-rescue rate. In contrast, the cesarean delivery rate is over 30% and over the past 20 years surveys have indicated that fetal distress or nonreassuring heart rate tracing was associated with 2% to 10% of all cesarean deliveries. Data from the 2009 and 2010 Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project, a 20% sample of U.S. hospitals containing 1,475,457 births, showed that a diagnosis of fetal distress (defined as Clinical Classifications Software [CCS] code 190) was applied to 10% of all births and that the cesarean delivery rate within that group was 59%, compared with 30% for deliveries not associated with that diagnosis. A 2016 report using data from the Consortium of Safe Labor study from 2002 to 2008 showed nonreassuring fetal heart tracing was the indication in 23% of primary cesarean deliveries. These

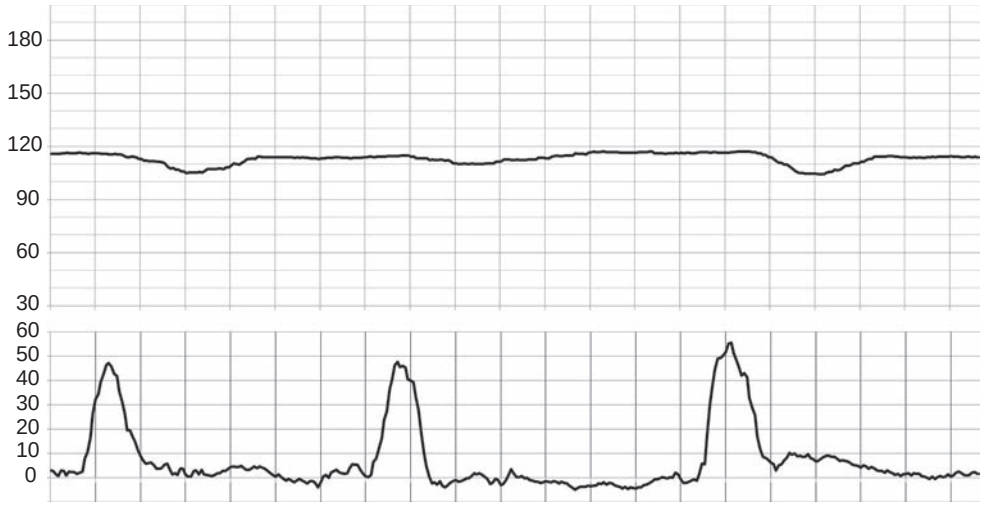

Fig. 56.1 The electronic fetal heart rate tracing demonstrates absent variability and recurrent late decelerations, especially evident after the first and third contractions. This is a Category III tracing. The grid shows 1-minute intervals; the upper tracing shows heart rate as beats per minute, and the lower tracing shows uterine contractions as mm Hg pressure.

data show that a diagnosis of fetal distress or nonreassuring FHR tracing is not uncommon and is associated with a high probability of cesarean delivery but not a certainty of it. For each case of fetal distress or nonreassuring FHR tracing, more patient-specific information is needed to determine the type of delivery and the urgency of delivery.

Implications

Uncorrected severe hypoxia in the fetus will eventually lead to profound acidosis; neurologic injury, including seizures, coma, hypotonia, encephalopathy, or cerebral palsy; and, ultimately, death.

MANAGEMENT

The first response to clinical signs of intrauterine hypoxia should be to initiate in utero fetal resuscitation. This includes supplemental oxygen administration, maternal repositioning (left or right lateral decubitus, knee-chest position, etc.), assessment and treatment of maternal hypotension or hypovolemia, discontinuation of oxytocin, or other actions to treat conditions that may be contributing to poor fetal oxygen delivery.

Statistics indicate that many deliveries that are labeled as including fetal distress or nonreassuring fetal heart tracing occur as vaginal deliveries, but most are cesarean deliveries. It is not clear how many are performed as true emergency cesarean deliveries with the primary objective being to make the "decision to incision" time as short as possible. It is obvious, however, that the anesthetic choices in many cases of fetal distress need not be driven primarily by the decision of which technique provides surgical anesthesia most rapidly.

When called for assistance with fetal distress the anesthetist should be prepared to assist with either vaginal or cesarean delivery and must decide which anesthetic is the most appropriate. Category III FHR tracings containing severe or prolonged bradycardia, as well as unstable maternal conditions such as massive hemorrhage or catastrophic uterine rupture, require immediate surgical intervention. Communication among the obstetric team, the anesthesia team, and the patient is imperative in cases of emergent cesarean delivery. The urgency of delivery, the anesthetic risk factors in the mother, the effects of anesthesia on the mother and the fetus, and the needs and expectations of the obstetrician and the patient all factor into the choice of anesthesia.

FHR monitoring should be continued following transfer to the delivery room and, if possible when a scalp electrode is used, until delivery. This information helps guide the choice and management of anesthetic. Fetal bradycardia that resolves in the operating room before anesthesia is induced might lead the obstetrician to reconsider whether to proceed with cesarean delivery, or it might affect the decision whether to proceed with general anesthesia or neuraxial anesthesia.

The relative risks of general and regional anesthesia must be carefully considered in each patient. General anesthesia can be induced more rapidly but is associated with a higher incidence of fatal and nonfatal maternal complications.

When the patient has an epidural catheter already in place and it has been working well it can be used to establish surgical anesthesia. Administration of 15 to 20 mL of 2% lidocaine or 3% chloroprocaine in 5-mL increments is usually sufficient to produce a T4 level of surgical anesthesia. Onset of epidural anesthesia is usually slow compared with the onset of spinal anesthesia but it can be expedited. Epinephrine (1:200,000) is often added to local anesthetics, especially lidocaine, where it extends the duration and improves the quality of the block, but commercial preparations of lidocaine with epinephrine have a lower pH than preparations of lidocaine alone and the result is slower onset of action. Epinephrine can be added directly to preparations of plain lidocaine, keeping the pH higher, or the pH can be adjusted with addition of sodium bicarbonate. Adding 1 mL of sodium bicarbonate (8.4%) to each 10 mL of 3% chloroprocaine or 2% lidocaine (with or without epinephrine) speeds onset by increasing the fraction of the drug in the nonionized form. Mean times needed to achieve surgical anesthesia using alkalinized chloroprocaine or lidocaine of 5 minutes or less have been reported in some studies. Alkalinized chloroprocaine has the fastest onset of any epidural anesthetic, but 3% chloroprocaine as it comes in the bottle is almost as fast and avoids both the time needed to prepare the mixture and the risk of mixing errors or contamination that might be associated with preparing drug combinations hastily. It is a good option if alkalinized chloroprocaine or lidocaine is not already available or if mixing drugs is being avoided.

Epidural bupivacaine 0.5% and ropivacaine 0.5% provide good anesthesia for cesarean delivery, but their onset is much slower than lidocaine or chloroprocaine, decreasing their appeal for emergency

BOX 56.1 Fetal Heart Rate Features

Baseline

A normal baseline FHR is defined as 110 to 160 beats per minute. Changes from that range suggest increased vagal or sympathetic tone.

Variability

Fetal heart rate variability is the fluctuation in the FHR. Previously, FHR variability was categorized as short term (beat to beat) and long term (over the course of 1 minute), but this distinction has been abandoned. The presence of normal FHR variability reflects normally functioning pathways in the fetal cerebral cortex, midbrain, vagus nerve, and cardiac conduction system.

Accelerations

Abrupt changes in the FHR ≥15 beats per minute above the baseline, lasting ≥15 seconds.

Antepartum FHR accelerations are a response to fetal movement and viewed as a sign of fetal well-being; their presence indicates a reactive nonstress test.

Intrapartum FHR accelerations indicate no significant fetal metabolic acidemia.

Decelerations

Early Deceleration

- Visually apparent, usually symmetric, *gradual* decrease and return of the FHR associated with a uterine contraction.
- A *gradual* FHR decrease is defined as one from the onset to the FHR nadir of ≥30 seconds.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The nadir of the deceleration occurs at the same time as the peak of the contraction.
- In most cases the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.
  - Probably due to reflex vagal responses to mild hypoxia.
  - Not considered to be ominous.

Variable Deceleration

- Visually apparent *abrupt* decrease in FHR.
- An *abrupt* FHR decrease is defined as from the onset of the deceleration to the beginning of the FHR nadir of <30 seconds. The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The decrease in FHR is ≥15 beats per minute, lasting ≥15 seconds, and <2 minutes in duration.
- When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.
  - Probably vagal responses to baroreceptor or chemoreceptor signals triggered by such things as cord compression or head compression in the second stage of labor.
  - Mild to moderate (≥80 beats per minute) variable decelerations are usually well tolerated, but prolonged severe (<60 beats per minute) decelerations may lead to fetal compromise.

Late Deceleration

- Visually apparent usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction.
- A *gradual* FHR decrease is defined as from the onset to the FHR nadir of ≥30 seconds.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.
  - Probably a response to hypoxemia but may also be a reflection of myocardial failure.
  - Possibly oversensitive as an indicator of fetal asphyxia, but in combination with decreased or absent FHR variability it is a reliable signal of fetal compromise.

FHR, Fetal heart rate.

Modified from Macones GA, Hankins GD, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol* 112(3):661-666, 2008.

BOX 56.2 Three-Tier Fetal Heart Rate Interpretation System

Category I (Normal)

Category I fetal heart rate (FHR) tracings include all of the following:

- Baseline rate: 110–160 beats per minute
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

Strongly predictive of normal fetal acid-base status at the time of observation

Category II (Indeterminate)

Category II FHR tracings include *all FHR tracings not categorized as Category I or Category III.* Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of Category II FHR tracings include any of the following:

Baseline Rate

- Bradycardia not accompanied by absent baseline variability
- Tachycardia

Baseline FHR Variability

- Minimal baseline variability
- Absent baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations

- Absence of induced accelerations after fetal stimulation

Periodic or Episodic Decelerations

- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration ≥2 minutes but <10 minutes
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," or "shoulders"

Not predictive of abnormal fetal acid-base status, but without adequate evidence to classify as normal or abnormal.

Category III (Abnormal)

Category III FHR tracings include either:

- Absent baseline FHR variability and any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

Predictive of abnormal fetal acid-base status at the time of observation and thus requiring prompt evaluation.

Modified from Macones GA, Hankins GD, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol* 112(3):661-666, 2008.

cesarean delivery. Alkalinization of these drugs with bicarbonate is not recommended because it easily precipitates the drugs out of solution.

If the decision to proceed to cesarean delivery is made in the labor room, the initial dose(s) of local anesthetic can be given before the patient is transported to the operating room. This shortens the time until surgical anesthesia is achieved, potentially decreasing the need for a general anesthetic. However, it also carries the risk that an adverse response (high block, hypotension, intravenous injection, etc.) can occur in an environment where it is harder to recognize and to treat than in the operating room. The relative risk and benefit must be weighed for each patient.

Spinal anesthesia should also always be considered for urgent or emergent cesarean delivery. As with epidural anesthesia the urgency of the delivery and the ability to provide surgical anesthesia within that time frame are critical to the choices made. In the case of spinal anesthesia the potential delay is most likely the time needed to place the block. The skill of the anesthesiologist, the patient's anatomy, the

ability of the patient to assume and maintain the necessary positions, and the acceptance of neuraxial anesthesia by the patient and obstetrician must all be part of the decision whether spinal anesthesia is appropriate. Onset of spinal anesthesia is usually rapid after the dose has been administered. It is usual to administer a large intravenous fluid preload of a non–dextrose-containing crystalloid solution before spinal anesthetic administration, but the American Society of Anesthesiologists (ASA) Practice Guidelines for obstetric anesthesia advise that failure to complete fluid preloading does not justify delaying spinal anesthesia when it is the most appropriate method for the patient.

When neither epidural nor spinal anesthesia is considered appropriate, general anesthesia is chosen. It is widely believed that general anesthesia carries a higher risk of serious complications or death in obstetric patients. This is supported by retrospective studies that look at maternal mortality and find a higher incidence in patients who received general anesthesia compared with regional anesthesia. The results may be somewhat biased by the fact that general anesthesia has historically been favored in emergency surgeries and in other high-risk surgeries, factors that independently increase the maternal morbidity and mortality, but most observers agree this is unlikely to account for most of the difference in risk. A major part of the morbidity and mortality associated with general anesthesia is related to airway management (e.g., failed intubation, pulmonary aspiration, or hypoventilation). These problems are usually avoided with regional anesthesia. Obstetric patients carry a higher risk of these problems than the general population. Failed intubation has been reported to occur with a frequency of 1 in 300 obstetric patients, compared with 1 in 2000 general surgical patients. When a failed intubation occurs during anesthesia for fetal distress, the condition of the fetus is part of the airway management algorithm. If intubation has failed but ventilation is maintained, and there is no fetal distress, the patient should be allowed to wake up and either a regional anesthetic or awake intubation should be pursued. If there is continued fetal distress, however, the preferred choice would be to proceed with inhalation anesthesia using a facemask or laryngeal mask airway when maternal oxygenation and ventilation can be maintained.

PREVENTION

Early diagnosis of patients at high risk of developing fetal distress can lead to early epidural placement, and early diagnosis of category II or even category III FHR tracings might allow for less urgent decisions about operative delivery. Good communication between the obstetric and anesthesia providers can help ensure optimal care and the best maternal and fetal outcomes.

ACKNOWLEDGMENT

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Foreign Body Aspiration

57

Paul G. Firth

Case Synopsis

A 3-year-old boy is booked for an urgent rigid bronchoscopy for evaluation and removal of a suspected aspirated foreign body. He has previously been treated unsuccessfully with bronchodilators and antibiotics for a week-long history of coughing, wheezing, and mild tachypnea. The parents thought they recalled a prior episode of choking while he was eating peanuts. Chest x-ray showed localized right-sided air trapping and emphysema.

PROBLEM ANALYSIS

Definition

Aspiration of a foreign body is a significant cause of accidental death in young children, particularly those 1 to 4 years old. Most aspirated objects are pieces of food or other organic material. Nuts (particularly peanuts) and seeds (especially sunflower and watermelon seeds) are the most frequently aspirated types of objects. Death may occur acutely through complete mechanical airway obstruction or severe laryngospasm. Survivors may develop pneumonia or empyema if the object is not removed. Bronchoscopy with general anesthesia to remove an aspirated foreign body from a small child is hazardous if performed by inexperienced clinicians, with a worldwide mortality rate of about 0.4%. Loss of airway, hypoventilation and hypoxia are the main contributors to mortality under anesthesia.

Recognition

Diagnosis is typically made through a combination of history, examination, and radiologic investigation, although bronchoscopy is the most definitive investigation.

A history of a witnessed choking event is highly suggestive of an aspiration event. Although the positive predictive value is high, the negative predictive value is much lower, because many aspiration episodes are unnoticed by caregivers.

Frequent presenting signs and symptoms include persistent cough, wheeze (often localized), and tachypnea; cyanosis and stridor are less common.

A chest x-ray may be suggestive of a foreign object in the airway. As organic matter is the most common type of aspirated material, most inhaled bodies are radiolucent. A substantial minority of x-rays are reported as normal. Common abnormalities induced by luminal obstruction, however, include localized emphysema and air trapping, or atelectasis and infiltrate (Fig. 57.1). Pneumothorax and pneumomediastinum are rare.

Computed tomography and virtual bronchoscopy (reformatted three-dimensional imaging) are methods to examine the airways if the diagnosis is not clear, although radiation exposure and cost limit these investigations. Rigid and flexible bronchoscopy can also be used to confirm or exclude the presence of a cryptic foreign body.

Risk Assessment

The anesthesiologist should determine (1) where the aspirated object is lodged, (2) what was aspirated, and (3) when it was aspirated. A clinical assessment of gas exchange is an additional important preprocedural objective.

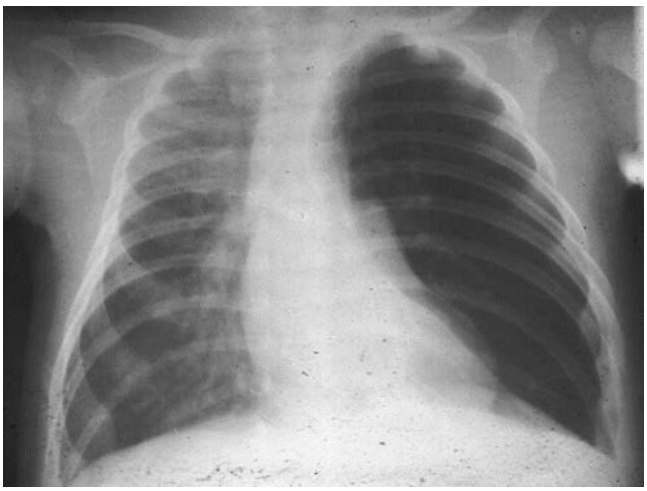

Fig. 57.1 An end-expiration chest x-ray, demonstrating left-sided air trapping by a radiolucent bronchial foreign body. (Courtesy Dr. Peter Masiakos, MD, Department of Surgery, Massachusetts General Hospital, Boston, MA.)

Implications

Most objects (>85%) lodge in the bronchial tree, predominantly on the right side. Those that are stuck in the larynx or trachea may produce complete airway obstruction, and typically should be removed urgently or emergently. Proximal objects are typically easier to locate and remove, whereas more distal objects may require more time to extract. A distal object can produce atelectasis and pneumonia, compromising gas exchange and making anesthetic delivery more challenging.

An organic object can swell as it absorbs fluid from the airway wall, producing progressive obstruction. If the foreign body is lodged above the carina, this can lead to delayed total airway obstruction and fatal asphyxia. Nut oils can cause marked local inflammation. Sharp objects can occasionally pierce the airway and cause a pneumomediastinum or pneumothorax that may be exacerbated by positive pressure ventilation.

The time delay since the aspiration may affect the difficulty of extraction and associated length of the required anesthetic. Mucosal edema, localized inflammation, and infection may make removal more difficult and time consuming.

TABLE 57.1 Complications of Bronchoscopy and Anesthesia to Remove Foreign Body

Complication	Comment
Loss of airway	Tracheal obstruction by foreign body
	Shift/dropping of foreign body into the trachea
	Laryngospasm
	Hypoxic bradycardia
	Cardiac/respiratory arrest
Inadequate ventilation	Coughing/breath holding
	Bronchospasm
	Pneumonia
Airway laceration	Pneumothorax
	Pneumomediastinum
	Bleeding
	Bronchial rupture
Failed extraction	Tracheotomy
	Thoracotomy
Laryngeal edema	Postoperative stridor
	Postoperative arrest

MANAGEMENT

Bronchoscopy is associated with significant morbidity and mortality, either from the offending object, the bronchoscope, or the anesthetic (Table 57.1). The anesthesiologist should ensure that the airway is patent and that ventilation is adequate; maintain arterial oxygenation despite gas exchange potentially being impaired by airway obstruction, atelectasis, or pneumonia; and prevent coughing, bucking, and airway trauma during the stimulus of bronchoscopy.

The object can be removed with a flexible or rigid bronchoscope. If a rigid bronchoscope is used, oxygenation occurs directly down the scope. Induction is typically done by inhalation, with intravenous access previously established. The vocal cords are topicalized with local anesthetic and the rigid bronchoscope is then inserted.

There are a variety of techniques for the maintenance of anesthesia, with no one method universally accepted. Total intravenous anesthesia is one common approach, with propofol (200 to 400 μg/kg/min) and supplemental opioid such as a remifentanil infusion (0.05 to 0.2 μg/kg/min). Sevoflurane in oxygen is another frequently used method.

There are also differences in practice with respect to ventilation. Both controlled and spontaneous ventilation, or a combination of the two, have been used successfully. It is unclear which technique best prevents intraoperative hypoxemia and coughing or bucking.

If flexible bronchoscopy is used, a laryngeal mask can be inserted and the scope introduced via a side port. Bronchoscopy down an endotracheal tube may also be feasible. Nasal passage of the bronchoscope following aerosolized lidocaine has also been described. However, limitations in the size of bronchoscopy equipment or airway lumen mean that flexible bronchoscopy is not feasible for all patients.

Postoperatively the patient must be closely observed for airway obstruction and respiratory embarrassment. Laryngeal edema may progress to total airway obstruction. Clinical condition will determine the optimal time for discharge home.

PREVENTION

Maintenance of airway and ventilation while ensuring optimal conditions for removal of the foreign body are the fundamental anesthetic objectives. A variety of anesthetic techniques are feasible to achieve these aims. Close cooperation and clear communication between anesthesiologist, bronchoscopist, and assistants are essential to ensure safe extraction of the mislocated object.

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Head Injury

58

Armagan Dagal • Arthur M. Lam

Case Synopsis

A 22-year-old previously healthy man sustained a head injury, as well as an unstable pelvic and femur fracture, following a motorcycle accident. He was initially combative but quickly became obtunded with a Glasgow Coma Scale (GCS) score of 9 (E3V3M3; see Table 58.1). His blood pressure was 95/40 mm Hg, and his heart rate was 100 beats per minute. He had a dilated, unreactive right pupil. Tracheal intubation was performed at the scene, and he was transported to the trauma center. A computed tomography scan revealed a large right epidural hematoma with a midline shift. Initial hematocrit was 32% after the administration of 2 L of crystalloid. His blood pressure was 130/80 mm Hg and his heart rate was 120 beats per minute. He was scheduled for emergent evacuation of the epidural hematoma, followed by open reduction and internal fixation of the femur and pelvis.

PROBLEM ANALYSIS

Definition

Traumatic brain injury (TBI) is an acquired insult to the brain tissue due to an external blunt or penetrating mechanical force that may evolve into transient or long-term impairment of cognitive, physical, and psychosocial functions. In addition, TBI is often accompanied by other extracranial injuries.

Incidence

The incidence of head injury is rising. The Centers for Disease Control and Prevention (CDC) estimated that TBI accounted for approximately 2.5 million emergency department (ED) visits. From these presentations, approximately 87% (2,213,826) patients were treated in and released from EDs, another 11% (283,630) were hospitalized and discharged, and approximately 2% (52,844) died.

Falls are the leading causes of nonfatal TBI (35%), followed by motor-vehicle–related injuries (17%) and strikes or blows to the head from or against an object (including sports related) (17%). Overall, motor-vehicle traffic incidents constitute the most common cause of TBI-related deaths, followed by self-inflicted/suicide and falls.

TBI is the commonest cause of death and disability among people under age 40. Improved understanding of the disease process and technologic advancements have reduced the TBI mortality rate by 8.2% in the last decade.

Initial damage to neural tissue directly due to trauma is considered the primary injury and includes cerebral contusion, diffuse axonal injury, hemorrhage into the epidural or subdural space, and intraparenchymal hemorrhage. *Secondary injury* is defined as any insult to the brain occurring after the initial injury that results in further neuronal damage. Although cerebral ischemia or hypoxia is the ultimate cause of secondary brain injury after TBI, systemic or local insults such as elevated intracranial pressure (ICP), systemic hypotension, and hypoxemia often contribute to secondary injury.

Neuronal death is likely mediated by complex biochemical processes involving the release of excitatory amino acids (e.g., glutamate) and the cellular influx of calcium. Actual cell death may be necrotic or apoptotic in nature. Preventing or reducing secondary brain injury is the focus of most medical management strategies, both in the operating room and subsequently in the intensive care unit (ICU).

TBI is often associated with other injuries (as illustrated in the case synopsis). Thus anesthesiologists may care for a patient during initial resuscitation, surgical intervention for TBI (e.g., evacuation of subdural hematoma, decompressive craniectomy), and/or during laparotomy or fixation of incidental orthopedic injuries, as well as subsequently in the ICU.

Recognition

Primary Traumatic Brain Injury

TBI is suspected when head trauma is associated with any of the clinical signs affecting the consciousness, memory, mental status, and/or neurologic function. Severity of TBI is commonly assessed by the GCS, which assigns a score to the patient's best motor, verbal, and eye-opening abilities (Table 58.1). A total score of 8 or less indicates severe TBI. Use of the GCS to evaluate patients with TBI reduces interobserver variability and allows for the comparison of serial examinations to evaluate disease resolution or progression. However, it is evident from the prior description that severe TBI is a heterogeneous disease, and patients with different pathophysiologic mechanisms can manifest with the same GCS score. In addition, use of the GCS as a prognostic indicator is controversial, and assignment of a GCS score is appropriate only after adequate cardiopulmonary resuscitation, especially when it is accompanied by severe hypotension or hypoxia.

Along with the GCS, the pupils should be examined for pupil size, symmetry, and reactivity to light. With acute unilateral mass lesions, an ipsilateral dilated and unreactive pupil suggests uncal herniation. In contrast, bilateral fixed and dilated pupils suggest severe intracranial hypertension that may result in brain herniation.

Vital signs may reflect the patient's overall clinical status aside from any TBI. For example, hypotension and tachycardia may be due to concealed hemorrhage with a large bone fracture, and hypertension may be due to pain. Vital signs also provide

TABLE 58.1 Glasgow Coma Scale Score

Eye Opening		Verbal Response		Motor Response	
Spontaneous	4	Oriented	5	Obeys commands	6
To speech	3	Confused	4	Localizes to pain	5
To pain	2	Inappropriate	3	Withdraws to pain	4
None	1	Incomprehensible	2	Flexes to pain	3
		None	1	Extends to pain	2
				None	1

significant insight into the nature of TBI. Severe hypertension may be a compensatory phenomenon (i.e., to preserve cerebral perfusion pressure [CPP] with elevated ICP; CPP is mean arterial pressure [MAP] minus ICP). Severe systemic hypertension with bradycardia is an ominous sign (Cushing reflex). It signifies impending brain herniation and requires immediate therapeutic intervention.

Computed Tomography Findings

Cranial computed tomography (CT) is highly sensitive for detecting intracranial hemorrhage and acute mass lesions. CT findings that support a significantly elevated ICP include the following:

- Mass lesion greater than 25 mL
- Midline shift of 5 mm or more
- Compression of the basal cisterns or lateral ventricles
- Medial displacement of the uncus

Secondary Brain Injury

Secondary brain injury can be caused by either systemic or cerebral factors (Table 58.2). Among these, hypoxia and hypotension are most likely to have an adverse effect on TBI outcome. However, the neurologic and systemic manifestations of primary TBI may obscure the signs of secondary injury due to cerebral hypoxia or ischemia. Although the calculation of CPP (which requires an arterial line and ICP monitor) is useful with abnormal head CT findings, even a normal CPP does not preclude the development of secondary ischemia or cerebral hypoxia.

Technologic advances have allowed the clinician to gain better insights about the injured brain and its functions.

Cerebral Perfusion and Oxygenation Monitors

Intracranial Pressure Monitor

Either a fiberoptic intraparenchymal probe or an intraventricular catheter can be used to monitor ICP. With continuous intraarterial pressure monitoring, CPP (CPP = MAP – ICP) can be continuously displayed in specialty monitors and allow optimal management of brain perfusion pressure. Although recent literature suggests that vigilant clinical management based on imaging can achieve similar patient outcome as ICP-based management, for now ICP monitoring remains the cornerstone of management of TBI patients and can still be considered the gold standard, allowing judicious clinical decisions based on instant feedback.

Jugular Venous Oximetry

A jugular venous bulb oximetric catheter (JBC) continuously measures brain venous oxygen saturation ($SjvO_2$). Inadequate brain perfusion increases oxygen extraction, causing a decrease in $SjvO_2$, whereas nonfunctioning brain tissue extracts little oxygen, resulting in high $SjvO_2$ values (luxury perfusion). Thus $SjvO_2$ less than 55% or greater than 75% is associated with a poor prognosis. $SjvO_2$ catheters are especially useful to monitor cerebral metabolic rate (CMR) when global intervention such as deliberate hyperventilation is used to reduce global cerebral blood flow (CBF) and consequently ICP. JBC lactate concentrations may also reveal increased anaerobic brain metabolism if they are higher than simultaneously drawn arterial lactate concentrations. A limitation of JBC is that it monitors only global CBF-CMR balance. $SjvO_2$ values can be normal despite small regional areas of ischemia or infarction. Despite initial enthusiasm, this has been largely superseded by brain tissue oxygen tension sensors.

TABLE 58.2 Risk Factors for Secondary Brain Injury

Cerebral Factors	Systemic Factors
Increased intracranial pressure	Hypotension
• Expanding mass lesions	Hypoxemia
• Hypercapnia	Anemia
• Hypoxemia	Hypovolemia
• Venous obstruction (cervical collar, poor positioning)	Hyperglycemia
• Systemic hypotension (compensatory cerebral vasodilation)	Hyponatremia
Excessive hyperventilation	Hypo-osmolar state
Posttraumatic vasospasm (traumatic subarachnoid hemorrhage)	Coagulopathy
Seizures	Fever

Brain Tissue Oxygen Tension

Brain tissue oxygen tension ($PbrO_2$) sensors provide a continuous measurement of brain parenchymal oxygen tension. This reflects the balance between local brain supply and demand for oxygen. The normal $PbrO_2$ is in the range of 23 to 35 mm Hg. A $PbrO_2$ value of less than 20 mm Hg represents compromised brain tissue oxygenation and is the threshold at which an intervention should be considered. The BOOST II trial has shown that the addition of $PbrO_2$ monitoring to existing ICP/CPP-guided management results in a statistically significant decrease in duration and severity of brain hypoxia, along with a 10% reduction in mortality and a trend toward reduced mortality and improved neurologic outcome at 6 months. This is an invasive monitor, and for it to be optimally effective it should be placed in the brain tissue most at risk, that is, the ischemic penumbra—a feat that is seldom accomplished. Instead it is often placed in the frontal lobe, in combination with the ICP monitor.

Near-Infrared Spectroscopy

Near-infrared spectroscopy is based on reflectance spectroscopy; it measures the light reflected from chromophobes in the brain (hemoglobin) to derive the regional oxygen saturation. It provides information on the balance between flow and metabolism. It is generally accepted that normal range varies between 60% and 75%, with a coefficient of variation of almost 10%. Extracranial contamination of light reflection is a potential source of artifact.

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography (TCD) allows estimation of cerebrovascular resistance, displaying increased pulsatility with elevated ICP, and can be a confirmatory test for intracranial circulatory arrest. Recent studies suggest that continuous monitoring of flow velocity with TCD may allow optimal blood pressure (BP) management by determining the BP range where cerebral autoregulation is most robust.

Microdialysis

Microdialysis catheters are placed in brain parenchyma, where they continuously perfuse the brain with a perfusate and sample small volumes of fluid (the dialysate), which is tested for lactate and pyruvate, glutamate, glucose, and glycerol concentration. Lactate-to-pyruvate ratios greater than 40 suggest insufficient cerebral oxygen delivery, inadequate glucose supply, or underlying neuronal mitochondrial dysfunction. However, a time lapse of at least an hour is needed to collect and analyze samples, and this time lag hinders real-time clinical decision making. It remains essentially a research tool at the present time.

Risk Assessment and Implications

Hypoxemia and Hypercapnia

TBI patients are at increased risk for airway obstruction and hypoventilation. These lead to hypoxemia and hypercapnia, which cause cerebral vasodilation. The latter may aggravate any elevated ICP.

Elevated Intracranial Pressure

An acute mass lesion increases ICP and reduces CPP. Increased ICP can lead to brain herniation, with catastrophic consequences.

Systemic Hypotension and Hypovolemia

Adults usually do not become hypovolemic and hypotensive as a result of blood loss from TBI alone. In contrast, small children can lose enough blood with TBI to become hypotensive. Other injuries (e.g., splenic rupture, large bone fractures) can make TBI patients hypotensive and further compromise CPP in those with increased ICP. Compensatory hypertension and bradycardia (Cushing reflex) with elevated ICP may further complicate the clinical picture. Thus in patients with TBI, normotension and tachycardia can still be compatible with severe hypovolemia, with the latter "concealed" by increased systemic vascular resistance (Cushing reflex). Thus an "adequate" blood pressure may give clinicians a false sense of security regarding the progress of resuscitation. Should the elevated ICP be relieved by decompressive craniectomy or evacuation of an intracranial hematoma, sudden profound hypotension or cardiac arrest may occur.

Of all the factors associated with secondary brain injury, systemic hypotension is likely the most significant. With impaired cerebral autoregulation, it invariably leads to reduced CPP. Patients with intact autoregulation but reduced intracranial compliance are also at risk for impaired CPP with hypotension. A reduced MAP indirectly dilates cerebral vasculature to maintain cerebral blood flow, resulting in increased cerebral blood volume and ICP. This increase in ICP further compromises CPP, leading to further compensatory cerebral vasodilation. This vicious circle is referred to as the vasodilator cascade (Fig. 58.1).

Impaired Cerebral Autoregulation

Cerebral autoregulation is a homeostatic mechanism that maintains near-constant perfusion of the brain over a wide range of MAPs. In normal adults, this range is 60 to 160 mm Hg. Autoregulation may be impaired in patients with TBI, and although the frequency of impaired autoregulation is higher in patients with severe TBI, it is clinically impossible to predict which patients will be affected. Even minor TBI may impair autoregulation. If so, CBF becomes directly proportional to blood pressure. Loss of cerebral autoregulation is associated with worse outcomes in severe TBI.

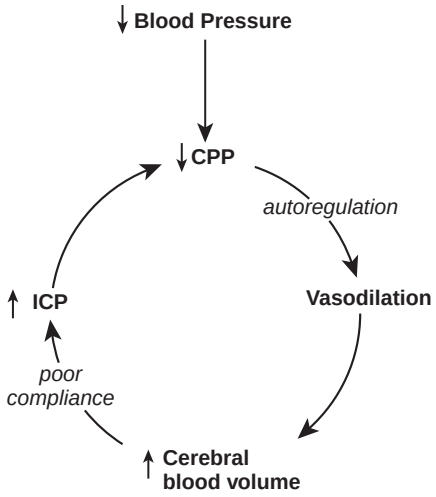

Fig. 58.1 Vasodilator cascade showing the potential interaction between systemic hypotension and intracranial hemodynamics when autoregulation is intact. A cascade in the opposite direction also occurs when blood pressure is increased. *CPP,* Cerebral perfusion pressure; *ICP,* intracranial pressure.

Coagulopathy

Severe TBI liberates enough thromboplastin from damaged neurons to cause coagulopathies, which may be mild to severe. They can increase surgical morbidity and mortality, which can preclude or delay extracranial surgical procedures, and are associated with poorer outcomes.

Pyrexia

Fever raises the CMR, increasing the risk for ischemia and neural injury, especially when cerebral perfusion is marginal. Cerebral blood volume increases with pyrexia owing to flow-metabolism coupling, exacerbating any elevated ICP. Although human studies do not conclusively link body temperature to outcome in TBI, both animal and human studies have linked brain infarct size and fever in ischemic brain injury.

Hyperglycemia

Hyperglycemia in TBI and stroke is associated with a poor prognosis, although a cause-effect relationship has not been clearly established. In experimental cerebral ischemia, detrimental effects of hyperglycemia have consistently been shown. Further, in one prospective trial, van den Berghe and colleagues found that critically ill patients with lax glucose control had worse outcomes than those with tight control. However, tight glucose control is often accomplished at the risk of severe hypoglycemia, which is equally detrimental.

Fluid and Electrolyte Abnormalities

Acute fluid and electrolyte disturbances occur in TBI patients, often due to inappropriate fluid administration. They can also be caused by diabetes insipidus. Hyponatremia and excessive free water will worsen cerebral edema, thereby increasing ICP. Isotonic fluid should be used for volume replacement, and colloids including albumin should be avoided. Blood transfusion threshold remains controversial, but a restricted approach is generally preferred (Table 58.3).

TABLE 58.3 Intravenous Fluids

Fluids	Osmolality (mOsm/kg)	Oncotic Pressure (mm Hg)	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Ca^{2+}/Mg^{2+} (mEq/L)	Glucose (g/L)
Plasma	289	21	141	103	4–5	5/2	
Crystalloid							
0.9% NS	308	0	154	154			
0.45% S	154	0	77	77			
3% HTS	1027	0	515	515			
7.5% HTS	2400	0	1200	1200			
23.4% HTS	8008						
LR	273	0	130	109	4	3/0	
D_5LR	527	0	130	109	4	3/0	50
D_5W[a]	252	0					50
D_5 NS[a]	586	0	154	154			50
$D_5$0.45% S[a]	406	0	77	77			50
Normosol/Plasmalyte	295	0	140	98	5	0/3	
Mannitol (20%)	1098	0					
Colloid							
Hetastarch (6%)	310	31	154	154			
Albumin (5%)	290	19					
Plasmanate	270–300	?	145	100	0.25		

[a]The osmolality of these dextrose solutions decreases as glucose enters the cells.
D_5W, 5% dextrose in water; *HTS,* hypertonic saline; *LR,* lactated Ringer's; *NS,* normal saline; *S,* saline.

Associated Extracranial Injuries

As many as 10% of patients with TBIs also have spine injuries. Spinal evaluation is often delayed if the patient requires emergent neurosurgical intervention (e.g., evacuation of epidural or subdural hematoma). For this reason, the spine should be protected at all times when moving or positioning patients before the completion of a spine injury workup. TBI patients may also have undiagnosed extremity and solid organ injuries.

MANAGEMENT

Refer to Box 58.1 for a list of general management targets.

BOX 58.1 List of General Management Targets

pH 7.35–7.45
Pa_{O_2} 100–300
Pa_{CO_2} 35–40 mm Hg
Temperature 36°–37.5°C
Systolic blood pressure 100–180 mm Hg
Intracranial pressure <20 mm Hg
Cerebral perfusion pressure 60–70 mm Hg
$SjvO_2$ 50–75 mm Hg
$PbtO_2$ ≥20 mm Hg
Glucose 120–180 mm Hg
Hemoglobin >7 g/dL
Platelets ≥75 × 103/mm^3
International normalized ratio ≤1.4
Sodium 135–145 mmol/L

Airway and Ventilation

Immediate tracheal intubation is necessary for severely head-injured patients, particularly those with GCS scores of 8 or less. Establishment of a definitive airway prevents aspiration of gastric content, allows control of end-tidal CO_2, and facilitates patient care and transfer.

Both hypoxemia (Pa_{O_2} <60 mm Hg) and hyperoxia (Pa_{O_2} >300 mm Hg) produce deleterious effects, and normal Pa_{O_2} should be targeted at all times. Moderate hyperventilation therapy (Pa_{CO_2} 30–35 mm Hg) is only indicated as a temporizing, lifesaving intervention in impending cerebral herniation pending definitive care, or to facilitate neurosurgical procedures. All other times the ideal target range for Pa_{CO_2} should be 35 to 45 mm Hg.

Anesthetic Agents

Hemodynamic stability is paramount; therefore judicious use of induction agent is indicated. The usual full induction dose is seldom necessary in brain-injured patients. Both propofol and etomidate can be used safely when titrated carefully to the patient's response. Both drugs decrease CBF and $CMRO_2$ and lower ICP. However, etomidate has a lower risk of untoward hypotension in TBI patients with polytrauma. A useful alternative is ketamine. The safety of ketamine in a controlled ventilation setting and in combination with other sedative agents has been established, as studies did not demonstrate any increase in ICP. A short-acting muscle relaxant should be used. Succinylcholine is preferred, and rocuronium is used when succinylcholine is contraindicated.

There are many options with regard to maintenance anesthetic agents and techniques in TBI patients. A combination of an opioid and a volatile anesthetic may be appropriate if the concentration of the volatile agent is kept less than 1 minimum alveolar concentration (MAC). Higher concentrations may cause cerebral vasodilation, or "luxury perfusion." Total intravenous anesthesia is the preferred option, as propofol is a potent indirect cerebral vasoconstrictor, but vasopressors may be needed to support blood pressure. Thiopental is equally effective, but it is no longer available in North America. Nitrous oxide is best avoided because it can increase the CMR and worsen ischemia; also, it may exacerbate existing pneumocephalus. It should be mentioned that anesthesia-induced pharmacologic neuroprotection so far has not yielded beneficial results in human studies.

Maintaining Adequate Cerebral Perfusion Pressure

The updated Brain Trauma Foundation guidelines (2007) advise keeping CPP between 50 and 60 mm Hg. To maintain CPP, there must be good intravenous access, and fluid resuscitation must replete intravascular volume as needed. Fear of worsening cerebral edema should never dissuade one from providing adequate fluid resuscitation. Ideally fluid resuscitation volumes should be goal directed, and close attention should be given to cumulative fluid balance in the first 96 hours after TBI.

Vasopressors and inotropes are often used along with fluid resuscitation to maintain CPP. However, they should be used with caution because they may increase the risk for acute respiratory distress syndrome. BP should be monitored and hypotension (systolic BP <90 mm Hg) avoided.

Ischemia is likely the final pathway in secondary brain injury. Therefore ideally the hematocrit should be between 21% and 25% to provide adequate oxygen delivery, although the threshold for transfusion remains controversial. If Cushing reflex is present in patients with acute subdural or epidural hematoma, BP may decline precipitously with surgical decompression. This is anticipated based on clinical findings (e.g., low GCS score, significant midline shift on CT, abnormal pupils), and preemptive intravenous fluid resuscitation should be undertaken. Prompt treatment of hypotension after surgical decompression with intravenous fluids and vasopressors or inotropes is essential.

Reducing Intracranial Pressure

Intracranial hypertension is defined as a sustained (>5 minutes) elevation of ICP above 20 mm Hg. To optimize CPP, ICP should be kept below 20 mm Hg while maintaining CPP in the 50 to 60 mm Hg range. An ICP monitor is indicated in patients with severe TBI who are comatose after resuscitation (GCS score <9) and have either abnormalities on cranial CT scan or meet at least two of the following three criteria: age greater than 40 years; systolic BP less than 90 mm Hg; or abnormal posturing. A recent international multidisciplinary consensus conference recommended that ICP and CPP should be monitored in patients at risk for ICP elevation based on clinical and/or imaging features to guide medical and surgical interventions.

Mannitol (0.25 to 1 g/kg) is useful for reducing brain tissue bulk and may decrease the production of cerebrospinal fluid; both of these effects reduce ICP. Mannitol is given after volume repletion. Hypertonic saline (HTS) (3% or 7.5%) appears to result in less rebound edema, longer-lasting effect, and fewer systemic side effects than mannitol, although it has not been shown to decrease mortality rates or improve ICP compared with other solutions in a recent meta-analysis.

Cerebral blood volume is reduced with acute hyperventilation, as CBF decreases by about 3% for each 1 mm Hg decline in arterial carbon dioxide tension. There is the potential for cerebral ischemia with excessive hyperventilation. Arterial carbon dioxide tension should not be decreased to less than 30 mm Hg, except for brief periods (e.g., impending herniation). Otherwise, normocapnia or slight hypocapnia (35 to 40 mm Hg) is desirable when ICP is less than 20 mm Hg. Other important techniques to reduce ICP are slight head-up and neutral neck positions to promote venous drainage and prevent venous obstruction, an often overlooked cause of elevated ICP. Many TBI patients have cervical collars in place, and it is important to inspect the collar to ensure that it does not impede venous drainage; a collar that is too tight can increase ICP. Circumferential endotracheal tube ties should be avoided for the same reason. In patients with increased ICP that is refractory to medical management, a decompressive craniectomy may be indicated.

Barbiturates or propofol given to suppress CMR can reduce ICP. Effects are optimal with burst suppression or an isoelectric electroencephalogram. Vasopressors may be required to support blood pressure with maximal CMR suppression. Low-dose propofol infusion is often used in TBI, because this allows effective ICP control while permitting prompt neurologic evaluation when required. However, metabolic syndromes characterized by myocardial dysfunction and lactic acidosis have been observed after prolonged propofol infusions, especially in children.

External ventricular drainage of cerebrospinal fluid can reduce ICP if the ventricles are not too compressed to prevent insertion. Lumbar spinal drainage catheter has also been reported with success, but the inherent risk of brainstem herniation is ever present with this technique, and therefore it is not advocated.

Mild to moderate hypothermia (33°C) has been extensively investigated both as a neuroprotective technique and as treatment for elevated ICP. Although positive results for the former indication continue to elude us, the efficacy for the latter indication is well established. For this to be effective, shivering must be treated vigorously, and ICP must be monitored closely during the rewarming phase.

Decompressive craniectomy (DC) should be considered in patients whose ICP elevation is refractory to medical management. This can be primary (bone flap removal during evacuation of intracranial hematoma) or secondary (subsequent removal because of sustained elevated ICP). This remains controversial, as improved survival is attained at the expense of increased proportions of patients with severe disability and poor quality of life. Both primary and secondary DC are subjects of ongoing clinical trials.

Correcting Coagulopathies and Managing Anemia

Acute coagulopathy of trauma and TBI-associated coagulopathy are both well-recognized phenomena and may result in significant coagulation dysfunction. Consumption coagulopathy and endogenous fibrinolysis appear to play a key role in the development of acute coagulopathy of trauma. In TBI large quantities of brain tissue thromboplastin is released into the bloodstream, causing disturbance in coagulation processes. In addition, damaged cerebral endothelium activates platelets, as well as clotting cascades, to produce intravascular thrombosis and depletion of coagulation factors.

Coagulopathies increase the morbidity associated with any surgery in TBI patients. Coagulation should be followed closely, and any deficient factors should be replaced aggressively. Some surgeons advocate early replacement of platelets and clotting factors based solely on clinical observations.

A recent meta-analysis based on two tranexamic acid (TXA) trials demonstrated a statistically significant reduction in intracranial hematoma progression but no statistically significant improvement in clinical outcome. An international, multicenter, phase III trial (CRASH-3) is currently underway to evaluate the use of TXA on death and disability in 10,000 patients with TBI.

Anemia is common in the acute period after TBI, affecting up to 50% of patients. Currently available evidence supports a target hemoglobin threshold level of 7 to 9 g/dL. Targeting hemoglobin levels greater than 10 g/dL after TBI has not been shown to result in improved neurologic outcomes and is associated with an increased risk of thromboembolic events and progressive hemorrhagic injury.

Treating Hyperglycemia

Dextrose-containing intravenous solutions should be avoided during fluid resuscitation. They may cause hyperglycemia and worsen cerebral ischemic injury. Current guidelines advise keeping blood glucose at 120 to 180 mg/dL. Patients under general anesthesia require frequent assessment of the serum glucose levels.

Restoring Normothermia

Clearly, hyperthermia is harmful to patients at risk for ischemic brain injury. Any beneficial effects of hypothermia are less clear. Despite having the potential to improve ICP, functional recovery has been reported to be poor and multiple clinical trials in TBI have demonstrated the futility of hypothermia utilization in addition to standard care. As mentioned, hypothermia may still be indicated to enhance the beneficial effects of pharmacotherapeutics when used in conjunction with other techniques to reduce ICP (e.g., DC, mannitol, propofol, barbiturate coma). The efficacy may vary, depending on specific patient populations, injury severity, and injury characteristics (focal vs. diffuse). However, hypothermia may cause coagulopathy, which is undesirable in patients who are already susceptible to such abnormalities. Hypothermia also increases the risk of infection, and cooling patients to less than 35°C may lower $PbrO_2$ owing to a leftward shift of the hemoglobin-oxygen dissociation curve. Given the inconclusive evidence for hypothermia, we advise keeping temperature in a low-normal range (35°C to 36°C), unless indicated for control of elevated ICP.

Delaying Nonemergent Medical Procedures and Systemic Effects of TBI

In general, the benefits of nonneurosurgical procedures in patients with severe TBI and unstable ICP must be weighed against the risk of further injury to the brain. Nonemergent procedures should be delayed in unstable TBI patients. These patients should be admitted to the ICU, where they can be resuscitated, their coagulation parameters normalized, and ICP brought under control. It is important to recognize that even in the absence of direct extracranial injury, more than 80% of patients with severe TBI may develop significant organ dysfunction involving the cardiovascular, respiratory, immunologic, hematologic, and endocrinologic systems, among others. Systemic complications influence the early management and are independently associated with worse outcomes.

Borderline patients may undergo damage control orthopedic procedures using external fixation to minimize further insult to the body while the patient's physiology recovers from the initial trauma.

MANAGEMENT OF THE CASE SYNOPSIS

This patient should be assessed quickly for volume status and resuscitation implemented if indicated. Severe pelvic fracture may result in exsanguinating blood loss and should be investigated promptly. It may require immediate interventional radiology for intravascular occlusion. Invasive arterial BP monitoring should be instituted, but placement of a central venous catheter is optional and should not cause delay in the surgical procedure. Blood should be available for transfusion. A total intravenous anesthetic with propofol and opiates is an appropriate anesthetic regimen. Hypotension following decompression may occur, and good communication between the surgical and anesthetic team is essential. Coagulation should be monitored and any abnormality immediately corrected. Normothermia to mild hypothermia should be maintained. Serum glucose should be monitored and treated as indicated. A primary DC may be indicated, and it is optimal to transport the patient directly from the operating room to the neurocritical care unit postoperatively for further management. At the end of the case an ICP monitor may or may not be inserted, depending on the brain condition and whether primary DC was performed.

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59 Hemodilution and Blood Conservation

Bryan S. Ahlgren • Glenn P. Gravlee

Case Synopsis

A 61-year-old, 80-kg man is scheduled for removal and replacement of a total hip prosthesis. He is concerned about blood transfusion and the transmission of infectious diseases, particularly human immunodeficiency virus (HIV). He requests that transfusion of homologous blood be avoided, if possible. He predonated 2 units of autologous blood. During surgery, blood loss is more than 2000 mL, and the hemoglobin level is 7.5 g/dL after both units of autologous blood are given. Vital signs and urine output remain within normal limits. An additional 500 mL of intraoperative blood loss is expected.

PROBLEM ANALYSIS

Definition, Recognition, and Risk Assessment

Complications arising from the transfusion of homologous (also called allogeneic) blood products have been recognized since the beginning of modern transfusion therapy. Bacterial blood contamination was fairly common before the introduction of refrigerated storage and sterile plastic bags. Subsequently, contamination with viruses (e.g., cytomegalovirus, hepatitis B and C, HIV, and human T-cell lymphotropic virus) became a source of greater morbidity. Now, West Nile virus and possibly variant Creutzfeldt-Jakob disease have been added to the list of viral diseases transmissible by blood transfusion. Fortunately, improvements in donor screening and blood component testing have reduced the risk of both HIV and hepatitis C transmission to less than 1 per 1 million units, and that for hepatitis B to about 1 per 137,000 units. Cytomegalovirus remains prevalent in the blood pool, but its transmission is generally not a problem in the absence of clinical immunosuppression. Nevertheless, many blood banks now routinely apply leukoreduction techniques to all cellular blood components before dispensing them, which has greatly reduced the risk of cytomegalovirus transmission. Thus viral transmission by blood transfusion is now so rare that bacterial contamination once again poses the highest risk for infectious complications, which is 1 in 30,000 red blood cell (RBC) units and 1 in 2000 to 3000 platelet units, although transmission of actual clinical infection rates are substantially lower than that (approximately 1 in 5 million for RBC units and 1 in 100,000 platelet units). Blood group incompatibility and anaphylactic reactions remain rare.

Implications

Considerable evidence supports immunosuppression as a significant consequence of blood transfusion. This increases the risk of cancer recurrence and of bacterial infection among transfusion recipients.

Large blood loss and hemodilution also raise the question of what constitutes a reasonable minimum hemoglobin level in an anesthetized patient with acceptable intravascular volume and vital signs. This is a surprisingly complex issue, but in general, healthy patients safely tolerate hemoglobin concentrations as low as 6 g/dL. Sicker patients may require hemoglobin concentrations as high as 10 g/dL.

Assuming that the hypothetical patient described in the case synopsis is otherwise healthy, the limiting factor may be the rate and predictability of blood loss, because some margin of safety is desirable if sudden additional blood loss should occur. Also, one must consider the possibility of significant postoperative bleeding. Consequently, the patient's hemoglobin concentration of 7.5 g/dL signals the possible need for homologous transfusion, unless shed blood is being effectively salvaged.

MANAGEMENT

This section focuses on available techniques (Table 59.1) and a cost-benefit analysis of autotransfusion techniques that may reduce or avoid the need for homologous RBC or blood component therapy.

Autologous Predonation

Patients can donate blood up to 42 days before operation, which constitutes the maximum storage period for modern anticoagulant and storage solutions. The frequency and amount of donation depend on the patient's ability to tolerate serial phlebotomy while maintaining an adequate hemoglobin level. Typically, a patient donates 2 units of blood per week starting 2 to 4 weeks before surgery. The minimum recommended hemoglobin level for donation is 11 g/dL. To maintain this level, patients are routinely given iron supplementation. Erythropoietin can be used to increase hemoglobin levels during predonation, which enables patients to donate more units; this is expensive, however, costing approximately $800 per unit of erythropoietin "manufactured." Erythropoietin augmentation of autologous predonation may be justified if some combination of the following factors exists:

TABLE 59.1 Autotransfusion Techniques

Technique	Cost	Risk	Advisability[a]
Autologous predonation	Moderate	Low	Yes
Acute normovolemic hemodilution	Low	Low	No
Intraoperative salvage	High	Low	Yes
Postoperative salvage, unwashed	Low	Moderate	No
Postoperative salvage, washed	Moderate	Low	Yes

[a]For the patient described in the case synopsis.

- The preoperative timeline is short (e.g., cancer resection).
- Homologous transfusion is not possible (e.g., Jehovah's Witness).
- The patient is anemic.
- The anticipated surgical blood loss is large (>2000 mL).

Autologous predonation is most effective at avoiding homologous transfusion when used in combination with other autotransfusion techniques, such as intraoperative blood salvage. The cost-effectiveness of autologous donation varies widely, but it often fails to meet the usual standards of efficacy. For this reason, its popularity has waned. The donation itself carries a hospitalization risk of approximately 1 in 17,000, which is 12 times that for community donations by healthy individuals. Even though the blood is autologous, its use still incurs some of the usual homologous transfusion risks, including bacterial contamination or clerical errors leading to incompatible blood transfusions. Compared with allogeneic blood units, autologous units typically require the same testing procedures but more complex storage and identification procedures, so the cost for each unit is higher.

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) involves the removal of blood just before or after the induction of anesthesia, combined with volume replacement using crystalloid or colloid. The technique requires standard anesthesia monitors (electrocardiogram, blood pressure, pulse oximetry, and temperature) and large-bore intravenous access with a 14- or 16-gauge peripheral or central venous catheter. Blood is collected into standard citrate-phosphate-dextrose bags. Collected blood can then safely be stored at room temperature for up to 8 hours or frozen if not transfused. Whole blood stored at room temperature should be constantly agitated (placed on shaker) to ensure platelet function.

The rationale for ANH is that the patient will be losing fewer RBCs into the surgical field because shed blood has a lower hematocrit due to hemodilution. Assuming that the lowest hematocrit remains acceptable (>20%) and that intravascular volume also remains intact, tissue perfusion will be maintained (and perhaps enhanced). Also, oxygen delivery will be sufficient owing to reduced blood viscosity. Additional clinical advantages include low cost, simple storage, and ease of transportation and record keeping.

Acute normovolemic hemodilution risks hypovolemia if volume replacement is inadequate. Further, the obligatory drop in hemoglobin concentration could induce unanticipated end-organ ischemia if there is an undiagnosed condition such as critical stenosis of a coronary artery or carotid artery. Mathematical analyses strongly suggest that the blood loss savings are fairly minor unless this technique is used quite aggressively—for example, hemodilution from a starting hematocrit of 40% to one of 20% or lower. Typically, this would require withdrawing 6 to 10 500-mL bags of blood. One study found no difference in allogeneic transfusion exposure when 3 units of acute normovolemic hemodilution were compared with a similar volume of autologous predonation in patients undergoing total hip arthroplasty.

Postoperative Blood Salvage

This technique involves the collection and reinfusion of blood shed postoperatively. The blood is collected through a relatively large filter and reinfused through a small-pore filter. This blood can be reinfused unmodified ("unwashed"), or it can be washed and concentrated in the same way as for intraoperative blood salvage.

Reinfused blood typically contains very low concentrations of plasma coagulation factors and platelets. It also contains elevated levels of fibrin degradation products, free hemoglobin, and inflammatory products such as cytokines. With total hip arthroplasty, it might also contain fat and bone spicules. As a result, many clinicians elect to administer salvaged blood only after it has been washed. This somewhat controversial technique reduces the need for allogeneic blood only when postoperative blood losses are large (e.g., >1000 mL), because postoperatively shed blood typically has a hematocrit of 15% to 20%.

Intraoperative Blood Salvage

This method involves using a suction apparatus to collect the patient's blood as it is shed intraoperatively into the surgical field. An anticoagulant solution is added to the shed blood, and it is then stored in a filtered reservoir. Once an adequate amount of blood has been collected (typically >700 mL), it is washed and concentrated so that the final product usually has a hematocrit between 55% and 70%.

Because intraoperative blood salvage conserves RBCs but not plasma or platelets, a dilutional coagulopathy should be anticipated if blood losses approach or exceed one blood volume. Otherwise, the risks of this technique are low if appropriate procedures and standards are followed and the blood is not contaminated with bacteria. The ability to conserve RBCs with this technique depends largely on the surgeon's ability to capture shed blood using suction. In this regard, total hip arthroplasty is in an intermediate category between laparotomy for aortic aneurysm repair, where blood pools in a body cavity and is easily captured, and a more superficial procedure such as reduction mammoplasty, where blood typically runs off the surgical field onto the drapes or is absorbed by sponges.

PREVENTION

Often, clinicians fail to appreciate how much blood loss can be safely tolerated by patients before the need for transfusion. This can be estimated using the following formula:

$$ABL = V \times (H_i - H_d) / H_m$$

where ABL is allowable blood loss; V is blood volume; H_i and H_d are the initial and lowest desired hematocrit values, respectively; and H_m is the hematocrit average of H_i and H_d. Assuming a blood volume of 5600 mL (80 kg × 70 mL/kg), an H_i of 40%, and an H_d of 25%, the patient in the case synopsis can tolerate a blood loss of almost 2600 mL without transfusion therapy. Intraoperative RBC salvage increases this figure in direct proportion to the efficacy of salvage.

Autologous Predonation

In retrospect, if one could have predicted the amount of blood loss experienced by the patient in the case synopsis based on the surgeon's track record with reoperative hip arthroplasties, the patient should have been given supplemental iron therapy and predonated 3 or 4 units

of autologous blood over 3 to 4 weeks before surgery. If the patient's original hematocrit was less than 40%, supplementation with erythropoietin would have been reasonable, although health insurance policies often do not cover the cost of erythropoietin used for this purpose.

Acute Normovolemic Hemodilution

Arguably, the most common application of this procedure is to withdraw 2 units in smaller patients (e.g., those <70 kg) and 3 units in larger ones. This saves 1 to 2 units of allogeneic packed RBCs if the intraoperative blood loss is between 3000 and 6000 mL, which crudely approximates one-half to one normal blood volume. As blood losses exceed 6000 mL, the number of units saved gradually diminishes (to 0.5 to 1 unit) with this technique.

Initially, one bag containing approximately 450 mL of blood is collected. As this is occurring, either 500 mL of colloid solution or about 1500 mL of crystalloid solution is infused into the patient to maintain intravascular volume. Hypotension or tachycardia suggests inadequate volume replacement. The exchange continues to the desired end point, as long as the patient tolerates the procedure. Checking the hematocrit or hemoglobin concentration periodically is advisable to reassess the appropriateness of the calculated end point. The blood is then stored at room temperature if it will be used within 8 hours; otherwise, refrigerated storage is required.

Intraoperative Blood Salvage

In the case presented here, intraoperative blood salvage may offer the best chance of respecting the patient's wish to avoid homologous blood. Further, effective use of this technique tends to override any theoretical benefits of acute normovolemic hemodilution. Alternatively, if the patient is otherwise completely healthy, one might "tough it out" to a hematocrit as low as 20%. Considering this patient's age, however, reducing the hematocrit below that level is probably ill advised.

Postoperative Blood Salvage

Because the cost of this technique is low and the likelihood of substantial postoperative bleeding is high in the patient described in the case synopsis, postoperative salvage is appropriate. Wound drainage contains various undesirable elements, however, so washing the product before reinfusion is advisable. Bacterial contamination can also occur, so this strategy should be avoided unless the drainage exceeds 500 mL over an 8-hour period. After this time, the collection device should be replaced if reinfusion is planned.

Alternative Blood Conservation Techniques

Other potential blood-conserving options are listed in Table 59.2. Moderate deliberate hypotension is reasonable if the patient is otherwise healthy; for a patient in his 60s, however, setting a relatively conservative lower mean arterial pressure limit, in the range of 70 mm Hg for 1 to 2 hours, might be prudent.[a] Another reasonable approach for deliberate hypotension might be to reduce the mean arterial pressure by about 20% below the patient's preoperative baseline level, which could probably be safely sustained for several hours if necessary. Tranexamic acid can also reduce blood loss with a low risk of complications, and has been shown in numerous studies to decrease the need for allogeneic blood transfusion in joint arthroplasty procedures.

TABLE 59.2 Other Potential Blood Conservation Techniques

Technique	Cost	Risk	Advisability[a]
Induced hypotension	Varies	Varies	Questionable; patient's age is cause for some concern
Prophylactic tranexamic acid	Moderate	Low	Unclear; reduces blood loss, but expensive
Spinal or epidural anesthesia	Low	Low	Facilitates blood pressure control; reduces deep vein thrombosis

[a]For the patient described in the case synopsis.

[a] Because our hypothetical patient is male and older than 60 years, and assuming no coronary artery disease or risk factors for it (hyperlipidemia, hypertension, or smoking history), another way to estimate the minimal acceptable pressure for deliberate hypotension (i.e., that required to maintain coronary perfusion pressure) is diastolic blood pressure minus left ventricular end-diastolic pressure = 50 mm Hg. The value for adequate coronary perfusion pressure may be higher in patients with advanced age, diastolic heart failure, or a strong family history of coronary artery disease, hypertension, or other heart disease (all associated with some amount of elevated left ventricular end-diastolic pressure).

Further Reading

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Intracranial Aneurysms: Rebleeding

60

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Case Synopsis

A 55-year-old man undergoing craniotomy for clip-ligation of a right anterior communicating artery aneurysm 12 hours after initial subarachnoid hemorrhage becomes acutely hypertensive and experiences bradycardia during the induction of anesthesia.

PROBLEM ANALYSIS

Definition

Intracranial aneurysms are outpouching of arteries developing secondary to turbulent flow and hemodynamic stress. *Aneurysmal rebleeding* is defined as a rerupture of the aneurysm, causing sudden clinical deterioration (a decrease in Glasgow Coma Scale [GCS] score in awake patients) with a concomitant increase of subarachnoid, intracerebral, or intraventricular blood.

Rebleeding raises intracranial pressure (ICP), leading to impairment of cerebral perfusion, causing neurologic deterioration. Many complications may ensue (Table 60.1). Sudden clot deposition throughout the subarachnoid space blocks the passage of cerebrospinal fluid (CSF) through the basal subarachnoid cisterns, producing acute hydrocephalus. Brain infarction may also occur due to direct, hematoma-induced brain destruction or shifts in the intracranial contents, along with vascular compromise. The larger the volume of subarachnoid blood and the greater the ICP, the more likely it is that cerebral blood flow (CBF) will be reduced and the patient's neurologic condition will worsen. Subarachnoid hemorrhage (SAH) also impairs autoregulation, the ability of the brain to maintain CBF fairly constant over mean arterial pressures (MAPs) between 50 and 150 mm Hg.

Epidemiology

Overall prevalence of unruptured intracranial aneurysms is 3.2%, and subarachnoid hemorrhage (SAH) from the rupture of an intracranial aneurysm (ICA) occurs with a frequency of 0.002% to 0.016% in most Western populations. Rates of ICA rupture are 0.05% to 6% per year, depending on the size and location of the aneurysm. Most (80% to 85%) of the ICAs are located in the anterior circulation, with a propensity to rupture when larger than 7 mm. The risk of rupture is 11 times greater in patients who present with a previous SAH than in those patients who present with symptomatic unruptured aneurysms.

Rebleeding following SAH can be catastrophic, with poor prognosis for functional recovery in survivors, and carries a mortality rate of greater than 60%. The risk of rebleeding is maximal in the first 2 to 12 hours, with up to 13.6% within the first 24 hours and up to 23% over the first 72 hours. In fact, more than one-third of rebleeds occur within 3 hours and nearly half within 6 hours of symptom onset, and early rebleeding is associated with worse outcome than later rebleeding. Van Donkelaar and colleagues suggested that a modified Fisher grade of 3 to 4 (Table 60.2) was a predictor for an in-hospital rebleeding within 24 hours after onset of prodromal signs. Also, the initiation of external cerebrospinal fluid drainage was independently associated with a rebleeding within 24 hours. In their study, cumulative in-hospital rebleeding rates were 5.8% within 24 hours and 1.2% between 24 to 72 hours after onset of prodromal signs. Early treatment of the ruptured aneurysm can reduce the risk of rebleeding. In the Cerebral Aneurysm Rerupture After Treatment (CARAT) study, recurrent aneurysmal SAH (aSAH) was predicted by incomplete obliteration of the aneurysm and occurred a median of 3 days after treatment but rarely after 1 year. Patients with adequately obliterated aneurysms after aSAH have a low risk of recurrent aSAH for at least 5 years, although some coiled aneurysms require retreatment. In patients presenting later for definitive treatment, during the vasospasm window, delayed obliteration of aneurysm is associated with a higher risk of rebleeding than early obliteration of aneurysm. If untreated, 50% of ruptured ICAs rebleed within 6 months of the initial SAH. About 20% to 30% of ruptured ICAs rebleed within 30 days of the initial SAH. Another 10% to 15% of patients rebleed during the ensuing 5 months.

The incidence of intraoperative aneurysm rupture (IAR) ranges from 6% to 8%. It varies among institutions and depends on the size and location of the aneurysm. It results from a complex interaction of etiologic factors of aneurysm formation, as well as factors related to anesthesia, surgery, or other interventions. Surgical causes of aneurysm rupture and rebleeding, in decreasing order of frequency, are dissection, brain retraction, hematoma evacuation, and opening of the dural and arachnoid membranes. Induction of anesthesia can precipitate IAR (1% to 2% incidence), with very poor prognosis and mortality rate of 75%. The majority of ruptures occurred during coughing on intubation, indicating that airway manipulation and the resultant sympathetic surge could be the contributing factor.

Recognition

Signs of rebleeding with reruptured ICAs are largely due to intracerebral hemorrhage. This is because adhesions from the prior SAH seal off the aneurysm from the subarachnoid space and deflect any new bleeding into the brain parenchyma.

After ICA rebleeds, the level of consciousness (GCS score) deteriorates in an awake patient, and patients develop focal neurologic deficits (aphasia, hemiplegia), abnormal vital signs (hypertension, bradycardia, arrhythmias, irregular respirations), and temperature elevation. They also have fluid and electrolyte imbalance (especially hyponatremia), and retinal hemorrhage may be evident on ophthalmologic examination (Box 60.1). Patients in an already poor clinical condition

TABLE 60.1 Complications of Subarachnoid Hemorrhage

Early	Late
Hematoma, ↑ ICP, rebleeding, seizures, hydrocephalus	Rebleeding, hydrocephalus, vasospasm, infarction, epilepsy
Nerve palsy, hemiparesis, reduced LOC	Permanent hemiparesis, cognitive disabilities
Cardiac arrhythmias	Myocardial infarction, pneumonia, hepatic and renal dysfunction
Transient ↑ BP	Persistent ↑ BP
Impaired vision	Vitreous hemorrhage
Fluid and electrolyte imbalance	Neurologic deterioration, death

BP, Blood pressure; *ICP,* intracranial pressure; *LOC,* level of consciousness.

TABLE 60.2 The Fischer Scale (Computed Tomography Scan Appearance of Hemorrhage)

Group 1	No blood detected
Group 2	Diffuse deposition of subarachnoid blood less than 1 mm thick
Group 3	Localized clots and/or vertical layers of blood 1 mm or greater in thickness
Group 4	Diffuse or no subarachnoid blood, but intracerebral or intraventricular clots are present

and who are intubated and sedated and closely monitored in the intensive care unit may already have an external ventricular catheter. In case of a sudden change of blood pressure (BP), pupil size, or fresh blood coming out of the CSF drainage system, computed tomography would confirm a rebleeding.

If ICA rebleeding occurs during or immediately after the induction of anesthesia, the patient's BP will increase, and the heart rate may or may not decrease. It is important to realize that the ICP will also increase. At this juncture, ICA rupture is diagnosed by intracranial Doppler ultrasonography, and the efficacy of management is monitored thereafter. Intraoperative rupture of an ICA is readily apparent. Rebleeding after completion of the operation is signaled by failure to awaken from anesthesia or by further neurologic deterioration after awakening (e.g., decrease in level of consciousness, development of new focal neurologic deficits or aphasia).

Risk Assessment

ICA rerupture is one of the major causes of neurologic deterioration after initial SAH (Box 60.2). Hypertension is the most important risk factor for aneurysm rupture and rebleeding. The likelihood of rebleeding is directly related to the patient's systolic BP in the post-SAH period. For patients who have already had multiple rebleeding episodes, the likelihood of further rupture and death is much greater. Risk of early rebleeding is higher in patients with poor-grade SAH, longer time to aneurysm treatment, worse neurologic status on admission, initial loss of consciousness, larger aneurysms, sentinel bleeds, possibly systolic BP greater than 160 mm Hg, and those who undergo angiography within 3 hours of the onset of symptoms. Genetic factors, although related to the occurrence of ICAs, do not appear to be related to an increased incidence of rebleeding. Other risk factors include female gender (twice the incidence of rebleeding versus males), poor medical condition, older age, posterior ICA, higher rates of intracerebral or intraventricular hematoma, and abnormal clotting parameters. During pregnancy, the risk of rebleeding from an unsecured ICA is 33% to 50%. Although this is fatal in 50% to 68% of patients, there is no evidence that the rebleeding rate in pregnant patients is different from that in the general population.

BOX 60.1 Effects of Aneurysmal Rebleeding

- Direct brain destruction
- Disturbance of CSF flow → hydrocephalus
- ↑ ICP from hematoma, intracerebral hemorrhage, intraventricular hemorrhage
- Cerebral infarction from ↓ CBF
- Fluid and electrolyte imbalance
- Cardiac arrhythmias, ↑ BP
- Respiratory impairment

BP, Blood pressure; *CBF,* cerebral blood flow; *CSF,* cerebrospinal fluid; *ICP,* intracranial pressure.

BOX 60.2 Causes of Neurologic Deterioration After Subarachnoid Hemorrhage

- Rebleeding—intracranial hypertension
- Hematoma
- Hydrocephalus
- Cerebral edema
  - Seizures
  - Meningitis
- Disordered autoregulation
- Disordered carbon dioxide responsiveness
- Acid-base disturbances
- Fluid and electrolyte disturbances
- Vasospasm
- Delayed ischemic deficit
- Cerebral infarction—secondary cerebral insults
  - Hypotension
  - Hypoxemia
  - Hyperglycemia
  - Intracranial hypertension (beyond initial hemorrhage)

BOX 60.3 Predictors of Mortality After Acute Subarachnoid Hemorrhage

- Poor clinical status or grade on admission—directly related to size of hematoma
- Decreased level of consciousness
- Elevated blood pressure
- Rebleeding
- Delayed ischemic deficit (vasospasm)
- Thickness of subarachnoid clot on initial computed tomography scan
- Basilar aneurysm
- Older age
- Preexisting medical illness

Implications

Pathophysiologic sequelae and complications of rebleeding after initial aneurysmal SAH are considerable. Because a recurrent hemorrhage is usually more severe than the initial one, mortality rate with recurrent hemorrhage doubles to 80%, with significant associated morbidity in the surviving patients. The size of the hematoma is the most critical factor in determining outcome (Box 60.3). Patients with large subdural hematomas and more of a midline shift on computed tomography scanning have a poorer prognosis, as do those with associated intracerebral or intraventricular hemorrhage.

Because the majority of rebleeding takes place within the first 6 to 24 hours after the initial SAH, early intervention to secure the aneurysm (whether by surgical clipping or endovascular coiling) has become the mainstay of treatment for rebleeding. Thus diagnosis and treatment of rebleeding must be accomplished quickly

and efficiently. Further, because increased experience with SAH, its sequelae, and its treatment improves patient care, collaborative relationships between community hospitals and centers specializing in the surgical and endovascular treatment of ICAs are mandatory.

PREVENTION

The American Heart Association (AHA) and the Neurocritical Care Society (NCS) released guidelines for the management of aneurysmal subarachnoid hemorrhage in 2012 to provide evidence-based guidelines for the care of patients presenting with SAH. Rebleeding is associated with very high mortality, with poor prognosis for functional recovery. The highest risk of rebleeding occurs within the first 12 hours. Early surgical or procedural treatment of a ruptured aneurysm reduces the risk of rebleeding. The International Subarachnoid Aneurysm Trial (ISAT) provides convincing evidence that coiling provided better clinical outcomes that clipping, though clipping should be considered with large intraparenchymal hematomas and middle cerebral aneurysms. Institution of emergency neurologic life support includes prompt and early recognition of SAH, control of pain and anxiety, Hunt and Hess or World Federation of Neurologic Surgeons Scoring, early airway management (including intubation for deteriorating neurologic score), inability to protect airway, and need for hyperventilation for treatment of intracranial hypertension or treatment of hypoxia. Other measures to reduce risk of rebleeding include close BP control with maintaining cerebral perfusion pressure, early treatment with a short course of antifibrinolytics, and seizure prophylaxis. In a prospective randomized study of use of tranexamic acid that included early treatment with a short course of antifibrinolytics (tranexamic acid), early rebleeding rates and adverse outcomes were reduced when the drug was administered immediately after SAH.

Though the incidence of seizure is low, if seizures do occur, the result can be catastrophic. Seizures may result in rebleeding of aneurysm and will cause increase in ICP. AHA and NCS recommend consideration of prophylactic anticonvulsants in the immediate posthemorrhagic period. Routine use of seizure prophylaxis remains controversial, however. Prophylactic phenytoin was independently associated with worse cognitive outcomes. Phenytoin and other anticonvulsants have been associated with vasospasm, delayed cerebral ischemia, and fever.

Therapy for rebleeding after an initial SAH is designed to maintain cerebral perfusion, reduce intracranial hypertension and volume, control systemic blood pressure, and decrease transmural pressure (MAP – ICP) across the aneurysm wall. Within this context, optimization of brain O_2 delivery depends on total arterial O_2 content and necessitates the maintenance of normal hemoglobin concentrations and arterial O_2 saturations.

Avoidance of lumbar puncture and rapid ventricular drainage before ICA clip-ligation may also protect against rebleeding. However, these measures are sometimes used to lower ICP (as a calculated risk), when cerebral perfusion is seriously compromised by intracranial hypertension.

Interventions to prevent rebleeding are also necessary during ICA manipulation for clip-ligation. Temporary proximal occlusion of the parent vessel is used to decrease the turgor of the ICA sac, and the blood pressure is maintained in the patient's high-normal range to enhance distal and collateral perfusion. Of course, if the temporary clip is removed before the aneurysm has been secured, blood pressure must be quickly returned to the patient's low-normal range to prevent aneurysmal rupture.

To the regimen of normotension, normovolemia, and mannitol, some neurosurgeons have added electroencephalographic burst suppression, with reported benefit. Propofol, if administered to provide burst suppression before temporary ICA occlusion, may also confer cerebral protection. Normoglycemia and relative hypothermia to 35°C may also reduce the ischemic risk with temporary occlusion of cerebral vessels.

MANAGEMENT

Intraoperative or Intraprocedural Aneurysmal Rupture

There is little literature or data that guides the anesthesiologist in the immediate management of an intraoperative or intraprocedural aneurysmal rupture. Chowdhury and colleagues provide a nice review of the controversies surrounding the management of these patients. Hypertension is the most important risk factor for rupture. Systemic hypertension increases the transmural pressure gradient (TMPG) when ICP remains the same. Sudden fluctuations in TMPG can cause rupture. TMPG can increase if systemic BP increases suddenly or intracranial pressure decreases suddenly. It is vital that both BP and ICP are controlled.

Monitoring and controlling BP is necessary to balance risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure. Invasive arterial BP monitoring, along with agents to control hypertension, is necessary on induction of anesthesia. Be aware of perioperative episodes that may acutely increase cause hypertension: intubation, positioning, skull pin fixation, skin incision, and periosteal dissection.

It is unknown what the optimal BP is that would reduce the risk of rebleeding, though AHA/NCS guidelines suggest that BP less than 160 mm Hg is reasonable. There are many titratable antihypertensive medications available to use. Nicardipine, a dihydropyridine calcium-channel blocking agent similar to nifedipine, is a popular and smooth agent to use to control BP. It has been studied in controlling BP in patients with SAH. Nicardipine also seems to be safe except for very few transient and easily addressed complications, such as hypotension, arrhythmia, and tachycardia. Nicardipine is more selective for cerebral and coronary blood vessels. Furthermore, nicardipine does not intrinsically decrease myocardial contractility. Additionally, intravenous nicardipine reduced the incidence and severity of delayed cerebral arterial narrowing in patients following aneurysmal SAH.

Labetalol, a mixed α-/β-adrenergic antagonist, is commonly used to control hypertension in patients with SAH. Labetalol decreases BP by decreasing systemic vascular resistance with little effect on stroke volume, heart rate, and cardiac output. Studies have evaluated the efficacy in BP control between labetalol and nicardipine. Ortega-Gutierrez and colleagues found both agents to be equally effective and safe for BP control in SAH and intracranial hemorrhage during the initial admission hours, though for better BP control a combination of both agents may be needed. However, other investigators found nicardipine to be superior. Nicardipine led to a more rapid response to therapy and fewer treatment failures associated with superior BP control versus labetalol in SAH.

Clevidipine, an ultrashort-acting calcium channel blocker, is another option. Clevidipine controlled systolic BP in all patients with aneurysmal SAH in less than 22 minutes and kept it within the elective range 70% of the time without major complications. Clevidipine is currently undergoing a phase 2 study to determine whether it will decrease or have an effect on vasospasm.

Other agents used to treat increased BP include boluses of intravenous medication such as hydralazine 10 mg via intravenous push or enalapril 1.25 mg intravenously. Nitroprusside, once commonly used, has now been replaced by the newer titratable antihypertensives.

Controlling ICP is as important as controlling hypertension in preventing increases in TMPG. ICP can be measured using a lumbar drain or an intraventricular bolt and is helpful in balancing BP and ICP to maintain cerebral perfusion pressure (MAP-ICP) and guides BP management. Decrease in ICP may result from rapid administration of mannitol or from excessive hyperventilation before dural opening. Rapid draining of CSF from a drain may also change ICP. Few data suggest that changes in ICP are a major cause of aneurysmal rupture; nonetheless, it is advisable to proceed with maneuvers that decrease ICP slowly and with caution.

The management of a ruptured aneurysm depends on the time of the rupture intraoperatively.

Rupture Before Dural Opening

Aneurysmal rupture in a closed skull produces sudden increases in ICP and risk of cerebral perfusion, leading to cerebral ischemia and neuronal injury. Management goals would be to decrease ICP and institute neuroprotective strategies.

Decrease ICP: Hyperventilation, intravenous anesthetics using remifentanil, propofol-induced burst suppression

Neuroprotective strategies: Secondary neuroprotection—control BP, prevent hematoma expansion, optimize tissue oxygenation (cerebral oxygenation monitoring may help guide hyperventilation), control hyperglycemia (avoid blood sugar >150), and avoid hypoglycemia (blood sugar <80)

Primary neuroprotection that targets processes such as excitotoxicity, oxidant stress, and inflammation has not been promising to date.

Hypothermia is a potent mechanism to decrease cerebral metabolism and stabilize neuronal membrane potentials. The International Hypothermia for Aneurysm Surgery Trial (IHAST) evaluated mild systemic hypothermia as a treatment to protect the brain against ischemic injury during craniotomy for treatment of ruptured cerebral aneurysm. IHAST concluded that mild systemic hypothermia (33°C) does not improve neurologic outcomes compared with maintaining normothermia (target temperature 36.5°C) and should not be routinely applied. Any increase in temperature above normal should be promptly reduced.

Prompt surgical rescue clipping is the key factor in determining outcome.

Intraprocedural Rupture of Cerebral Aneurysm During Embolization

Intraprocedural aneurysm rupture may cause a sudden and massive rise in BP with or without bradycardia.

Prompt reversal of heparin anticoagulation: platelet administration to reverse antiplatelet activity

Minimize cerebral metabolism: intravenous anesthetics using remifentanil and propofol-induced burst suppression

Control abrupt increases in ICP: modest hyperventilation, osmotic diuresis

BP control: lower BP below 160 mm Hg—avoid aggressive control as it may induce cerebral ischemia

Surgical intervention

Rupture After Dural Opening

An open skull and dura may better accommodate an intraoperative rupture. Most ruptures occur during dissection, clip placement, dural opening, or retractor placement.

Neuroprotective strategies: Intravenous anesthetics using remifentanil and propofol-induced burst suppression, optimize tissue oxygenation (cerebral oxygenation monitoring may help guide hyperventilation), and control hyperglycemia.

Maintain normotension: Prompt reduction in BP to MAP 50 to 60 mm Hg has been advocated in the past, but this strategy may have a detrimental effect on cerebral perfusion pressure, especially in the setting of impaired cerebral autoregulation. Minimize the degree and duration of hypotension.

Maintain normovolemia: Any blood loss is replaced immediately with blood products to keep hemoglobin between 8 and 10 g/dL, colloid (albumin), or crystalloid. It is essential to maintain normal blood volume.

Maintain euglycemia and normal electrolyte balance.

Clip application or temporary occlusion: This can be difficult depending on the time of the rupture. This may be facilitated by transient flow arrest using adenosine. Recommended starting dose of adenosine is 0.3 to 0.4 mg/kg with remifentanil- and propofol-induced burst suppression.

Postoperative Management

In the immediate postoperative period, cerebrovascular imaging may be necessary. The patient who has experienced a rebleed should remain intubated and be monitored with continued intensive treatment for stroke-related conditions in the intensive care unit.

After securing the ICA, the patient can receive prophylaxis against or treatment for cerebral vasospasm, such as hypertensive hypervolemic hemodilution ("triple H therapy"), without fear of ICA rerupture. Vasospasm following SAH is a very important source of morbidity and mortality. Initiation of nimodipine and maintenance of normovolemia and avoiding hypotension is critical in minimizing delayed cerebral ischemia associated with vasospasm. Too often, the first sign is a neurologic deficit, which may be too late to reverse. Transcranial Doppler ultrasonography assists in the clinical decision making regarding further diagnostic evaluation and therapeutic interventions. If the patient deteriorates neurologically from cerebral vasospasm before the ICA is secured, triple H therapy (see earlier) must be instituted with caution. To avoid rebleeding, the systolic pressure is increased modestly from 120 to 150 mm Hg, central venous pressure from 10 to 12 mm Hg, and pulmonary capillary wedge pressure from 12 to 16 mm Hg.

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61 Intracranial Aneurysms: Vasospasm and Other Issues

Ehab Farag • Alex M. Witek • Mark Bain

Case Synopsis

A 58-year-old female patient with a past medical history significant for hypertension, type 2 diabetes, and smoking developed a severe headache and was admitted to the emergency department. Computed tomography (CT) of her head showed a subarachnoid hemorrhage Fisher grade 3. The patient's cerebral angiogram showed a ruptured wide neck aneurysm in the anterior communicating artery region. The patient underwent endovascular occluding of the aneurysm using a flow diversion system (pipeline embolization device) with coiling. Four days after the procedure the patient developed hemiparesis and impaired mental status. The patient's transcranial Doppler examination showed increased velocities in the anterior cerebral artery up to 170 cm/s from baseline on admission at 110 cm/s. The diagnosis of cerebral vasospasm and delayed cerebral ischemia was confirmed using CT angiography, which showed vasospasm of small distal cerebral blood vessels. In addition, the patient underwent magnetic resonance imaging (MRI) that showed multiple cerebral infarcts. The patient was managed by oral nimodipine, euvolemia, and induced hypertension.

PROBLEM ANALYSIS

Subarachnoid Hemorrhage

Despite stroke dropping from third to fourth place among the most common causes for mortality, subarachnoid hemorrhage (SAH) from intracranial aneurysm has not declined and still affects 9 per 100,000 people per year in the United States, with about 600,000 cases annually worldwide. The intracranial aneurysm is more predominant in the female gender compared with the male gender by a 3:1 ratio. In addition, female patients have a higher incidence of developing multiple aneurysms. Estrogen is essential for promoting normal endothelial function and its effect on vascular structure, with the fall in estrogen during menopause resulting in a peak of SAH between 50 and 59 years of age. In males, both unruptured and ruptured aneurysms present at an earlier age.

Factors associated with poor outcome are older age, poor neurologic examination on admission, and amount of blood seen on the initial head CT imaging by Fisher grade. The Fisher scale has four grades: 1, 2, 3, and 4. Fisher grade 3 (diffuse subarachnoid blood on CT) itself is significantly associated with the development of cerebral vasospasm. Two clinical scales used for SAH patient evaluation are the Hunt and Hess and the World Federation of Neurological Surgeons (WFNS). Hunt and Hess grade ranges from grade 1, denoting a person who is normal except for mild headache, to grade 5 in a person who is comatose. The WFNS combines the Glasgow Coma Scale and focal neurologic signs for a score of 1 to 5. Higher scores predict poorer outcomes.

Noncontrast head CT is 98% to 100% sensitive for diagnosing SAH within 12 hours, but this rate drops to 93% at 24 hours and may be as low as 57% at 6 days. If the CT scan is negative and clinical suspicion exists, a diagnostic lumbar puncture should be performed.

The blood pressure should be closely monitored and controlled to a maximum systolic blood pressure of 150 to 160 mm Hg in the presecuring phase. The risk of rebleeding within 24 hours of initial SAH may be 15%, with recurrent hemorrhage fatality around 70%. Therefore early treatment of a ruptured aneurysm is recommended to reduce rebleeding and to facilitate treatment of cerebral vasospasm using induced hypertension.

Treatment of Intracranial Aneurysms

Aneurysm treatment is indicated in patients with aneurysmal SAH given the risk of early rebleeding. There are a variety of treatment options for intracranial aneurysms. Microsurgical clipping involves performing a craniotomy to place a metallic clip across the neck of the aneurysm (Fig. 61.1). Endovascular coiling is an alternative to clipping that was introduced in the 1990s, and the number of coiling procedures has greatly increased over the past 2 decades. Coiling involves accessing the aneurysm with a microcatheter and deploying platinum coils to occlude the aneurysm sac (Fig. 61.2). Adjuncts to coiling include balloon- and stent-assisted techniques, which can prevent coil prolapse and decrease the risk of recurrence. More recently, flow-diverting stents have emerged as a useful tool for the treatment of aneurysms that were previously difficult to treat with either clipping or coiling (Fig. 61.3). Flow-diverting stents have a lower porosity than other intracranial stents, which causes stasis of blood flow within the aneurysm, leading to thrombosis and eventually occlusion, while at the same time permitting patency of branch vessels that are covered with the stent.

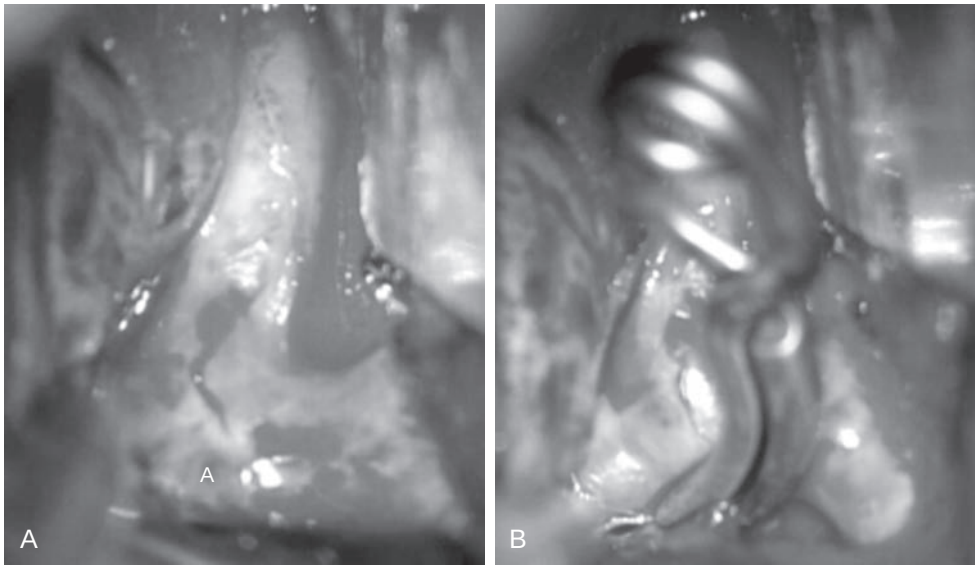

Fig. 61.1 **A,** Microsurgical view after opening the Sylvian fissure, demonstrating an aneurysm *(A)* located at the middle cerebral artery bifurcation. **B,** A titanium clip has been placed across the neck of the aneurysm to occlude it.

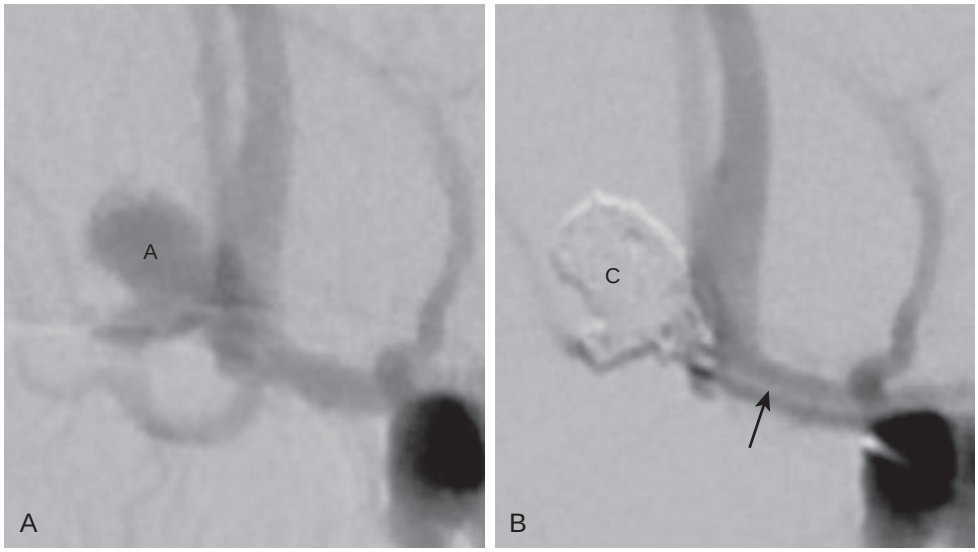

Fig. 61.2 **A,** Digital subtraction angiogram demonstrating an aneurysm *(A)* of the anterior communicating artery. **B,** Digital subtraction angiogram obtained during coil embolization of the aneurysm. A microcatheter *(arrow)* has been placed into the aneurysm, through which platinum coils *(C)* have been packed into the dome of the aneurysm, which no longer fills with contrast.

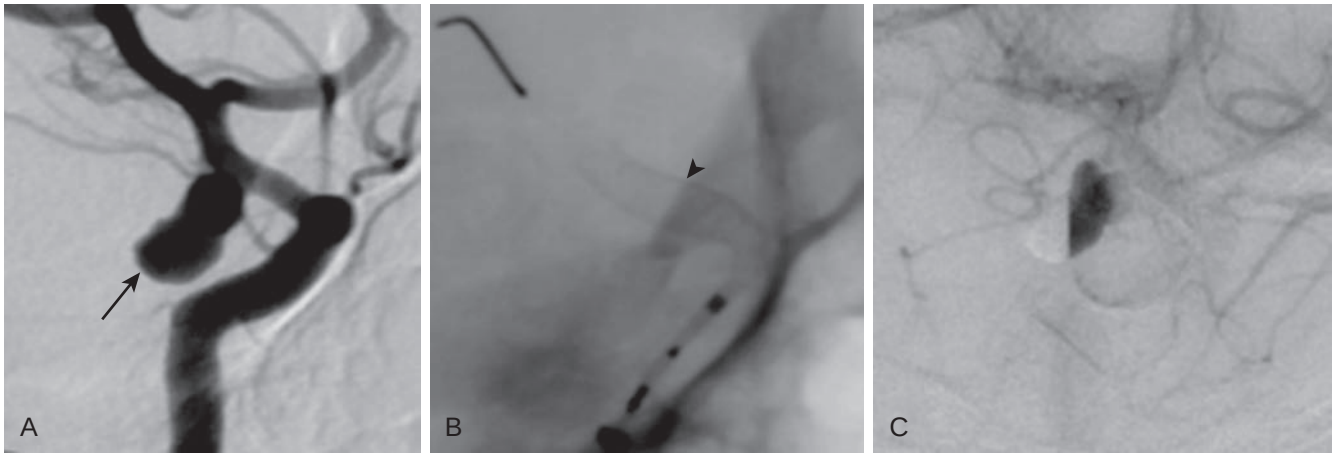

Fig. 61.3 **A,** Digital subtraction angiogram demonstrating an aneurysm *(arrow)* originating from the communicating segment of the internal carotid artery. **B,** Fluoroscopic view of a Pipeline embolization device *(arrowhead)* being deployed in the ICA, covering the neck of the aneurysm. **C,** Digital subtraction angiogram after placement of the Pipeline embolization device, demonstrating stasis of flow in the treated aneurysm.

The choice between treatment modalities is complex and depends on multiple factors, including aneurysm location, aneurysm shape, patient clinical status and comorbidities, and preference of the patient and surgeon. Although there have been three randomized studies comparing clipping to coiling for ruptured aneurysms, there are insufficient data to draw strong conclusions for most aneurysms. The International Subarachnoid Aneurysm Trial (ISAT) is the largest of these trials and found a lower rate of death or dependency in patients who underwent coiling (11%) versus those who underwent clipping (14%); however, only 22% of eligible patients were randomized. Furthermore, the follow-up study of death and clinical outcomes in 1644 patients at 22 UK neurosurgical centers showed that the patients in the coiling group were more likely to be alive and independent at 10 years than were the patients in the clipping group. The Barrow Ruptured Aneurysm Trial (BRAT) reported better outcomes for coiling compared with clipping for patients with posterior circulation aneurysms, but no difference for anterior circulation aneurysms. Aneurysm morphology is an important consideration, with a narrow neck being a favorable characteristic for coiling. Older age, medical comorbidities, and poor clinical grade may favor endovascular therapy as these patients may be at higher risk for adverse events associated with craniotomy.

Clipping tends to be a more durable treatment and has been associated with lower recurrence rates and less likelihood of requiring retreatment. The potential for complications is an important consideration when treating both ruptured and unruptured aneurysms. Common periprocedural complications for patients undergoing neurosurgical or endovascular treatment of aneurysms include intraoperative rupture and stroke. Clipping requires a craniotomy, which adds morbidity and prolonged recovery time. Patients undergoing stent placement (including stent-assisted coiling and flow diverters) require dual antiplatelet therapy for several months to prevent in-stent thrombosis during the period of epithelialization. Furthermore, flow diversion does not offer immediate protection from rehemorrhage. For these reasons, stents and flow diverters are used sparingly in patients with SAH, but they may be necessary in special circumstances.

In summary, there are a variety of options for the treatment of cerebral aneurysms. Although the interpretation of randomized trials of clipping versus coiling is confounded by selection bias and crossover, it appears that coiling has more favorable outcomes for ruptured posterior circulation aneurysms. Surgical decision making continues to rely heavily on operator experience.

Cerebral Vasospasm and Delayed Cerebral Ischemia

Delayed cerebral ischemia (DCI) is a common and serious complication after SAH. DCI occurs in approximately 20% to 40% of patients and is associated with an increased incidence of cerebral infarction and mortality. It is usually caused by vasospasm. Vasospasm is a reversible narrowing of the subarachnoid arteries. It usually occurs from the 3rd to 5th day to the 15th day after the hemorrhage, with the peak at the 10th day. It is observed in 70% of patients on angiographic scans but causes symptoms in only 20% to 30%. Therefore vasospasm primarily describes findings on diagnostic studies, whereas DCI should be used to describe clinical deterioration such as hemiparesis, aphasia, and altered consciousness after SAH diagnosed by a decrease of at least 2 points on the Glasgow Coma Scale.

Angiographic Vasospasm

Angiographic narrowing is mainly due to vasoconstriction caused by subarachnoid blood clot. Angiographic vasospasm always resolves, although arterial fibrosis, endothelial thickening, and reduced compliance can persist. Although arterial narrowing of proximal intracranial vessels can be observed in up to 60% to 70% of patients with SAH, only 30% will experience DCI. Of note, development of DCI depends on the extent and severity of angiographic vasospasm, as well as on preexisting collateral and anastomotic blood flow, cerebral metabolic demand, and blood pressure.

Pathophysiology of Delayed Cerebral Ischemia

Genetic Factors

Plasminogen activator inhibitor–1 (PAI-1) is the main inhibitor of tissue plasminogen activator (t-PA). It inhibits the conversion of plasminogen into active plasmin. The 4G allele in the PAI-1 gene is correlated with higher PAI-1 levels. Elevated PAI-1 levels are associated with poor outcome after SAH as it enhances microthrombosis.

The endothelium nitric oxide synthetase (eNOS) 27 VNTR (particularly the "4a" allele) is significantly associated with the occurrence of aneurysmal SAH. The eNOS T-786C SNP (particularly the "C" allele) is significantly associated with the occurrence of cerebral vasospasm.

Microthrombi

The presence of microthrombi induced by platelet aggregates in parenchymal microvessels after SAH has been identified as one of the main culprits for DCI. The process of platelet activation is associated with the release of proteases such as matrix metalloproteinase 9 that digests collagen IV in the blood vessel lamina. Of note, the constriction of cortical and/or intraparenchymal arterioles usually precedes the thrombus formation either acutely or days after SAH.

In addition to formation of microthrombi within hours of SAH, large-artery angiographic vasospasm induces endothelium injury that enhances platelet aggregation and microthrombi formation. Furthermore, the activation of the clotting process after SAH, which contributes to cessation of the hemorrhage, could generate more emboli in the distal circulation. Finally, the systemic hypercoagulable response to SAH enhances the formation of microthrombi in the cerebral circulation.

Subarachnoid Blood and Inflammation

After SAH, the presence of free hemoglobin in the subarachnoid space induces the expression of cell adhesion molecules in the endothelial cells, which in turn facilitates the migration of leukocytes into the subarachnoid space, inducing inflammation, scavenged nitric oxide (NO), and impaired NO-mediated vasodilation.

The reactive oxygen species (ROS) formed during hemoglobin auto-oxidation constitute a major etiologic factor underlying the development of cerebral vasospasm. ROS oxidize bilirubin to bilirubin oxidation products, which in turn inhibit eNOS and NO production.

Haptoglobin (Hp) is an iron-recycling protein that mediates clearance of extracorpuscular free hemoglobin after hemorrhage. Hp counters hemoglobin toxicity by capturing the released hemoglobin and directing it to CD163 receptor–expressing macrophages, which internalize the free hemoglobin. In humans, two Hp alleles exist and therefore three possible genotypes are possible: Hp 1-1, Hp 1-2, and Hp 2-2. The Hp 2-2 genotype appears to promote a proinflammatory state and is cleared slowly by leukocytes, an effect that greatly prolongs NO scavenging. Therefore patients with the Hp 2-2 genotype are at higher risk of developing symptomatic cerebral vasospasm after SAH.

L-citrulline injection to supplement NO in animals with the Hp 2-2 genotype has been shown to prevent vasospasm.

Blood in the subarachnoid space and lipid peroxidation initiate a significant inflammatory response. Activated leukocytes in the cerebrospinal fluid of patients with SAH synthesize release endothelin-1 (ET-1) in addition to other cytokines such as interleukin-6 (IL-6), interleukin-1β, tumor necrosis factor–α, and oxygen-free radicals. The intercellular adhesion molecule–1 (ICAM-1) and vascular adhesion molecule–1 (VCAM-1) are necessary for leukocytes to adhere to the endothelium and enter the subarachnoid space, inducing the inflammatory response after SAH. Cerebrospinal fluid and serum concentrations of ICAM-1 and VCAM-1 are correlated with the development of vasospasm diagnosed by transcranial Doppler. Ibuprofen, which inhibits ICAM-1 and VCAM-1 upregulation, was found to reduce experimental vasospasm. However, the doses of ibuprofen required to prevent ICAM-1 and VCAM-1 upregulation can produce systemic toxic effects. Ibuprofen polymers implanted into the subarachnoid space releasing high and controlled sustained drug concentrations in a monkey SAH model prevented the development of angiographic vasospasm without signs of local or systemic toxicity. However, despite the detrimental effects of inflammation process after SAH, it can have beneficial effects in repairing processes after SAH.

Blood-Brain Barrier Disruption

Blood-brain barrier disruption after SAH probably contributes to brain injury after SAH, but it might have beneficial effects. Therefore activation of matrix metalloproteinases that acutely disrupt the blood-brain barrier may facilitate brain repair at a later stage.

Cortical Spreading Ischemia

Cortical spreading depression (CSD) has been posed as the putative mechanism for DCI after SAH. CSD is a depolarization wave in cerebral gray matter that propagates a slow velocity of 2 to 5 mm/min. This mass depolarization of cells results in the redistribution of ions and neurotransmitters, leading to a cycle that ends in neuronal inactivation followed by a period of transient depression in the cortex. In the normal brain, CSD is usually associated with an increase in regional cerebral blood flow (CBF) and oxygen delivery as a means of delivering the necessary energy required for the ionic pumps driving neuronal repolarization. However, after SAH, the hyperemia coupled with CSD does not occur, leading to a reduction of CBF and inducing the spread of ischemia.

Patients with SAH after clipping of ruptured cerebral aneurysm developed DCI associated with clusters of CSD despite the absence of angiographic vasospasm in some patients. The number and duration of CSD clusters correlated significantly with the development of DCI.

CSD is accompanied by a marked rise in cytosolic calcium. It depolarizes neuronal mitochondria and triggers the rise in oxygen use via the calcium uniporter mitochondria membrane. CSD also activates glycolytic pathways, which increase cortical lactate production. An increased extracellular potassium level due to erythrocyte lysis directly depolarizes arteriolar smooth muscle cell and increases intracellular calcium via voltage-gated calcium channels, thus causing vasoconstriction. Furthermore, depolarization of neurons removes the magnesium block of *N*-methyl-D-aspartate (NMDA) receptors and sensitizes the receptor to small increases in interstitial glutamate. The interaction of glutamate with the NMDA receptor triggers further release of potassium and glutamate with further propagation of the CSD. The presence of blood in the subarachnoid space avidly scavenges NO and enhances the development of CSD. Arterial hypotension prolongs the duration of CSD, whereas hypertension reduces it. Therefore maintaining cerebral perfusion pressure after SAH is very important to mitigate the harmful effects of CSD after SAH.

Predictors of Delayed Cerebral Ischemia

Thick subarachnoid blood clots, poor clinical condition on admission, and loss of consciousness at ictus increase the risk of DCI. Strong evidence suggests that smoking increases the risk of DCI, and moderate-strength evidence indicates that diabetes, systemic inflammatory response syndrome, hyperglycemia, and hydrocephalus also increase the risk. ET-1, IL-6, and some markers of thrombin activation in the cerebrospinal fluid might be useful for predicting DCI after SAH.

DIAGNOSIS AND MANAGEMENT OF DELAYED CEREBRAL ISCHEMIA

Delayed neurologic deterioration after SAH (3 to 14 days) occurs in up to 50% of patients, with only about 5% of cases occurring after day 10. Clinical diagnosis of DCI can be difficult, especially in poor-grade patients who may be sedated and ventilated. DCI can be asymptomatic in patients who are not diagnosed clinically with DCI; however, CT scanning and MRI reveal cerebral infarcts in 10% to 20% and 23%, respectively, of patients. Cerebral infarction has a strong relationship with poor outcome, and the two most common causes of infarction are the aneurysm-securing procedure and DCI.

Elderly patients with WFNS grades 1 to 3 on admission, with no or thin SAH on CT, have low risk for DCI and therefore might be candidates for less-frequent monitoring.

Angiography

Catheter angiography remains the gold standard for detection of angiographic vasospasm, but it is being replaced by CT angiography. The most accurate combination of tests for angiographic vasospasm, with accuracy almost similar to catheter angiography, is the qualitative assessment of artery narrowing on CT angiography combined with CT perfusion mean transit time (mean time it takes for blood to perfuse a region of tissue) of more than 6.4 seconds.

Transcranial Doppler Ultrasound

Transcranial Doppler ultrasound (TCD) can be used to screen and diagnose cerebral vasospasm. Mean velocities of TCD in the 120s to 130s cm/s for anterior cerebral artery and middle cerebral artery (MCA) suggest mild vasospasm, 140s to 170s moderate vasospasm, and 180 and higher severe vasospasm in conjunction with a Lindegaard ratio (MCA to extracranial internal carotid artery mean velocities) of more than 3.

TCD technique has some limitations in that it only assesses a small number of large arteries, is operator dependent, and has technical factors such as inability to obtain temporal windows. False positives can occur when the blood pressure is augmented. False negatives can be seen in cases with very severe artery narrowing owing to low blood flow.

Electroencephalogram and Other Techniques

Continuous electroencephalogram can be very helpful to detect the epileptiform discharges and to help in their early management. Moreover, reduced relative variability in alpha-wave activity to other waves was shown to be 100% sensitive and 50% specific for vasospasm as diagnosed by other techniques such as TCD and angiography.

Near-infrared spectroscopy is a noninvasive method that measures cerebral blood saturation and can be used to diagnose DCI.

The xenon (Xe)–enhanced CT scan technique is a useful noninvasive technique to measure regional cerebral blood flow (rCBF). Symptomatic vasospasm can be diagnosed with this technique if the mean Xe-rCBF value is less than 32 mL/100 g/min in the presence of angiographically verified vasospasm, indicating hemodynamically relevant vasospasm.

Invasive Brain-Tissue Monitoring

Brain microdialysis is an invasive monitoring method that might be useful for identification and monitoring of DCI. Cerebral ischemia is associated with elevated glutamate and glycerol levels and an increased lactate-to-pyruvate ratio. These compounds can be measured by microdialysis probe if it is inserted in the vicinity of the ischemic region.

Thermal diffusion flowmetry probe is another invasive technique, and it is useful to measure the regional cerebral blood flow (rCBF). Reduced rCBF measured by this technique is more sensitive and a specific marker of DCI.

PREVENTION

Systemic Delayed Cerebral Ischemia

Cilostazol

Cilostazol is a selective inhibitor of phosphotriesterase-3 and exerts a vasodilatory and antithrombotic effect. Cilostazol 100 mg orally twice daily for 14 days was able to improve clinical outcome measured by the modified ranking scale (mRS) at discharge. No serious adverse effects of cilostazol, such as hemorrhagic complications or refractory hypotension, were reported.

Clazosentan

Clazosentan is a selective endothelin receptor–A antagonist that has been tested to reduce vasospasm-related mortality. Three large randomized controlled trials, the Clazosentan to Overcome Neurological Ischemia and Infarction (CONSCIOUS-1, -2, and -3) studies, were performed to test the effect of clazosentan on cerebral vasospasm. CONSCIOUS-1 showed a dose-dependent reduction in moderate or severe angiographic vasospasm, and a dose of 15 mg/h resulted in a 65% risk reduction. The promising results of this trial were further explored in CONSCIOUS-2 and CONSCIOUS-3 patients treated with surgical clipping or endovascular coiling, respectively, after SAH. CONSCIOUS-2 failed to show a significant difference in mortality or the incidence of new cerebral infarcts and DCI. These negative results have led to the premature halt of the CONSCIOUS-3 trial after enrolling 571 patients with SAH. The dose of clazosentan of 15 mg/h in the CONSCIOUS-3 trial reduced incidence of vasospasm-related mortality and all-cause mortality compared with the placebo group (15% vs. 27%; $p = 0.007$). Further study is required to fully understand the potential usefulness of clazosentan in patients with SAH.

Eicosapentaenoic Acid

Omega-3 fatty acids such as eicosapentaenoic acid (EPA) reduce platelet reactivity and have vasodilatory effects. The efficacy of EPA has been tested for cerebral vasospasm after clipping in patients with SAH. The treatment group had a significantly lower incidence of symptomatic vasospasm and cerebral infarction but without a difference in clinical outcome measured by mRS.

Erythropoietin

Erythropoietin (EPO) has been shown to increase brain oxygen tension in patients with cerebral vasospasm within hours of its use. EPO stimulates eNOS, therefore it increases the blood flow to the ischemic areas. The restoration of cerebral autoregulation and antiinflammatory potency has been postulated as possible underlying mechanisms.

Fasudil

Fasudil is a Rho-kinase inhibitor exerting a vasodilatory effect. It reduced the relative incidence of symptomatic vasospasm by 30% and angiographic vasospasm by 38%. The drug is the standard prophylactic treatment in Japan because nimodipine is not approved there. In a randomized controlled trial, there was no difference between fasudil and nimodipine in the incidence of clinical vasospasm or the occurrence of CT hypodensities. However, patients in the fasudil group showed more favorable clinical outcome after 1 month, as measured by a Glasgow Coma Scale score.

Heparin

Heparin has antiinflammatory effects via its actions to enhance the integrity of endothelial glycocalyx and the endothelial function. In addition, its anticoagulant effects make heparin an interesting therapy in preventing DCI. The use of heparin in the dose of 8 U/kg/h was shown to reduce symptomatic vasospasm significantly compared with the control group. No hemorrhagic complications were reported in the study group.

Nimodipine

Nimodipine is a voltage-gated calcium channel antagonist that inhibits calcium entry into smooth muscle cells and neurons. Prophylactic use of nimodipine in SAH to diminish the risk of DCI and poor outcome is recommended by the latest guidelines of the American Heart Association/American Stroke Association (AHA/ASA) (Class I, Level of evidence A). Nimodipine improves functional outcome in patients with SAH, however, with no effect on reducing angiographic vasospasm. Its neuroprotective effect is attributed to the fact that it attenuates the neuronal calcium increase after cellular ischemia, which causes cortical spreading ischemia and cell death. Nimodipine increases fibrinolytic activity by decreasing PAI-1 levels in plasma. It also inhibits platelet function as it diminishes the release of thromboxane B_2. Nimodipine is orally given at a dose of 60 mg every 4 hours for 21 days starting from the admission into the intensive care unit.

Magnesium

Magnesium is a physiologic calcium antagonist and therefore exerts a vasodilatory effect. However, the trials for using intravenous magnesium sulfate for aneurysmal subarachnoid hemorrhage (MASH-1 and -2) failed to show any effects of cerebral vasospasm.

Statins

Statins increase cerebral blood flow via the expression of cerebral endothelial nitric oxide synthase. The use of simvastatin in aneurysmal subarachnoid hemorrhage (STASH trial) either at 40 mg or 80 mg once daily for 21 days failed to show any benefit on the incidence of DCI or the favorable outcome at 6 months measured by mRS.

Albumin

Albumin has multiple physiologic functions in the body. It helps to maintain the integrity of the vascular barrier via its action on the endothelial glycocalyx. It helps transfer the sphingosine-1 phosphate (S1P) produced by the red blood cells to the endothelial cells. S1P helps to maintain the tight junctions between the endothelial cells and thereby maintains the integrity of the vascular barrier. Moreover, S1P stimulates the production of NO from the endothelial cells. Of note, albumin is the main carrier of NO in the blood. Albumin helps to decrease platelet aggregation and therefore helps to increase the blood flow to the ischemic regions. In addition, it is considered the main antioxidant in the body. Therefore albumin was shown to have neuroprotective effects in animal models of focal cerebral ischemia.

The use of 25% human albumin in a subarachnoid hemorrhage (ALISAH) trial at a dose of 1.25 g/kg/day reduced the incidence of vasospasm measured by TCD, DCI, and cerebral infarcts.

Nicardipine Controlled Release Implants

Nicardipine is a calcium channel blocker. The use of nicardipine-release implants is only applicable in patients treated by surgical clipping. The use of nicardipine 4 mg slow-release pellet implantation along the exposed vessels was shown to reduce the incidence of DCI in patients with Fisher grade 3 SAH treated by surgical clipping.

Induced Hypertension

Hemodynamic augmentation including hypervolemia, hypertension, and hemodilution (triple-H therapy) to overcome the increased resistance to flow of spastic vessels has been the mainstay of the medical treatment of cerebral vasospasm for decades. However, induced hypervolemia or hemodilution causes several complications including pulmonary edema, heart failure, cerebral edema, hyponatremia, and coagulopathy related to the use of the nonalbumin colloid solutions. The most effective way to increase brain oxygenation in the presence of DCI and cerebral vasospasm is induced hypertension. In the healthy brain, decreased pressure from large artery constriction or systemic hypotension is compensated for by dilation of these arterioles, a process that maintains tissue perfusion within normal ranges. Small vessels also dilate to deliver nutrients required for tissue metabolic requirements. However, this mechanism is impaired in SAH. Therefore induced hypertension is the most effective way to maintain cerebral perfusion in the presence of DCI. The recent recommendation is to maintain strict euvolemia and to refrain from hypervolemia. Transfusion is recommended in patients with initial hemoglobin levels less than 9 g/dL.

An intraaortic balloon pump (IABP) improves cardiac function and CBF in SAH patients with vasospasm who are unable to tolerate induced hypertension due to cardiac failure refractory to vasopressors and inotropic infusions. This can be seen in elderly patients or in patients with neurogenic stunned myocardium after SAH. The use of IABP may be associated with ipsilateral lower extremity ischemia, infection, thrombocytopenia, pseudoaneurysm, and aortic dissection. The use of IABP is absolutely contraindicated in the presence of aortic dissection or aortic aneurysm. The use of anticoagulants with IABP is generally unnecessary during the first 48 hours. After the first 48 hours low-dose heparin therapy is recommended.

Subarachnoid Blood Clearance

The positive relation of the amount of the blood in the subarachnoid space and the development of cerebral vasospasm has been established. The clearance techniques of the blood from the subarachnoid space, such as lumbar drainage and cisternal irrigation with thrombolytic agents, might be helpful to reduce the incidence of cerebral vasospasm and DCI. Kinetic therapy for subarachnoid blood clearance using a head shaker or lateral rotational therapy with local thrombolytic therapy has been shown to decrease DCI.

Interventional Neuroradiologic Treatments

Interventional neuroradiologic procedures are considered rescue measures for cerebral vasospasm refractory to medical management. Balloon angioplasty has a longer-lasting effect and it is performed safely in the proximal vasospasm such as in the internal carotid artery; M1 and M2 segments of the middle cerebral artery; A1 and A2 segments of the anterior cerebral artery; and P1 and P2 segments of the posterior cerebral artery, vertebral artery, and basilar artery. Angioplasty is associated with a 5% risk of major complications, including a 1% risk of vessel rupture. Intraarterial spasmolysis has a transient effect but is suitable for more distally located and diffuse spasms. An intraarterial combination of milrinone and nimodipine appeared to have good spasmolytic effects. In addition, the use of intraarterial calcium blockers such as nicardipine and verapamil was shown to be successful as arterial vasodilator agents. Use of papaverine as a vasodilator was abandoned based on its deleterious effects, such as increased cerebral hypertension, blindness, and neurotoxicity.

Novel Therapeutics

Tamoxifen is a breast cancer chemotherapeutic agent that has neuroprotective effects in models of spinal cord injury, intracerebral hemorrhage, brain ischemia, and hypoxic-ischemic brain injury. Tamoxifen administration in a rat SAH model decreased inflammation, and the rats demonstrated no evidence of early brain damage such as cortical edema and blood-brain barrier disruption. Most strikingly, tamoxifen-treated rats had complete reversal of their SAH-induced spatial working memory dysfunction compared with the control group.

Glibenclamide (glyburide) is an antidiabetic agent that selectively inhibits the sulfonylurea receptor 1–transient receptor potential melastatin 4 (Sur1-TRPM4) channel that is involved in neuroinflammation. Therefore glibenclamide is now currently in phase II trials of acute central nervous system injury.

Ultrasound can improve blood flow in cerebral vasospasm by dilating spastic cerebral blood vessels by enhancing endothelium nitric oxide synthetase and neuronal nitric oxide synthetase activity via induction of shear stress in the vessel wall. Therefore MRI-guided transcranial ultrasound is proposed as a therapeutic option for cerebral vasospasm.

Seizures and Prophylactic Anticonvulsant Use

Risk factors for the development of seizures in SAH are clipping of aneurysmal SAH in patients older than 65 years of age, thick subarachnoid clot, and possibly intraparenchymal hematoma or infarction. The use of anticonvulsants, especially phenytoin, may worsen outcome after SAH. If anticonvulsant prophylaxis is used, a short course (3 to 7 days) is recommended.

Cardiac Complications

The heart and brain are intimately connected through the vasculature and nerves. Once the brain becomes damaged from SAH, parasympathetic dysfunction may contribute to cardiac arrhythmias, leading to the release of inflammatory cytokines that enter the vasculature.

Inflammatory factors released from the damaged heart can induce inflammation in the brain. In addition, adipokines from excess fat storage can increase neuroinflammation susceptibility after brain injury. Therefore atherosclerosis and diabetes can prime the immune system and exacerbate the inflammatory response during SAH.

Cardiac manifestations of SAH include abnormalities on the electrocardiogram such as QT-interval prolongation and T-wave inversion, disturbances of cardiac rhythm, and left ventricle (LV) dysfunction.

Takotsubo Cardiomyopathy

Stress cardiomyopathy or Takotsubo cardiomyopathy (TC) was first described in the early 1990s in Japan. Its Japanese name was derived from the characteristic appearance of the left ventricle, as evidenced by ventriculography during diagnostic coronary angiography for evaluation of acute coronary syndrome. This classic left ventricular shape had a round bottom and narrow neck due to stunning of the apical ventricular segments, thus resembling a Japanese octopus trap known as *takotsubo,* explaining why TC also is known as "transient apical ballooning syndrome." The postulated pathophysiology of TC in patients with SAH involves excessive release of catecholamines by myocardial sympathetic nerve terminals after SAH-induced hypothalamic injury. The incidence of TC after SAH ranges between 1% and 6%. It affects predominantly postmenopausal women. It is associated with cardiac enzyme elevation and ST-segment deviation, including, infrequently, elevation and T-wave inversion on the electrocardiogram. TC is characterized by nonobstructive coronary artery disease in coronary angiography. SAH-induced LV impairment usually resolves within 2 to 4 weeks and is not associated with adverse sequelae.

Management of TC is supportive such as inotropic support, intraaortic balloon counterpulsation, and aggressive diuresis. Severe cases of TC may be complicated by left ventricular apical thrombus formation, which may pose a dilemma with the need for anticoagulation in the context of SAH.

Hyponatremia

Hyponatremia is very common in patients with SAH, occurring in up to 57% of patients with SAH. Clinical manifestations of hyponatremia range from inattention and gait disturbance in mild hyponatremia to seizures, increased cerebral edema, and even death in acute severe hyponatremia. Hyponatremia has been associated with several disorders, notably cerebral wasting syndrome (CSW), first described in 1950, and the syndrome of inappropriate antidiuretic hormone (SIADH). CSW involves renal salt loss and natriuresis by increased circulating natriuretic peptide, thus leading to negative sodium balance, hyponatremia, and intravascular depletion. The SIADH is caused by increased antidiuretic hormone secretion with resultant inability to appropriately excrete free water, resulting in euvolemia or hypervolemia. Both disorders are associated with inappropriately elevated urine osmolality and urine sodium concentration. Accordingly, distinguishing between SIADH and CSW is primarily based on an assessment of the patient's volume status and urine output.

Hyponatremia should not be corrected faster than 12 to 24 mmol/L in 24 hours to avoid central pontine myelinolysis. Maintaining euvolemia during hyponatremia management is crucial to avoid DCI; therefore fluid restriction should be used with caution in SAH patients. Conivaptan is a vasopressin-receptor antagonist and can be used for the treatment of hyponatremia caused by SIADH in SAH patients. Demeclocycline hydrochloride also may be used. Use of the corticosteroids fludrocortisone and hydrocortisone is effective in limiting excessive natriuresis and hyponatremia, especially in cases of CSW. The use of 3% saline has been tried in the management of hyponatremia.

Hypernatremia

Hypernatremia is less common in SAH than hyponatremia. It is probably a result of either hypovolemia or the administration of hypertonic saline or mannitol for treatment of cerebral edema. Diabetes insipidus can be another cause for hypernatremia in the setting of hypovolemia and hypotonic urine.

Hyperglycemia

Liberal glucose management of more than 220 mg/dL in patients with SAH was associated with increased risk of infection. However, tight glucose control (80 to 110 mg/dL) with insulin infusions was found to increase the episodes of hypoglycemia, and this was associated with more vasospasm and less favorable 3-month outcome. The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial found worsened outcomes in patients treated with tight glucose using insulin infusions. The common recommendations are to avoid hypoglycemia (serum <80 mg/dL) and to maintain serum glucose below 200 mg/dL. If microdialysis is being used for monitoring, serum glucose may be adjusted to avoid low cerebral glucose.

Pulmonary Complications

Pulmonary complications represent almost half of all fatal medical complications and have been mostly associated with cerebral vasospasm treatment with hypervolemia and hemodilution. Impaired oxygenation is the most common pulmonary abnormality and is present in up to 80% of patients when it is defined as alveolar-arterial gradient of greater than 100 mm Hg or a Pao_2:Fio_2 ratio of less than 300. The main causes for impaired oxygenation in SAH patients are acute lung injury (ALI) and acute respiratory distress syndrome. Neurogenic pulmonary edema in SAH patients is commonly due to a catecholamine surge that occurs in early stages in SAH, affects both pulmonary vascular endothelium and myocardium, and may account for an important portion of patients with ALI in SAH.

Other common pulmonary complications include pneumonia (15% to 20%), congestive heart failure (8%), pneumothorax (3%), and pulmonary embolism.

Prevention is better than treatment of these complications. Therefore prophylactic measures against hospital-acquired and ventilator-associated pneumonia, deep venous thrombosis, and ventilator-associated lung injury are essential to prevent pulmonary complications in SAH patients. Routine use of a lung-protective, low tidal volume strategy with positive end-expiratory pressure should be used in mechanically ventilated SAH patients. Keeping the patients euvolemic with avoidance of fluid overload is crucial in avoiding iatrogenic pulmonary edema and in limiting neurogenic pulmonary edema.

CONCLUSION

SAH comprises only 5% of all strokes, but the case fatality rate is high (40%), owing in part to DCI and neurologic complications after SAH. SAH affects the heart, lungs, and other body systems. Early recognition and management of these complications will help improve patient outcomes.

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62 Laryngoscopy and Microlaryngoscopy

Joshua H. Atkins

Case Synopsis

A 62-year-old obese man (body mass index 41) with a history of laryngeal cancer presents for microdirect laryngoscopy, esophagoscopy, and bronchoscopy to evaluate a positron emission tomography (PET)–positive lesion on recent surveillance scanning. He has a history of chronic obstructive pulmonary disease on 2 L home oxygen, hypertension, hyperlipidemia, 35 pack-year smoking, and laryngeal cancer for which he underwent transoral robotic surgery and subsequent radiation. He underwent nasopharyngolaryngoscopy in the surgical clinic, which demonstrated no overt mass and significant laryngeal edema and scarring. After induction of general anesthesia with propofol and remifentanil, mask ventilation is difficult but adequate to maintain oxygen saturation greater than 90%. The airway is immediately turned over to the ear, nose, and throat (ENT) specialist. Surgical laryngoscopy with a Jackson laryngoscope provides no view of the larynx. Mask ventilation is resumed and subsequent exposure with an anterior commissure scope is sufficient to introduce a 4% lidocaine laryngeal tracheal applicator and a metal suction catheter through the glottic opening. High-frequency jet ventilation is initiated through the metal suction catheter (frequency 120, driving pressure 22 psi, inspiratory time 40%, Fio_2 100%). Hypotension (blood pressure 90/50 mm Hg) and bradycardia (heart rate 48 beats per minute) are treated with 10 mg of intravenous ephedrine, and the procedure is completed with no biopsies or bleeding. A 6.0 endotracheal tube is placed through the anterior commissure scope by the surgeon, and the patient is extubated after fully awake. A difficult airway bracelet is applied, and the patient is taken to the recovery area.

PROBLEM ANALYSIS

Preoperative Considerations

Patients presenting for microdirect laryngoscopy (MDL) and related procedures often have significant comorbidities. Life expectancy has improved with advanced diagnostic and therapeutic interventions for laryngeal and related cancers. Airway-related complications, especially loss of airway, are the most concerning for the perioperative team. More patients who have undergone prior airway surgery, radiation, or a combination of surgery and radiation are presenting to the operating room (OR) for surveillance biopsy or evaluation for PET-positive recurrence. Laryngeal masses can occlude the airway after induction, obstruct glottic view and impede direct passage of the endotracheal tube through the glottic opening, or bleed due to trauma during laryngoscopy. Radiation causes fibrosis, edema, and reduced tissue mobility that may be critical for glottic exposure. Surveillance frequently includes esophagoscopy and flexible fiberoptic bronchoscopy in addition to laryngoscopy. Abnormal airway anatomy, especially when due to reduced laryngeal mobility after radiation therapy, may also make tracheostomy or emergency cricothyroidotomy difficult.

MANAGEMENT

Operative Planning and Management

The otolaryngologist may perform a repeat awake nasopharyngolaryngoscopy in the OR immediately before induction to reassess the airway. Although this will not be directly informative with regard to the ability of laryngoscopy to expose the glottis, it provides information on the extent of edema and friable tissue, size and position of masses, and the feasibility of a transnasal fiberoptic intubation for rescue. Assessment of tongue protrusion and mobility of the larynx at the thyroid cartilage by external manipulation is also recommended. Laryngeal displacement to align the glottis with tube/laryngoscopic view may not be possible if the thyroid cartilage is fixed and the neck fibrosed. The landmarks for an emergency tracheostomy should be identified before induction. These include the cricothyroid membrane and lower trachea. These landmarks may be difficult to palpate or covered with inflamed scar tissue after radiation therapy. Ultrasound is emerging as an effective tool for the identification of the cricothyroid ligament, although use in the irradiated neck is not well described. Consideration in this case should be given to "awake look" laryngoscopy. After airway topicalization with 2% to 4% nebulized lidocaine a videolaryngoscope can be introduced gently into the mouth. If a reasonable view can be obtained the patient can be intubated in this fashion or the laryngoscope removed and general anesthesia induced. The ENT specialist should be present in the OR during any airway procedures, including "awake look" and induction of general anesthesia, and a surgical airway tray should be immediately available in the OR. An inhalational induction with sevoflurane can be considered when intubation, but not ventilation, is potentially difficult. Once an adequate plane of anesthesia is achieved with maintenance of spontaneous ventilation, an initial laryngoscopy can be performed to assess the airway by either surgeon or anesthesiologist. If an inadequate view is obtained the patient can be intubated fiberoptically through an supraglottic airway

(SGA) or intubating oral airway. The SGA may be more difficult to seat or seal in the setting of altered anatomy from prior airway surgery, although there is little guidance from the literature regarding this question. We prefer an approach in which the surgeon proceeds directly to surgical laryngoscopy after induction of general anesthesia so as to minimize the number of attempts and have the expertise needed to rescue the surgical airway immediately available at bedside. If surgical exposure/intubation/laryngoscopy is difficult and the surgeon believes there is a likelihood for worsening of edema, vocal cord dysfunction, or tumor growth, a tracheostomy for postoperative airway protection should be considered. Otherwise, extubation should be performed only after fully awake and with surgical laryngoscopy equipment and the ENT specialist immediately available. A detailed team approach to airway assessment and planning, as outlined previously, is integral to reducing airway complications in this setting.

Aside from loss of airway, other potential complications from MDL, bronchoscopy, and esophagoscopy include esophageal perforation, pneumothorax, dental injury, and hemodynamic changes. Esophageal perforation is extremely rare. Dental injury is more common. Patients with a Maryland bridge of the front of the teeth may be especially susceptible to such damage due to the pressure placed on the bridge during laryngoscopic suspension even when a dental guard is used. Pneumothorax is often mentioned as a complication of high-frequency jet ventilation. This is secondary to overinflation that is the consequence of high driving pressure (especially in pediatrics or Sanders-type injector) or absence of an open egress channel for delivered oxygen, which results in breath stacking and pressure-related injury. In the context of MDL the latter scenario is highly unlikely due to the direct visualization of the glottis throughout the procedure. If a patient has severe distal tracheal stenosis, breath stacking could still occur. An automated jet ventilator such as the Acutronic Monsoon reduces the risk of such complications. A pressure sensor at the end of the oxygen delivery line will trigger an alarm and turn off the delivery if a high pressure threshold is reached. Driving pressure should be limited to less than 2 atm (28.4 psi) to limit the risk of pneumothorax. The most common hemodynamic changes are hypertension from stimulation or bradycardia from profound vagal tone associated with laryngoscopy. Propofol is an excellent agent, particularly in combination with remifentanil, to suppress the sympathetic response to the laryngoscopy. Remifentanil can be associated with bradycardia. Ephedrine, glycopyrrolate, and low-dose atropine are all reasonable options to treat hemodynamically significant bradycardia.

Laser ablation of laryngeal lesions is commonly performed for treatment of nonmalignant vocal cord lesions or papilloma. Principal risks associated with this approach include airway fire and laser burns to the patient or providers in the OR, including eye injury. Protective eyewear should be worn by the patient and providers, and the patient's eyes and face covered with moist towels. Inspired oxygen concentration should be lowered at or below 30% during periods of laser use. A laser-resistant endotracheal tube, jet ventilation via metal suction catheter, or intermittent apnea technique can each be considered. An air-oxygen blender should be used whenever lasering takes place near the airway under sedation or local anesthesia. In the event of a laser-related airway fire, ventilation should cease immediately, flammable airway devices should be removed, and flames should be extinguished with saline. Mask ventilation should be performed and the airway assessed with flexible bronchoscopy to guide further management.

PREVENTION

Postoperative Considerations

Constant vigilance is also required to detect postoperative airway compromise. Symptoms such as stridor, shortness of breath, or coughing of blood should be rapidly assessed at the bedside by physical examination and nasopharyngoscopy. A difficult airway in the OR is likely to be even more challenging to repeat in the emergent, out-of-OR context. Adequate preparation of equipment and communication of management details will be a crucial factor. A difficult airway designation system (e.g., bracelet) with a written plan for emergent reintubation should be considered. This will also be helpful for the planning of subsequent anesthetics.

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63 Major Organ System Dysfunction After Cardiopulmonary Bypass

M. Tracy Zundel • Paul S. Pagel

Case Synopsis

A 67-year-old man with critical aortic valve stenosis (aortic valve area of 0.5 cm^2), severe mitral regurgitation, coronary artery disease, left ventricular systolic dysfunction (ejection fraction of 30%), and chronic renal insufficiency (serum creatinine concentration of 1.89 mg/dL) underwent aortic valve replacement, mitral valve annuloplasty, and two-vessel coronary artery bypass graft (CABG) surgery. Cardiopulmonary bypass (CPB) time was 235 minutes. The patient was hypotensive (mean arterial pressure of 40 mm Hg) during an initial attempt at weaning from CPB. Transesophageal echocardiography demonstrated profoundly depressed myocardial function. CPB was reinitiated. Intravenous infusions of epinephrine and norepinephrine were begun, but a second attempt at weaning from CPB was also unsuccessful despite these interventions. An intraaortic balloon pump was inserted through the right femoral artery, and the patient successfully separated from CPB while continuing to receive intravenous inotropic support. Transfusion of fresh frozen plasma, platelets, and cryoprecipitate was necessary to obtain hemostasis before the patient's chest was closed and he was transferred to the intensive care unit. Mechanical circulatory support and vasoactive medications were required to maintain adequate mean arterial pressure and cardiac output after surgery. The patient was combative and required conscious sedation with dexmedetomidine after emerging from anesthesia. Postoperative serum creatinine concentrations progressively increased, and the patient eventually required continuous venovenous dialysis for management of acute kidney injury. He had persistent hypoxemia despite high inspired oxygen concentrations (Pao_2/Fio_2 ratio <100), a lung-protective mechanical ventilation strategy, permissive hypercapnea, and 15 cm H_2O positive end-expiratory airway pressure. A chest radiograph was consistent with acute respiratory distress syndrome. The patient also developed atrial fibrillation on the third postoperative day.

PROBLEM ANALYSIS

Definition

Mechanical effects and alterations in physiology combine to cause CPB-related organ system dysfunction. Obstruction to blood flow, embolization of air or particulate matter, and vascular injury may result because of exposure to bypass equipment, whereas a profound systemic inflammatory response mediates the adverse physiologic consequences of CPB during and after cardiac surgery. Surgical trauma, blood loss, and hypothermia contribute to this inflammatory response. Three distinct mechanisms produce the intense proinflammatory state resulting from CPB. First, the interaction of blood with foreign bypass surfaces (e.g., plastic tubing and cannulae, oxygenator components) causes humoral and cellular immune responses through generation of proinflammatory cytokines (e.g., interleukin-6 and interleukin-10, tumor necrosis factor–alpha), stimulation of the complement cascade, and activation of cytotoxic leukocytes. Second, myocardial ischemia-reperfusion injury results from placement and removal of the aortic cross-clamp, which also contributes to the production of inflammatory mediators and large quantities of reactive oxygen species from activated neutrophils. Third, hypoperfusion during CPB causes damage to gastrointestinal mucosal barriers, thereby facilitating bacterial translocation and immune system activation. The systemic inflammatory response to CPB fundamentally alters microvascular perfusion and the functional integrity of vascular endothelium. These actions contribute to compromised end-organ blood flow concomitant with enhanced capillary permeability after CPB (Fig. 63.1).

Recognition

The mechanical complications of CPB are capable of producing catastrophic injury. Obstruction to arterial blood flow or venous drainage, air embolism, acute aortic dissection, dislodgment and embolism of aortic debris, and malposition of inflow and outflow cannulas are major mechanical consequences of CPB (Table 63.1). The clinical manifestations of the inflammatory response to CPB may be more subtle, but are most often attributed to the consequences of hypotension and malperfusion in myocardial, pulmonary, renal, splanchnic, and central nervous system vascular beds resulting from activation of the complement cascade and production of proinflammatory cytokines. For example, renal function may deteriorate after CPB

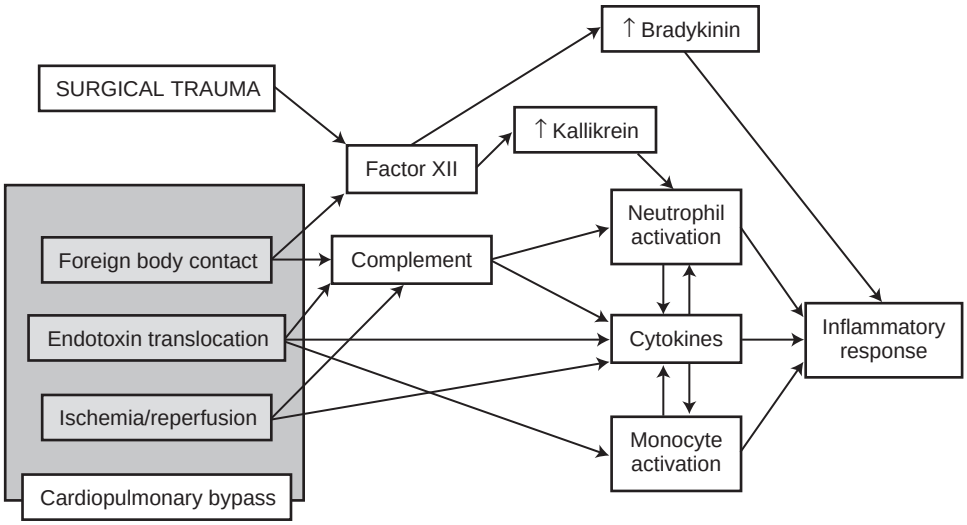

Fig. 63.1 Pathways of inflammatory activation during cardiopulmonary bypass.

TABLE 63.1 Detection of Mechanical Complications of Cardiopulmonary Bypass

Complication	Detection
Aortic dissection	Visual inspection of cannula or aorta
	Abnormal inflow pressure
	Alterations in peripheral arterial waveform
Dislodgment of aortic debris	Chest radiography
	Aortography
	Transesophageal or epivascular echocardiography
	Direct palpation
Obstruction to venous drainage	Inspection of head and jugular veins
	Sudden or unexpected changes in CVP while on CPB
Embolization	Transesophageal echocardiography
	Transcranial Doppler
	Bubble detectors in CPB circuit
	Arterial line filters
Cerebral hypoperfusion	Arterial pressure and flow monitoring during CPB
	Hypothermia
	Mixed venous oxygen saturation monitoring
	Electroencephalography

CPB, Cardiopulmonary bypass; *CVP*, central venous pressure.

and subsequently progress to acute renal failure of sufficient severity to require temporary or, less commonly, permanent hemodialysis. Increased permeability of pulmonary capillary vascular endothelium contributes to the development of pulmonary edema in which reduced lung compliance and compromised gas exchange are characteristic features. Microvascular occlusion from leukocyte aggregates in cerebral microvessels adversely affects mental status, produces delirium, or causes cognitive impairment in the absence of focal neurologic findings. Depression of myocardial contractility with or without atrial or ventricular arrhythmias may also occur that further contribute to hemodynamic instability, hypotension, end-organ malperfusion, and the need for circulatory support with vasoactive medications.

Because the insult imposed by CPB is primarily mediated by systemic inflammation, clinical signs and symptoms are often quite similar to those resulting from other causes of inflammation. Nevertheless, the manifestations of this inflammatory response may not be consistently observed in all organ systems. Fever may or may not be present, and the white blood cell count may remain within the normal range despite a CPB-induced proinflammatory state. Urine output may be reduced with or without evidence of acute tubular necrosis in sediment analysis. Alterations in pulmonary compliance and gas exchange are generally nonspecific, may be variable in severity, and typically resemble those of acute respiratory distress syndrome resulting from other etiologies. Agitation, delirium, and impaired cognition may also be variably present, but these findings are more commonly encountered than focal neurologic deficits per se. Arterial hypotension is often present, resulting from reduced cardiac output, systemic vascular resistance, or both, but again, it is important to emphasize that such hemodynamic derangements are not consistently present in all patients with a CPB-induced systemic proinflammatory state.

Risk Assessment

Exposure to CPB invariably causes some degree of systemic inflammation in all patients undergoing cardiac surgery, but several factors present before or occurring during CPB are associated with a clinically relevant systemic inflammatory response.

Preoperative Factors

Coronary artery disease, poorly controlled diabetes mellitus, and preexisting left ventricular systolic dysfunction increase the intensity of the proinflammatory cytokine response to CPB. This response has been correlated with postoperative hemodynamic instability and a greater risk of major adverse cardiovascular events. Preoperative renal insufficiency also intensifies the inflammatory response to CPB, most likely by attenuating clearance of proinflammatory mediators. In general, patients with more severe coexisting disease are more likely to develop a more pronounced inflammatory response when exposed to CPB during cardiac surgery. For example, the plasma concentrations of proinflammatory cytokines are substantially higher in patients undergoing heart or lung transplantation, at least in part, because of the presence of refractory heart failure or end-stage pulmonary disease.

Intraoperative Factors

Duration of CPB

The incidence and severity of CPB-related complications, including systemic inflammation, are directly dependent on the duration of CPB. The duration of CPB is correlated with plasma interleukin concentrations and the magnitude of neutrophil adhesion; these factors increase the risk of complications after CPB. Persistent decreases in blood flow also contribute to end-organ damage associated with

prolonged CPB. For example, splanchnic hypoperfusion increases gastrointestinal mucosal permeability during CPB, and the untoward consequences of this effect (e.g., ileus, bacterial translocation, endotoxin exposure) are more frequently apparent when CPB is prolonged. Similarly, pulmonary ischemia-reperfusion injury, pulmonary vascular endothelial dysfunction, and clinically significant hypoxemia are more likely as CPB duration increases.

Factors Associated With CPB

It is unclear whether the type of oxygenator, pump, or extracorporeal circuit or the degree of hypothermia used during CPB affects the duration and extent of the resulting inflammatory response. For example, membrane oxygenators produce less inflammation than bubble oxygenators, but this difference does not appear to translate into clinically meaningful improvements in postoperative pulmonary function. Similarly, no clear effect on outcome has been observed based on the components of CPB prime or the type of pump used for CPB. Pulsatile CPB blood flow is associated with less endotoxin release and lower cytokine concentrations, but again, these factors do not appear to substantially affect clinical outcome compared with a continuous flow technique. Warm compared with cold CPB increases the inflammatory response to CPB. In contrast, warm cardioplegia reduces the consequent inflammation.

Anesthetic Drugs and Technique

Anesthetics exert immunomodulatory actions, but the relative clinical importance of these effects in patients exposed to CPB remains unresolved. Volatile anesthetics, including sevoflurane and isoflurane, reduce inflammatory cytokine activity and attenuate the cytotoxic effects of neutrophils on vascular endothelial function in the presence of ischemia-reperfusion injury. Propofol also inhibits neutrophil activation and may facilitate production of antiinflammatory cytokines. Despite these potentially beneficial effects of propofol, the highly selective α_2-adrenoceptor agonist dexmedetomidine was recently shown to reduce the incidence and severity of postoperative delirium (a neurologic complication often associated with CPB-mediated inflammation) compared with propofol when used for conscious sedation in patients after cardiac surgery. Opioids including morphine also modulate the inflammatory response to CPB by downregulating immune cell function and suppressing the antibody response. Thoracic epidural anesthesia decreases the perioperative stress response; this technique does not substantially affect the cytokine response to CPB.

Transfusion

Allogeneic blood transfusion increases the intensity of the inflammatory response to CPB. Autotransfusion of recovered mediastinal blood also increases the inflammatory response because this blood frequently contains elevated proinflammatory cytokine concentrations. Washing (cell-saver) devices significantly reduce the concentrations of inflammatory mediators, but more neutrophils are usually present in washed blood than are observed in the native circulation. The use of these washing devices does not affect the incidence of CPB-related complications.

Implications

The effects of systemic inflammation associated with CPB may be profound. CPB causes neutrophil sequestration into the lungs, resulting in pulmonary epithelial and endothelial injury. The consequent increase in pulmonary vascular endothelial permeability produces interstitial and alveolar edema, reducing oxygenation and lung compliance. Pulmonary function tests are adversely affected, and acute lung injury occurs in 12% and 3%, respectively, of patients exposed to CPB patients. There is a direct correlation between the duration of CPB and the incidence and severity of resulting lung injury. Postoperative neurologic dysfunction is also linked to the CPB inflammatory response. Cerebrovascular microembolization, endothelial damage resulting from neutrophil activation, and dysfunctional vasomotor control in cerebral microvessels mediated by abnormal nitric oxide metabolism are putative mechanisms that may be responsible for neurologic injury. Postoperative delirium and cognitive impairment may occur in approximately one-third and two-thirds of patients after CPB, respectively, whereas focal neurologic deficits are less frequently encountered (1% to 3%). Postoperative cognitive impairment may be transient or permanent, is associated with substantial morbidity, and has profound consequences for quality of life after cardiac surgery.

Perioperative renal insufficiency occurs in 7% to 13% of patients exposed to CPB and markedly increases the risk of mortality, especially when hemodialysis is required. The specific mechanisms by which inflammatory response of CPB causes acute kidney injury are incompletely understood, but ischemia-reperfusion injury and impaired vascular regulation may play essential roles in this pathophysiology. Coagulation disorders after CPB may also be linked to the systemic inflammatory response. Platelet dysfunction, activation of the complement and fibrinolytic cascades, and elevated proinflammatory cytokine concentrations have been implicated the coagulopathic effects of CPB. Notably, lower concentrations of proinflammatory cytokines during CPB are associated with reductions in postoperative blood loss after cardiac surgery. These data provide indirect evidence relating CPB-mediated systemic inflammation and coagulation deficits that occur after CPB.

MANAGEMENT

Primary prevention and secondary supportive care for end-organ dysfunction are the major principles of the management of the inflammatory state after CPB. A number of potentially useful strategies have been proposed to achieve these objectives, but no single specific intervention has been identified to date to definitively attenuate the inflammatory response to CPB and reduce associated morbidity and mortality.

Avoidance of Cardiopulmonary Bypass/Aortic Cross-Clamping

Off-pump CABG reduces but does not entirely abolish the systemic inflammatory state associated with on-pump CABG. However, this difference in inflammation between off- versus on-pump CABG most likely does not contribute to meaningful improvements in morbidity and mortality, as several recent large randomized clinical trials have demonstrated that these two techniques produce essentially equivalent outcomes.

Heparin-Coated Bypass Circuits

Heparin-coated bypass circuits reduce contact-mediated complement, factor XII, and neutrophil activation. Leukocyte filtration further enhances these beneficial effects. Clinical trials suggest that high-risk patients may benefit from these interventions, especially when prolonged CPB and aortic cross-clamp times are present.

Selective Gastrointestinal Decontamination

The results of early clinical trials suggested that preoperative oral administration of nonabsorbable antibiotics reduces endotoxin

concentrations resulting from gastrointestinal bacterial translocation and may decrease the risk of postoperative infection after CPB. Despite these promising initial results, this approach has not been definitively linked to a reduction in mortality in patients undergoing cardiac surgery.

Hemofiltration

Intentional removal of inflammatory mediators from the circulation using hemofiltration decreases the severity of the CPB-mediated inflammatory response. Hemofiltration attenuates renal injury and reduces the magnitude of pulmonary complications after CPB, but this technique does not appear to significantly influence overall outcome.

Corticosteroids

Studies conducted in experimental animals suggest that corticosteroids may decrease inflammatory consequences of CPB on pulmonary, cardiac, renal, and hematologic function. Corticosteroids have also been shown to reduce proinflammatory cytokine and endotoxin concentrations after CPB in small clinical trials. Despite these findings, perioperative administration of corticosteroids provide no demonstrable clinical benefit and do not improve outcome in patients exposed to CPB.

Supportive Care

Mitigation of the inflammatory consequences of CPB is the mainstay of supportive care. Maintenance of hemodynamic stability clearly reduces the extent of subsequent ischemia-reperfusion injury. A lung-protection approach to mechanical ventilation for treatment of adverse pulmonary effects of CPB is recommended to avoid alveolar overdistention, barotrauma, and further damage. Acute kidney injury related to CPB may require hemodialysis until renal function improves; continuous venovenous hemodialysis may provide distinct advantages compared with other dialysis techniques in patients with cardiovascular instability. Hyperglycemia requires aggressive treatment (most often using an intravenous infusion of insulin) with target blood glucose concentrations ranging between 110 and 180 mg/dL because persistently elevated blood glucose concentration is associated with morbidity and mortality in cardiac surgery patients. Maintenance of normal electrolytes, administration of perioperative β_1-adrenoceptor blockers, or temporary left or biatrial pacing may reduce the incidence of postoperative atrial fibrillation in high-risk patients. Finally, it is important to emphasize that sepsis may closely mimic the clinical presentation of CPB-related systemic inflammation. The presence of vasodilation, hypotension, increased pulmonary capillary permeability with hypoxemia, acute renal insufficiency, and myocardial dysfunction after CPB not only requires supportive care but should also prompt investigation for systemic infection. Catheter-related sepsis, mediastinitis, endocarditis, and pulmonary or urinary tract infections are possible sources of infection in postoperative cardiac surgery patients that should be carefully excluded.

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64 Mediastinal Masses

Rebecca M. Gerlach • Jerome M. Klafta

Case Synopsis

A 23-year-old previously healthy man is scheduled for cervical mediastinoscopy for tissue diagnosis of a mediastinal mass. He presents with a 3-month history of fatigue and dyspnea on exertion and reports that he cannot sleep on his left side because it makes him feel short of breath. Chest computed tomography (CT) demonstrates a 10 × 8 × 5 cm mass adjacent to the right atrium, ascending aorta, and main pulmonary artery, with no other abnormalities. After induction with propofol and succinylcholine, the patient is easily intubated but rapidly becomes hypoxic. Vigorous manual ventilation fails to improve oxygenation, and the patient becomes progressively hypotensive.

PROBLEM ANALYSIS

Definition

Patients with anterior mediastinal masses are prone to develop certain potentially life-threatening complications because of the influence of these masses on neighboring structures (superior vena cava, tracheal bifurcation or mainstem bronchi, main pulmonary artery, aortic arch, and heart). Principal anesthetic considerations for patients with anterior mediastinal masses involve the following three potential complications:

- Tracheobronchial tree compression or obstruction
- Superior vena cava syndrome
- Compression of the heart and pulmonary vessels

Also, patients may present for anesthesia or monitored anesthesia care for a variety of reasons, including the following:

- Excision of intrathoracic tumor (primary or metastatic)
- Lymph node biopsy (for tissue diagnosis)
- Central line placement (for chemotherapy)
- Biopsy of intrathoracic mass (open or thoracoscopic)
- Any other procedure, either related to the disease (e.g., open reduction and internal fixation of pathologic fracture) or not (cesarean section)
- Imaging studies (children)

Although these masses are referred to as "anterior," they are often at the confluence of the anterior, superior, and middle mediastina (Fig. 64.1).

Recognition

Tracheobronchial Tree Compression or Obstruction

Tracheobronchial tree compression or obstruction is the most common of the three potential complications arising from anterior mediastinal masses. There can be both static and dynamic components to such compression or obstruction. The dynamic components may not be unmasked until after supine positioning (Fig. 64.2), induction of general anesthesia, or administration of paralytic agents (Table 64.1). Difficulty in mask ventilation in the absence of upper airway obstruction or difficulty ventilating despite successful endotracheal intubation are classic scenarios.

Preoperative features may include the following:

- History of orthopnea, positional dyspnea
- Chest radiograph showing large mass, airway compression
- Chest CT scan showing compression of airway or other structures (Fig. 64.3)
- Flow-volume loops with truncation of expiratory and possibly inspiratory limbs (Fig. 64.4)

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome occurs as a result of tumor compression or direct invasion of the superior vena cava and has the following features:

- Facial or upper extremity edema
- Dilated facial or upper extremity veins with collateralization
- Respiratory symptoms (nasal congestion, cough, orthopnea)
- Central nervous system effects (mental status changes, headache)
- Collateralization evident on chest CT with contrast enhancement

Compression of Heart and Pulmonary Artery

Compression of the heart or pulmonary artery is a rare but life-threatening complication. A history of syncope with a Valsalva maneuver is suggestive and merits at least a focused preoperative transthoracic echocardiographic examination looking specifically for extrinsic compression of cardiac chambers or of the pulmonary artery.

Risk Assessment

Generally, the larger the mass, the greater physiologic embarrassment it is likely to cause. However, the ability to prospectively identify which patients with mediastinal masses are at high risk for perioperative cardiorespiratory complications with general anesthesia (GA) is limited, because GA is usually avoided in patients with the highest anticipated risk based on historical or case-derived factors. In population-based studies in both children and adults, local anesthesia and sedation is often the technique chosen for patients in the highest risk groups, thus limiting conclusions regarding the safety of GA.

Patients are stratified as high risk for perioperative complications by the presence of symptoms (severe postural symptoms, stridor, cyanosis); tracheal compression greater than 50% or associated bronchial

compression; pericardial effusion; or SVC syndrome. In adults, the presence of a pericardial effusion or mixed pattern of obstructive and restrictive pulmonary disease are factors associated with the highest rate of perioperative respiratory complications. In children, the presence of orthopnea, upper body edema, great vessel compression, and mainstem bronchus compression has been associated with the greatest risk.

Overall, the incidence of perioperative complications may be significantly higher in pediatric patients than adults. This can be explained by the fact that infants and small children are more susceptible than adults to extrinsic airway obstruction because their airways are more compressible and because small decreases in airway diameter result in proportionally greater effects on airway cross-sectional area and resistance. In children, tracheal cross-sectional area (as measured by CT) less than 50% to 66% of predicted has been suggested as a cutoff below which GA should be avoided if possible. The only symptom that has been shown to strongly correlate with the degree of tracheal narrowing is orthopnea; however, its value in predicting intraoperative airway collapse is questionable. Adults with tracheal compression greater than 50% may not have intraoperative airway collapse, but are at elevated risk of postoperative respiratory complications.

Abnormalities on pulmonary function testing may provide a surrogate marker for detecting airflow compromise and risk of complications. In children, peak expiratory flow rates below 50% predicted may be more sensitive than tracheal cross-sectional area alone in detecting airflow compromise. In adults, a mixed obstructive and restrictive pattern indicates a mass is large enough to compress the lung parenchyma and also a main airway; however, a CT scan may show this more readily. Blunting of the expiratory limb of a flow-volume loop, although classically considered pathognomonic, does not accurately predict complications.

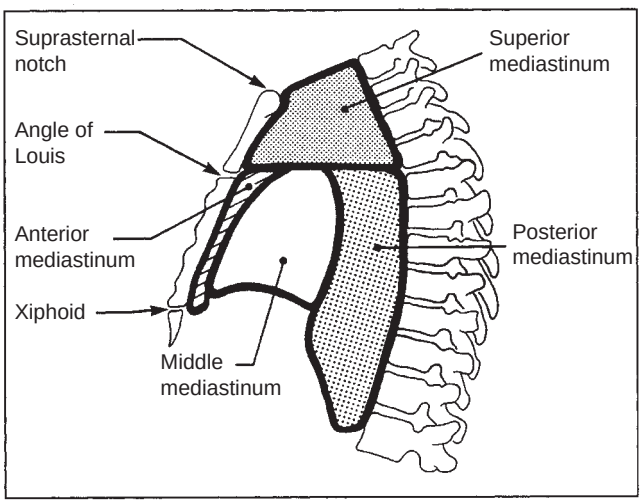

Fig. 64.1 The mediastinum is divided into superior and inferior portions. The inferior mediastinum is divided into anterior, middle, and posterior portions. (From Benumof JL: *Anesthesia for thoracic surgery,* 2nd ed. Philadelphia, WB Saunders, 1995, p 39.)

Implications

- Tracheobronchial tree compression
  - Inability to ventilate or oxygenate, with hypercarbia or hypoxia
  - Possible cardiorespiratory arrest
- SVC syndrome
  - Excessive bleeding if the surgical site involves the head, neck, or upper extremities
  - Unreliable drug or fluid delivery via upper extremity intravenous (IV) lines
  - Relative contraindication for jugular or subclavian central IV access
  - Potential for airway edema
- Compression of heart and pulmonary vessels
  - Hypotension or cardiovascular collapse

MANAGEMENT

Tracheobronchial Tree Compression

The best approach is prevention. However, if tracheobronchial tree compression does occur, the following maneuvers should be attempted:

- Change the patient's position to a lateral or semi-Fowler's position.
- Resume spontaneous ventilation.

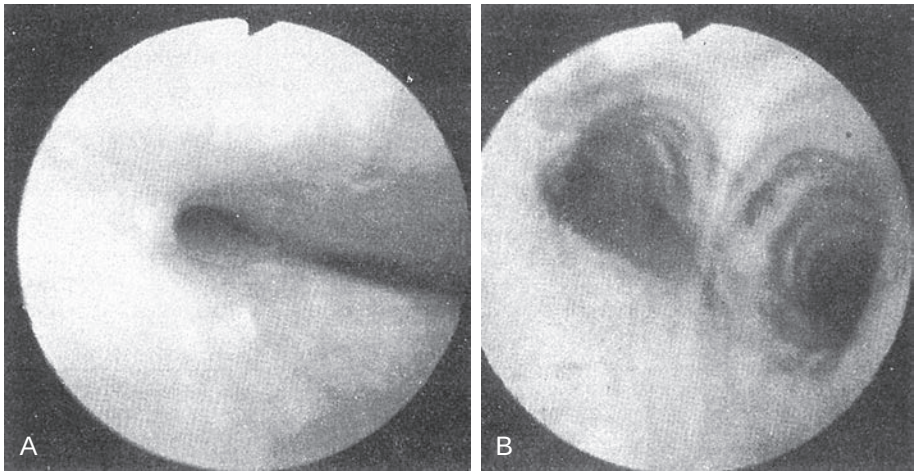

Fig. 64.2 Fiberoptic bronchoscopic appearance of the lower trachea in an anesthetized patient in the supine position (A) with a large anterior mediastinal mass that almost totally obstructs the trachea in the anteroposterior plane. With the patient in the sitting position (B), the lumen appears normal. (From Prakash UBS, Abel MD, Hubmayr RD: Mediastinal mass and tracheal obstruction during general anesthesia. *Mayo Clin Proc* 63:1004-1011, 1988.)

- Attempt to advance the endotracheal tube past the obstruction.
  - Consider using fiberoptic bronchoscopic guidance or an endotracheal tube changer.
  - Consider a smaller, flexible endotracheal tube.
- Attempt to bypass the obstruction and ventilate with a rigid bronchoscope.
- Oxygenate via femorofemoral cardiopulmonary bypass (unlikely to be successfully implemented in adequate time if not prepared for preoperatively).

Superior Vena Cava Syndrome

- Recognize the effect of associated airway edema on intubation, and consider awake fiberoptic intubation if difficulty is anticipated.
- Elevate the head of the bed to reduce venous pressure.
- Use lower extremity IV access as a more reliable route to the central circulation.
- Consider the use of diuretics and steroids or preoperative endovascular SVC stent.

Compression of Heart and Pulmonary Artery

- Perform intraoperative echocardiography to assess the degree of impairment.
- Position the patient to minimize compression (lateral or even prone, whatever the patient identified preoperatively as the least symptomatic position).
- Maintain venous return, pulmonary artery pressure, and cardiac output as needed with fluids, pressors, and inotropic agents.
- Spontaneous ventilation may help.
- Plan for emergent implementation of cardiopulmonary bypass (cannulate the femoral vessels under local anesthesia before induction of anesthesia).

TABLE 64.1 Perioperative Complications That May Arise From Mediastinal Masses

Complication	Manifestation	Mechanism
Airway compromise	Difficult intubation	SVC obstruction causing upper airway edema
	Upper airway obstruction	Mass effect or surgical trauma to recurrent laryngeal causing vocal cord dysfunction/paralysis
Respiratory compromise	Tracheobronchial obstruction	Distortion, malacia, or dynamic collapse of the trachea and/or mainstem bronchi leading to difficult ventilation/oxygenation
	Pulmonary edema	Left atrial compression causing increased pulmonary venous pressure
Hemodynamic compromise	Decreased preload	Cardiac compression of the right or left atrium or right ventricle impairing cardiac filling
	Right ventricular strain/failure	Compression of right ventricular outflow tract or pulmonary artery causing right ventricular pressure overload
	Hemorrhage	Bleeding from tumor after surgical manipulation, potentially exacerbated by SVC obstruction

SVC, Superior vena cava.

PREVENTION

In patients with significant vascular, cardiac, or airway compromise, preoperative radiation therapy to shrink the tumor or local anesthesia for the procedure (if feasible) should be strongly considered. A potential disadvantage of preoperative radiation therapy is that it may obscure the histologic diagnosis and jeopardize treatment. CT-guided transsternal core biopsy is an alternative diagnostic technique at some centers. A multidisciplinary approach (oncology, radiation oncology, surgery, and anesthesiology) is required to make an intelligent decision regarding the risk-benefit ratio for proceeding with therapy.

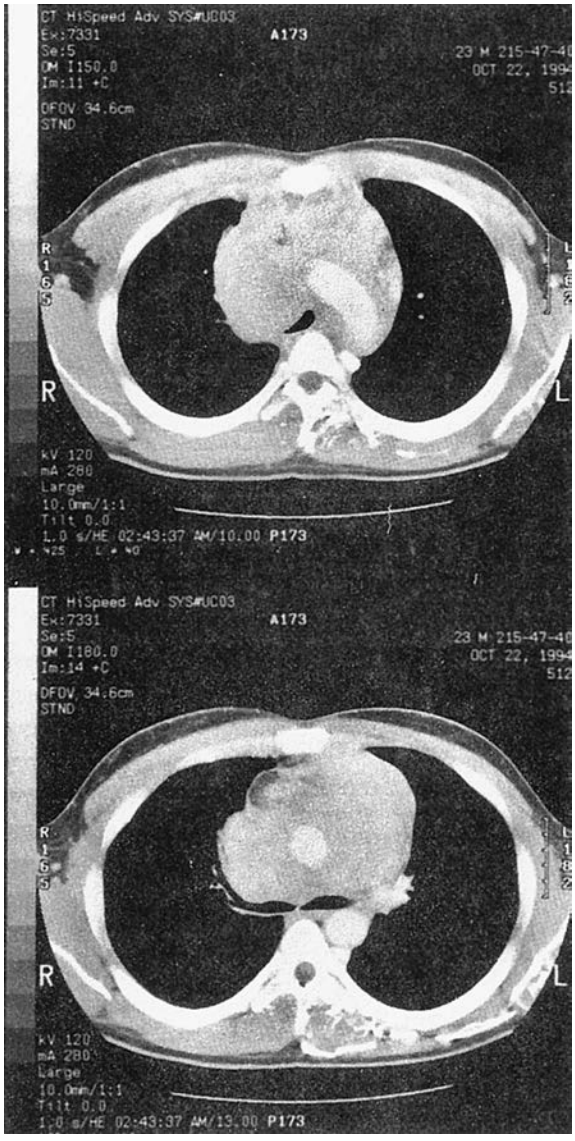

Fig. 64.3 Chest computed tomography scan showing extrinsic compression at the level of the trachea *(top)* and mainstem bronchi *(bottom).*

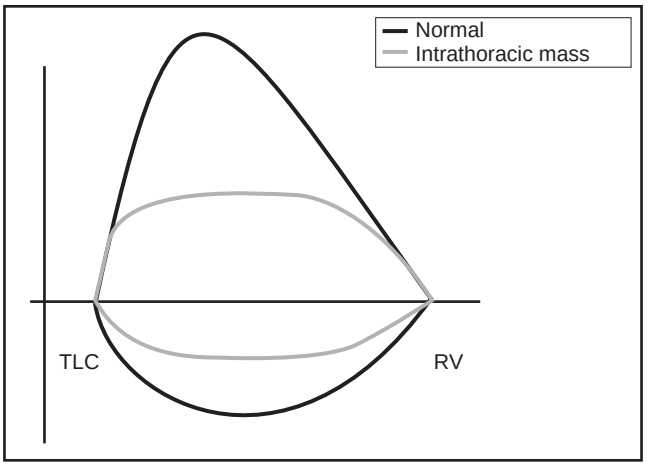

Fig. 64.4 Flow-volume loop for a patient with a normal airway and for a patient with an intrathoracic mass. *TLC,* Total lung capacity; *RV,* residual volume. (From Pullerits J, Holzman R: Anaesthesia for patients with mediastinal masses. *Can J Anaesth* 36:681-688, 1989.)

The anesthetic plan and required setup vary, depending on the proposed operation (and surgical approach), the severity of the patient's symptoms, and other coexisting conditions and diseases. For high-risk patients, the least invasive surgical plan is chosen and, when possible, local anesthesia and sedation planned. Medications that maintain the patient's respiratory drive, such as ketamine, dexmedetomidine, or midazolam, are frequently helpful. When GA is required, the following guidelines can be used:

- Have a low threshold for placing a preinduction arterial line in patients undergoing general anesthesia who have any symptoms or other evidence (e.g., CT scans) of airway compression. This will provide beat-to-beat blood pressure monitoring in the event of respiratory or hemodynamic compromise.
- A rigid bronchoscope should be prepared for use with the attending surgeon in the operating room for induction if there is particular concern about airway collapse.
- In the absence of contraindications (e.g., aspiration risk, difficult mask airway), slow induction of general anesthesia is preferred (IV or inhalation). Maintain spontaneous ventilation until effective positive-pressure ventilation is confirmed. If needed, perform tracheal intubation with succinylcholine (unless contraindicated); its short duration of action is advantageous in the event that muscle relaxation has a deleterious effect on the ability to ventilate the patient. Also, use the smallest dose of succinylcholine necessary (≤1.0 mg/kg).
- If feasible, perform fiberoptic intubation in an awake, spontaneously breathing patient. The fiberoptic bronchoscope can also be used to assess positional or dynamic airway collapse.
- Aim for a very smooth emergence and extubation sequence, because excessive coughing and straining can exacerbate both airway obstruction and the symptoms of SVC syndrome.
- If central venous access or monitoring is required (indications are related to coexisting disease), access should be obtained via the femoral route.
- Cardiopulmonary bypass on "standby" is unlikely to be implemented in time to prevent catastrophic neurologic injury in the event of airway obstruction or cardiovascular collapse, even with a prepared team and primed pump. Femoral cannulation before induction is a reasonable approach in the highest-risk patients.

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65 Methylmethacrylate

Bridget Perrin Pulos • Nabil M. Elkassabany

Case Synopsis

A 75-year-old woman presents for hemiarthroplasty after a femoral neck fracture. She has a history of hypertension, coronary artery disease, moderate pulmonary hypertension, and osteoporosis. Her medications include lisinopril and clopidogrel. The patient undergoes induction of general anesthesia, and the surgery proceeds uneventfully. During cementing of the prosthesis the patient develops severe hypotension, hypoxemia, and tachycardia.

PROBLEM ANALYSIS

Definition

Methylmethacrylate (MMA) is a pressurized bone cement used in orthopedic surgery. It is a polymer that is formed by mixing methylmethacrylate monomer in liquid form with an accelerator in powdered form. MMA is used in total hip and total knee replacement to implant the prosthesis, as well as for cemented hemiarthroplasty for femoral fractures, among other procedures. The cement is thought to undergo an exothermic reaction and then expand in the space between the prosthesis and the bone.

MMA is associated with bone cement implantation syndrome (BCIS). BCIS is a potentially fatal condition characterized by hypotension and hypoxia, with possible progression to pulmonary hypertension and right ventricular (RV) failure, loss of consciousness, arrhythmia, and even cardiac arrest. It is thought that increased pulmonary vascular resistance causes an acute decrease in RV ejection fraction and a distended right ventricle. The distended right ventricle may bulge into the left ventricle causing decreased left ventricular filling and lowering the cardiac output (Table 65.1). The syndrome can be seen at the time of cementation, femoral reaming, prosthesis insertion, joint reduction, or tourniquet deflation. Until recently there was no widely accepted standardized definition for BCIS, despite the well-known symptoms attributed to it. Therefore the true incidence of the syndrome is unknown. Additionally, there is likely underreporting of lesser degrees of BCIS.

In 2009 Donaldson and colleagues proposed a BCIS severity classification system to allow better characterization of the incidence and risk factors associated with the syndrome. Grade 1 was defined as moderate hypoxia or hypotension; grade 2 as severe hypoxia or hypotension or an unexpected loss of consciousness; and grade 3 as cardiovascular collapse requiring cardiopulmonary resuscitation (Table 65.2).

In 2014 Olsen and colleagues used this classification system to perform a retrospective study of 1016 patients undergoing hemiarthroplasty and found the overall incidence of BCIS to be 28%. The incidence of grades 1, 2, and 3 BCIS was 21%, 5.1%, and 1.7%, respectively. Importantly, they found that both 30-day and long-term mortality rates were significantly higher after a moderate or severe episode.

The pathophysiology of BCIS is not completely understood; however, several theories have been proposed, and it is possible that different mechanisms may play a role. The monomer-mediated model proposed that circulating MMA monomers cause vasodilation, leading to the observed hemodynamic changes. Although MMA is known to be a peripheral vasodilator, the amount that is released during orthopedic procedures is considerably less than that shown to cause hypotension in experimental models. The newer embolic model involves acute pulmonary microembolization. This model proposes that an increase in intramedullary pressure during cementing and reaming leads to embolization. The hemodynamic consequences of these emboli are thought to result from both mechanical obstruction to the pulmonary circulation and endothelial damage. This damage to the endothelium leads to vasoactive mediator release and increased vascular tone. Embolic showers can be seen in the right atrium, right ventricle, and pulmonary artery when intraoperative transesophageal echocardiography (TEE) is used. In one study the embolic load was shown to be greater for cemented versus uncemented arthroplasty. However, the embolic model also does not explain all aspects of BCIS. Embolization is not always associated with hemodynamic changes, and hypotension has been reported with MMA use in procedures where large amounts of embolism are not likely (such as percutaneous vertebroplasty). Some of the endothelial damage that is seen in these cases may be the result of release of various inflammatory mediators. It is likely that the true pathophysiology is a combination of these different mechanisms.

There are also occupational exposure issues related to MMA use. The US Environmental Protection Agency has set the permissible limit for occupational exposure to 100 parts per million over the course of an 8-hour work period. Acute exposure to very high levels of MMA can cause toxicity to the liver, as well as pulmonary edema. At very high levels, MMA has been shown to be teratogenic in mice, and there is a concern for toxic effects to the fetus for operating room personnel who are pregnant. Personal protective helmet systems and local suction can help minimize exposure to MMA in the operating room.

Diagnosis

BCIS is characterized by hypoxia, hypotension, or both occurring at certain times during surgery using MMA cement. The clinical signs and symptoms are similar to those that would be seen with pulmonary or fat embolism (Table 65.3). In an awake patient, mental status changes or loss of consciousness may be seen. There is a wide range of severity of BCIS, from a transient but significant decrease in arterial oxygen saturation, to cardiovascular arrest. If there is a large embolus, end-tidal CO_2 may decrease. Emboli can also cause petechiae and anuria, although these would be later signs.

TABLE 65.1 Bone Cement Implantation Syndrome Systemic Effects

Organ System	Effect
Cardiac	Decreased MAP, decreased stroke volume with increasing pulmonary vascular resistance → decreased RV ejection fraction
	Pulmonary hypertension → right-sided heart failure and eventually left-sided heart failure
	Cardiac arrhythmia
Pulmonary	Pulmonary emboli → increased pulmonary pressures and V/Q mismatch
Hematology	Activation of coagulation cascade and release of vasodilatory mediators
	Increased platelet aggregation → increased thrombosis
Central nervous system	Confusion, loss of consciousness
	If patient has PFO, potential for paradoxic emboli and stroke

MAP, Mean arterial pressure; *PFO,* patent foramen ovale; *RV,* right ventricular; *V/Q,* ventilation/perfusion.

TABLE 65.2 Donaldson and Colleagues' Severity Classification of Bone Cement Implantation Syndrome

Grade 1	Moderate hypoxia (arterial oxygen saturation <94%) or Moderate hypotension (decrease in systolic blood pressure >20%)
Grade 2	Severe hypoxia (arterial oxygen saturation <88%) or Severe hypotension (decrease in systolic blood pressure >40% or An unexpected loss of consciousness
Grade 3	Cardiovascular collapse requiring cardiopulmonary resuscitation

TABLE 65.3 Differential Diagnosis of Bone Cement Implantation Syndrome

Pulmonary Embolism	Fat Embolism
Myocardial infarction	Tachyarrhythmia
Stroke (neurocognitive changes)	Other cardiac or pulmonary conditions leading to pulmonary hypertension

Risk Assessment

Patients who are higher risk for BCIS may benefit from more invasive monitoring. Those patients include the elderly, patients with preexisting pulmonary hypertension or preexisting cardiac disease, and patients with osteoporosis. Surgical factors that are thought to increase the risk are pathologic fractures, intertrochanteric fractures, and long-stem arthroplasty. Additionally, anesthesia providers should be even more vigilant at certain key higher-risk times during the surgery, such as during cementing, prosthesis insertion, reduction of the joint, or tourniquet deflation.

MANAGEMENT

The mainstay of treatment of BCIS is supportive care. In patients who experience the greatest severity of symptoms, this may include intubation; invasive monitoring with an arterial line, central line, and/or pulmonary artery catheter; volume replacement; and pressors as needed. In some patients, TEE may be used to help guide management related to intravascular volume status and RV function. Patients should be placed on 100% Fio_2 to help minimize the increased pulmonary vascular resistance.

PREVENTION

For the highest-risk patients, the possibility of using an uncemented prosthesis should be discussed with the surgeons. If this is not possible, there may be other surgical techniques that can be used to minimize the embolic load such as lavaging the marrow cavity or placing a vent hole in the bone to reduce intramedullary pressure during reaming. In high-risk patients, preemptive invasive monitoring with an arterial line and/or a central line may be warranted to help manage BCIS should it occur. Although these measures will not prevent BCIS, maintaining appropriate volume status throughout the procedure will optimize patients for further resuscitation efforts if needed.

ACKNOWLEDGMENT

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66 One-Lung Ventilation

Danielle Shafiepour • Peter D. Slinger

Case Synopsis

A 72-year-old man is scheduled for robotic-assisted right upper lobe wedge resection for adenocarcinoma. His medical history is notable for stable coronary artery disease treated with coronary artery bypass grafting and a bare metal stent and hypertension treated with an angiotensin-converting enzyme (ACE) inhibitor. Preoperative pulmonary function testing reveals a forced expiratory volume in 1 second (FEV_1) of 85% predicted, a diffusing capacity of 56% predicted, and a ventilation/perfusion (V/Q) scan showing 65% of perfusion to the right lung. After intubation with a left double-lumen tube, the patient is positioned laterally, and lung isolation is achieved after reconfirmation of tube placement with a bronchoscope. Within 5 minutes of lung isolation, the patient begins to desaturate, gradually reaching a nadir of 88% at 30 minutes despite initial maneuvers to improve oxygenation on one lung.

PROBLEM ANALYSIS

Definition and Recognition

Hypoxemia used to be a frequent occurrence during one-lung ventilation (OLV) before the use of routine fiberoscopy and modern inhaled anesthetic agents that have less of an inhibitory action on hypoxic vasoconstriction. Although the majority of cases requiring OLV now proceed without significant desaturation when lung isolation is achieved successfully, significant desaturation may still occur in 1% to 10% of patients even when maintained on a fraction of inspired oxygen (Fio_2) of 1.0. This case illustrates how hypoxia may still pose a significant challenge to the anesthesiologist. An understanding of the determinants of lung perfusion during OLV and a systematic approach to dealing with hypoxia as outlined in this chapter will provide the anesthesiologist with strategies to manage cases such as the one described.

In the absence of endotracheal tube or bronchial blocker malposition, hypoxia during OLV is caused primarily by shunting of blood through the nonventilated lung. The development of atelectasis in the ventilated lung further worsens this by creating additional areas of low V/Q. The blood flow from these nonventilated areas then mixes with that from the ventilated lung segments and causes a decrease in Pao_2. Interestingly, no threshold saturation has been universally adopted as a safe lower limit during OLV; however, generally a saturation of 90% is often accepted, and in patients without significant comorbid disease, desaturations to the high 80s may be tolerated for short periods.

Optimal V/Q matching during OLV is achieved by maximizing perfusion to the dependent lung and maximizing pulmonary vascular resistance (PVR) in the nondependent lung. Many factors are at play in determining the proportion of pulmonary perfusion that flows through the nonventilated lung during OLV, and several are amenable to influence by the anesthesiologist (Fig. 66.1). Lung volumes influence PVR in a hyperbolic manner; at extremes the PVR increases whereas at functional residual capacity (FRC) it is at its lowest, which is ideal for the dependent lung. During anesthesia, atelectasis tends to develop in the dependent lung because of mechanical compression in the lateral position and gas absorption, particularly after inspiring pure oxygen during preoxygenation and before OLV. The end-expiratory volume of the dependent lung therefore trends toward residual volume in the absence of positive pressure to counteract these factors. Despite maintaining positive end-expiratory pressure (PEEP), a pig model of OLV demonstrates that much of the ventilated lung remains suboptimally aerated at end-expiration (Fig. 66.2). Position of the patient is an additional factor influencing the distribution of pulmonary blood flow, due to the effect of gravity. More recent studies call into question the magnitude of this effect on distribution of pulmonary perfusion as opposed to other characteristics, suggesting that gravity's effects are superimposed on a background of heterogeneous perfusion due to the underlying structure of the vascular bed. At least to some extent, lateral positioning does allow for a gravity-induced increase in perfusion to the dependent ventilated lung, thereby minimizing shunt.

The pulmonary vasculature itself is not a passive bystander; on the contrary, it assumes an active role in determining regional perfusion via hypoxic pulmonary vasoconstriction (HPV). In response to low alveolar oxygen tensions, pulmonary arterial smooth muscle constricts increasing regional resistance though the pulmonary vascular bed and redistributing flow away from hypoxic areas. This mechanism optimizes V/Q matching and is most effective when the hypoxic fraction of lung tissue corresponds to between 30% and 70% of the lung. The onset of this response is rapid, plateauing over approximately 20 minutes, followed by a delayed phase beginning after 40 minutes. The magnitude of this response in experimental settings (breathing 5% O_2 into the test lung) has been shown to increase pulmonary vascular resistance in the test lung by threefold to fivefold and decrease perfusion to that lung by 30% to 45%. Debate exists in the literature with regard to the presence of a preconditioning effect whereby the sensitivity of the response to hypoxia increases on repeat exposure; these disparities in results may reflect differences in experimental conditions such as duration of hypoxic exposure and interval before reexposure. HPV is attenuated by ACE inhibitors.

Surgical manipulation itself may influence the distribution of pulmonary blood flow. Although local release of vasoactive mediators may oppose HPV, retraction and mechanical interference with pulmonary blood flow can decrease perfusion of the nondependent (operated) lung.

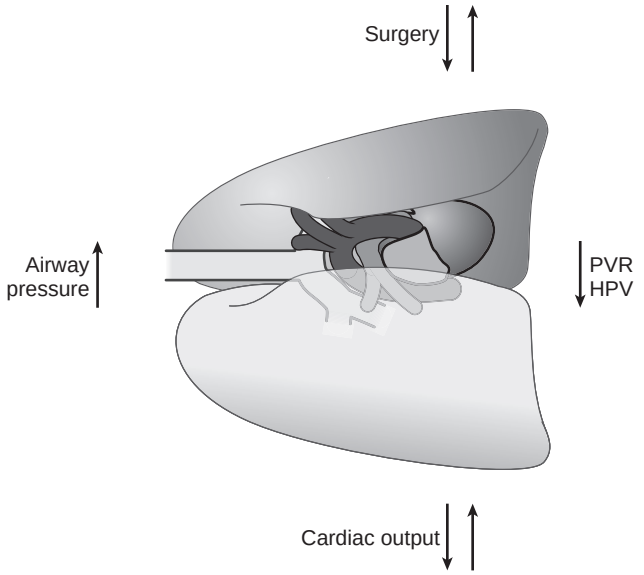

Fig. 66.1 The factors shown can influence pulmonary blood flow distribution during OLV in the lateral position according to the direction of the adjacent arrows. *HPV,* Hypoxic pulmonary vasoconstriction; *PVR,* pulmonary vascular resistance. (From Slinger PD, Campos JH: Anesthesia for thoracic surgery. In Miller RD, editor: *Miller's anesthesia,* 8th ed. Philadelphia, Elsevier, 2015, pp 1942–2006.)

Risk Assessment

As mentioned, the majority of patients when maintained on an Fio_2 of 100% with adequate positioning of a double-lumen tube or bronchial blocker will not have significant hypoxemia. Several factors listed in Box 66.1 have been identified that may predict desaturation during OLV.

Most of these factors relate directly to the proportion of blood that will be shunting through the nonventilated lung. A higher percentage of ventilation or perfusion to the operative lung and surgery on the larger right lung result in relatively more blood being shunted through the collapsed lung. Supine positioning will remove the beneficial effect of gravity to increase perfusion to the dependent ventilated lung.

Perhaps surprisingly, obstructive airflow limitation correlates inversely with risk of desaturation on OLV. Mechanisms that have been proposed include delayed collapse of the nondependent lung, persistent end-expiratory airflow in the dependent lung contributing to auto-PEEP, and altered mechanisms of hypoxic pulmonary vasoconstriction. The most significant factor correlating with hypoxia on OLV is the intraoperative Pao_2 on two-lung ventilation (TLV) before OLV. The TLV Pao_2 serves as a gauge of the ability of the respiratory system to optimize V/Q matching when faced with factors that promote mismatch such as general anesthesia, positive-pressure ventilation, and the lateral position.

As most of these factors are known well in advance of the surgery, this allows the anesthesiologist to be prepared for potential difficulty with oxygenation during such cases and apply prophylactic measures for prevention of hypoxia as outlined in the following section.

PREVENTION

Adoption of optimal ventilation strategies will help achieve adequate oxygenation in most cases and help reduce postoperative hypoxia from acute lung injury (ALI) for which OLV is understood to be a risk factor. Although most of this chapter deals with intraoperative hypoxia, the role of ventilatory strategy in minimizing ALI and postoperative hypoxia is one that deserves some attention. Damage to alveoli during OLV may result from barotrauma, volutrauma, atelectrauma from sequential tidal recruitment of collapsed alveoli, biotrauma related to the release of inflammatory mediators, and capillary shear stress. In an evidence-based review of OLV management, Brassard and colleagues propose a protective strategy with the following recommendations:

1. TLV period before OLV:
   - Ventilation with Fio_2 100% to afford a higher margin of safety at induction and to promote surgical lung collapse
   - Recruitment maneuvers after periods where derecruitment may occur such as bronchoscopy, noting that the optimal timing and level of pressure have not been established
   - Use of small tidal volumes (Vt) of 6 to 8 mL/kg calculated according to ideal body weight (IBW)
   - PEEP of 3 to 10 cm H_2O
2. OLV period:
   - Recruitment maneuver following lung isolation
   - Use of small Vt of 4 to 6 mL/kg (IBW)
   - Maintaining peak pressures less than 30 cm H_2O and plateau pressures less than 20 cm H_2O
   - Use of PEEP 3 to 10 cm H_2O

   Note the caveat that although this has a role in preventing lung injury, inappropriately low or high PEEP may worsen hypoxia. This may occur by increasing end-expiratory lung volume above FRC, thereby increasing PVR and diverting blood to the nonventilated lung. Inadequately low PEEP can promote derecruitment and atelectasis, increasing shunt in the ventilated lung.
   - PEEP should be titrated to optimize lung compliance, and evidence of auto-PEEP should be sought by observing for interrupted expiratory flows
   - Titrating Fio_2 to an Spo_2 of 92% to 96% to avoid oxygen toxicity and atelectasis, noting that 0.5 to 0.8 is adequate in most cases
   - Ventilating with a respiratory rate of 12 to 16 breaths per minute to avoid both excessive hypercapnia with low respiratory rates and auto-PEEP and high ventilator pressures due to short expiratory and inspiratory times with high respiratory rates
   - Maintenance of anesthesia with desflurane or sevoflurane as these agents do not impair HPV as much as older inhalation agents and may have lung protective effects
3. Reexpansion of operative lung:
   - Selective unilateral reexpansion to avoid overdistention of the more compliant nonoperative lung, slowly pressurizing to only 20 cm H_2O in the presence of lung resection
   - Using minimal Fio_2 to reexpand as this may attenuate reperfusion injury
4. TLV after OLV:
   - Maintenance of protective lung ventilation with small Vt (depending on the extent of resection)
   - Maintenance of PEEP and positive pressure until extubation because of resistant double-lumen tubes (DLTs) and tendency toward atelectasis in the newly expanded lung
   - Titration of Fio_2 to 92% to 96% to avoid hyperoxia and atelectasis
   - Postextubation consideration of continuous positive airway pressure (CPAP) for prevention of hypoxia in high-risk patients and for rescue in respiratory failure

In addition to optimizing ventilation, attention should be paid to the circulation during OLV. The relationship between cardiac output and its effect on oxygenation during OLV involves an understanding of both its effects on distribution of perfusion and its effects on the mixed venous oxygen saturation (Svo_2). Increasing cardiac output can cause dilation of the pulmonary bed and counteract HPV,

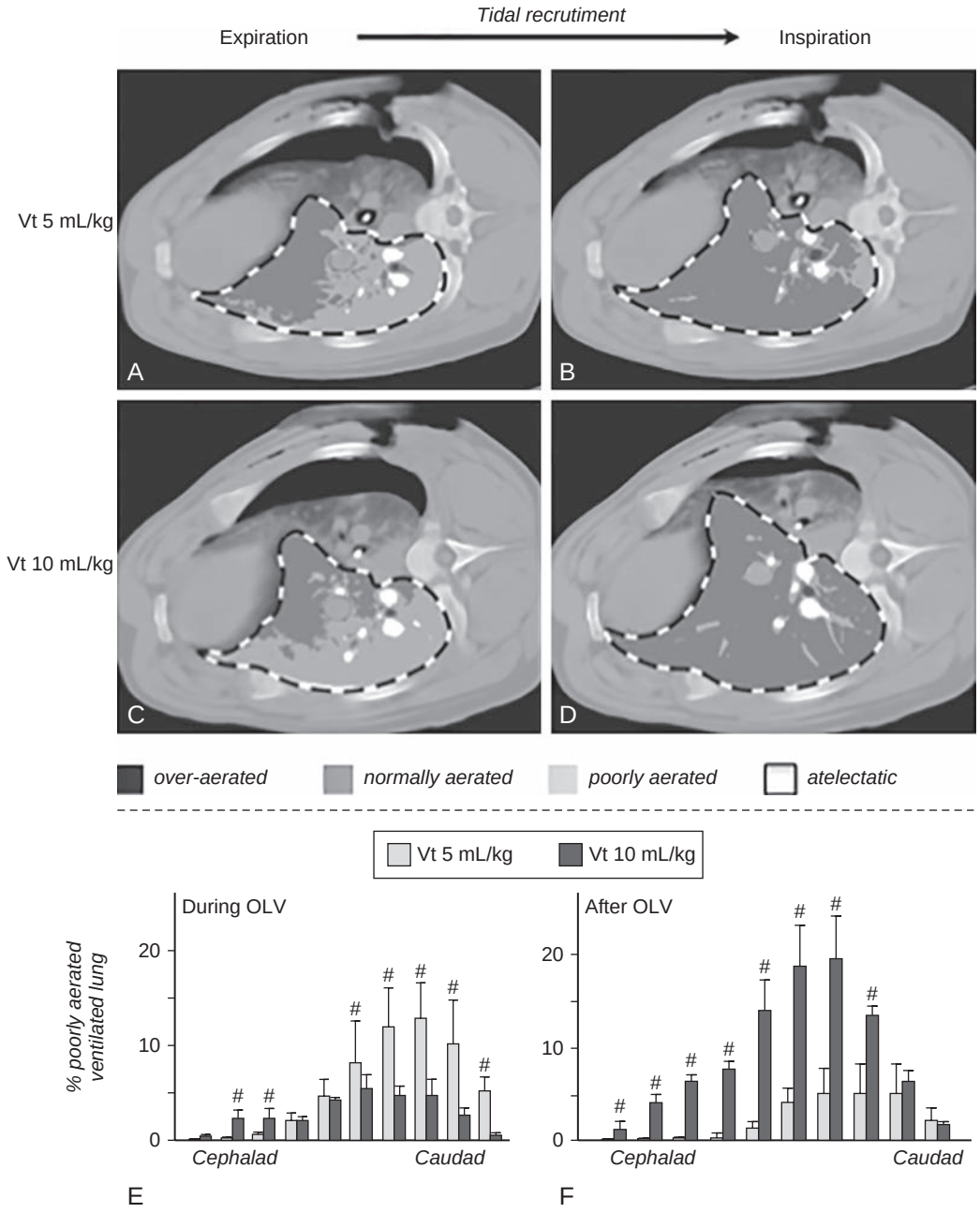

Fig. 66.2 A–F, A pig model of OLV shows that with PEEP of 5, there remains significant alveolar collapse at end-expiration with tidal volumes of both 5 and 10 mL/kg. In the period after OLV, there is more collapse in the higher tidal volume (Vt) group, which is attributed to repeated tidal recruitment with each breath. (From Lohser J, Slinger P: Lung injury after one-lung ventilation: a review of the pathophysiologic mechanisms affecting the ventilated and the collapsed lung. *Anesth Analg* 121[2]:302-318, 2015.)

thereby increasing shunt fraction and worsening oxygenation. It will also increase Svo_2 provided oxygen consumption is stable, which in the presence of significant shunting as seen in OLV can improve oxygenation. The net effect is that both increasing and decreasing cardiac output will have detrimental effects on oxygenation, and it should therefore be maintained at a normal level.

MANAGEMENT

The typical pattern of changes in arterial oxygenation observed during OLV consists of a Pao_2 nadir at 20 to 30 minutes followed by a stabilization or increase thereafter during the second phase of HPV. In the event of an abrupt or severe desaturation, restoring oxygenation is a priority, and resumption of TLV with Fio_2 of 1.0 may be necessary with deflation of the bronchial blocker or bronchial cuff on a DLT. Failure of appropriate lung isolation is a likely culprit and can be verified bronchoscopically once oxygenation has been restored. Proceeding without lung isolation may be an option in some cases; however, many thoracic procedures such as robotic and video-assisted thoracoscopic surgery require good lung isolation. Once oxygenation has been restored to an acceptable level and tube dislodgment has been ruled out, other techniques may be applied.

BOX 66.1 Factors That Increase Likelihood of Hypoxia During One-Lung Ventilation

- High percentage of ventilation or perfusion to the operative lung on preoperative V/Q scan
- Poor Pao_2 during two-lung ventilation, particularly in the lateral position intraoperatively
- Right-sided thoracotomy
- Normal preoperative spirometry (FEV_1 or FVC) or restrictive lung disease
- Supine position during one-lung ventilation

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *V/Q*, ventilation/perfusion.

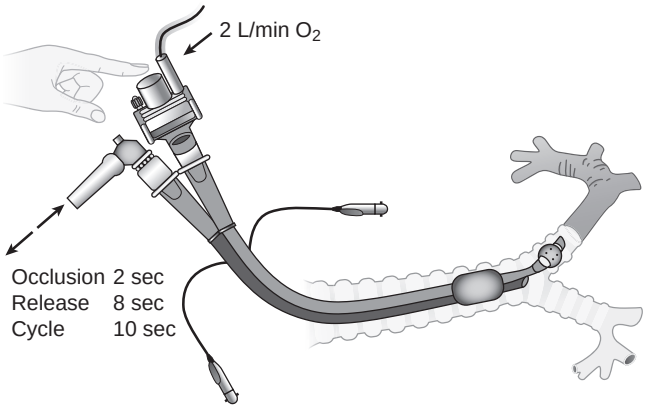

Fig. 66.3 Intermittent insufflation of oxygen into the nonventilated lung can be achieved by intermittent brief occlusion of a bacteriostatic filter attached to the nonventilated lumen of the DLT with O_2 flowing at 2 L/min into the gas sampling port on the filter. (From Slinger P: *Principles and practice of anesthesia for thoracic surgery.* New York, Springer, 2011.)

Acute decreases in cardiac output are not uncommon in thoracic surgery due to manipulation of the heart and great vessels and should be ruled out by assessing the blood pressure and communicating with the surgical team. Recruitment of the ventilated lung may be attempted as atelectasis often develops due to the high Fio_2 and mechanical compression; however, it must be noted that a transient decrease in saturation may be observed due to shifting of perfusion to the nonventilated lung during recruitment of the lower lung. Recruitment may be accomplished with either sustained pressures (e.g., gentle increase of pressure to 30 cm H_2O maintained for at least 10 seconds as advocated by Brassard and colleagues) or cycling maneuvers consisting of gradual stepwise increases in PEEP and peak pressure. It is possible that sustained pressure maneuvers may be more injurious to the alveolar-capillary interface. Additional PEEP to the ventilated lung may be considered, and although a starting value of 5 cm H_2O is often recommended, a more fine-tuned approach may be possible by performing a PEEP decrement trial seeking the maximum dynamic compliance as described by Ferrando and colleagues. If hypoxia persists an arterial gas should be sent to ensure that ventilation is adequate because respiratory alkalosis can impair the efficacy of HPV, and significant respiratory acidosis may increase PVR disproportionately in the ventilated lung, also worsening shunt.

If these measures do not adequately improve oxygenation, consideration should be given to applying CPAP with oxygen to the nondependent lung. This can be accomplished with a commercial circuit or simply a PEEP valve with an oxygen source. CPAP of only 2 cm H_2O has been shown to improve oxygenation provided that it is applied following a recruitment maneuver of the nonventilated lung as atelectatic alveoli have a high opening pressure (>0 cm H_2O). The recruitment will require transient interruption of the surgical procedure, and with thoracoscopic procedures even a small amount of CPAP may impair surgical view. Other methods have been described for intermittent insufflation of oxygen to the surgical lung. One such description involves attaching a standard bacterial filter to the nonventilated lumen of the DLT and connecting oxygen flowing at 2 L/min to the gas sample analyzer port (Fig. 66.3). By manually occluding the open end of the filter for 2 seconds, approximately 66 mL of oxygen will flow into the nonventilated lung, which did not negatively affect the surgical exposure in a series of 26 thoracotomy patients.

If CPAP is not practical or sufficiently effective, various methods exist to partially ventilate the nonventilated lung. Suggested mechanisms include the following:

1. *Oxygen insufflation to selective segments* (Fig. 66.4): Attaching 5 L/min of O_2 to the suction port on a bronchoscope allows the operator to selectively insufflate portions of the operative lung that are remote from the surgical site by pressing the suction trigger. The surgeon can alert the anesthesiologist to any overinflation observed on the videoscope.
2. *Selective lobar collapse:* Directing a bronchial blocker into one lobar bronchus to occlude only a specific lobe will allow for ventilation to the remaining portion of that lung. The blocker has to be placed in the correct lobar bronchus at the time of intubation. This will interfere with surgical exposure in some cases.

Improving V/Q matching can also be achieved by mechanically restricting perfusion to the operative lung. The surgeon may be asked to clamp the pulmonary artery on the operative side, bearing in mind that this represents an acute afterload increase to the right side of the heart.

Finally, the degree of shunting can be influenced by pharmacologic factors. Although the modern volatile anesthetics do not adversely affect HPV as much as older ones, limiting their use to 1 MAC may be beneficial. Additional systemic vasodilators should be discontinued as appropriate because they may augment the shunt fraction by preferentially dilating the vasculature of the more constricted nonventilated lung.

The selective administration of vasodilators to the vascular bed of the ventilated lung has been attempted via the inhalational route with or without the addition of systemic vasoconstrictors to enhance the HPV effect in the nonventilated lung. Inhaled nitric oxide (iNO), a selective pulmonary vasodilator, has been studied for this purpose. Although it has failed to consistently show an oxygenation benefit when used alone, the combination of iNO at 20 ppm and the intravenous vasoconstrictor almitrine at 4 μg/kg/min has been shown to improve oxygenation during OLV in humans. The relative contribution of each drug is not clear from these results, however, and a small randomized study of 16 patients showed a significant benefit from almitrine alone on Pao_2 in OLV. This is of theoretic interest only as almitrine, previously marketed as a respiratory stimulant, is not commercially available in North America. Other inhaled vasodilators have been studied including both prostacyclin (PGI_2, also known as flolan) and the more rapidly cleared prostaglandin E_1 (PGE_1). A trial of PGE_1 in lung transplant patients during the first lung implantation after pulmonary artery clamping (during OLV and perfusion) showed that PGE_1 improved pulmonary artery pressure (PAP); however, it also improved the Pao_2/Fio_2 ratio and decreased shunt within the ventilated lung presumably by preferentially vasodilating better ventilated portions of the lung. Inhaled PGI_2, which can be delivered directly to a ventilator circuit via nebulization, has been shown to reduce PAP similarly to iNO in heart and lung transplant patients and is an appealing alternative as it is cheaper to deliver than iNO. The combination of inhaled PGI_2 (50 ng/kg/min) and intravenous phenylephrine has been reported in a case study to cause a dramatic improvement in oxygenation in a hypoxemic patient undergoing a video-assisted thoracoscopic surgery (VATS) procedure. Proposed benefits include permitting patients with marginal lung function to undergo OLV with increased safety and helping to reduce the need for cardiopulmonary bypass in lung transplant recipients.

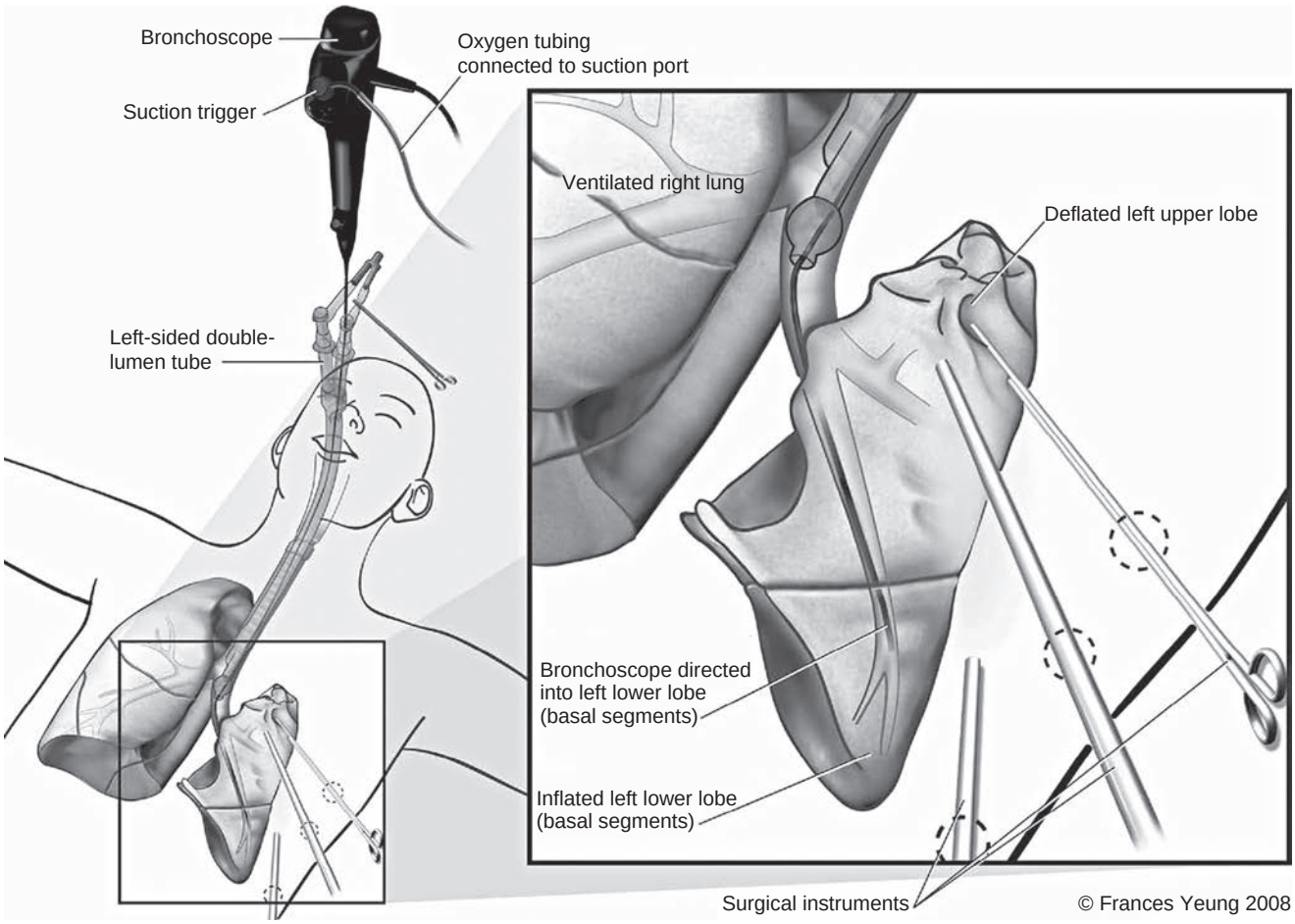

Fig. 66.4 Oxygen can be insufflated into selected lobes or segments by attaching O_2 tubing flowing at 5 L/min to the suction port of a fiberoptic bronchoscope and pressing the suction trigger when the bronchoscope has been introduced to the appropriate lung segment. (From Slinger P: *Principles and practice of anesthesia for thoracic surgery*. New York, Springer, 2011.)

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67 Open Globe Injury

Alvaro Andres Macias

Case Synopsis

A 35-year-old man presents to the emergency department complaining of left eye pain and loss of vision after being hit by a nail in the left eye while working in a construction project. He had eaten a full lunch 1 hour before the accident.

PROBLEM ANALYSIS

Definition

Eye injuries are most commonly caused by a foreign body (35% of cases), open wounds (25% of cases), contusions (25% of cases), and burns (15% of cases). Approximately 35% of eye injuries occur in patients younger than 17 years old. Eye injury is the most common cause of monocular blindness in the United States.

Recognition

Generally, the diagnosis of open globe injury can be surmised from the history and physical examination. Trauma to the head or face, foreign bodies such as metal or wood pieces, and industrial accidents are usually identified during the initial assessment.

In any patient who sustains trauma to the head, the globe and vision must be evaluated.

Risk Assessment

The goals of anesthesia for eye surgery are to provide anesthesia and profound analgesia; avoid coughing, retching, or vomiting; and avoid forceful blinking or crying. Damaging increases in intraocular pressure (IOP) (Box 67.1) can cause extrusion of the ocular contents in patients with an open globe.

The most common risk and concern associated with open globe injury besides extrusion of the eye contents is a full stomach. This risk involves not only the possibility of aspiration of gastric contents but also the fact that drugs or maneuvers used to manage the patient can cause an increase in IOP. Another significant concern is the occurrence of endophthalmitis. Most guidelines recommend that the eye should be repaired within 24 hours of the eye injury. Antibiotics should be started as soon as possible.

BOX 67.1 Drugs or Factors That May Increase Intraocular Pressure

Hypoxemia, hypercarbia, acidosis
Hypertension
Coughing, vomiting, laryngoscopy, tracheal intubation
Excessive cricoid pressure
Ketamine, succinylcholine
Increased extraocular muscle tone
Increased extraocular contents (tumor, hemorrhage)

Normal blinking increases IOP by approximately 5 to 10 mm Hg from baseline (normal IOP ranges from 10 to 20 mm Hg). Hypoxemia may raise IOP via vasodilation of the choroidal arteries. Sustained hypertension may increase IOP, and induced hypotension may decrease IOP. Vomiting, coughing, or "bucking" causes the most dramatic increase in IOP by causing congestion in the venous system, impeding the outflow of aqueous humor, and increasing the volume of choroidal blood. This increase in pressure may be as high as 30 to 40 mm Hg. In poorly anesthetized patients, laryngoscopy can increase IOP by up to 20 mm Hg.

Implications

Following induction of anesthesia, the administration of succinylcholine increases IOP by approximately 5 to 10 mm Hg for about 5 to 10 minutes. IOP returns to baseline after that period of time. In the open globe, however, the IOP is atmospheric pressure. There are no reports of extrusion of ocular contents in patients who presented with a ruptured globe and received succinylcholine for intubation.

MANAGEMENT

Preoperatively, a detailed history of previous medical conditions should be obtained, and any previous reactions to anesthesia should be noted. The clinician should take measures to decrease and avoid increasing IOP (Box 67.2). Large doses of narcotics should be avoided because they can cause nausea and vomiting and lead to respiratory depression and CO_2 retention with subsequent increase in IOP. Prophylaxis against aspiration may include a nonparticulate antacid, metoclopramide to enhance gastric emptying, and an H_2-receptor antagonist to elevate gastric fluid pH and reduce gastric acid production.

Periocular local anesthesia with intravenous sedation may be considered in patients with anterior chamber injuries (foreign body), but it is important to remember that eye blocks increase the IOP and subsequently the risk of eye content extrusion. In pediatric cases, general anesthesia is the preferred technique. The use of a local anesthetic technique depends on the patient's status, the surgeon's willingness, associated injuries, and the severity of the open globe injury. General anesthesia is usually preferred, however. The patient should be preoxygenated, and pressure on the eye by the facemask should be avoided. Although the use of succinylcholine is controversial, the rise in IOP can be lessened by pretreatment with remifentanil in doses of 1 to 3 μg/kg, lidocaine 1 to 1.5 mg/kg, and an induction dose of propofol 1.5 to 3 mg/kg or fentanyl 1 to 2 mcg/kg.

Rapid-sequence induction can be accomplished without succinylcholine, using a nondepolarizing agent after preoxygenation,

BOX 67.2 Drugs or Factors That May Decrease Intraocular Pressure

Hypothermia
Inhalational anesthetics
Hyperventilation (hypocarbia, alkalosis)
Reduced extraocular muscle tone

cricoid pressure, and induction with propofol or sodium pentothal. Rocuronium 1.2 mg/kg can be used for rapid-sequence induction (thereby shortening the time to relaxation to approximately 60 seconds). The previous concern of a prolonged motor block when rocuronium is used for rapid-sequence induction is no longer a concern since the recent approval of sugammadex in the United States.

Ketamine's effect on IOP is controversial; however, it may cause nystagmus and blepharospasm and therefore should not be used in ophthalmologic surgery. Etomidate may decrease IOP, but it can cause unpredictable myoclonus, with consequent elevation of IOP. General anesthesia can be maintained with either inhaled anesthetics or a total intravenous anesthesia (TIVA) technique, which could be beneficial in avoiding postoperative nausea and vomiting.

Postoperatively, before extubation, the stomach should be decompressed, the oropharynx suctioned, and an antiemetic such as a serotonin antagonist administered. Intravenous lidocaine (1.5 mg/kg) may be given to reduce coughing during emergence. If the patient has been NPO for more than 8 hours, a deep extubation technique can be considered.

PREVENTION

- Take the necessary precautions to prevent coughing, straining, bucking, and vomiting.
- Try to minimize hypercarbia, hypoxia, and increases in blood pressure.
- Attempt to minimize the risk of aspiration while ensuring the patient's safety.
- Provide prophylaxis for postoperative nausea and vomiting with H_2-receptor antagonists, metoclopramide, and nonparticulate antacids.

ACKNOWLEDGMENT

The author wishes to thank Dr. Stacey L. Allen and Dr. Ellen Duncan for their contributions to the previous edition of this chapter.

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68 Perioperative Psychological Trauma

Zeev N. Kain

Case Synopsis

A 4-year-old boy presents for inguinal hernia repair. In the preoperative holding area, he appears scared and agitated and refuses to leave his mother's lap. On separation, he cries and tries to escape from the anesthesiologist. One week after surgery, the mother reports major behavioral changes in the boy since his operation, including nightmares and temper tantrums.

PROBLEM ANALYSIS

Definition

The perioperative period is frequently an extremely traumatic time for both children and parents. Subjective feelings of tension, apprehension, and worry characterize preoperative anxiety in children. Preoperative anxiety stimulates sympathetic, parasympathetic, and endocrine systems, leading to increases in heart rate, blood pressure, and cardiac excitability. These reactions reflect the child's fear of separation from parents and the home environment, loss of control, and fear of unfamiliar routines, surgical instruments, and hospital procedures. Thus it is no surprise that up to 65% of all children undergoing anesthesia and surgery develop extreme anxiety and fear during the perioperative period.

Of perhaps greater importance than the child's behavior in the preoperative holding area is the child's behavior after the surgery. Clinicians and investigators have long recognized postoperative psychological reactions such as general anxiety, nighttime crying, enuresis, separation anxiety, and temper tantrums. These behavioral changes are of particular concern if they persist for an extended period and negatively affect the child's responses to subsequent medical care or interfere with his or her emotional and cognitive development.

Recognition

Children having anesthesia and surgery express many forms of anxiety. Some explicitly verbalize their fears, whereas others express their anxiety behaviorally. Many children look scared, become agitated, breathe deeply, tremble, stop talking or playing, or begin to cry. Others may wet themselves unexpectedly, have increased motor tone, and actively attempt to escape from medical personnel. The specific maladaptive behaviors in any particular child can vary widely. However, the most common ones are separation anxiety, eating problems, increased fear of doctors and hospitals, bad dreams or nightmares, and temper tantrums.

Perioperative anxiety is associated with increased levels of serum cortisol, epinephrine, growth hormone, and adrenocorticotropic hormone. Reports show a significant correlation between increased heart rate and blood pressure and behavioral ratings of anxiety. Preoperative anxiety is often associated with a relative vagal predominance in sympathovagal-mediated heart rate variability.

Risk Assessment

The incidence of preoperative anxiety in young children is reported to range from 40% to 60%. Children of anxious parents, shy and inhibited children, children with a history of previous surgery, children with a history of previous poor-quality medical encounters, and children ages 4 to 7 years are at increased risk for the development of preoperative anxiety.

Postoperative maladaptive behavioral responses, such as general anxiety, nighttime crying, enuresis, separation anxiety, and temper tantrums, occur in 13% to 40% of children 2 weeks after surgery; 3% to 20% of these children continue to demonstrate maladaptive behaviors 6 months after surgery (Fig. 68.1). More significant behavioral changes, such as new-onset enuresis, are rare and present in only 0.8% of children. It is important to emphasize that although a large number of young children develop negative behavioral responses in the immediate postoperative period, the magnitude of these changes is limited, and only a minority of children have persistent, long-term maladaptive behavioral responses.

The child's age, baseline temperament, number of siblings, enrollment in day care, and preoperative anxiety are all independent predictors for postoperative maladaptive behaviors in multivariate models (Tables 68.1 and 68.2). Genitourinary surgery is associated with the highest incidence of postoperative behavioral changes. Pressure-equalizing myringotomy and tympanic membrane tube placement have the lowest incidence of postoperative negative behavioral changes.

Implications

Preoperative anxiety may be a hardship on both the child and the parents and lead to immediate postoperative negative behavioral responses. Long-lasting psychological effects that influence the child's response to subsequent medical care and interfere with normal development have been described. Although reports are conflicting, they suggest that preoperative anxiety may delay gastric emptying and increase gastric acidity; therefore some practitioners consider this response to be a risk factor for aspiration pneumonitis. Preoperative anxiety is also associated with an increased risk of

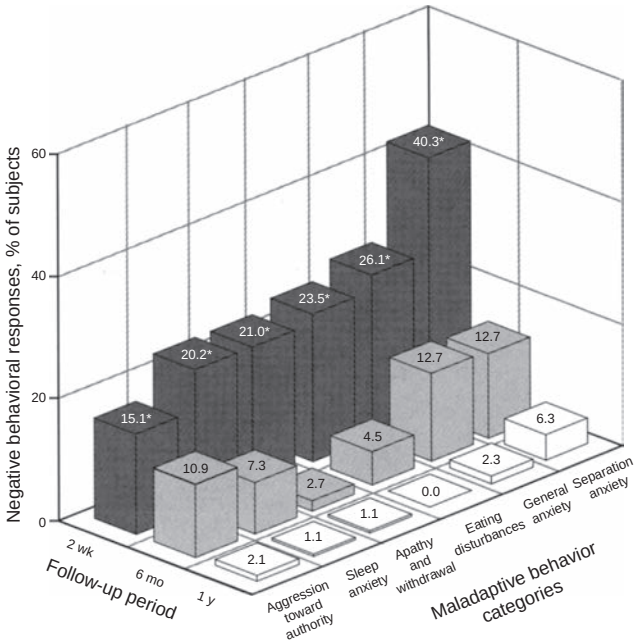

Fig. 68.1 Changes over time in the prevalence of negative behavioral responses based on the Posthospitalization Behavior Questionnaire. Separation anxiety was the most common maladaptive behavior reported by parents at both 2 weeks (40.3%) and 6 months (6.3%). The prevalence of behaviors in all six categories decreased significantly from 2 weeks to 6 months and 1 year (numbers in bars represent percentages of total subjects). *$P < .05$. (From Kain ZN, Mayes LC, O'Connor T: Preoperative anxiety in children. Predictors and outcomes. *Arch Pediatr Adolesc Med* 150[12]:1238-1245, 1996.)

TABLE 68.1 Risk Factors for Negative Behavioral Changes 2 Weeks After Surgery

Predictor Variables	Outcome	Relative Risk (95% CI)
4 vs. 6 years of age	Separation anxiety	9.4 (1.2–39)
	General anxiety	3.3 (1.1–7.8)
Not enrolled vs. enrolled in a day-care facility	Separation anxiety	6.6 (1.2–29)
Very anxious mother vs. calm mother in the holding area[a]	Apathy and withdrawal	6.6 (1.6–19.1)
	Sleep anxiety	3.9 (1.1–14)
	Separation anxiety	3.4 (1.2–6.7)
Child who is very anxious on separation vs. one who is calm on separation[b]	Eating anxiety	4.2 (1.3–8.7)
No siblings vs. siblings	Separation anxiety	3.5 (1.3–9.6)
Child who is very impulsive vs. one who is not very impulsive[c]	General anxiety	2.7 (1.1–6.8)

CI, Confidence interval.
[a]"Very anxious" is defined as an anxiety score in the upper 25th percentile on the State-Trait Anxiety Inventory (STAI) state subscale; "calm" is defined as a score in the lower 25th percentile on the same scale.
[b]Measured by the Clinical Anxiety Rating Scale.
[c]"Very impulsive" is defined as an impulsivity score in the upper 25th percentile on the Emotionality, Activity, Sociability, Impulsivity Instrument; "not very impulsive" is defined as a score in the lower 25th percentile on the same instrument.
From Kain ZN, Mayes LC, O'Connor T: Preoperative anxiety in children. Predictors and outcomes. *Arch Pediatr Adolesc Med* 150(12):1238-1245, 1996.

TABLE 68.2 Risk Factors for Negative Behavioral Changes 6 Months After Surgery

Predictor Variables	Outcome	Relative Risk (95% CI)
No siblings vs. siblings	General anxiety	3.0 (1.4–6.9)
	Separation anxiety	2.0 (1.1–3.5)
	Aggressiveness	2.0 (1.1–4.1)
Very anxious child vs. calm child in the holding area[a]	Eating anxiety	NA[b]
Very anxious mother vs. calm mother in the holding area[c]	Sleep anxiety	4.8 (1.2–20.4)

[a]"Very anxious" is defined as an anxiety score in the upper 25th percentile on the Venham Picture Test; "calm" is defined as a score in the lower 25th percentile on the same test.
[b]Not applicable; relative risk cannot be calculated because of a 0 value—0% vs. 17% ($P = .04$).
[c]As measured with the State-Trait Anxiety Inventory (STAI) state subscale.
CI, Confidence interval.
From Kain ZN, Mayes LC, O'Connor T: Preoperative anxiety in children. Predictors and outcomes. *Arch Pediatr Adolesc Med* 150(12):1238-1245, 1996.

symptoms of emergence delirium on awakening from anesthesia, as well as altered cortisol and epinephrine responses over the first 24 hours after surgery.

MANAGEMENT

Behavioral modification and pharmacologic agents are the two preoperative interventions directed toward reducing perioperative anxiety.

Behavioral Modification

Parental presence during the induction of anesthesia has been suggested as an alternative to preanesthetic medication. The potential benefits of parental presence include the following:

- Avoidance of screaming and struggling (separation anxiety)
- Reduction in the child's anxiety during induction
- Potential reduction of the long-term behavioral effects of surgery

Common objections to parental presence include the following:

- Disruption of the operating room routine
- Compromise of operative sterility
- Crowded operating rooms
- Additional stress on the anesthesiologist

Experimental data do not support the routine use of this intervention. Although earlier studies suggested reduced anxiety, more recent reports indicate that routine parental presence during the induction of anesthesia is not always beneficial. Children who benefit are the following:

- Generally, those older than 4 years
- Those with a shy and inhibited personality
- Those with a calm parent

Most parents prefer to be present during the induction of anesthesia, regardless of the child's age or previous surgical experience (even those whose children received sedative premedication at a previous surgery). Among parents present during the induction of anesthesia, the vast majority believe that they were of some assistance to the child and the anesthesiologist. However, more than 90% of parents report feeling some degree of anxiety during induction. Although this is clinically significant, it is not sufficiently debilitating to cause concern for the parents' health. Parental presence during the induction of anesthesia is increasing in the United States, even though available data indicate that it is beneficial for only some children. All factors and circumstances should be considered whenever the question of parental presence arises. Research in this area is now focusing more on what

parents do during induction of anesthesia rather than their mere presence or absence.

Pharmacologic Agents

Sedative premedication before surgery is an effective and widely used method for decreasing anxiety in young children. The primary goal of such premedication is to facilitate smooth and anxiety-free parental separation. A detailed discussion of preanesthetic medication in children is beyond the scope of this chapter. Only the most commonly used agents are discussed.

Midazolam is by far the most commonly used agent for premedication. It has a rapid onset and offset of action and has predictable effects, without causing cardiorespiratory depression. It can be given by any route, depending on the clinical setting. However, when used for preoperative anxiety, it is most commonly administrated orally (0.5 mg/kg) or nasally (0.2 mg/kg). When the drug is mixed with flavored syrup or Tylenol and administered orally, midazolam provides excellent sedation and anxiolysis in 20 to 30 minutes. Despite the high incidence of crying on nasal instillation, this provides predictable effects within 10 minutes. Midazolam can also be given per rectum (0.3 to 0.4 mg/kg), although older children may object to this route.

Ketamine is especially useful as a premedication or induction agent for uncooperative patients. When mixed with a cola-flavored soft drink and given orally (6 mg/kg), ketamine provides predictable sedation in 20 to 25 minutes. The nasal route provides good sedation at similar doses.

Fentanyl's lipid solubility makes it ineffective as an oral premedication. However, oral transmucosal absorption in the form of a fentanyl lollipop can produce effective preoperative sedation and facilitate the inhalational induction of anesthesia. Transmucosal fentanyl (10 to 15 μg/kg) has been reported to cause facial pruritus, and perioperative nausea and vomiting occur in a significant number of children.

Finally, it is important to emphasize that routine preoperative administration of sedatives to all children may result in increased pharmacy costs and the need for additional nursing staff and appropriately equipped bed space in the holding area. It is therefore important to identify the population at high risk for preoperative anxiety and use preoperative sedatives only for those children.

PREVENTION

Preoperative behavioral preparation programs are available, but increasingly fewer US hospitals routinely offer them. These programs consist of child and family preoperative teaching, an orientation tour, and role-playing using dolls to allow the child to become familiar with a new and anxiety-provoking environment. This familiarity may enhance cooperative behavior and lessen anxiety in the preoperative holding area and operating room. Although most studies suggest that behavioral preparation of children reduces stress and enhances coping mechanisms, other reports indicate that such programs may actually "sensitize" younger children.

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Peripheral Vascular Surgery 69

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Case Synopsis

A 74-year-old woman with a long-standing history of insulin-dependent diabetes, hypertension, chronic kidney disease, and a 50 pack-year smoking history requires right lower limb surgical revascularization due to lifestyle-limiting claudication. The patient is on carvedilol, simvastatin, lisinopril, and insulin. She describes chronic angina after ascending over two flights of stairs that resolves with rest. A dobutamine stress echocardiogram demonstrates a single segment of basal inferior hypokinesis at rest and on stress imaging. General anesthesia with endotracheal intubation is planned. There is a possibility of using upper extremity vessels as graft material. An hour after uneventful surgery, while the patient is in the recovery unit, the surgeon recognizes impending graft thrombosis after the loss of Doppler signals. The graft must be reexplored in the operating room.

PROBLEM ANALYSIS

Definition

Peripheral arterial disease (PAD) is characterized by atherosclerotic occlusive disease of the lower extremities. PAD, cerebrovascular disease, and coronary artery disease are the three major syndromes of atherosclerosis. PAD affects at least 8 to 12 million Americans and is associated with significant morbidity and mortality and decreased quality of life.

The strongest risk factors for PAD are diabetes and smoking. Other well-known risk factors are advanced age (>60 years), hypertension, and hyperlipidemia. The Fontaine and Rutherford classification systems are used to grade the severity of clinical symptoms reported by patients, with a higher grade indicating a higher severity of disease. The Rutherford scoring system is more commonly used in newer scientific literature. These two classification systems are based on an ischemia model to assess the risk of amputation versus the benefit of revascularization and hence may not provide the same prognostication in diabetic patients with threatened limbs.

When PAD is symptomatic, the most common complaint is intermittent claudication (IC). However, most patients are either asymptomatic or have symptoms other than IC.

On the other end of the spectrum are patients who present with life-threatening or acute limb ischemia (ALI), manifested by pain at rest; gangrene; and chronic, nonhealing wounds. In reality, ALI is a complex interplay of multiple pathogenetic mechanisms rather than progressive atherosclerosis. *Acute limb ischemia* (ALI) is defined as a sudden (<2 weeks) decrease in limb perfusion that threatens the viability of the limb. The degree of ischemia is related to the extent of occlusion, distal runoff, and maturity of collateral arteries. Limb viability is acutely threatened in ALI as opposed to chronic limb ischemia (CLI) because there is insufficient time for collateral blood supply to circumvent the occlusion.

The incidence of ALI requiring hospitalization in the United States is approximately 26 per 100,000 compared with approximately 200 per 100,000 per year for CLI. Patients who present with acute limb ischemia are systemically ill and have three times higher risk of perioperative mortality (approximately 10% to 25%) compared with patients with CLI. Hence, accurate and prompt diagnosis is essential to increase the chances of limb preservation and to decrease mortality. These patients require emergent revascularization within 6 hours to prevent complete limb ischemia and extensive tissue necrosis.

Clinical features of acute limb ischemia are commonly grouped into a mnemonic known as the six *P*s: paresthesia (or anesthesia), pain, pulselessness, pallor, poikilothermia (limb's temperature equalizes with ambient temperature), and paralysis. Apart from paralysis and anesthesia, these clinical signs and symptoms are often nonspecific and have poor correlation with completeness of vascular occlusion. Pain on squeezing the affected muscle indicates infarction and impending irreversible tissue damage. If the patient still has the ability to wiggle his or her fingers or toes and sensations are still present, the limb is likely salvageable with urgent revascularization within 6 hours. Attempting revascularization 10 to 12 hours after severe ischemia is often unsuccessful due to sequelae of the systemic inflammatory response and ischemia-reperfusion injury.

Causes of acute limb ischemia can be broadly categorized into (1) acute emboli (60% of cases), from the heart (80%) or a diseased artery (20%), and (2) acute thrombosis (30% of cases) of a limb artery (e.g., popliteal aneurysm) or bypass graft. Other causes include trauma (blunt or penetrating), malperfusion (due to aortic or isolated peripheral artery dissection), iatrogenic injury (postprocedural, intraarterial drug injection), coagulopathy (e.g., heparin-induced thrombocytopenia [HIT] syndrome), and sepsis (particularly pneumococcal and meningococcal). Of note, venous gangrene may be mistaken for acute limb ischemia.

At presentation, 25% of patients with ALI will be treated medically, 50% to 60% will undergo revascularization, and 25% will undergo primary amputation. The major treatment goals for ALI include limb salvage, wound healing, pain control, reduction in overall cardiac risk, and improvement in quality of life. Because such patients are at risk for imminent limb loss, surgery is semiurgent or urgent. During revascularization, aortoiliac (inflow) or distal (outflow) obstructions are bypassed with axillofemoral or femoropopliteal distal bypass grafts, respectively. Also, successful surgery and long-term survival of the graft depend on blood flow through the graft, blood coagulability, and the future development of atherosclerotic changes in the graft. Anesthesia care can have an important impact on immediate and longer-term outcomes.

Recognition

Peripheral vascular surgery, particularly suprainguinal operations, are classified as high-risk procedures. Therefore careful attention to metabolic and cardiac status is critical. This, combined with the high prevalence of clinical risk factors, translates into increased risk for perioperative cardiac complications. These risk factors (Revised Cardiac Risk Index [RCRI]) include a history of ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes with preoperative treatment with insulin, and serum creatinine greater than 2 mg/dL. A patient with three or more risk factors has a 5.4% risk of major cardiac complication. Perioperative myocardial infarction (MI) has a complex pathophysiology, but the major contributing factors arise from coronary plaque rupture (type I MI, T1MI) and the mismatch of myocardial oxygen supply demand (type II MI, T2MI). All patients who present with active cardiac conditions, including unstable coronary syndromes, decompensated heart failure, significant arrhythmias, and severe valvulopathies, should undergo evaluation and treatment before surgery.

Risk Assessment

Perioperative MI is the most common cause of death after major vascular surgery. Several studies suggest that perioperative MI is often asymptomatic and commonly occurs within the first 48 hours after surgery, with strong association for transitioning into a symptomatic MI and increased 30-day mortality. Angiotensin-converting enzyme (ACE) inhibitors may have a protective role in the modification of renin-angiotensin system (RAS)–induced atherosclerosis. Drugs that target the RAS, such as ACE inhibitors and angiotensin-II receptor blockers (ARBs), are widely used to lower blood pressure. Newer research based on animal models suggests they may also have an additional role in decreasing atherosclerosis that is independent of their blood-lowering effect. The Heart Outcomes Prevention Evaluation (HOPE) trial of 9297 patients over 55 years of age established that high plasma renin activity was a major predictor of vascular events and mortality, which suggests that these patients could benefit from the inhibition of the RAS.

Patients with PAD are often on cardiovascular medications that have been recommended to decrease cardiovascular risk, including antiplatelet drugs, β-blockers and statins. High-risk patients (i.e., those with an RCRI index score ≥3 on aspirin, β-blocker, and statin therapy) had a threefold reduction in risk of perioperative MI and mortality at 30 days and 1 year. Additionally, there was no demonstrable increase in moderate or severe bleeding due to aspirin use in these patients. The survival benefit of antiplatelet and statin therapy preoperatively and at discharge was present at 5 years after vascular surgery. In a large prospective study that queried the association between bleeding complications from peripheral vascular surgery and antiplatelet use (aspirin and/or clopidogrel), the authors demonstrated the risk of reoperation for bleeding to be not significantly different across antiplatelet regimens.

According to the 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Centers for Disease Control and Prevention (CDC) guidelines, a blood pressure goal of 139/89 mm Hg or less was recommended regardless of age. Other guidelines, such as the JNC-8, suggest a higher cutoff of less than 150/90 mm Hg for patients over age 60 years. This less stringent recommendation may change depending on the results from the SPRINT trial of 2015—a randomized controlled trial with more than 9000 patients over age 50 years that was ended early due to evidence that a more aggressive blood pressure target of 120/80 mm Hg had a significant impact on reducing cardiovascular and cerebrovascular morbidity and mortality. Generally speaking, patients with stage I hypertension (systolic blood pressure [SBP] 140 to 159 mm Hg or diastolic blood pressure [DBP] 90 to 99 mm Hg) or stage II hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) should be treated with lifestyle modification, and if not adequately controlled at 6 months, a thiazide diuretic alone or in combination with an ACE inhibitor, ARB, or calcium channel blocker should be initiated.

Smoking cessation should be encouraged due to its deleterious effects on vascular inflammation, accelerated atherosclerosis, and ultimately bypass graft failure. Long-term outcomes associated with active smoking include increased risk of limb loss, MI, and death. With respect to pulmonary complications, smoking cessation initiated less than 4 to 8 weeks before surgery does not carry additional risk compared with patients who continue smoking until surgery. To better predict pulmonary complications in patients who smoke, pulmonary function tests may be appropriate.

Monitoring

Indicated monitoring includes at least a two-lead electrocardiogram with precise placement of V_4 or V_5 leads, surface pulse oximetry, end-tidal carbon dioxide and inhalational anesthetic monitoring, and noninvasive blood pressure monitoring. Invasive monitoring is indicated for some patients, especially those with symptomatic or severe cardiovascular disease (e.g., stage III or IV heart failure, symptomatic arrhythmias). Such monitoring includes an arterial line, central venous pressure, transesophageal echocardiography, and possibly a pulmonary artery catheter. These are placed before or after anesthesia induction. With severe hypertension, poor left ventricular function (ejection fraction ≤0.35), or symptomatic coronary artery disease, preinduction invasive monitoring allows tighter control of hemodynamic changes during induction and tracheal intubation and during periods of increased cardiovascular stress. The anesthetic technique (regional anesthesia [RA] vs. general anesthesia [GA]) should not affect the decision to institute central venous pressure or pulmonary artery catheter monitoring. Central lines may be required for patients with poor peripheral access or when arm veins will be used as conduits for surgery. Transesophageal echocardiography is useful for monitoring cardiac function and volume status when GA is used, especially for hemodynamically unstable patients or if a cardiac (atrial fibrillation) or aortic (unstable plaque) source for thromboembolism is present.

MANAGEMENT

Regarding anesthetic technique, primary concerns focus on the surgical revascularization procedure, the patient's tolerance of the anesthetic and surgery (which often takes many hours), and preoperative cardiopulmonary risk factors. Another important concern is the effect of anesthetic technique—RA versus GA—on the success of revascularization and perioperative outcomes. The following factors should be considered.

Sympathectomy

This procedure dilates the venous capacitance bed to reduce cardiac preload, thus increasing fluid requirements to maintain cardiac output. It also reduces systemic vascular resistance. If this decreases cardiac afterload and work, it may improve global and regional left ventricular function for the duration of the sympathetic block. For example, a cardiac sympathectomy induced by a thoracic epidural would increase myocardial oxygen supply and decrease cardiac work by lowering wall tension, heart rate, and afterload. Furthermore, these patients exhibit lower levels of electrocardiographic evidence of myocardial ischemia compared with controls.

Sympathetic block may also reduce stress-related hypercoagulability and the frequency of venous thromboembolism. Tuman and colleagues reported a 2.5% versus 20% graft failure rate randomly comparing RA and GA, respectively, suggesting that neuraxial anesthesia during limb revascularization has beneficial effects on maintaining graft patency and viability in the early postoperative period.

TABLE 69.1 Summary of Studies Comparing Regional Anesthesia and General Anesthesia for Peripheral Vascular Surgery

	NUMBER OF PATIENTS		PERIOPERATIVE MORTALITY		CARDIOVASCULAR COMPLICATIONS		PVS GRAFT FAILURE		
Study	**GA**	**RA**	**GA**	**RA**	**GA**	**RA**	**GA**	**RA**	**Remarks**
Ghanami et al. 2013	4768	694	37.3%	34.0%	2.8%	2.2%	7.3%	7.2%	Choice of anesthetic type did not appear to affect outcomes after lower-extremity bypass for CLI. Anesthetic choice should be governed by local expertise and practice.
Dodds et al. 2007	37	45	4%	0%	16%	11%	13%; 16% (day 7; day 30)	0%; 5% (day 7; day 30)	Significantly more patients in the GA group required a reoperation for limb or graft salvage within 7 days of the index surgery, a difference that was statistically significant ($P = 0.02$).
Singh et al. 2006	9757	503	—	—	1.8 (1.32–2.48) (OR; 95% CI) GA vs. RA		1.43 (1.16–1.77) (OR; 95% CI) GA vs. RA		There was a higher incidence of cardiac events, graft failure, and return to the operating room, although this did not translate into a statistically longer length of stay or an increase in 30-day mortality rate.
Tuman et al. 1991	40	40	0	0	27	10	—	—	GA with postoperative epidural analgesia vs. GA with postoperative PCA; controls ($N = 40$) were randomly selected GA patients (non-CV surgery), but no PVD
Christopherson et al. 1993	51	49	3.9	4.1	7.8	8.2	21[a]	4[a]	EA for surgery followed by epidural analgesia, or GA for surgery and IV PCA 11 (GA) vs. 2 (RA) patients had regrafting or embolectomy

CI, Confidence interval; *CLI*, chronic limb ischemia; *GA*, general anesthesia; *OR*, odds ratio; *PVS*, peripheral vascular surgery; *RA*, regional anesthesia.
[a]$P \leq .05$.

Stress Response

The stress response activated during surgery may be attenuated by RA. Spinal anesthesia may produce a greater reduction in the neuroendocrine stress response than epidural anesthesia as evidenced by lower levels of intraoperative cortisol, noradrenaline, and total catecholamine levels in the former group. Furthermore, there are profound changes to the metabolic, immune, and neurohormonal systems that RAs may favorably influence—mismatches in myocardial oxygen supply-demand, arterial vasoconstriction, hypercoagulability and fibrinolysis, reduced urinary output, hyperglycemia, sodium and water retention, wound infections, cancer recurrence, and postoperative delirium and cognitive dysfunction. Additionally, epidural analgesia with a combination of local anesthetic and opioid initiated before incision will abolish stress response to surgery on the lower limbs greater than systemic opioids alone.

Regional Versus General Anesthesia

Although it is difficult to compare studies of anesthetic techniques, medications, and surgical factors related to peripheral vascular disease (PVD), recent prospective randomized trials have found no difference in mortality rates between spinal or epidural RA and GA (Table 69.1). The lack of reported differences in outcome may be attributed to improved cardiovascular management in these trials compared with earlier ones.

RA continued as postoperative analgesia may improve graft patency, as indicated by a reduced need for regrafting, thrombectomy, or amputation. Two studies in Table 69.1 (Tuman and Christopherson) showed marked differences in graft failure rates between GA alone and RA with or without GA; the other studies found no such difference. Conflicting outcomes may be ascribed to differences in methodology, type of graft material, extent of distal vessel disease, and adjunct anesthetic drugs. Thus RA for PVD surgery may benefit patients at highest risk for early graft failure or those who require reoperation for whatever reason. For limb salvage surgery, hypercoagulable states and prosthetic conduits are independent risk factors for graft failure.

RA may have beneficial effects on some procoagulant parameters (e.g., platelet function, fibrinogen, and plasminogen activator inhibitor levels). Furthermore, serologically proven hypercoagulability is known to be associated with inferior long-term graft patency and lower rates of limb salvage and survival after infrainguinal bypass grafts. However, whether RA protects against graft thrombosis remains controversial.

Although multiple anesthetic techniques have been evaluated to date, the ideal technique for lower limb revascularization surgery, especially femoral-popliteal-tibial (distal) bypass grafting, remains unclear. Nonetheless, a number of medical and surgical factors may help determine the best technique for a particular patient. The duration of surgery is one important consideration. Surgeons may expend considerable time harvesting the patient's own veins because acute and chronic patency is significantly enhanced with these grafts compared with frozen veins or prosthetic materials. Repeat revascularization procedures are typically longer and more complex. Certainly RA may still be possible, because continuous epidural infusions and spinal catheters are available and routinely employed. However, patients may have difficulty tolerating intravenous sedation for long periods. Use of the modified semi-Fowler positioning and back supports may help reduce discomfort or reduce or eliminate orthopnea.

Another consideration is whether arm veins will be harvested, particularly for reoperations. Reconstructions of this type may preclude the use of RA alone, but combined RA and GA may be appropriate.

If it is determined that RA is optimal for a patient, the use of perioperative anticoagulation must be given consideration. Guidelines of the American Society of Regional Anesthesia and Pain Medicine address the implications of anticoagulation and offer advice for the prevention and management of bleeding complications with RA.

The superiority of RA or GA for preventing adverse cardiovascular outcomes, graft thrombosis, or mortality has not been established. Although one trial demonstrated that vascular patients who underwent general endotracheal anesthesia were more likely to develop postoperative pneumonia than those who received neuraxial anesthesia. Another trial showed that RA may decrease the incidence of postoperative cognitive dysfunction and mortality in the elderly, although more research study is needed. As discussed earlier, a number of proposed mechanisms may

explain the trend toward improved outcomes with RA, but these have not been firmly established. Thus the choice of anesthetic management should be made on a case-by-case basis after discussions with both the surgeon and the patient. Medical and surgical factors, as well as patient preferences, can help determine the best strategy for each patient.

Maintaining Hemodynamic Goals

Sustained tachycardia is one of the least tolerated hemodynamic alterations. It is important to determine and correct the cause, such as surgical stimulation or excessive or rapid blood loss (the latter often occurs during thrombectomy). Emergence from GA is a common time for perioperative myocardial ischemia to occur. It may be associated with hypertension and tachycardia due to subconscious or conscious pain awareness. Labetalol or esmolol can attenuate elevated heart rate responses. These drugs, as well as nitroglycerin, hydralazine, or nicardipine, can be used to reduce blood pressure or treat ischemia if it persists after a favorable heart rate has been restored. Changing anesthetic depth and administering β-blockers are often first-line therapies. Patients at high risk for cardiovascular complications may benefit from perioperative β-blockade, especially when GA is used. Heart rate control, which serves to maintain the benefits of myocardial ischemia protection, continued 48 hours postoperatively after vascular surgery has been associated with a significant reduction and/or elimination of ST depression in high-risk patients.

Fluid Management

Perioperative fluid management should be tailored to patient and procedural factors to maintain hemodynamic stability and minimize complications. There are limited data to support the use of liberal versus goal-directed therapy in major adult surgery, although perioperative outcomes were more favorable with the latter, specifically pneumonia and renal complications. Although liberal fluid strategy theoretically improves organ perfusion, it is associated with a higher risk of pulmonary edema, pneumonia, and longer hospital stay. In patients undergoing major surgery, the most important factor in optimizing patient outcome was not the absolute amount of perioperative fluid administered, but rather the titration of fluid to achieve a targeted and objectively measurable hemodynamic parameter of adequate intravascular resuscitation, such as cardiac output, pulse pressure variation (PPV), and esophageal Doppler FTc (flow-corrected time). Arterial wave-form analysis may be used to obtain PPV or systolic volume variation values in mechanically ventilated patients. Sufficient venous access is critical for patients undergoing major surgery for rapid drug or fluid administration.

Intraoperative blood loss should be replaced with crystalloid or colloid solutions to maintain intravascular volume before red blood cell transfusion is given to maintain adequate oxygen carrying capacity. Preoperatively, a complete blood count, prothrombin time/international normalized ratio, and partial thromboplastin time should be obtained. Maximum blood loss calculation using the patient's ideal body weight and estimated blood volumes of 65 to 75 mL/kg in the average male or female may be used as a rough estimate. The potential for significant hemorrhage is present for aortobifemoral surgery but less so for infrainguinal procedures. Regular assessments for hemoglobin concentration and blood coagulation via thromboelastrogram may be incorporated to guide therapy. A restrictive transfusion threshold of 8 g/dL is a reasonable set point to maintain oxygen delivery in a patient population with a high prevalence of coronary artery disease. Intraoperative cell salvage and autologous blood transfusion should be utilized barring patient refusal or specific contraindications.

Vascular surgeons are especially cognizant of the fact that reduced blood viscosity increases blood flow through the bypass graft. Thus some degree of anemia may be beneficial for high-risk grafts; however, it is also associated with reduced vital organ and tissue oxygen delivery. A reasonable trade-off for intraoperative hemoglobin concentration is maintaining a hematocrit of 28 in high-risk patients.

Normothermia

Temperature homeostasis is an important consideration, particularly when understanding the detrimental cardiovascular effects associated with perioperative hypothermia. Thus forced-air warming blankets, a warm operating room, warmed intravenous fluids, a humidifier on the ventilator circuit, and/or low fresh gas flows are appropriate for maintaining normothermia.

Operative Treatment

Between 1998 and 2009, the incidence of ALI among the US Medicare population declined significantly, and the percentage of patients treated with endovascular techniques markedly increased. During this same time, 1-year amputation rates declined. Furthermore, although in-hospital mortality rates declined after presentation with ALI, 1-year mortality rates remained unchanged.

Peripheral limb bypass, however, remains a complementary modality for patients with acceptable surgical risk. Bypass grafts are usually reconstructed from high-quality saphenous veins, although the failure rate remains stubbornly high at 30% to 50% after 5 years. Continued smoking after bypass surgery has been implicated to cause at least a threefold increase in graft failure, which illustrates the importance of smoking cessation in preventing PAD and maintaining graft patency. Other upcoming modalities for treatment of CLI include gene and cell-based therapies that promote neovascularization and vasculogenesis.

Patients with acute limb ischemia are systemically ill, often requiring critical care monitoring postoperatively. General anesthesia with rapid-sequence induction and cricoid pressure may be indicated given the high perioperative risk and inadequate fasting time.

Induction agents that maintain hemodynamic stability are preferred. Once arterial blood supply is restored to the ischemic tissue, reperfusion injury may cause cardiac and metabolic disturbances. Systemic hypotension and myocardial depression mediated by the release of vasoactive mediators may occur. Treatment with inotropes and/or continuous infusions of vasopressor medications may be required to correct persistent hypotension. These perturbations should be anticipated by frequent monitoring of potassium and arterial blood gases. Administration of intravenous calcium gluconate, sodium bicarbonate, and/or insulin with dextrose may be required to correct hyperkalemia and acidosis. Increases in end-tidal carbon dioxide may be corrected with adjustments in ventilation. Rhadbomyolysis and renal injury from the release of creatinine kinase should be treated with hydration and urine alkalinization. If severe muscle necrosis is present, primary amputation may be indicated.

PREVENTION

Any patient having lower extremity PVS is presumed to have generalized atherosclerotic disease and coronary artery disease. Therefore preoperative considerations are similar to those for patients with known cardiac disease having major noncardiac surgery. Aggressive preventive strategies such as risk-factor modification and drug therapy (e.g., β-blockers, lipid-lowering agents, antiplatelet drugs) are needed. Antiplatelet drugs and RA may reduce the rate of postoperative graft thrombosis. β-Blockers reduce the risk for myocardial ischemia and myocardial infarction, which are responsible for most of the morbidity

associated with PVS, although they should not be started acutely the morning of surgery, and many experts would suggest that you need at least 1 week of titration to avoid the increased incidence of stroke observed in some studies.

The superiority of RA or GA for preventing adverse cardiovascular outcomes, graft thrombosis, or mortality has not been established. As discussed earlier, a number of proposed mechanisms may explain the trend toward improved outcomes with RA, but these have not been firmly established. Thus the choice of anesthetic management should be made on a case-by-case basis after discussions with both the surgeon and the patient. Medical and surgical factors, as well as patient preferences, can help determine the best strategy for each patient.

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Pituitary Tumors: Diabetes Insipidus

70

Chad D. Courtemanche • Melissa A. Laxton

Case Synopsis

A 58-year-old man undergoes transsphenoidal hypophysectomy for resection of a prolactin-secreting pituitary adenoma with suprasellar extension. Ten hours after surgery, urine output exceeds 3 L/h, and the serum sodium level is 150 mEq/L.

PROBLEM ANALYSIS

Definition

Diabetes insipidus is a syndrome characterized by polyuria, thirst, and polydipsia triggered by plasma hyperosmolarity. Neurogenic, or "central," diabetes insipidus results from insufficient antidiuretic hormone (ADH) secretion, secondary to damage to the hypothalamic-neurohypophysial axis. Loss of approximately 90% of ADH-secreting neurons is needed for the development of clinically relevant polyuria. In contrast, nephrogenic diabetes insipidus is characterized by renal resistance to the action of ADH. Gestational diabetes insipidus usually occurs later in pregnancy and resolves 4 to 6 weeks postpartum.

An absolute deficiency of ADH results in impaired urine concentrating ability, polyuria, and a tendency toward dehydration. Most patients have incomplete neurogenic diabetes insipidus and retain a limited ability to concentrate urine and conserve free water. However, if access to water is impaired (e.g., unconsciousness, perioperative nothing-by-mouth status), hypertonic dehydration and hypernatremia may develop. Signs and symptoms of hypernatremia include psychomotor agitation, neuromuscular irritability, lethargy, coma, and seizures.

Recognition

Diabetes insipidus occurs in as many as 70% of adult patients in the first 24 hours following transsphenoidal pituitary surgery. However, the syndrome is usually transient in this setting, and studies suggest that 20% of patients are discharged with the diagnosis of diabetes insipidus. Perioperative glucocorticoid replacement may facilitate the development of polyuria. Laboratory findings characteristic of diabetes insipidus are as follows:

- A 24-hour urine volume greater than 50 mL/kg
- Urine osmolarity less than 300 mOsm/kg H_2O
- Urine specific gravity less than 1.010
- Serum osmolarity greater than 300 mOsm/kg
- Hypernatremia (serum sodium >142 mEq/L

Chronic polyuria causes the hypertonic renal medullary concentration gradient to be "washed out." Additional urine-concentrating mechanisms become impaired, so that polyuria increases. Alternative causes of polyuria must be eliminated to make the diagnosis of primary neurogenic or nephrogenic diabetes insipidus with confidence (Box 70.1).

BOX 70.1 Causes of Polyuria Other Than Primary Neurogenic or Nephrogenic Diabetes Insipidus

Chemical diuresis
Mannitol
Urea
Radiocontrast agents
Hyperglycemia
Furosemide, thiazides, ethacrynic acid
Acute renal failure
Drug-induced nephrogenic diabetes insipidus (e.g., cisplatin, lithium)
Postobstructive diuresis
Postresuscitation diuresis

Risk Assessment

As noted earlier, transient diabetes insipidus occurs in up to 20% of discharged patients following transsphenoidal hypophysectomy. However, it becomes permanent in about 2% of cases. A macroadenoma with suprasellar extension may be associated with a higher risk for postoperative diabetes insipidus than is a lesion confined to the sella. Recent data suggest that an endoscopic transsphenoidal approach for resection of pituitary tumors may decrease both the short- and long-term incidence of diabetes insipidus compared with the traditional, direct transsphenoidal approach. The secretory type of tumor appears to have no effect on the postoperative occurrence of diabetes insipidus.

Diabetes insipidus follows three patterns postoperatively: transient, triphasic, and permanent. Postoperative diabetes insipidus is usually recognized within 12 to 24 hours of the initial insult, but delays of days to weeks have been recorded. In approximately 70% of cases, diabetes insipidus is transient, lasting only 3 to 5 days. More rarely, it may last several weeks, followed by gradual resolution. This pattern is more common after resection of pituitary adenomas confined to the sella. After transcranial approaches to pituitary macroadenomas with suprasellar extension, or procedures in which proximal damage to the pituitary stalk is likely, both complete and partial diabetes insipidus have been observed; in some cases, it takes several years for this condition to improve or resolve as neuronal elements regenerate.

A small group of patients (5% to 10%) exhibits a classic triphasic response to injury. This pattern most commonly follows hypophysial stalk injury due to severe head trauma or the resection of extensive suprasellar tumors. The initial phase is characterized by an abrupt cessation of ADH release. This is manifest by polyuria, which usually begins within 12 to 24 hours after injury and lasts for 4 to 8 days.

An antidiuretic phase, lasting 5 to 6 days, follows. It is characterized by concentrated urine, with plasma hypo-osmolarity and hyponatremia as a result of free water reabsorption. Profound hyponatremia and its attendant complications may develop if there is a delay in recognizing this phase. Symptoms of hyponatremia include nausea, headaches, and seizures. Excessive release of stored ADH from degenerating neurohypophysial tissues is the likely explanation for this antidiuretic phase. Once this stored ADH release is complete, diabetes insipidus frequently recurs. Although usually persistent, sometimes it may improve or resolve.

Implications

A patient with diabetes insipidus is unable to concentrate urine and retain water. Without treatment, intravascular volume depletion results, cardiac stroke volume declines, and heart rate increases in an effort to maintain cardiac output. Hypoperfusion may be signaled by weak peripheral pulses; orthostatic hypotension; cold, clammy skin; rapid, shallow respirations; and a reduced level of consciousness. Hypernatremia may manifest as seizures and hyperreflexia. Because patients are usually discharged within days of surgery, careful counseling regarding the signs and symptoms of diabetes insipidus is of utmost importance.

MANAGEMENT

Owing to the predominantly transient nature of perioperative diabetes insipidus, some mild cases are managed with oral fluid replacement, especially if the patient is cooperative and the thirst mechanism is intact. However, if the patient is unable to cooperate and there is associated hypokalemia and concern about "washout" of the renal medullary concentration gradient, more aggressive therapy may be warranted.

Exogenous replacement of ADH is with either desmopressin or aqueous vasopressin. After transsphenoidal resection, desmopressin is usually administered either subcutaneously in a dosage of 1 to 2 μg every 8 to 12 hours or intravenously 250 to 500 ng infused over 2 hours. Desmopressin preferentially acts at the V2 receptor and therefore lacks the vasoconstrictor effects of vasopressin and is less likely to cause the hypertension or abdominal cramping associated with V1 receptors. For patients requiring long-term ADH replacement, both intranasal and oral preparations are available. However, due to significant variability in response to treatment, the dose must be titrated individually.

Although desmopressin is clearly the drug of choice for the chronic treatment of diabetes insipidus, its duration of action is 12 to 18 hours. Some clinicians prefer aqueous vasopressin due to its short half-life of approximately 20 minutes if diabetes insipidus is likely to be transient. Aqueous vasopressin is formulated as 20 pressor U/mL of solution. The peak effect occurs by 1 to 2 hours, and the duration of action is 4 to 8 hours. The usual starting dosage is 2 to 5 U subcutaneously or intramuscularly every 4 to 6 hours as needed, or as an infusion starting at 0.25 to 1.0 μU/kg/h. Alternative therapeutic options include carbamazepine, chloropropamide, clofibrate, and thiazide diuretics.

Careful assessment of fluid intake; urine output, osmolarity, and specific gravity; plasma osmolarity; serum sodium concentration; and body weight should guide therapy with vasopressin or desmopressin. Clinicians must be alert to the possible development of an antidiuretic phase of hormonal dysfunction, complicated by water intoxication.

PREVENTION

Meticulous surgical resection is the best means of preventing perioperative diabetes insipidus. Anesthesiologists should maintain a high index of suspicion for the development of diabetes insipidus, especially when there is suprasellar extension of a pituitary tumor or other endocrine abnormalities in a neurosurgical patient.

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Posterior Fossa Surgery

71

Diana Ayubcha • Dimitry Y. Baranov

Case Synopsis

A 53-year-old woman undergoes posterior fossa craniotomy for removal of a right acoustic schwannoma. Preoperative symptoms included tinnitus, episodic vertigo, headache, facial asymmetry, and loss of coordination and balance. The surgeon will use a retrosigmoid approach and is planning for supine elevated right shoulder position and the intraoperative use of somatosensory evoked potentials (SSEPs); brainstem auditory evoked potentials (BAEPs); and facial, hypoglossal, accessory, and masseter electromyography (EMG). During the surgery, the neurophysiologist is unable to evoke EMG activity of the facial nerve. After extubation, the patient has a right-sided facial droop.

PROBLEM ANALYSIS

Definition

The posterior fossa is a small volume compartment with low compliance containing a number of vitally important neural structures, which are uniquely different in function and pathology. Traditionally in neurosurgical and neuroanesthesia literature, discussions on procedures related to the pathology found in the posterior fossa are combined into one chapter, although one may argue this approach as arbitrary at best but potentially also misleading. Each procedure performed on the various anatomic structures found in the posterior fossa carries its own dramatically unique challenges and the risk for potential complications. Intimate knowledge of these challenges and close cooperation and communication with the neurosurgical and neurophysiologic teams is required in order to design and execute the perioperative anesthesia care plan for each particular surgical intervention. Considering how extensive the list of pathologies found in the posterior fossa is (Box 71.1), it is beyond the scope of this chapter to provide a full comprehensive review necessary to address every aspect of anesthesia care for these procedures. However, some common principles in regard to anticipating, recognizing, and managing anesthesia perioperative complications in the posterior fossa surgery are covered in this chapter.

Surgery in the posterior fossa, with the presence of vital neuronal and vascular structures within a limited space, presents challenges for both the surgeon and the anesthesiologist. It contains critical respiratory, vasomotor, and cardiac control centers, specifically within the brainstem. In addition to the midbrain, medulla, and pons, which form the brainstem, the cerebellum, lower cranial nerves, and many critical vascular structures are found in the posterior fossa. The vascular anatomy includes arteries of the vertebrobasilar circulation and venous sinuses traversing the fossa, including the sigmoid, transverse, and occipital. Manipulation of these regions, as seen with surgical retraction, can significantly influence respiratory drive, resting vascular tone, blood pressure, and heart rate. Small increases in volume within this space, mainly as a result of postoperative hematoma or edema, can result in rapid elevation of compartmental pressure, and subsequent life-threatening brainstem compression. Intraoperative goals are aimed at facilitating surgical access, accommodating requirements for reliable neurophysiologic monitoring of nervous tissue and cranial nerve integrity, and maintaining respiratory and cardiovascular stability. The cerebrospinal fluid (CSF) conduit is exceptionally narrow through the cerebral aqueduct. Minimal obstruction can result in significant increases in intracranial pressure. Patients with lesions in the posterior fossa have a varied presentation depending on the exact location and structures involved. As an example, a small lesion impinging on the cerebral aqueduct may result in obstructive hydrocephalus, with presenting symptoms of headache and altered mental status. Similarly, a small lesion located in the lateral pons may result in isolated cranial nerve dysfunction. Therefore it is critical in the

BOX 71.1 Posterior Fossa Pathologies and Surgical Approaches

- Cerebellopontine angle lesion surgery
  - Schwannoma
  - Meningioma
  - Acoustic neuroma
  - Glomus jugulare tumors
- Microvascular decompression and vascular surgery
  - Trigeminal neuralgia
  - Hemifacial spasm
  - Posterior cerebellar artery aneurysm
  - Vertebral/vertebrobasilar aneurysm
  - Basilar tip aneurysm
  - Arteriovenous malformations
- Cerebellar lesion surgery
  - Astrocytoma
  - Arachnoid cysts
  - Hemangioblastoma
  - Cerebellar convexity meningioma
  - Cerebellar arteriovenous malformation
- Petroclival lesion surgery
  - Chordoma
  - Meningioma
- Axial lesion surgery
  - Medulloblastoma
  - Cerebellar astrocytoma
  - Brainstem glioma
  - Ependymoma
  - Choroid plexus papilloma
  - Dermoid tumors
- Cyst excision
  - Epidermoid cyst
  - Arachnoid cyst

preoperative setting to identify the exact location of the lesion, as well as structural involvement, and any associated neurologic or systemic compromise.

Recognition

When discussing complications related to posterior fossa surgery, it is important to point out the predominantly surgical and non–life-threatening nature of these complications. In a recent review of 500 cases, the overall complication rate was under 32% with the vast majority of those being CSF leaks, meningitis, wound infection, and cranial nerve palsies. Hydrocephalus and cerebellar hematoma represent a small percentage of all surgical complications. Overall mortality rate was less than 3%. Most of these complications are unlikely to be related to the anesthetic management. Serious perioperative complications that are not directly related to surgical technique or approach (such as venous air embolism) are traditionally and arguably considered to be in the domain of anesthesia management and are quite rare. Transitory hemodynamic instability, although more frequently observed in this type of surgery, can usually be treated promptly without consequences and should not be considered a complication. Most of the anesthesia complications can be divided into a number of broad, and sometimes overlapping, categories: (1) complications related to positioning for posterior fossa surgery; (2) failure to provide adequate anesthetic for complex intraoperative neurophysiologic monitoring needed to monitor the integrity of neuronal pathways at risk; (3) severe hemodynamic disturbances related to compression or irritation of vasomotor centers in the brainstem; and (4) postoperative complications related to an expanding hematoma and parenchymal edema, especially in patients with an unsecured airway.

Surgical exposure in the posterior cranial fossa is a well-recognized challenge. Both sitting and variations of horizontal positions are being used. In the past, the sitting position was viewed as providing superior surgical exposure and anatomic orientation with the CSF and blood being gravitationally drained from the operative field, improved venous drainage, decreased blood loss, free diaphragmatic movement, and easier access to the endotracheal tube and the airway. However, this has fallen out of favor in many centers due to potentially severe complications associated with this position and the risk of malpractice claims. Sitting craniotomy complications are well known and include venous air embolism (VAE), paradoxic air embolism (PAE), tension pneumocephalus, lingual and laryngeal edema, quadriparesis, peripheral nerve injuries, severe hemodynamic instability, and decreased cerebral perfusion. Use of horizontal positioning such as lateral, prone, or bench positions decreases the rate of VAE and PAE but presents its own challenges. Frequent use of extreme neck flexion to improve exposure may result in higher risk of cervical spinal cord ischemia, macroglossia, and airway edema. Prone position leads to increased intraabdominal and intrathoracic pressure, impaired venous drainage, and risk of postoperative vision loss. Bench and lateral positions can be associated with brachial plexus injury if appropriate measures are not undertaken to minimize the stretch and the compression in the dependent arm. All of these positions demand special equipment and significant expertise and experience, which is uncommon considering how increasingly rare the use of these positions has become. The most common approach in acoustic neuroma excision is retromastoid, where the patient remains supine with an elevated ipsilateral shoulder using a sandbag. This position is not associated with the increased risk of the aforementioned complications. A comprehensive discussion on the management of each individual position and complications related to it is beyond the scope of this text. Just a description of monitoring modalities and management of VAE and PAE would deserve a whole chapter. The practitioner faced with the planning for surgery involving any of these positions would be wise to allocate the right amount of time to make adequate preparations for this challenge, including close communication with the members of the team involved in the procedure.

The use of neurophysiologic monitoring to improve neural function preservation during posterior fossa surgery may involve somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), and electromyography (EMG). Various anesthetic agents affect neurophysiologic monitoring to a different degree, and appropriate anesthetic management is needed to provide the best monitoring conditions. Failure to appreciate the specific monitoring needs for the proposed surgery may result in inadequate patient monitoring and suboptimal outcomes.

A profound hemodynamic instability is often expected in posterior fossa surgery. Surgical irritation or damage to brainstem cardiac and vasomotor centers can lead to rapid and unpredictable hemodynamic changes. Extreme heart rate and blood pressure alterations are common with surgical manipulation, and rapid recognition and treatment are required. The important caveat to remember is that the surgeons might rely on changes in blood pressure and heart rate for early detection of surgical damage to the important brainstem structure and cranial nerves. Therefore prophylactic treatment of hemodynamic changes must be undertaken only in agreement with surgical colleagues.

Finally, there are no adequate intraoperative monitors for a large number of important brainstem functions, such as airway maintenance and protection, swallowing, and respiratory control. Patients emerging after posterior fossa surgery are at increased risk of an endangered airway, respiratory compromise, and sudden neurologic deterioration due to rapid compression of the brainstem in the presence of even fairly small postoperative edema or hematoma. Thus anesthetic management must be planned to ensure rapid and clear emergence to allow reliable evaluations of the airway reflexes and neurologic status before extubation can be undertaken. The patient care team should discuss the range of acceptable hemodynamic parameters, expected neuronal or bulbar dysfunction, and measures needed to address anticipated alterations in airway protection and respiratory function should the need arise. Postoperative ventilatory support, intubation, or diagnostic studies (e.g., angiography, computed tomography, magnetic resonance imaging) should be discussed before emergence, and appropriate plans must be developed in light of those discussions and relayed to the intensive care unit team.

Risk Assessment

Knowledge of the anatomic location of the lesion of interest, the planned surgical procedure, and the actual structures involved in the surgery are all critical elements of posterior fossa surgery. Risk assessment is possible only after a review of the individual patient's history and physical examination, an evaluation of radiologic studies, and a discussion with the neurosurgeon. The greatest risks are associated with tumors directly involving the brainstem (e.g., pons and medulla), lesions with direct involvement of the cranial nerves required for airway maintenance and protection, lesions involving the facial nerve, and surgeries conducted with the patient in the sitting position. The actual events encountered during surgery are impossible to predict, which contributes to the challenge of providing anesthesia for neurosurgery in general and for posterior fossa surgery in particular. At a minimum, plans for the diagnosis and management of hemodynamic instability, respiratory dysfunction, alterations in cranial nerve function, and venous air embolism should be made before starting any posterior fossa surgery.

Implications

As previously discussed, the risks to patients undergoing posterior fossa surgery have direct implications for the preoperative preparation, type of monitoring, and anesthetic technique necessary to secure optimal perioperative outcomes. Before surgery, patients must be carefully monitored and sedative-hypnotic and analgesic drugs must be titrated with extreme care. Intraoperative risks are predominantly hemodynamic instability and cardiovascular collapse. Especially with surgery involving the pons and medulla, extreme hemodynamic variability in heart rate and blood pressure may result in patient instability. This instability is usually limited to periods of direct surgical retraction and manipulation, but it can be clinically important. Hemodynamic collapse and cardiac arrest have resulted from venous air entrainment, and both are a constant risk during all posterior fossa (and skull base) surgeries, even in patients who are horizontally positioned. Use of an arterial line and right atrial catheter is warranted when needed. Anesthetic regimen based on modern short-acting intravenous agents (total intravenous anesthesia) such as propofol, remifentanil, and dexmedetomidine, with low stable levels of desflurane, would allow superior conditions for SSEPs and cranial nerve EMG monitoring. The BAEPs are resistant to the effects of most anesthetic agents in the doses used today.

MANAGEMENT

A full understanding of the patient's condition and anticipated surgical requirements represents an important part of management. Failure to understand the specific location and effect of the posterior fossa lesion severely limits the delivery of optimal therapy. Overall anesthesia care is similar to that in surgical procedures performed on patients with supratentorial lesions. The emphasis is on preparedness to treat sudden and profound hemodynamic instability and ensure careful attention to details when positioning these patients to avoid multiple complications related to these positions.

Postoperatively, to determine the need for ongoing monitoring and support, all cranial nerve and brainstem functions associated with the site of surgery should be specifically evaluated once the patient is awake. This requires that the anesthetic technique permit neurologic examination at the conclusion of surgery, preferably in the operating room before transport to the intensive care unit. Coincidentally the anesthetic agents used to provide optimal conditions for neurophysiologic monitoring tend to secure a rapid and reliable emergence.

The time course and presenting signs and symptoms of posterior fossa deterioration may be different from those associated with supratentorial surgery. With supratentorial lesions, deterioration (usually due to an expanding mass or hydrocephalus) generally progresses over time, so serial monitoring is appropriate. For posterior fossa surgery, rapid localized deterioration may occur, leading to a loss of bulbar function, respiratory arrest, or hemodynamic collapse. Thus vigilance and a high index of suspicion must be maintained into the postoperative period. It is important to reevaluate the airway after extubation in order to prepare all necessary equipment for a potentially difficult airway in the postoperative setting.

PREVENTION

Careful evaluation of the patient and discussion with the surgeon about location, impact, and proposed surgical approach are required for the optimal management of patients undergoing posterior fossa surgery. Anticipation of the more common severe complications, such as postoperative VAE and airway or respiratory dysfunction, is a critical part of anesthetic management, as is the recognition of the need for specialized monitoring techniques. Although serious complications associated with posterior fossa surgery are uncommon with current surgical procedures, a high index of suspicion and constant vigilance are the most important aspects of perioperative care.

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72 Postpartum Hemorrhage

Joanna David • Perumal Tamilselvan

Case Synopsis

A 29-year-old woman, gravida 4, para 2, has been delivered of a 4200-g infant. Her labor had been augmented after high maternal temperatures and foul-smelling liquor. The anesthesiologist is called 2 hours after delivery of the placenta when the patient is noted to be increasingly hypotensive, tachycardic, and pale. On arrival, the anesthesiologist is informed that she has had a heavier-than-normal lochia resulting in a slow but persistent loss per vaginum.

PROBLEM ANALYSIS

Definition

Primary postpartum hemorrhage (PPH) has been defined as the loss of 500 mL or more of blood within 24 hours of delivery. PPH can be minor (500 to 1000 mL) or major (>1000 mL). Major can be further divided into moderate (1000 to 2000 mL) or severe (>2000 mL).

Most of the cases that cause morbidity or mortality or that present challenges in management have a blood loss greater than 1000 mL.

Although primary PPH is the most common form of obstetric hemorrhage, secondary PPH should not be forgotten. This is defined as abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally.

Recognition

PPH occurs in as many as 10% of deliveries. Blood loss may be obvious, such as per vaginum or loss from the surgical wound. However, it can also be concealed and contained within the uterus, soft tissues, or peritoneum. The patient may exhibit the following:

- Anxiety, confusion, or unresponsiveness
- Hypotension
- Tachycardia (beware of patients on β-blockers who may have a normal pulse or bradycardia)
- Poor peripheral perfusion
- Oliguria
- Unexplained metabolic acidosis
- High ongoing fluid requirement to maintain blood pressure

Risk Assessment

Most patients with PPH will have no identifying risk factors. The risk factors are stated in Tables 72.1 and 72.2 and may result in direct blood loss or coagulation failure. Other risk factors include the following:

- Polyhydramnios
- Precipitous labor
- Augmented labor
- High parity
- Use of tocolytic agents
- Inhalational anesthetics at high concentrations

The most common cause of PPH is uterine atony. At term, blood flow through the placental vasculature is approximately 600 mL/min. After delivery, the primary mechanism that controls blood loss is contraction of the uterine myometrium. This tamponades disrupted blood vessels at the former placental site. Failure of this mechanism can result in massive and rapid blood loss.

Retained placenta is also a common cause of both early and delayed PPH, although not all cases result in significant blood loss. Retained placental fragments may be unrecognized and thus bleeding may be insidious. Patients who have had a prior retained placenta or who deliver well before term are likely to be affected.

Trauma associated with delivery can result in PPH and should be considered in all postpartum patients with continued blood loss despite a firm, contracted uterus. Traumatic bleeding can occur at the following sites:

- Vagina
- Cervix
- Uterus (poor handling during cesarean section, disrupted sutures)
- Perineum (laceration or episiotomy)
- Other structures—tearing of the broad ligament, ovarian artery disruption

Uterine inversion is a rare cause of PPH but can be catastrophic. It should be suspected in any case of PPH when there is significant hypotension.

Implications

Patient outcome depends on early recognition, the rate and severity of blood loss, and timely anesthetic or obstetric intervention. It is worth remembering that PPH is a major cause of morbidity and remains one of the top five causes of maternal death in both developed and developing countries.

MANAGEMENT

Basic Management

Communication

It is important to call for help immediately and inform the senior anesthetist and obstetrician. Also inform the blood bank, hematologist, and porter. Be sure to allocate a team leader and a scribe.

TABLE 72.1 Major Risk Factors for Postpartum Hemorrhage

Antenatal Presentation	Approximate Odds Ratio for PPH (99% CI)
Placental abruption	13 (7.61–12.9)
Placenta previa	12 (7.17–23)
Multiple pregnancy	5 (3.0–6.6)
Preeclampsia/gestational hypertension	4
Previous PPH	3
Ethnicity	2 (1.48–2.17)
Obesity (BMI >35)	2 (1.24–2.17)
Macrosomia (>4 kg)	2 (1.38–2.60)
Anemia (hemoglobin <90 g/L)	2 (1.63–3.15)
Age >40	1.4 (1.16–1.74)
Factors That Become Evident During Labor	
Cesarean section, emergency	4 (3.28–3.95)
Cesarean section, elective	2 (2.18–2.80)
Induction of labor	2 (1.67–2.96)
Retained placenta	5 (3.36–7.87)
Mediolateral episiotomy	5
Operative vaginal delivery	2 (1.38–2.60)
Prolonged labor (12 hours)	2
Pyrexia in labor	2

BMI, Body mass index; *CI,* confidence interval; *PPH,* postpartum hemorrhage.

TABLE 72.2 Relationship Between Etiology of Postpartum Hemorrhage and Predisposing Factors

Etiology	Predisposing Factors
Uterine atony	Multiple gestation, macrosomia, polyhydramnios, chorioamnionitis, prolonged labor, precipitous labor, augmented labor, multiparity, use of tocolytics, use of potent inhalational anesthetics
Retained placenta	Prior history of retained placenta, second-trimester delivery, abnormal placentation
Trauma	Precipitous delivery, instrumented delivery, macrosomia
Uterine inversion	Uterine atony, inappropriate umbilical cord traction, uterine anomalies, abnormal placentation

Resuscitation

Basic resuscitation follows the ABCDE model. The patient should be systematically assessed and supported as the assessment progresses.

- A: High-flow oxygen should be given to the patient if conscious. If her airway is not being maintained, provide airway support and oxygenation until intubation can be performed.
- B: Provide support ventilation if required; pulse oximetry.
- C: Use two large-bore intravenous cannulae. Take blood for group and crossmatching and baseline blood tests including venous blood gas. Give 2 L of warm crystalloid intravenously, and give blood, if indicated, as soon as possible. Assess blood pressure and electrocardiogram. Control any bleeding, and elevate legs if appropriate.
- D: Check the patient's Glasgow Coma Scale score, pupils, and blood glucose.
- E: Expose the patient to ensure a full assessment. Record temperature.

Definitive Management

This is a multidisciplinary effort that requires good communication and is helped by the establishment of in-house protocols and drills.

Pharmacologic Management

Oxytocic Agents

The primary treatment for uterine atony is the use of uterotonic medications. Oxytocin is the first choice for both the treatment and prophylaxis of uterine atony. Prophylactic oxytocics reduce the risk of PPH by about 60%. Prophylactic oxytocin is administered as 5 to 10 IU intramuscularly during the third stage of labor. It is given as 5 IU slow intravenous injection at cesarean section. An intravenous infusion can help to maintain uterine contraction after delivery as an infusion of 10 IU per hour diluted in 0.9% sodium chloride. It can cause vasodilation, hypotension, nausea, and flushing when administered.

Ergot alkaloids are second-line medications for the treatment of uterine atony and are usually administered in combination with oxytocin. Ergometrine produces tetanic uterine contractions, most likely mediated by α-adrenergic receptors. The usual dose is 0.5 mg intramuscularly. Effects are observed within a few minutes and last several hours. These agents may cause extreme hypertension, especially in hypertensive patients or those receiving concomitant vasopressor therapy. Such ergot-induced hypertension may be severe enough to cause intracranial hemorrhage, stroke, or seizures.

If these methods fail to relieve uterine atony, 15-methyl prostaglandin F_2 (Carboprost) can be used to treat refractory cases. However, it may cause bronchospasm and alter lung ventilation-perfusion ratios, causing hypoxemia. The usual dose is 250 μg administered intramuscularly or intramyometrially. It can be repeated every 15 to 30 minutes, but the total dosage should not exceed 2 mg. Misoprostol, another prostaglandin, has been investigated for safety and efficacy in the treatment of PPH. A dose of 1000 μg per rectum has been shown to be effective for severe PPH unresponsive to standard uterotonic agents. Recently several case reports have described the successful use of recombinant factor VIIa (20 to 40 μg/kg) in patients with severe, refractory PPH.

Tocolytic Agents

These agents facilitate relaxation of the uterus and, in the context of PPH, allow the obstetrician to perform manual extraction or replace the inverted uterus. In normovolemic patients, intravenous nitroglycerin (50 to 100 μg) provides uterine relaxation in about 45 seconds and lasts approximately 60 seconds. Nitroglycerin spray can be used as an alternative to intravenous administration. Each spray delivers about 400 μg of nitroglycerin sublingually, and careful attention to the patient's blood pressure is essential. If nitroglycerin is ineffective or the cervical os has closed (i.e., does not permit a transvaginal or other operative procedure), deep general anesthesia may be needed. After rapid-sequence induction and tracheal intubation, a potent volatile agent provides uterine relaxation, but the agent should be discontinued as soon as possible after the intervention.

Correction of Coagulation

In addition to the resuscitation of the patient and the administration of the anesthetic, the anesthetist is also responsible for ensuring the correction of any coagulation abnormalities. This includes, but is not limited to, the following:

- Ensuring early assessment of coagulation and request for blood products
- Early administration of fibrinogen
- Tranexamic acid administration
- Liaising with the hematologist and furnishing him or her with blood samples as requested
- Checking and administering blood, platelets, fresh frozen plasma, cryoprecipitate, and recombinant factor VIIa as required
- Fluid balance

The aim is to achieve the following:
- Hemoglobin greater than 8 g/dL
- Platelet count greater than 75×10^9/L
- Prothrombin less than 1.5 × mean control
- Activated prothrombin times less than 1.5 × mean control
- Fibrinogen greater than 1.0 g/L

Operative Management

To achieve hemostasis, intervention may be needed. Hemostatic obstetric procedures are as follows:
- External uterine massage (or internal if at cesarean section) plus oxytocics
- Manual removal of placenta
- Repair of genital tract trauma
- Uterine packs
- Rusch balloon
- Exploratory laparotomy with or without modified B-Lynch suture with or without hysterectomy with or without any necessary life-saving procedure
- Resolution of uterine inversion
- Interventional radiology—may be necessary if the bleeding point cannot be identified on laparotomy

With the exception of laparotomy and cases of major hemorrhage, most of these procedures can be performed under regional anesthesia. Repair of vaginal or perineal lacerations can also be performed with local anesthetic infiltration by the obstetrician.

If the blood loss is great and/or continuing, a general anesthetic will be required and a rapid-sequence induction with cricoid pressure and tracheal intubation is the anesthetic of choice.

These may be prolonged surgical procedures with massive blood loss. Regional anesthesia can be used, but it is generally not recommended.

Postresuscitation Care

The parturient should be monitored until stable. This should be in an obstetric high-dependency unit or in an intensive care unit as appropriate. Regular assessments should be performed according to local guidelines.

PREVENTION

Active management of the third stage of labor with the use of oxytocics should be standard for all women.

As previously mentioned, PPH usually occurs without warning. Prevention of associated morbidity and mortality requires vigilance, a high index of suspicion, and preparedness for a rapid response.

The use of early-warning scores such as the Modified Early Obstetric Warning Score (MEOWS) has enabled staff of all levels and experience to quickly identify, assess, and respond to deteriorating patients and thus facilitate early resuscitation and support.

Patients who are at risk should be identified and counseled ahead of delivery. Consultant anesthetic and obstetric staff should attend when the patient presents to be delivered.

If the risk is great (e.g., patients with a placenta accreta), the parturient should be referred to a facility with the expertise and resources to manage a major hemorrhage. These include cell salvage, interventional radiology, appropriate surgical expertise, and access to intensive care. The delivery should be timed to ensure the presence of consultant staff.

Major obstetric hemorrhage protocols have also been developed to respond quickly to unanticipated major bleeding.

In specific patient groups (e.g., Jehovah's Witnesses), it is essential to speak with the patients both at booking and on presentation for delivery to determine what blood products they will accept. This should be carefully documented in the patient notes along with any advance directives.

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Preterm Labor

73

Amanpreet Kaur

Case Synopsis

A 28-year-old woman, gravida 2, para 1, with an estimated gestational age of 28 weeks presents with a new onset of regular uterine contractions. She is admitted to the hospital for intravenous hydration and tocolytic therapy.

PROBLEM ANALYSIS

Definition/Epidemiology

Centers for Disease Control and Prevention (CDC) data from 2014 reveal preterm deliveries of 9.57%. Data from 2012 reported 450,000 preterm births; that is 1:9 for every live birth in the United States. *Preterm birth* is defined as birth before 37 weeks of pregnancy. Preterm-related death accounted for 35% of all infant deaths in 2010 and is a leading cause of neurologic disabilities in children. Some problems include breathing problems, feeding difficulties, cerebral palsy, developmental delay, and vision and hearing impairment (Box 73.1). Current obstetric practices aim at delaying such delivery as much as possible.

Recognition

The American Congress of Obstetricians and Gynecologists (ACOG) definition is as follows:

- *Preterm labor* is defined as regular uterine contractions occurring at least once every 10 minutes and resulting in cervical dilation or effacement before 37 weeks' gestation (Table 73.1).
- A preterm infant is any infant delivered before 37 weeks' gestation.
- Any infant weighing less than 2500 or 1500 g at birth is a low-birth-weight (LBW) or very-low-birth-weight (VLBW) infant, respectively, regardless of gestational age.
- At 29 weeks' gestation, more than 90% of estimated fetal weights are less than 1500 g.
- Although survival at 23 weeks of gestational age may be as high as 25%, most of these survivors have significant long-term neurologic impairment.
- Delay of delivery from a gestational age of 23 to 31 weeks improves neonatal survival rate from just over 25% to 96%.

Risk Assessment

The initial assessment of a patient with preterm labor consists of a thorough physical examination to eliminate treatable medical conditions that may have precipitated labor and a pelvic examination to rule out premature rupture of membranes. Bed rest, intravenous hydration, continuous fetal heart rate monitoring, and tocography are almost universally indicated. Bed rest and hydration alone are effective in a large number of patients. If these conservative measures are ineffective, ultrasonography, and occasionally amniocentesis, is undertaken to establish gestational age and fetal maturity. Lecithin/sphingomyelin (L/S) ratio is seen as a marker of fetal maturity. L/S ratio greater than 2 is a marker of fetal lung maturity.

Once the diagnosis is established, the obstetrician must decide whether to institute pharmacologic tocolytic therapy. This decision is based on the estimated gestational age, fetal weight, and the presence or absence of a reassuring fetal heart rate. In general, a gestational age between 20 and 34 weeks and a fetal weight of less than 2500 g in the presence of a reassuring fetal heart rate trace and absence of fetal distress are indications for tocolytic therapy. Sometimes waiting to finish the two doses of dexamethasone or betamethasone therapy 24 hours apart for lung maturity is warranted.

The tocolytic agents currently in use have the potential for significant interactions with commonly used anesthetic agents. In addition, prematurity may have implications for the route of delivery (whether vaginal or abdominal).

Implications

To understand the mechanisms of pharmacologic intervention to stop preterm labor, physiology of uterine contraction and role of calcium is important.

Although the processes that initiate labor are incompletely understood, much is known about the physiology of uterine contractions. The myometrium contains myosin and actin filaments that generate contractile force. Pacemaker cells within the myometrium are capable of initiating spontaneous contractile activity, which spreads throughout the myometrium via gap junctions between cells.

Calcium plays a critical role. Before contraction, intracellular calcium concentration increases due to release of calcium from the sarcoplasmic reticulum or flux across the sarcolemma. Calcium interacts with calmodulin, activating myosin light-chain kinase. The activated myosin light-chain kinase phosphorylates myosin, which then binds with actin. Adenosine triphosphate (ATP) is hydrolyzed by myosin adenosine triphosphatase (ATPase), resulting in movement of the actin-myosin elements and myometrial contraction. A reduction in intracellular calcium concentration, or dephosphorylation of myosin, inhibits the actin-myosin interaction, causing relaxation (Box 73.2).

This cascade offers several opportunities for pharmacologic intervention. Activation of β_2-adrenergic receptors within the myometrium activates adenyl cyclase, converting ATP to cyclic adenosine monophosphate (cAMP). Increased cAMP decreases intracellular calcium, inhibiting myosin light-chain kinase and decreasing contractile activity and hence relaxation (Box 73.3).

Magnesium sulfate decreases uterine activity, probably decreasing intracellular free calcium concentration through competition for binding sites. It may also activate adenyl cyclase, increasing synthesis of cAMP.

BOX 73.1 Sequel of Prematurity

Breathing problems
Feeding difficulties
Cerebral palsy
Developmental delay
Vision problems
Hearing impairment

TABLE 73.1 Definition of Commonly Used Terms in Preterm Labor

Term	Definition
Preterm labor	Regular uterine contraction every 10 minutes leading to changes in cervical examination at 20–37 weeks
Preterm infant	Infant born before 37 weeks' gestation
LBW infant	Weight less than 2500 g at birth
VLBW infant	Weight less than 1500 g at birth
PROM	Rupture of membranes before initiation of labor
Pre-PROM	PROM before 37 weeks' gestation

LBW, Low birth weight; *PROM,* premature rupture of membranes; *VLBW,* very low birth weight.

BOX 73.2 Flowchart Depicting Contraction

Pacemaker cells within myometrium initiate spontaneous myometrial activity → release of calcium from sarcoplasmic reticulum or influx from sarcolemma → intracellular calcium increases → Ca^+ calmodulin complex → activates myosin light-chain kinase → phosphorylation of myosin → ATP hydrolyzed by myosin ATPase → actin-myosin interaction and contraction.

BOX 73.3 Flowchart Depicting Relaxation

Uptake of Ca by sarcoplasmic reticulum → reduction in intracellular Ca → dephosphorylation of myosin → inhibition of actin myosin interaction, causing relaxation.

By blocking voltage-dependent calcium channels in the cell membrane (or altering intracellular uptake and release mechanisms), calcium-channel blocking agents decrease the concentration of free calcium within the myometrium.

Prostaglandins $F_{2\alpha}$ and $E_{2\alpha}$ are potent stimulators of uterine activity. During labor, their concentration increases in maternal blood and amniotic fluid. The nonsteroidal antiinflammatory agents that inhibit prostaglandin synthetase can inhibit the production of these prostaglandins.

MANAGEMENT

None of the tocolytic agents currently available is uniformly successful for tocolytic therapy, and it is difficult to compare their efficacy. Each has its own side effects that can limit its usefulness (Table 73.2). They include magnesium sulfate, β_2-adrenergic agonists, prostaglandin synthetase inhibitors, and calcium-channel blockers (Box 73.4). Also, a novel agent, the oxytocin antagonist atosiban, has been in use in Europe.

Oxytocin Antagonists

Atosiban [1-(3-mercaptopropionic acid)-2-[3-(p-etoxyphenyl)-D-alanine]-4-L-treonine-8-L-ornitineoxytocin] is an oxytocin antagonist. It is a competitive inhibitor of oxytocin that binds to both myometrial and decidual receptors. As it does not alter the subsequent sensitivity of the myometrium to oxytocin, the risk for postpartum uterine atony and hemorrhage is minimal or none.

Phase II and III studies demonstrate atosiban as an effective tocolytic agent. It has fewer maternal side effects, undergoes minimal placental transfer, and does not increase maternal blood loss at delivery. Atosiban has not yet been approved by the Food and Drug Administration for use in the United States because of a higher rate of perinatal deaths in the atosiban arm of the study that it reviewed.

There are no data on the interaction between atosiban and anesthetic agents. However, given the hemodynamic profile of this agent, one would not expect significant interactions. Atosiban is widely used in Europe.

TABLE 73.2 Maternal and Fetal Side Effects of Common Tocolytic Agents

Tocolytic Drug	Maternal Side Effect	Fetal Side Effect
Atosiban	None to minimal	Possible increase in perinatal death
Magnesium sulfate	Dose based (see Table 73.3)	Respiratory depression, hyporeflexia, decreased tone, loss of fetal heart rate variability, low biophysical score
β_2 agonist	Hypotension, increased cardiac output, hyperglycemia, hypokalemia, tachyarrythymia, pulmonary edema	Tachyarrhythmia
Prostaglandin inhibitors	May affect maternal coagulation	Premature closure of fetal ductus arteriosus decreased urinary secretion, oligohydramnios, renal failure
Calcium-channel blockers	Hypotension, reflex tachycardia, headache, nausea	Minimal

BOX 73.4 Common Tocolytic Agents

Magnesium sulfate
β_2-adrenergic agonists
Prostaglandin synthetase inhibitors
Calcium-channel blockers

Magnesium Sulfate

Magnesium is the intravenous tocolytic agent of choice in most centers because of its low cost and relatively low incidence of serious side effects. At the neuromuscular junction, magnesium inhibits release of acetylcholine and decreases sensitivity of the postsynaptic endplate to acetylcholine. Magnesium sulfate decreases uterine activity, probably decreasing intracellular free calcium concentration through competition for binding sites. It may also activate adenyl cyclase, increasing synthesis of cAMP.

The normal serum magnesium concentration ranges from 1.6 to 2.4 mg/dL. Therapy is initiated with an intravenous bolus of 4 to 6 g, followed by a continuous infusion of 1 to 2 g/h. The infusion is titrated to maintain a serum concentration of 4 to 8 mg/dL; although usually sufficient to inhibit uterine activity, this is not always successful.

Magnesium causes peripheral vasodilation, and parturients often experience warmth, flushing, and nausea, particularly with the onset of therapy. Maternal tachycardia and hypotension may result, but they are transient. At higher serum concentrations, other effects are seen. Widening of the QRS complex and prolongation of the PR interval are uncommon below concentrations of 10 mg/dL, but can be seen at therapeutic levels. At concentrations of 12 mg/dL or more, deep tendon

TABLE 73.3 Maternal Side Effects of Magnesium Based on Serum Concentration

Magnesium Serum Concentration (mg/dL)	Maternal Side Effects
4–8 (therapeutic concentration)	Warmth, flushing, and nausea; transient tachycardia and hypotension
>10	Widening of QRS complex and PR interval
>12	Loss of deep tendon reflexes
>18	Respiratory arrest
>25	Cardiac arrest

reflexes are lost. A concentration of 18 mg/dL can result in respiratory arrest, and at 25 mg/dL cardiac arrest may occur (Table 73.3). Fetal effects are infrequent; decreased fetal heart rate variability has been reported, as has a reduced biophysical profile score. Respiratory depression, hyporeflexia, and decreased tone have been reported in neonates following prolonged maternal magnesium therapy.

As a result of vasodilation, hypotension may occur in these patients during neuraxial block. Careful attention to maternal blood pressure allows the use of either epidural or spinal anesthesia, but a slower onset may make epidural techniques preferable. Parturients receiving magnesium are more susceptible to muscle relaxants when general anesthesia is necessary. Following the use of succinylcholine, the train-of-four response must be closely followed with a peripheral nerve stimulator to guide further use of relaxants. When necessary, further relaxants should be administered in very small doses because of their exaggerated effect. Although magnesium at therapeutic concentrations has been shown to decrease the minimum alveolar concentration of halothane at therapeutic concentrations, this is not a clinically significant effect. Following delivery, uterine atony and postpartum hemorrhage may result. Early detection and prompt treatment should be initiated.

β_2-Adrenergic Agents

Both ritodrine and terbutaline are used as tocolytic agents, but only ritodrine is approved by the Food and Drug Administration for tocolysis. Ritodrine is administered by continuous intravenous infusion and titrated in response to the uterine contraction pattern. Terbutaline is administered as a single intravenous or subcutaneous dose for prompt but temporary inhibition of uterine activity, and may be continued as oral therapy.

Although β_2 activity is responsible for tocolytic effects, both drugs have significant β_1-adrenergic effects, which account for the majority of side effects. β_2-Adrenergic activity can cause vasodilation (resulting in hypotension) and hyperglycemia. Direct β_1-adrenergic activity increases myocardial contractility and heart rate, leading to increased cardiac output, which may be protective against hypotension during regional anesthesia. The most significant side effects of β-agonist therapy are cardiac. Pulmonary edema, either cardiogenic or noncardiogenic in nature, may occur in up to 4% of patients. Fortunately, it usually resolves with discontinuation of therapy. Likewise, myocardial ischemia has been reported, manifesting as chest pain and electrocardiographic changes; this also resolves with discontinuation of therapy. Tachyarrhythmias (both maternal and fetal) may occur. Finally, hyperglycemia and hypokalemia are frequently seen in these patients.

When anesthesia is required, a period of at least 60 to 90 minutes between discontinuation of therapy and administration of anesthetic is ideal; unfortunately, a delay of this magnitude may jeopardize the fetus. Aggressive hydration is avoided due to concerns over pulmonary edema, and vasopressor therapy (ephedrine) is used more aggressively to maintain maternal blood pressure.

Prostaglandin Synthetase Inhibitors

Prostaglandins $E_{2\alpha}$ and $F_{2\alpha}$ are potent stimulators of uterine activity, and they also cause softening ("ripening") of the cervix near term. Prostaglandin synthetase inhibitors prevent the conversion of arachidonic acid into the active prostaglandins. Although all drugs in this class possess this capacity, only indomethacin is widely used in the treatment of preterm labor. It can be administered both orally and rectally and continued for several weeks.

In contrast to magnesium and β-agonists, indomethacin has few maternal side effects. It may affect maternal coagulation, but this does not seem to be of major clinical importance. In an otherwise healthy parturient without clinical evidence of impaired hemostasis, further evaluation of maternal coagulation status is generally not indicated.

These agents may have significant fetal effects, however. Prostaglandin synthetase inhibitors may result in premature closure of the fetal ductus arteriosus in utero; this effect appears to be related to gestational age and is less of a problem before 32 weeks' gestation. Indomethacin may cause decreased fetal urine excretion, leading to oligohydramnios and, rarely, neonatal renal failure. Finally, an increased incidence of necrotizing enterocolitis, intracranial hemorrhage, and bronchopulmonary dysplasia has been noted in neonates following in utero indomethacin therapy.

Calcium-Channel Blockers

By inhibiting transmembrane calcium flux, the calcium-channel blockers reduce myometrial contractility. Nifedipine is most widely used for tocolysis. The drug has a rapid onset following sublingual administration, and therapy is maintained via the oral route.

Maternal side effects of nifedipine therapy are generally mild. Nifedipine has few cardiac effects, but vasodilation and decreased blood pressure are often seen. These may be associated with reflex tachycardia, headache, and nausea.

PREVENTION

Despite aggressive therapy, tocolysis often fails and labor progresses. When delivery becomes inevitable, a choice as to the best route of delivery must be made. Most obstetricians consider the lower limit of viability to be around 24 to 25 weeks of gestational age. Routine cesarean delivery is undertaken for LBW, VLBW, breech presentation, and gestational age less than 32 weeks. Surgical delivery aims to prevent head trauma and subsequent intracranial hemorrhage. Fetuses under 32 weeks of estimated gestational age with breech presentation, when delivered vaginally, are prone to cord prolapse, muscle trauma, and head entrapment. The advantages of surgical delivery for the fetus must, however, be weighed against the increased morbidity of cesarean delivery for the mother.

For cesarean delivery, neuraxial anesthesia is preferred over general anesthesia. Most anesthetic agents that are used for induction and maintenance of general anesthesia cross the placenta and have a depressant effect on the fetus. Preterm infants exposed to neuraxial anesthesia for cesarean delivery have higher 1- and 5-minute Apgar scores than similar infants exposed to general anesthesia. Some data from animal studies have suggested that exposure of the immature brain to anesthetic agents such as propofol, thiopental, ketamine, and inhalation agents can trigger significant brain cell apoptosis in the developing fetal/neonatal brain and cause functional learning deficits later in life. The role of supplemental oxygen to the mother for neuraxial block is controversial in a setting of no fetal distress.

It is important to note that the uterine-relaxant properties of tocolytics, with the exception of atosiban, persist after the delivery. Depending on the duration of therapy and the half-life of the agent, all may contribute to uterine hypotonia intraoperatively. Vigorous therapy may be necessary to restore uterine tone and prevent significant maternal blood loss. Two or more large-bore intravenous accesses should be obtained. Type and cross for blood transfusion should be available, along with drugs to restore uterine tone; these drugs include oxytocin, methergin, prostaglandin F2α antagonist, and misoprostol.

Whenever a vaginal delivery is planned for a VLBW infant, good pelvic relaxation can be provided via neuraxial anesthesia. Depending on the skills of the provider, whenever possible the neuraxial block in preterm cases with dilated cervix with or without bulging membranes should preferably be done in a lateral position. Pudendal block or local infiltration of the perineum does not help labor pain. Neuraxial analgesia decreases maternal concentrations of catecholamines, and may even improve uteroplacental perfusion as long as hypotension is avoided. An advantage of early initiation of neuraxial analgesia is also the ability to rapidly convert labor analgesia to surgical anesthesia in the event of an emergent cesarean.

Nevertheless, the best predictors of neonatal survival in planning the delivery of the very premature infant is to ensure the presence of trained neonatal personnel for resuscitation and ready access to a neonatal intensive care unit for subsequent care. In conclusion, a team effort of the obstetrician, anesthesiologist, and neonatologist is required to improve maternal and particularly preterm fetal outcomes.

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Pulmonary Hypertension

74

Andrew Roscoe

Case Synopsis

A 55-year-old man with end-stage lung disease undergoes bilateral lung transplantation for usual interstitial pneumonitis. After reperfusion of the second lung the patient develops ischemia-reperfusion injury with acute graft dysfunction, pulmonary hypertension, and right ventricular failure.

PROBLEM ANALYSIS

Definition

Pulmonary hypertension (PHT) is defined as an increase in mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest. It can be subdivided according to the pulmonary artery wedge pressure (PAWP) into precapillary PHT (PAWP ≤15 mm Hg) and postcapillary PHT (PAWP >15 mm Hg).

PHT can be graded as mild, moderate, or severe:

- Mild: mPAP 25 to 40 mm Hg
- Moderate: mPAP 40 to 55 mm Hg
- Severe: mPAP greater than 55 mm Hg

The relationship of mPAP to cardiac output (CO) and pulmonary vascular resistance (PVR) is described by the following equation:

$$\text{mPAP} = \text{CO} \times \text{PVR}$$

Therefore an increase in mPAP is due to an increase in either CO or PVR, or both. However, in the normal individual, the pulmonary circulation has high compliance, and an increase in CO is accompanied by pulmonary vessel recruitment and a decrease in PVR. This results in little increase in mPAP.

In postcapillary PHT the transpulmonary gradient (TPG) can be used to identify high-risk patients:

$$\text{TPG} = \text{mPAP} - \text{PAWP}$$

Patients with postcapillary PHT initially have a normal TPG (<12 mm Hg) but may progress to develop a mixed precapillary/postcapillary PHT with an elevated TPG. As TPG is influenced by cardiac output, PVR may provide a better indicator of mixed PHT. A normal PVR is less than 3 Wood units (<240 dynes/s/cm^5).

PHT can be classified based on pathology and pathophysiology (Box 74.1).

Recognition

Acute PHT can be readily detected by the presence of a pulmonary artery catheter (PAC).

In the absence of a PAC, transesophageal echocardiography (TEE) can assist in the diagnosis. In the presence of tricuspid regurgitation (TR) and interrogation of the TR jet peak velocity (V_{TR}) with continuous-wave Doppler, the simplified Bernoulli equation can be applied to estimate the systolic pulmonary artery pressure (sPAP):

$$\text{sPAP} = 4V^2_{TR} + \text{CVP}$$

In the absence of significant TR, pulse-wave Doppler (PWD) interrogation of pulmonary artery (PA) blood flow can be used to measure the PA acceleration time (PAAT), from which the mPAP can be derived:

$$\text{mPAP} = 73 - (0.42 \times \text{PAAT})$$

The morphology of the PA PWD waveform may also help to distinguish between precapillary and postcapillary etiologies. In addition, TEE plays a key role in the prompt diagnosis of right ventricular (RV) failure and detecting any contribution from left ventricular (LV) dysfunction. TEE can also exclude any mechanical cause for postcapillary PHT, such as stenosis of a pulmonary vein anastomosis.

Risk Assessment

Primary graft dysfunction (PGD) after lung transplantation is characterized by pulmonary edema, hypoxemia, and PHT. It occurs in up to 25% of lung transplants. Risk factors include donor variables (age >45 years, female, head trauma); recipient variables (pulmonary arterial hypertension, body mass index >25); and operative factors, such as prolonged ischemic time and the use of cardiopulmonary bypass. PGD is associated with prolonged postoperative ventilation and increased early mortality.

In the nontransplant population 75% of PHT is secondary to left-sided heart failure.

Implications

In the noncardiac setting, PHT is not a recognized risk factor in perioperative cardiovascular morbidity and mortality risk scoring. However, patients suffering from PHT are known to have a significant increase in perioperative complications. Patients with moderate PHT may have as high as a 7% mortality rate and 42% morbidity rate when undergoing noncardiac surgery. In cardiac surgery, PHT is a well-recognized prognostic factor and has a clear association with perioperative mortality.

MANAGEMENT

The principles of PHT management include optimization of RV preload, augmentation of RV contractility, maintenance of right coronary artery (RCA) perfusion pressure, and measures to reduce PVR.

Right Ventricular Preload

In the presence of an increased PVR and RV dysfunction, volume loading usually proves to be detrimental to hemodynamics. The

BOX 74.1 Clinical Classification of Pulmonary Hypertension

1 Pulmonary arterial hypertension
- **1.1** Idiopathic
- **1.2** Inherited
- **1.3** Drug-induced

1′ Pulmonary veno-occlusive disease

1″ Persistent pulmonary hypertension of the newborn

2 Secondary to left-sided heart disease
- **2.1** Systolic dysfunction
- **2.2** Diastolic dysfunction
- **2.3** Valvular disease

3 Secondary to lung disease/hypoxia
- **3.1** Chronic obstructive pulmonary disease
- **3.2** Interstitial lung disease
- **3.3** Mixed restrictive/obstructive lung disease
- **3.4** Sleep disorders

4 Chronic thromboembolic pulmonary hypertension

5 Multifactorial mechanisms
- **5.1** Hematologic disease
- **5.2** Systemic disorders
- **5.3** Metabolic disorders

BOX 74.2 Pulmonary Vasodilators

Inhaled
- Nitric oxide
- PGI_2 analogs
- Milrinone

Intravenous
- Nitroglycerin
- Adenosine
- PGI_2 analogs
- Dobutamine
- Milrinone
- PDE-5 inhibitors

Oral
- PDE-5 inhibitors
- PGI_2 analogs
- ET antagonists
- Riociguat
- Hydralazine
- CCBs
- Hydralazine

CCBs, Calcium-channel blockers; *ET,* endothelin; *PDE,* phosphodiesterase; *PGI_2,* prostacyclin.

right ventricle has a flatter Starling curve than the left ventricle, so an increase in preload produces RV dilation with only small increases in stroke volume. The sequelae of this RV dilation include the following:

- Increase in free wall tension, causing an increase in oxygen demand
- Decrease in RCA perfusion pressure, reducing oxygen delivery
- Tricuspid annular dilation, worsening tricuspid regurgitation and exacerbating volume overload
- Interventricular shift to the left, impeding LV diastolic filling and reducing LV stroke volume, resulting in systemic hypotension

Preload may be affected by positive-pressure ventilation, especially if high airway pressures and positive end-expiratory pressure (PEEP) are employed to overcome hypoxemia.

Treatment involves reducing preload with diuretics or hemodialysis, typically to a central venous pressure (CVP) less than 15 mm Hg.

Right Ventricular Contractility

RV systolic dysfunction may be secondary to overstretching of the free wall or myocyte ischemia due to reduced perfusion and oxygenation. Inotropic agents are frequently used to augment RV contractility, but they increase oxygen consumption and may lead to tachyarrhythmias, so judicious use is warranted:

- Dopamine (5 to 10 μg/kg/min) and epinephrine improve RV contractility while maintaining systemic arterial pressures, with little effect on PVR.
- Low-dose dobutamine (5 to 10 μg/kg/min) has been shown to augment RV contractility and improve right ventricle–pulmonary artery coupling. However, at higher doses, β_2-mediated systemic vasodilation reduces RCA perfusion pressure.
- Milrinone, a phosphodiesterase-3 inhibitor, has some attractive properties: positive inotrope and pulmonary vasodilator, but causes significant systemic vasodilation. Its use is better suited to treating postcapillary PHT and biventricular failure.
- The calcium sensitizer levosimendan is a potent inodilator, which may improve RV diastolic function, but also results in significant systemic vasodilation.

Right Coronary Artery Perfusion

In the normal heart, RV myocardial perfusion occurs throughout systole and diastole. As PA pressures approach systemic pressures, RCA perfusion becomes limited to diastole and is determined by systemic arterial and RV diastolic pressures. RV volume overload and dilation, coupled with a decrease in systemic arterial pressures, will worsen myocardial perfusion. The mainstay of treatment is to ensure adequate systemic blood pressure:

- Norepinephrine mainly acts on α_1 receptors, causing vasoconstriction, but also has some β_1 activation, enhancing RV contractility, and has been shown to improve right ventricle–pulmonary artery coupling in some studies.
- Vasopressin acts on V1 receptors and at low dose (<0.03 U/min) causes pulmonary vasodilation but at higher doses causes pulmonary and coronary artery vasoconstriction, and carries no inotropic effect. It may be useful as an adjunct to norepinephrine in maintaining systemic arterial pressures.

Reduction of Pulmonary Vascular Resistance

Basic measures to reduce PVR include avoiding hypoxia, hypercapnia, and acidemia; maintaining normothermia; recruitment maneuvers to reduce ventilation/perfusion (V/Q) mismatch; ventilating with low tidal volumes, because PVR is minimal at functional residual capacity; and administration of pulmonary vasodilators (Box 74.2).

The inhaled pulmonary vasodilators, nitric oxide (NO) and prostacyclin derivatives, have the advantage of reducing PVR with minimal effect on systemic arterial pressure. Although their use improves pulmonary hemodynamics, an outcome benefit is still unproven.

Intravenous pulmonary dilators have the disadvantage of significant systemic side effects and may blunt hypoxic pulmonary vasoconstriction, worsening V/Q mismatch. Calcium-channel antagonists may have a negative inotropic effect and should be avoided in the presence of RV dysfunction. Endothelin receptor antagonists are used extensively in the management of idiopathic PHT and chronic thromboembolic PHT, but have been shown to increase mortality in postcapillary PHT.

Mechanical Circulatory Support

If RV failure persists despite maximal pharmacologic therapy, extracorporeal life support (ECLS) can proffer temporary assistance. If PHT is solely

due to hypoxemia, the institution of venovenous ECLS to provide oxygenation should reduce PVR, with subsequent improvement in RV function. If other mechanisms of PHT are present, venoarterial ECLS allows for both cardiac and respiratory support. ECLS provides temporary support, and should only be instigated when there is a potentially reversible cause.

PREVENTION

Basic maneuvers can be employed to mitigate the severity and effect of PHT on RV function:

- Ensure adequate oxygenation
- Avoid hypercapnia
- Avoid acidemia
- Maintain normothermia
- Low tidal-volume ventilation
- Recruitment maneuvers to reduce V/Q mismatch

The prophylactic use of inhaled NO has been studied in lung transplantation, left ventricular assist device, and pneumonectomy surgeries, with mixed results.

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75 Retrobulbar Block

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Case Synopsis

Monitored anesthesia care is provided for an active 70-year-old patient undergoing phacoemulsion of a cataract with intraocular lens implantation. The patient has stable hypertension, coronary artery disease, mild emphysema, and renal insufficiency. Sedation with 1 mg midazolam is administered along with verbal reassurance while the anesthesiologist performs a retrobulbar block. Five minutes later the patient becomes unresponsive, is hypotensive with a heart rate of 35 beats per minute, and is breathing irregularly with oxygenation saturation of 83%.

PROBLEM ANALYSIS

Definition

Cataract surgery is likely to remain the most frequently performed surgical procedure in industrialized nations with their burgeoning Baby Boomer populations. Yet many anesthesiologists are unaware of the potential sight- and life-threatening complications associated with ophthalmic regional anesthesia, either from a lack of technical familiarity or from a lack of follow-up in predominantly same-day surgical patients. Anesthesiologists must be aware of these rare but possibly fatal consequences of local anesthesia injected into a patient's eye to anticipate complications and treat them appropriately.

A review of the literature reveals an evolving practice to less invasive ocular anesthesia. From Knapp's use of 4% retrobulbar cocaine in 1884, Atkinson advocated the "modern" approach in 1936 of a blind insertion of a needle into the intraconal space. In 1986 Davis and Mandel described the posterior peribulbar technique as an alternative. In 1992 Stevens published an article about cataract extraction by a medial quadrant sub-Tenon capsular infiltration. Subconjunctival and topical anesthesia are useful in modern ophthalmic surgical techniques that do not mandate total ocular akinesia and analgesia.

Retrobulbar block combined with facial nerve block provides superior akinesia, anesthesia, and analgesia compared with other regional techniques. Indications include the following:

- Avoidance of general anesthesia in elderly patients who have multiple medical comorbidities
- Achievement of optimal surgical conditions for extracapsular cataract extraction, phacoemulsification, intraocular lens implantation, and open globe surgery (e.g., vitrectomy, glaucoma treatment, repair of retinal detachment)
- Prolonged, difficult surgeries (e.g., previous eye surgeries) or in patients with hard cataracts or nystagmus

Contraindications to retrobulbar block include the following:

- True allergy to local anesthetic drugs
- Patient refusal, despite explanations regarding the use of intravenous sedation to minimize pain and lack of perioperative awareness
- Patient inability to cooperate

The operating room team must determine its own level of comfort concerning contraindications to local anesthetic blocks. The spectrum of "uncooperative" patients includes impaired mental status, youth, dementia, deafness, severe emphysema or congestive heart failure, excessive anxiety, inability to keep still from Parkinson tremor or restless legs syndrome, or inability to lie flat. Which of these patients may be managed safely with regional anesthesia, minimal intravenous sedation, or verbal reassurance and which patients will require general anesthesia care should be answered by discussion among the ophthalmologist, anesthesiologist, and patient.

Coagulation abnormalities must also be considered. Evidence suggests that patients who take nonsteroidal antiinflammatory drugs, aspirin, or warfarin can undergo eye surgery safely.

Recognition

Complications

Sight-threatening injuries include predominantly needle-related penetration into the globe, the optic nerve, central retinal vein and artery, and muscles surrounding these structures. Wrong (nonsurgical) eye injection has occurred. Injection of anesthetic into the surgical globe has resulted in scleral perforation, vitreous hemorrhage, loss of vitreous fluid and hypotony, diminished red reflex, and retinal detachment. Local anesthetic into the optic nerve sheath has been postulated to cause transient vision loss of the nonsurgical eye due to spread of the anesthetic agent through the subarachnoid space to the optic chiasm to the contralateral optic nerve. Hemorrhage from the central vein and artery cause occlusion of the blood vessels, as well as compression and ischemia of the optic nerve. Immediate, delayed, and partial-to-total visual losses have been reported. Injections into the inferior rectus and superior rectus muscles have resulted in diplopia, vertical tropia, and permanent myopathies leading to persistent strabismus because of unopposed antagonist muscle contractures. Subconjunctival hematomas or hyphemas in the anterior chamber of the eye are visually striking but of a lesser danger to patients.

Life-threatening injuries have been reported with retrobulbar, peribulbar, and even the less invasive ophthalmic anesthetic techniques. Brainstem anesthesia from direct subarachnoid injection of local anesthetic can be immediate, the ultimate high spinal anesthetic, requiring cardiopulmonary resuscitation for bradycardia or asystole, apnea, and hypotension. More difficult to diagnose is a slow onset of brainstem anesthesia (described earlier) when the patient demonstrates mild confusion, gradual unresponsiveness to verbal or painful stimuli, shivering or convulsive fit, bilateral ocular nerve palsy and amaurosis,

hemiplegia to quadriplegia, respiratory depression, and hemodynamic instability. Acute pulmonary edema and trigeminal nerve blockade and "coma," severe orbital cellulitis in immunocompromised patients, myopic staphylomas, and chemosis after retrobulbar block have been reported anecdotally. Should the patient already be under surgical drapes, diagnosis and treatment may be delayed unless a vigilant anesthesia provider is focused to detect these possibilities. Adequate resuscitative capabilities should always be within reach to prevent death.

During a retrobulbar or peribulbar block, activation of the oculocardiac reflex–related bradycardia, asystole, or other arrhythmias may be confused with brainstem anesthesia. Ocular injection, pressure on the globe, or traction on the extraocular muscles, conjunctiva, or globe transmits signals through the ophthalmic branch of the trigeminal nerve to the vagus nerve. Young children who have not received atropine pretreatment are especially prone to the oculocardiac reflex.

Other medical causes such as angina, poorly controlled hypertension, insidious onset of myocardial infarction, or stroke must be recognized as strong differential diagnoses in the predominantly geriatric population. In the absence of eye injection or ocular pressure a vasovagal episode from starting intravenous access can occur. Diabetic patients with retinopathies may be symptomatic from hypoglycemia or slipping into diabetic ketoacidosis. Appropriate preanesthetic assessments and optimization of patient health may reduce some of the confounding perioperative factors.

Complication rates with regional anesthesia are very low. They range from 1 in 1300 to 1 in 16,000 for globe perforation and 1 in 300 to 1 in 500 for brainstem anesthesia (Box 75.1). More recent observational studies in the United Kingdom suggest an incidence for ocular perforation between 0.009% and 0.13%, and between 0.09% and 0.79% for brainstem depression. There was a 0.25% incidence of anesthesia-related diplopia in one retrospective review, with retrobulbar block accounting for 0.39% of cases.

Unfortunately, similar compromise of patient safety and ocular damages continue despite less invasive ocular techniques. A 2007 prospective, observational study of routine ocular practice in the United Kingdom estimated cataract surgery to comprise 92% local anesthetics without sedation. Of approximately 375,000 local anesthetics, 30.6% were peribulbar, 42.6% sub-Tenon, 3.5% retrobulbar, 1.7% subconjunctival, 9.9% topical, and 11.0% topical-intracameral. The UK cataract national data set audit of 55,567 surgeries published in 2009 showed that sub-Tenon anesthesia was the most widely used anesthetic technique. Peribulbar anesthetics averaged 19.5%, and the retrobulbar technique decreased to 0.5%. A statistically significant increased risk of serious complications with sharp-needle anesthesia compared with sub-Tenon blunt cannula was noted.

Less invasive techniques allow anxious patients to squeeze eyelids or be a moving surgical target for the ophthalmologists. Globe perforation when dissecting with sharp scissors for a sub-Tenon injection has occurred along with posterior capsular tear requiring anterior vitrectomy.

BOX 75.1 Complications of Retrobulbar Block

- Retrobulbar or peribulbar hemorrhage
- Globe penetration or perforation
- Optic nerve damage leading to visual changes, including blindness
- Central nervous system depression leading to brainstem anesthesia
- Severe symptomatic activation of oculocardiac reflex
- Diplopia and eye muscle imbalance

Anatomic Considerations

To understand how complications occur with retrobulbar block and other regional anesthesia techniques used for ophthalmic surgery, a brief review of the ocular anatomy is necessary (Fig. 75.1). The extraocular muscles surround the globe and form the cone. The lateral rectus is supplied by the abducens (sixth cranial) nerve, the superior oblique by the trochlear (fourth cranial) nerve, and the other muscles by the oculomotor (third cranial) nerve. The nasociliary, oculomotor, abducens, and optic nerves run within the cone behind the globe, along with the central retinal artery and vein. Importantly, the dural cuff surrounds the optic nerve.

The ophthalmic division of the intracranial trigeminal nerve divides into the lacrimal, frontal, and nasociliary nerves. Extraconal and conjunctival sensations are supplied by the first two of these nerves. Branches of the nasociliary provide innervation to the intraconal portion, cornea, sclera, iris, and ciliary body of the eye. Block of the anterior ethmoidal nerve, another branch of the nasociliary nerve, results in nasal stuffiness.

The ciliary ganglion of the nasociliary nerve lies near the apex of the retrobulbar cone; therefore it is associated with the optic nerve and artery. Parasympathetic fibers from the Edinger-Westphal nucleus accompany the oculomotor nerve and synapse in its ganglion, whereas sensory and sympathetic fibers from T1 continue through the ganglion. Its efferent nerve, the short ciliary nerve, travels anteriorly to provide sensation to the globe and autonomic motor function to the iris.

Technique

All sensory and motor nerves can be blocked by injection into either the optic cone (retrobulbar block) or the orbital fat (peribulbar block). For retrobulbar block, the needle is placed from the inferolateral orbital rim to past the equator of the globe, before turning medially and inward. Ideally, the needle enters between the inferior and lateral rectus muscles, behind the globe, and within the space bounded by

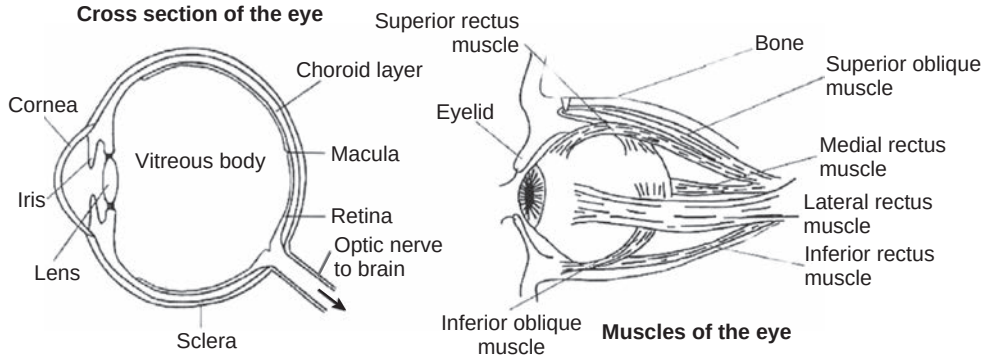

Fig. 75.1 Anatomy of the eye relevant to the performance of retrobulbar block.

the extraocular muscles. On injection, the pulsatile ocular blood flow decreases, even in the absence of changes in intraocular pressure. The patient maintains a primary gaze, looking straight ahead.

Placement of retrobulbar blocks uses external anatomic landmarks and tactile sensations. A 1995 paper describing the use of ultrasound during retrobulbar block demonstrated that the needle tips are perilously closer to the globe than envisioned by the operator. Perhaps the increasing use of ultrasound-guided peripheral nerve blocks will extend to routine use during invasive eye blocks.

Risk Assessment

The following are risk factors implicated in complications associated with retrobulbar block:

- Technical inexperience on the part of the surgeon or anesthesiologist
- Use of a sharp needle longer than 35.0 mm and an insertion depth greater than 25 mm
- Long axial length of a myopic eye (long, thin globe) or axial length greater than 24 mm
- Left inferior rectus muscle injection by a right-handed physician
- Use of excessive volume (≥4 to 5 mL) of local anesthetic, which may lead to "compartment syndrome"
- Presence of staphylomata at the site of injection as detected by ultrasound
- Multiple injections
- An uncooperative patient who is either overly anxious or oversedated

It is unclear how the type of local anesthetic used or the inclusion of hyaluronidase affects the risk of complications. A 1999 UK observational survey concluded that serious adverse events, though rare, were seen with all ocular techniques using local anesthetics. Lidocaine was used significantly less in the group who had serious adverse events.

Implications

Skills required for deep ocular injections may diminish from lack of use. Ultrasound-guided injections can potentially reduce the devastating sight- and life-threatening complications.

The use of subconjunctival and topical anesthesia has increased due to ease of administration, rapid placement, lack of painful injections, and minimal complications. Unfortunately, the eye is not akinetic, and the patient must be cooperative despite possibly experiencing pain with the superior rectus fixation suture and during cautery of scleral vessels. General anesthetics in selected patients, either uncooperative or highly myopic, may be a safer option than retrobulbar/peribulbar blocks.

MANAGEMENT

An anesthesiologist's presence continues to be vital to the well-being of any patient undergoing ophthalmic surgery. Maintaining communication with the patient (e.g., through intermittent hand squeezes) is as important as monitoring the blood pressure, electrocardiogram, capnography, and pulse oximetry.

In the event of extensive ocular hemorrhage or global perforation, the opinion of the ophthalmologist should guide further treatment. Surgery may be deferred or changed (e.g., progressed to a scleral buckle procedure). Early referral to tertiary retinal care may alleviate the catastrophic effects of diminished visual acuity.

The alert anesthesiologist should be able to manage cardiopulmonary resuscitation. Airway management and circulatory support with vagolytic or anticonvulsive medications may be used until the patient returns to his or her preoperative status.

PREVENTION

Knowledge of ocular anatomy and its proximity to intracranial structures and a continuing dedication to improve one's ocular regional anesthesia skills can reduce the incidence of serious complications. Tracking the location of the needle via ultrasound may protect the globe and its neurovascular and muscular structures. The use of short, 2.5- to 3-cm blunt needles and small volumes (3 to 4 mL) of local anesthetics is prudent. A minimal needle insertion depth (<25 mm) and stopping the insertion if the patient complains of severe pain can lower the likelihood of touching the globe or the dura. The eye should remain in the primary neutral gaze or in a slightly down and outward gaze during injection. The patient must be cooperative. Verbal reassurance to minimize the need for intravenous sedation and vigilant monitoring will promote patient and ocular safety.

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76 Sedation of Pediatric Patients

Mary Landrigan-Ossar • Joseph P. Cravero

Case Synopsis

An obese 10-year-old child with enlarged tonsils and a history of sleep apnea is scheduled to undergo magnetic resonance imaging (MRI). She is sedated by the hospital sedation service, which is staffed by pediatric intensive care physicians. The child is given 2.5 mg/kg of propofol as a bolus, and a 200 μg/kg/min infusion is started. After falling asleep, the child is placed in the scanner. Ten minutes into the MRI scan, the child's oxygen saturation decreased from 98% to 86%, and (although there appears to be respiratory effort) there is no reading on the end-tidal CO_2 monitor.

PROBLEM ANALYSIS

Definition

Sedation may be described as a continuum of states of depressed consciousness. The American Academy of Pediatrics (AAP), the American Society of Anesthesiologists (ASA), and the Joint Commission (TJC) have agreed on standardized definitions to describe sedation depth including *minimal sedation, moderate sedation, deep sedation,* and *general anesthesia.* Definitions of sedation states and patient responsiveness are presented in Table 76.1. The possible "states" or "depths" of sedation have been correlated to the risk of complications based on the extent to which natural airway/vascular tone and protective reflexes have been depressed. Deeper levels of sedation have greater likelihood of depressing airway tone, protective reflexes, respiratory drive, and cardiac function, inherently resulting in greater risks of complications.

Because sedation is a continuum and patient responses to sedating medications are unpredictable, emphasis has been placed on practitioners' ability to rescue patients from at least one level of sedation deeper than intended. As such, practitioners who administer drugs to achieve minimal sedation must have the skills to rescue a patient who becomes moderately sedated, and practitioners who intend to achieve deep sedation must have the skills to rescue patients from a state of general anesthesia. Because most sedation-related adverse events in children are related to airway compromise or loss of respiratory effort, the most important skills are the appropriate recognition of inadequate ventilation and subsequent advanced airway management. For practical purposes, most children require deep sedation to produce acceptable conditions for prolonged diagnostic or therapeutic procedures. Therefore it is good practice to use the guidelines for deep sedation from the outset of the sedation process.

Sedation adverse events (complications) have been well documented in a number of studies, notably in a report from the Pediatric Sedation Research Consortium (PSRC). In a report of over 30,000 prospectively observed sedation encounters, this group reported the observed complications, which included (but were not limited to) apnea, airway obstruction, laryngospasm, hypoxia, prolonged recovery, and aspiration. There were also a small number of patients with hypotension and bradycardia (Table 76.2). Although the rates for serious adverse events were low, the data confirm that sedation of children involves alterations of consciousness that are associated with partial or complete loss of protective reflexes and more profound changes in central nervous system and cardiopulmonary physiology.

TJC and the Centers for Medicare and Medicaid Services (CMS) have recognized anesthesiologists as experts in managing all levels of sedation/anesthesia, and both organizations have mandated that departments of anesthesia lead the way in developing institutional policies regarding the sedation of all patients, whether adult or pediatric. The intention is to create uniform standards of care regarding the management of patients undergoing sedation/anesthesia within each institution.

Recognition

Appropriate monitoring is critical to recognizing the onset of airway obstruction or changes in cardiovascular stability. The AAP and ASA have set forth appropriate monitoring criteria based on depth of sedation outlined in Table 76.3. For deeply sedated patients, monitoring electrocardiogram, blood pressure, and pulse oximetry is recommended. Perhaps most important is monitoring of respiration, which can be accomplished through multiple devices/techniques. Most commonly used are impedance plethysmography, direct observation, precordial stethoscopy (or amplified breath sounds), and end-tidal CO_2 detection/capnography. The use of CO_2 detection has been widely described and adopted because it can be used in a wide range of sedation environments (including remote locations), and it detects air exchange rather than simply chest wall movement. The use of capnography allows for early detection and correction of impaired ventilation before the onset of hypoxemia.

Monitors alone will not detect complications. The presence of an independent observer who tracks the monitor output and records trends is a critical aspect of sedation complication prevention and management. This observer must have training both in the recognition of potential adverse situations and in appropriate responses to restore patients to a safe baseline. Simulation is a useful tool both to teach basic and advanced sedation skills and to test organizations' approach to adverse events.

Likewise, sedation often does not end with the completion of a procedure. Patients should be monitored in a fully equipped and staffed recovery area with strict and uniform discharge criteria identical to those used for patients recovering from general anesthesia.

TABLE 76.1 Expected Patient Responses With Minimal, Moderate, or Deep Sedation

	Minimal Sedation[a]	Moderate Sedation[b]	Deep Sedation[c]
Responsiveness	Normal to verbal stimulation	Purposeful to verbal or light tactile stimulation	Purposeful following repeated or painful stimulation
Airway	Unaffected	No intervention required	May require intervention
Spontaneous ventilation	Unaffected	Adequate	May be inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained

[a]Drug-induced state equivalent to anxiolysis.
[b]Drug-induced depression of consciousness equivalent to conscious sedation.
[c]Drug-induced depression of consciousness during which patients cannot be easily aroused.
Modified from the American Society of Anesthesiologists. Available at http://www.asahq.org.

TABLE 76.2 Complications Recorded in the Pediatric Sedation Research Consortium—Data on 30,000 Sedation Cases Prospectively Evaluated for Complications During or Immediately After a Procedure

	Incidence per 10,000	*N*	95% CI
Complications			
Death	0.0	0	0.0–0.0
Cardiac arrest	0.3	1	0.0–1.9
Aspiration	0.3	1	0.0–1.9
Hypothermia	1.3	4	0.4–3.4
Seizure (unanticipated) during sedation	2.7	8	1.1–5.2
Stridor	4.3	11	1.8–6.6
Laryngospasm	4.3	13	2.3–7.4
Wheeze (new onset during sedation)	4.7	14	2.5–7.8
Allergic reaction (rash)	5.7	17	3.3–9.1
Intravenous-related problems/complication	11.0	33	7.6–15.4
Prolonged sedation	13.6	41	9.8–18.5
Prolonged recovery	22.3	67	17.3–28.3
Apnea (unexpected)	24.3	73	19.1–30.5
Secretions (requiring suction)	41.6	125	34.7–49.6
Vomiting during procedure (non-GI)	47.2	142	39.8–55.7
Desaturation—below 90%	156.5	470	142.7–171.2
Total adverse events	339.6 (1 per 29)	1020	308.1–371.5
Unplanned Treatments			
Reversal agent required—unanticipated	1.7	5	0.6–3.9
Emergency anesthesia consultation for airway	2.0	6	0.7–4.3
Admission to hospital—unanticipated (sedation related)	7.0	21	4.3–10.7
Intubation required—unanticipated	9.7	29	6.5–13.9
Airway (oral) (unexpected requirement)	27.6	83	22.0–34.2
Bag-mask ventilation (unanticipated)	63.9	192	55.2–73.6
Total unplanned treatments	111.9 (1 per 89)	336	85.3–130.2
Conditions Present During Procedure			
Inadequate sedation, could not complete	88.9 (1 per 338)	267	78.6–100.2

CI, Confidence interval; *GI*, gastrointestinal.
From Cravero JP, Blike GT, Beach M, et al: Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. *Pediatrics* 118(3):1087-1096, 2006.

TABLE 76.3 Guidelines for Recognition of Complications Related to Sedation

	Moderate Sedation	Deep Sedation
Monitoring	Pulse oximetry—continuous Heart rate—continuous Respiratory rate every 15 min Level of consciousness every 15 min Blood pressure every 15 min	Pulse oximetry—continuous[a] Heart rate—continuous Respiratory rate every 5 min Level of consciousness every 5 min Blood pressure every 5 min[b]
Charting	Pulse oximetry every 15 min Heart rate every 15 min Respiratory rate every 15 min Level of consciousness every 15 min[c] Blood pressure every 15 min	Pulse oximetry every 15 min Heart rate every 5 min Respiratory rate every 5 min Level of consciousness every 5 min Blood pressure every 5 min
Personnel	Same individual may observe patient and assist with procedure	Dedicated patient observer may not assist with procedure
Equipment	Pulse oximeter Blood pressure measuring device	Pulse oximeter Blood pressure measuring device Electrocardiograph and defibrillator immediately available

[a]Note whether and how oxygen is administered.
[b]Blood pressure may be taken less frequently if other vital signs are stable and taking blood pressure would interfere with the procedure.
[c]Assessment of the level of consciousness may not be practical during some procedures, such as magnetic resonance imaging or computed tomography, if awakening the patient would prevent a successful scan.

Risk Assessment

Landmark work by Coté and colleagues has identified the fact that most serious complications relating to sedation involve one or more of the following factors:

- The same person performing the procedure and sedating the child
- Residual drug effects combined with inadequate monitoring during recovery
- Lack of appreciation for drug-drug interactions and drug dosing errors
- Having parents administer a sedating medication at home and then having no one observe the child for signs of airway obstruction

A detailed analysis of sedation accidents conducted by these investigators found that approximately two-thirds of children were younger than 6 years of age, and half received more than one sedating medication. This study also found that adverse outcomes were associated with all routes of drug administration (oral, rectal, nasal, intramuscular, intravenous, inhalation). Twelve patients suffered an adverse event or outcome either on the way to the medical facility (two patients who received sedation at home) or after discharge from medical supervision (10 patients). All patients who suffered an adverse event after discharge had received long-acting sedation medications.

In a series of studies evaluating sedation complications from the PSRC, Cravero and colleagues confirmed the existence of higher-risk pediatric subgroups undergoing sedation. These include young patients, ASA status III or IV, obesity, and those sedated with potent agents such as propofol. High-risk procedures such as bronchoscopy and upper gastrointestinal procedures have also been identified. Serious adverse events were not associated with a particular provider type versus any other. The authors suggest that the relatively low rates of serious adverse outcomes in their data are the result of coordinated sedation services that identify high-risk patients and have excellent monitoring, quality improvement processes, and teamwork.

In response to the data on complications that occur after procedures are completed, Malviya and colleagues examined recovery in toddlers following chloral hydrate sedation for echocardiograms. They found that using discharge criteria based on the patient's ability to remain awake for 20 consecutive minutes in a soporific environment and on the University of Michigan Sedation Scale resulted in a mean discharge time 75 minutes later than when using standard discharge criteria. This observation suggests that prolonged observation (perhaps in a step-down unit) may improve safety when long-acting medications are used for pediatric sedation.

In summary, the collected literature on sedation clearly supports the concept that sedation risk varies with patient subgroups and procedures, thus requiring a systematic assessment of children requiring sedation, with the goal of significantly reducing anesthetic-related morbidity and mortality.

Implications

It is impossible to simply convince infants, toddlers, and many children to cooperate with diagnostic and therapeutic procedures. Pharmacologic control is required. A long list of medications has been employed over the years in the pursuit of this goal. This includes barbiturates, chloral hydrate, butyrophenones, opioids, phenothiazines, benzodiazepines, and hypnotics such as propofol and dexmedetomidine. For some of these medications or medication combinations, there is a paucity of information regarding pediatric safety and efficacy. This is particularly true as the sedation strategy trends toward deep sedation.

Because there are insufficient numbers of anesthesiologists to provide all of the sedation required for diagnostic and therapeutic procedures in children, many receive procedural sedation from pediatric subspecialists other than anesthesiologists. Propofol sedation provided by providers who are not anesthesiologists has raised concerns regarding the appropriateness of these individuals administering this medication. Anesthesiologists have attempted (in the not-distant past) to restrict the use of propofol and all deep sedation by nonanesthesiologists. Currently, the provision of deep sedation by emergency physicians and other nonanesthesiologists using propofol or other drug regimens is well established. This practice is supported by large-scale studies performed by the PSRC, which have demonstrated that, at least within the confines of established sedation programs, deep sedation can be safely administered outside the specialty of anesthesiology. The ASA has established guidelines for the use of deep sedation and propofol (specifically) by nonanesthesiologists. It is up to our specialty to educate and train these individuals. Indeed TJC and CMS have recognized the importance of anesthesia oversight of sedation in the hospital setting. Regardless of the medications being employed, sedation needs to be provided by physicians and/or nurses who have been appropriately trained to administer it and to recognize and treat its complications.

MANAGEMENT

Long-term safe sedation of multiple patients requires a robust system that encompasses patient selection, intraprocedural management, preparation for adverse events, and appropriate recovery. As mentioned, the AAP first developed guidelines for the sedation of pediatric patients both inside and outside the hospital environment in 1985. The guidelines were revised in 1992, and since then they have been augmented by two ASA practice guidelines and multiple revisions, most recently in 2016.

A systematic approach to a practice of sedation means organizing care in such a way that a number of checks and balances are in place so that vital pieces of information are not lost and responses to emergency situations are determined before the need for them exists. For the sedation of pediatric patients, such an approach involves a number of important components:

- All patients must be treated with the same degree of care, and consistent criteria must be established to determine which patients require care by an anesthesiologist and which can be referred to other specialist sedation services. This includes consideration of age, ASA physical status, airway anatomy, obesity, and medical comorbidities such as cardiac or respiratory disease.
- Adequate review of the patient's history, physical examination (including a focused airway examination), current medications, allergies, and past medical and surgical records is essential, and mandated by various regulatory bodies.
- Presedation given at home before traveling to the site where the procedure will be performed is strictly prohibited. Children must be under medical supervision before being given any drugs.
- Before sedation, ensure the availability of age- and size-appropriate and functioning equipment to manage the airway; medications to effectively manage emergencies, including reversal agents for opioids and benzodiazepines; and adequate means of delivering positive-pressure ventilation with sufficient oxygen reserves for at least 1 hour.
- Monitoring of patients during sedation should be appropriate for their level of sedation (see Table 76.3) and should be recorded such that other practitioners can easily interpret the course of the sedation.
- Response to adverse events and emergency situations should be standardized as much as possible, particularly with regard to activation of code response and availability of backup for difficult airway management. Simulation of such events can be utilized to highlight latent issues with a system.
- Recovery of patients after sedation should be held to the same standard as that for patients recovering from anesthesia, and discharge criteria should be standardized.
- Sedation programs should participate in ongoing safety reviews and quality improvement efforts, tracking not only adverse events but ideally also monitoring quality of sedation and the experience from the viewpoint of patients and their families.

PREVENTION

Complications associated with sedation of pediatric patients and the interventions required to prevent complications are well described. Data from the studies by Coté and colleagues, as well as the PSRC, clearly outline the critical competencies required to deliver safe sedation care. Sedation providers (regardless of specialty or background) must be able to recognize hypoventilation or apnea. They must be

able to open an airway and clear any obstruction. They must be able to provide ventilation and support cardiovascular depression. The most important (and successful) strategy for the prevention of complications is to ensure that all sedation providers are specifically trained and (confirmed) capable in these critical skills.

In many institutions, the appointment of a "sedation team" is an effective method ensuring safe and effective sedation—thus preventing complications. When the sedation team is provided appropriate resources (ideally with a central procedure unit), the same sedation process can be used for patients undergoing a wide variety of procedures. Sedation teams (or services), by virtue of their training and experience, work together to develop techniques to facilitate safe sedation and patient, parent, and physician satisfaction. Training courses for these teams have been described and should include didactic teaching, as well as simulation and hands-on practical experience with testing for critical competency before independent practice.

Anesthesiologists have a critical role in preventing sedation complications. When anesthesiologists do not have the workforce to provide sedation for children, it is critical that they participate in creating the sedation education, training, support, and continuing surveillance for sedation providers from other specialties. Regardless of how pediatric sedation services are structured, institutional sedation safety and quality must be consistent across all sedation sites. There should be one administrative director for all sedation/anesthesia, and, logically, this responsibility should rest with the director of anesthesiology services.

Case Synopsis and Summary

The case synopsis illustrates the key concepts of this chapter. First is the need to perform a presedation evaluation and recognize increased risk associated with anesthesia. The patient had multiple risk factors for airway obstruction, including obesity and obstructive sleep apnea. In addition, appropriate monitoring is illustrated by the use of end-tidal CO_2 monitoring in a situation where it is not possible to be close to the patient. Finally, we recognize the complication of airway obstruction by the presence of chest wall movement in the absence of CO_2 on the capnography. Intervention and prevention of more serious consequences can only be accomplished by sedation providers who recognize this complication and intervene to open the airway. Appropriate training of sedation providers and system oversight should make this potentially dangerous complication a minor interruption in the scan.

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77 Spinal Cord Injury

Tod B. Sloan • Antoun Koht

Case Synopsis

A 32-year-old man presents to the emergency department following a motorcycle accident in which he was thrown to the roadside. He is mildly obtunded, smells of alcohol, and is difficult to examine neurologically, but he appears to have loss of sensation and motor activity below the C5 dermatome. Lateral neck films fail to identify bony injury or subluxation. Vital signs reveal hypotension (90/40 mm Hg), bradycardia (50 beats per minute), respiratory difficulty, and an oral temperature of 36.2°C. He is taken to the operating room emergently for repair of an open tibial fracture.

PROBLEM ANALYSIS

Definition

Spinal cord injury (SCI) is defined as injury to the spinal cord with neurologic dysfunction, with or without spinal column disruption. Anesthesia care is often required shortly after injury for resuscitation or surgical intervention. Later, anesthesia care may be required for surgery in patients with chronic SCI. Care may also be needed for patients who have recently sustained iatrogenic SCI (e.g., corrective surgery for scoliosis, aortic reconstructive surgery). Acute SCI occurs most frequently with trauma. Most of the problems accompanying SCI are a result of the neurologic loss, and they evolve over time.

Early recognition of SCI is important if devastating late complications are to be reduced or prevented. Acutely, the spinal cord distal to the level of injury is nonfunctional (e.g., areflexia, muscle flaccidity). Loss of thoracic sympathetic outflow leads to the spinal shock syndrome; this is characterized by hypotension and bradycardia due to unopposed vagal parasympathetic tone. After several days to 8 weeks, spinal reflexes in the uninjured cord become functional, but it is isolated from higher neural influence (i.e., cephalad spinal cord, brainstem, brain). This leads to uncontrolled spinal reflexes, muscle spasticity, and, ultimately, contractures. Such changes distinguish acute from chronic SCI and explain the attendant neurophysiologic differences between acute and chronic phases of injury.

Recognition

All patients with multiple trauma should be evaluated for acute SCI, especially those with neck complaints or neurologic abnormalities; those who are comatose, with hypotension and absent reflexes; and any trauma patient with apparent hypovolemic shock without the expected compensatory tachycardia. Most traumatic acute SCI occurs in the more flexible cervical and thoracolumbar regions, but especially in the cervical spine. Radiographic films of the lateral cervical spine (C1–C7) and anteroposterior open-mouth ("swimmer's view") films usually confirm any bony injury. However, an unstable cervical spine may be missed in as many as 30% of cases. Thus clinical symptoms and computed tomography or magnetic resonance imaging may be required to identify all cervical injuries. Acute SCI can also occur without ligamentous or bony injury, especially in children; this is called spinal cord injury without radiographic abnormality (SCIWORA).

SCI is evaluated according to the following parameters:

- Level of injury
- Time since injury
- Presence of spinal instability
- Degree and type of neurologic impairment
- Associated injuries (especially head injury) and medical problems

The level of injury is usually related to the mechanism of injury and the site of trauma. It is inferred by the neurologic examination and confirmed by any of the aforementioned radiographic procedures. The SCI level defines the potential complications and has implications for management. Up to 20% of patients (80% when cervical) have more than one level of injury.

The time since injury is usually apparent from the trauma event itself or the onset of neurologic findings. Early recognition of acute SCI is important, because early treatment may reduce the degree of irreversible injury. As time progresses, the spectrum of residual injury changes (see later).

Recognition of spinal instability (especially in the cervical spine) is important for patient positioning and movement, including during airway management and tracheal intubation. However, spine injury can occur without bony or ligamentous instability (e.g., spinal hematomas and abscesses; intraoperative injuries; trauma in children). Finally, the degree and type of neurologic impairment define the potential neurologic sequelae.

Risk Assessment

Certain surgical procedures are associated with a recognized risk of acute SCI. The neurologic risk in spinal column correction procedures is approximately 1% to 4%; however, the risk approaches 75% for the correction of severe kyphosis and is high with the removal of spinal cord tumors. Surgery involving the thoracic aorta also has a high risk (see Chapter 79). In surgical patients, early detection of the injury by intraoperative monitoring (sensory and motor evoked potentials) may allow correction before the injurious process (often ischemia) causes irreversible injury.

Acute SCI should be suspected in all trauma victims. Major trauma victims have a 2.6% risk of acute SCI, and patients with head trauma have a 4% to 5% risk of associated cervical spine injury. Traumatic

acute SCI is thought to occur in 12 to 53 persons per million yearly, more often in males (4:1 predominance), and most commonly at C4 to C6. The second most commonly injured spine region is T11 to L2. The most frequent cause is motor vehicle accidents, often associated with alcohol or drug consumption. Falls in elderly persons and diving accidents are among the other important causes. Of patients with cervical spine injuries, about 25% become quadriplegic, and 40% have no residual neurologic impairment. That leaves about 35% with some degree of residual neurologic impairment.

Patients with acute SCI who show no resolution of neurologic impairment progress to chronic SCI. In obtunded patients, a careful history and neurologic examination may be needed to distinguish chronic SCI from cerebral injury. A better understanding of the mechanisms of SCI and its management has reduced overall mortality rate from 80% (World War I era) to less than 2% by the early 1980s.

Implications

The complications of SCI depend on the level of injury and the particular syndrome of injury, defined by the zone of injury in the spinal cord. The greatest number of complications occur with neurologically complete SCI (comparable to spinal cord transection). This is characterized by initial loss of all neurologic function at and below the level of injury. With high spinal cord injury (C4–C6), pulmonary function studies usually reveal reduced total lung capacity, vital capacity, expiratory reserve volume, and forced expiratory volume and increased residual lung volume. Vital capacity is an excellent measure of pulmonary compromise; patients with a vital capacity less than 15 mL/kg often require tracheal intubation and ventilatory support.

A variety of factors contribute to ventilatory compromise, which occurs in 67% of acute SCI patients within the first few days after injury (Box 77.1). Acute SCI patients ventilate better when supine, because the abdominal contents tent the diaphragm, allowing for better mechanical action (except when distended bowel or stomach hinders diaphragmatic movement). Retained airway secretions and atelectasis are common. Ventilation may improve with chronic SCI due to strengthening of the chest wall and abdomen by intercostal and abdominal muscle contractures.

Cardiovascular function is markedly altered in acute cervical SCI by the associated loss of sympathetic tone of the heart and vasculature. Consequent venodilation leads to relative hypovolemia and reduced preload. This is aggravated by traumatic or surgical blood loss. Peripheral vasodilation reduces systemic vascular resistance. The reduction in both preload and systemic vascular resistance contributes to a hypotensive state known as spinal shock. Loss of cardiac sympathetic innervation (cardiac accelerators T1–T4/T5) leads to the inability to increase contractility and heart rate in response to hypovolemia or blood loss. Resulting unopposed vagal tone enhances the potential for bradycardia and escape rhythms. Either may occur with sudden increased blood pressure (i.e., hyperactive carotid sinus reflex) or airway manipulation and may necessitate atropine or temporary or permanent pacing. In addition to the potential for bradycardia and hypotension, patients with acute SCI are at risk for acute heart failure and pulmonary edema. Experimental evidence suggests that myocardial injury may occur at the time of SCI due to a catecholamine surge with an acute and transient increase in afterload.

There is greater cardiovascular stability with chronic SCI. However, with lesions above T7, sensory stimuli below the level of SCI may provoke exaggerated sympathetic spinal reflexes (i.e., autonomic hyperreflexia), causing intense vasoconstriction, bradycardia, and acute hypertension (see Chapter 85).

In addition to cardiovascular dysfunction, there are other types of injury or defects associated with acute SCI (Box 77.2). Impaired temperature regulation, caused by loss of sympathetic-mediated changes in vascular tone, leads to a poikilothermic condition with inability to control sweating. Denervation of skeletal muscle leads to neuromuscular junction hypersensitivity and premature receptors, so that depolarizing muscle relaxants (e.g., succinylcholine) cause exaggerated potassium release. This begins in 6 to 12 hours but usually does not reach a high enough level to lead to complications for 24 to 48 hours of acute SCI and lasts until muscle atrophy with chronic SCI abolishes the effect. Succinylcholine was generally considered safe after 1 year from the onset of acute SCI; however, recent studies indicate that this may be a lifelong condition. In traumatic acute SCI, patients may have associated injuries (e.g., head trauma with increased intracranial pressure; chest, abdominal, or orthopedic injuries). Other conditions associated with chronic SCI include the following:

- Renal failure (from recurrent urinary tract infection or amyloidosis)
- Drug or alcohol abuse or dependence (owing to depression or pain syndromes)
- Decubitus ulcers

Also with chronic SCI, spinal reflex action below the lesion may lead to uncontrolled muscle contractures (i.e., the "mass reflex"). Patients with both acute and chronic SCI are prone to develop deep venous thrombosis (up to 80% to 85% in cervical injuries). Thus pulmonary thromboembolism is a common cause of death in patients with acute SCI and may prompt the placement of a vena cava filter.

MANAGEMENT

Initial priorities in acute SCI victims are securing the airway, ensuring adequate oxygenation and ventilation, and providing circulatory support. Further medical management is for coexisting injuries and the prevention of secondary ischemic SCI. The unstable spine should

BOX 77.1 Factors Contributing to Ventilatory Compromise in Acute Spinal Cord Injury

Limitation of diaphragmatic motion by gastric distention and ileus
Aspiration pneumonitis
Reduced expiratory reserve and ability to cough, secondary to loss of abdominal (T2–L1) and intercostal (T1–T11) muscle control
Fat emboli with long bone fractures
Chest trauma (rib fractures, pulmonary contusion, pneumothorax, hemothorax)
Loss of spinal input to the phrenic nerve (C3–C5) and control of the diaphragm
Depressed consciousness from head injury, alcohol, or drugs
Neurogenic edema from head injury
Pulmonary edema secondary to cardiovascular dysfunction

BOX 77.2 Injuries or Defects Associated With Acute Spinal Cord Injury

Cardiovascular dysfunction (spinal shock)
Impaired temperature regulation (poikilothermic)
Neuromuscular junction hypersensitivity
Head injury (raised intracranial pressure)
Chest trauma (pneumothorax, cardiac contusion)
Myocardial injury
Aspiration pneumonitis
Pneumothorax, pneumomediastinum
Hematoma compromise of airway in neck trauma
Long bone fractures with blood loss and fat emboli
Renal failure
Muscle contractures
Deep venous thrombosis and pulmonary thromboembolism

be stabilized in a neutral position, with traction deferred until the neurologic evaluation is complete. Traction can lead to further injury, including disk herniation, C1–C2 ligamentous laxity, or ankylosing spondylitis.

The first priority is to secure the airway. Ideally, a controlled, nasal awake intubation (if not contraindicated) is associated with the least neck movement and allows neurologic observation during intubation. However, if immediate tracheal intubation using direct laryngoscopy is necessary, midline stabilization (not traction) can minimize the degree of cervical spine movement. If facial trauma prohibits oral intubation, a surgical airway (tracheostomy or cricothyrotomy) or transtracheal ventilation may be needed. In patients with head trauma, nasal intubation should be avoided, if possible, until a basilar skull fracture has been ruled out.

After establishment of the airway, adequate oxygenation and ventilation must be confirmed. Any hypotension, which could be secondary to loss of sympathetic tone from acute SCI, hypovolemia, and trauma, should be treated with intravenous fluids to restore adequate cardiac output and blood pressure. Pulmonary artery catheterization may be needed, especially with quadriplegia, because excessive fluids may cause pulmonary edema. Vasoconstrictors (e.g., dopamine, ephedrine, phenylephrine) are used to augment cardiovascular dynamics when volume alone is ineffective. (Note that phenylephrine may be advantageous. It is primarily an α-adrenergic agonist. Thus it increases both systemic vascular resistance and preload via constriction of the venous capacitance bed.) Myocardial inotropic support may also be necessary, because acute SCI may cause myocardial injury from brief, explosive autonomic discharge with hypertension due to mechanical compression of the descending sympathetic nerves. Transient bradycardia is treated with atropine or β-adrenergic agonists, with provision for pacing in patients with persistent bradycardia or escape rhythms. The use of high-dose methylprednisolone to improve outcome is currently controversial (see later discussion).

Sudden changes in position may cause postural hypotension (head-up tilt) or pulmonary edema (head-down tilt) due to reduced cardiovascular compensation. The clinician should monitor the patient's temperature and use warming blankets or adjust the ambient temperature as needed. Unexplained hypotension may also be due to previously unrecognized intraabdominal or retroperitoneal bleeding.

Associated major injuries occur in about two-thirds of patients with traumatic acute SCI. Of special concern are thoracoabdominal injuries, which may be nonapparent owing to sensory loss or head injury. Thoracoabdominal injuries occur in as many as 25% to 50% of patients with acute SCI. Other aspects of postinjury care relate to complications of acute SCI, such as gastric erosions, deep venous thrombosis, and pulmonary embolism.

Emergency surgery in cases of traumatic acute SCI is usually for injuries other than those to the spinal cord. However, emergency spinal cord surgery may be required if vertebral bony alignment cannot be achieved by traction (e.g., due to "locked" facets) or when bone fragments or protruding disk material is impinging on the spinal cord. Anesthetic management for such surgery involves maintaining adequate spinal cord perfusion. Outcomes are improved if mean blood pressure is greater than 85 mm Hg, central venous pressure is 5 to 10 mm Hg, arterial oxygen tension is greater than 100 mm Hg, and normoglycemia and normocarbia are maintained. Extubation should be delayed until adequate unsupported ventilatory function is ensured. Postoperative mechanical ventilatory support may be needed. Emergency reintubation is undesirable in patients with acute cervical spine injury due to the need for additional neck manipulation.

If acute SCI is related to recent spinal or aortic surgery, time is of the essence if deleterious effects are to be reversed. Some surgeons use steroids, such as methylprednisolone or dexamethasone, at this time. Removal of spinal instrumentation or exploration of the spinal canal for hematomas may be required within a few hours. If so, electrophysiologic monitoring (i.e., sensory or motor evoked potentials) may be necessary to warn of further SCI.

Anesthesia for surgery in patients with chronic SCI is often for decubitus ulcers or kidney stones. Local, regional, or general anesthesia may be sufficient, depending on the site of surgery and the degree of neurologic impairment. However, many chronic SCI patients (85%) with lesions above T7 are prone to autonomic hyperreflexia and associated hypertension, which can occur when no anesthesia or local anesthesia alone is used; both regional and general anesthesia can block this phenomenon, and potent direct vasodilators may be needed to treat the episode in addition to removing the trigger cause. Although less successful than subarachnoid block for urologic or general surgery, epidurals have been used successfully during labor. Positioning problems may be anticipated in chronic SCI patients due to either contractures or positions that compromise ventilation. In patients with chronic SCI, the blood volume is often contracted (60 mL/kg), making them prone to orthostatic hypotension. Other procedures that may require anesthesia care and are common in patients with chronic SCI are placement of pulse generators for phrenic nerve or spinal cord stimulation (i.e., to improve ventilatory mechanics or for pain control, respectively) and intrathecal baclofen for the management of spasticity.

PREVENTION

Once acute SCI has occurred, efforts should be directed toward reducing additional injury due to secondary causes (e.g., hypoxemia, impaired spinal cord perfusion, bony impingement). The use of high-dose steroid after acute SCI is currently controversial because it does not appear to improve neurologic function and its use is associated with significant side effects. Such steroid use is not advised with penetrating abdominal injuries because of the probable or assumed contamination of the spinal canal with bowel flora. Prompt intervention for acute SCI related to spinal cord surgery, or to relieve compression, can also reduce the degree of injury. Intraoperative measures that help reduce acute SCI include maintaining normal blood pressure, arterial carbon dioxide tension, and glucose concentrations throughout surgery and the immediate postoperative period. Finally, spinal cord function monitoring with evoked sensory and motor potentials may reduce any additional (iatrogenic) injury, especially during spinal decompression and fusion.

Currently substantial effort is being made to maximize function through rehabilitation and functional aides, and studies are under way to increase the spinal cord's ability for regeneration.

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78 Thermally Injured Patients

Katarzyna Luba

Case Synopsis

You are an anesthesiologist on call, and a surgical resident covering the burn unit books an emergency extremity fasciotomy. The patient, a 40-year-old homeless man, was rescued from a burning garage and admitted to the burn unit the night before. He was found unresponsive at the scene, with a toxic blood ethanol level and deep burns covering about 80% of his total body surface area (TBSA). He is on ventilatory support in volume-control mode, with a fraction of inspired oxygen (Fio_2) of 0.8, positive end-expiratory pressure (PEEP) of 15 cm H_2O, and a tidal volume of 400 mL. As you prepare to transport the patient to the operating room (OR), you notice that his peak airway pressure is high. You are concerned about decreased chest compliance and your ability to effectively ventilate and oxygenate the patient during transport and in the OR. You share your concerns with the attending surgeon, who decides to perform chest and abdominal escharotomies.

PROBLEM ANALYSIS

Definition

Burn injuries are caused by heat, electric current, or caustic or corrosive chemicals. The severity of injury is determined by the extent and depth of tissue destruction. Thermal burns result from contact of the skin or mucous membrane and the underlying tissues with the heat source for the extent of time sufficient to produce injury. The severity of the thermal burn is directly proportional to the temperature of the heat source and the duration and surface area of the contact, and is inversely proportional to the thickness of the skin and the blood supply to the contact area. Chemical burns result from a chemical reaction of an offending agent with tissue components, dehydration, or corrosion. Electrical burns occur by arcing of electrical current across two points of body surface resulting in external injuries, or by conduction of heat along vessels and nerves to produce deep injuries. A secondary thermal burn may result from ignition of clothing by arcing of electrical current.

Recognition

The number of burn injuries occurring annually in the United States is estimated at between 1 million and 2 million. Each year, nearly 500,000 people seek treatment for burn injury, of whom 40,000 to 80,000 are hospitalized and 3500 to 5000 die. Most burned patients present in emergency departments of general hospitals without a dedicated burn center. Challenges in the initial care of patients with major burn injury include airway and ventilatory management, vascular access, fluid resuscitation, and pain management.

The severity of burn injury is determined by the percentage of *total body surface area* (TBSA) involved, depth of the burn, and the presence or absence of inhalational injury. TBSA burned is estimated using the "rule of nines" (Fig. 78.1) or the Lund-Browder chart (Fig. 78.2). The Lund-Browder chart is a diagram that accounts for age-specific changes in how the surface of various body parts contributes to TBSA, and thus it is better suited to estimate the size of burn injury in a child. The depth of a burn is defined as first, second, or third degree, based on whether there is superficial, partial-thickness, or full-thickness destruction of the skin.

First-degree burns (e.g., sunburn) are limited to the epidermis, appear as erythematous areas of otherwise intact skin, and may be painful, but heal without a specific intervention. Second-degree burns, or partial-thickness burns, partially involve the dermis, form blisters and moist, weeping lesions, blanch with pressure, and may be extremely painful. Second-degree burns require specific wound therapy including skin grafting. Third-degree or full-thickness burns involve the entire thickness of the dermis and may penetrate into the subcutaneous tissue.

The third-degree burn appears white, waxy, and is often speckled with red dots (i.e., heat-congealed hemoglobin). Sensory nerve endings are destroyed, so third-degree burns are insensate. Left untreated, third-degree burns heal by scarring that may result in severely disfiguring and crippling contractures; therefore third-degree burns should be excised and grafted early to preserve function. Inappropriate therapy, in particular, inadequate fluid resuscitation, may convert a second-degree burn injury to a full-thickness (third-degree) injury. Fourth degree is used to describe burns that involve deep structures, such as muscle, fascia, and bone.

Inhalation injury is present in 20% to 35% of hospitalized burn victims and is responsible for 60% to 70% of burn-related fatalities. It is important to recognize the inhalation injury as soon as possible. Inhalation injury should be suspected if the circumstances of the injury involve an exposure to fire and smoke in an enclosed space, especially in combination with loss of consciousness or intoxication. Findings on physical examination, including burns over the face, blisters on the lips and oral mucosa, singed nasal or facial hair, carbonaceous sputum, dysphagia, hoarseness, tachypnea, intercostal retraction, rales, and wheezing, point to the possibility of an inhalation injury. Early hypoxia may follow. Chest radiographs may be normal until the development of infection or atelectasis. Fiberoptic bronchoscopy may reveal carbonaceous debris, erythema, or ulcerations of the airway mucosa.

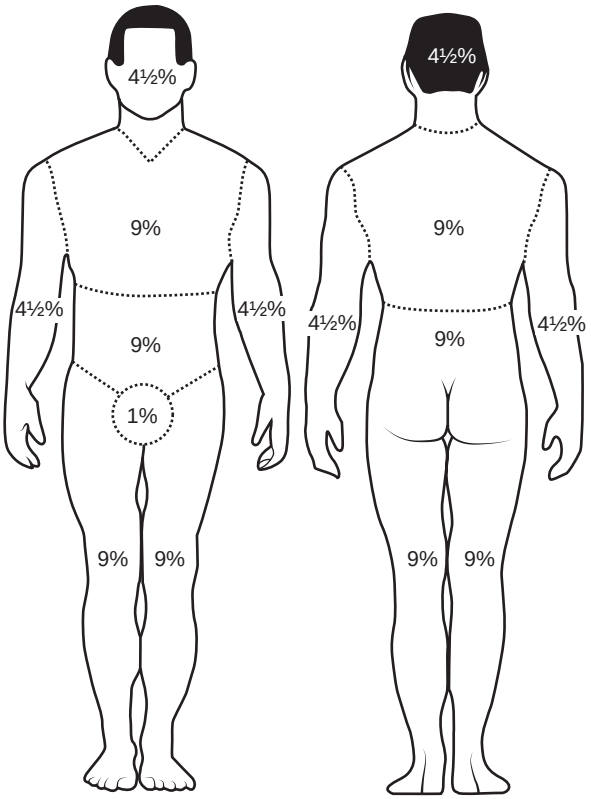


Fig. 78.1 Estimate of %TBSA: "rule of nines."

Risk Assessment and Implications

Burn Injury Pathophysiology

Major burns cause profound, generalized pathophysiologic changes. In the early postburn phase, tissue destruction at the site of the injury activates a cytokine-mediated systemic inflammatory response, characterized by increased capillary permeability and edema. When burn injury exceeds about 25% of TBSA, generalized edema develops. Loss of intravascular fluid due to generalized capillary leakage and weeping of fluids out of burned surfaces denuded of skin may quickly result in shock, with impaired tissue and organ perfusion. Burn shock occurs not only because of depletion of intravascular volume, but also because of increased systemic and pulmonary vascular resistance (due to release of catecholamines and vasopressin) and direct myocardial depression. Biochemical markers of the burn shock phase include hemoconcentration, lactic acidosis, and mixed venous desaturation. Shock leads to a decrease in glomerular filtration rate and stimulation of the renin–aldosterone–antidiuretic hormone axis, manifesting as acute oliguria. Hypothermia develops as a result of loss of thermoregulatory function of the dermis.

Within 48 to 72 hours after burn injury, the increased capillary leakage resolves, and edema formation significantly decreases. Fluid loss continues through open burn wounds. The shock phase is followed by the hypermetabolic phase, which starts a period of increased oxygen consumption, carbon dioxide production, increased protein catabolism, and insulin resistance. The hemodynamic picture during this phase is characterized by supranormal cardiac output, tachycardia, and low systemic vascular resistance. Patients with major burn injuries demonstrate increased requirements for most drugs, including sedatives, opioids, neuromuscular blocking agents, and antibiotics, owing to higher volume of distribution and increased clearance. The onset of sepsis, which may be extremely rapid and severe, aggravates the hyperdynamic state. Acute respiratory distress syndrome (ARDS) may develop.

Delayed consequences of burn injury include a persistent inflammatory state, immunosuppression, and severe protein catabolism, which continues until the closure of the burn wound. Burn wound infection is a leading cause of death in patients with burns exceeding 60% of TBSA. Early and repeated debridement of infected burn wounds is mandatory to maximize the patient's chances of surviving the injury.

A full-thickness burn forms a rigid eschar over the burned area. Circumferential eschars of extremities may lead to compartment syndrome when edema forms under an eschar during an early phase of injury. Aggressive fluid resuscitation, essential in the management of the burn shock, may precipitate the development of the compartment syndrome. Unrecognized compartment syndrome may result in extensive muscle necrosis, rhabdomyolysis, secondary acute kidney injury, and the loss of affected extremities. Close monitoring of at-risk extremities and timely escharotomies are necessary to prevent secondary ischemic injury. Circumferential eschars of the trunk may result in a dramatic decrease in chest compliance and interfere with ventilatory mechanics. Such eschars also may require early escharotomies to enable effective ventilatory support.

Electrical injury often results in extensive, deep soft tissue damage that significantly increases resuscitative fluid requirements. Bone has the highest resistance to flow of electrical current, so the high heat produced by electrical current reaching the bone causes extensive damage of deep muscle surrounding the bone. Deep muscle injury may result in edema, compartment syndrome, muscle necrosis, and rhabdomyolysis. Myoglobinuria resulting from extensive muscle necrosis may lead to acute renal failure. Electrical shock often causes arrhythmia and myocardial damage similar to myocardial contusion.

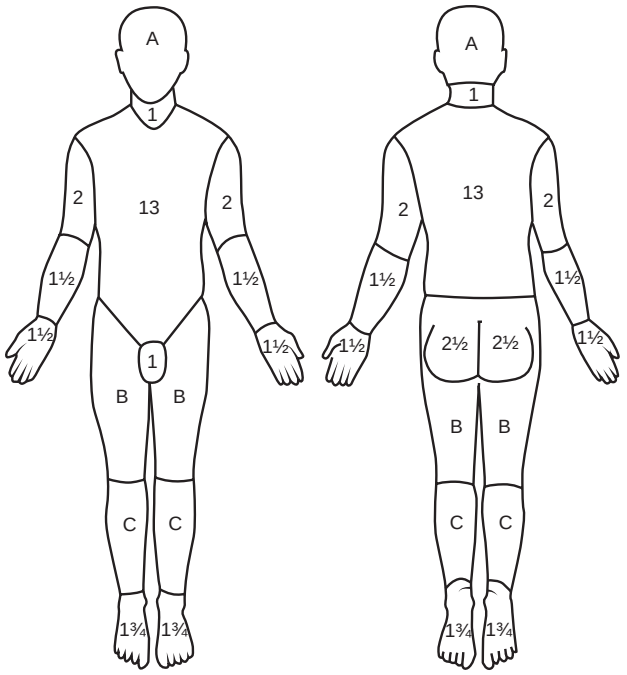
Abdominal Compartment Syndrome

Massive fluid resuscitation in a setting of increased capillary permeability (sepsis, trauma, burn) results in retroperitoneal, mesenteric, and bowel edema and intraabdominal hypertension (IAH), manifesting as a progressive decrease in lung compliance, oliguria unresponsive to fluid resuscitation, hypotension, and acidosis. If untreated, it may be rapidly fatal by progressing to abdominal compartment syndrome (ACS) with acute renal failure, ventilatory compromise, bowel ischemia, and multiorgan system failure (MOSF). ACS may be prevented by maintaining a high suspicion index in the appropriate clinical setting (such as major burn injury), monitoring of intraabdominal pressure, and limiting the total volume of intravenous fluid resuscitation.

An increase in intraabdominal pressure above 20 mm Hg signals the onset of IAH. Management of IAH consists of deep sedation, permissive hypercapnia, chest and abdominal escharotomies, neuromuscular blockade, and percutaneous drainage of ascites. If conservative measures fail to prevent the progression of IAH, an emergency decompressive laparotomy may be necessary to prevent ACS.

Inhalation Injury

Inhalation injury occurs as a combination of (a) scalding of the face and upper airway by inhalation of steam and/or hot gases; (b) chemical injury to the trachea, bronchi, and pulmonary interstitium by the toxic components of the smoke; (c) impairment of oxygen transport processes by carbon monoxide poisoning; and (d) inhibition of oxygen utilization by inhalation of cyanide. Inhalation injury significantly contributes to morbidity and mortality related to burn injury. Scalding of the face and upper airway results in massive edema of the face, tongue, epiglottis, and vocal cords, and may rapidly lead to airway



	%	
Region	**PTL**	**FTL**
Head		
Neck		
Anterior trunk		
Posterior trunk		
Right arm		
Left arm		
Buttocks		
Genitalia		
Right leg		
Left leg		
Total burn		

Relative percentage of body surface area affected by growth

Area	**0**	**1**	**5**	**10**	**15**	**Adult**	**Age**
A=½of head	9½	8½	6½	5½	4½	3½	
B=½of one thigh	2¾	3¼	4	4½	4½	4¾	
C=½of one leg	2½	2½	2¾	3	3¼	3½	

Fig. 78.2 Estimate of %TBSA: Lund-Browder charts.

obstruction. Airway edema may be delayed by several hours. It may be precipitated by aggressive fluid resuscitation. A high index of suspicion and frequent assessment of respiratory function may help prevent a catastrophic airway obstruction.

Inhalation of smoke results in chemical injury of the tracheobronchial tree. Combustion products of the smoke from a house fire, such as hydrochloric acid, sulfuric acid, formaldehyde, acrolein, ammonia, and phosgene, are damaging to the trachea, bronchi, and alveoli. Paralysis of mucociliary transport impairs clearance of bacteria, mucus, and tissue debris. Atelectasis may rapidly occur because of loss of surfactant production and from plugging of small airways. ARDS may develop, especially if burn injury is complicated by MOSF. Mechanisms include inflammatory mediators from the burned area, effects of fluid resuscitation, and infection.

Carbon monoxide (CO) and cyanide present in inhaled smoke result in systemic toxicity. CO binds to oxygen-binding sites on hemoglobin with a 200-fold higher affinity. Binding of CO decreases oxygen-carrying capacity of hemoglobin and leads to tissue hypoxia. It also shifts the oxyhemoglobin dissociation curve to the left. Clinical symptoms of CO poisoning, including agitation, confusion, mental status depression, and coma, are nonspecific. A high index of suspicion helps with accurate diagnosis. A standard pulse oximeter does not distinguish carboxyhemoglobin from oxyhemoglobin. In a patient breathing supplemental oxygen, the Pao_2 may be normal in the presence of CO poisoning. Diagnosis of CO poisoning is confirmed by measuring the level of carboxyhemoglobin in arterial blood, or by measuring oxygen-carrying capacity of hemoglobin by cooximetry. Carboxyhemoglobin levels greater than 15% are toxic. Levels above 40% result in severe neurologic dysfunction and coma. Levels exceeding 60% result in fatal cerebral hypoxic injury. The half-life of carboxyhemoglobin is 4 hours for a person breathing room air. Breathing 100% oxygen reduces the half-life of carboxyhemoglobin to 1 hour. Hyperbaric oxygen therapy has been suggested to reduce the neurologic sequelae of CO toxicity. However, no convincing benefit has been demonstrated for hyperbaric oxygen therapy in CO poisoning.

Cyanide is produced by the burning of nitrogenous materials. Cyanide poisoning should be suspected in a burned patient with anion gap metabolic acidosis, a high serum level of lactic acid, and increased mixed venous oxygen saturation in the presence of apparently adequate oxygen delivery. Cyanide blocks the final step in the oxidative phosphorylation by binding to mitochondrial cytochrome oxidase and preventing the use of oxygen for metabolism of pyruvate to adenosine triphosphate. Adenosine triphosphate can only be generated by anaerobic metabolism, which results in lactic acidosis. The increased mixed venous oxygen saturation suggests mitochondrial poisoning and the inability of the cells to utilize oxygen. Concentrations of cyanide greater than 20 ppm are considered toxic. Concentrations of 100 ppm can lead to seizures, coma, respiratory failure, and death.

Mortality related to burn injury has improved over the past decades. The rate of survival for major burns has increased because of higher awareness and advances in resuscitation; early excision and grafting of burn wounds; progress in methods of wound coverage, anesthesia, and critical care; early diagnosis and aggressive treatment of infections; and the recognition of the role of aggressive nutritional support, particularly early and uninterrupted enteral feeding. Available data support linking of improved outcomes for

major burns with early referral to specialized burn units. Specialized expertise, personnel, and equipment required for effective care of patients with major burn injury are not available in low-volume centers and general hospitals. Mortality persists at a rate of approximately 4% for patients admitted to burn centers. A large analysis identified three risk factors predictive of death from burn injury: age older than 60 years, burn size greater than 40% TBSA, and inhalation injury. Mortality is a function of the number of risk factors present.

MANAGEMENT AND PREVENTION

A patient with a severe burn injury should be initially approached as a patient with multiple trauma. Management should start at the scene of injury and follow the trauma assessment according to the Advanced Trauma Life Support guidelines. This includes application of the basic ABCs (airway, breathing, circulation), initiation of resuscitation, and assessment for coexisting injuries. Up to 7% of patients referred to burn centers are found to have coexisting nonburn injuries. A thorough trauma assessment should be ongoing and continue in the emergency department, during transport to a specialized burn center, and after admission to the burn center.

Airway Management

Airway and breathing evaluation is the priority during initial assessment. Thermal injury of the upper airway results in edema that may rapidly worsen with aggressive fluid resuscitation and result in airway obstruction. As a general rule, the patient with thermal injury of the airway should be intubated early, before edema makes intubation difficult. In pediatric patients, progression of airway edema to airway obstruction may be very rapid due to small dimensions of the airway. Preemptive intubation, even in the absence of immediate indications, should be considered if a patient is to be transported to a different facility (e.g., to a burn center). Severely edematous airway should be managed with fiberoptic intubation and topical anesthesia while maintaining spontaneous ventilation. Sedation during fiberoptic intubation is necessary in all pediatric patients and in many adults. Sedatives that do not impair pharyngeal muscle tone and spontaneous ventilation, such as ketamine and dexmedetomidine, are useful options.

Patients in the immediate postburn period should be considered to have a full stomach. In the later phase of care of burn-injured patients, aspiration risk persists due to intestinal edema, sepsis, and opioid use, all of which delay gastric emptying. Edema of the face, pain, exudate, topical antibiotics, and dressings make for an inadequate mask fit and difficult or impossible mask ventilation. Alternative intubating techniques, such as awake fiberoptic intubation or the use of an intubating supraglottic airway, may allow avoiding mask ventilation altogether.

Facial burns make it difficult to secure the endotracheal tube (ETT) in a way that minimizes the risk of accidental extubation. Tape does not adhere to the burned skin. Alternative methods include placing a soft, circumferential tie around the patient's head, using wire or a surgical suture to secure the ETT to a tooth, or suturing the ETT to the gum.

Fluid Requirements

Burn shock and MOSF can only be prevented with immediate and aggressive fluid resuscitation. Among many formulas for estimating fluid requirements in burn injury, the Parkland formula is the one most commonly used in the United States. This formula recommends the use of crystalloids in the first 24 hours postburn and the use of colloids afterward. A recent trend is to administer colloids within the first 24 hours postburn. Lactated Ringer's solution (LR) is the crystalloid of choice in view of the risk of hyperchloremic acidosis associated with resuscitation with normal saline (0.9% NaCl). Dextrose 5% should be added to LR to prevent hypoglycemia in children.

The initial estimate of resuscitation fluid volume to be administered in the first 24 hours postburn, calculated according to the Parkland formula, is 4 mL per each kilogram of body weight multiplied by the size of the burn wound as percent of total body surface area (4 mL/kg/% TBSA burn). For example, a 70-kg person with a burn of 80% of TBSA requires 22,400 mL of crystalloid in the first 24 hours. Half of this volume should be administered over the first 8 hours postburn, followed by reassessment and titration of resuscitation volume.

Massive fluid resuscitation worsens burn-related tissue edema and carries the risk of abdominal compartment syndrome, as well as compartment syndrome of circumferentially burned extremities. Although aggressive fluid resuscitation is essential for survival of a patient with a major burn, the resuscitation needs should be constantly reassessed and titrated to a minimum necessary to maintain urine output between 0.5 and 1 mL/kg/h (2 mL/kg/h in children). Actual fluid needs may significantly exceed estimated resuscitation volume in patients with large-area, full-thickness burns, associated trauma, or electrical burns, and in patients in whom initial resuscitation was delayed. The presence of inhalational injury increases fluid requirements by up to 50%.

Anesthetic Management

Preoperative Evaluation

Surgical interventions commonly performed in burned patients include early decompression procedures, such as extremity fasciotomies and decompressive laparotomy, early and delayed debridement and grafting of the burn wound, reconstructive procedures, and general supportive procedures, such as tracheostomy, gastrostomy, or placement of dialysis access.

Preoperative evaluation should identify the time, extent, and circumstances of burn injury, current resuscitation plan and total fluid volume administered, upper airway injury and edema, presence of inhalation injury, respiratory status and ventilatory parameters, complications of burn injury such as sepsis and MOSF, and critical care management plan and goals. Discussing the surgical plan with the surgical team is essential to estimate the duration of the procedure and blood loss to plan necessary intravenous access, invasive monitors, and the availability of blood products.

Ventilation and Oxygenation

Burn injury is commonly associated with respiratory failure. Patients with inhalation injury require early intubation for airway patency, pulmonary toilet, and management of respiratory depression secondary to sedation and analgesia. Sloughing of airway mucosa due to inhalation injury requires aggressive pulmonary toilet and significantly increases the risk for occlusion of the ETT. Chest compliance may be reduced by circumferential burns of the chest and increased intraabdominal pressure due to aggressive fluid resuscitation. Inhalation injury may be complicated by atelectasis and pneumonia, leading to ventilation-perfusion mismatch and hypoxia. The hypermetabolic phase of burn injury with increased carbon dioxide production requires ventilatory support to provide high minute ventilation. A major burn injury, with or without inhalation injury, is often complicated by sepsis and MOSF including ARDS. In patients with lung injury, lung-protective

ventilatory strategy with the use of tidal volumes not exceeding 6 mL/kg ideal body weight, and plateau pressures of less than 30 cm H_2O, are recommended, and high levels of PEEP and Fio_2 are needed to maintain acceptable oxygenation.

Patients with inhalational injury and ARDS may be at risk for critical hypoxia during transport from the burn unit or intensive care unit (ICU) to the OR. A trial of manual ventilation at the bedside in the burn unit should be conducted before transport to test the patient's tolerance of manual ventilation. Some patients may require the use of a transport ventilator capable of generating a high level of PEEP to maintain adequate oxygenation. The anesthesia machine must be equipped with ventilatory capabilities equivalent to those in use in the ICU.

Blood Loss and Vascular Access

Excision of burn wounds is accompanied by major blood loss. Burn wounds are debrided down to intact tissue, frequently over a large area, and the amount of blood shed is typically difficult to quantify. Published estimates place the blood loss during burn excision between 2.6% and 3.4% of circulating blood volume for every 1% TBSA excised. Constant attention to intravascular volume status and serial monitoring of hemoglobin level and metabolic indices of tissue perfusion (pH, serum lactate level, mixed venous saturation) are necessary during excision of large burn wounds to guide blood transfusion decisions and fluid resuscitation. Early administration of fresh frozen plasma is justified to prevent coagulopathy in burned patients in whom massive blood loss is anticipated during wound excision. Wound debridement should be terminated and staged if the patient develops refractory hypotension, hypothermia, coagulopathy, or metabolic acidosis.

Securing of large-bore intravenous access is mandatory if major blood loss is anticipated. Venous access is challenging, because superficial veins are destroyed by the burn, so it is often necessary to access deep or central veins (antecubital, femoral, internal jugular, or subclavian) through the burned tissue. Ultrasonographic guidance is very helpful in localization of deep veins and safe placement of central venous catheters. Venous catheters may need to be sutured in place, especially if the venous access site is located within the surgical field.

Monitoring

Placement of standard monitors, such as electrocardiogram (ECG) electrodes, blood pressure cuff, and pulse oximeter, is challenging in patients with massive burns. ECG electrodes and adhesive pulse oximetry probes will not adhere to the burned surface, and may need to be affixed to the underlying tissue with surgical staples. Sites for placement of the pulse oximetry probe, other than fingers and toes, include the nose, tongue, ears, and lips. Intact sites for a blood pressure cuff on the extremities may not be available, and a sterile cuff may need to be carefully placed over a grafted wound area. Alternatively, an arterial line may be placed through a burned site and sutured in place. Pulse pressure variation is useful to monitor and manage intravascular volume status. Placement of an arterial line for continuous blood pressure monitoring and blood sampling should be considered in patients in an early phase of a major burn injury, patients with sepsis, or when major blood loss is anticipated during an extensive burn wound excision.

Hypothermia

Patients with burn injury are prone to hypothermia due to dysfunctional central thermoregulatory mechanisms and loss of thermoregulatory function of the skin destroyed by the burn. Hypothermia during debridement of burn wounds can exacerbate blood loss and catabolic response to the injury. Methods of maintaining normal body temperature in the OR include warming the OR above 30°C; use of heat lamps, fluid warmers, warming blankets, and heated and humidified inspired gases; and wrapping the patient's head and extremities with insulation materials. Severe hypothermia (<35°C) should prompt rapid termination of the procedure.

Pharmacology

Burn injury alters the pharmacokinetics and pharmacodynamics of most drugs. During the acute postburn phase, metabolism and elimination of drugs by the liver and kidney decrease owing to decreased cardiac output and organ blood flow, and patients may demonstrate increased sensitivity to many drugs used in anesthesia. During the hyperdynamic phase that follows, blood flow to the kidneys and liver increases along with increased cardiac output. Thus clearance of many drugs increases, so their dosage needs to be adjusted.

Generalized edema increases the volume of distribution of most drugs. Increased volume of distribution and increased clearance results in a decreased sensitivity of burn-injured patients to most drugs used in anesthesia (sedatives, opioids, antibiotics, muscle relaxants). In addition, burn-injured patients rapidly develop tolerance to benzodiazepines and opioids and require escalation of doses.

Burn injury significantly alters the pharmacology of muscle relaxants. Within 24 hours after injury, there is a proliferation of extrajunctional acetylcholine receptors. Exposure to succinylcholine after the first postburn day may cause hyperkalemia leading to cardiac arrest. Contraindication to succinylcholine in burn-injured patients should be observed for up to 1 year after complete recovery from the burn. Concomitant decrease in sensitivity to nondepolarizing muscle relaxants is multifactorial. It results from extrajunctional proliferation of acetylcholine receptors and the expression of immature, fetal-type receptors, enhanced hepatic and renal clearance, and increased binding to α_1-acid glycoprotein, an acute-phase reactant.

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Thoracic Aortic Aneurysm

79

Justin Tawil

Case Synopsis

An 80-year-old man with previous abdominal aortic aneurysm (AAA) repair presents with abrupt-onset back pain starting 1 hour ago. He is alert, diaphoretic, tachycardic, and hypertensive. He is given oxygen, nitroglycerin, and morphine. He was found to have a dissecting thoracoabdominal aortic aneurysm (TAAA) on a computed tomography (CT) scan. There is absence of blood flow to the left kidney. Large peripheral intravenous access was placed, and with blood pressure control his pain resolved. He has multiple medical problems including hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and diabetes.

PROBLEM ANALYSIS

Definition

Serious aortic disease falls into four categories: aneurysm, dissection, rupture, and coarctation. Coarctation, narrowing of the aorta, is typically a pediatric disease recognized and treated before adulthood. Recurrent stenosis and proximal aneurysm may require intervention in adulthood. Arteritis, atherosclerosis, and trauma may rarely give rise to acquired coarctation.

Congenital diseases that contribute to aortic pathology are the inherited connective tissue disorders: Marfan, Ehlers Danlos, and Loyes Dietz syndromes and others. These diseases weaken the aortic wall structure producing aneurysm, dissection, and rupture. Other diseases associated with TAAA include hypertension, smoking, polycystic kidney disease, steroid use, and arteritis (syphilis, giant cell, Behçet disease). Aneurysm is usually defined as an aortic dilation to a diameter greater than 4.5 cm or more than twice its normal size. Aneurysms may be true, if they contain all three layers (intima, media, adventitia), or false. Aneurysms are classified by the Crawford classifications (Fig. 79.1). TAAA is a progressive disease with a growth rate of 0.05 to 0.3 cm per year depending on the size and cause. As aneurysms grow, wall tension and risk of rupture increase via the law of LaPlace. Aneurysms occur following half of acute dissections.

Aortic dissection is a disruption in the aortic wall such that blood is pumped from the true lumen into a false lumen created within the medial or adventitial layers. If the lesion extends through the adventitial layer, an aortic rupture has occurred. This false channel is separated from the true lumen by an intimal flap. Without an outflow track, any blood entering the false lumen causes the dissection to extend. As the false lumen grows, it compresses the true lumen, and may disrupt blood flow to branch arteries.

Dissections are defined by the DeBakey and Stanford classifications (Fig. 79.2). Rupture or dissection is the eventual result of progressive aneurysm. Dissections may be simple or complicated. Complicated dissection produces malperfusion to organs or limbs, or unrelenting pain despite control of hemodynamics.

Aortic rupture, with or without previous aneurysm, is seen spontaneously, with vigorous activity, or with deceleration injury. Iatrogenic rupture may occur during reparative manipulation or rarely from manipulation of the airway during intubation. Aortic rupture represents failure of the entire thickness of the aorta such that blood is pumped directly into the adjacent space. Rupture is frequently fatal but may be contained before exsanguination by adjacent structures, hematoma, or rising compartment pressures.

Recognition

Rapid and specific diagnosis can be lifesaving. Untreated, the mortality rate is 1% per hour and 50% at 48 hours. Missed diagnosis may occur in up to 38% of acute aortic presentations because of its rarity and variable symptoms that mimic more common diseases (coronary artery disease, cholecystitis, pyelonephritis). Presenting symptoms of dissection are listed in Table 79.1. Patients rarely present classically with ripping, migratory back pain, hypotension, and malperfusion syndromes. Many aneurysms are found incidentally. Large thoracic aneurysms may present with hoarseness, dysphagia, dyspnea, or arrhythmia.

Imaging is an important tool for rapid and specific diagnosis. Acute management requires information about anatomic extent, localization, perfusion of branch arteries, effusions, rupture, and tamponade. Demonstration of an intimal flap is diagnostic for dissection. Noninvasive imaging has replaced aortography for diagnosis. Currently, contrast CT is the tool of choice because it is noninvasive, fast, and available in most centers. Magnetic resonance imaging (MRI) does have incrementally greater specificity than CT imaging but is not universally available, takes longer, and has increased cost. Widened mediastinum on chest x-ray is neither sensitive nor specific to dissection but may help raise the index of suspicion in symptomatic patients. Transesophageal echocardiography (TEE) holds specificity on par with CT and MRI. TEE is frequently used intraoperatively to locate the proximal flap, to assess operational success, to identify correct wire-guided access of the true aortic lumen for distal circulatory support devices (DCS), and to guide hemodynamic management. Transthoracic echocardiography is not well suited for diagnosis of TAAA.

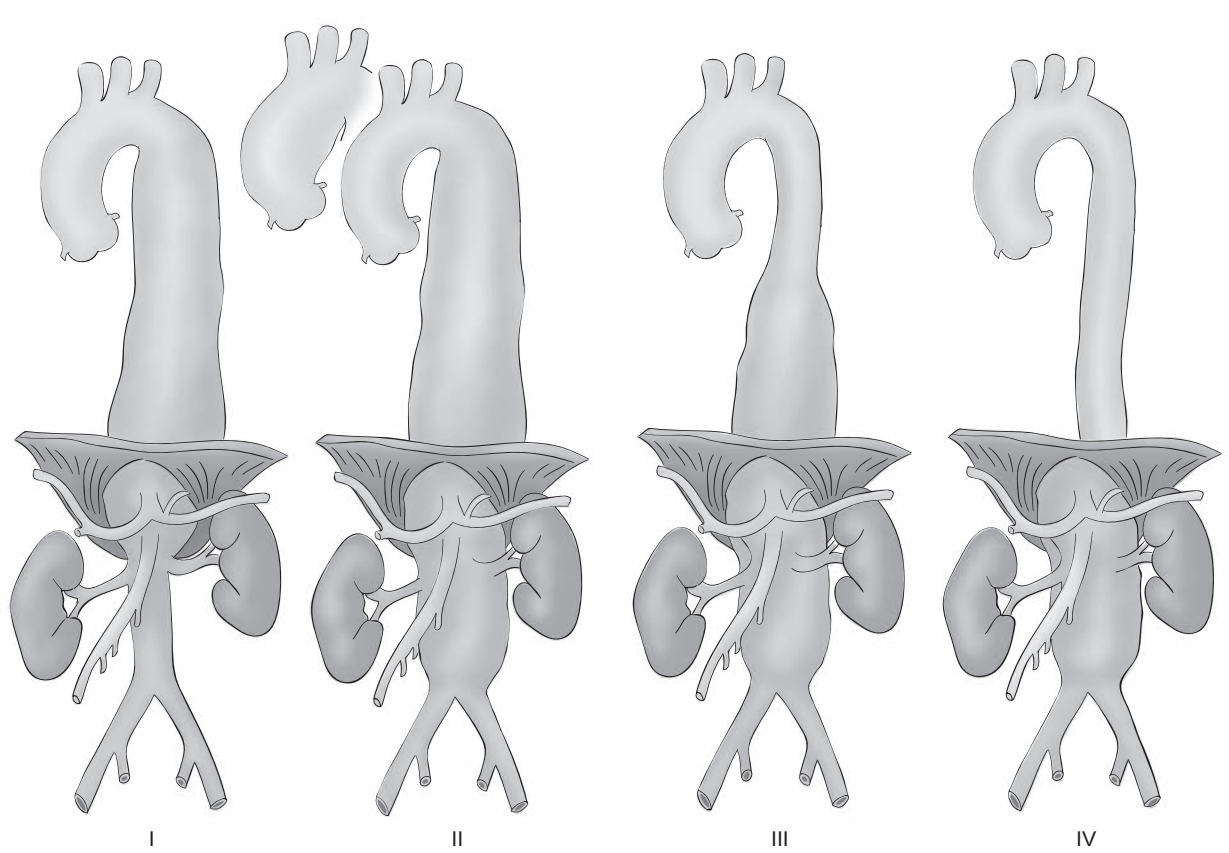

Fig. 79.1 Crawford classification of aortic aneurysms. (From Norris EJ, Frank SF: Anesthesia for vascular surgery. In Miller RD, editor: *Anesthesia,* 5th ed. Philadelphia, Churchill Livingstone, 2000, p 1870.)

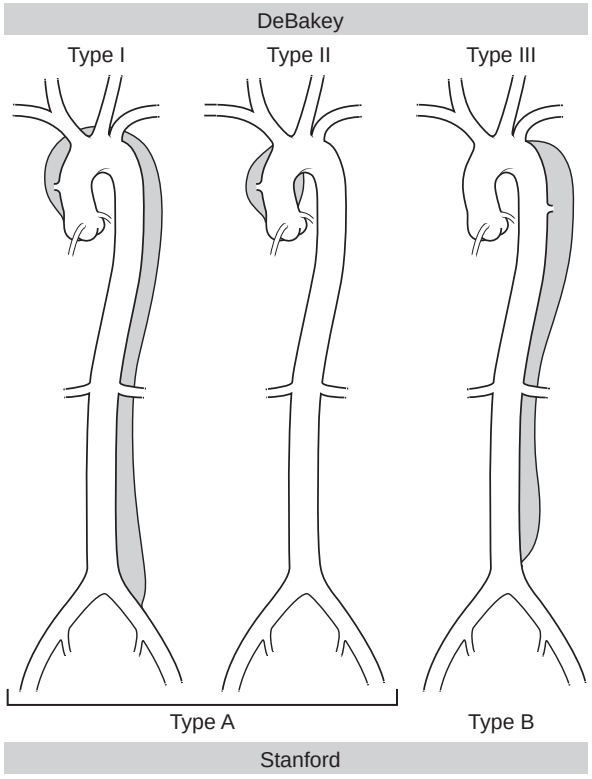

Fig. 79.2 DeBakey (types I, II, IIIA, and IIIB) and Stanford (types A and B) classifications of aortic dissection. (From Ibe R, Baig K, Chukwuemeka A: Surgery of the thoracic aorta. *Surgery [Oxford]* 30[1]:28-31, 2012.)

TABLE 79.1 Signs and Symptoms of Acute Dissection

Diagnosis	Postmortem[b]	28%
Neurologic	Paraplegia[a]	3%
	Syncope[b]	13%
	Pain free[b]	6%
Cardiovascular	Chest/back pain[a]	85%
	Hypotension[a]	Type A: 27% Type B: 3%
	Abdominal pain only[b]	5%
Renal	Acute kidney injury[a]	60%

[a]Gallo A, Davies RR, Coe MP, et al: Indications, timing, and prognosis of operative repair of aortic dissections. *Semin Thorac Cardivasc Surg* 17:224-235, 2005.
[b]Tsai TT, Trimarchi S, Nienaber CA: Acute aortic dissection: perspectives from the International Registry of Acute Aortic Dissection (IRAD). *Eur J Vasc Endovasc Surg* 37:149-159, 2009.

TABLE 79.2 TAAA/Dissection Baseline Demographics

Transient ischemic attack[a]	15%
Stroke[b]	5%
Intracranial hemorrhage[b]	2%
Male[c]	66%
Hypertension[a,c,d]	70%–80%
Prior computed tomography surgery[c]	16%–21%
Prior dissection or aneurysm with repair[c,e]	2%–25%
Coronary artery disease[a,c,d]	40%–70%
Coronary artery bypass graft or stenting[a]	33%
Recent cocaine[c]	0.5%–37%
Hyperlipidemia[a]	43%
Smoking[a]	63%
Chronic obstructive pulmonary disease[a,d]	33%–41%
Chronic renal failure (Creatinine ≥1.5)[a,d]	14%–18%
Diabetes mellitus[a,c]	4%–7%

[a]Kulik A, Castner CF, Kouchoukos NT: Outcomes after thoracoabdominal aortic aneurysm repair with hypothermic circulatory arrest. *J Thorac Cardiovasc Surg* 141:953-960, 2011.
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TABLE 79.3 Outcomes in TAAA Repair

Open repair	Hospital mortality[a,b]	Elective: 3%–12% Nonelective: 20%–45%
	1-/5-/10-/20-year survival[a,b]	85%/78%/72%/23%
	10-year freedom from reoperation[b]	60%
	Stroke[a,c]	2%–5%
	Intracranial hemorrhage[c]	2%
	Spinal cord ischemia (SCI)[a,b,c,d]	Elective: 0%–8% Emergent: 15%–40%
	Tracheostomy[b]	11%
	Congestive heart failure[b]	9%
	Myocardial infarction[c,e]	1%–2%
	Atrial fibrillation[c]	15%
	Acute respiratory distress syndrome[c]	14%
	Acute respiratory failure[c,f]	12%–20%
	New hemodialysis[b,c,f,g]	7%–14% 4% of survivors
	Deep venous thrombosis/pulmonary embolism[b]	5%
	Gastrointestinal bleeding/mesenteric ischemia[b,f,h]	0%–9%
	Sepsis[b]	5%
Endovascular repair	6-month mortality[b]	15%
	Stroke[b,i]	3%
	SCI[b,i,j,k]	0%–8% Prior AAA repair: 14%
	HD[b]	3%

[a]Achneck HE, Rizzo JA, Tranquilli M, et al: Safety of thoracic aortic surgery in the present era. *Ann Thorac Surg* 84:1180-1185, 2007.
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Risk Assessment

At baseline patients carry multiple comorbidities (Table 79.2). In nearly every reported series there is a theme that older, sicker patients, with hemodynamic instability at any point perioperatively, perfusion deficits on presentation, and those in need of emergent or prolonged operations do much worse than the overall data suggest. Crawford II and III patients tend to be older, with more extensive disease and comorbidity, and have the worst outcomes. Annual risk of rupture increases with size from 5% at 4 cm, 6% at 5 cm, and then exponentially to 14% at 6 cm.

Overall mortality rate is difficult to assess, varies widely between reports, and is probably underestimated. With 60% of study patients presenting as referrals, and autopsy being optional in most locations, many deaths are lost to statistical analysis. Mortality from complicated type B dissections may be 50%. Operative mortality increases ninefold when not elective.

Aortic repair has implications on all organ systems. See Table 79.3 for a summary of outcomes. Concerns about bleeding, stroke, spinal cord ischemia (SCI), renal failure, and gastrointestinal (GI) insults prompt most of the early attention. Respiratory failure, cardiac events, infection, and nutritional status have significant longer-term effects. Your surgeon is likely the best resource for assistance prioritizing efforts directed at organ protection based on patient-specific risk factors. Adjunctive anesthetic and surgical techniques have been introduced to improve major outcomes. Techniques are generally not studied in isolation, and high-quality data of individual measures are lacking.

Neurologic events, particularly SCI and stroke, are feared consequences of aortic surgery. Stroke may be more common in endovascular approaches as retrograde wires and catheters increase embolic burden. Stroke is associated with procedure duration, female sex, and obesity. Stroke correlates with the duration of hypothermic arrest and increases dramatically at 40 minutes. Covering the left subclavian with stents in the absence of dominant left vertebral artery or left internal mammary artery use in prior coronary artery bypass graft is reportedly safe. Advances in circulatory arrest and endovascular techniques have reduced stroke risk over time.

SCI and the resulting paraplegia/paraparesis may be immediate, when noted on awakening from anesthesia, or delayed, when a normal examination is documented before onset. Delayed SCI is often

preceded by hypotension, which may result from operative or GI bleeding, pain management, systemic inflammatory response syndrome (SIRS), sepsis, or cardiac causes. Reactive cerebrospinal fluid (CSF) drainage following the onset of symptoms is only partially effective. In the emergency setting, SCI risk may be as high as 40%. SCI carries a loss in quality of life, high cost of care, and a 70% 1-year mortality rate. A number of measures are taken to reduce the risk of SCI. Ischemia results from a mismatch in metabolic supply and demand. This mismatch is multifactorial (preexisting vascular disease, obligatory surgical ischemia, vasospasm, increased intracranial pressure [ICP], postreperfusion edema) and so matching a cause with an adjunctive therapy is difficult in real time.

A variety of rational surgical, pharmacologic, hemodynamic, CSF drainage, and monitoring techniques offer an endless combination of possible interventions. Evoked potentials require special consideration and complicate the anesthesia plan. Although motor evoked potentials (MEPs) are a better monitor of the anterior cord, somatosensory evoked potentials (SSEPs) usually reflect significant changes in spinal cord blood flow and predict ischemia well. Use of these monitors is variable, but may optimize neuroprotection in real time.

Intercostal artery reimplantation guided by imaging, back-bleeding, or evoked potentials reduces SCI in some studies but is not universally demonstrated. This variability may result from increased ischemic time and added technical complexity. Postoperative bleeding may require reoperation in as many as 5% of patients with reimplantation. Others report that immediate ligation of intercostals actually improves SCI. This technique stops steal/back-bleeding from the spinal cord during ischemia. This might explain why SCI is not higher in patients with endovascular techniques where intercostals are covered. Collateral flow to the cord via the anterior spinal artery comes from the vertebral, subclavian, intercostal, lumbar, and hypogastric arteries (Fig. 79.3). Animal studies show that a totally desegmented cord is viable solely from collaterals. Unfortunately these networks are compromised in atherosclerotic, hypertensive vasculopaths. Induced hypertension during cross-clamp increases collateral circulation.

Particular attention is given to the arteria radicularis magna (Adamkiewicz), which arises classically at T10. Cadaver data suggest an origin more commonly (70%) at lumbar levels. This explains the particularly high rate of SCI in patients with prior AAA repair. Higher risk of SCI is also correlated with emergent operations, perioperative hypotension, obesity, diabetes mellitus, old age, long stent repair, external iliac injury, hypogastric or subclavian occlusion, and renal failure.

CSF drainage reduces ICP and improves perfusion pressure and SCI outcomes. Cord and cerebral perfusion are defined by the following equation: Perfusion pressure = MAP – (the greater of CVP

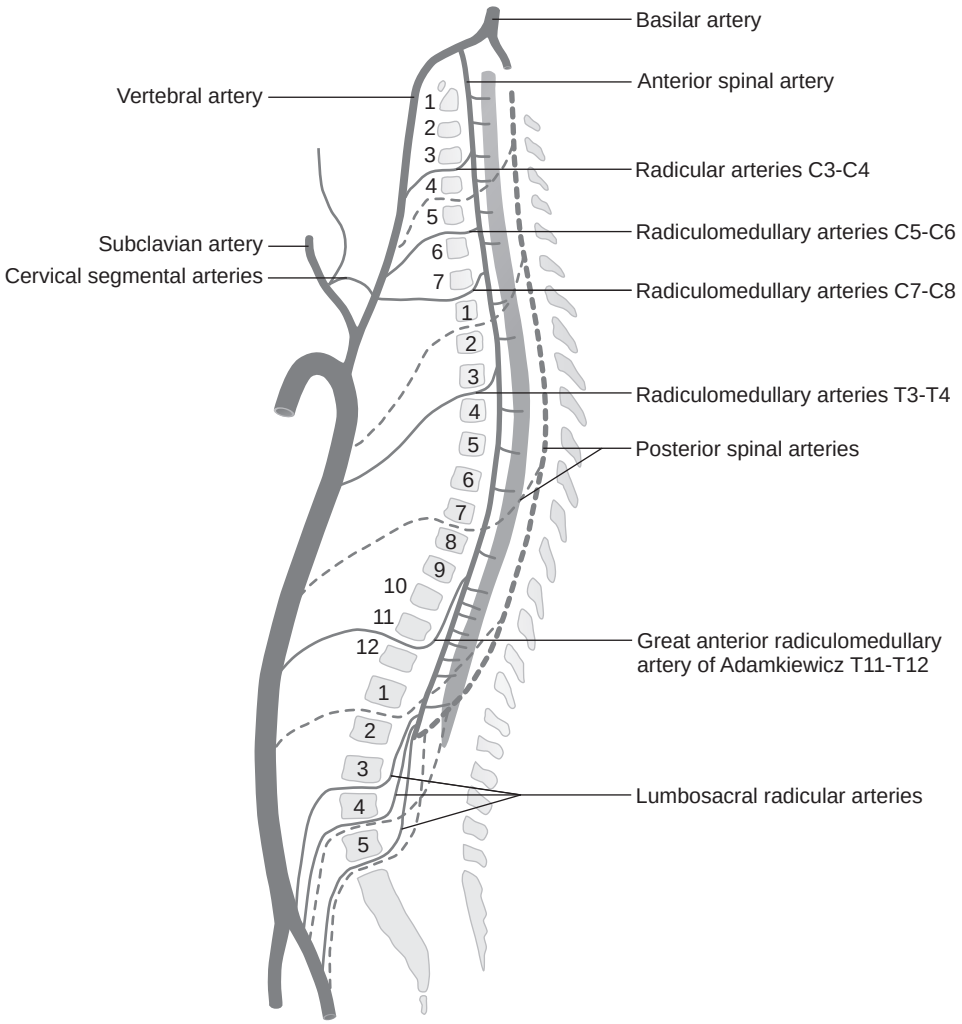

Fig. 79.3 Blood supply of the spinal cord. (From Marijic J, El-Magharbel I, Weiss L, et al: Anesthesia for patients with thoracic aortic disease. In Leung J, editor: *Cardiac and vascular anesthesia: the requisites in anesthesiology.* Philadelphia, Mosby, 2004, p 180.)

or ICP). This suggests that any reduction in ICP below CVP has no benefit. It also implies that venodilators may offer benefit over arteriodilators for hypertension management.

Coronary disease, high-risk surgery, and unequaled physiologic stress may result in myocardial ischemia, infarction, and heart failure. Increased systemic vascular resistance (SVR) during cross-clamp reduces coronary perfusion by elevation in left ventricular end-diastolic pressure and increases demand. The combination of narcotic, barbiturate, esmolol, and nitroglycerin-based blood pressure control may increase coronary flow and reduce left ventricle stroke work with less effect on autoregulation than direct arterial dilators. Arrhythmia is common, but serious cardiac events are reportedly lower than one might expect.

Respiratory failure is a major cause of morbidity and mortality. Smoking, COPD, and lung compromise from mechanical ventilation, transfusion, and fluids are all common. Large thoracotomy incisions are painful and require careful management to optimize atelectasis. Acute respiratory distress syndrome, prolonged ventilation, and ventilator-acquired pneumonia add significant complexity to the postoperative course of these patients. Pulmonary embolism as a result of disseminated intravascular coagulation, immobility, SIRS, and prothrombotic transfusion also occur.

Chronic kidney disease is common in this population. TAAA lesions often involve ischemia to the renal vessels and have the highest risk of acute renal failure and new hemodialysis. As many as half of patients with fulminant acute renal failure are in multiorgan failure and die. Contrast CT imaging for diagnosis, and postoperative surveillance, adds additional insult. Most published studies use less sensitive screening tools for kidney injury and likely represent an underestimation.

Visceral involvement of the celiac, superior mesenteric artery disease, or inferior mesenteric artery disease is not unusual in vasculopaths. Cross-clamping, embolization and coverage of these vessels provide operative ischemia. Ischemia generates acidosis which contributes to hemodynamic disturbance. Mortality from visceral ischemia and GI bleeding is uncommon but has been reported. Intraoperative mechanical perfusion, arterioplasty, and sequential cross-clamping may reduce these risks.

Implications

Arch lesions are predominantly, but not universally, surgical diseases. Medical management, clamp and sew, DCS, and endovascular techniques offer variable complication profiles that should be tailored to the patient's anatomy and physiology. Patients may present following meticulous management or emergently. Some patients are relatively hopeless, such as those in full arrest before incision, but an understanding of the patient and disease guide optimal care.

MANAGEMENT

Initial management of all patients with aortic disease is focused on hemodynamics. Those patients with simple dissection require intensive care unit admission for aggressive blood pressure control. The vast majority, 73% to 90%, of these patients can be treated successfully with medical management alone. Uncomplicated dissections and incidentally discovered aneurysms are in large part treated medically because interventions carry a high morbidity. Medically treated patients have hospital mortality rates around 1%. Medical therapy revolves around reducing aortic wall stress. Aggressive control of blood pressure and heart rate has been shown to reduce the rate of expansion and risk of rupture for aneurysmal disease. β-Blockers, specifically labetalol, are well studied and often first-line therapy.

Patients with large aneurysms, complicated dissections, or unrelenting symptoms require operative intervention. With these characteristics comes a risk of morbidity and mortality that usually outweighs conservative medical treatment. This class of patients has such a high-risk natural course that the number needed to treat for survival at 5 years is two patients.

The management of TAAA varies greatly between surgeons and institutions. There is frequently debate among providers as to the treatment of choice for a given patient. With therapies that overlap cardiothoracic surgery, vascular surgery, and interventional radiology/cardiology it is common for disagreement between providers. Randomized controlled trials do not exist to clearly define best practice. Long-term quality-of-life outcomes do not differ between open and endovascular techniques.

The decision on whom and when to intervene is a complex decision. Although there are published guidelines based on aneurysm size, they are superficial and inadequate. Many dissections and ruptures occur before guidelines would recommend intervention. Risks of an individual's natural course must be balanced against those expected for interventional outcomes. The method chosen for repair, skills of the team, and adjuncts used play heavily into this assessment. Outstanding short- and intermediate-term outcomes have presented in the literature for both endovascular and open options. Age and connective tissue diseases also play a significant part in the decision making. Most connective tissue patients are young, require a more durable repair, and are often excluded from endovascular options. Open repair has well-demonstrated durability beyond 20 years. Older or high-risk patients, especially those with advanced pulmonary disease, may benefit most from endovascular repair. Institutional knowledge about outcomes allows a more meaningful discussion of risks and benefits. It follows that even lower-risk patients should be referred early to high-volume centers with good outcome data because those surgeons are best able offer tailored council.

Orr and colleagues provide an excellent review of endovascular stenting options and their technical differences. New stents and deployment devices continue to broaden applicability and improve complication profiles. The benefits claimed by proponents of endovascular techniques are shorter operative time, faster time to intervention, less blood loss, potential avoidance of general anesthesia, and avoidance of thoracotomy.

Endovascular treatment requires preservation of involved branch arteries. Initially straight tube grafts relied on avoidance of, or collateral flow to, important structures. Newer branched and fenestrated options allow more flexibility. Manufacturers have been able to create stents based on patient-specific anatomy. Anatomic factors limit the application of endovascular techniques for some patients. Grafts require that certain portions of the aorta be normal as "landing zones." Access and aortic vessel size and course must be large and straight enough to accommodate these tools.

Complications specific to endovascular techniques include graft collapse, endoleak, migration, kinking, and access vessel injury. Endoleak, or communication between the aneurysmal sack and arterial pressure/flow, results from a variety of sources. Endovascular repair requires more frequent surveillance imaging and additional procedures are common. Long-term durability after 10 years is not well documented.

Anesthetic Management

Operative management of open TAAA is the greatest challenge in all of anesthesia. TAAA surgery is high-risk surgery. Anesthetic success in this high-risk population requires flawless application of a range of procedural skills, control of dramatic alterations in physiology,

and consideration for insults to every organ system. Techniques vary widely between providers and institutions. Communication about the intended procedure, major risk factors, and planned adjuncts should be clear between surgical and anesthesia teams.

The initial assessment should focus on airway, hemodynamics, and the planned operative procedure. Reassurance with verbal and pharmacologic anxiolytics and tight control of hemodynamics are paramount to reducing the risk of rupture before operative intervention in the emergent setting. Prexoygenation and standard monitors are then applied.

Spinal drain placement, below the conus at L3–L5, is preferred in the awake patient to minimize neurologic injury. Spinal drains should be covered with an occlusive dressing. Bloody tap is not a contraindication to drain placement or operation but may increase the risk of epidural hematoma, especially in heparinized patients. Changes in patient positioning or transfer should prompt clamping of the spinal drain to prevent unintended drainage.

Vascular access with large-bore peripheral catheters and arterial catheterization should precede induction. The operation may involve dissection or clamping of the left subclavian artery, so the right upper extremity is preferred for arterial monitoring. Central aortic pressure by femoral arterial monitoring is useful with DCS. Central access with or without Swan-Ganz catheter may also be placed before induction in some patients.

Following preoxygenation, induction focuses on prevention of hypertension. Titration of fentanyl provides sympathectomy, and the usual reductions in heart rate are helpful. Any hypotension should not be overcorrected. Intubation should proceed as indicated by history and physical examination. Lung isolation is, briefly, required to improve exposure and reduce retractor injury. Double-lumen tube placement obligates the provider to postoperative endotracheal tube exchange when the patient is in critical condition, often after significant transfusion. Aneurysm rupture has been reported following airway manipulation, which should be considered preoperatively based on imaging and symptoms.

The patient is placed in a semi–right-lateral position with surgical approach via a left thoracotomy incision that extends down and toward the midline. Care should be taken to avoid pressure points and stretch injury to the brachial plexus during positioning. Catheters and spinal drain should be checked for patency after position change.

Advanced neuromonitoring dictates anesthetic maintenance. CSF drainage is an invasive procedure with a 5% complication rate, including headache, nerve injury, subdural hematoma, CSF leak, meningitis, catheter fracture, and intracranial hemorrhage. Some do not drain CSF in the absence of evoked potential changes, whereas others drain 5 to 20 mL/h targeting ICP values until SCI is ruled out. If blood is noted in the CSF, the drain should be clamped until imaging can identify a source. Temperature is reduced to a goal of 32 to 34 degrees. Pharmacologic adjuncts may also be employed.

Inotropes, β-blockers, pressors, vasodilators, antiarrhythmics, insulin, electrolytes, and internal/external defibrillation should be available. TEE and pulmonary artery catheters help optimize hemodynamics and monitor for ischemia. At the time of cross-clamping, SVR increases relative to the proximity of the clamp. Supraciliac clamping is the most dramatic. Patients with DCS or preexisting axillary bypass have a reduced response to clamping. Before clamping, temperature and spinal drainage should be at goal, and systolic blood pressure is lowered to 90 to 100 mm Hg with volatile anesthetics, esmolol and nitroglycerin infusions, fentanyl, and barbiturates as appropriate. Application of the cross-clamp should be coordinated with these efforts. Left ventricular strain is mitigated as best as possible and observed closely. Mild hyperventilation and infusion of bicarbonate will control acidosis. Venous drainage from clamped structures persists despite arterial exclusion so both CVP and ICP increase. MAP should target 80 to 110 mm Hg during this period. TEE and frequent blood gases help monitor this critical time.

Just before unclamping, anesthesia is lightened, and MAP is maintained at the upper limits. Bolus vasoconstrictors, calcium, and bicarbonate should be readied. Slow release of the cross-clamp exposes the patient to maximally dilated arteries, acidosis, and hypoxic metabolites. Volume loading before unclamping helps fill exsanguinated arterial systems.

TAAA operations may result in rapid loss of blood at any point. Excessive bleeding results from heparin administration, surgery, hypothermia, fibrinolysis, and DCS. Blood products, cell-saver, and rapid transfusion devices should be available. Intraoperative transfusion is almost universal so blood, plasma, platelets, and cryoprecipitate in the range of 5 to 10 units each should be expected. In the case of major bleeding, goal-directed transfusion and monitoring with international normalized ratio, fibrinogen, complete blood count, and thromboelastography is useful.

Renal protection consists of providing perfusion pressure and cardiac output while avoiding nephrotoxins. Cold crystalloid perfusion and DCS reduce ischemic injury during open procedures. Time between intravenous dye injection and urinary excretion predict postoperative renal recovery. Urine output and bladder temperature should be monitored.

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80 Toxic Ingestion

Casey D. Bryant • Jeffrey S. Kelly

Case Synopsis

A 25-year-old restrained male driver involved in a rollover motor vehicle accident presents acutely for repair of bilateral open tibia fractures. Loss of consciousness was reported at the scene. The patient is currently alert but disoriented, with a Glasgow Coma Scale score on examination of 14. He also exhibits slurred speech and injected conjunctivae. He admits to ingestion of alcohol and amphetamines just before the accident. He is stable hemodynamically, and a thorough trauma evaluation is undertaken after completion of the primary and secondary surveys (including a negative computed tomography [CT] scan of the head, cervical spine, chest, abdomen, and pelvis), making other significant injuries much less likely. Other findings are as follows: blood pressure 110/50 mm Hg, pulse 124 beats per minute, respiratory rate 24 breaths per minute, temperature 37.1°C, and pulse oximetry 100% on room air. Significant laboratory findings include hematocrit 24%, pH 7.27, base deficit of –10 mEq/L, and blood alcohol content 279 mg/dL.

PROBLEM ANALYSIS

Definition and Recognition

Exposure to toxic substances occurs commonly, as evidenced by the 3.1 million calls received by poison control centers in 2013. Such calls typically involved an acute (88%), unintentional (80%), oral (79%) exposure to a single toxin (89%) by a child (57%) at a private residence (91%). Although almost 70% of such cases in 2013 were managed outside the health care system, toxic ingestions still resulted in 601,642 physician visits, 228,230 hospital admissions, 99,117 critical care admissions, and 2113 deaths. These data are even more impressive given that poison control center information likely underestimates the true incidence of both toxic exposure and adverse poisoning outcomes due to underreporting. Drug classes associated with the largest number of deaths in 2013 (in descending order of frequency) were analgesics, stimulant/street drugs (heroin, methamphetamine, and cocaine), cardiovascular drugs, antidepressants, and sedatives/hypnotics/antipsychotics.

Risk Assessment

Most poisoning ingestions tend to follow one of two general patterns. Children (<12 years of age) usually take small quantities of a single toxin unintentionally and seldom manifest significant morbidity or mortality. In contrast, adolescents and adults typically ingest larger amounts of multiple toxins intentionally and suffer higher rates of morbidity and mortality.

Large series of mixed adult overdoses suggest that the coingestion of ethanol occurs in approximately 50% of cases, and alcohol significantly confounds the initial clinical assessment in a similar percentage of trauma patients. Ethanol-related motor vehicle accidents in the United States during 2013 caused nearly one-third (31%) of all traffic-related deaths and resulted in an associated cost of over $59 billion. To complicate things, drugs other than alcohol are reportedly involved in approximately 18% of motor vehicle driver deaths.

The clinician should therefore maintain a high index of suspicion that adolescent and adult trauma victims have some form of acute intoxication and should evaluate the patient for evidence of substance abuse during the initial history, physical examination, and diagnostic workup. Important historical data include the specific toxin or toxins, quantity taken, ingestion time, signs and symptoms since ingestion, past medical and psychiatric history (including suicidal intent), current medications, allergies, and trauma (accidental, incidental, or self-inflicted). Because the history can often be unreliable or incomplete in acute poisoning situations, supplemental data from other sources (e.g., public safety personnel, family, medical records, area pharmacies, local poison control centers, state narcotic databases) may be helpful in diagnosing toxic exposures. A rapid, systematic, and thorough physical examination is mandatory, given the vague history that often surrounds poisoning and trauma scenarios. Barrier precautions should be exercised where appropriate to prevent self-intoxication (such as cutaneous exposure to organophosphate insecticides). The assessment should initially focus on the ABCs (airway, breathing, and circulation), with aggressive intervention to stabilize any abnormalities discovered. Additional assessment considerations are as follows:

- *Gag reflex.* This has implications for airway protection and possible aspiration in overdose patients, but contributes little to clinician assessment and the Glasgow Coma Scale regarding the possible need for intubation.
- *Core temperature disturbances.* Multiple etiologies may be involved, including toxic (salicylates, stimulants), environmental, and/or infectious causes.
- *Neurologic examination abnormalities.* Detection of central nervous system dysfunction (such as confusion, coma, or delirium) should prompt the clinician to pursue additional diagnostic imaging such as CT or magnetic resonance imaging to evaluate for other potential causes such as cervical spinal cord injury, ischemic stroke, or intracranial hemorrhage.
- *Incidental trauma and stigmata of substance abuse.* The patient should be examined for puncture wounds, needle tracks, and nasal septal perforation.
- *Constellation of signs and symptoms ("toxidromes").* The ingestion of certain toxins may present as characteristic toxidromes typically involving abnormal vital signs, altered mental status, pupillary changes, and a variety of miscellaneous effects that can be attributed

TABLE 80.1 Common Toxidromes

Syndrome	Common Clinical Signs	Potential Toxic Agents
Anticholinergic	Tachycardia, fever, dry skin, urinary retention, ileus, mydriasis, delirium, seizures	Antihistamines, phenothiazines, tricyclic antidepressants, antipsychotics, atropine, scopolamine, jimsonweed, amantadine, antiparkinson drugs, *Amanita* mushrooms, baclofen
Cholinergic	Bradycardia, diaphoresis, urinary or fecal incontinence, emesis, miosis, central nervous system depression, weakness, fasciculations, wheezing	Organophosphate and carbamate insecticides, physostigmine, pyridostigmine, edrophonium, certain mushrooms
Sympathomimetic (stimulants)	Tachycardia (bradycardia with pure α-agonist), hypertension, mydriasis, diaphoresis, piloerection, fever, delusions, paranoid ideation, restlessness, agitation	Cocaine, amphetamines, over-the-counter decongestants (pseudoephedrine, phenylpropanolamine, phenylephrine)
Narcotic	Mental status depression, hypoventilation, miosis, ileus, hypotension, bradycardia	Opioids
Sedative-hypnotic	Confusion, slurred speech, mental status depression, respiratory depression, ataxia, hypothermia	Benzodiazepines, barbiturates, ethanol, antipsychotics, anticonvulsants
Serotonin	Fever, diaphoresis, flushing, diarrhea, hyperreflexia, tremor, myoclonus, trismus	Selective serotonin reuptake inhibitors, trazodone, clomipramine, meperidine, methadone, dextromethorphan, linezolid, tramadol, others.
Hallucinogenic	Hallucinations, psychosis, paranoid ideation, panic, fever, mydriasis	Cocaine, amphetamines, cannabinoids, phencyclidine (PCP), lysergic acid diethylamide (LSD), antihistamines
Extrapyramidal	Tremor, rigidity, opisthotonos, torticollis, choreoathetosis, trismus, hyperreflexia	Typical and atypical antipsychotics

Data from Hoffman RS, Howland MA, Lewin NA, et al., editors: *Goldfrank's toxicologic emergencies,* 10th ed. New York, McGraw-Hill, 2015; and Levine M, Brooks DE, Truitt CA, et al.: Toxicology in the ICU: part 1: general overview and approach to treatment. *Chest* 140:795-806, 2011.

to the known pharmacologic properties of the particular drug class. Examples of specific toxidromes are provided in Table 80.1.

Laboratory evaluation should be based on the suspected ingestion (i.e., drug levels, blood alcohol level) and should include consideration of acetaminophen and salicylate levels in overdose situations. Urine drug screens may occasionally provide diagnostic clues about possible ingestions, although results are typically not available in a timely manner, and the substances detected will vary between institutions.

Concomitant trauma and poisoning may confound the accurate assessment of each individual entity, as exemplified by the case synopsis. Normal blood pressure and pulse pressure in the presence of anemia, tachycardia, and metabolic acidosis likely reflects hypovolemic shock that is partially masked by amphetamine-associated vasoconstriction.

MANAGEMENT

The vast majority of acutely poisoned patients have satisfactory outcomes when given appropriate supportive care, with an emphasis on aggressive, early intervention to stabilize vital organ function. Initial efforts should focus on maintaining a stable, patent airway, establishing adequate ventilation and oxygenation, and stabilizing cardiovascular function, just as one would do for other medical emergencies. All patients with depressed mental status should receive oxygen if hypoxia is present, consideration of intravenous naloxone if there is clinical concern for opioid overdose, and intravenous dextrose if the finger-stick blood glucose level is low. Hypoglycemia should be corrected as early as possible even in patients with suspected thiamine deficiency, as recent literature does not support the classical practice of thiamine administration before glucose to avoid precipitating Wernicke's encephalopathy. Tonic-clonic seizures that are suspected to be the result of a toxin or drug are best treated with benzodiazepines, often at higher doses than those required for traditional epileptic seizures. Intravenous barbiturates are acceptable second-line agents given their γ-aminobutyric acid (GABA)–agonist activity. Given the high incidence of ethanol abuse in both poisoning and trauma patients, early monitoring for alcohol withdrawal should be implemented with appropriate initiation of benzodiazepine therapy as indicated.

Definitive poisoning management typically involves the early use of specific antidotes (where appropriate) and decontamination techniques. Gastrointestinal decontamination primarily revolves around activated charcoal, which should be considered for potentially toxic ingestions of agents known to adsorb to charcoal. It should be administered as early as possible (ideally within 1 hour of ingestion) and only in patients who have an appropriate mental status or secured airway. Repeat dosing of charcoal is currently recommended only in patients who have ingested life-threatening amounts of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Repeat charcoal dosing for aspirin overdose remains controversial, but may be considered by the clinician. Other more historical decontamination techniques such as gastric emptying (using either syrup of ipecac or gastric lavage) and decreasing intestinal transit time using osmotic cathartics have continued to fall out of favor due to persistent absence of evidence-based literature support. Syrup of ipecac administration has been completely abandoned, and the risks of gastric lavage limit its utilization to extremely rare situations of massive enteral overdoses where skilled personnel with proper training and experience in this therapy are present to initiate it early after ingestion. Evidence supporting whole bowel irrigation using large volumes of isosmotic cathartics is also weak, but it may be considered for ingestions involving enteric-coated/sustained-released medications, illicit drug packets, or substances not adsorbed to activated charcoal (e.g., lithium, iron, potassium). Hemodialysis is reserved for dialyzable toxins with clinically significant effects or levels (e.g. salicylates, lithium, metformin). (Table 80.2; Boxes 80.1 and 80.2).

TABLE 80.2 Selected Poisoning Antidotes

Toxin	Antidote
Opiates	Naloxone
Benzodiazepines	Flumazenil (beware of precipitating seizures in patients taking chronic benzodiazepines)
Anticholinergics	Physostigmine (in consultation with a Toxicologist)
Cholinesterase inhibitors	Atropine, pralidoxime (for insecticides)
Calcium channel blockers	Calcium chloride, glucagon, consider high dose insulin therapy
β-Blockers	Glucagon, consider high dose insulin therapy
Digoxin	Digoxin-specific antibody
Acetaminophen	*N*-acetylcysteine
Methanol	Fomepizole, ethanol
Ethylene glycol	Fomepizole, ethanol
Isoniazid	Pyridoxine
Cyanide	Amyl nitrate, sodium nitrite, sodium thiosulfate, hydroxocobalamin
Methemoglobin	Methylene blue
Iron	Deferoxamine

Data from Brooks DE, Levine M, O'Connor AD, et al: Toxicology in the ICU: part 2: specific toxins, *Chest* 140:1072-1085, 2011; and Hoffman RS, Howland MA, Lewin NA, et al, editors: *Goldfrank's toxicologic emergencies,* 10th ed. New York, McGraw-Hill, 2015.

BOX 80.1 Poisoning Treatment: Activated Charcoal

Indications

Single dose: Ingestions of drugs or toxins that bind to activated charcoal, when no contraindications exist and an improved outcome is expected.

Multiple doses: Ingestions of drugs or toxins that bind to activated charcoal and (1) a prolonged absorption phase is expected, (2) potential toxicity is great, and (3) patient has ingested life-threating amounts of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Repeat dosing for aspirin overdose remains controversial.

Dose[a]

Initial Dose (Single or Multiple)

Adults and children: 1 g/kg body weight or 10:1 ratio of activated charcoal to drug, whichever is greater.

Following massive ingestions: 2 g/kg may be indicated if such a large dose can be easily administered and tolerated.

Repeated Doses[a]

Adults and children: 0.5 g/kg body weight every 4–6 hours for 12–24 hours, in accordance with the dose and dosage form of drug ingested (larger doses and shorter dosing intervals may occasionally be indicated).

Procedure

Add 8 parts water to the selected amount of powdered form; all formulations, including prepacked slurries, should be shaken well for at least 1 min to form a transiently stable suspension before drinking or instillation via orogastric or nasogastric tube.

If the patient vomits the dose of activated charcoal, it should be repeated if one can do so safely. Smaller, more frequent doses or continuous nasogastric administration may be better tolerated and an antiemetic may be needed.

If a nasogastric or orogastric tube is used for multiple-dose administration, allow time for the last dose to pass through the stomach before suctioning the remaining activated charcoal and removing the tube as this may prevent aspiration of activated charcoal.

Contraindications

Patient at risk for aspiration who has an unprotected airway

Caustic ingestion (activated charcoal is ineffective as an adsorbent in these cases and may accumulate in burned areas, interfering with endoscopy)

Ileus (a contraindication for multiple dosing)

Adverse Effects

Aspiration pneumonitis

Emesis

Obscuring of gastrointestinal mucosa (for endoscopy)

Constipation

[a]Can be given orally or via an orogastric or nasogastric tube.

Adapted from Hoegberg LCG, Gude AB: Techniques used to prevent gastrointestinal absorption. In Hoffman RS, Howland MA, Lewin NA, et al, editors: *Goldfrank's toxicologic emergencies,* 10th ed. New York, McGraw-Hill, 2015.

BOX 80.2 Poisoning Treatment: Whole Bowel Irrigation

General Indications

Whole bowel irrigation with polyethylene glycol electrolyte lavage solution may be helpful in managing poisonings and overdoses when (1) the ingestion involves enteric-coated/sustained-released medications, illicit drug packets, or substances not amenable to activated charcoal decontamination (such as lithium, iron, potassium), and (2) it is desirable or necessary to rapidly clear the entire gastrointestinal tract without emesis or causing fluid or electrolyte disturbances.

Specific Indications

Intoxication with a sustained-release medication

Slowly dissolving substances (e.g., iron tablets, paint chips, bezoars, concretions)

Drug packets (e.g., heroin, crack vials, cocaine) swallowed by "body packers" or "body stuffers"

Drugs or toxins not adsorbed by activated charcoal (e.g., lithium, iron, potassium)

Dose[a]

Adults: 1–2 L/h for 4–6 hours, or until the rectal effluent is clear

Children: 25–40 mL/kg/h for 4–6 hours, or until the rectal effluent is clear

Note: Activated charcoal should be administered before and during whole bowel irrigation if a charcoal-adsorbable drug or toxin is involved; an antiemetic such as metoclopramide or a serotonin antagonist may be indicated to achieve compliance.

Contraindications

Gastrointestinal pathology (e.g., ileus, perforation, obstruction)

Caustic ingestion

Patients at risk for pulmonary aspiration

Adverse Effects

Rectal itching

Vomiting (especially with rapid administration)

Bloating

Decreased efficacy of activated charcoal

Desorption of toxin from activated charcoal

[a]Can be given orally or via nasogastric tube.

Data from Hoegberg LCG, Gude AB: Techniques used to prevent gastrointestinal absorption. In Hoffman RS, Howland MA, Lewin NA, et al., editors: *Goldfrank's toxicologic emergencies,* 10th ed. New York, McGraw-Hill, 2015; and Levine M, Brooks DE, Truitt CA, et al.: Toxicology in the ICU: part 1: general overview and approach to treatment. *Chest* 140:795-806, 2011.

The signs and symptoms of amphetamine use in the patient described in the case synopsis were obscured by the concomitant effects of central nervous system depressants (i.e., ethanol), hypovolemia from long bone fractures, and environmental exposure to low ambient temperatures. Classic physical findings of amphetamine toxicity are consistent with a diffuse hyperadrenergic state and include hypertension, tachycardia, hyperthermia, diaphoresis, mydriasis, and hyperactivity. Psychiatric symptoms may include agitation, paranoid ideation, and hallucinations. Specific therapy is directed toward "pharmacologic cooling" with benzodiazepines (e.g., diazepam 10 mg intravenously as needed and aggressively titrated until the patient is calm). Goals of treatment are to (1) decrease motor agitation and treat tonic-clonic seizures with GABA agonists, (2) provide active physical cooling maneuvers to treat significant hyperthermia, (3) initiate intravenous hydration with isotonic crystalloid with a goal urine output of 1 to 2 mL/kg per hour in cases involving rhabdomyolysis, and (4) control severe hypertension that is unresponsive to benzodiazepine sedation by using agents such as nicardipine or nitroprusside. Nitroprusside should be administered with caution, because long-term amphetamine abuse contributes to relative intravascular volume depletion in a manner similar to chronic hypertension. As with pheochromocytoma and cocaine abuse, the use of β-blockers in cases of amphetamine abuse may lead to unopposed α-adrenergic stimulation and possible exacerbation of hypertension. Hyponatremia resulting from certain amphetamine congeners should be corrected with caution, and 3% saline should be reserved for life-threatening situations (such as seizures) believed to be due to severe hyponatremia.

Because the patient lacked significant amphetamine-related symptoms, definitive therapy for this gentleman consisted simply of aggressive supportive care. He was admitted postoperatively to an adequately staffed telemetry area trained in the care of complicated trauma patients. Monitoring for signs and symptoms of alcohol withdrawal was carried out, but significant withdrawal would be relatively uncommon in a patient this age.

PREVENTION

It would be unethical to conduct prospective, controlled trials to assess complications arising from toxic ingestion. Epidemiologic studies, retrospective data, and case reports provide sufficient insight into the consequences of specific toxic ingestions. Thus, prevention of toxic sequelae requires a thorough and systematic clinical assessment, as

well as familiarity with the specific pharmacology, pharmacodynamics, and pharmacokinetics of the ingested agents.

Further Reading

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81 Troubleshooting Common Problems During Cardiopulmonary Bypass

John R. Cooper, Jr.

COMPLICATIONS OF AORTIC ROOT CANNULATION: ACUTE AORTIC ROOT DISSECTION

Case Synopsis

A 75-year-old man with a history of calcific aortic stenosis was scheduled for valve replacement. Induction of anesthesia, sternotomy, and insertion of perfusion cannulas were uneventful. However, the aortic tissue appeared thin and calcified. The aortic purse strings and cannula appeared well placed, but when cardiopulmonary bypass (CPB) was initiated, the pump arterial line pressure increased, and systemic blood pressure (radial artery) decreased. The aorta appeared acutely dilated and bluish.

PROBLEM ANALYSIS

Definition

Acute aortic dissection is a very serious complication of aortic cannulation for bypass. Although rare, it can occur at any time, even in experienced hands. It is fatal unless a diagnosis is made early; thus it requires a high degree of vigilance. Dissection can also occur during CPB or after decannulation.

For dissection to occur, blood under pressure must gain access to the media of the aortic wall. In this case the cannula orifice was unintentionally placed within the media of the arterial wall rather than the true lumen during cannulation. When CPB was begun, the resulting increase in pressure created a dissection.

Additional manipulation of the ascending aorta (e.g., placement of the aortic cross-clamp, antegrade cardioplegia line, or proximal bypass grafts) may increase the risk of dissection. Predisposing factors that also increase the risk of acute aortic dissection include conditions that weaken the aortic wall, such as the following:

- Cystic medial necrosis or other genetically related tissue weakness
- Elastic or medial degeneration associated with aging
- Thin or friable aorta tissue, as with poststenotic dilation (aortic stenosis)
- Atheromatous disease

Dissection can also occur spontaneously in the operating room or during the postoperative period in the intensive care unit.

Recognition

In cases of intraoperative dissection, a sudden, unexplained decrease in mean arterial pressure and venous return is usually seen, along with an acute elevation in arterial line pressure as measured at the pump and bluish discoloration and enlargement of the aortic root. Myocardial ischemia, aortic insufficiency, or both may develop, and signs of organ hypoperfusion (including oliguria and pupil asymmetry) may be present if the dissection extends to other major arterial vessels. If transesophageal echocardiography is used, dissection may be evident on examination of the thoracic aorta (Fig. 81.1).

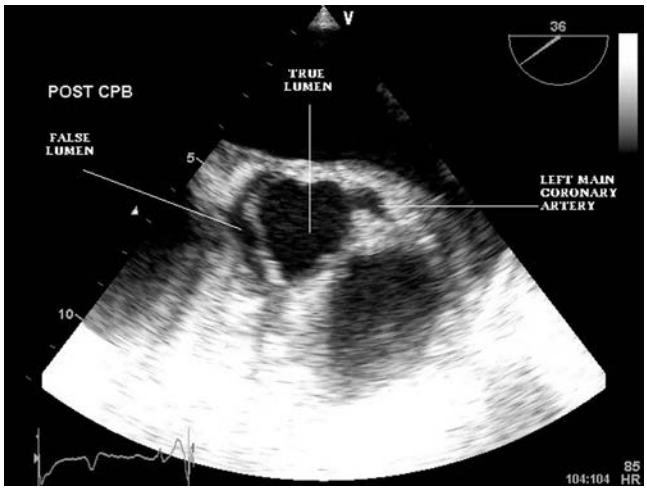

Fig. 81.1 Transesophageal echocardiography of the ascending aorta just distal to the aortic valve, with an intraoperative aortic dissection evident showing true and false lumens. This dissection propagated from the antegrade cardioplegia administration site.

MANAGEMENT

Once dissection is recognized, CPB must be discontinued immediately. The surgeon must then either reposition or replace the arterial cannula so that it is inside the true lumen at a more distal site on the aortic arch or (more often) switch to femoral artery cannulation. Surgical repair of the aortic dissection is almost always necessary; such repair should include coronary artery reimplantation if the patency of the coronary arteries is compromised.

PREVENTION

Measures that may be effective in reducing the risk of aortic dissection during cannulation include the following:

- Blood pressure control (to avoid hypertension) at the time of cannulation
- Inserting the cannula at a right angle to the aorta to prevent dissection of tissue planes
- Special care in positioning the tip in the true lumen of the aorta
- Blood pressure reduction when the aortic cross-clamp is applied or removed
- Use of atraumatic clamps, with as few applications to the aorta as possible
- Continuous monitoring of arterial cannula pressure by the perfusionist

INNOMINATE OR CAROTID ARTERY HYPERPERFUSION

Case Synopsis

A 58-year-old woman underwent CPB for coronary artery bypass grafting. After successful aortic and venous cannulation by the surgeon, the anesthesiologist noted right-sided facial blanching. Further examination showed the presence of a right carotid thrill.

PROBLEM ANALYSIS

Definition

Pump flow can be directed primarily into the carotid or innominate artery instead of the aorta. This can result in cerebral edema or arterial rupture due to high perfusion pressure or the creation of an intimal flap that obstructs arterial flow.

Recognition

Signs of innominate artery cannulation include ipsilateral facial blanching, pupillary dilation, and conjunctival chemosis. Hypotension may be detected with a left radial or femoral artery catheter, but a right radial artery catheter may show hypertension.

MANAGEMENT

Repositioning of the cannula is necessary. Measures to reduce cerebral edema may be indicated, such as administering diuretics or placing the patient in a head-up position.

PREVENTION

Using a short aortic cannula with a flange to prevent insertion too far into the aorta is usually effective. The anesthesiologist can check for bilateral carotid pulses without thrills after cannulation and initiation of CPB, but this may not reliably detect problems caused by carotid or innominate artery hyperperfusion. With certain types of cannulas, transesophageal echocardiography may be useful in determining position.

OBSTRUCTION OF VENOUS RETURN TO THE PUMP

Case Synopsis

In a 60-year-old man, CPB was initiated after uneventful aortic cannulation and insertion of a single venous cannula into the right atrium. There was an immediate decrease in pump-oxygenator venous reservoir volume and thus the pump's ability to maintain a normal flow rate. Adding volume to the circuit did not resolve the issue. Obvious venous engorgement in the patient's face and neck was noted on examination.

PROBLEM ANALYSIS

Definition

Obstruction of venous return to the pump-oxygenator may have several causes:

- An "air lock" created by the presence of large air bubbles within the venous cannula or tubing
- Failure to remove a venous line clamp
- Lifting of the heart within the chest by the surgeon
- Use of venous cannulas too small for the patient's size
- Presence of thrombus or tumor in the right atrium
- Kinked or malpositioned cannula (most common)

When two cannulas are used, the superior vena cava cannula may be placed in the azygos vein or, if the cannula is advanced too far cephalad, the innominate vein. The inferior vena cava cannula can be inserted into the hepatic vein. In this case the single cannula was inserted so far into the inferior vena cava that there could be no venous return from the superior vena cava.

Recognition

Poor venous return to the pump-oxygenator and the resultant decrease in venous reservoir volume are the first signs. Failure to reduce pump flow immediately can result in emptying of the venous reservoir, incurring a risk of massive arterial air embolism. Central venous pressure increases; there is obvious venous engorgement in the face and neck and, later, conjunctival chemosis. Also, lack of drainage from the right side of the heart may result in distention of the right ventricle and compression of the left ventricle; these changes are detected by direct visualization or evidenced by an increase in pulmonary artery or left atrial pressure.

MANAGEMENT

Pump flow should be reduced until the cause of obstruction to venous return is found. The surgeon can propel an air lock through the venous tubing by progressively raising and tapping the tubing downstream from the bubble. Malpositioned venous cannulas must be repositioned. Only after adequate venous return is established and volume in the venous reservoir has recovered can full-flow CPB be continued.

PREVENTION

The surgeon should inspect the venous cannula for large bubbles and ensure proper venous cannula position; however, cannula malposition can be subtle. The anesthesiologist should routinely check the patient's face, external jugular veins, and conjunctiva for signs of high venous pressures. Monitoring central venous pressures may not detect a superior vena cava obstruction because the catheter tip may be below the obstruction point.

MASSIVE GAS EMBOLISM

Case Synopsis

In a 65-year-old woman undergoing mitral valve replacement, CPB was initiated after uneventful insertion of aortic and venous cannulas. Before the aortic cross-clamp was applied, the surgeon inserted a vent cannula into the left atrium via the left superior pulmonary vein. Blood initially drained normally toward the venous reservoir but then reversed direction, and a large quantity of air entered the heart and was ejected systemically.

PROBLEM ANALYSIS

Definition

Systemic gas embolism is the most common serious adverse event associated with CPB and is largely preventable. Principal causes include the following:

- Vortexing—air being pumped out of an empty or nearly empty oxygenator reservoir
- Reversed roller-pump tubing in the vent line or arterial cannula
- Disconnection, leak, oxygenator disruption, or line occlusion proximal to the arterial pump, with air entrainment or cavitation
- Development of positive pressure in the cardiotomy reservoir, producing retrograde airflow into the heart or aorta
- Injection of air into the aortic root from the cardioplegia delivery system
- A thrombus in the oxygenator or a runaway pump head
- Ejection of blood before the removal of air from the heart, opening the left side of a beating heart, or opening the right side of a beating heart when there is a right-to-left connection (i.e., a patent foramen ovale)
- Disconnection or rupture of the oxygenator or lines during CPB
- Failure to clamp the aortic line at the end of CPB, resulting in air infusion if the pump head is accidentally restarted

Recognition

Air in the arterial cannula is usually visually apparent, but signs of myocardial or other organ ischemia may also appear. Rarely, withdrawal of air from an arterial pressure monitoring line indicates air embolism.

MANAGEMENT

If the embolus is massive, CPB must be discontinued after recognition. The patient is then placed in a steep Trendelenburg position, the aortic cannula is removed, and the CPB circuit is reprimed. Retrograde perfusion of the superior vena cava is initiated (Fig. 81.2). Then CPB is restarted with hypothermia, increasing perfusion pressure, and 100% oxygen. Consideration can then be given

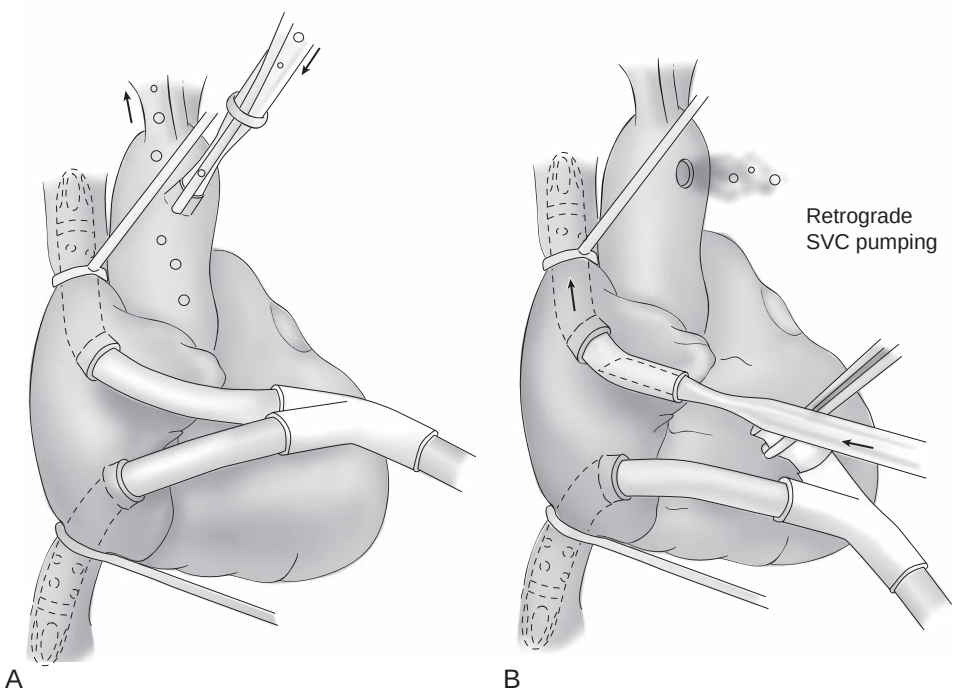

Fig. 81.2 A, Massive air embolus through the aortic cannula (*circles* represent the aortic root). **B,** The aortic cannula is removed, purged of air *(circles),* and inserted into the divided superior vena cava (SVC) cannula. Retrograde perfusion at 1200 mL/min at 20°C is carried out for 1 to 2 minutes. Air exits the aortic cannulation site. (From Mills NL, Ochsner JL: Massive air embolism during CPB: causes, prevention and management. *J Thorac Cardiovasc Surg* 80:713, 1980.)

to pharmacologic interventions to reduce cerebral injury, including mannitol, steroids, and barbiturates. Postoperative interventions may include initiating hyperbaric oxygen treatment, placing the patient in the reverse Trendelenburg position, initiating slight hyperventilation, inducing hypothermia, and preventing hyperglycemia and hyponatremia.

PREVENTION

Continual attention must be paid by the perfusionist to maintaining a safe volume of blood in the oxygenator reservoir. The use of low-level alarms and bubble detectors is now standard. The surgical team must protect the venous lines and communicate with the perfusionist whenever venous return is likely to be compromised. Other possible measures include the following:

- Centrifugal pumps
- Arterial line filters
- Bubble traps with an open air-purge line guarded by a one-way valve
- Collapsible reservoirs
- One-way valves placed in the left heart vent line

PUMP OR OXYGENATOR FAILURE

Case Synopsis

A 68-year-old man underwent CPB for combined mitral valve replacement and coronary bypass grafting. Five minutes after CPB was initiated, dark blood was observed in the aortic cannula by the anesthesiologist. An immediate blood gas sampling revealed low arterial oxygen tension (Pa_{O_2}).

PROBLEM ANALYSIS

Definition

This arterial inflow desaturation can be caused by failure of the gas supply system or the oxygenator itself, or by specific patient characteristics or pathophysiology.

Pump failure can be a fourth cause of low Pao_2. This can result from electrical or mechanical failure, tubing rupture or disconnection, or automatic shutoff by the bubble or reservoir level detector. A runaway pump head may inappropriately raise the pump flow rate to maximum. If the occlusion of a roller pump is improperly set, excessive regurgitation can cause reduced forward blood flow, hypotension, and metabolic acidosis.

Recognition

Oxygenator failure results in dark blood in the arterial cannula and severe vasodilation. Blood leaking into the heater-cooler water may also be seen with oxygenator rupture. With pump failure and low Pao_2, one observes hypotension, metabolic acidosis, and possibly hemolysis.

MANAGEMENT

If oxygenator failure is suspected, a blood gas measurement should be obtained from the arterial inflow line, and the perfusionist should increase oxygen gas flows and determine the adequacy of mechanical pump flow. Additionally, the following actions should be taken:

- Careful inspection of the gas circuit, including gas sources, all connections, tubing, gas line filter, and anesthetic vaporizer
- Inspection of the oxygenator for appropriate blood levels and examination of a hard shell device for leaks or cracks
- Inspection of the venous and arterial cannulas for appropriate patient connections
- Ensuring adequate muscle relaxation, appropriate patient temperature, and depth of anesthesia

If the heart is still beating, one should consider allowing it to eject blood into the pulmonary circulation for additional oxygenation and continuing to ventilate the lungs until arterialization of blood is apparent in the aortic cannula. It may be necessary to exchange the oxygenator, which is a difficult procedure.

If there is mechanical pump failure, a hand crank can be used until a replacement is obtained or tubing is replaced. In the case of a runaway pump head, the machine must be unplugged, and the tubing must be switched to a different roller head. If flow will be low or absent for more than a few minutes and the patient cannot be weaned immediately from CPB, hypothermia should be induced and the head and heart packed in ice for additional protection.

PREVENTION

Vigilance is paramount. Using a pump arterial line oxygen saturation monitor, an oxygen partial pressure analyzer, or both may be beneficial. Backup equipment should always be available.

THROMBOSED OXYGENATOR OR CIRCUIT

Case Synopsis

A 60-year-old man underwent aortocoronary bypass and concurrent abdominal aortic aneurysm repair. After weaning from CPB, while the aneurysm was being repaired, the CPB circuit was used for blood salvage and reinfusion. After 1 hour, as blood was being given through the aortic cannula, a large clot was discovered in the oxygenator. The patient's activated clotting time was greater than 400 seconds.

PROBLEM ANALYSIS

Definition

This adverse event can prevent CPB flow, cause a massive gas embolus, and interfere with gas exchange. Causes include inadequate heparinization, blood stagnation in the bypass circuit (e.g., no flow in the circuit during circulatory arrest), and, occasionally, addition of nonheparinized blood products during CPB.

Recognition

Visual inspection of the circuit for clots is most reliable, but the observation of air exiting from the oxygenator or high arterial cannula pressure may also indicate a large clot.

MANAGEMENT

If possible, stop CPB and reheparinize the patient by using a different lot of heparin. Hypothermia should be initiated, and open cardiac massage should be performed if the patient cannot be acutely weaned from CPB. The oxygenator may need to be replaced. The protocol for massive air embolism should be followed, if appropriate.

PREVENTION

The surgical team should ensure adequate heparin administration and monitoring in prolonged cases, and the circuit and arterial line filter should be inspected visually for clots. Heparinizing any blood products added to the circuit should be considered, and stagnant blood

pooling in the CPB circuit should be avoided, even if heparinization appears adequate by laboratory measurements.

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82 Antibiotics

Huong Le • Timothy E. Morey

Case Synopsis

A 23-year-old man presents for reduction and fixation of an open tibial fracture after falling off a horse. During the presurgical briefing/time-out, the surgeon requests that the patient be given vancomycin, 1 g, before incision. After propofol and succinylcholine administration and successful endotracheal intubation, anesthesia is maintained with sevoflurane, N_2O 50%/O_2 50%, and fentanyl, 2 μg/kg/h. Four minutes after vancomycin is given, the patient suffers cardiovascular collapse.

PROBLEM ANALYSIS

Definition

Anesthesiologists frequently administer antibiotic prophylaxis to surgical patients to ensure patient benefits related to the Surgical Care Improvement Project (i.e., SCIP-Inf 1). For this reason, anesthesiologists should be knowledgeable regarding indications, dosage, complications, and interactions of antibiotics with anesthetics and other medications used in the perioperative period. Antibiotics possess a diverse spectrum of side effects and interact with a number of anesthetic adjuvants (Table 82.1). Antibiotics also account for the majority of self-reported drug-allergy entries. For these reasons, anesthesiologists must understand and anticipate possible complications associated with antibiotic administration.

Vancomycin is a glycopeptide antibiotic commonly used for bacterial prophylaxis in orthopedic, neurologic, and vascular surgery and as an alternative antibiotic for patients allergic to penicillin-based antibiotics and cephalosporins or for patients harboring drug-resistant organisms. When a life-threatening reaction occurs after the initiation of vancomycin, the possibility of a hypersensitivity reaction must be considered. Vancomycin administration can lead to multiple types of hypersensitivity reactions, two of which are (1) "red man" syndrome (RMS) and (2) anaphylaxis.

Red Man Syndrome

RMS or "red neck" syndrome manifests as hypotension, cutaneous flushing, erythema, urticaria, pruritus, and maculopapular rash, primarily of the face, neck, arms, and chest. The constellation of symptoms may be mild in its presentation or severe to the point of life threatening. Signs may occur as early as 4 to 10 minutes after the start of infusion and can be precipitated by an infusion rate of less than an hour in duration. An unusual feature of vancomycin is its ability to nearly double histamine release from basophils and cutaneous mast cells through a poorly understood dose-dependent mechanism. Although it may be clinically indistinguishable from anaphylaxis in the operating room, RMS does not involve immunoglobulin E (IgE) sensitization. Previously described as an anaphylactoid reaction, it is currently described in the literature as non-IgE immunologic anaphylaxis. Diagnosis relies primarily on (1) the exclusion of other intraoperative events that may produce hypotension; (2) the temporal relationship of cardiovascular instability to vancomycin infusion and the observation of other manifestations of histamine release, such as perioral, periocular, and facial edema; (3) bronchospasm due to stimulation of bronchial histamine receptors; and (4) hypoxia secondary to histamine-induced inhibition of hypoxic pulmonary vasoconstriction and subsequent formation of pulmonary shunts. Attention should be given to other histamine-inducing drugs that may potentiate the symptoms of RMS (see Table 82.1). As a marker for immunologic mast-cell activation, tryptase release does not occur in vancomycin-induced anaphylactoid reactions. Assays for histamine release are usually impractical because histamine concentrations peak 5 minutes after onset and return to baseline within an hour after release.

The liberated histamine causes dilation of peripheral blood vessels and simultaneously increases cardiac output, stroke volume, and pulmonary artery blood pressure. However, the peripheral vascular dilation is the most prominent physiologic feature and may induce severe hypotension and cardiovascular collapse. Treatment options become more aggressive with later detection, more histamine release, and more severe hypotension. Management options include the following:

- Discontinue or slow the vancomycin infusion
- Administer an intravenous (IV) fluid bolus
- Discontinue or decrease concentrations of other agents capable of inducing hypotension (e.g., anesthetics or sodium nitroprusside)
- Administer H_1-antihistamines (e.g., diphenhydramine)
- Consider inhaled β-agonists if bronchospasm is present
- Administer vasopressors (e.g., ephedrine, phenylephrine, and epinephrine) for severe hypotension
- Initiate advanced cardiac life-support maneuvers in case of cardiac arrest

Immunoglobulin E–Mediated Anaphylaxis

The potential cause of cardiovascular collapse after vancomycin infusion may also be related to IgE-mediated anaphylaxis. Signs of anaphylaxis include rapid-onset morbilliform rash or hives, urticaria, flushing, angioedema, vomiting, diarrhea, rhinoconjunctivitis, and tachycardia. These symptoms may persist for up to 48 hours. Because these signs are more difficult to detect in a patient covered in surgical drapes and sedated or under general anesthesia, the presence of hypotension and bronchospasm in a patient previously exposed to vancomycin should immediately result in the consideration of IgE-mediated anaphylaxis as a cause (Box 82.1). Previous exposure to vancomycin results in the production of vancomycin-specific IgE and, on repeat

TABLE 82.1 Complications of Antibiotics Commonly Used for Prophylaxis

	COMPLICATIONS		
Antibiotic	**Common**	**Occasional**	**Rare**
Aminoglycosides	Nephrotoxicity Ototoxicity	Rash Nausea, vomiting Potentiation of neuromuscular blockade	Peripheral neuritis Anaphylaxis Electrolyte disturbances
Cephalosporins	Painful when given intramuscularly (IM)	Nausea Drug fever Diarrhea Phlebitis	Anaphylaxis Hypotension Bronchospasm Angioedema Urticaria
Clindamycin		Diarrhea Pseudomembranous colitis Rash Metallic taste Inhibition of neuromuscular transmission Potentiation of neuromuscular blockade	Anaphylaxis Cardiac arrest Erythema Granulocytopenia Thrombocytopenia
Erythromycin	Phlebitis when given intravenously Painful when given IM	Nausea, vomiting Diarrhea Pseudomembranous colitis	Long QT syndrome Fever Rash Eosinophilia
Metronidazole	Nausea, vomiting Metallic taste Disulfiram-like reaction if alcohol consumed	Burning tongue Urethral/vaginal burning Dark urine Rash	Convulsions Ataxia Peripheral neuropathy Encephalopathy Cerebellar dysfunction
Penicillin G, ampicillin		Rash Drug fever Diarrhea Leukopenia	Anaphylaxis Bronchospasm Angioedema Electrolyte disturbances Interstitial nephritis
Trimethoprim-sulfamethoxazole		Rash	Erythema multiforme Diarrhea Aplastic anemia Neutropenia Thrombocytopenia
Vancomycin	Phlebitis Severe pain when given IM	"Red man" syndrome "Pain and spasm" syndrome Hypotension Anaphylaxis Nephrotoxicity Ototoxicity	Neutropenia

Adapted from Cheng, EY, Nimphius N, Hennen ER: Antibiotic therapy and the anesthesiologist. *J Clin Anesth* 7:425-439, 1995.

administration, the sensitized mast cells release histamine, leukotriene C_4, and prostaglandin D_2. Cytokines such as tumor necrosis factor–alpha and interleukins 4, 5, 6, 8, and 13 may amplify the type-I hypersensitivity reaction as the inflammatory cascade escalates. Cytotoxic T cells may play a part in the pathogenesis of the morbilliform rash. Serum β-tryptase levels, a marker of IgE-crosslinked mast-cell degranulation, should be performed 1 to 2 hours after the onset of the reaction. Total serum tryptase levels (α-protryptase and β-tryptase) above 25 μg/L, an increase of 2 ng/mL or 135% above baseline levels, and a ratio or peak total tryptase to peak β-tryptase greater than 10 are suggestive of IgE-mediated anaphylaxis. Another blood sample should be drawn for comparison at least 2 days after the initial draw because the expectation is that levels will return to baseline values within 12 to 14 hours.

Management options should be tailored to the presenting symptoms and include the following:

- Discontinue the vancomycin infusion
- Administer epinephrine promptly at an initial dose of 10 to 200 μg depending on the severity of the reaction
- Administer an IV fluid bolus
- Discontinue or decrease concentrations of other agents capable of inducing hypotension
- Administer H_1 antihistamines (e.g., diphenhydramine) and H_2 antihistamines (e.g., ranitidine) for urticaria and angioedema
- Consider inhaled β-agonists if bronchospasm is present
- Consider corticosteroids to mitigate bronchospasm and prevent late-phase shock
- Initiate advanced cardiac life-support maneuvers in case of cardiac arrest
- Follow up with an allergist for skin tests (the prick test and intradermal test; the serum-specific IgE and radioallergosorbent test is less sensitive)
- Document transparently in the patient's medical history, and discuss with the patient

MANAGEMENT

In the differential diagnosis of profound hypotension after vancomycin administration, anesthesiologists must distinguish between RMS and anaphylaxis because differences in their respective management can affect patient outcomes. RMS is the more common syndrome, having been reported in 14% of children and 80% to 90% of volunteers administered 1 g of vancomycin over 1 hour.

BOX 82.1 Signs of Intraoperative Anaphylaxis/Vancomycin Adverse Effects/Histamine Inducers

Signs of Intraoperative Anaphylaxis
Hypotension
Bronchospasm
Tachycardia (may be masked by β-blocker administration)
Cardiovascular collapse
Erythema
Angioedema

Vancomycin Adverse Effects
Linear immunoglobulin A (IgA) bullous dermatosis
DRESS[a] syndrome
Nephrotoxicity
Ototoxicity
Neutropenia
Agranulocytosis
Thrombocytopenia
Phlebitis
Immune thrombocytopenia

Histamine Inducers
Antibiotics (i.e., ciprofloxacin, vancomycin)
Barbiturates
Morphine or meperidine
Pancuronium or atracurium
Succinylcholine benzylisoquinolinium compounds
Plasma expanders (i.e., dextran, polygeline [Haemaccel])
Radiocontrast agents

[a]Drug rash with eosinophilia and systemic symptoms.

In general, the risk of hypotension related to RMS is greater when vancomycin and a volatile anesthetic are administered concurrently (i.e., vancomycin infusion after anesthetic induction) because both agents can potentially depress blood pressure. Additionally, hypotension during vancomycin infusion related to RMS is more common in anesthetized patients than nonanesthetized patients. Interestingly, bacteremia, critical-care status, malignancy, and diabetes mellitus may diminish the rate and severity of cardiovascular side effects, which is explained in part by depletion of histamine from previous liberation in response to illness, perioperative stress, and protamine administration. Comparatively, perioperative anaphylaxis is a rarely occurring event but is associated with a mortality rate of up to 9%. Approximately 70% of all hypersensitivity reactions that occur during anesthesia are IgE mediated. As the first-line agent in type-I hypersensitivity reactions, epinephrine stabilizes mast cells, inhibits histamine release, and reduces histamine-related vasodilation and capillary permeability. For patients with severe hypotension related to RMS, epinephrine is appropriate for cardiovascular support.

PREVENTION

In patients with a history of RMS or type-I hypersensitivity reactions to vancomycin, using alternative antibiotics is the first choice for prevention of these reactions. Quinupristin/dalfopristin is a macrolide-lincosamide-streptogramin that is bactericidal vitro against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis*. It can be used in adults to treat complicated skin and skin-structure infections caused by *Staphylococcus aureus* (methicillin susceptible) or *Streptococcus pyogenes*. Linezolid, an oxazolidinone, is active against streptococci, vancomycin-resistant enterococci, and methicillin-resistant MRSA. There is evidence that it is more effective than vancomycin for treating patients with skin and soft-tissue infections, including those attributed to MRSA.

For patients requiring vancomycin, who experience severe RMS or present with anaphylaxis, protocols for vancomycin desensitization have been developed to allow this patient population to safely receive IV vancomycin. This treatment revolves around gradual desensitization of mast cells to vancomycin by gradually increasing the serum concentration of this antibiotic and can be accomplished in a short interval of 24 hours for acutely ill patients. This preventive protocol is, of course, reserved for patients in duress and requires planning before the day of surgery if operative prophylactic vancomycin administration is envisioned. The protocol must be repeated with every vancomycin infusion and include the use of antihistamines and corticosteroids. There is some evidence that the combination of H_1 and H_2 is preferred over H_1 alone in the prevention and treatment of the histamine release in these patients. Vancomycin may be safely administered to patients in the perioperative period before or after the induction of anesthesia. Prudent anesthesiologists will attempt to follow recommendations regarding the duration of infusion of vancomycin, especially in patients with greater risk (e.g., children) or patients who poorly tolerate even mild hypotension (e.g., those with aortic stenosis), and be aware of the drug's other adverse effects (see Box 82.1). Hemodynamic depression requires prompt detection and treatment to avoid potentially life-threatening cardiovascular collapse.

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Antiemetics

Mahmoud I. Wagih

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Case Synopsis

A 30-year-old female patient was scheduled for hysteroscopy as a day-case procedure. She has no past medical history of relevance. Metoclopramide 10 mg and ondansetron 4 mg were administered followed by propofol/fentanyl via intravenous induction and sevoflurane for maintenance of anesthesia. Postoperatively she had intractable vomiting that delayed her discharge from the postanesthesia care unit and was only controlled through the use of a combination of around-the-clock antiemetics for the following 48 hours, resulting in unplanned hospital admission.

PROBLEM ANALYSIS

Definition

One in three patients suffers postoperative nausea and vomiting (PONV). The incidence is higher for certain procedures (45% of gynecologic procedures and 80% in high-risk groups). PONV is rated by most surgical patients as the worst aspect of their perioperative experience (pain was second on the list). In the era of day-case surgery, the logistic and financial implications of unplanned overnight stay/readmission caused by severe PONV can be significant. Approaches to prophylactic and therapeutic measures are both inconsistent and of varying effectiveness.

Recognition

Nonanesthetic factors, such as mechanical bowel obstruction, pharmacologic agents, and increased intracranial pressure, can cause nausea and/or vomiting in the perioperative period. These factors should be considered independently as their pathophysiology and therapeutic approach are different.

Prevention and control of PONV has both prophylactic and therapeutic aspects and entails pharmacologic and nonpharmacologic measures. Almost all antiemetics are receptor agonists/antagonists that act centrally (and peripherally in case of metoclopramide).

Understanding their mechanism of action is crucial to appreciating the repertoire of their side effects.

Risk Assessment

Recent literature review has changed the perception of "traditional" risk factors for PONV.

Patient-Related Factors

Strong association exists between the patient age group (<50 years, >3 years) and PONV. There is sufficient evidence to indicate that female sex and history of PONV are considerable risk factors. The risk is reduced in smokers.

Historically, a number of factors were perceived to be significant contributors to the risk of PONV. Recent literature reviews have shed doubt on them, such as American Society of Anesthesiologists physical status, duration of perioperative fasting, use of nasogastric tube, early enteral intake/duration of fasting, anxiety, migraine, body mass index, and menstrual cycle phase.

Surgical Factors

Abdominopelvic surgery is associated with a significant risk of PONV (cholecystectomy, gynecologic and laparoscopic procedures).

In pediatric patients, strabismus surgery is associated with the highest risk, as well as procedures lasting more than 30 minutes. There is limited or no evidence for other procedures as independent risk factors.

Anesthesia-Related Factors

Strong association exists between general anesthesia (and its duration and depth) and PONV. Volatile agents, opioids, and nitrous oxide were identified early in anesthetic practice as offending agents. Despite the general perception, the level of experience of the anesthetist and the use of neuromuscular reversal agents are not associated with PONV.

MANAGEMENT

Considering the range of side effects of antiemetics (from headache to case records of torsade de pointes) and the consequences of PONV (poor patient satisfaction, unplanned admissions, and medical complications), a tailored plan of management after deploying an objective risk assessment system is highly recommended.

General Measures to Decrease Baseline Risk of PONV

Early identification of high-risk patients is mandatory. Different health systems have adopted scoring methods to ratify the risk of PONV.

Avoidance of general anesthesia (GA) and the established offending agents is a practical prophylactic approach. Total intravenous anesthesia is a sensible choice in patients with a history of severe PONV. If GA is a must, propofol offers advantages as an induction agent. The use of nitrous oxide is slowly declining, especially with a greater percentage of procedures performed as day-case surgery where PONV can significantly complicate a patient's care. Opioid-sparing techniques using other modes of analgesia are becoming standard practice. Examples include regional techniques, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and medications classically used for treatment of neuropathic pain. Good hydration and prompt treatment of hypotension are not only good standards of care; both can significantly reduce the risk of PONV. The debate is still ongoing regarding the routine use of prophylactic antiemetics. The implications for the patients and the health system have to be balanced against the incidence of side effects and the feasibility/affordability. The evidence for prophylactic agents is that efficacy is similar among the commonly used agents, and combination therapy is more effective than single-agent therapy.

Interventional Measures

Although low-risk patients may not require any measures beyond those listed previously, high-risk patients would benefit from prophylactic measures, and both groups will require an antiemetic strategy as part of their perioperative care plan.

A summary of the characteristics of different antiemetic groups follows.

Serotonin (5-HT_3) Receptor Antagonists

This group includes ondansetron, dolasetron, granisetron, tropisetron, ramosetron, and palonosetron. They are generally more effective against vomiting than nausea, so to maximize their effectiveness they are better administered at the end of surgery. They have a range of side effects such as headache, elevated liver enzymes, constipation, and prolonged QT interval (dose related). Few case records of clinically significant arrhythmias were linked to 5-HT_3 receptor antagonists. Overall the low incidence of side effects led to their widespread use. Dolasetron is no longer available in the United States.

Neurokinin-1 Receptor Antagonists

These agents are the newest group of antiemetics to find a niche in anesthesia after their introduction for chemotherapy-induced nausea and vomiting. The well-established members are aprepitant, casopitant, and rolapitant.

They have an extended duration of action (48 to 72 hours) so can be used on induction of anesthesia. Their side effects are relatively mild and include dizziness, weakness, and nonspecific mild symptoms. No cardiovascular side effects have been documented.

Corticosteroids

Both dexamethasone and methylprednisolone have been used for managing PONV. Considering their pharmacokinetic profile—mainly their duration of action—they are to be used after induction of anesthesia, and no further doses are recommended if the initial dose is ineffective. Recent studies suggest that higher doses of dexamethasone (8 mg) are more effective. Positive effects on quality of recovery (including quality of pain control) have been documented.

The side effects of their short-term use are limited. Phosphate preparation causes severe perineal itching and pain (50% of patients, females greater than males). Dexamethasone causes an increase in blood glucose 6 to12 hours after a single dose, making it relatively contraindicated in labile diabetic patients.

Butyrophenones

Droperidol and haloperidol are the two main butyrophenones used for PONV management. They are effective when used at the end of surgery. Because of the side-effect profile, they are recommended as rescue therapy only.

Prolongation of QT interval in a pattern and to an extent similar to ondansetron is the most serious side effect (2001 droperidol black box warning by the Food and Drug Administration [FDA]). Sedation occurs in the higher range of doses. Haloperidol has a lower incidence of prolonged QT interval, but its use for PONV is not an FDA-approved indication.

Antihistamines

Dimenhydrinate, meclizine, and cyclizine (United Kingdom) are established feasible antiemetics. There is no consensus regarding the optimum time for their administration. Their side effects are related to their anticholinergic properties (tachycardia, blurred vision, hallucinations, and occasionally urinary retention), especially in the elderly. Sedation is another common side effect.

Anticholinergics

Transdermal scopolamine is the main agent in this category. The patch is effective for up to 24 hours. It can be applied the night before surgery or on the same day. Its side effects are generally mild and include visual disturbances and dizziness.

Antidopaminergics

Phenothiazines such as prochlorperazine and perphenazine are no longer used as antipsychotics. Their use for PONV should be in combination with other agents or as rescue therapy considering the potential serious (and dose-related) side effects. Sedation is comparable to a placebo when used within the recommended dose for PONV. They are also associated with a low incidence of neuroleptic malignant syndrome and anticholinergic side effects.

Metoclopramide

Recent evidence shows poor effectiveness of metoclopramide within the therapeutic dose (10 mg). Effectiveness improves when the dose is increased to 30 mg but still below that of other drug groups. Unfortunately, the incidence of extrapyramidal side effects increases significantly with higher doses (number needed to harm 140).

Acupuncture

Recent literature review has shown that P-6 stimulation using different modalities of acupuncture was associated with lower incidence of PONV and less need for rescue therapy. This effect was maintained both in adults and children and in invasive and noninvasive approaches to acupuncture and was not dependent on the timing of stimulation. Neuromuscular stimulation of the median nerve (particularly in the tetanic mode) has shown similar efficacy.

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84 Antihistamines: H_1- and H_2-Blockers

Michael Feduska

Case Synopsis

A 90-year-old man with a past medical history of multiinfarct dementia presented with hematuria and is found to be confused and agitated in the postanesthesia care unit after cystourethroscopy. The patient received midazolam preoperatively, fentanyl and propofol on induction, and 50 mg of diphenhydramine after an episode of erythema.

PROBLEM ANALYSIS

Definition

The antihistamine drug class can be divided into four separate types based on interaction with four known receptor subtypes (H_1, H_2, H_3, H_4). H_1- and H_2-receptor antagonists or "blockers" are in fact inverse agonists that shift equilibrium of the receptor-drug complex toward inactivity. Histamine receptors are located at multiple sites, including smooth muscle, exocrine glands, and the central nervous system (CNS). First-generation H_1 antihistamines have additional activity at muscarinic receptors, α-adrenergic receptors, and serotonergic receptors. Primary uses for H_1 antihistamines include treatment of allergic rhinitis, allergic conjunctivitis, and urticaria; prevention of hypersensitivity reactions; treatment of motion sickness; and as a sleep aid.

The H_1 antihistamine class was modified to increase H_1 specificity and to limit adverse effects. Second-generation H_1 antihistamines do not cause anticholinergic symptoms to the same degree as their predecessor and have a limited ability to cross the blood-brain barrier, thus attenuating CNS effects. The second-generation H_1 antihistamines are now the preferred treatment for allergic symptoms.

Histamine-stimulated release of gastric acid is unchanged by H_1-receptor activity. The absence of this reaction led to the discovery of the H_2-receptor subtype and the development of H_2 antihistamines. H_2 antihistamines act to prevent histamine release from enterochromaffin cells in the stomach, which halts parietal cell secretion of gastric acid. H_2 antihistamines provide treatment for patients with mild peptic ulcer disease, gastroesophageal reflux disease, and stress ulcer prophylaxis (Table 84.1).

TABLE 84.1 Commonly Encountered Antihistamines

First-Generation H_1 Antihistamines	Second-Generation H_1 Antihistamines	H_2 Antihistamines
Dimenhydrinate	Cetirizine	Cimetidine
Diphenhydramine	Desloratadine	Famotidine
Doxylamine	Fexofenadine	Ranitidine
Hydroxyzine	Levocetirizine	Nizatidine
Meclizine	Loratadine	Rupatadine
Promethazine		

Recognition

Anticholinergic effects predominate in the first-generation H_1 antihistamines due to their action at muscarinic receptors. Symptoms of anticholinergic activity include mydriasis, CNS disturbances, erythema, hyperpyrexia, and urinary retention. The anticholinergic toxidrome can be recalled by the mnemonic "blind as a bat, mad as a hatter, red as a beet, hot as a hare, dry as a bone." Mild CNS changes can occur with therapeutic doses leading to sedation, impaired cognition, and hyperexcitability with confusion and combativeness (particularly in pediatric patients). Dystonia has been reported after administration of therapeutic doses of diphenhydramine. CNS effects and anticholinergic effects occur in first-generation H_1 antihistamines to a much greater degree than in second-generation medications.

The severity of symptoms varies with dosage, but toxic thresholds are not well defined by the literature. First-generation H_1 antihistamine overdose is encountered when used in suicide attempts or when used as a recreational drug. These patients may present with agitation or hallucinations followed by seizures, coma, respiratory depression, rhabdomyolysis, and cardiac arrhythmias.

H_2 antihistamine side-effect symptoms include diarrhea, constipation, myalgia, and drowsiness. CNS changes such as delirium and hallucinations have been noted with intravenous administration of H_2 antagonists in geriatric populations. Hypotension may occur with rapid intravenous administration (Table 84.2).

Risk Assessment and Implications

When evaluating causes of postoperative agitation, administration of H_1 antihistamines must be considered along with the patient's baseline mental status, daily medication regimen, intraoperative medications, and procedural risk factors. Treatment of postoperative nausea and vomiting, urticaria, or mild allergic reactions with promethazine or diphenhydramine may prolong cognitive recovery, compounding the effects of other amnestic agents. Pediatric patients, geriatric patients, and patients with hepatic or renal dysfunction are at increased risk for CNS changes. Urine output and fluid input should be carefully monitored in the perioperative period. Postoperative urinary retention has multifactorial causes with contributions from patient pathology, the operative procedure, and medications.

TABLE 84.2 Adverse Reactions to Antihistamines

Reaction	First-Generation H_1 Antihistamines	Second-Generation H_1 Antihistamines	H_2 Antihistamines
Cardiovascular	Tachycardia, prolonged QT, hypotension	N/A	Hypotension, AV block, bradycardia
Central nervous system	Sedation, confusion, seizures, dystonia, mydriasis, coma	Minimal cognitive effects	Drowsiness, headache, delirium
Pulmonary	N/A	N/A	Increased incidence of pneumonia
Gastrointestinal/metabolic	Diarrhea, nausea/vomiting, constipation, weight gain, fever	Diarrhea, nausea/vomiting, constipation	Diarrhea, constipation, elevated LFTs, hepatitis
Genitourinary	Urinary retention	Minimal effects	Impotence
Hematologic	N/A	N/A	Pancytopenia, thrombocytopenia, agranulocytosis

AV, Atrioventricular; *LFTs,* liver function tests.

QT prolongation can occur with many first-generation H_1 antihistamines and may precipitate torsades de pointes. Diphenhydramine is associated with sodium channel blockade resulting in reduction of phase 0 of the cardiac action potential precipitating wide complex tachycardia.

The second-generation H_1 antihistamines are considered "nonsedating" with less pronounced CNS and negligible anticholinergic side effects. Care should be taken to monitor for cognitive impairment, particularly when used in combination with medications with similar side-effect profiles, such as monoamine oxidase inhibitors and tricyclic antidepressants. Second-generation H_1 overdose is not linked to the severe CNS effects and cardiac toxicity seen with first-generation medications.

The H_2 antagonists cimetidine and, to a lesser degree, ranitidine are prone to drug-drug interactions via CYP enzyme inhibition. Cimetidine causes weak inhibition in cytochrome P450 (CYP3A4), which causes increased plasma levels of P450-metabolized drugs (warfarin, phenytoin, theophylline, valproic acid). Rare cases of thrombocytopenia, pancytopenia, and agranulocytosis have been associated with H_2 medications.

MANAGEMENT

Management of anticholinergic effects in H_1 antagonists will be aimed at symptomatic relief. A bladder ultrasound may be necessary to delineate urinary retention from other causes of decreased output. Straight catheterization should be attempted initially, and a Foley catheter should be placed in the event of recurrent retention. A urology consultation may be warranted.

Postoperative delirium can be managed with frequent reorientation, one-to-one monitoring, and family contact when appropriate. Benzodiazepam drugs may be used for treatment of agitation, but should be avoided in any population at risk for a paradoxic response. Haloperidol can be used after an evaluation of the QT interval by 12-lead electrocardiogram (ECG) before administration.

Cardiac arrhythmias should be evaluated by a 12-lead ECG and treated using the advanced cardiac life-support protocol. Treatment of diphenhydramine-induced wide complex tachycardia with sodium bicarbonate has been successful.

Though rare, thrombocytopenia and pancytopenia have been associated with famotidine, particularly in the intensive care unit setting. The H_2 antihistamine class association with thrombocytopenia may warrant monitoring of the patient's platelet count.

PREVENTION

Prevention of side effects from this drug class is best achieved by avoiding at-risk patient populations. Limiting the dosage in patients with renal or liver dysfunction, preexisting mental deficits, and extremes of age is prudent if the medication is deemed necessary.

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85 Autonomic Hyperreflexia

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Case Synopsis

A 34-year-old male veteran who sustained a complete spinal cord injury at C5 during combat 10 years ago underwent a cystoscopy with ureteral stent placement under conscious sedation. During the procedure the patient became hypertensive to 260/120 mm Hg and bradycardic with a heart rate of 42 beats per minute. He complained of headaches and blurred vision and started becoming agitated and confused.

PROBLEM ANALYSIS

Definition

Autonomic hyperreflexia, also known as autonomic dysreflexia, is a clinical syndrome associated with cervical and thoracic spinal cord injuries (SCIs). Autonomic hyperreflexia episodes are usually characterized by an acute, and often dramatic, increase in blood pressure in association with a stimulus below the level of the spinal cord lesion. This elevation in blood pressure can be accompanied by bradycardia or (more rarely) tachycardia. The clinical criteria for an autonomic hyperreflexia episode includes an increase from baseline systolic blood pressure of at least 20% associated with at least one of the following symptoms: sweating, chills, goose bumps, flushing, or headache. Intensity of an autonomic hyperreflexia episode can vary from asymptomatic to a life-threating hypertensive emergency. During an episode of autonomic hyperreflexia, an offending stimulus below the level of the spinal cord lesion leads to sympathetic nervous system activation that is no longer opposed by inhibitory descending parasympathetic pathways, as occurs in patients without SCI. This sympathetic activation below the SCI lesion leads to extensive vasoconstriction of the peripheral circulation and of the splanchnic vasculature that accounts for the majority of the vascular capacitance in humans. It also causes mild to malignant elevations in blood pressure.

An autonomic hyperreflexia episode can be triggered by activation of pain fibers below the level of the spinal cord lesion whether the patient has sensation or not. Such stimuli can include distention or contraction of hollow organs such as bowel or bladder, with bladder distention being the most common cause of autonomic hyperreflexia episodes overall. Gastroesophageal reflux, gastritis, gallstones, fecal impaction, hemorrhoids, obstruction or manipulation of indwelling urinary catheters, urologic procedures, pregnancy, childbirth, and surgical procedures have all been implicated in triggering autonomic hyperreflexia. Other triggering events can include spasms, temperature alterations, sexual intercourse, bone fractures, or hip dislocation.

Recognition

Increased muscle tone, spasms, and pilomotor erection indicative of increased sympathetic activity may be observed below the SCI level. Above the spinal cord lesion, patients can have flushing and sweating of the skin, nasal congestion, headache, and bradycardia or other arrhythmias. These symptoms are caused by the activation of the parasympathetic nervous system after baroreceptors in the aortic arch or carotid sinus that are cephalad to the SCI lesion sense a rise in blood pressure. The parasympathetic system then counteracts the sympathetic-driven vasoconstriction below the SCI level by causing vasodilation above this level. Symptoms of an episode of autonomic hyperreflexia can range from asymptomatic to severe. More ominous symptoms and signs may include dyspnea and chest pain from the acute left ventricular afterload, as well as blurred vision, headaches, and confusion signaling that the upper limit of cerebral autoregulation has been surpassed and that the cerebral vasculature can no longer compensate for this acute rise in blood pressure (Box 85.1).

Risk Assessment

Awareness of the risk of autonomic hyperreflexia when caring for surgical patients with SCI is paramount to a safe and effective anesthetic. Despite the fact that many patients will have little or no sensation below their SCI, surgery or instrumentation can still lead to an episode of autonomic hyperreflexia. Episodes usually take place during the chronic stage of SCI, which tends to be greater than 1 month after the SCI occurs but may occur as early as a few weeks after injury. Autonomic hyperreflexia typically occurs in patients with spinal cord lesions at or above the level of T6 because the vast majority of sympathetic efferents arise below T5–T6. Approximately 20% to 70% of SCI patients with lesions at or above T6 have been estimated to exhibit autonomic hyperreflexia. Episodes are more likely in patients with complete spinal cord lesions compared with incomplete lesions, and more severe reactions tend to occur in patients with a higher level of SCI. An SCI level below T10 is unlikely to exhibit autonomic hyperreflexia because there are very few sympathetic efferents below this level.

Surgical site is important as urologic procedures with distention of the bladder are one of the most common triggers. Surgical sites above the level of the SCI lesion have a relatively low risk of autonomic hyperreflexia from the procedure itself, but other triggers such as an obstructed urinary catheter or other stimuli below the SCI lesion may precipitate an episode. Uterine contractions during labor can elicit intense sympathetic outflow, making this group of patients at high risk as well.

BOX 85.1 Signs, Symptoms, and Sequelae of an Autonomic Hyperreflexia Episode

Signs Below the Spinal Cord Injury Level
Pilomotor erection
Blanching
Spasms

Signs and Symptoms Above the Spinal Cord Injury Level and Sequelae
Nausea
Sweating
Chills
Headache
Nasal congestion
Flushing
Dyspnea
Confusion
Blurred vision
Chest pain
Hypertension (systolic blood pressure >20% from baseline)
Bradycardia
Tachycardia
Arrhythmias
Asystole
Conduction
Ischemic electrocardiogram changes
Seizures
Hypertensive encephalopathy
Hemorrhagic or ischemic stroke
Myocardial infarction
Acute left ventricular failure
Pulmonary edema

Implications

Blood pressure elevations can be life threatening, and if not treated promptly can lead to seizures, myocardial infarction or acute left ventricular failure with pulmonary edema from massive afterload, hypertensive encephalopathy, hemorrhagic or ischemic stroke, or death. Autonomic hyperreflexia episodes during labor or delivery endanger the fetus and the mother as the intense vasoconstriction may cause uteroplacental insufficiency and fetal hypoxia.

MANAGEMENT

The best practice for prompt management of an episode of autonomic hyperreflexia requires recognition of the risk of an episode so that appropriate preventive measures can be taken, a heightened alertness for symptoms and signs of an episode is established with all health care providers, and appropriate nonpharmacologic maneuvers and pharmacologic treatments are readily available.

Nonpharmacologic Management

The first line of treatment for an episode of autonomic hyperreflexia should be the identification and removal of the triggering stimulus. If the triggering stimulus is thought to be the surgical manipulation and the blood pressure has reached dangerous levels, having the surgeons pause (e.g., drain the bladder during a cystoscopy) while the anesthetic is deepened and blood pressure control can be obtained is recommended if possible. Placing the patient in an upright position can increase venous pooling and cause an orthostatic decrease in blood pressure. This may not be possible in the operating room, but may be an effective nonpharmacologic treatment in the recovery room. Removing constrictive devices or binders can also lower blood pressure by the same mechanism. However, these maneuvers may be minimally successful, and pharmacologic treatment for malignant hypertension should not be delayed while these attempts are made. When the triggering stimulus cannot be identified or the blood pressure remains elevated despite its removal, pharmacologic therapy with antihypertensive medications should be initiated.

Pharmacologic Management

Pharmacologic management of blood pressure may be needed when trigger elimination, deepening the anesthetic, and nonpharmacologic maneuvers fail to reduce blood pressure or when a trigger cannot be identified. Antihypertensive medications used to treat autonomic hyperreflexia–induced blood pressure elevations should ideally have quick onset and short duration of action. Medications that fit this profile and that are usually readily available in the operating room include nitrates, esmolol, and nicardipine. Nitrates have multiple modes of administration (intravenous, sublingual, translingual spray, and transdermal). Nitrates also have a quick onset and short duration of action and are ideally suited to be given to an awake or an anesthetized patient. However, nitrates, when combined with sildenafil, can cause protracted decreases in systemic blood pressure and even decrease coronary blood flow in at-risk vessels. Given this, one should rule out sildenafil use before administration of nitrates. Nicardipine and esmolol have quick onset and short duration of action; however, caution should be advised when giving β-blockers as they can worsen bradycardia associated with autonomic hyperreflexia. Other antihypertensive medications that are usually readily available in the operating room are labetalol and hydralazine. Both medications are longer acting and can lead to hypotension when the triggering stimulus is removed. Furthermore, the same issues with worsening bradycardia can occur with labetalol, and caution should be advised. Regardless of which medication is chosen, one should have choices immediately available so that treatment of hypertension is not delayed.

PREVENTION

As many as 90% of patients with SCI undergoing surgery with topical or no anesthesia develop autonomic hyperreflexia. A study of patients with SCI above T7 examined blood pressures during surgery. The patients who received sedation, topical anesthesia, or no anesthesia had, on average, significantly higher intraoperative blood pressure than baseline. Those patients who received general anesthesia had no significant change in blood pressure intraoperatively, whereas those who received spinal anesthesia had significantly lower intraoperative blood pressures compared with baseline. Furthermore, 79% of patients who were given sedation, topical anesthesia, or no anesthesia had hypertensive episodes, whereas only 23% of patients given general anesthesia and 7% of patients given spinal anesthesia had hypertensive episodes intraoperatively. Though regional anesthesia is superior to general anesthesia for preventing an episode of autonomic hyperreflexia, it is difficult to assess the level of blockade in SCI patients, and prior spinal instrumentation may make neuraxial anesthesia difficult.

Every attempt should be made to ensure adequate depth of anesthesia, whether general or neuraxial/peripheral blockade, and to ensure that pain control is satisfactory in the perioperative period. If an episode of autonomic hyperreflexia is triggered by surgical stimulation, deepening the anesthetic with volatile anesthetics, opioids, and/or propofol may

be helpful. If the patient has an epidural or peripheral nerve catheter, it can be bolused with local anesthetic. However, conversion to a general anesthetic may be needed to alleviate the episode of autonomic hyperreflexia if the additional local anesthetic is unsuccessful.

Advances in medical and rehabilitative science have enabled more women with SCI to become pregnant and deliver babies. Many of these women will be at risk for autonomic hyperreflexia during labor and delivery, whether spontaneous vaginal, instrumented, or cesarean section, and can be managed with spinal, epidural, or general anesthesia. When spinal or epidural anesthesia is used for labor, an anesthetic level extending to at least the T10 level can block stimuli that arise from pelvic organs and is thought to be the most reliable way of preventing autonomic hyperreflexia. Continual blood pressure and electrocardiogram monitoring is recommended for parturients with high SCI levels. Direct arterial blood pressure monitoring may be indicated for specific high-risk patients or those with certain coexisting diseases. Continuing the neuraxial anesthetic into the early postpartum phase is important as uterine contractions will continue after delivery.

Emergence and Postoperative Management

Emergence from general anesthesia should occur in the usual fashion, and extubation should occur when those criteria are met. Procedures done under regional or neuraxial anesthesia can proceed to the recovery room when the procedure finishes. Blood pressure should be monitored frequently in the postoperative period regardless of anesthetic type, as autonomic hyperreflexia can be triggered when the effects of general and/or local anesthesia subside. Continuous epidural or peripheral nerve catheters may be needed for several days postoperatively to avoid triggering an episode of autonomic hyperreflexia. Informing all perioperative team members of the risk of autonomic hyperreflexia will allow those caring for these patients to be vigilant and potentially recognize and treat episodes of autonomic hyperreflexia, or even prevent them from occurring.

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Further Reading

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Barbiturates: Porphyrias

86

Nicolas N. Algarra • Christoph N. Seubert

Case Synopsis

An anxious 24-year-old woman presents with nausea, vomiting, and abdominal pain and is scheduled for exploratory laparotomy. Past history is remarkable for a negative exploratory laparotomy 2 years ago. Blood pressure is 150/90 mm Hg, and pulse is 105 beats per minute; the physical examination reveals abdominal tenderness. Electrolyte levels and white blood cell count are normal. With direct questioning about family history, the patient declares that her mother may have had porphyria.

PROBLEM ANALYSIS

Definition

A good understanding of the basic deficiency and interaction with anesthesia and the stresses of surgery can prevent an acute attack in susceptible patients with inducible porphyria.

Porphyrias are a heterogeneous group of genetic disorders where a deficiency in an enzyme combined with environmental stresses can produce an acute attack and accumulation of intermediary products of heme synthesis that can cause mild to life-threatening symptoms. Although porphyrias can be classified on the basis of the underlying genetic defect (Fig. 86.1), the simple clinical division into inducible/acute and noninducible/chronic forms remains useful. An example of the latter is porphyria cutanea tarda (PCT), the most frequent form of porphyria. Apart from the friability of the patient's skin and the association with hepatitis C, human immunodeficiency virus, or alcohol abuse, PCT presents no anesthetic concerns and does not restrict the choice of drugs. In contrast, all patients with acute/inducible porphyrias are at risk of porphyric crisis, particularly in the perioperative period. Drugs administered in the perioperative period, the condition requiring surgery, stress, and/or fasting may precipitate acute attacks of porphyria. If the attack goes untreated or unrecognized, it can be fatal. Conversely, control of precipitating factors and/or prompt treatment averts or mitigates the attack and allows the safe conduct of surgery. Therefore acute porphyrias present important anesthetic concerns.

Porphyrin synthesis occurs in all cells and is of particular importance in bone marrow and the liver. Porphyrins are essential components of proteins involved in the utilization, transport, and storage of oxygen. These proteins include the ubiquitous cytochrome oxidases of the respiratory chain, the hepatic cytochrome P450 enzymes, and oxygen storage and transport proteins such as hemoglobin. Synthesis of porphyrins involves a series of enzymes (see Fig. 86.1). Genes for key enzymes of porphyrin synthesis are duplicated in the genome, allowing for the separate regulation of heme synthesis in the liver and bone marrow. In the liver, most heme is used for the production of cytochrome P450 enzymes. Therefore regulation of heme synthesis and P450 production are regulated in a coordinated fashion.

The four acute porphyrias are acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and δ-aminolevulinic acid dehydratase–deficient porphyria (ADP). The gene defects that underlie the acute porphyrias are loss-of-function mutations and typically reduce enzyme activity by half. This reduction results from a pattern of inheritance that is recessive for the rare ADP or dominant with variable penetrance for the three more frequent acute porphyrias (Table 86.1). Although the location of the defective hepatic enzyme in the synthetic pathway for heme varies among the acute porphyrias (see Fig. 86.1), all four

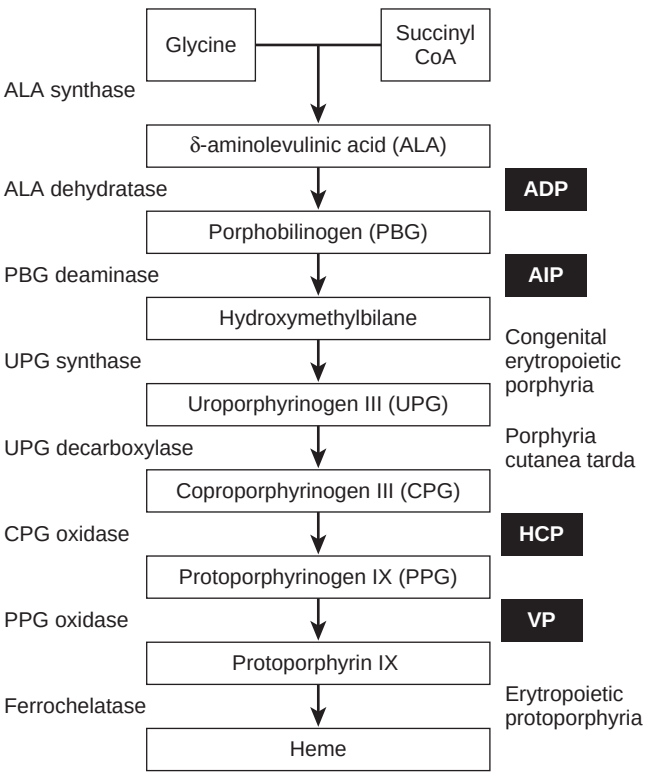

Fig. 86.1 The human heme biosynthetic pathway. The enzymes that catalyze the steps are denoted on the left, and the porphyria that results from a defective enzyme is denoted on the right. Acute porphyrias are highlighted by a black box. *ADP,* δ-aminolevulinic acid dehydratase–deficient porphyria; *AIP,* acute intermittent porphyria; *HCP,* hereditary coproporphyria; *VP,* variegate porphyria.

TABLE 86.1 Acute/Inducible Porphyrias

Porphyria	Incidence	Inheritance	Neurovisceral Symptoms	Photosensitivity
δ-Aminolevulinic acid dehydratase–deficient porphyria (ADP)	Exceedingly rare	Autosomal recessive	++	–
Acute intermittent porphyria (AIP)	1:10,000 Higher in Scandinavia	Autosomal dominant	+++	–
Hereditary coproporphyria (HCP)	Rare 1:1,000,000	Autosomal dominant	++	+
Variegate porphyria (VP)	1:300,000 Higher in South Africa	Autosomal dominant	++	+

TABLE 86.2 Symptoms of a Porphyric Crisis

		SYMPTOMS
Peripheral nervous system	Sensory	Abdominal pain
	Motor	Proximally accentuated weakness, may involve cranial nerves and respiratory muscles
	Autonomic	Tachycardia Hypertension
Central nervous system	Psychiatric	Anxiety Hallucinations Paranoia
	Endocrine	SIADH
	Neurologic	Seizures
Miscellaneous	Nausea/vomiting Hyponatremia	
Laboratory	Increased ALA and PBG in urine Light-exposed urine turns dark red/pink	

ALA, δ-aminolevulinic acid; *PBG*, porphobilinogen; *SIADH*, syndrome of inappropriate secretion of antidiuretic hormone.

may present with acute attacks that are similar in symptoms and treatment. It is unclear why enzymatic defects in chronic or erythropoietic porphyrias do not lead to acute attacks. HCP and VP may cause accumulation of excess porphyrins in the skin, where excitation by ultraviolet light causes blistering and scarring skin lesions.

Recognition

Because symptoms can be nonspecific and varied, acute attacks of inducible porphyrias are difficult to recognize in the perioperative period. Typical symptoms and frequency of occurrence are summarized in Table 86.2. Attacks rarely occur before puberty and seldom recur throughout adult life. They last for several days and are characterized by intense, steady, and poorly localized abdominal pain. The intensity of the pain contrasts sharply with the paucity of physical findings, sometimes resulting in emergent exploratory laparotomies. Nausea, vomiting, and decreased bowel sounds are common but do not dominate the clinical picture, whereas fever, leukocytosis, and/or abdominal tenderness is usually absent. Acute attacks of inducible porphyrias may involve the peripheral nervous system in the form of a proximally accentuated motor weakness. This weakness occasionally occurs after resolution of the abdominal pain and may resemble Guillain-Barré syndrome without the characteristic albumin increase in cerebrospinal fluid. Cranial nerves and sensory nerves may be affected, and progression of neurologic involvement to respiratory and bulbar paralysis and death is possible. In one-quarter of patients, the central nervous system can also be involved in the form of psychiatric symptoms such as anxiety, hallucinations, and/or paranoia. Generalized seizures may occur as a neurologic manifestation of central nervous system involvement or as a manifestation of severe hyponatremia caused by inappropriate secretion of antidiuretic hormone and/or vomiting. If suspected, the diagnosis of acute porphyria can be confirmed by screening for and quantifying the porphyrin precursors δ-aminolevulinic acid and porphobilinogen in the urine. Daylight can convert the colorless porphobilinogen to porphyrins that cause a darkening and red-to-purple discoloration of the urine. Resolution of symptoms is usually rapid, but weakness may persist for days or months.

In asymptomatic patients, the perioperative diagnosis of acute porphyrias relies on a detailed family history. Because the more frequent forms are all inherited as autosomal dominant diseases, many susceptible patients know of blood relatives with a diagnosis of acute porphyria. In contrast, laboratory investigations may be negative, because the patient's metabolic situation has compensated. Therefore positive interval diagnosis of porphyria belongs in the hands of a specialist. (Information can be found on the American Porphyria Foundation website: http://www.porphyriafoundation.com or the website of the University of Cape Town, South Africa: http://www.porphyria-professionals.uct.ac.za/.)

Risk Assessment

The prevalence of acute porphyrias (see Table 86.1) is difficult to estimate because as many as 80% of affected patients may never experience an acute attack in their lifetime. The prevalence of AIP is estimated to be about 1:10,000 in North America, but may reach 1:1000 in Scandinavia or in people of Scandinavian descent. Clinically, it accounts for three-quarters of acute attacks. VP is less prevalent, except in South Africans of Dutch descent, where more than 20,000 cases have been traced to a single immigrant couple. HCP is rare, with an estimated prevalence of 1:1,000,000. Only seven cases of ADP have been reported.

More important to risk assessment than the prevalence rate is the fact that acute attacks are always multifactorial. Even prior uneventful exposure to porphyrinogenic drugs does not rule out a diagnosis of acute porphyria. Therefore a high index of suspicion is justified if the constellation of symptoms (see Table 86.2) may fit that of an acute attack of porphyria.

Implications

Failure to diagnose and treat an acute attack of porphyria confers a mortality risk of up to 10%. Such failure not only prolongs the attack, but also puts the patient at risk of further morbidity:

- Further upregulation of hepatic heme synthesis because of decreased glucose intake
- Progression of motor involvement to include respiratory muscles and cranial nerves
- Residual paresis that persists even after resolution of the attack
- Seizures, which may be treated with porphyrinogenic drugs

- Exposure to porphyrinogenic drugs for other supportive treatment
- Unwarranted surgery

MANAGEMENT

Perioperative care of patients with porphyria involves more than avoidance of barbiturates. Preoperative assessment should identify whether symptoms of an acute attack are present. In fact, as shown in the case synopsis, surgery may be unwarranted, and medical care should be focused only on treatment of the porphyric crisis. In the absence of an acute attack, the prescription of the anesthetic should consist of nonporphyrinogenic drugs. Details, as well as additional measures to minimize the risk of an acute attack, are discussed later. If the preoperative assessment suggests an acute attack of porphyria, both symptomatic and specific therapies should be instituted in an appropriate inpatient setting.

Acute Attack of Porphyria in the Perioperative Period

Specific therapy for acute attacks of porphyria consists of three interventions: the administration of hematin and glucose (as they both inhibit δ-aminolevulinic acid synthase and thus correct the metabolic abnormality) and identification and removal of the precipitating factor, which decreases enzyme induction. Hematin (Panhematin, Ovation Pharmaceuticals, Deerfield, IL) contains alkaline heme from processed human red blood cells. It is a lyophilized powder that is best reconstituted in albumin to form a stable solution and minimize thrombophlebitis and anticoagulation. Depending on the severity of an attack, hematin is given at a dose of 3 to 4 mg/kg for up to 4 days. Hematin replenishes the hepatic heme pool and normalizes the activity of the heme synthesis pathway by providing negative feedback (see Fig. 86.1). Given the mortality risk and the potential for severe or protracted neurologic symptoms of acute attacks of porphyria, hematin therapy should be initiated as early as possible. Glucose, at a dose of 300 to 400 g/day, is less effective than hematin, but has been shown to decrease the excretion of porphyrin precursors. Furthermore, fasting and low-carbohydrate diets can precipitate acute attacks. Although glucose is effective when administered enterally, the nausea and decreased intestinal motility of an acute attack make parenteral administration more feasible. Identification and removal of precipitating factors should at the very least include a careful assessment of drug therapy (Table 86.3). Given that the causes of an acute attack may be multifactorial, complete removal of precipitating factors may not be attainable.

Supportive therapy should focus on the symptoms that are associated with the attack. Pain should be treated with opiates. Electrolyte imbalances should be corrected. Cranial nerve involvement may require aspiration prophylaxis, whereas involvement of respiratory muscles may require mechanical ventilation or at least close monitoring in an intensive care unit. Seizures present a particular challenge because barbiturates, phenytoin, and some other antiseizure drugs are potent triggers for an acute attack. Hyponatremia should be excluded as a cause, and midazolam or clonazepam can safely be used to stop seizure activity.

Anesthetic Management of Patients With Acute Porphyria

Assessment of the safety profile of drugs in porphyria is difficult. On one hand, drugs are the most frequent precipitating factor of acute attacks; on the other hand, not every exposure of susceptible patients to porphyrinogenic drugs results in such an attack. Information about drug safety in porphyria is derived from the following three sources, listed in order of decreasing clinical applicability: (1) actual human cases that suggest a temporal or causal relationship, (2) animal models of induced porphyria, and (3) cell culture. The latter two sources tend to overstate the risks to patients and are frequently the source of conflicting information. (More detailed drug information and lists of safe and potentially unsafe drugs can be found on the following websites: http://www.drugs-porphyria.org/ and http://www.porphyriafoundation.com/drug-database.) Volatile anesthetics, for example, are porphyrinogenic in animal models, but clinical experience with halothane and isoflurane suggests that their use is safe. Therefore many drugs can be used with caution provided that they are indicated and potential benefits outweigh the risks.

TABLE 86.3 Safety of Drugs in Patients With Acute Porphyria[a]

Unsafe/Avoid	Use With Caution/Avoid	Probably Safe
Barbiturates	Ketorolac	Opiates
Etomidate	Macrolides	Neuromuscular blockers
Phenytoin	Tetracyclines	Glycopyrrolate
Valproic acid	Quinolones	Atropine
Succinimides	Hydralazine	Neostigmine
Pyrazolone	Calcium channel blockers	Naloxone
Clindamycin		Midazolam
Erythromycin		Flumazenil
Doxycyclin		Nitrous oxide
Sulfonamides		Volatile anesthetics
Amiodarone		Local anesthetics
		Procainamide
		β-Blockers
		Scopolamine
		Diphenhydramine
		Phenylephrine
		Ondansetron

[a]*Note:* This list is incomplete. Unlisted drugs cannot be assumed to be safe. The categories are intended to provide guidance and not to replace the clinical judgment of the prescribing physician. Some drugs are categorized based on clinical experience, irrespective of the absence or presence of warnings in the package insert. Porphyrics should be treated with the minimum number of drugs necessary. See text for details.

The anesthetic plan for patients with porphyria should avoid agents that are known to precipitate acute attacks. These are summarized in Table 86.3. Similarly, suitable agents that are considered safe in patients with porphyria should be considered (see Table 86.3). For general anesthesia, propofol can be considered the induction agent of choice, whereas barbiturates and etomidate should be avoided. We do not have sufficient data regarding the safe use of dexmedetomidine in porphyria. Sugammadex has been used successfully during an acute porphyric attack. Muscle relaxants and opioids are safe. Clinically, volatile agents are safe, although data on sevoflurane and desflurane are limited. Local and regional anesthesia can be safely used in patients with porphyria, although during an acute attack, autonomic instability, psychiatric symptoms, weakness, and hypovolemia may present relative contraindications. Clinical experience suggests that both amide- and ester-type local anesthetics are safe, even though lidocaine increases δ-aminolevulinic acid synthase activity in tissue culture.

PREVENTION

Perioperative prevention of acute attacks in patients with acute porphyria requires careful planning and good communication among

all caregivers. Admission on the night before surgery allows prophylactic administration of glucose, thus minimizing the impact of the preoperative fast. Reassurance and premedication can relieve anxiety and stress. Drug administration should be minimized, and each drug should be assessed for its risk of precipitating an acute attack. Because a porphyric crisis may develop with a delay of 3 to 5 days to the precipitating event, discharge instructions should stress the symptoms of a porphyric crisis among reportable postoperative complaints. The workup for symptoms should contain screening for and quantitation of the urinary porphyrin precursors δ-aminolevulinic acid and porphobilinogen. Such an integrated approach allows the safe conduct of surgery in patients with acute porphyria.

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Disorders of Potassium Balance

87

Richard J. Novak

Case Synopses

Hypokalemia

A 70-year-old man with hypertension is anesthetized for emergency surgery for a bowel obstruction. His only daily medication is hydrochlorothiazide. His preoperative serum potassium concentration was 3.4 mEq/L. Intraoperative oliguria is treated with 10 mg of intravenous furosemide. He produces 900 mL of urine in the next hour, and his electrocardiogram (ECG) shows new U waves and five premature ventricular systoles per minute. A repeat serum potassium concentration is 2.8 mEq/L.

Hyperkalemia

A 55-year-old woman with end-stage renal disease presents for revision of a left femoral-popliteal artery bypass. She was dialyzed this morning via her left forearm arteriovenous fistula. Her serum potassium before surgery was 5.6 mEq/L. At hour 4 of surgery the femoral artery cross-clamp is released, and her ECG develops peaked T waves and widened QRS complexes. A repeat serum potassium is 7.0 mEq/L.

Potassium plays an important role in the resting membrane potential of excitable cells such as cardiac myocytes, and disorders of potassium balance can cause life-threatening arrhythmias. Hypokalemia occurs in up to 20% of hospitalized patients and is associated with a tenfold increased mortality risk, chiefly due to arrhythmias and cardiovascular events. Hyperkalemia is reported in 1% to 10% of hospitalized patients, and 10% of these have severe hyperkalemia with a K^+ greater than 6.0 mEq/L. Hyperkalemia accounts for 2% to 5% of deaths in patients with end-stage renal disease.

Perioperative serum potassium concentration abnormalities are common, and the recognition and treatment of hypokalemia and hyperkalemia are important skills. Maintenance of total body potassium is accomplished by a balance between the intake of K^+ and the renal or gastroenterologic excretion of K^+. Potassium is the principal intracellular cation. More than 98% of the total body potassium is located within cells, largely in muscle cells. Total body potassium stores equal 50 mEq/kg; thus a 70-kg man contains approximately 3500 mEq of K^+. The normal serum potassium concentration is 3.5 to 5.3 mEq/L. The normal intracellular potassium concentration is about 30 to 40 times higher than the serum concentration. The Na^+-K^+-ATPase pump inside cell membranes actively pumps sodium out of cells and potassium into cells and maintains the extracellular-intracellular ratio of potassium.

Any change in the extracellular-intracellular K^+ concentration ratio is of greater concern than the measured extracellular K^+ serum concentration. Acute changes in the ratio are more dangerous than chronic changes. The most significant risks are to cardiac electrophysiology, resulting in both arrhythmias and depressed contractility. The clinical history that accompanies acute serum potassium decrease or increase is of critical importance, as the two case synopses illustrate.

HYPOKALEMIA

PROBLEM ANALYSIS

Definition

The first case synopsis illustrates chronic hypokalemia complicated by acute hypokalemia. Chronic hypokalemia is associated with a reduction in both total body stores and measured serum potassium levels, while a normal ratio of extracellular to intracellular potassium concentration is maintained. Diuresis with furosemide causes the renal loss of potassium, with a drop in the serum K^+ from 3.4 mEq/L to 2. 8 mEq/L. This acute hypokalemia causes a change in the extracellular-intracellular ratio, which leads to an increased resting potential, hyperpolarization across the cell membrane, and a predisposition to cardiac arrhythmias.

Recognition

In the awake patient the most common symptoms of a serum K^+ less than 3 mEq/L are weakness and fatigue. Other symptoms relate to cardiovascular, central nervous system, neuromuscular, renal, or metabolic function (Box 87.1). In a patient under general anesthesia, ECG changes, decreased cardiac output, or a decreased response to vasopressors may be the initial presentations of hypokalemia. Abnormal ECG changes or a clinical scenario such as the acute diuresis in the first case synopsis prompt the clinician to measure a serum K^+ and confirm the diagnosis of hypokalemia. ECG changes in hypokalemia may include the following (Fig. 87.1):

- The appearance of U waves
- Flattened or inverted T waves, concave ST-segment depression
- Increased amplitude of QRS complexes
- Premature atrial or ventricular extrasystoles

BOX 87.1 Symptoms or Effects of Hypokalemia

Cardiovascular
Decreased cardiac contractility
Electrical conduction abnormalities
Orthostatic hypotension and decreased response to vasopressors
Increased risk of digitalis toxicity

Neuromuscular and Central Nervous System
Weakness and fatigue
Confusion and depression
Respiratory depression (at serum K^+ <2.5 mEq/L)
Peripheral neuropathy and hyporeflexia
Potentiation of neuromuscular blocking drugs
Rhabdomyolysis (at serum K^+ <2.0 mEq/L)

Renal and Gastrointestinal
Polyuria; reduced urine concentrating ability
Hypoperistalsis

Metabolic
Glucose intolerance
Potentiation of hypomagnesemia and hypocalcemia

BOX 87.2 Causes of Hypokalemia

Inadequate Dietary Intake
Malnutrition
Alcoholism

Gastrointestinal Losses
Diarrhea
Vomiting

Renal Losses
Diuretic therapy
Glucocorticoid excess
Mineralocorticoid excess
Magnesium deficiency
Excessive dialysis

Intracellular Shift of K^+
Acute respiratory or metabolic alkalosis
β_2-Catecholamine agonists
Increased insulin levels

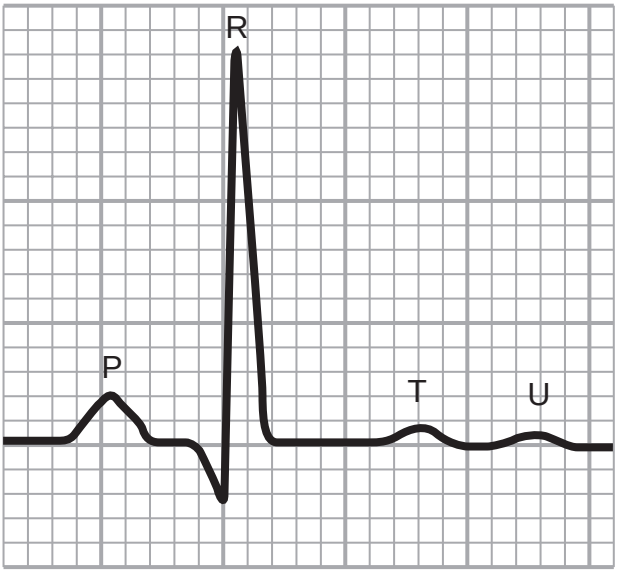

Fig. 87.1 ECG changes accompanying an acute decrease in serum potassium K^+ concentration. Note flattening of the T wave and the appearance of a U wave.

- With severe hypokalemia, supraventricular tachycardias, atrial fibrillation, atrial flutter, and potentially ventricular tachycardia or fibrillation

Risk Assessment

Causes of hypokalemia are listed in Box 87.2. These include inadequate oral intake due to alcoholism or malnutrition, potassium loss via the gastrointestinal tract due to excessive diarrhea, potassium loss via the kidney because of thiazide or loop diuretics, glucocorticoid or mineralocorticoid excess, and potassium loss due to excessive dialysis. An extracellular to intracellular shift of potassium is caused by acute alkalosis, β_2-catecholamine therapy, or insulin therapy.

Implications

The patient in the first case synopsis developed arrhythmias at a serum K^+ of 2.8 mEq/L. There is no empiric serum K^+ concentration below which the risk of arrhythmias is a certainty. The clinical implication of any low K^+ level depends on the following factors:

- The medical comorbidities of the patient
- Whether the potassium deficiency is acute or chronic
- The cause of the hypokalemia
- The planned surgery or procedure
- Whether scheduled surgery is urgent or emergent
- Any additional acute imbalance that urgent or emergent surgery/anesthesia may bring

Clinically important arrhythmias are the chief risks of hypokalemia. Acute decrease in the extracellular-intracellular potassium ratio increases the transmembrane K^+ gradient and transmembrane potential of excitable cells, which can stimulate automatic, triggered, or reentrant arrhythmias in cardiac cells.

MANAGEMENT

With a chronic decreased serum K^+ level such as the preoperative K^+ of 3.4 mEq/L in the first case synopsis, the risk of rapid potassium replacement exceeds the risks of the chronic K^+ depletion. Preoperative hypokalemia presents the clinician with two problems: (1) whether to proceed with or postpone the surgery and (2) how to treat the low K^+ concentration.

Whether to Proceed With Anesthesia and Surgery

In two studies, mild to moderate chronic preoperative hypokalemia (K^+ = 2.6 to 3.4 mEq/L) was not associated with a higher incidence of intraoperative arrhythmias in noncardiac surgery. The decision whether to proceed with surgery and anesthesia in patients with hypokalemia is dependent on the acuteness of the change and on the clinical scenario. Considerations regarding proceeding with surgery or anesthesia in patients with hypokalemia include the following:

- The duration of the hypokalemia
- The urgency and severity of the planned surgery
- The presence of other relevant physiologic or metabolic imbalances
- Concurrent medical comorbidities that may be aggravated by hypokalemia
- The presence of renal insufficiency, uncontrolled hypertension, heart failure, or coronary artery disease

BOX 87.3 Treatment of Hypokalemia

Correction of the Underlying Cause
Stop diuretics
Correct alkalosis
Discontinue β-adrenergic or insulin administration

Nonurgent Potassium Replacement
KCl orally, 40–100 mEq daily

Urgent Potassium Replacement
KCl intravenously, 10 mEq per hour (maximum replacement rate of 20 mEq per hour), may be given via a central venous catheter with continuous ECG monitoring. The concentration of KCl should not exceed 40 mEq/L via peripheral venous catheter. The concentration of KCl may be increased to 20 mEq/100 mL via a central venous administration.

When a low serum K^+ concentration is detected, the abnormal K^+ laboratory value test should be repeated. If hypokalemia is confirmed, a reasonable preoperative management for noncardiac surgery is as follows:

- If the serum K^+ concentration is below 2.5 mEq/L, all but true emergency surgeries should be canceled, especially if ECG changes are present. During the postponement, the cause of the hypokalemia should be determined, and the patient should be treated with supplemental potassium.
- If the serum K^+ concentration is between 2.5 and 3.0 mEq/L and the patient has any abnormal ECG changes of hypokalemia, the surgery should be delayed, the cause of the hypokalemia should be determined, and the patient should be treated with supplemental potassium. If the proposed surgery is urgent or emergent, the surgery may proceed along with intravenous potassium administration, monitoring of K^+ levels, and monitoring for hypokalemia- or hyperkalemia-related arrhythmias.
- If the serum K^+ concentration is between 3.1 and 3.5 mEq/L, providing there has not been an acute decrease of 0.5 mEq/L or more and there are no abnormal ECG changes of hypokalemia, there is little risk to proceeding with surgery and anesthesia. Exceptions may include patients with a severe cardiac history such as acute myocardial infarction, heart failure, acute catecholamine excess, or digitalis toxicity.

Treatment of Hypokalemia (Box 87.3)

Potassium must pass from the extracellular space into the cells to replete intracellular stores, so overly rapid potassium replacement is dangerous. When hypokalemia is chronic and surgery is not urgent or emergent, oral repletion with potassium chloride (KCl) is advised over several weeks' time. A typical oral potassium chloride dose may range from 40 to 100 mEq/day. In the setting of normal kidney function, the serum K^+ decreases by about 0.27 mEq/L for every 100 mEq deficiency in total body stores. The repletion of a preoperative deficit from K^+ = 3.4 mEq/L to K^+ = 4.4 mEq/L may require 400 mEq of KCl or more over a time frame of days.

Intraoperative hypokalemia accompanied by ECG changes and premature ventricular ectopy requires acute treatment. Intravenous KCl is typically administered at a rate no faster than 10 to 20 mEq per hour. If the potassium depletion is known to be both acute and large (e.g., due to acute diuresis such as in our case synopsis) and is accompanied by arrhythmia, intravenous KCl may be administered at up to 20 mEq per hour. Continuous ECG monitoring must accompany rapid KCl repletion therapy, and frequent repeat serum K^+ concentrations should be measured.

Treatment for hypokalemia can include correction of alkalosis and discontinuation of drugs that exacerbate the condition (e.g., potassium-wasting diuretics, β-adrenergic agents, or insulin). Certain conditions and drugs cause delayed movement of supplemental K^+ into cells and result in serum hyperkalemia during the treatment of hypokalemia. These conditions include patients with diabetes, acidemia, or renal tubular acidosis, as well as patients receiving angiotensin-converting enzyme inhibitors, β-adrenergic blockers, or nonsteroidal antiinflammatory drugs.

Hypomagnesemia can accompany hypokalemia and aggravates hypokalemia by impairing K^+ conservation. Hypomagnesemia is most often seen in critically ill patients with chronic alcoholism, acute myocardial infarction, diarrhea, cachexia, malnutrition, or starvation. A magnesium level should be measured in these patients, and supplemental magnesium should be administered as indicated.

The treatment in our first case synopsis includes an intraoperative infusion of KCl at 10 mEq of KCl per hour, with a recheck of the serum K^+ each hour. If ECG changes continue unabated or if further arrhythmias develop, KCl may be administered via a central line at a rate up to 20 mEq of KCl per hour. Overly rapid intravenous potassium replenishment can produce arrhythmias more severe than those produced by hypokalemia itself.

PREVENTION

Clinicians need to be knowledgeable regarding the various causes of hypokalemia, with particular vigilance directed to critically ill patients or patients receiving potassium-wasting diuretics. Clinicians should be familiar with the ECG changes of hypokalemia, and monitor and treat decreased K^+ concentrations in these patients as indicated.

HYPERKALEMIA

PROBLEM ANALYSIS

Definition

Hyperkalemia is defined as a serum potassium greater than 5.3 mEq/L. In the second case synopsis, the etiology of hyperkalemia is renal insufficiency accompanied by intraoperative lower limb ischemia after a prolonged revascularization. A rise in serum potassium concentration is of critical importance because it can cause severe cardiac arrhythmias, conduction disorders, and depressed myocardial contractility.

Recognition

A high index of suspicion is required to diagnose hyperkalemia. There are few early symptoms. Because hyperkalemia partially depolarizes the cell membrane, awake patients may manifest muscular weakness. The initial diagnosis of hyperkalemia is often made by detection of an elevated potassium level during a routine serum potassium measurement, with or without ECG abnormalities. ECG changes associated with elevated serum K^+ include the following (Fig. 87.2):

- Narrowed, peaked T waves
- Prolongation of the PR interval and decrease in P wave amplitude
- Progressive widening of the QRS complex as hyperkalemia worsens

With severe hyperkalemia there are a loss of P waves and widened QRS complexes that merge with the T waves, giving the ECG a sine-wave appearance. This rhythm may progress to ventricular tachycardia, fibrillation, or asystole.

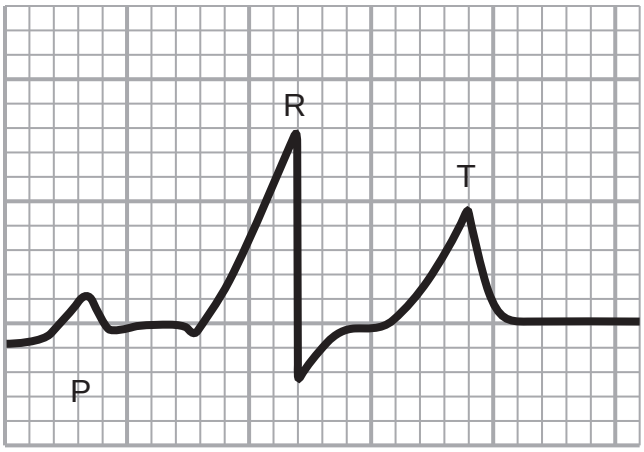

Fig. 87.2 ECG changes accompanying an acute increase in serum potassium K^+ concentration. The T wave becomes peaked, the QRS widens, and the P-R interval is prolonged. As the serum potassium increases further, the QRS and T waves merge, giving the ECG a sine-wave appearance.

BOX 87.4 Causes of Hyperkalemia

Increased Intake
Iatrogenic excessive KCl therapy
Administration of stored packed red blood cell transfusion

Decreased Renal Excretion
Acute or chronic renal insufficiency
Potassium-sparing diuretics
Primary hypoaldosteronism: adrenal insufficiency
Secondary hypoaldosteronism: angiotensin-converting enzyme inhibitors, angiotensin-receptor blocking agents, nonsteroidal antiinflammatory agents, heparin

Intracellular to Extracellular Release of Potassium
Acidosis
Major trauma or tissue necrosis
Extensive burns
Rhabdomyolysis
Hemolysis
Reperfusion after ischemia and cell death (e.g., infarcted bowel, release of an aortic cross-clamp)
Administration of succinylcholine to patients with skeletal muscle myopathies, major burns, multiple trauma, muscle denervation, or upper motor neuron injury

Risk Assessment

Causes of hyperkalemia are listed in Box 87.4. Renal failure patients are at the highest risk for hyperkalemic complications. Patients receiving potassium-sparing diuretics along with potassium replacement are also a high-risk population. Massive transfusion can cause hyperkalemia due to the administration of potassium accumulated during blood preservation. Overzealous or accidental iatrogenic injections of intravenous KCl in a hospital setting have caused deaths due to acute hyperkalemia.

Acidosis exacerbates hyperkalemia. An acute 0.1 decrease in pH causes about a 1.0 mEq/L increase in serum K^+, due to movement of intracellular potassium out of cells. Causes of perioperative metabolic acidosis include hypoperfusion secondary to hemorrhagic, septic, cardiac, or anaphylactic shock. Perioperative respiratory acidosis is due to hypoventilation.

Massive cell necrosis or disruption of cell membranes cause potassium leak and hyperkalemia. Examples include major trauma, large third-degree burns, rhabdomyolysis, and hemolysis. Reperfusion of ischemic areas after release of an aortic cross-clamp or reperfusion of ischemic bowel releases potassium. The resultant hyperkalemia is worsened by any concurrent ischemic metabolic acidosis.

Succinylcholine muscle depolarization causes a transient elevation in serum K^+ of approximately 0.45 mEq/L, which may be clinically important in the setting of preexisting hyperkalemia. Succinylcholine is contraindicated in patients with neuromuscular disorders, myopathies, and after the acute phase of injury causing extensive denervation of skeletal muscle, hemiplegia, upper-motor neuron injury, or major burns. These conditions alter the kinetics of potassium channel opening in cell membranes such that potassium channels remain open longer and may cause massive life-threatening hyperkalemic surges.

Implications

The chief perioperative risks of hyperkalemia are life-threatening cardiac complications, which include the following:

- First-, second-, or third-degree atrioventricular (AV) heart block
- Bradycardia or asystole
- Ventricular or AV junctional escape rhythms
- Ventricular tachycardia or fibrillation
- Impaired contractility

Acute elevations of K^+ levels are associated with a higher prevalence of arrhythmias than chronic elevated K^+ levels.

MANAGEMENT

The management of hyperkalemia is dependent on the acuteness of the change and on the clinical scenario. The decision of whether to proceed with surgery or anesthesia depends on the following factors:

- The duration of the hyperkalemia
- The urgency and severity of the planned surgery
- The presence of other physiologic or metabolic imbalances
- Concurrent medical comorbidities that may be aggravated by hyperkalemia
- The presence of renal insufficiency, uncontrolled hypertension, congestive heart failure, or coronary artery disease

No empiric K^+ value mandates treatment for hyperkalemia, and correlations between clinical ECG changes and K^+ values are inconsistent. A study of patients with end-stage renal disease and preoperative potassium levels of higher than 6 mEq/L demonstrated no adverse outcomes during surgery and anesthesia for dialysis vascular access procedures. Hyperkalemia associated with cardiac conduction disturbances, arrhythmias, or decreased contractility is a medical emergency. Continuous ECG monitoring and acute therapy are necessary (Box 87.5).

The cardiac effects of hyperkalemia are reduced by calcium gluconate or calcium chloride, which antagonize the effect of elevated K^+ on cardiac cell membranes. Administration of intravenous glucose and insulin rapidly decreases the serum K^+ concentration by shifting K^+ intracellularly. β_2-Adrenergic agonists such as albuterol also redistribute K^+ intracellularly.

Furosemide decreases total body potassium via renal excretion. Sodium polystyrene sulfate (Kayexalate) or patiromer decrease the total body potassium via gastrointestinal excretion. These latter two drugs work more slowly. Hemodialysis can remove 25 to 30 mEq/L of potassium per hour, and is indicated in patients with severe renal failure or patients with severe cardiac physiologic dysfunction. It is imperative to measure K^+ serum concentration repeatedly to avoid hypokalemia due to overtreatment.

BOX 87.5 Treatment of Hyperkalemia

Stabilize the Electrical Effects on Cardiac Membranes

Calcium gluconate, 10 mL of a 10% solution 3–6 g IV over 2–3 minutes; or

Calcium chloride, 3–4 mL of a 10% solution over 2–3 minutes (effect begins in 1–3 minutes and lasts 30–60 minutes; dose may be repeated if there is no change in ECG abnormalities)

Transfer Potassium Intracellularly

Regular insulin (10–20 units) with 50–100 mL of 50% dextrose IV (effect begins in 10–20 minutes, peaks at 30–60 minutes, and lasts 4–6 hours)

Albuterol 10–20 mg in 4 mL of saline, nebulized and inhaled over 10 minutes (effect begins in 30 minutes, peaks at 90 minutes, and lasts 2–6 hours)

Remove Potassium From the Body

Slow removal from the gastrointestinal tract via cation exchange resins:

Sodium polystyrene sulfate (Kayexalate) 15–30 g PO (full effect may take 24 hours; may require repeat doses every 4–6 hours); or

Patiromer 4.2–8.4 g PO one to two times daily

Furosemide

Hemodialysis against a hypokalemic solution

ECG, Electrocardiogram; *IV,* intravenously; *PO,* orally.

In the second case synopsis, initial treatment of the ECG abnormalities would include intravenous calcium gluconate, followed by insulin/glucose and inhaled albuterol. The arterial blood gas should be checked and any acidosis corrected. Postoperative repeat dialysis would be the definitive treatment.

PREVENTION

Clinicians should be knowledgeable regarding the various causes of hyperkalemia, with particular vigilance directed to patients with chronic renal failure. Clinicians should be familiar with the ECG changes of hyperkalemia, and monitor serum K^+ concentrations in high-risk patients. Peaked T waves precede the more dire complications of AV heart block, bradycardia, arrhythmias, or decreased myocardial contractility. In patients with elevated K^+ concentration, avoid potassium supplementation, potassium-sparing diuretics, acidosis, and succinylcholine.

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88 Intrathecal Opioids

Reza Salajegheh • Bhiken I. Naik

Case Synopsis

An otherwise healthy 26-year-old woman undergoes cesarean section for delivery of a breech infant. Spinal anesthesia is used, consisting of 1.6 mL of 0.75% hyperbaric bupivacaine (12 mg) with preservative-free morphine (0.3 mg). The surgery is uneventful, and the infant has Apgar scores of 9 and 9 at 5 and 10 minutes, respectively. The patient remains in the recovery room for 2 hours and is then transferred to the floor. She is treated with diphenhydramine 50 mg intravenously (IV) for generalized pruritus 6 hours after surgery and promethazine 25 mg IV for vomiting 7 hours after surgery. Ten hours after surgery, she complains of persistent pruritus, noting that the diphenhydramine had no effect.

PROBLEM ANALYSIS

Definition

Intrathecal administration of opioids is an effective means of providing analgesia both intraoperatively and postoperatively. A combination of opioids and local anesthetics is often coadministered in an effort to reduce doses of both classes, thereby limiting the side effects. Morphine is commonly chosen for intrathecal administration, as a single dose may provide analgesia for up to 24 hours. Side effects of intrathecal opioids include early and late respiratory depression, nausea and vomiting, pruritus, sedation, and urinary retention (Table 88.1).

Early respiratory depression occurs in the first 2 hours after intrathecal administration of opioids and is believed to be due to vascular uptake and redistribution. Delayed respiratory depression, which occurs 6 to 12 hours after intrathecal administration, is thought to be due to the rostral spread of opioid in the cerebrospinal fluid (CSF). Similarly, nausea and vomiting is due to the rostral spread of the opioid in the CSF with stimulation of the area postrema in the fourth ventricle. Sedation is related to the spread of opioids through the CSF to the thalamus, limbic system, or cerebral cortex. Sedation may be exacerbated by hypercarbia with carbon dioxide narcosis. Urinary retention is due to the inhibition of sacral parasympathetic outflow with relaxation of the bladder detrusor muscle and concomitant inability to relax the sphincter.

Pruritus, either generalized or localized, can occur frequently in patients receiving intrathecal opioids. *Pruritus* is defined as an unpleasant sensation that results in the desire or reflex to scratch. It typically first occurs in the area of the nose, eyes, and face, likely related to the relatively high concentration of opioid receptors at the spinal nucleus of the trigeminal nerve. Notably, this effect occurs more commonly after epidural and spinal administration than with systemic administration. Although the mechanism is not fully understood, histamine release is not postulated to be a causative factor.

Recognition

Although the most serious complication of intrathecal opioid administration is respiratory depression, respiratory depression of clinical significance occurs in less than 0.5% of cases. Though not life threatening, pruritus remains the most common patient complaint, occurring in 83% of postpartum patients and 69% of nonpregnant patients. This can lead to significant patient discomfort. In some cases, the resulting pruritus can be more unpleasant for the patient than the pain itself.

Although the true mechanism of pruritus induced by intrathecal administration of opioids is not fully understood, there are several theories. One theory points to the relationship between nociception and pruritus and the method by which these signals are transmitted. Both nociception and pruritus are transmitted by C fibers, whose signaling is potentiated by prostaglandins. Given the small unmyelinated nature of C fibers, both pruritus and nociceptive sensations can be attenuated by "rubbing." This is consistent with the gate theory of pain, which asserts that increased activity of large myelinated Aβ sensory fibers diminishes transmission of nociceptive (and potentially pruritic) stimuli carried by small unmyelinated C fibers, by modulation of thalamic projection neurons. Another theory suggests that nociception-specific neurons in the dorsal horn inhibit pruritus-specific neurons in the spinothalamic tract. This can be observed by the decrease in pruritus that occurs with an increase in nociception, however slight, in the form of scratching. The addition of opioids may weaken this inhibition, resulting in an increased sensation of pruritus. There are additional theories involving serotonergic pathways, but the exact mechanisms are unknown. What is known is that there is a high concentration of μ and serotonin receptors in the dorsal horn of the spinal cord and the spinal tract of the trigeminal nerve in the medulla. The spinal trigeminal nucleus is thought to be an integrative "itch center" for sensory input from the face. Supporting this are studies demonstrating reduction in pruritus with ondansetron and propofol, which has strong noncompetitive inhibition of serotonin channel activity. However, no single unifying theory can fully explain opioid-induced pruritus.

Though effectively preventing and addressing pruritus remains a challenge, a careful understanding of treatment options and known mechanisms of action is important to ensuring maximum patient satisfaction in the perioperative period.

Risk Assessment

Careful selection of patients for the administration of intrathecal opioids is important. Discussion should be had with the patient regarding

TABLE 88.1 Cause and Treatment of Complications of Intrathecal Medications

Complication	Cause	Treatment
Early respiratory depression	Rapid vascular uptake and redistribution	Ventilatory support, naloxone
Late respiratory depression	Rostral CSF spread to brainstem respiratory center	Ventilatory support, naloxone
Pruritus	Unknown (unlikely due to histamine release)	Naloxone, antihistamines (controversy), mixed opioid agonist-antagonists
Nausea, vomiting	Rostral CSF spread to vomiting center or chemoreceptor trigger zone in fourth ventricle	Naloxone, antiemetics, droperidol, transdermal scopolamine
Urinary retention	Inhibited sacral parasympathetic outflow	Naloxone (large doses), urinary catheterization
Sedation	Rostral spread in CSF to thalamus, limbic system, or cortex; hypercarbia	Naloxone

CSF, Cerebrospinal fluid.

the potential for pruritus and the patient's level of tolerance for this side effect. The parturient is at higher risk for pruritus after neuraxial administration of opioids, with an incidence of 60% to 100%. By comparison, orthopedic patients have an incidence of 30% to 60%.

Lipid-soluble opioids such as fentanyl have a shorter duration of pruritus compared with opioids such as intrathecal morphine, likely due to the increased systemic uptake of the former. Not surprisingly, the incidence of pruritus also increases with escalating doses of intrathecal opioids. Utilization of concomitant local anesthetics in the intrathecal bolus may result in a decreased severity of pruritus by reducing the dose of intrathecal opioid necessary to achieve appropriate analgesia. However, utilization of epinephrine in the intrathecal bolus may potentially result in worsening pruritus by reducing systemic uptake of the opioid via local vasoconstriction, resulting in increased peak CSF concentrations.

MANAGEMENT

Management of neuraxial opioid-induced pruritus remains a significant challenge, with the primary goal necessitating a balance of the analgesic and pruritic side effects of these drugs. Traditionally, antihistamines have been used to treat opioid-induced pruritus; however, H_1 blockers have been shown to have limited success in treating central pruritus. Occasionally, the sedative effect of the first-generation antihistamines is misinterpreted as an improvement in symptomatology.

Multiple agents have been shown to be effective in the treatment of opioid-induced pruritus; however, the degree of efficacy and level of evidence are variable. These include opioid antagonists, mixed agonist/antagonists, serotonin antagonists, nonsteroidal antiinflammatory drugs (NSAIDs), propofol, and dopamine antagonists.

The largest body of evidence supports opioid receptor antagonists, such as naloxone. A continuous infusion of naloxone was found to be most effective in preventing variability in serum concentrations, due to its relatively short half-life. Low-dose naloxone infusions (less than 2 μg/kg/h) are ideal in reversing pruritus without significant reversal of analgesia.

Mixed opioid agonists-antagonists (e.g., nalbuphine and butorphanol) have been shown to be effective in treating opioid-induced pruritus; however, they can be associated with an increased risk of sedation. Furthermore, their efficacy in treating pruritus in the pediatric population is questionable.

The intravenous administration of serotonin receptor antagonists, such as ondansetron (0.1 mg/kg), has also been shown to reduce the degree and incidence of pruritus with neuraxial opioids. Serotonin receptor antagonists have been shown to be less effective after neuraxial administration of the more lipophilic opioids.

There is some conflicting evidence for the use of NSAIDs in diminishing pruritus, with one study showing success with rectally administered diclofenac and another study showing no benefit with celecoxib 200 mg. The role of propofol in reducing neuraxial opioid-induced pruritus has demonstrated mixed results.

PREVENTION

Preventing opioid-induced pruritus begins at the time of administration of neuraxial opioids. Using adjuvant medications can minimize the intrathecal opioid dose required for optimal analgesia. Frequent assessment and aggressive management including a multimodal approach may be required to minimize the onset and severity of pruritus.

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89 Ketamine

Madhuri S. Kurdi

Case Synopsis

A 22-year-old woman is posted for an emergency appendectomy. She is hemodynamically stable and administered a spinal anesthesia. The surgeon makes the abdominal incision, but on deeper dissection the patient cries out in pain. The anesthesiologist administers bolus ketamine intravenously (2 mg/kg) and asks the surgeon to go ahead. Soon after the bolus dose, there is respiratory depression and apnea for a few seconds, which recedes with intermittent positive-pressure ventilation. After some time, the surgeon complains of tightness of the abdominal muscles and inability to continue with the surgery. He demands better relaxation. The patient's limbs are tight. She is clenching her teeth tightly, and there is a slight rise in her arterial pressure and heart rate. Oral secretions appear. She is suctioned and administered intravenous (IV) glycopyrrolate (0.02 mg/kg). Laryngospasm ensues, and the arterial oxygen saturation falls. The anesthesiologist administers IV succinylcholine 1.5 mg/kg, intubates her trachea, and maintains further muscle relaxation with IV vecuronium. She is reversed and extubated at the end of the surgery. In the recovery room, soon after shifting, she is frequently blushing, shows lip-smacking movements, is casting coy glances here and there, and is repeatedly shouting loudly, "What? What is it? Where are you?" Her cry is disturbing to all the staff and patients in the recovery area. She repeatedly tries to get up from her bed, pulls out her nasogastric tube, and has a bout of vomiting. The anesthesiologist and recovery room doctor administer IV midazolam 0.05 mg/kg and IV ondansetron (0.15 mg/kg). Her agitation soon decreases.

PROBLEM ANALYSIS

Definition

Ketamine is a phencyclidine derivative that produces pharmacologic effects such as dissociative anesthesia, sedation, catalepsy, profound somatic analgesia, amnesia, bronchodilation, and sympathetic nervous system stimulation. It is currently being widely used as a sedative premedicant, sole anesthetic or adjunct anesthetic, perioperative analgesic, sedative for procedural sedation, and an analgesic cum antidepressant in pain medicine. Though ketamine has an excellent safety profile, some unique adverse effects can cause complications during its use (Table 89.1).

Recognition

The case synopsis illustrates significant complications of ketamine use: (1) tachycardia and increase in arterial pressure, (2) skeletal muscle hypertonia, (3) increased salivation, (4) laryngospasm, (5) emergence phenomenon, and (6) nausea and vomiting.

Tachycardia and Increase in Arterial Pressure

Ketamine administration leads to centrally mediated increase in sympathetic tone and release of catecholamines from the adrenal medulla, thus causing an indirect increase in the blood pressure (BP) and heart rate. The episodes of tachycardia and hypertension are short. In the absence of depressant premedication, the rise in heart rate is about 15% to 25%, and the rise in systolic pressure in adults receiving clinical doses of ketamine is about 20 to 40 mm Hg (10% to 50% above preanesthesia values) with a slightly lower rise in diastolic pressure. The BP rises steadily over 3 to 4 minutes after injection and then declines to normal limits over the next 10 to 20 minutes.

Increase in Skeletal Muscle Tone

This is most prominent after an initial IV bolus and gradually decreases.

Respiratory Depression/Apnea

This may occur due to rapid administration of a normal dose/administration of an unusually large dose and concurrent use of sedative drugs. It is transient and appears 1 to 2 minutes after rapid IV administration due to unusually high central nervous system levels. Midazolam when coadministered can increase the likelihood of apnea.

Laryngospasm

Increased salivation can lead to laryngospasm. The chances of laryngospasm are more after intramuscular (IM) ketamine administration, especially in children, in children with upper respiratory tract infection/airway anomalies/airway procedures, and in adults receiving high IM doses. The laryngospasm may be transient, but sometimes may be intractable and repetitive.

Nausea and Vomiting

It usually occurs late during the recovery phase when the patient is alert and can clear the airway without assistance.

TABLE 89.1 Complications of Ketamine

Intraoperative/During the Infusion	Postoperative/After Discontinuing Infusion	After Prolonged and Repeated/Recreational Use
Increase in arterial pressure and heart rate	Emergence phenomenon	Hemorrhagic cystitis, hydronephrosis, papillary necrosis
Increase in oral and tracheobronchial secretions, laryngospasm, airway obstruction	Nausea and vomiting	Abdominal cramps ("K" cramps)
Increase in skeletal muscle tone (opisthotonus, bizarre postures, clonus), purposeless movements		Mild transient increase in liver enzymes
Slight rise in ICP and IOP, seizures, nystagmus, transient diplopia		Neurocognitive impairment, memory and attention deficits, emotional blunting, impaired language skills
Transient apnea, respiratory depression, hiccups		Tolerance
Negative cardiovascular (direct cardiac depressant) effects in critically ill and severely stressed patients/with high-dose ketamine		Withdrawal syndrome with psychosis after discontinuation, dependence

ICP, Intracranial pressure; *IOP,* intraocular pressure.

Emergence Reactions

These are undesirable psychomimetic reactions that complicate recovery from ketamine anesthesia. They occur secondary to ketamine induced depression of auditory and visual relay nuclei, leading to misinterpretation or misperception of auditory and visual stimuli. They can be of varying severity and types. They abate within a few hours. The common clinical manifestations include agitation, pleasant and unpleasant hallucinations, confusion, euphoria, fear, disorientation, sensory and perceptual illusions, nightmares (up to 3 to 30 postoperative days), delirium, excitation, aggressive behavior, out-of-body sensation, paresthesia, short-lasting delusions, feeling of a sensation of light throughout the body, colorful vision, distorted shape and size of body parts, novel experiences concerning body consistency as made of dry wood/plastic/foam rubber, melting together with someone/environment, feeling energized and getting a strong urge to move around and talk to people, monosyllable mumble, feeling of numbness in the extremities, losing of sense of time and identity, "giggliness," feelings of estrangement or isolation, negativism, hostility, and repetitive motor behavior. The recovery agitation is mild in 6.3% of cases and clinically important in 1.4% of cases. The differential diagnosis includes alcoholic delirium tremens, head injury–induced delirium, postoperative cognitive dysfunction/postoperative delirium/atropine-induced delirium in the elderly, and postoperative delirium due to sevoflurane/isoflurane/desflurane in children.

Risk Assessment

The hemodynamic effects are seen at anesthetic doses and are not measurable at subanesthetic doses. The increase in salivation is particularly seen in children and at higher doses. Ketamine-associated laryngospasm and respiratory depression/apnea are transient and the incidence is 0.3% and 0.8%, respectively, in children. The incidence of ketamine-induced vomiting is more in adults (5% to 15%) compared with children, and the peak age for vomiting is early adolescence. High IV doses, anesthetic doses, and the IM route are associated with a higher rate of vomiting. The incidence of emergence reactions ranges from 3% to 100% and is more and of a larger magnitude in adult patients (age >15 years and <65 years; 30% to 50%) compared with children (5% to 15%) and in women compared with men. Incidence is less after oral administration. Also, it is higher in patients with psychotism/known schizophrenia. There is a dose-effect relationship between the ketamine dose and the intensity of the psychomimetic effects. The psychomimetic effects increase at doses above 0.3 mg/kg IV bolus. Complications such as increase in intracranial pressure and intraocular pressure (IOP) may be exacerbated in the presence of hypercarbia. Nystagmus and diplopia occur at all doses of ketamine. IM/IV ketamine–associated seizures have been reported in both healthy and epileptic patients with premedication and induction doses. However, the drug has shown both proconvulsant and anticonvulsant effects.

Implications

The cardiovascular-stimulating properties of ketamine can produce an undesirable hemodynamic response to intubation; hinder intraoperative elective hypotension, especially in the first 15 minutes after ketamine administration; play havoc with the surgical field; cause life-threatening engorgement of vascular tumors of the tongue and resultant airway obstruction; and prove disastrous in patients with preexisting hypertension or cardiovascular disease/intravascular aneurysms. The skeletal muscle hypertonia produced by ketamine can make operating conditions very difficult for the surgeon, especially during intraabdominal and intrathoracic operations. The hypersalivation caused by ketamine can cause laryngospasm and airway obstruction, make taping of the endotracheal tubes difficult, and may impair visualization during fiberoptic intubation. The purposeless limb movements, muscle rigidity, rise in pulse rate and blood pressure, increased salivation, and laryngospasm are sometimes misdiagnosed as signs of light anesthesia leading to administration of high doses of ketamine, which can cause further complications. Because ketamine can sometimes disturb patency of the airway and cause vomiting, it should be avoided for procedures in the prone position and in patients with a full stomach. The increase in IOP and nystagmus make ketamine unsuitable in surgeries for glaucoma and open eye injuries. Emergence reactions can be frightening and disturbing to the patient, the anesthesiologist, the surgeon, recovery room staff, other neighboring patients, and relatives and cause damage to the surgical site and drains.

MANAGEMENT

In clinical settings, ketamine is well tolerated. Most of the complications are transient and can be managed (Table 89.2).

PREVENTION

Ketamine-induced complications will be less if careful patient and surgical procedure selection with proper patient monitoring are done, the drug is administered by an anesthesiologist, the dose is lowered and titrated, and appropriate prophylactic drugs (e.g., glycopyrrolate) and benzodiazepines (e.g., midazolam) are administered (see Table 89.2).

TABLE 89.2 Prevention and Management of Complications Caused by Ketamine

Complications	Prevention	Management
Tachycardia and increase arterial pressure	• Coadministration of propofol/midazolam/dexmedetomidine/clonidine/β-blocker/inhalational anesthetic along with low-dose ketamine • Prior modest doses of diazepam/midazolam/opioid-hyoscine • Use continuous microdrip ketamine infusion	• Usually transient • If troublesome, inject β-blocker (e.g., IV metoprolol) or increase dose of anesthetic agents such as sevoflurane/isoflurane/halothane/propofol/dexmedetomidine
Increased salivation	• Prophylactic atropine 20 μg/kg IM 30 minutes preoperatively or 10–20 μg/kg at induction/IV glycopyrrolate 0.004 mg/kg at induction	• Suctioning • Antisialogogues such as IV atropine 0.02 mg/kg, glycopyrrolate 0.01–0.02 mg/kg
Laryngospasm and airway obstruction	• Reduce/prevent secretions • Avoid as a sole agent in children less than 3 months old/in patients with URTI/in procedures involving mechanical stimulation of pharynx • Avoid large IM doses	• Assisted ventilation with 100% oxygen, succinylcholine
Respiratory depression/apnea	• Inject bolus ketamine at a slow rate over 60 seconds	• Oxygenate and give bag-valve-mask ventilation
Nausea and vomiting	• Coadminister propofol • Metoclopramide/ondansetron	• IV ondansetron 0.1 mg/kg, IV metoclopramide 0.1 mg/kg
Emergence phenomenon	• Premedicate with IV midazolam (0.03 mg/kg)/promethazine/haloperidol/opioid/opioid-hyoscine/opioid-droperidol • Avoid rapid administration of large doses of ketamine • Consider patient recovery in a quiet area with muted lighting • Include propofol/thiopentone/inhaled anesthetics/dexmedetomidine in the anesthesia protocol • Proper patient selection, preemptive discussion of potential complications and positive suggestion • Use of S (+) ketamine • IV midazolam 0.07 mg/kg toward end of anesthesia	• Titrated benzodiazepines such as midazolam/diazepam/lorazepam • Oral/subcutaneous haloperidol or subcutaneous midazolam if on long-term ketamine treatment • Small dose of thiopentone • Lamotrigine • Usually abates within a few hours; only sometimes recurrences can take place up to 24 hours
Raised intracranial pressure (ICP)	• Avoid use in those with raised ICP and on spontaneous ventilation	• Institute controlled ventilation/hyperventilate
Convulsions	• Always premedicate or coadminister a benzodiazepine like midazolam/diazepam	• Stop further ketamine administration • Give IV benzodiazepine/barbiturate
Skeletal muscle hypertonicity	• Coadminister benzodiazepines • Avoid as a sole anesthetic in abdominal/intrathoracic surgery	• Give IV muscle relaxants and IPPV • IV midazolam 0.05 mg/kg

IM, Intramuscular; *IPPV,* intermittent positive-pressure ventilation; *IV,* intravenous; *URTI,* upper respiratory tract infection.

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Magnesium

Richard C. Month

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Case Synopsis

A 23-year-old pregnant woman at 34 weeks and 3 days' gestation with severe preeclampsia is brought emergently to the operating room for cesarean delivery under general anesthesia. She is currently receiving a magnesium infusion for treatment of her preeclampsia. Forty-five minutes after uneventful rapid-sequence induction with propofol and rocuronium, followed by an uneventful delivery, the patient has continued profound neuromuscular blockade (train of four 0/4 with no posttetanic facilitation). After waiting 30 minutes in the operating room with no improvement, she is brought intubated to the intensive care unit; she is extubated 6 hours later.

PROBLEM ANALYSIS

Definition

Magnesium Homeostasis

Magnesium is the fourth most abundant cation in the body, with total body stores of about 2000 mEq. Normal serum magnesium (Mg^{2+}) concentrations are between 1.4 and 2.1 mEq/L, equivalent to 1.7 and 2.5 mg/dL, respectively (see Table 90.1 for unit conversions); however, serum Mg^{2+} concentrations correlate poorly with total body stores, reflecting less than 1% of the total. Gastrointestinal absorption in the duodenum and jejunum represents the principal source of Mg^{2+} (8 to 9 mEq/day). The amount of Mg^{2+} lost from the body via gastrointestinal secretions is relatively constant (2 mEq/day). In contrast, the kidney can dramatically affect losses in response to lowered serum Mg^{2+} concentrations due to reabsorption of Mg^{2+} in the proximal renal tubules and the loop of Henle.

Role in Cellular Function

Magnesium serves as an essential cofactor for many important cellular enzymes (e.g., adenylyl cyclase, Na^+,K^+-ATPase). In addition, the magnesium complex, with adenosine triphosphate, serves as a substrate for the enzymatic reaction mediating muscle contraction and relaxation. Magnesium also regulates cellular function by antagonizing the effects of calcium and modulating several potassium currents (Box 90.1).

Alterations in serum Mg^{2+} concentrations affect multiple organ systems. For example, hypermagnesemia causes relaxation of vascular smooth muscle by directly competing with Ca^{2+} to inhibit smooth muscle contraction, increasing the release of prostacyclin and decreasing catecholamine release after sympathetic stimulation. At the motor neuromuscular junction, increased Mg^{2+} causes presynaptic inhibition of Ca^{2+} release, inhibiting acetylcholine release, which in turn depresses sarcolemmic excitability. In the heart, reduced Mg^{2+} slows the heart rate by suppressing automaticity and depressing atrioventricular conduction. Hypermagnesemia also reduces the amplitude of early afterdepolarizations to oppose triggered arrhythmias (see later). In the brain, increased Mg^{2+} serves as an anticonvulsant by blocking neuronal Ca^{2+} channels associated with the *N*-methyl-D-aspartate (NMDA) receptor.

Role in Therapeutics

Magnesium infusions may be therapeutic in the case of triggered ventricular arrhythmias. They are also used as adjunct therapy for atrial fibrillation in cardiac surgery, as tocolytic agents in preterm labor, and to prevent seizures with preeclampsia.

The frequency of automatic or triggered ventricular arrhythmias with hypomagnesemia (e.g., torsades de pointes, digitalis ventricular arrhythmias) is reduced by intravenous magnesium infusions that double the serum Mg^{2+} concentration. Thus such infusions may increase inwardly rectifying potassium currents to reduce the amplitude of the early afterdepolarizations that serve as the triggers for torsades de pointes. Proposed mechanisms for magnesium's effect on digitalis-induced ventricular arrhythmias include improved function of the Na+,K+-ATPase pump and reduction in the amplitude of delayed afterdepolarizations owing to a reduction in the intracellular rise of Ca^{2+}. However, most ventricular arrhythmias are due to reentry

TABLE 90.1 Unit Conversions for Magnesium Compounds and Serum Concentrations

Compound	Unit Conversions
Magnesium sulfate ($MgSO_4$)	1 g = 8.13 mEq of Mg^{2+}
Magnesium oxide (MgO)	1 g = 46 mEq of Mg^{2+}
Magnesium acetate ($MgC_4H_6O_4$)	1 g = 9.35 mEq of Mg^{2+}
Magnesium chloride ($MgCl_2$)	1 g = 9.75 mEq of Mg^{2+}
Serum concentrations (all compounds)	1 mg/dL = 0.83 mEq/L = 0.415 mmol/L

BOX 90.1 Mechanisms for Magnesium's Effect on Cellular Function

Ca^{2+} Antagonism
- Modulates handling of Ca^{2+} by sarcoplasmic reticulum
- Inhibits Ca^{2+} influx into myocyte through sarcolemmal channels
- Modulates second messenger system (i.e., adenyl cyclase–adenosine monophosphate)
- Competes with Ca^{2+} for high affinity site on actin

K^+ Current
- Enhances function of Na^+,K^+-ATPase
- Blocks outward K^+ current to result in an increase in inward rectifying K^+ current
- Mediates inwardly rectifying properties

TABLE 90.2 Correlation Between Serum Magnesium Concentration and Systemic Effects

Concentration (mEq/L)	Systemic Effects
<0.8	Arrhythmias may be resistant to therapy
	When associated with hypocalcemia: disorientation, muscle twitching, choreiform movements, seizures
1.4–2.1	Normal range
3–4	Flushing
	7%–13% increase in PR interval
	0%–11% increase in QRS interval
	No change in Q-T interval
5–6	Slight reduction in blood pressure
	Slight increase in heart rate
	10% reduction in FEV_1 and FVC
	Blurred vision from diminished accommodation and convergence
	Lethargy
10	Loss of deep tendon reflexes
20	Respiratory arrest
	Atrioventricular conduction block
	Progressive QRS widening and bradycardia
>25	Cardiac arrest

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity.

and do not respond to intravenous magnesium. In contrast, preoperative β-blockers and calcium channel antagonists with adjunct Mg^{2+} therapy can reduce the occurrence of atrial fibrillation in postoperative cardiac surgery patients. Hypomagnesemia can result from hemodilution with cardiopulmonary bypass and diuretic therapy.

Increasing the serum Mg^{2+} concentration has been used extensively in obstetrics. Increasing serum magnesium levels by 4 to 6 mEq/L decreases uterine activity by direct smooth muscle relaxation. In addition, magnesium infusion is the therapy of choice for preeclampsia, as it decreases systemic vascular resistance (by inhibition of vascular smooth muscle contraction and decreasing catecholamine release after sympathetic stimulation) and reduces the risk of seizure activity (by NMDA-receptor inhibition and avoidance of regional ischemia by increasing vascular flow). Finally, magnesium is administered for neuroprotective benefits and avoidance of cerebral palsy in patients at risk for premature delivery.

Recognition

Hypomagnesemia

Alterations in serum Mg^{2+} concentrations are often unrecognized and occur with alterations in other serum electrolytes, such as calcium and potassium. Hypomagnesemia is best diagnosed by recognizing those conditions associated with it (e.g., chronic ethanol abuse, diuretic or digitalis therapy). Hypomagnesemia alone does not result in electrocardiogram changes; however, the associated disturbances in calcium and potassium may do so.

Hypermagnesemia

Hypermagnesemia is most often diagnosed by associating the timing of adverse effects with the administration of magnesium. In patients with gastrointestinal diseases leading to increased absorption or renal dysfunction leading to decreased excretion, large doses of cathartics, antacids, or analgesics containing magnesium salts may result in significant hypermagnesemia. Under these conditions, the temporal association with magnesium administration is often not apparent.

Hypermagnesemia is also diagnosed by recognizing the progressive pattern of its adverse effects and then confirming that suspicion with serum Mg^{2+} measurements. Hypermagnesemia can produce the following adverse effects:

- Generalized vasodilation
- Lethargy
- Muscle weakness
- Respiratory depression
- Sinus bradycardia
- Atrioventricular block
- Asystole

Table 90.2 lists common adverse effects of hypermagnesemia and the associated serum Mg^{2+} concentration at which these effects first appear. It is noteworthy that the serum concentration at which a particular adverse reaction occurs in a given individual varies considerably, depending on the associated metabolic disturbances.

Risk Assessment

Hypomagnesemia

Hypomagnesemia has an incidence of 470 per 1000 individuals suspected of having serum electrolyte abnormalities. Persons with congestive heart failure who are treated with diuretics and digitalis have a 7% to 37% incidence of hypomagnesemia. Alcoholics have a 30% to 40% incidence of hypomagnesemia.

Hypermagnesemia

Hypermagnesemia has an incidence of 57 per 1000 individuals suspected of having serum electrolyte abnormalities. Because of the kidney's remarkable ability to reduce the reabsorption of magnesium, respiratory and cardiac arrests are extremely rare during continuous magnesium infusions for arrhythmias, tocolysis, or treatment of preeclampsia. To prevent the adverse effects of hypermagnesemia, it is best to avoid administering magnesium to individuals with renal dysfunction.

Implications

Ventricular arrhythmias resulting from increased automaticity or triggered activity due to magnesium deficits clearly warrant the replacement of those deficits. The use of magnesium infusions to reduce the risk of acute myocardial infarction is controversial and is still under investigation. The use of magnesium for preterm labor tocolysis seems to be a safe alternative to β-sympathomimetics, though may not be as effective. In comparison to phenytoin, magnesium is more efficacious in preventing seizures in women with preeclampsia. Nondepolarizing muscle relaxants are synergized by magnesium, by reduction of the available acetylcholine released into the motor endplate.

MANAGEMENT

The key to the management of both hypomagnesemia and hypermagnesemia is recognition. Hypomagnesemia can be treated either orally or parenterally. Table 90.1 gives the elemental content of the various magnesium-containing formulations used to treat hypomagnesemia. In patients with normal renal function, 16 to 32 mEq of magnesium sulfate can be infused intravenously over 30 minutes to 1 hour for rapid correction or over 8 to 24 hours for slower correction.

As serum Mg^{2+} represents less than 1% of the total body stores of magnesium, achieving sustained elevations in serum Mg^{2+}

concentrations with hypomagnesemia involves multiple doses to replete total body stores. In contrast, the treatment of hypermagnesemia includes any or all of the following:

- Removal of all potential ex vivo sources of magnesium
- In cases of respiratory arrest, intubation and support of ventilation
- Administration of furosemide and magnesium-free salt solutions to increase the renal excretion of magnesium
- Calcium chloride (5 to 10 mEq every 5 to 10 minutes) to antagonize hypermagnesemia
- Dialysis with magnesium-poor dialysate

PREVENTION

The best prevention for hypermagnesemia is to not give magnesium-containing salts or compounds to patients with renal failure. Magnesium-containing compounds include the following:

- Cathartics (e.g., magnesium citrate)
- Antacids (e.g., magnesium oxide)
- Analgesics (e.g., buffered aspirin)
- Magnesium supplements

During the administration of cathartics to individuals with gastrointestinal disturbances (e.g., paralytic ileus, ulcerative colitis, perforated duodenal ulcer), massive amounts of magnesium absorption can occur.

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91 Magnetic Resonance Imaging

Herodotos Ellinas

Case Synopsis

A 4-year-old boy with a 10-day history of persistent nausea, vomiting, and otitis media requires magnetic resonance imaging (MRI) of the brain to evaluate possible intracranial process. The anesthesiology consultant was called to evaluate and assist with the anesthetic.

PROBLEM ANALYSIS

Definition

MRI is a noninvasive diagnostic imaging modality that produces precise images of the body. It is free of ionizing radiation and does not, by itself, produce any known biologically deleterious effects. It is based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy, which are then emitted as radio waves and reconstructed into computerized images. Magnetic field strengths generally range from 0.2 to 3 tesla (T), although magnetic field strengths up to 7 T have been used for research purposes. The patient is required to lie still within a small space while multiple images are obtained. MRI requires a longer time to obtain than computed tomography scanning; therefore any movement by the patient degrades the image quality. In fact, any change in the patient's position may affect the homogeneity of the magnetic field, which is optimized at the beginning of the scan. Studies can take from 45 minutes to more than 2 hours, with individual sequences taking from 3 to 10 minutes. The scanner is noisy, and the restricted space and lack of movement can induce claustrophobia in some patients. Patients may also experience localized or systemic increase in temperature, and the strength of the magnetic field can induce inadvertent injuries.

There are four zones within the MRI suite, defined based on screening around magnet safety:

1. Zone I—Free access to public
2. Zone II—Greeting zone, under supervision from MRI staff
3. Zone III—Restricted to screened public and personnel
4. Zone IV—Magnet room

Recognition

Most adults and children older than 6 years are capable of lying still for the scan. With the use of headphones and music, MRI is a well-tolerated procedure. However, there are several groups of patients who may require anesthesia for the scan to be performed (Box 91.1).

Risk Assessment

Box 91.2 lists some common contraindications to MRI. They are related either to the possibility of the magnet causing a ferromagnetic object to move or heat up or to the induction of an electrical current from the radiofrequency pulses and magnetic gradients used to generate the images. The effect on the unborn fetus is unknown, but concerns have been expressed regarding hearing loss and teratogenicity. MRI should probably be avoided in the first trimester unless absolutely indicated based on the patient's medical condition. Permanent cosmetic makeup and tattoos can cause skin irritation, burns, and swelling during MRI scanning.

Anesthesia risk is increased because the patient is in a remote location, with limited airway access and visibility. The presence of gastroesophageal reflux, seizures, or raised intracranial pressure affects the choice of anesthetic. Other potential problems that may arise are listed in Box 91.3.

Implications

Monitors must be suitable for use in the MRI suite. They should be nonferromagnetic, and cables should be screened from electromagnetic interference (fiberoptic is ideal). The signal should be filtered to avoid radiofrequency interference, which affects image quality. Despite specialized technology, some problems still remain (Table 91.1).

BOX 91.1 Indications for Sedation/General Anesthesia for Magnetic Resonance Imaging

- Very young or anxious/agitated patients
- Patients who have failed an oral anxiolytic regimen
- Claustrophobic patients
- Patients with severe comorbidities (e.g., obstructive sleep apnea, gastroesophageal reflux)
- Prolonged study (multiple scans)
- Intensive care unit patients

BOX 91.2 Absolute or Relative Contraindications to Magnetic Resonance Imaging

- Aneurysm clips
- Cardiac pacemaker[a]
- Implantable cardioverter-defibrillator (ICD)[a]
- Cochlear implant[a]
- Electronic implanted devices (e.g., insulin pump)
- Epidural catheters (some are MRI conditional, e.g., Flex Tip plus)[a]
- Foreign bodies, metallic objects near vital organs
- Neurostimulator[a]
- Penile prosthesis
- Permanent contraceptive devices

[a]Consult the device manufacturer for product classification for MRI safety.

BOX 91.3 Potential Problems Related to Magnetic Resonance Imaging

Malfunction of anesthesia equipment
Malfunction of monitoring equipment
Anesthesia equipment interfering with image quality
High-velocity ferromagnetic projectile from loose objects
Disruption of electronic devices
Nephrogenic systemic fibrosis (in patients with acute/severe renal insufficiency)

TABLE 91.1 Monitoring Problems in Magnetic Resonance Imaging

Monitor	Problem
Electrocardiogram (ECG)	T waves and ST segments are often altered, and qualitative information is lacking during MRI scanning cycle; ECG cables may cause burn injury; special ECG electrodes are required to avoid burn injury
Pulse oximeter	Malfunction; heating of probe may cause burn injury; fiberoptic connection to patient is best
Capnograph	Requires long tubing, resulting in prolonged upsweep and delay in display of real-time measurements; respiratory rate and trends are still useful
Temperature	Requires a fiberoptic sensor
Blood pressure	Noninvasive: connections for cuff and hoses should be plastic Invasive: use fiberoptic system and transducers with nonferrous components

All anesthesia equipment, as well as the pulse oximeter, intravenous line pole, and anesthesia cart, should also be nonferromagnetic. MRI-safe anesthesia machines, laryngoscopes (lithium batteries), and stethoscopes are available. Any equipment with a transformer must be kept out of the magnetic field. Gas cylinders must be aluminum. If inhalation anesthesia is used, a suitable scavenging system should be available. "MRI-safe" vaporizers may have minimal amounts of ferromagnetic materials and should not be taken into the MRI suite unless mounted on the anesthesia machine or ventilator. The area surrounding a magnetic field stronger than 5 gauss (marked on the floor of the MRI suite) should not contain any ferromagnetic items.

MANAGEMENT

As with any anesthesia induction, the monitoring standards of the American Society of Anesthesiologists should be adhered to. To avoid problems due to monitoring cables, it is advisable to place them as near as possible to the center of the long axis of the MRI magnetic field. They also should be placed on the part of the patient that is most distant from the radiofrequency field with avoidance of coiled or crossed wires. The anesthetic technique is dictated by the age of the patient and concurrent diseases (Box 91.4).

Vaporizers are accurate in the MRI suite. Newer intravenous infusion pumps are nonferromagnetic and can be used within the 5-gauss limit for magnetic fields with remote monitoring from the control room. Ferromagnetic pumps can be used via long infusion tubing.

The use of a contrast agent (gadolinium) is often required and should be used with caution in patients with acute or severe renal insufficiency due to the risk for nephrogenic systemic fibrosis.

If a patient comes from the intensive care unit, special care must be taken to ensure that all cables and transducers are carefully screened and ferromagnetic objects are removed (e.g., Foley catheter clips). Cables should be straightened to prevent burns. If cardiac arrest occurs, cardiopulmonary resuscitation should be initiated, and the patient should be removed from the magnetic field and moved to a designated area with resuscitation equipment. It is essential that the code team remains outside zone IV to avoid the release of any potentially harmful projectile objects.

If a fire or inadvertent or controlled shutdown of the magnet (quench) occurs, institutional protocols should be followed to prevent harm to both patients and staff. Quenching the magnet can lead to release of helium and intense heat production, leading to both fires and possible asphyxiation in the magnet room.

BOX 91.4 Anesthetic Options for Magnetic Resonance Imaging

Sedation for Pediatric Patients
Oral chloral hydrate (<3 years old) 75–100 mg/kg for procedures up to 1 hour
Dexmedetomidine 1 μg/kg bolus and infusion 1–2 μg/kg/h
Pentobarbital 2.5–5 mg/kg intravenously (maximum 100 mg/dose)
Propofol bolus of 2–3 mg/kg and infusion of 150–200 μg/kg/min

Benzodiazepines for Sedation and Anxiolysis in Adults
Midazolam, lorazepam, or diazepam orally or intravenously
Good technique for patients with few medical problems and an easily maintained airway
Rapid recovery; little nausea or vomiting

General Anesthesia With Endotracheal Tube Ventilation
Inhalation anesthesia or propofol infusion
Good for very young patients or those with gastroesophageal reflux, full stomach, or raised intracranial pressure

General Anesthesia and Spontaneous Respiration With Laryngeal Mask Airway
Inhalation anesthesia or propofol infusion

PREVENTION

To prevent complications in the MRI suite, one must be aware of the MRI contraindications (see Box 91.2). Good communication between the radiology and anesthesiology departments is essential to ensure that the correct anesthesia and monitoring equipment is available from the outset and that at-risk patients undergo prescan anesthesia evaluations. The anesthesia staff involved with providing care for MRI should be aware of all the potential technical problems that may arise in this unique environment. Safety education should be put in place based on existing guidelines and updated frequently based on technology improvements.

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Muscle Relaxants

92

Constance L. Monitto

Case Synopsis

A 2-year-old boy presents for inguinal herniorrhaphy. During mask induction with oxygen, nitrous oxide, and sevoflurane, he develops laryngospasm, which is treated with intramuscular succinylcholine. A wide-complex QRS tachycardia is subsequently noted on the electrocardiogram monitor.

PROBLEM ANALYSIS

Definition

There can be complications with all neuromuscular relaxant drugs; however, the potential for serious complications is greatest with succinylcholine (SCh). Although these complications have limited its routine use, SCh retains a role in pediatric anesthesia because of its unparalleled speed of onset, its brief duration of action, and its ability to be administered intramuscularly when intravenous access has not been obtained. These properties continue to justify its availability for emergency intubation and management of laryngospasm that does not resolve with conservative airway interventions.

Significant complications associated with SCh use in children include the following:

- Cardiac arrhythmias
- Elevations in intragastric, intraocular, and intracranial pressure
- Rhabdomyolysis and myoglobinemia
- Unanticipated prolonged duration of action
- Masseter spasm
- Malignant hyperthermia (see Chapter 195)

Nondepolarizing muscle relaxants (NDMRs) generally belong to one of two chemical classes: the aminosteroids (e.g., pancuronium, vecuronium, rocuronium, rapacuronium) or the benzylisoquinolinium compounds (e.g., d-tubocurarine, mivacurium, atracurium, cisatracurium). Complications with NDMRs include profound muscle weakness and impaired respiration with residual neuromuscular blockade (see Chapter 95). Prolonged myopathy after extended infusion of aminosteroid relaxants in the intensive care unit has been reported. Life-threatening anaphylactic reactions and bronchospasm have also been observed. However, the most common side effects of the NDMRs result from their histaminergic, cholinergic, and muscarinic effects. None of these reactions is unique to pediatric patients.

Recognition

Depolarizing Muscle Relaxants

Although decamethonium was the first depolarizing muscle relaxant introduced into clinical practice in the late 1940s, it is no longer used in patient care, so this discussion is limited to SCh. Because of its structural similarity to two acetylcholine molecules joined together, succinylcholine initially stimulates acetylcholine receptors at the neuromuscular junction. Subsequently, as occurs in the presence of excess acetylcholine, these receptors remain inactive until the drug diffuses away and is broken down by local pseudocholinesterase.

Arrhythmias, most commonly sinus bradycardia or junctional rhythm, frequently accompany the administration of SCh. Bradycardia is due to SCh's similarity to acetylcholine's parasympathetic action on the heart. Its occurrence is particularly relevant in pediatric practice because it can cause significant hypotension in infants and children whose cardiac output is largely heart-rate dependent or, in the case of junctional rhythm, dependent on properly timed atrial contractions to augment ventricular filling (e.g., hypertrophic, dilated, or restrictive cardiomyopathy or arrhythmogenic right ventricular dysplasia; see Chapter 39). Further, asystole has been reported in patients of all ages after SCh administration. Life-threatening ventricular arrhythmias heralding severe rhabdomyolysis, hyperkalemia, or malignant hyperthermia occur less frequently.

Succinylcholine can cause elevations in intragastric, intraocular, and intracranial pressure as a result of muscle fasciculations and elevations in cerebral blood flow and metabolism.

Rhabdomyolysis and myoglobinemia can be detected in a significant proportion of children following SCh administration. Although some patients may have detectable myoglobinuria, in the vast majority, rhabdomyolysis is a benign sequela of SCh. In high-risk populations, however, including patients with congenital muscle disease or malignant hyperthermia sensitivity, SCh-induced rhabdomyolysis can be life threatening due to associated electrolyte disturbances, renal failure, or disseminated intravascular coagulation.

Prolonged neuromuscular blockade can occur after administering SCh to patients with heterozygous or homozygous genetic abnormalities in the butyrylcholinesterase gene (pseudocholinesterase deficiency) (see Chapter 98). Because the short-acting, nondepolarizing muscle relaxant mivacurium (which is no longer marketed in the United States) is also metabolized by butyrylcholinesterase, its use may produce this response as well.

Masseter spasm (or trismus) is characterized by an exaggerated increase in the tension of the masseter muscle that prevents mouth opening after SCh administration. Careful investigations have shown that masseter muscle tone is commonly increased after SCh administration. Hence, trismus may represent an extreme in the normal dose-related increase in muscle tension after SCh. As a result, masseter rigidity alone is not considered diagnostic of malignant hyperthermia. Recognition and management of malignant hyperthermia are discussed in Chapter 195.

Nondepolarizing Muscle Relaxants

Intraoperative anaphylaxis to neuromuscular blocking agents is a rare but serious complication. Although at times difficult to diagnose,

clinical signs include flushing, hypotension, tachycardia, and bronchospasm following administration of the agent.

Histamine release occurs with some benzylisoquinoline relaxants, and is recognized by skin flushing, hypotension, and tachycardia. Alternatively, the increased heart rate and hypertension observed with pancuronium is thought to involve blockade of muscarinic M2 receptors with associated vagolytic effects, as well as blockade of neuronal reuptake of norepinephrine.

Life-threatening episodes of bronchospasm, characterized by profound difficulty in ventilation with absent end-tidal carbon dioxide, as well as some deaths due to irreversible bronchospasm, were reported after the introduction of the aminosteroid NDMR rapacuronium bromide to clinical practice in 1999. Subsequent laboratory studies suggested that clinically relevant concentrations of rapacuronium may provoke bronchospasm due to muscarinic airway effects, and the drug was withdrawn from the market in 2001, less than 2 years after Food and Drug Administration (FDA) approval.

Risk Assessment

Succinylcholine

Vagally mediated arrhythmias, including sinus or atrioventricular junctional bradycardia, sinus pause, and transient asystolic arrest, may occur in as many as 40% to 60% of children after a single intravenous dose of SCh, but they are infrequently associated with intramuscular administration. As in adults, repeated doses may elicit more frequent and severe bradyarrhythmias.

Malignant ventricular dysrhythmias and even cardiac arrest after SCh may occur as a result of exaggerated potassium release in patients with acute or progressive denervation injury (e.g., spinal cord transection, peripheral neuropathy, stroke), extensive tissue damage (e.g., burns, crush injury), prolonged immobilization, or neuromuscular disease, as these disorders are associated with an elevated number of extrajunctional acetylcholine receptors. Many of these conditions are evident before induction of anesthesia, but this is not always the case with progressive neuromuscular disease in young boys. For example, Duchenne muscular dystrophy affects approximately 1 in 3600 boys. Although both sexes can carry the disease-causing genetic mutation, because it is an X-linked recessive gene, females are rarely clinically affected. Laboratory testing can identify children who carry the mutated gene at birth, but in cases in which the disease results from a spontaneous germ cell mutation, the diagnosis may not be made until the child is old enough to manifest symptoms.

Historically, rhabdomyolysis after SCh administration was detected by serum myoglobin elevation in 40% of children anesthetized with halothane, and as many as 8% had associated myoglobinuria. Case reports also describe its occurrence in patients receiving enflurane, isoflurane, or sevoflurane. Although far more common in pediatric patients than in adults, rhabdomyolysis appears to be a benign process in the overwhelming majority of children. Nevertheless, children with myopathic processes can exhibit life-threatening hyperkalemia, arrythmias, acute renal injury, and disseminated intravascular coagulation. Because the underlying myopathy may be undiagnosed in young children, cardiac arrest in apparently healthy children has been reported after SCh administration.

Butyrylcholinesterase/pseudocholinesterase is synthesized in the liver. Although several medical conditions, including hepatic failure, may result in striking reductions in circulating concentrations of normal cholinesterases, reduced concentrations of normal enzyme have a far less dramatic impact than the presence of a genetically defective enzyme. Approximately 1 in 3000 patients presents with (frequently) occult genetic variants of pseudocholinesterase of the type that can result in markedly prolonged neuromuscular blockade after the administration of SCh or mivacurium.

The frequency of masseter muscle spasm remains controversial. Some cite a 1% incidence rate, whereas others say that it never occurs. In 1994 Hannallah and Kaplan reported incomplete relaxation in 4.4% and masseter rigidity in 0.2% of children anesthetized with halothane and succinylcholine, but observed no episodes of trismus (inability to open the jaw). Linking SCh-induced masseter spasm and malignant hyperthermia remains a matter of controversy. Of real concern, though, is the finding that in a select population of patients referred to the North American Malignant Hyperthermia Group, 50% of children with masseter spasm who were screened for malignant hyperthermia sensitivity by muscle biopsy tested positive. Of these patients, approximately 10% developed clinical signs of malignant hyperthermia perioperatively. Therefore severe masseter spasm must be viewed with concern.

Nondepolarizing Muscle Relaxants

The true incidence of anaphylactic reactions to neuromuscular blocking agents (NMBs) is hard to accurately quantify. Anaphylaxis is reported to occur in 1 in 10,000 to 20,000 anesthesias, and 50% to 70% of these episodes are thought to be related to NMBs. Incidences vary among different patient populations, but reactions may occur more commonly after SCh and rocuronium administration and less frequently after vecuronium or benzylisoquinoline NDMR administration. A prior history of drug exposure is not necessary. Patients with an allergic history or a history of anaphylaxis may be more susceptible to histamine release from NDMRs that are associated with histamine release (Table 92.1).

Implications

Succinylcholine

Bradyarrhythmias usually are benign and self-limited or respond to vagolytic therapy. However, if they are protracted or associated with hemodynamic compromise, intervention may be required. In contrast, malignant ventricular arrhythmias and cardiac arrest seen with exaggerated potassium release after SCh have projected mortality rates as high as 60% and require prompt diagnosis and treatment.

Because small children have limited muscle mass, changes in intragastric pressure resulting from SCh-induced muscle fasciculations are generally minor and clinically unimportant. Increases in intraocular pressure are transient, but may be clinically relevant in patients presenting with an open globe for surgery as they may result in extrusion of vitreous contents.

Rhabdomyolysis rarely has lasting consequences except in myopathic patients, in whom the consequences can be dire.

Children with atypical pseudocholinesterase who receive succinylcholine eventually recover neuromuscular function without sequelae. In the short term, they may require ventilatory assistance until they have regained sufficient strength to maintain adequate ventilation. However, long-term implications have more to do with genetic counseling and awareness of the condition.

Masseter spasm usually has few immediate implications, because the spasm is localized to the masseter. If, however, the patient is at risk for malignant hyperthermia, the implications for future management of both the child and the family are substantial.

Nondepolarizing Muscle Relaxants

Intraoperative anaphylaxis from NDMRs is a serious concern, with a mortality rate of approximately 3% to 6%. NDMRs that release

TABLE 92.1 Intubating Dose, Primary Clearance, and Side Effects of Muscle Relaxants in Children

Muscle Relaxant	Intubating Dose (IV mg/kg)	Primary Method of Clearance	Cholinergic Effects	Histamine Release
Succinylcholine	2–3 (infants) 2 (children) 4 (IM)	Plasma cholinesterase	Stimulates	Rare
Mivacurium	0.2–0.4	Plasma cholinesterase	No effect	+ (doses >3 × ED_{95})
Atracurium	0.3–0.5	Ester hydrolysis; Hofmann degradation	No effect	++ (doses >3 × ED_{95})
Cisatracurium	0.15–0.2	Ester hydrolysis; Hofmann degradation	No effect	Minimal
Vecuronium	0.1 0.4 (rapid sequence)	Hepatic	No effect	None
Rocuronium	0.6 1.0 (rapid sequence) 1.0 IM (infants) 1.6 IM (children)	Hepatic	No effect	None
d-Tubocurarine	0.3–0.6	Renal	No effect	+++
Pancuronium	0.1	Renal	Blocks ++[a]	None

[a]Also causes sympathetic stimulation.
IM, Intramuscular; *IV,* intravenous.

histamine are best avoided in patients with asthma, a significant right-to-left shunt, or valvular stenosis. Owing to the potential for tachycardia, pancuronium is best avoided in patients in whom tachycardia might be detrimental (e.g., severe mitral, tricuspid, or aortic stenosis; coronary strictures or anomalous left coronary artery; accelerated, juvenile coronary artery disease).

MANAGEMENT

Succinylcholine

Persistent or hemodynamically disadvantageous bradyarrhythmias are treated with atropine or (in more critical situations) chest compressions, epinephrine, and/or pacing, particularly in infants. Dysrhythmias with hyperkalemia are treated with cardiopulmonary resuscitation, alkalization, calcium, and glucose-insulin. Successful resuscitation may be prolonged, and extracorporeal circulation may be needed for extreme cases, at least until potassium is eliminated by excretion or dialysis.

Increases in intraocular or intracranial pressure can be attenuated by pretreatment with an NDMR, and elevations in intracranial pressure can also be ameliorated by interventions aimed at decreasing cerebral blood flow and metabolism.

Rhabdomyolysis that goes undetected requires no specific therapy in most patients. For those with myopathy, full cardiac resuscitation and measures to promote myoglobin excretion (e.g., furosemide, mannitol) may be required.

Children with clinically suspected pseudocholinesterase deficiency require ventilatory support until neuromuscular function returns, at times up to 4 to 8 hours after NMB administration. Absolute pseudocholinesterase activity and the dibucaine and fluoride numbers should subsequently be determined to guide future anesthetic management.

Isolated masseter spasm usually requires no specific treatment because the spasm recedes within a few minutes. Reports suggest that it is safe to proceed with anesthesia and surgery with careful documentation of capnography and patient temperature, adequate hydration and monitoring of serum electrolytes, acid-base status, myoglobin, and creatine phosphokinase levels. Because masseter rigidity alone is not diagnostic of malignant hyperthermia, it is no longer considered an indication to change to a nontriggerering anesthetic. However, surgery should be aborted if signs of persistent rigidity, increasing metabolic rate, or malignant hyperthermia develop. Further testing may be required.

Nondepolarizing Muscle Relaxants

Routine management of anaphylaxis includes removal of the antigen source when possible, inhibition of mediator production and release (e.g., steroid administration), and interventions to modulate the effects of the mediators. These may include histaminergic blockade, treatment of bronchoconstriction with β_2-agonists, and the administration of intravenous fluids and epinephrine to decrease bronchial hyperresponsiveness and support the circulation. Postoperative confirmatory laboratory data include elevated serum tryptase, histamine, and (drug-specific) immunoglobulin E levels at the time of the reaction and 6 weeks later.

Hypotension due to histamine release is treated with intravenous fluids and vasopressors. Treatment of symptomatic tachycardia not associated with hypotension may include a deepening of anesthesia, opioids, and a β-blocker.

PREVENTION

Succinylcholine

In light of reports of profound SCh-induced rhabdomyolysis, cardiac arrest, and death in apparently healthy children ultimately diagnosed with myopathic disease, drug manufacturers sought to ban routine SCh use in children in 1993. In response to protests from anesthesiologists who were aware of the drug's still-unique attributes, the FDA held an open committee meeting from which compromise labeling for SCh emerged (Fig. 92.1). However, because life-threatening hyperkalemia can only be prevented by avoiding SCh in high-risk patients (who cannot always be identified preoperatively), expert recommendation states that routine use of succinylcholine in infants and children should be avoided. Administration of the drug to infants and children is only recommended for emergency control of the airway.

Considering alternatives, intramuscular administration of rocuronium has been studied, but its duration of action is significantly longer than succinylcholine, and intubating conditions are not consistently satisfactory. Hence it is not considered an acceptable substitute when intravenous access is not available. However, when an intravenous line is in place, a recent Cochrane review identified no difference in intubating conditions between intravenously administered rocuronium and SCh in children undergoing modified rapid-sequence induction, as well as in adults administered 1.2 mg/kg rocuronium. Although SCh was deemed superior because of its short duration of action, this limitation is now

BOXED WARNING

Rare reports of acute rhabdomyolysis w/ hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death in healthy pediatric patients w/ undiagnosed skeletal muscle myopathy; most frequently Duchenne's muscular dystrophy. Often presented w/ peaked T-waves and sudden cardiac arrest w/in min after administration to healthy-appearing pediatric patients (most frequently ≤8 yrs of age) and adolescents. Treatment of hyperkalemia should be instituted; administer IV Ca^{2+}, bicarbonate, and glucose w/ insulin, w/ hyperventilation. Appropriate treatment should be instituted when signs of malignant hyperthermia are present. Reserve use in pediatric patients for emergency intubation where securing airway is necessary (eg, laryngospasm, difficult airway, full stomach, or for IM use when suitable vein is inaccessible).

Fig. 92.1 Boxed warning concerning the association between succinylcholine chloride (Anectine) and hyperkalemic cardiac arrest. (From Anectine (succinylcholine chloride)—drug summary. PDR.net, 2016. Available at http://www.pdr.net/drug-summary/Anectine-succinylcholine-chloride-680. Accessed June 16, 2016.)

less significant because sugammadex has been commercially available in Australia and Europe since 2008, and the FDA approved its use in the United States in late 2015. Sugammadex is a γ-cyclodextrin that reverses aminosteroid (rocuronium and vecuronium) neuromuscular blockade by encapsulating the drug in its central core. This noncovalent bonding is able to reverse the effects of rocuronium in less than 3 minutes, leaving open the possibility of emergency reversal of neuromuscular blockade in a time frame comparable to that seen with succinylcholine.

Nondepolarizing Muscle Relaxants

Because of its histamine-releasing properties, atracurium has been replaced in clinical practice by its metabolite cisatracurium, which is 1.5 times more potent but does not release histamine even at very high doses. Similarly, use of rocuronium or vecuronium precludes the hyperdynamic effects seen with pancuronium administration.

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Nitrous Oxide: Neurotoxicity

93

Ka Chun Suen • Daqing Ma

Case Synopsis

A 7-week-old infant underwent a Kasai procedure for the diagnosis of biliary atresia. The patient received isoflurane and nitrous oxide, and the operation was uneventful. Five days after the surgery, the patient developed hypotonia, hyporeflexia, and apnea. Computed tomography showed severe cerebral atrophy, and homocysteine was detected in the infant's urine.

PROBLEM ANALYSIS

Definition

Nitrous oxide (N_2O), also known as laughing gas, was first discovered in 1772 by John Priestly. In 1798 the Pneumatic Institute was founded by Thomas Beddoes, which aimed to study the use of gases in medicine. Humphry Davy, who worked as an assistant in the institute, noticed the reduction in pain that was caused by an eruption of a wisdom tooth after inhaling N_2O. He later published a book on N_2O in which he stated, "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations where too great an effusion of blood does not take place." However, his discovery was not widely accepted at that time. Later, Horace Wells, an American dental surgeon, also noticed the anesthetic effect of N_2O as he saw that Gardner Quincy Colton injured his leg without feeling any pain while receiving the gas. Wells later requested to get his tooth removed while inhaling N_2O, in which he reported that the surgery was a painless experience. Nonetheless, Wells failed to show the same effect during a demonstration at Massachusetts General Hospital. Hence, it was not until about 20 years later that Colton reintroduced the use of N_2O with the improved apparatus, and since then it has become popular.

Recognition

N_2O is a colorless, sweet-smelling gas, which has been used for more than 150 years as an anesthetic (Table 93.1). It is considered to be the least potent inhalational anesthetic in current practice, with 104% of minimal alveolar concentration. Because of its low potency, N_2O is often used as an additional inhalation agent to augment the effect of the anesthesia. For example, evidence has shown that pretreatment of N_2O with 50% oxygen enhances the speed of induction of sevoflurane. N_2O has a relatively low partition coefficient of only 0.47, which allows rapid equilibrium between the partial pressures of blood and gas. For this reason, the speed of onset and offset of N_2O is relatively quick. Furthermore, N_2O gives a "second gas effect" in which it increases the speed of onset of other gaseous anesthetics. For instance, the speed of onset of desflurane is increased by the concurrent administration of N_2O. This "second gas effect" is due to the lower lipid solubility of N_2O than nitrogen, which allows rapid diffusion of N_2O into blood. This causes an increased concentration of the volatile anesthetics in the alveolar space and thus the increased speed of onset. N_2O is also transported freely in the blood as it does not bind to hemoglobin. The elimination of this inhalation agent is therefore rapid.

Mechanism of Action

Although nitrous oxide has been used for more than a century, its mechanism of action is still not completely understood. As an anesthetic agent, it has been shown that N_2O interacts with different receptors and channels, including γ-aminobutyric acid type A ($GABA_A$), *N*-methyl-D-aspartate receptor (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazole-propinate receptor (AMPA). However, there is only weak or no potentiation of N_2O on the $GABA_A$ channel. NMDA and AMPA receptors are believed to be the major sites of action, in which N_2O antagonizes their action to inhibit the postsynaptic current. As an analgesic agent, N_2O binds to different subtypes of opioid receptor. Whereas N_2O competitively inhibits the μ-opioid receptor, it noncompetitively inhibits the κ-opioid receptor.

Effect on the Cardiovascular System

N_2O has minimal effect on heart rate and arterial blood pressure but mildly depresses the myocardial contraction that is offset by sympathetic activation. Despite its minimal effect on different physiologic parameters, the safety of N_2O regarding its effect on the cardiovascular system has been questioned recently. Evidence showed that intraoperative administration of N_2O can increase the rate of myocardial ischemia that is associated with an increased level of homocysteine in patients. The ENIGMA-I trial studied different complications that are associated with the use of N_2O, in which it showed that there is a trend of increase of myocardial infarction (MI) in those who have received N_2O. The follow-up study of the ENIGMA-I trial confirmed this as it demonstrated that there is an increased risk of MI after the administration of N_2O. Nonetheless, the ENIGMA-II study, a large multicenter randomized controlled trial on the effect of N_2O on the risk of perioperative cardiovascular adverse events, in contrast to the ENIGMA-I trial, showed that there is no increase in the rate of death or stroke in those who have used N_2O.

Effect on the Respiratory System

N_2O also has minimal effect on the respiratory system in which it does not affect the minute ventilation or cause bronchodilation.

TABLE 93.1 Physical and Chemical Properties of Nitrous Oxide

Boiling point	–88°C
Molecular weight	44
Minimal alveolar concentration	104%
Blood:gas partition coefficient	0.47
Fat:blood partition coefficient	2.3
Color	Colorless
Smell	Sweet smelling

Data from Brown SM, Sneyd JR: Nitrous oxide in modern anesthetic practice. *BJA Educ* 16(3):87-91, 2015; Becker DE, Rosenberg M: Nitrous oxide and the inhalation anesthetics. *Anesth Prog* 55(4):124-131, 2008.

Risk Assessment

Use in Pediatric Anesthesia

N_2O has multiple functions in clinical practice as it has anesthetic, analgesic, and anxiolytic properties. Therefore it is a popular choice in young patients. It has been shown to be safe and effective as an analgesic in different procedures in pediatric patients. Equimolecular mixture of oxygen and nitrous (EMONO) is a safe intervention that provides analgesic and anxiolytic properties for pediatric patients who undergo different procedures, including lumbar puncture, bone marrow aspiration, fibrotic bronchoscopy, and laceration repair. Adverse reaction concerning N_2O administration is scarce in pediatric patients with only 0.2% of serious adverse events such as airway obstruction and oxygen desaturation; the majority of adverse events are nausea, vomiting, and euphoria.

Neurotoxicity of Nitrous Oxide Use in Young Patients

Despite the safe profile of nitrous oxide, neurotoxicity is a major concern. In vivo studies have shown that aged brains and perinatal brains are more vulnerable to neurotoxicity than brains of any other ages. During the early stage of life, different species undergo crucial brain development. Synaptogenesis is a process where apoptosis of neurons takes place to allow maturation and the development of synapses. Whereas synaptogenesis happens in the first 2 weeks of life in rats, it lasts from the third trimester of pregnancy to about 2 years after birth in humans. Evidence has shown that N_2O can cause widespread neuroapoptosis in multiple parts of the brain, including the cerebral cortex, hippocampus, and thalamus in young rats, causing cognitive damage that leads to long-term memory and learning impairment. Shu and colleagues have shown that pretreatment of 7-day-old rats with N_2O and isoflurane under hypoxic condition causes a decrease in the antiapoptotic factor, Bcl-2 and an increase in the proapoptotic factor, P53, most prominently in the hippocampus. An increase in the level of cytochrome c, a key factor in activating apoptosis, is also observed. N_2O can also cause an increased level of c-fos, a neuronal marker of tissue damage, as well as swellings in intracellular organelles such as mitochondria and endoplasmic reticulum in posterior cingulate and retrosplenial cortices. A similar effect can be seen in postnatal day 5 to 6 rhesus monkeys exposed to a combination of N_2O and isoflurane, in which neuroapoptosis can be observed in the temporal gyrus, hippocampus, and frontal cortex. It is important to recognize that the locations where N_2O affects the brain in rhesus monkeys are different from those in rats. This may be due to the different time course of brain development between rats and rhesus monkeys. In humans, although there are limited clinical studies, in utero studies demonstrated that the administration of N_2O during pregnancy could cause hydrocephalus and encephalocele and is associated with increased muscle tone.

Mechanism of Neurotoxicity Caused by Nitrous Oxide

Although the causes of neurotoxicity are not fully understood, evidence has shown that it is due to the antagonistic characteristic of N_2O to NMDA receptors located on neurons with GABA channels. This triggers the abnormal release of acetylcholine (ACh) that affects some parts of the brain. In physiologic condition, the action of NMDA promotes the inhibitory action of GABAergic neurons so that the release of ACh is inhibited. However, when N_2O is administered, the action of NMDA receptors is prohibited and therefore allows the release of ACh, which in turn affects some regions of the brain, including the basal ganglia.

Another cause is the increased level of homocysteine that is associated with the administration of N_2O. N_2O can irreversibly bind to cobalt atom in vitamin B_{12}, which is a cofactor for methionine synthase that is responsible for the conversion of homocysteine to methionine. Impairment of methionine synthase function leads to an increased homocysteine level. Homocysteine can act as an agonist on the NMDA receptor for a longer period of time than the antagonism of N_2O, which can lead to respiratory, cardiovascular, and neurologic complications and death. Moreover, the binding of homocysteine to NMDA receptors also induces the release of intracellular Ca^{2+}. This in turn causes the release of reactive oxygen species, including superoxide, that can damage almost all parts of the brain.

MANAGEMENT AND PREVENTION

Although there is vast amount of preclinical evidence indicating that N_2O is neurotoxic, particularly in the young, clinical data are still lacking per se. Therefore more clinical study is warranted to enhance our understanding. Seeking an ideal inhalation anesthetic with no side effects to replace the clinical use of N_2O is what anesthetists are aiming for. Xenon and dexmedetomidine, an α_2-adrenoceptor agonist, may be free from neurotoxicity but clinical studies are needed for confirmation. Until then, the use of N_2O remains controversial and some authors have suggested avoiding its use whereas others advocate continuing to use it.

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94 Nonbarbiturate Anesthetics

Kristen Burton • Gaurav Malhotra

Case Synopsis

A 53-year-old, 75-kg man with a past medical history significant for poorly controlled hypertension and non–insulin-dependent diabetes is scheduled for an external fixation of a femur fracture sustained after a fall off a ladder 2 days ago. The patient has been NPO since the accident and on maintenance fluids of lactated Ringer's solution at 75 mL/h. He has no known drug allergies and takes hydrochlorothiazide, lisinopril, and metformin at home. On arrival to the operating room, his heart rate is 96 beats per minute, his blood pressure is 105/50 mm Hg, and he is saturating 98% on 2 L nasal cannula. During induction, he receives 150 μg of fentanyl, 80 mg of lidocaine, 150 mg of propofol, and 8 mg of vecuronium. After easy mask ventilation, the airway is secured with an endotracheal tube. Postinduction blood pressure is 65/43 mm Hg with a heart rate of 108 beats per minute. Minimal response is noted to initial boluses of 100 μg of phenylephrine and 10 mg of ephedrine. Ultimately, the patient's hemodynamics stabilized after a bolus of 1 L of crystalloid solution.

PROBLEM ANALYSIS

Definition

In addition to ketamine (see Chapter 89), nonbarbiturate anesthetics include midazolam, dexmedetomidine, etomidate, and propofol. Midazolam and dexmedetomidine are more commonly used as sedative-anxiolytic agents and often as adjuncts to other induction agents. Both etomidate and propofol are used as intravenous (IV) induction agents; the former is often preferred for patients with or at risk for hemodynamic instability.

Recognition

Mechanism of Action

Benzodiazepines, propofol, and etomidate all exert their effect via interaction with γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the central nervous system. Midazolam is a benzodiazepine that increases the frequency of chloride channel opening by facilitating GABA-receptor binding, causing cell membrane hyperpolarization and thus producing an inhibitory effect on neural function.

Dexmedetomidine is an α_2-agonist that causes activation in the locus coeruleus and spinal cord that results in a decrease in sympathetic nervous system outflow (norepinephrine and epinephrine) and cellular hyperpolarization through the reduction of cyclic adenosine monophosphate.

Etomidate is an imidazole derivative. It also causes hyperpolarization of the neuronal cell membrane, thereby inactivating the reticular activating system. Etomidate may also increase GABA-receptor availability.

Propofol is an alkylphenol. It is presumed to act on GABA receptors in the central nervous system to increase the frequency of chloride channel opening. Thus propofol too has a neuroinhibitory action.

Pharmacokinetics

Midazolam is short acting, water soluble in a buffered acid medium (pH = 3.5), and highly lipophilic at physiologic pH. Midazolam has a fast onset of action and is highly protein bound. The short duration of action is secondary to redistribution and hepatic metabolism; however, because midazolam is excreted by the kidneys, its effects may be extended in renal failure.

Dexmedetomidine, a lipophilic and highly protein-bound imidazole compound, has a rapid onset of action and a short duration of action secondary to redistribution. Dexmedetomidine undergoes metabolism in the liver and thus should be used with caution in patients with hepatic impairment. Its inactive metabolites are primarily renally excreted. Dexmedetomidine is diluted in a crystalloid solution and can be given as a loading dose over 10 minutes followed by a maintenance infusion.

Etomidate is water soluble and is dissolved in 35% propylene glycol. Its short duration of action is the result of redistribution after an initial distribution time of 3 minutes. It is metabolized by the liver into inactive metabolites that are excreted by the kidneys (85%) and in the bile (13%). Age decreases its clearance, whereas in cirrhosis, clearance is normal, but the volume of distribution and elimination half-time are doubled.

Propofol is highly lipophilic and is formulated in a soybean oil–egg yolk–lecithin emulsion. Pharmacodynamic properties of propofol are dependent on the plasma concentration of the drug. The induction dose of propofol in adults is 1 to 2.5 mg/kg, producing blood concentrations of 2 to 6 μg/mL. Awakening is rapid even after prolonged infusions and typically occurs at plasma concentrations of 1.0 to 1.5 μg/mL. Steady-state propofol blood concentrations are generally proportional to infusion rates. The context-sensitive half-time of propofol is minimally influenced by infusion duration, owing to rapid metabolic clearance. Biotransformation occurs in the liver. Clearance exceeds hepatic blood flow, suggesting the existence of extrahepatic metabolism, most significantly by the lungs. Metabolites are secreted in the urine. Hepatic or renal dysfunction does not reduce the clearance of the parent drug.

Other pharmacokinetic data for propofol, dexmedetomidine, etomidate, and midazolam are listed in Table 94.1.

Risk Assessment

When choosing a nonbarbiturate anesthetic for induction of general anesthesia or sedation, there are several options, including midazolam, dexmedetomidine, etomidate, propofol, and ketamine (see Chapter 89).

TABLE 94.1 Pharmacokinetic Data for Propofol, Etomidate, Midazolam, and Dexmedetomidine

	DRUG			
Parameter	**Propofol**	**Etomidate**	**Midazolam**	**Dexmedetomidine**
Distribution half-life (minutes)	2–8	Initial: 3 Late: 29	3–10	Approximately 6
Elimination half-life (hours)	0.5–1.5	2–5	1–4	2–3
Biotransformation	Hepatic; extrahepatic (lungs)	Hepatic	Hepatic	Hepatic
Metabolites	Inactive	Very weakly active	Inactive	Inactive
Excretion	Renal	Renal (85%); bile (13%)	Renal	Renal; fecal (4%)
IV induction dose	1–2.5 mg/kg	0.2–0.5 mg/kg	0.1–0.2 mg/kg	0.5–1 μg/kg over 10 min
IV maintenance dose	50–150 μg/kg/min	2.5–10 μg/kg/min	0.05–0.1 μg/kg/min	0.2–0.7 μg/kg/h

IV, Intravenous.

The most commonly used drug is propofol, owing to its rapid onset of action and recovery and lack of serious side effects. However, when choosing among these nonbarbiturates as IV induction agents, one must consider whether any of the following is present or possible:

- Hypovolemia or circulatory shock
- Cardiovascular disease
- Respiratory insufficiency
- Central nervous system injury or impairment
- Hepatic or renal impairment and any related pharmacokinetic implications
- Drug interactions
- Concern for difficult airway or other circumstance requiring awake intubation or preservation of spontaneous ventilation, including cervical spine instability or large mediastinal mass

Midazolam

Midazolam has little effect on hemodynamic parameters (Table 94.2). At a dose of 0.2 mg/kg, midazolam appears to be safe in patients with cardiovascular disease. Any increase in heart rate is likely a reflex-caused response to modestly decreased stroke volume and blood pressure, with reduced sympathetic tone secondary to anxiolysis. Hypovolemia accentuates these effects. In contrast, midazolam can cause apnea and decrease the ventilatory response to carbon dioxide (CO_2), especially after bolus dosing. Midazolam is commonly given with an opiate (e.g., fentanyl) for sedation, which can potentiate its effect on respiration, so patients receiving this combination of drugs must be closely monitored for signs of respiratory insufficiency.

Other considerations include the following:

- Slight reduction in cerebral O_2 consumption, with little or no decrease in cerebral blood flow
- Small decrease in intracranial pressure (ICP)
- Maintains cerebral autoregulation
- Large decrease in intraocular pressure (IOP)
- Shortens seizure duration and increases seizure threshold
- Slower loss of consciousness and longer recovery period for return of cognitive functions
- Potential for coughing, hiccups, or involuntary skeletal muscle movements when used for induction of anesthesia

Dexmedetomidine

Dexmedetomidine is a highly selective agonist of the α_2-adrenoreceptor; however, rapid bolus dosing may elicit vasoconstriction with baroreceptor-mediated bradycardia secondary to cross-reactivity with α_1-receptors at high doses. The sympatholytic effects of dexmedetomidine predominate with maintenance infusions, leading to hypotension and bradycardia in addition to sedation and anxiolysis. Dexmedetomidine should therefore be used cautiously in patients with baseline hypotension, hypovolemia, bradycardia, or heart block; patients with autonomic dysregulation; the elderly; and patients taking atrioventricular nodal blocking agents. Rebound hypertension may be seen with abrupt discontinuation after prolonged infusion. When used as a sole agent, dexmedetomidine produces minimal depressant effects on the respiratory system. This ability to preserve spontaneous ventilation, in addition to its anxiolytic and sedative properties, make dexmedetomidine an ideal drug for use during awake/sedated fiberoptic intubations when there is concern for a difficult airway.

Other considerations include the following:

- Analgesic properties when used as an adjunct to regional and general anesthesia
- Reduces anesthetic requirements when used as a supplement in general anesthesia
- Decreases ICP, cerebral blood flow, and cerebral O_2 consumption
- Decreases IOP
- Reduces shivering
- May be useful in cardiac surgery secondary to sympatholytic effects
- Useful in children to help prevent emergence delirium

Etomidate

Etomidate does not affect sympathetic activity or the baroreceptor reflex function. It confers reliable hemodynamic stability in patients with or without cardiac disease. The myocardial oxygen (O_2) supply-demand ratio is maintained. In hemorrhagic shock models, etomidate is associated with increased survival compared with thiopental. However, some studies suggest that the cardiovascular depression with etomidate is similar to that with propofol. It has been shown to increase mortality risk in critically ill patients secondary to adrenal suppression. Finally, etomidate is less likely to cause apnea or decrease the ventilatory response to CO_2 than is midazolam.

Other considerations include the following:

- No analgesic properties
- Increased incidence of nausea and vomiting
- Irritation at peripheral vein injection site
- Clinically significant adrenocortical inhibition with prolonged infusions and possibly even a single dose
- Can cause myoclonus and involuntary skeletal muscle movements, may be attenuated by premedication with opioids or benzodiazepines
- Increases seizure duration, therefore can be used for electroconvulsive therapy
- Decreases cerebral blood flow and cerebral metabolic rate ($CMRO_2$)
- May reduce IOP and ICP, but this can be counteracted by myoclonus, mydriasis, or coughing

TABLE 94.2 Hemodynamic, Respiratory, and Other Effects of Propofol, Etomidate, Midazolam, and Dexmedetomidine

	DRUG			
Parameter	**Propofol**	**Etomidate**	**Midazolam**	**Dexmedetomidine**
Heart rate	↓	0/↑	0/↑	↓
Mean arterial pressure	↓↓	0/↓	0/↓	Transient ↑ with bolus followed by ↓ with maintenance infusion
Systemic vascular resistance	↓↓	0/↓	0/↓	↑/↓ as above
Mean pulmonary artery pressure	0	0/↑	0	0/↓
Cardiac index	↓↓	0/↑	0/↓	↓
Stroke volume	↓↓	0/↓	0/↓	↓
Myocardial contractility	0/↓	0/↓	0/↓	0
Apnea	↑↑↑	↑	↑↑	0
Ventilatory response to CO_2	↓↓↓	↓	↓↓	0
Bronchodilation	+ in COPD	0	0	+ (intravenous administration)
Nausea and vomiting	Decrease	Increase	Minimal	Minimal
Analgesia	Minimal	Minimal	Minimal	Moderate when used as adjunct
Pain on injection	Severe	Possible	Minimal	Minimal

COPD, Chronic obstructive pulmonary disease.

Propofol

Propofol has potent cardiovascular depressant effects. It decreases mean arterial pressure by as much as 40% due to myocardial depression and vasodilation. Preload and afterload are reduced secondary to decreased venous return and systemic vascular resistance, respectively. This is brought about by propofol's action to reduce sympathetic tone and directly relax vascular smooth muscle. Propofol's negative inotropic effects are due to reduced myocardial intracellular calcium availability, caused by Ca^{2+} influx inhibition. However, the myocardial O_2 supply-demand balance is maintained. Propofol also impairs the vasoconstrictor reflex in acute hemorrhage.

Propofol produces dose-dependent respiratory depression that is potentiated with the use of opioids and benzodiazepines. Further, it has a high potential to impair the ventilatory response to CO_2 and cause apnea (see Table 94.2). Continuous infusions reduce both the tidal volume and the frequency of breathing. Propofol has a bronchodilating effect, and it decreases the intraoperative incidence of bronchospasm with reactive airways disease.

Other considerations include the following:

- Vein irritation and pain on injection (lidocaine helps reduce this)
- Antiemetic, antipruritic, and anxiolytic properties
- Lipid emulsion supports bacterial growth
- Coughing, hiccups, and involuntary skeletal muscle movements with induction
- Reduction in cerebral O_2 consumption, blood flow, ICP, and IOP
- No effect on seizure threshold
- No analgesic properties
- Risk of propofol infusion syndrome in patients given high doses (>4 mg/kg/h) for prolonged duration (>48 hours); manifested by metabolic acidosis, rhabdomyolysis, arrhythmias, myocardial and renal failure, fatty liver, and death; increased risk in younger and critically ill patients
- Reports of delayed neuroexcitatory side effects that may cause seizures, hallucinations, and opisthotonos

Implications

Regular induction doses of propofol in patients with cardiovascular disease or hypovolemia place them at an increased risk for cardiovascular collapse and myocardial ischemia or infarction. As mentioned previously, propofol has significant cardiovascular depressant effects that are potentiated in a hypovolemic patient. If possible, effort should be made to volume resuscitate the patient before induction. In severely hypovolemic or hemodynamically compromised patients, carefully titrated doses of any induction agent may be used to limit hemodynamic effects. The goal is to preserve end-organ perfusion.

MANAGEMENT

Selection of an appropriate nonbarbiturate IV induction agent must take the following issues into consideration:

- Address hypovolemia or hypotension due to hemorrhage or other causes of intravascular volume depletion by restoring preload using crystalloid or colloid.
- Anticipate the need for vasoactive drugs during induction depending on the patient's comorbidities and volume status.
- Consider the need for invasive monitoring, including arterial line, central venous pressure, and transesophageal echocardiography.
- Optimize ventilation and oxygenation.
- Consider the need for maintaining spontaneous ventilation during induction in cases with potential for difficult airway management, large mediastinal masses, or unstable cervical spine.
- Assess the need for rapid or modified rapid-sequence intubation.
- Consider the need for avoidance of large increases in ICP or IOP.

Hypovolemia and Airway Management

Goals of induction include securing an airway, optimizing O_2 delivery, restoring intravascular volume, and maintaining hemodynamic stability. A rapid-sequence induction may be necessary to minimize the risk of aspiration. In the case of a difficult airway, unstable cervical spine, or large mediastinal mass, an awake intubation may be indicated. As previously mentioned, dexmedetomidine is frequently used in this scenario as it provides sedation and anxiolysis while maintaining spontaneous ventilation. The choice of an IV anesthetic is dictated by its cardiovascular, cerebrovascular, and pharmacokinetic effects (see Tables 94.1 and 94.2). Of the agents discussed here, etomidate is probably the safest agent for patients with significant hypovolemia or blood loss to minimize the risk of immediate cardiovascular collapse. However, regardless of which agent is selected, its dose must be reduced and carefully titrated in the presence of significant hemorrhage or reduced intravascular volume.

Increased Intracranial or Intraocular Pressure

Midazolam, etomidate, and propofol exert a beneficial decrease in ICP, in contrast to ketamine, which increases ICP. However, slower

emergence with midazolam can hinder early postoperative neurologic assessment. Dexmedetomidine has minimal effect on ICP.

Midazolam, dexmedetomidine, and propofol decrease IOP. Etomidate has the same effect, but it can be counteracted by myoclonic activity, mydriasis, and cough caused by etomidate. Ketamine increases IOP.

Adrenal Suppression

Etomidate use has been associated with adrenal suppression in humans. Even a single dose has been known to inhibit cortisol production and thus must be used with caution in critically ill patients.

PREVENTION

Avoidance of complications with nonbarbiturate IV induction agents requires attention to the following issues:

- Volume repletion and administration of blood or blood products, if indicated.
- Appropriate selection of the IV anesthetic induction agent. Consider time of onset and emergence, amnesia, analgesia, coronary and cerebral perfusion, systemic blood pressure, myocardial and cerebral O_2 consumption, onset of apnea, and effects on ICP and IOP.
- Slow titration and adjustment of induction doses. Careful titration to effect generally prevents abrupt, deleterious changes in blood pressure; a vasopressor may be needed for the patient to tolerate the induction. Doses of IV induction agents should be adjusted based on the patient's age, ideal weight, and hepatic and renal function.
- Side effects and relative contraindications of the various IV anesthetic induction agents.

The patient described in the case synopsis presents with a low-normal blood pressure in the setting of a baseline history of hypertension. The patient has a long bone fracture with probable poor oral intake while in the hospital. Such patients are at high risk for intravascular volume depletion and, as seen in this scenario, are at risk for significant hypotension after standard induction doses of propofol. Had this been recognized before induction, appropriate resuscitation with crystalloid or colloids, as well as carefully titrated doses of propofol, could have helped to mitigate such cardiovascular collapse. The need for vasoactive agents should also be anticipated.

Further Reading

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95 Nondepolarizing Neuromuscular Block

Mohammad El-Orbany

Case Synopsis

Following emergence and tracheal extubation after general anesthesia with neuromuscular relaxation, a 52-year-old woman with a history of chronic renal insufficiency has labored breathing with paradoxic movement of the chest wall and abdomen and intermittent upper airway obstruction.

PROBLEM ANALYSIS

Definition

The incidence of postextubation residual neuromuscular block (RNMB) has been estimated to be above 40%. This common problem may result in serious postoperative respiratory complications if not recognized and properly managed. Prolonged weakness occurs due to either inadequate reversal of neuromuscular block at the time of tracheal extubation or a prolonged block beyond its expected duration of action. It has been agreed that this complication occurs when the train-of-four (TOF) ratio is below 0.9 at the time of tracheal extubation. Residual weakness can result in a wide spectrum of manifestations ranging from discomfort, diplopia, and swallowing difficulty at one end of the spectrum to aspiration and complete respiratory arrest on the other end (Box 95.1).

In an ideal world, each neuromuscular blocking drug (NMBD) is metabolized and excreted at a predictable rate based on its pharmacokinetic profile. Clinically, however, it is important to recognize that coexisting disease processes, intraoperative events, and some concurrent drug therapy may prolong the duration of action of NMBDs and make its reversibility difficult.

Recognition

The degree of neuromuscular block/strength can be assessed using the following measures:

- *Clinical tests:* head lift for 5 seconds, sustained hand grip, tongue protrusion test
- *Subjective monitors (simple nerve stimulators):* visual or tactile evaluation to assess the degree of fade to TOF, double-burst, or tetanic stimulation
- *Objective (qualitative) monitors:* acceleromyography, mechanomyography, electromyography, and kinemyography to qualitatively assess the exact degree of block/muscle strength

Probably the use of multiple assessment modalities can provide a more accurate estimate to the degree of recovery from RNMB and indicate the best time when tracheal extubation can be safely performed without any RNMB. So if, after anesthesia and reversal drug administration, the patient is still unable to sustain head lift for 5 seconds; demonstrates fade in response to 50-Hz tetanic, TOF, or double-burst stimulation; or the TOF ratio is below 0.9 as indicated by an objective monitor, a certain degree of RNMB still exists, and if tracheal extubation is performed at this point, the patient will suffer from any of the complications associated with RNMB. The safest course of action in this situation is to wait until the patient regains adequate muscle power before tracheal extubation (TOF ratio ≥0.9) while considering the following factors that may contribute to prolonged neuromuscular recovery:

- Coexisting diseases or conditions that may affect NMBD elimination or metabolism
- Expected recovery times relative to the dose administered and timing of administration (Table 95.1)

With routine neuromuscular monitoring (with a simple nerve stimulator or preferably with an objective monitor), titration of NMBD doses and timing of administration based on surgical requirements and findings from the monitor, and administration of proper doses of reversal drugs when a certain degree of recovery has been established (at least three responses to TOF stimulation), the incidence of RNMB can be significantly reduced.

Risk Assessment

Whether by known, unknown, or postulated mechanisms, all the following conditions can potentiate the actions of NMBDs and increase the difficulty of reversal:

- Concurrent drug interaction: antibiotics (especially aminoglycosides), loop diuretics (e.g., furosemide), magnesium sulfate, lithium salts, calcium channel blockers, quinidine, or procainamide
- Renal or hepatic insufficiency or failure altering the duration of action of the drugs that depend on these organs for metabolism/elimination including NMBDs (Table 95.2)
- Hypothermia
- Acid-base imbalance

Implications

Prolonged block can increase operating room times, especially when tracheal extubation must be performed before admission to the postanesthesia care unit (PACU), as required in some ambulatory surgery centers. When RNMB is diagnosed before tracheal extubation, postoperative mechanical ventilatory support may be needed for some time in PACU until full recovery is achieved. If so, the patient must

BOX 95.1 Complications of Residual Neuromuscular Block

- Impairment of pharyngeal coordination and force of contraction
- Swallowing dysfunction
- Reductions in upper esophageal sphincter tone
- Increased risk of aspiration
- Decreased inspiratory air flow
- Upper airway obstruction
- Impaired hypoxic ventilatory drive and increased risk of postoperative hypoxemia
- Symptoms of muscle weakness (visual disturbances, facial weakness, difficulty speaking and drinking, generalized weakness)
- Higher risk of critical respiratory events in the PACU
- Delays in PACU discharge
- Prolonged postoperative ventilatory support and increased intubation times
- Increased risk of postoperative pulmonary complications (atelectasis or pneumonia)

PACU, Postanesthesia care unit.

TABLE 95.1 Approximate Recovery Times for Different Nondepolarizing Neuromuscular Blocking Drugs

	Dose Range (mg/kg)	Recovery Time From Low Dose[a] (min)	Recovery Time From High Dose[a] (min)
Long-Acting NDMRs			
Pancuronium[b]	0.1		40–60
Doxacurium	0.05–0.08	50–130 (mean 91)	74–268 (mean 177)
Intermediate-Acting NDMRs			
Vecuronium	0.10		25–45
Rocuronium	0.6–1.2	15–85 (mean 31)	38–160 (mean 67)
Atracurium[b]	0.5		20–45
Cisatracurium[c]	0.15–0.20	28–65 (mean 46)	31–103 (mean 59)
Short-Acting NDMRs			
Mivacurium[b]	0.25	11–29 (mean 19)	

NDMRs, Nondepolarizing muscle relaxants.
[a]Approximate duration of recovery based on package inserts and variability in manufacturers' definitions of recovery. Unless otherwise specified, the value given is for recovery to 25% of twitch height.
[b]Range for recovery time from high dose is that until a first maintenance dose is needed.
[c]Value for recovery to 5% of twitch height.

TABLE 95.2 Routes of Metabolism or Elimination for Nondepolarizing Neuromuscular Blocking Drugs

	ROUTE			
Drug	Renal	Hepatic	Ester Hydrolysis	Hoffman Elimination
Pancuronium	Major	Intermediate	Negligible	Negligible
Doxacurium	Major	Major	Negligible	Negligible
Vecuronium	Minor	Major	Negligible	Negligible
Rocuronium	Minor	Major	Negligible	Negligible
Atracurium	Negligible	Negligible	Major	Major
Cisatracurium	Minor	Minor	Negligible	Major
Mivacurium	Minor	Minor	Major	Negligible

All categories were derived from data on elimination and metabolism from package inserts.

be sedated to avoid subsequent recall of unpleasant events due to partial or complete paralysis.

If RNMB is not recognized and the trachea is extubated as mentioned earlier, patients may suffer from further complications, some of which may be serious or even life threatening. Patients may have insufficient motor strength to protect the airway, increasing the risk for pulmonary aspiration. This can also cause respiratory insufficiency, hypercarbia, and hypoxemia. Collectively, these conditions may cause hemodynamic instability, arrhythmias, or respiratory arrest.

MANAGEMENT

Early recognition and prompt management are keys to reducing morbidity and mortality that might be associated with RNMB. If adequate doses of reversal drug had been administered after a single initial intubating NMBD dose and the desired level of recovery is not achieved, the cause of the drug's reduced elimination or potentiation must be sought and corrected, if possible.

If prolonged neuromuscular block is not detected until the case's conclusion but before tracheal extubation, the patient is kept sedated while arrangements are made for postoperative ventilatory support in the PACU. Evidence of inadequate neuromuscular recovery includes the following:

- Inability to sustain a head lift for at least 5 seconds
- Fade after TOF, 50-Hz tetanic, or double-burst stimulation
- A TOF ratio below 90% on an objective monitor

While in the PACU, the patient should remain sedated until head lift or results of peripheral nerve stimulation indicate adequate recovery of motor strength.

An unfortunate occurrence is described in the case synopsis. Tracheal extubation was performed without ensuring adequate recovery of neuromuscular functions. Apparently, the patient was not adequately assessed before extubation, so the clinician was confronted with a patient struggling to breathe in the PACU. In this situation, prompt recognition of the problem and immediate action are needed to ensure adequate oxygenation and ventilation. This can be achieved with facemask ventilation, bilevel positive airway pressure, or insertion of a laryngeal mask while preparing for reintubation. The latter is usually needed, and the patient should be frequently assessed to ensure regaining adequate muscle strength before tracheal extubation. Left unattended, RNMB can lead to grave complications, including aspiration or complete respiratory arrest and/or obstruction.

PREVENTION

RNMB can be a preventable complication by adopting some simple rules, the first of which is avoiding NMBDs when muscle relaxation is not needed (as in some peripheral surgeries). When muscle relaxation is indicated, the choice of the NMBD should be based on an understanding of the comorbidities that may affect hepatic or renal elimination, concurrent drug therapy, and other factors that may affect clinical duration.

Intraoperative monitoring of the magnitude of neuromuscular block with a peripheral nerve stimulator (subjective monitoring) or one of the commercially available quantitative (objective) monitors should be routine when NMBDs are administered. These monitors can guide the clinician as to the proper timing of tracheal intubation after induction, ensure maintaining the proper degree of surgical relaxation intraoperatively, and indicate the proper timing of safe tracheal extubation when the desired degree of recovery from the block has been achieved. Any monitoring site that avoids misleading effects of direct muscle stimulation is acceptable, bearing in mind that there are slight differences in recovery times among the various muscle groups. The most common sites for neuromuscular monitoring are the ulnar nerve at the wrist, the facial nerve, or the posterior tibial nerve because all of them are superficial enough to be easily stimulated.

Although visual or tactile evaluation of the TOF response can be useful during induction and maintenance, they poorly predict adequate

recovery from NMBDs. Even experienced clinicians cannot detect fade in response to TOF stimulation when using either visual or tactile assessment when the TOF ratio is above 0.4. Selecting double-burst stimulation or 5-second, 50-Hz tetanus, combined with clinical signs, provides better sensitivity for the detection of RNMB but still not enough to eliminate the complication. To avoid RNMB, the T_4/T_1 ratio should be at least 0.9 at the time of tracheal extubation, which can only be ascertained with the use of an objective monitor. The last recommendation for prevention of RNMB is to use reversal drugs routinely whenever an NMBD has been administered and only when a certain degree of spontaneous recovery has been demonstrated (three or preferably four responses to TOF stimulation). It must be noted, however, that even with anticholinesterase therapy, the time to full recovery is dependent on full metabolism and elimination of the NMBD. Further, there may be active metabolites contributing to block prolongation. If these or the parent drug has slow metabolism or elimination, the recovery time can be more prolonged, and tracheal extubation should be delayed until adequate recovery has been demonstrated.

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Perioperative Fluid Management

96

Donald S. Prough • Christer H. Svensén

Case Synopses

Case 1
A 72-year-old man is scheduled to undergo transverse colectomy and primary reanastomosis for a nonobstructing carcinoma. He has a history of hypertension that is well controlled by a diuretic and is otherwise healthy.

Case 2
A 35-year-old woman is scheduled to undergo laparoscopic cholecystectomy for cholelithiasis. Other than mild obesity (preoperative weight 88 kg), she is healthy.

PROBLEM ANALYSIS

Definition

Fluid administration is probably the most ubiquitous intervention in surgical settings. The topic is highly controversial, and despite decades of research, there is still uncertainty on when, what amount, and at what rate fluids should be given. Complications are related to either insufficient or excessive fluid therapy, and in both instances complications can range from relatively minor to life threatening. Recent studies strongly suggest that both the frequency and the importance of complications of perioperative fluid therapy have been underestimated in the past. However, in the last decade, goal-directed protocols have been implemented, and although the evidence for critically ill patients is weak, there is more convincing evidence for elective surgical patients.

Life-threatening complications of insufficient fluid therapy are hypoperfusion and related vital organ system complications. Acute renal failure and multisystem organ failure are associated with the worst outcomes. Less serious complications are postoperative thirst, dizziness, nausea, vomiting, fatigue, and drowsiness. Postoperative exercise capacity and pulmonary function may be transiently impaired by insufficient fluid therapy.

The most feared complication of excessive fluid therapy is primary or secondary pulmonary edema. With primary pulmonary edema, there is increased venous return and right ventricular preload. This leads to increased right ventricular outflow and pulmonary artery flow and, ultimately, increased pulmonary capillary hydrostatic pressure. If this increase is sufficient and sustained, it can cause pulmonary alveolar capillary leak and alveolar flooding. This mechanism is similar to that associated with naloxone over reversal of opiates. Secondary pulmonary edema is due to left ventricular overload and "forward" (cardiogenic) failure. This is more likely in patients with at least some left ventricular functional impairment. Less threatening but still bothersome late complications related to excessive fluid therapy include peripheral edema, periorbital edema, and impaired gastrointestinal function or wound healing. These occur after discharge from the postanesthesia care unit or in the intensive care unit and are thus less readily apparent to anesthesia personnel.

Historical Perspective

The first efforts to administer fluids into the circulation were to reverse dehydration caused by diarrhea or vomiting in cholera patients. In the early 20th century, fluid restriction was the predominant strategy of perioperative fluid management until the mid-1960s. Colloids were introduced in the mid–20th century initially as intravascular replacement by albumin during World War II. In the 1960s Shires and colleagues emphasized the concept that extracellular fluid volume was decreased during hemorrhage or major surgery and required replacement with crystalloid fluids. This was called "third spacing" of fluids—a concept that now has been widely abandoned. As a consequence of their studies, infusion of large amounts of crystalloids became the standard of care for combat casualties during the Vietnam conflict. This caused interstitial accumulation and peripheral edema (notably acute respiratory distress syndrome [ARDS]), but the method was also associated with an apparent reduction in the rate of renal failure and was subsequently adopted for the perioperative management of civilian surgical patients.

Although a strict cause-and-effect relationship between increased fluid resuscitation and ARDS has never been established, the possible association has troubled clinicians. In 1999 Arieff reported 13 patients who developed postoperative pulmonary edema. Of these, 10 were generally healthy, and 3 had serious medical comorbidities. However, collectively, the group had a net fluid retention of 67 mL/kg within the first 24 intraoperative and postoperative hours.

In 2003, Brandstrup and coworkers, in a landmark multicenter study, pointed to the importance of a restrictive fluid therapy during colorectal surgeries. Although this was more a colloid-crystalloid protocol, the apparent fact was that a low weight increase was a major benefit compared with earlier findings that correlated weight increase with higher rate of complications. Healthy subjects undergoing short procedures seem to benefit from a moderate infusion of a crystalloid to prevent postoperative nausea, whereas patients undergoing colorectal surgeries have benefited from zero-balanced protocols with a "restrictive" goal-directed protocol pattern even though the total amount of fluid could exceed that administered during day surgical protocols due to the length of surgery.

In recent years, enhanced recovery after surgery (ERAS) protocols, together with an increased development of both invasive and noninvasive devices for assessment of fluid responsiveness, have significantly reduced the amount of perioperative fluids. These protocols have included recommendations for colonic, pelvic/rectal, and pancreatic surgery. Goals have been to reduce hospital stay and time to resumption of normal activities and improve survival by more aggressive fasting rules, avoiding routine bowel preparation, preoperative carbohydrate intake, and early mobilization (see Lobo et al., 2002).

Recognition and Assessment

Clinicians can recognize the extremes of insufficient or excessive fluid therapy. Hypotension, tachycardia, and oliguria are obvious, though not specific, signs of hypovolemia; pulmonary edema is an obvious but not a specific sign of hypervolemia. Recognition of subtle hypovolemia or hypervolemia is often more difficult. A widely accepted rationale behind fluid therapy is to improve cardiac output and organ perfusion, thereby limiting organ dysfunction.

The clinical assessment of blood and extracellular volume begins with the recognition of deficit-generating situations, such as bowel obstruction, chronic diuretic use, sepsis, burns, and trauma. Physical signs suggesting hypovolemia include oliguria, supine hypotension, and a positive tilt test. Although oliguria implies hypovolemia, hypovolemic patients may be nonoliguric, and normovolemic patients may be oliguric because of renal failure or stress-induced endocrine responses. Supine hypotension implies a blood volume deficit of more than 30%, although a normal arterial blood pressure could represent relative hypotension in an elderly or chronically hypertensive patient. A positive tilt test is defined as an increase in heart rate of at least 20 beats per minute and a decrease in systolic blood pressure of 20 mm Hg or more when a patient assumes the upright position. However, young, healthy subjects can withstand acute loss of 20% of blood volume while exhibiting only postural tachycardia. In contrast, orthostasis may occur in 20% to 30% of elderly patients, despite normal blood volume.

Laboratory evidence that suggests hypovolemia or extracellular volume depletion includes azotemia, low urinary sodium, metabolic alkalosis (if hypovolemia is mild), and lactic acidosis (if hypovolemia is severe). Hematocrit is virtually unchanged by acute hemorrhage until fluids are administered or fluid shifts from the interstitial to the intravascular space occur. Blood urea nitrogen (BUN), normally 8 to 20 mg/dL, is increased by hypovolemia, high protein intake, gastrointestinal bleeding, or accelerated catabolism; it is reduced by severe hepatic dysfunction. Serum creatinine (SCr), a product of muscle catabolism, may be misleadingly low in elderly adults, females, and debilitated or malnourished patients; however, in muscular or acutely catabolic patients, it may exceed the normal range (0.5 to 1.5 mg/dL). A BUN/SCr ratio exceeding the normal range (10 to 20) suggests dehydration. In prerenal oliguria, enhanced sodium reabsorption should reduce urinary [Na^+] to 20 mEq/L or less. Enhanced water reabsorption should increase the urine concentration (urine osmolality >400; urine–plasma creatinine ratio >40:1). However, sensitivity and specificity of these urinary variables may be misleading.

Assessment of the adequacy of intraoperative fluid resuscitation integrates multiple clinical variables, including sodium concentrations, estimates of intraoperative blood loss and monitoring of heart rate, blood pressure, urine output, arterial oxygenation, pH, or central venous pressure. None of these parameters is fully helpful. Visual estimation of intraoperative blood loss is notoriously inaccurate. Moreover, tachycardia is an insensitive, nonspecific indicator of hypovolemia, as is central venous pressure. However, during profound hypovolemia, indirect blood pressure measurements may underestimate direct arterial pressure. Another advantage of direct arterial pressure monitoring may be the recognition of increased systolic blood pressure variation accompanying positive-pressure ventilation with hypovolemia. Urine output often declines precipitously during moderate to severe hypovolemia. Therefore in the absence of glycosuria or diuretic administration, a urine output of 0.5 to 1.0 $mL/kg^{-1}/hr^{-1}$ during anesthesia suggests adequate renal perfusion. Arterial pH may decrease only when tissue hypoperfusion becomes severe. Cardiac output may remain normal, despite severely reduced regional blood flow. Lactate may reflect tissue perfusion and mixed venous oxygen saturation (Svo_2) is a specific indicator of poor systemic tissue and vital perfusion; however, it reflects average perfusion in multiple organs and requires a pulmonary artery catheter placement. A surrogate parameter such as central venous oxygen saturation ($Scvo_2$) requires a central line placement. Neither of these can predict poor perfusion in specific organs. Newer techniques such as side-stream cameras for monitoring of the periphery are being developed (Fig. 96.1).

Individualized Goal-Directed Therapy

A more rational approach is to determine the *fluid responsiveness* of the patient. This has conventionally been done by individual hemodynamic monitoring and determining a clinical significant increase in stroke volume (SV). Individualized goal-directed therapy may incorporate the use of fluids or inotropes. A patient whose SV increases by 10% to 15% after a fluid challenge (250 to 500 mL) is considered to be a *fluid responder.* This is in accordance with the Frank-Starling principle—as the preload increases, SV increases until an optimal preload is achieved, at which point SV becomes constant. If the fluid load no longer contributes to an increased SV, there is no use to continue bolusing. Further loading will increase atrial pressure, increase venous and arterial hydrostatic pressure, cause a shift of fluid into the interstitial space, and create tissue edema. The tissue edema will further distort architecture and impair oxygen exchange, capillary flow, and lymphatic drainage. Increased atrial pressure is transmitted backward with increased venous pressure (mean circulatory filling pressure), which will affect the microcirculation.

Functional hemodynamic parameters such as stroke volume variation (SVV) and pulse pressure variation could possibly be used to guide fluid therapy. Both of these parameters are dependent on the interaction between the heart and the lungs (pulse contour analysis). In the spontaneously breathing patient, inspiration will reduce the intrathoracic pressure, which will augment venous return and the preload, thereby increasing stroke volume. In the mechanically ventilated patient, the reversed conditions will persist. This can be seen clinically by studying the arterial waveform during mechanical ventilation and observing how the curve moves. The movement of the curve can actually show the degree of hypovolemia. Variations imposed on the Frank-Starling curve can result in major alterations if imposed in the lower part of the curve, but only minor alterations will occur if imposed on the flatter part (Fig. 96.2). The main aim is thus to achieve an adequate circulating volume as well as an adequate function of the cardiovascular system. This can be substantially changed, however, during surgical conditions, changing body temperature, and different anesthetic conditions.

Advocates of goal-directed therapies argue that it is necessary, given that patients inevitably are different, to reduce provider variability, particularly among high-risk patients and those not in an ERAS program.

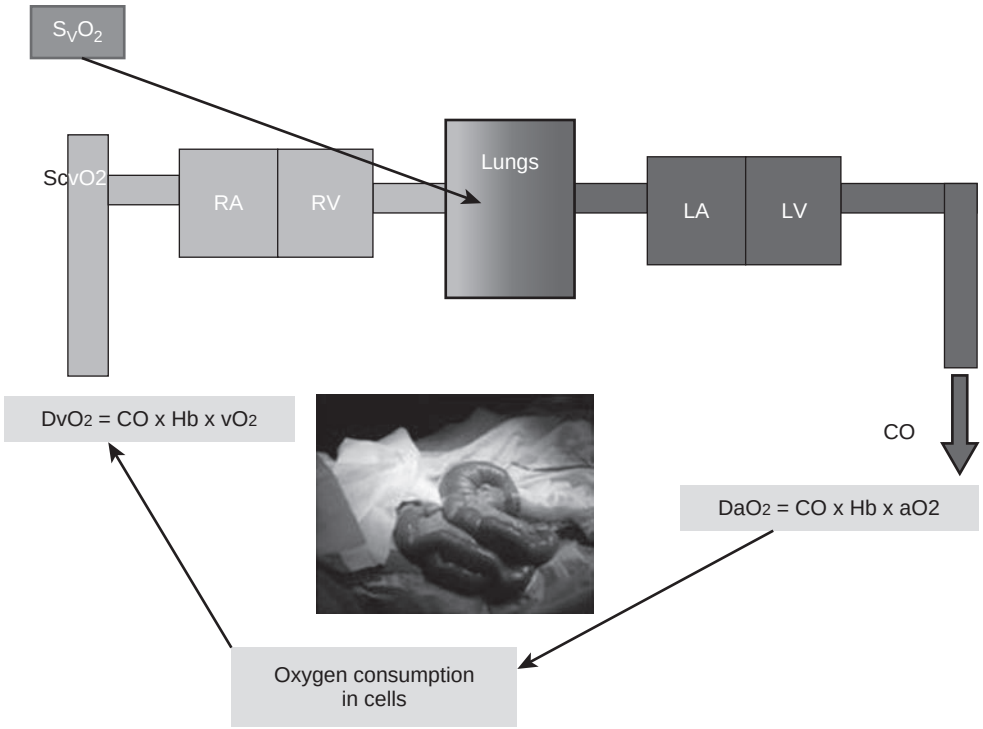

Fig. 96.1 Saturation of tissues. *LA,* Left atrium; *LV,* left ventricle; *CO,* cardiac output; DaO_2, arterial delivery of oxygen; *Hb,* hemoglobin; aO_2, arterial oxygenation; DvO_2, venous delivery of oxygen; vO_2, venous oxygenation; $ScvO_2$, central venous oxygenation; SvO_2, mixed venous oxygenation.

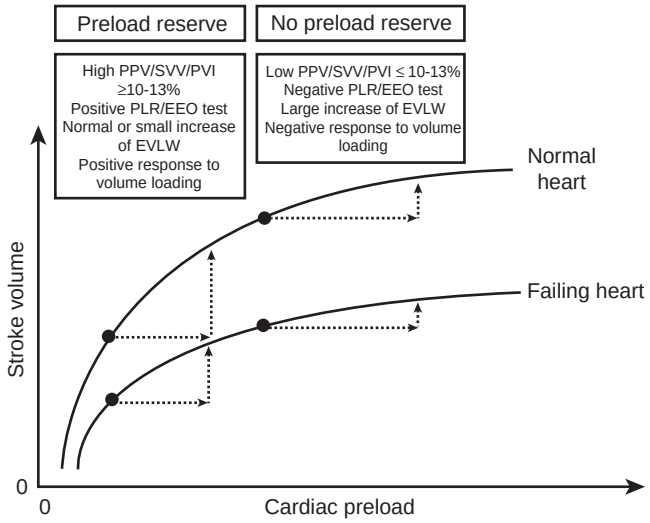

Fig. 96.2 The Frank-Starling curve describes the relationship between diastolic myocardial tension (preload) and systolic cardiac function. There is preload reserve when the ventricle function is on the steep part of the curve. Pulse pressure variation (PPV), stroke volume variation (SVV), and pleth variability index (PVI) are high at this part, and tests such as end-expiratory occlusion (EEO) and passive leg raising (PLR) are positive. When the ventricle is functioning near the flat part of the curve, there is no preload reserve. (From Aditianingsih et al.: Guiding principles of fluid and volume therapy. *Best Pract Res Clin Anaesthesiol* 28[3]:249-260, 2014.)

Different Monitoring Systems

An example of an invasive device is the PiCCO (Pulsion Medical Systems, Munich, Germany), which enables continuous hemodynamic monitoring using a femoral or axillary arterial catheter and a central venous catheter. Employing patented algorithms based on the assumption that the area under the systolic part of the aortic pressure waveform corresponds to the stroke volume curve, PiCCO combines real-time continuous monitoring through pulse contour analysis with intermittent thermodilution measurement via the transpulmonary method. This device is able to give measurements of the transpulmonary cardiac output, intrathoracic blood volume, extravascular lung water, and cardiac function. The latter parameters require a central venous line for injection of a cold bolus. The system, however, requires recalibrations, especially when rapid changes occur.

The LiDCO technique (LiDCO Ltd., London, UK) is another pulse contour method (or pulse power method) that is purported to present a linear relationship between net power and net flow in a vascular system provided that no major change in vascular compliance or resistance occurs. The LiDCO plus technique requires lithium dilution and shows reliable assessment of cardiac output and stroke volume provided the restrictions mentioned previously are met. The LiDCO rapid version does not require calibration and is used solely for monitoring cardiac output and stroke volume deviations from baseline.

The FloTrac or Vigileo (Edwards Inc., Irvine, CA) system requires a sensor attached to an arterial line. The system displays cardiac output and stroke volume variation on a continuous base, and this can be correlated to the Frank-Starling. For the Vigileo, the standard deviation of pulse pressure is correlated with a normal stroke volume based on an underlying database. Aortic impedance is also derived from historic data, but actual vascular compliance and resistance are determined using arterial waveform analysis. The device does not require calibration and is fairly easy to use but is hampered by the fact that it is less reliable when vasopressors are used. Even the latest software, version 3, is not accurate when a common vasopressor such as phenylephrine is used. Furthermore, an optimal arterial signal is needed for valid cardiac output measurement. SVV measurements are also limited by the requirement of mechanical ventilation with a tidal volume of at least 8 mL/kg. A device package that combines the SVV system with oximetry catheters to provide central venous oxygen saturation measurements ($Scvo_2$) gives both hemodynamic and volumetric data. The

use of this device has been approved by the Food and Drug Administration in the United States. All of these devices require optimal arterial signals and are unreliable when the patient has arrhythmias or is under intraaortic balloon pump treatment.

The esophageal Doppler-guided therapy technique uses Doppler ultrasound technology to analyze the blood flow in the descending aorta. A single-use probe is inserted into the esophagus and positioned to measure the blood flow for each heartbeat. The waveform is then compared with biometric data and gives the stroke volume and flow time corrected for heartbeat (FTc). Because the catheter is inserted in the lower esophagus, approximately 70% of the circulating blood flow is accounted for in the calculations. Using different algorithms, this provides the opportunity to measure fluid responsiveness. Most algorithms use small aliquots of colloids or crystalloids (2 to 3 mL/kg). The primary goal of the technique is to optimize the stroke volume according to the Frank-Starling curve. An increase in preload should cause an increase in cardiac output. By interpreting the curve, it is possible to analyze which patients are "responders" and which are "nonresponders" to fluid therapy in the context of cardiovascular performance. The stepwise fluid infusion is continued until the patient is considered a nonresponder to fluid. Usually this happens when stroke volume or cardiac output deviation becomes less than 10%. This has been validated against standard-of-care protocols and has shown reduced morbidity and reduced hospital stay. The esophageal Doppler-guided therapy technique has been used in high-risk and colorectal surgeries, but recent studies showed no differences between esophageal Doppler-guided therapy and a fixed protocol in more healthy patients or patients undergoing laparoscopic procedures.

Noninvasive devices have been presented, such as continuous noninvasive arterial pressure devices that visualize beat-to-beat waveforms. Currently, these devices are not precise enough to apply to current standards although they could probably be clinically useful to follow trends. Pulse oximetry waveform analysis could be used to assess fluid responsiveness. Pulse oximetric plethysmographic (POP) waveforms amplitude (delta POP) and plethysmographic variability index (PVI, where perfusion index is defined as the ratio of nonpulsatile to pulsatile blood flow through the peripheral capillary bed) have been developed.

Different Fluids

The basic fluid requirement consists of replacement for evaporation, loss of water and electrolytes through sweat (perspiratio sensibilis), and urine. Sodium has a crucial impact on the extracellular fluid volume. During anesthesia and surgery the level of antidiuretic hormone is increased, which reduces the elimination of free water. If the patient is administered hypotonic solutions, serum natrium (S-Na) will decrease with potentially dangerous hyponatremia. This could have deleterious effects on brain cells, particularly in small children.

Glucose

Pure glucose solutions distribute to all fluid compartments. Glucose solutions supply a basic amount of calories, which in many situations may help to prevent hypoglycemia. Adding acetate ion will lower the chloride content. As the chloride supply decreases and bicarbonate is formed when the acetate decomposes, this type of solution creates a certain buffering capacity, which explains the name "buffered glucose." The glucose content can vary (2.5% or 5%; i.e., 25 or 50 mg/mL) depending on the nutritional status of the patient. A certain amount of water is released during the metabolism of glucose and acetate, which makes a positive contribution to the total water balance.

Isotonic Sodium Chloride

Isotonic sodium chloride (9 mg/mL, 0.9% per volume of NaCl) is usually described as "normal" or "physiologic," reflecting that it has an osmolality similar to plasma and the interstitial space. It is made from common salt that has been dissolved in sterile water. The solution provides a chloride content that is higher compared with plasma. Consequently, isotonic sodium chloride will result in an excess of chloride ions and can lead to the development of hyperchloremic acidosis explained by the fact that strong ion difference (SID; the sum total of sodium, potassium, and magnesium minus the sum total of chlorides and lactate) determines pH in extracellular fluid (ECF). The SID is usually +40 in the ECF, but the equivalent total figure in isotonic sodium chloride is 0. Supplying sodium chloride will therefore decrease the SID and cause acidosis. In animals and healthy volunteers, it has been demonstrated that chloride induces vasoconstriction and decreases glomerular filtration rate. Administration of 0.9% saline thus results in hyperchloremia, which is associated with reduced cardiac contractility, decreased renal perfusion, reduced gastric flow, and impaired gut motility. Despite this, isotonic saline is still one of the most commonly used crystalloid solutions in the world. It is cheap and also compatible with blood.

Balanced Solutions

Balanced solutions mimic the composition of human plasma. Important features are also isotonicity and a chloride concentration close to that of human plasma.

Metabolizable anions could be acetate (acetic acid), lactate (lactic acid), gluconate (gluconic acid), malate (malic acid), or citrate (citric acid). Consuming H^+ ions and oxygen, these anions are metabolized in the liver (mainly lactate) or in muscle (mainly acetate and malate) to replace HCO_3^-. Replacing Cl^- with lactate decreases the total Cl^- load, and when lactate is metabolized in the liver, Na^+ is released, which could react with other anions. This is why Ringer solutions usually have a Cl^- level of 110 mmol/L compared with 154 mmol/L in isotonic saline.

Ringer's lactate (in the United Kingdom labeled as Hartmann's solution) is used almost everywhere in the world. In Scandinavia, researchers found that the decomposition of lactate is first and foremost dependent on the liver, but also to a certain degree on the kidneys. When lactate is supplied exogenously, the gluconeogenesis is the principal pathway for lactate. This could have implications for perioperative care. A report published by the National Academy of Sciences in the United States in the late 1990s suggested that lactated Ringer should be modified in particular because the D-lactate moiety available in most preparations had adverse effects in critically ill patients.

Acetate, on the other hand, can be metabolized by most cells in the body, which implies that it should be more suitable for critically ill patients. Compared with lactate, acetate produces HCO_3^- more quickly, creates moderate O_2 consumption, has a lower effect on the respiratory quotient, is unchanged in patients with diabetes, and can be used as a hypoxia marker. Like Ringer's lactate, the sodium level in Ringer's acetate is considerably lower compared with plasma. It has recently been addressed that there is a risk of postoperative hyponatremia when large amounts of fluid with low sodium content are administered. This is particularly apparent in the pediatric population. This has been regarded as a disadvantage and therefore the sodium level was increased in Ringerfundin to resolve this shortcoming. However, this solution also contains a higher concentration of chloride (127 mmol/L) compared with Ringer's acetate (110 mmol/L).

Plasma-Lyte

Plasma-Lyte is a solution with an osmolality and electrolyte content more similar to plasma. The buffering capacity consists of gluconate, which is a slow-acting weak buffer. Many think it is the "ideal" crystalloid. Currently, a large clinical trial in Australia and New Zealand has shown no differences in acute kidney injuries or death in critically ill patients when comparing buffered crystalloid to isotonic saline.

Colloids

The large molecules found in colloid solutions should ideally expand the plasma volume, resulting in a colloid osmotic pressure that is the equivalent of the natural pressure of the plasma. Colloid solutions are retained longer in the intravascular fluid compared with crystalloid solutions, which means that presumably smaller quantities are needed. As a result in an ideal situation, a positive effect is achieved more quickly than when the same volume of crystalloid is administered. In addition, there is presumably considerably less expansion of the interstitial fluid space, which in turn decreases the amount of edema, improves microcirculation, and therefore also provides better conditions for an adequate oxygen supply to the tissues. This applies to patients whose glycocalyx and endothelial barrier are intact.

Colloids are categorized either as natural or as artificial colloids. There has been debate ongoing for many years about which colloid, if any, to use and discussion of the merits of colloid solutions versus crystalloid solutions. The results of studies carried out do not indicate any general advantages of one solution over the other.

Plasma

Plasma infusion expands the intravascular fluid space slightly less than the volume of fluid supplied. Plasma is less effective with regard to volume expansion compared with an infusion of equivalent volumes of dextran, starch, or albumin solutions. This is because plasma contains elements that increase capillary permeability. Infusion of plasma causes activation of inflammatory responses, and cascade systems may be activated. As such, plasma should only be administered if there is justification to do so mainly to provide coagulation factors or coagulation inhibitors.

Albumin

Albumin is a natural colloid and the predominant protein in human plasma. Human albumin at 4% to 5% in saline is a colloid for volume resuscitation. Albumin accounts for 60% to 80% of the colloid osmotic pressure in the bloodstream. Normal transcapillary leakage is 5% to 10% per hour. The albumin is returned to the bloodstream via the lymphatic system. Leakage may increase in the event of trauma or septic conditions, which leads to redistribution of the albumin so that a much larger proportion ends up in the interstitial fluid space ("albumin trapping"). Extravascular edema may be formed as a result from the albumin binding the fluid, which impedes microcirculation and impairs oxygenation of the tissues. The Saline versus Albumin Fluid Evaluation (SAFE) study did not show any significant benefit in mortality rate at 28 days when the fluid was randomized in a critically ill setting. Additional studies in predefined subgroups, however, showed increased risk for traumatic brain injury but slight benefit for septic patients, although this effect has not been fully established in later studies.

Artificial Colloids

Dextran

Dextran consists of polysaccharides made of glucose. It is excreted to a certain degree through the kidneys, the rest being broken down in the plasma into carbon dioxide and water. The most common preparations are 6% dextran 70, 3% dextran 60, and 10% dextran 40. Its ability to expand plasma volume varies from between slightly less than infused volume (3% dextran 60) to more than the infused volume (10% dextran 40), and 6% dextran 70 has the longest duration. The maximum dose recommended is 1.5 g/kg body weight per 24-hour period. To reduce the risk of allergic reaction, low-molecular-weight dextran–1 (hapten) is administered to bind the reactive points on any antibodies directed toward dextran. Antibodies may have been created because of administration of dextran earlier in life, or they may be naturally occurring in the gastrointestinal system.

Dextran inhibits platelet aggregation, lowers factor VIII/von Willebrand factor levels, and reduces leukocyte adhesion. Dextran is no longer widely used.

Gelatine

Gelatine consists of polypeptides made from bovine gelatine with an average molecular weight of 30 to 35 kDa. They are safe in terms of coagulation and organ integrity except that they may elicit renal problems.

Hydroxyethyl Starch

Hydroxyethyl starch (HES) is an artificial polymer derived from hydroxyethyl substitution of amylopectin obtained from waxy maize or potato. There are several HES (6% or 10%) solutions differentiated by the molecular weight (70 to 450 kDa), molar substitutions, and C2/C6 ratios. The low-molecular-weight solutions (130 kDa) have until recently been the most used.

Starch molecules are to some extent broken down by amylase and then secreted via the kidneys. Other parts accumulate in the reticuloendothelial tissues and have been attributed to cause pruritus. Available preparations for perioperative use are low-molecular HES 130/0.4 (cornstarch) and HES 130/0.42 (potato starch). The potato starch is mixed with a balanced solution (Tetraspan), and cornstarch solutions are mixed either with a common salt solution (Voluven) or a balanced solution (Volulyte).

In the early 2000s it was suspected that HES with larger molecular sizes (>200 kDa) caused kidney problems. Although this was thought to be attributed to the molecular size per se, it has now been established that nephrotoxic problems also occur with lower-molecular-weight preparations in critically ill settings. Some of these studies have been criticized for inadequate design. There are conflicting data and reviews of the perioperative studies. Currently, HES has been widely restricted, and as of this writing, the products are black-boxed by many regulatory authorities around the world. It has been suggested that there may still be an intraoperative safe area to replace blood loss before the threshold of transfusion.

MANAGEMENT

For the 72-year-old man having transverse colectomy, a reasonable option is to manage fluids as in an ERAS concept. Using that approach, the patient would receive preoperative carbohydrates, no preload, and minimal crystalloid during induction. Monitoring could

be by the insertion of an esophageal Doppler catheter and assessment of SV and FTc. Postinduction hypotension, if it developed, would be treated with a pressor while awaiting the onset of surgical stimulation. Small aliquots (100 to 200 mL) of either crystalloids or colloids increase SV and decrease FTc. A thoracic epidural would be optimal. Maintenance fluids would consist of a crystalloid (lactated Ringer´s or Plasma-Lyte, 3 ml/h). All blood loss would be replaced with a colloid to minimize fluid load in a ratio of 1:1 unless blood loss exceeded 1500 mL, in which case blood components would be given as appropriate.

For the 35-year-old woman undergoing laparoscopic cholecystectomy, the fluid strategy would be somewhat different. Infusing 1 to 2 L of crystalloid over the course of the case would likely be more than enough. The available evidence suggests that this approach is associated with improved postoperative symptoms.

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Reversal Agents: Naloxone, Flumazenil, and Sugammadex

97

William J. Sauer • Juliana Barr

NALOXONE

Case Synopsis

An otherwise healthy 65-year-old, 80-kg man is given 2 mg of fentanyl intravenously (IV) during a 3-hour coronary artery bypass grafting procedure. Postoperatively, the patient remains intubated and mechanically ventilated and is transferred to the intensive care unit (ICU) in stable condition. The surgeons opt for early extubation of the patient, but he remains deeply sedated, does not respond to painful stimuli, and is not overbreathing the ventilator. He is given a total of 2 mg of naloxone IV, and over a 5-minute period becomes acutely hypoxemic, with increasing rales and frothy pulmonary secretions. A chest x-ray shows acute pulmonary edema. An electrocardiogram shows ventricular ectopy.

PROBLEM ANALYSIS

Definition

Naloxone (Narcan) is a nonselective, high-affinity opioid antagonist that is indicated primarily for use with (1) opioid-induced respiratory depression (i.e., in the postoperative period or in neonates secondary to maternal administration), (2) acute opioid overdose, and (3) opioid-induced pruritus (off-label indication). It is structurally related to morphine and oxymorphone, and competitively inhibits the effects of opioid agonists at all opioid receptors (mu > kappa = delta), though its primary clinical use focuses on reversal of sedation and respiratory depression (mu antagonism). Thus it must be titrated carefully (Table 97.1), as the analgesia effects of opioids can also be reversed, inducing severe pain and/or acute opioid withdrawal–like symptoms. Significant cardiopulmonary instability (i.e., hypertension, cardiac arrhythmias, pulmonary edema, and cardiac arrest), agitation, and seizures have been described with various doses of naloxone, though these side effects are rare and are more likely to occur at higher doses.

Intravenous injection is the most common form of naloxone administration, though endotracheal, subcutaneous, and intramuscular delivery is also effective. Low bioavailability secondary to a high (95%) hepatic first-pass effect renders oral intake of naloxone ineffective. It is fast acting (<2 minutes) and has a dose-dependent duration of effect (30 to 240 minutes; Table 97.2), with primary hepatic metabolism with renal excretion of inactive metabolites. Most opioid agonists have a longer half-life than naloxone, so repeated doses must be delivered to prevent renarcotization.

Recognition

Cardiovascular complications can occur rapidly (i.e., within minutes) after naloxone administration, especially when large doses (i.e., 0.4 to 2 mg IV) are given. This is thought to be secondary to neurogenic cardiovascular excitation with significant catecholamine release resulting in hypertension, arrhythmias, pulmonary and systemic vasoconstriction, pulmonary edema, and seizures. Furthermore, sedation and respiratory depression may reappear if naloxone is eliminated faster than the residual opiates (renarcotization), so cardiovascular monitoring should always be established and naloxone redosed as necessary.

Risk Assessment

Although the exact incidence of complications after naloxone is not known, postoperative events are exceedingly rare, especially when low doses are judiciously titrated. Events are more likely in patients with a history of chronic opioid use/abuse or seizures and when other symptoms of withdrawal are present (e.g., nausea, vomiting, diaphoresis, agitation). Adverse events are also more common in ICU patients, likely because of higher opioid doses administered in this patient population (e.g., significant cardiac or noncardiac surgeries, opiate overdose admissions). Finally, physiologic stress may play a role in naloxone toxicity, as all case reports of naloxone toxicity occurred in patients who were experiencing severe pain and stress at the time of the event.

The incidence of opioid-related deaths has skyrocketed over the past decade with an estimated 69,000 attributable deaths worldwide, resulting in the World Health Organization calling for broad community access to naloxone. Prior prospective studies have demonstrated that the emergent use of naloxone for opiate overdose treatment resulted in a 1.3% complication rate (median dose 0.2 mg IV), though causality cannot be guaranteed. Animal studies show that avoidance of significant hypercapnea (mask ventilation) before administration of naloxone may mitigate cardiopulmonary side effects.

Implications

Although initial recommendations for naloxone use were to rapidly administer large bolus doses IV, it is now recommended to judiciously administer low doses intermittently (see Table 97.1) to decrease the possibility of cardiovascular and neurologic complications. Cardiovascular monitoring should be continued after it is administrated for several hours to monitor for renarcotization.

TABLE 97.1 Dosing Reversal Agents for Postoperative Sedation and Respiratory Depression

Drug	Intermittent Dosing[a]	Continuous Intravenous Infusion[a]
Naloxone	Intravenous: 20–40 μg q 1–2 min (5–20 μg q 1–2 min)	4–8 μg/kg/h (4–8 μg/kg/h)
Flumazenil	Intravenous: 0.2 mg q 2–5 min, up to 1.0 mg; may repeat q 20 min; maximum dose = 3.0 mg/h (4–20 μg/kg)	0.5–1.0 μg/kg/min, up to 3 mg/h total dose (0.5–1 μg/kg/min)

[a]Pediatric doses are in parentheses.

TABLE 97.2 Clinical Pharmacology of Reversal Agents[a]

Drug	Onset (min)	Peak Effect (min)	Duration (min)	Elimination Half-Life (min)
Naloxone	1–2	5–15	60–240	40–60[b]
Flumazenil	1–2	2–10	45–90	50[c]

[a]Times are for intravenous dosing only; naloxone may be also given intravenously, intramuscularly, subcutaneously, or endotracheally although the onset, time to peak effect, duration of effect, and magnitude of effect may vary considerably between patients.
[b]Elimination half-life is doubled in neonates.
[c]Elimination half-life is halved in neonates and prolonged in patients with liver disease.

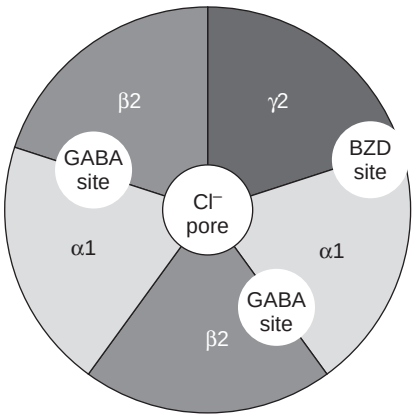

Fig. 97.1 $GABA_A$ receptor. (From Wikipedia.org. At https://en.wikipedia.org/wiki/GABAA_receptor#cite_note-pmid22446838-1.)

MANAGEMENT

If complications do develop, naloxone administration should be discontinued immediately. Support the patient's oxygenation and ventilation mechanically (bag-valve-mask, laryngeal mask airway, or endotracheal tube), and monitor and treat cardiovascular complications while arranging for transfer to the ICU.

PREVENTION

Avoid high doses of naloxone, and titrate carefully while monitoring hemodynamics closely. Small intravenous bolus doses (as little as 20 to 40 μg) or continuous infusions (4 to 8 μg/kg/h) may reverse opioid-induced respiratory depression and sedation without reversing the analgesic effects of opioids or precipitating cardiopulmonary instability. Intravascular administration is more predictable than other routes of administration and should be used whenever possible. Naloxone crosses the placenta and may precipitate acute withdrawal symptoms or seizures in neonates and in opioid-dependent mothers.

FLUMAZENIL

Case Synopsis

A 42-year-old man with a history of depression and anxiety is brought to the emergency department after being found unconscious at home next to empty prescription bottles of amitriptyline and diazepam. On arrival his vitals are notable for a heart rate of 95 beats per minute and a respiratory rate of 10 breaths per minute. He does not withdraw to painful stimuli, and his gag reflex is absent. He is given 1 mg of flumazenil IV, and several minutes later the patient experiences a grand mal seizure. Intravenous lorazepam is given with no response. The patient is emergently intubated for airway protection and admitted to the ICU.

PROBLEM ANALYSIS

Definition

Flumazenil (Romazicon), a 1,4-imidazobenzodiazepine derivative, is a nonselective, high-affinity, competitive γ-aminobutyric acid A ($GABA_A$) receptor antagonist that is used (1) for reversal of sedation with benzodiazepines and (2) as the antidote for a benzodiazepine overdose. It is given to reverse benzodiazepine-induced sedation, amnesia, disorientation, or hypoventilation. Because flumazenil only binds to the $GABA_A$ receptor (benzodiazepine site), it has no effect on opiates or other GABA-ergic substances such as barbiturates, ethanol, propofol, or other general anesthetics (Fig. 97.1). Because of the risk of seizures in patients with chronic benzodiazepine use/abuse, its use in the setting of an overdose has drastically declined (the risks outweigh the benefits).

After a single intravenous dose of flumazenil, its effect is seen within minutes (see Table 97.2). It can also be given intramuscularly, orally, or rectally, though nonintravenous routes are usually reserved for long-term flumazenil use. Because of its rapid hepatic clearance, flumazenil is short acting. It has no active or toxic metabolites. Flumazenil's duration of effect may be prolonged in patients with severe liver disease owing to reduced hepatic clearance. Similar to naloxone, flumazenil's duration of effect will usually end before the benzodiazepine in use (particularly in the ICU setting), resulting in resedation once the effects of flumazenil subside.

Recognition

Flumazenil can cause seizures or other signs of drug withdrawal in patients with a history of chronic benzodiazepine use, those undergoing benzodiazepine withdrawal, or those with tricyclic antidepressant (or other proconvulsant) use or overdose. This resulted in a black-box warning and a decreased utilization of flumazenil. There are, however, no reports of seizures after flumazenil administration in ICU patients who received benzodiazepines for chronic sedation.

The onset of flumazenil is rapid; however, the total dose of flumazenil needed to achieve a full and sustained reversal of the side effects of benzodiazepines may vary with the potency and residual plasma concentration of the benzodiazepine used. Respiratory depression may not be fully reversed, even with maximal doses of flumazenil. Like naloxone, resedation is a common event that requires close monitoring when flumazenil is in use.

Risk Assessment

Flumazenil is an effective means of reversing the residual sedative or respiratory depressant effects of benzodiazepines after the small doses typically used for anesthesia or conscious sedation. Because of flumazenil's short duration of action, ICU patients who receive chronic infusions or large doses of benzodiazepines may experience resedation and recurrent respiratory depression once flumazenil's antagonistic effects wear off. Therefore flumazenil should not be used to hasten the termination of benzodiazepine sedation in these patients. However, a trial of flumazenil may be diagnostically useful in critically ill patients who fail to awaken within a reasonable time frame after discontinuing benzodiazepines. If the patient fails to awaken after receiving the maximal dose of intravenous flumazenil (i.e., 3 mg IV administered in divided doses over 1 hour), other causes of the persistent sedation or respiratory depression should be considered. Patients who do respond to flumazenil should be carefully monitored for up to 2 hours after the last dose of flumazenil for signs of resedation or recurrent respiratory depression.

Implications

Aside from its use in low-dose sedation, many experts consider that the risk of seizures/adverse events when flumazenil is used as an antidote to benzodiazepine overdoses outweighs its potential benefits. Most patients with acute benzodiazepine overdose have less respiratory depression than with opioid overdose and, when necessary, mechanical ventilation and cardiovascular support can be provided until the overdose resolves. If flumazenil is used to treat a benzodiazepine overdose, these patients should be admitted to the ICU for close monitoring.

MANAGEMENT

Similarly to naloxone, if complications develop, stop the administration of flumazenil immediately. Seizures should be treated with antiepileptics, with the understanding that benzodiazepines will likely be ineffective at low doses after flumazenil administration.

PREVENTION

Flumazenil is safe and effective for reversing short-term sedation and respiratory depression with benzodiazepines, but not for chronically dependent patients. It should be given in small divided doses, and patients must be carefully observed for signs of resedation and respiratory depression for at least 2 hours. Small repeat intravenous boluses (0.2 mg) or a low-dose continuous intravenous infusion of flumazenil (i.e., 0.5 to 1 μg/kg/min, up to 3 mg/h) can be titrated to the desired level of sedation and ventilation. This more reliably prevents resedation of postoperative patients and also avoids abrupt or complete reversal of anxiolysis. Finally, avoid flumazenil in patients with chronic benzodiazepine dependence or in suspected cases of tricyclic antidepressant overdose.

SUGAMMADEX

Case Synopsis

An 87-year-old man is scheduled for urgent laparoscopic cholecystectomy and is intubated at the beginning of the case with rapid-sequence intubation–dosed rocuronium (1.2 mg/kg). Although the surgery only takes 1 hour to complete, the train-of-four (TOF) is still 0/4 even though no additional rocuronium is given for the remainder of the procedure. Sugammadex is given, and within 2 minutes, his neuromuscular blockade is completely reversed (i.e., TOF = 4/4 twitches with no fade), but the patient subsequently develops acute bradycardia (30 beats per minute). Glycopyrrolate (0.2 mg IV) is immediately given, and his heart rate returns to sinus rhythm at 74 beats per minute.

PROBLEM ANALYSIS

Definition

Sugammadex (Bridion) is a γ-cyclodextrin that selectively binds to steroidal neuromuscular blocking agents (NMBAs), making it the first selective muscle relaxant binding agent. Although it has been available internationally for several years, it recently received Food and Drug Administration (FDA) approval for (1) routine reversal of rocuronium- and vecuronium-induced neuromuscular blockade and (2) emergent reversal of rocuronium-induced neuromuscular blockade. This latter indication could change the management of patients who the anesthesiologist "cannot intubate, cannot ventilate" after induction of anesthesia with rocuronium. Unlike cholinesterase inhibitors (i.e., neostigmine, edrophonium), which traditionally have been the standard of method for "reversing" neuromuscular blockade with nondepolarizing agents in patients, sugammadex encapsulates the steroidal NMBAs, preventing rocuronium and vecuronium from interacting with nicotinic receptors (a true antidote, as opposed to merely increasing the amount of acetylcholine at the neuromuscular junction to compete with remaining NMBA) (Fig. 97.2).

The FDA declined approval of sugammadex three separate times due to concerns for hypersensitivity and bradycardia. But over 9 million patient exposures worldwide and follow-up repeat dosing trials have shown that serious adverse events are extremely rare (less than 1%) after sugammadex administration. If inadequately dosed, recurrence of neuromuscular blockade can occur. Other concerns have included an increased partial thromboplastin time (PTT) in coagulopathic patients, and possibly decreasing the concentration of estrogen and/or progesterone contraceptives. QTc prolongation has been reported with sugammadex administration as well. Common side effects include headache, nausea, vomiting, and dizziness.

Sugammadex has a rapid onset of effect (i.e., <3 minutes) when given IV and when dosed appropriately for the degree of neuromuscular blockade (Table 97.3). It is not metabolized by the liver, so hepatic dysfunction does not affect sugammadex dosing; however, coagulopathies should be considered. Nearly all of sugammadex is cleared by the kidneys with a half-life of approximately 2 hours (up to 19 hours in patients with severe renal impairment).

Recognition

Serious adverse events (e.g., hypersensitivity, bradycardia) usually occur within the first 5 minutes of drug administration, so vigilant monitoring should be performed immediately after the drug is given. Anticholinergic medications should be available, as well as typical hypersensitivity medications. Neuromuscular monitoring should be performed to ensure complete reversal, and recurrence of neuromuscular blockage has been described in prior studies (concern for underdosed sugammadex). If a patient who has received sugammadex needs redosing of NMBAs, a new class (i.e., a nonsteroidal NMBA) should be used instead, as sugammadex has no effect on the other classes of

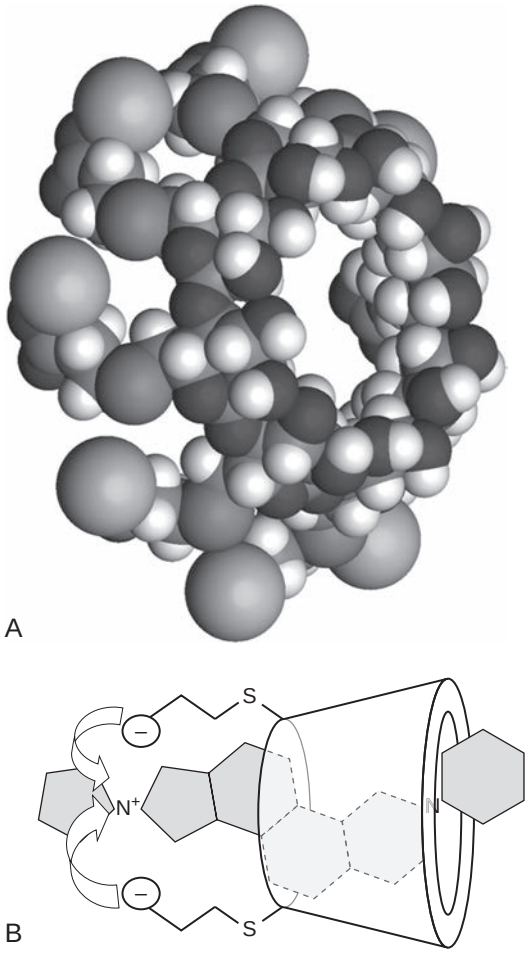

Fig. 97.2 Sugammadex (A) and schematic of sugammadex chelating steroidal neuromuscular blockade with rocuronium (B). (From Wikiwand. Available at http://www.wikiwand.com/en/Sugammadex.)

TABLE 97.3 Sugammadex (Steroidal Neuromuscular Blockade Reversal) Dosing

TOF >2	TOF <2	Immediate (TOF <0)[a]
2 mg/kg	4 mg/kg	16 mg/kg

[a]Immediate reversal has only been studied with rocuronium dosing (not vecuronium).
TOF, Train-of-four.

Risk Assessment

Although initial concerns for hypersensitivity reactions caused delays in FDA approval, a follow-up sugammadex repeat-dose trial with 299 patients revealed only one case of an anaphylactic reaction. Sugammadex should be avoided if possible in patients with significant coagulopathies, given the concern for PTT prolongation. If deep neuromuscular blockade has been reversed, muscle strength and respiratory efforts should be monitored closely.

Implications

Because sugammadex appears to provide a faster, more effective reversal of neuromuscular blockade than with cholinesterase inhibitors, its utilization will likely grow significantly in the coming years. Close monitoring of cardiopulmonary (ASA monitors) and neuromuscular (quantifiable TOF) status should be performed when administering any "reversal" agent.

MANAGEMENT

If bradycardia develops, anticholinergic medications (e.g., glycopyrrolate) should quickly be administered. Hypersensitivity reactions with bronchospasm or hypotension should be treated with appropriate medications immediately.

PREVENTION

Sugammadex should be avoided in patients where concern for hypersensitivity reaction could be present (prior reaction). If coagulopathies are present, it should be used with caution. Patients who are using estrogen and/or progesterone contraception should be informed that sugammadex can interfere with the efficacy of such medications.

Further Reading

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Succinylcholine

98

Eugene B. Freid

Case Synopsis

A 52-year-old woman with bipolar depression undergoes her first electroconvulsive therapy (ECT) treatment. Past history is otherwise pertinent only for hemiparetic, static encephalopathy as a result of meningitis in infancy and hypertension. Medications include lamotrigine, lurasidone, and lisinopril. Induction of anesthesia with 80 mg methohexital and 60 mg succinylcholine is uneventful, and she receives unilateral ECT. She is still apneic 15 minutes after the procedure and has no train-of-four response. She is sedated, intubated, and placed on mechanical ventilation. Sixty minutes later, she is clinically weak, with four diminished twitches and moderate fade on a train-of-four. Her trachea is extubated 2 hours after completion of ECT. Evaluation reveals a butyrylcholinesterase activity of 55% and a dibucaine number of 25, which is consistent with an atypical variant of butyrylcholinesterase.

PROBLEM ANALYSIS

Definition

For 50 years, the rapid onset and short duration of succinylcholine has afforded distinct advantages over other neuromuscular blocking drugs. Unfortunately succinylcholine also has numerous well-described complications that are related to its mechanism of action or pharmacokinetics or that occur as an idiosyncratic effect (Box 98.1). The most serious reactions are hyperkalemia, unanticipated prolonged muscle relaxation, and malignant hyperthermia (see Chapter 195). Hyperkalemia-induced cardiac arrest may develop soon after succinylcholine administration to patients with conditions that predispose to acetylcholine receptor upregulation (Box 98.2) or rhabdomyolysis.

Prolonged relaxation may occur after succinylcholine administration with the development of a phase II block or with decreased metabolism. After a single large dose, repeated doses, or a prolonged continuous infusion of succinylcholine, the postjunctional receptor may not respond normally to acetylcholine, even after the receptor-nicotinic channel has repolarized. This is termed a *phase II block*.

Under normal circumstances, the short duration of the effect of succinylcholine is the result of rapid hydrolysis by butyrylcholinesterase (BChE), also known as *pseudocholinesterase* or *plasma cholinesterase.* Ninety percent of an intravenous dose of succinylcholine is rapidly hydrolyzed to a nearly inactive metabolite in the plasma and liver by BChE. Neuromuscular block terminates by the diffusion of succinylcholine from the end plate into the extracellular fluid, where BChE influences the onset and duration of action by controlling the rate of hydrolysis. A prolonged duration of succinylcholine may occur when quantities of normal BChE are significantly decreased or when an abnormal variant of BChE is present.

Recognition

T-wave elevation, QRS complex prolongation and a sinusoidal QRS waveform (see Chapter 87), and asystole or ventricular fibrillation occurring shortly after succinylcholine administration are the characteristic alterations observed on the electrocardiogram (ECG) in patients with exaggerated potassium (K^+) release and hyperkalemia. Measurement of serum K^+ concentrations confirms hyperkalemia. However, if the ECG is abnormal, treatment should precede confirmation of serum K^+ concentrations.

The presence of abnormal BChE is frequently recognized only after failure to emerge from general anesthesia and prolonged muscle weakness occurs in an otherwise healthy patient who received a normal dose of succinylcholine. The presence of very low levels of a normal BChE or abnormal forms of BChE leads to variable prolongation of neuromuscular block (Table 98.1). These abnormalities are not uncommon. In a recent observational study in Switzerland, 16% of patients having rapid-sequence induction with 1 mg/kg succinylcholine had duration of block greater than 10 minutes. The diagnosis is confirmed by characteristic findings on peripheral nerve stimulation, including a train-of-four ratio (T_4/T_1) of less than 0.3 and the presence of fade and posttetanic facilitation typical of a phase II block caused by the elevated concentration of unmetabolized succinylcholine at the neuromuscular junction.

Risk Assessment

Potassium Release

Under normal conditions, depolarization of skeletal muscle occurs at acetylcholine receptors (AChRs) at the motor end plate and fluxes in K^+ after succinylcholine typically raise serum K^+ concentrations of up to 0.5 mEq/dL. In a number of pathologic conditions, however, exaggerated K^+ release after succinylcholine administration causes plasma K^+ concentrations to rise excessively (see Box 98.2). In susceptible patients, there is upregulation of immature AChRs and α7AChRs spreading throughout the muscle membrane. In effect, the entire muscle membrane acts as a motor end plate. The upregulated extrajunctional AChRs are more sensitive to succinylcholine, and the metabolism is slower, leading to sustained depolarization and exaggerated efflux of K^+ from the myocytes into the extracellular fluid. *Pretreatment with a nondepolarizing relaxant does not reliably abolish the hyperkalemic response.*

The timing of the development of exaggerated K^+ release with succinylcholine administration depends on the nature of the injury and

BOX 98.1 Complications of Succinylcholine Administration

- Cardiovascular
  - Tachycardia (ganglionic stimulation)
  - Bradycardia, sinus arrest, junctional rhythm (cardiac muscarinic)
- Hyperkalemia, exaggerated potassium release
- Fasciculations; myalgia[a]
- Myoglobinuria, elevated plasma creatine phosphokinase
- Sustained muscle contraction (myotonic dystrophy, congenital myotonia)
- Malignant hyperthermia
- Masseter muscle rigidity
- Prolonged relaxation
  - Phase II block
  - Inadequate pseudocholinesterase activity
- Increased intraocular pressure
- Increased intracranial pressure
- Increased intragastric pressure[a]
- Histamine release
- Allergy/anaphylactoid reactions

[a]May be reduced with succinylcholine pretreatment (defasciculation).

BOX 98.2 Conditions Predisposing to Exaggerated Potassium Release With Succinylcholine

- Thermal injury
- Upper or lower motor neuron defect
  - Spinal cord trauma
  - Hemiparesis, lower motor neuron lesions
  - Multiple sclerosis
  - Stroke
  - Guillain-Barré disease
  - Encephalitis with motor involvement
  - Central nervous system trauma
- Myopathy, muscular dystrophy
- Major trauma
- Disuse atrophy, prolonged chemical denervation
- Severe infection, tetanus

follows the timing of the development of AChR supersensitivity. Typically, it begins 5 to 15 days after thermal injury or trauma, peaks at 20 to 60 days, and persists for up to 3 months. In patients with upper and lower motor neuron disease, it begins at 7 days and persists for about 6 months, although it can occasionally persist for several years. In contrast, patients with static encephalopathy (e.g., cerebral palsy) typically do not have exaggerated K^+ release after succinylcholine, because their nervous system damage is remote and stable.

In patients with myopathy, rhabdomyolysis after succinylcholine administration can also cause life-threatening hyperkalemia. In infants and children, the myopathy may be clinically unapparent and is diagnosed only after succinylcholine-induced hyperkalemic cardiac arrest occurs.

Phase II Block

Clinically relevant phase II block can occur with total succinylcholine doses as low as 4 mg/kg, with either repeat dosing or continuous infusions. Development of tachyphylaxis often occurs concurrently with the development of clinically relevant phase II block.

Pseudocholinesterase

Reduced BChE activity occurs in the newborn and the elderly; with pregnancy, liver disease, malnutrition, malignancy, thermal injury; and with the use of certain medications and organophosphate pesticides. BChE levels may drop precipitously after plasmapheresis (Box 98.3). Low levels of a normal BChE generally do not prolong succinylcholine block to a clinically significant degree; this occurs only when normal BChE activity is reduced by at least 75% (normal, 4.9 to 12 IU/mL). In contrast, in patients with genetically abnormal BChE, the delay in return of normal neuromuscular function can range from mild (10 to 15 minutes) to severe (2 to 4 hours), depending on the variant. BChE is mediated by a single gene locus on chromosome 3q26. More than 50 mutations in BChE gene have been located, some replacing single amino acids resulting in an abnormal enzyme that does not function properly, others that prevent production of BChE. A single BChE gene may carry more than one mutation. The phenotypic difference between many, but not all of the abnormal BChE variants can be demonstrated using compounds (e.g., dibucaine, fluoride) that inhibit benzoylcholine hydrolysis by BChE under standard laboratory conditions. Benzoylcholine hydrolysis is inhibited 80% by dibucaine in the normal (Eu Eu) patient.

The most frequently occurring variants are the Kalow (K) and the Ea dibucaine resistant (atypical) variants (Table 98.1). In the atypical variant, benzoylcholine hydrolysis by dibucaine is reduced to less than 30%. Other qualitative forms of BChE include two fluoride-resistant variants and several "silent" variants in which a point mutation results in minimal BChE activity and shows neither dibucaine- nor fluoride-induced inhibition. There are also three quantitative variants, J, K and H, where BChE production is reduced. The k-polymorphism variant by itself only prolongs succinylcholine duration a small amount but may be combined with other mutations to markedly prolong neuromuscular block. Table 98.1 summarizes the characteristics of the normal and genetically abnormal BChE variants.

Implications

The consequences of succinylcholine-induced hyperkalemia include cardiac dysrhythmias and cardiac arrest. Prolonged relaxation after succinylcholine requires airway management and mechanical ventilation (with sedation) until the neuromuscular weakness subsides. Patients with abnormal BChE variants also demonstrate prolonged duration of mivacurium and ester local anesthetics. Because BChE is not involved in the metabolism of esmolol and remifentanil, their metabolism is unaffected in patients with atypical or abnormal BChE.

MANAGEMENT

Hyperkalemia

Asystole and ventricular fibrillation are treated with standard advanced cardiovascular life support (ACLS) protocols. In addition, the myocardium must be stabilized with calcium (chloride or gluconate) and hyperkalemia aggressively treated with hyperventilation and sodium bicarbonate and β-agonists. Because current ACLS protocols for asystole and ventricular fibrillation no longer contain calcium and sodium bicarbonate in the initial treatment, early consideration of hyperkalemia is critical. Calcium reduces the cellular effects of high K^+ concentrations in the heart, and hyperventilation, bicarbonate, and β-adrenergic receptor agonists (epinephrine) help drive K^+ intracellularly. Milder degrees of hyperkalemia are treated with hyperventilation, calcium, sodium bicarbonate, and parenteral or inhaled β-adrenergic receptor agonist therapy (albuterol or terbutaline). Glucose and insulin can

TABLE 98.1 Characteristics of Normal, Atypical, and Abnormal Butyrylcholinesterase

Genotype	Phenotype (Common Name)	Block Prolongation (90% T_1, min)	Dibucaine Number	Fluoride Number	Enzymatic Activity	Frequency
Eu Eu	Wild type (usual)	Normal 9.3 min (4–16)	70–80	60	100%	96%
Kalow (k) polymorphism	(K-variant)	Minimal 11.6 min (7–14)	80	60	67%	Eu/K: 1/4 KK: 1/63
Eu Ea		Slight 15 min (9–38)	60	50	77%	1/25
Eu Ef		Slight 15 min (11–23)	75	50	86%	1/200
Eu Es		Slight	80	60	50%	1/190
Ea Ef		Moderate 29 (23–36)	50	50	59%	1/20,000
Ef Es		Moderate	65	35	37%	1/15,000
Ef Ef	Fluoride resistant F1, F2	Moderate	65	35	74%	0.002 1/154,000
Ea Ea	Dibucaine resistant (atypical)	Very 130 (90–180)	20	20	43%	0.018 1/2000
Es Es	Silent S1, S2, S3	Very	—	—	0-slight	1/100,000
Ea Es		Very	20	20	22%	1/29,000

Data from Pantuck EJ, Pantuck CB: Prolonged apnea following succinylcholine administration. In Azar I, editor: *Muscle relaxants.* New York, Marcel Dekker, 1987, pp 206-229; Whittaker M: Plasma cholinesterase variants and the anaesthetist. *Anaesthesia* 35(2):174-197, 1980; Bretlau C, Sørenson MK, Vedersoe AL, et al.: Response to succinylcholine in patients carrying the K-variant of the butyrylcholinesterase gene. *Anesth Analg* 116(3):596-601, 2013.

BOX 98.3 Conditions Predisposing to Reduced Butyrylcholinesterase Activity

- Physiologic (newborn, pregnancy and elderly)
- Liver disease, malnutrition
- Malignancy (especially lung, gastrointestinal, and genitourinary)
- Thermal injury
- Medications (glucocorticoids, metoclopramide, estrogens, echothiophate, bambuterol, phenelzine, and cyclophosphamide)
- Organophosphate pesticides
- Plasmapheresis

also be used, but because their effects are more delayed, they are not considered first-line therapy. For children with hyperkalemic cardiac arrest, postoperative evaluation for occult muscle disease should be performed.

Prolonged Block

Because awareness during paralysis is still being reported in patients found to have genetically abnormal BChE, treatment for prolonged relaxation includes not only ensuring an adequate airway and gas exchange but also sedation/analgesia until phase II block is no longer evident and adequate muscle strength is present. Pure phase II block may be reversible with anticholinesterase. However, the block caused by succinylcholine overdose or with atypical or abnormal pseudocholinesterase is a mixed block (phase I and phase II), and anticholinesterase therapy may lengthen the duration of phase I block. Most practitioners simply continue ventilatory support until the block wanes and muscle strength has returned to its baseline level. Although banked blood and plasma contain active BChE, the risk associated with their transfusion outweighs the possible benefit of reversing prolonged block. Patients suspected of having atypical or abnormal BChE should be tested for BChE activity, dibucaine number, and genetic testing, if available, and made aware of their condition. There should be a note in the patient's chart indicating an "allergy" to succinylcholine, and the patient should wear a medical-alert bracelet.

PREVENTION

The best way to prevent complications with succinylcholine is to avoid it altogether, unless there is a compelling indication for or advantage to its use. This is especially true in young children, especially male, who might have clinically unapparent myopathy. In many countries, the availability of sugammadex has allowed the replacement of succinylcholine with rocuronium in most instances where succinylcholine is used. Several studies have demonstrated onset and recovery with high-dose rocuronium and sugammadex at least as rapid as, or even more rapid than, succinylcholine.

If repeated doses of succinylcholine are used, keeping the total dose under 5 to 6 mg/kg reduces development of phase II block. During the preoperative evaluation, a family history of prolonged weakness or delay in awakening from anesthesia should be elicited. There are some geographic regions in which genetic abnormalities of BChE are more common because of its hereditary nature. In these regions, preoperative laboratory screening for BChE activity may be useful.

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Volatile Anesthetics: Organ Toxicity

99

Evan D. Kharasch

Case Synopsis

A 53-year-old woman has laser excision of vocal cord papillomas under anesthesia with halothane and spontaneous ventilation. She has had several prior excisions, including one a month earlier, all with halothane; all were uneventful. However, 1 week after this surgery, she develops fever, nausea, and malaise, along with severe jaundice and markedly elevated serum transaminase concentrations.

PROBLEM ANALYSIS

Definition

Organ toxicity caused by volatile anesthetics is the result of alterations in cellular structure or function that persist beyond the period of anesthetic administration and elimination. Of greatest concern with volatile anesthetics are hepatic toxicity and renal toxicity.

Not discussed here, but worthy of mention, is the potential for volatile inhalational anesthetics to interact with desiccated carbon dioxide absorbents to form potentially toxic compounds, such as carbon monoxide and compound A. Pulmonary and renal toxicity can occur, and fires and explosions have also been reported. (For more details, see the works by Baum and Woehlck listed under "Further Reading.")

Hepatic Toxicity

Hepatic toxicity occurs most commonly after halothane administration, but it has also been observed with less frequency after enflurane, isoflurane, sevoflurane, and desflurane. Halothane causes two types of liver damage:

- Fulminant hepatic necrosis ("halothane hepatitis")
- Mild subclinical hepatotoxicity

Fulminant hepatic necrosis is clinically characterized by fever and jaundice, with grossly elevated serum transaminase levels. Liver biopsies show massive centrilobular necrosis. Today, fulminant hepatic necrosis is considered an immune phenomenon that is initiated by oxidative metabolism of halothane to an intermediate. This subsequently binds to liver proteins and induces trifluoroacetylation, which renders the proteins antigenic. These antigens stimulate the formation of antibodies that, on reexposure to halothane (or enflurane, isoflurane, or desflurane), initiate immune-mediated hepatic necrosis. Such necrosis is rare, occurring in 1 in 6000 to 35,000 persons after halothane administration and in 2 in 1 million persons after enflurane; there have been a few reports of cases after isoflurane and one confirmed case after desflurane. Hepatic dysfunction after sevoflurane administration has also been reported, but it is not thought to represent immune-mediated necrosis, and the relationship to anesthesia is unknown.

Mild hepatotoxicity occurs commonly after halothane administration (approximately 25% of cases) but not after the administration of other volatile anesthetics. It is characterized by mild, transient elevations in serum transaminase and glutathione-S-transferase concentrations and altered postoperative drug metabolism. However, clinically evident hepatocellular disease is not a characteristic of mild hepatic toxicity. Rather, it is attributed to reductive (anaerobic) halothane metabolism, with reactive metabolites causing lipid peroxidation and binding to cytochrome P-450. The two forms of hepatic anesthetic toxicity are thought to be unrelated.

Acute Renal Failure

Acute renal failure is a common perioperative problem, but it is now rarely the direct result of volatile anesthetics. Several terms require definition:

- *Renal failure* is a reduction in renal function sufficient to cause alterations in serum biochemistry; it may be oliguric, nonoliguric, or polyuric.
- *Renal insufficiency* is a lesser reduction in renal function with normal serum biochemistry.
- *Oliguria* is urine output less than 20 mL/h (in a 70-kg adult) and implies renal failure.
- *Nonoliguric renal failure* is more common than oliguric failure, and it is thought to represent a milder renal insult.
- *Polyuria* is urine output greater than 100 mL/h (in a 70-kg adult).

Both oliguric and nonoliguric renal failure may be postrenal (obstructive), prerenal (renal hypoperfusion due to hypovolemia, hypotension, decreased renal blood flow, or cardiovascular surgery), or intrinsic (caused by nephrotoxins such as aminoglycosides, myoglobin, hemoglobin, radiocontrast media, or nonsteroidal antiinflammatory agents). Polyuric renal failure with reduced concentrating ability is due to either central diabetes insipidus (insufficient antidiuretic hormone secretion, usually due to pituitary dysfunction) or nephrogenic diabetes insipidus (renal unresponsiveness to antidiuretic hormone).

Anesthesia-related renal insufficiency is often prerenal and is caused by hypotension or altered renal perfusion. It is limited to the duration of the anesthetic and is reversible. Renal failure specifically attributable to anesthetic agents has been observed only with methoxyflurane, which can cause vasopressin-resistant polyuria, hypernatremia, hyperosmolality, and dehydration; it also increases blood urea nitrogen (BUN) and creatinine levels. Methoxyflurane nephrotoxicity is due to dose-related methoxyflurane metabolism. Associated plasma

fluoride concentrations range from greater than 50 to 80 μM. A mild but reversible concentrating defect after prolonged enflurane use has been noted. Direct nephrotoxicity has not been observed with enflurane, isoflurane, desflurane, or sevoflurane, even with systemic fluoride concentrations far exceeding 50 μM. The role of systemic fluoride concentrations as a factor in nephrotoxicity has been discounted.

Recognition

Fulminant hepatic necrosis manifests clinically as fever, nausea, anorexia, chills, malaise, and rash that appear 3 to 6 days postoperatively, followed by severe jaundice that occurs 6 to 10 days postoperatively. Laboratory manifestations include grossly elevated serum transaminase levels, hyperbilirubinemia, and prolonged prothrombin time, but these are not specific for the disease. Pathologic findings include centrilobular and midzonal necrosis, but again, these findings are not specific. Mild hepatotoxicity after halothane is usually clinically silent, consisting of only mild, reversible increases in liver enzymes (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, and glutathione-S-transferase) on laboratory studies. These elevations appear 1 to 2 days postoperatively and usually resolve within days. However, levels may remain elevated for up to 2 weeks.

A specific diagnosis of anesthetic-related hepatitis is difficult at best. Both the clinical presentation and the morphologic features strongly resemble those of viral hepatitis. Indeed, the incidence of occult perioperative hepatitis (viral, infectious, alcoholic) is 1 in 700, and in 30% of these cases, postoperative jaundice develops; this is far greater than the incidence of anesthetic-related fulminant hepatitis. Positive serologic markers for hepatitis A, B, C, or D or other infectious agents (e.g., cytomegalovirus, Epstein-Barr virus) may help exclude anesthesia as the cause of postoperative hepatitis, but negative serologic findings are inconclusive, especially if infection is recent. A few laboratories can detect antitrifluoroacetylated protein antibodies in serum, which favors a diagnosis of anesthetic-related hepatitis. However, the assay lacks sufficient specificity and is not routinely available. Hepatitis C is the most common cause of postoperative hepatitis, but hepatic ischemia, other drugs, transfusion, and cholestasis should also be excluded.

The clinical characteristics of renal insufficiency and acute renal failure were listed earlier. Differentiation of central and nephrogenic diabetes insipidus is based on response to water deprivation and vasopressin. The cause of oliguric renal failure is determined by the BUN-creatinine ratio, urine sodium and osmolality, urine-plasma osmolality, urine-plasma creatinine, fractional excretion of sodium, and response to volume challenge. The diagnosis of renal failure specific to a volatile anesthetic is extremely rare in the post-methoxyflurane era.

Risk Assessment

Clinical risk factors for fulminant hepatic necrosis include the following:

- Repeated halothane exposure
- Prior history of postanesthetic fever or jaundice
- Obesity
- Female sex
- Middle age

Halothane is oxidatively metabolized by cytochrome P-450 2E1. Thus enzyme induction (alcohol, isoniazid, obesity) increases antigen formation and increases risk, whereas enzyme inhibition (disulfiram) reduces metabolism. Multiple, repeated exposures at short intervals (<6 weeks) is the greatest risk factor for halothane hepatitis.

Children are at greatly diminished risk, for unknown reasons, even after repeated halothane exposure. Liver disease itself is not a risk factor for halothane hepatitis. Clinical risk factors for mild hepatotoxicity are those that increase reductive halothane metabolism. Halothane is reduced anaerobically by P-450 3A4 and 2A6; thus enzyme induction (e.g., by barbiturates, phenytoin, valproic acid) increases metabolism, as does reduced hepatic blood flow. The latter is further reduced by halothane. Although enflurane, isoflurane, and desflurane also cause neoantigen formation, the degree of such formation is far less than with halothane, so the risk of hepatitis with these agents in halothane-sensitized patients is far less.

The only clearly identified clinical risk factors for postoperative renal failure are the following:

- Poor preoperative renal function (increased BUN or creatinine levels)
- Advanced age
- Cardiac failure

Treatment and prevention of hypovolemia and preoperative hydration are primary goals in ameliorating the cardiovascular and renal blood flow effects of volatile anesthetics in general. Mechanical ventilation and positive end-expiratory pressure are other factors peripherally related to volatile anesthetics that diminish renal function. Although not pertinent to contemporary anesthesia, certain inducers of drug metabolism (barbiturates, isoniazid, ethanol) potentiate methoxyflurane metabolism and toxicity.

Implications

Fulminant hepatic necrosis after halothane is fatal in nearly half of all cases. There are no known clinical implications of mild hepatotoxicity. Perioperative acute renal failure accounts for half of all patients who require acute dialysis and is associated with a 50% mortality rate. This has remained unchanged for decades.

MANAGEMENT

There is no specific management for either fulminant hepatic necrosis or mild hepatotoxicity. No therapy is needed for mild hepatotoxicity, whereas only supportive therapy and orthotopic liver transplantation are available for hepatic necrosis. Treatment for acute renal dysfunction includes restoration of normovolemia and renal blood flow; administration of mannitol, loop diuretics (controversial), dopamine, and fenoldopam (experimental); and dialysis.

PREVENTION

No measures for the prevention of mild hepatotoxicity are necessary. The only fail-safe method of preventing fulminant hepatic necrosis is total avoidance of halothane, enflurane, isoflurane, and desflurane in patients previously exposed to halothane. Hepatitis is rare in children and in adults with only a single exposure to halothane. A conservative approach is to avoid halothane in patients with known risk factors for fulminant necrosis, especially recent halothane anesthesia. The ultraconservative approach is to avoid halothane altogether.

The single most effective measure to prevent postoperative renal failure is to minimize renal ischemia by maintaining renal perfusion. Maintenance of adequate hydration is essential. Mannitol may be an effective prophylactic.

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100 Blood and Blood Products: Infections

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Case Synopsis

A 70-year-old man with a history of coronary artery disease and a new diagnosis of abdominal aortic aneurysm is being evaluated in the preoperative area for an open repair. His hemoglobin is 10 g/dL, and you decide to obtain his informed consent for the possibility of blood product transfusions. During the process of obtaining consent, he becomes visibly upset during the discussion. On further questioning, it becomes clear that the patient is very concerned over the chance of "catching something from the blood" and would like to know more information.

PROBLEM ANALYSIS

Definition

Blood-borne infections are a concern of patients, family members, and health care providers alike. Patients may be exposed to these infections through the transfusion of banked blood products. Additionally, the act of allogeneic blood transfusion alone may cause recipient immunomodulation that can confer an increased risk of infections. As the largest user of blood products of any physician group, it is especially important for the anesthesiologist to understand the risks of infections and their management.

Transfusion-transmitted infectious diseases (TTIDs) have been recognized for decades, with the most recent advances occurring since the 1980s and the discovery of blood-related human immunodeficiency virus (HIV) transmission. Blood products can transmit viral, bacterial, and parasitic infections. Several mechanisms are in place throughout the donation process to mitigate these risks, including donor screening and testing.

Recognition

The blood screening process begins with a medical history to detect patients with symptoms of current infections and those at high risk of carrying infection. Donated blood is then tested for several viral and parasitic pathogens through antibody and nucleic acid testing (Box 100.1). Additionally, donor platelets are subjected to an automated culture for 24 hours after donation to screen for bacterial contamination. Several notable infectious agents not tested for but known to be transmissible include variant Creutzfeldt-Jakob disease, malaria, dengue fever, and babesiosis. These are typically screened for during the blood donation interview process.

Bacterial Infections

Transfusion-transmitted bacterial infections (TTBIs) are more common in platelet components, owing to their room-temperature storage. TTBIs can be caused from a wide spectrum of organisms during the collection process, including donor blood or contamination during phlebotomy collection and subsequent processing. Both gram-positive and gram-negative organisms have been shown to grow in platelets, with the most common pathogen being *Yersinia enterocolitica.*

Transfusion-Related Immunomodulation

Transfusion-related immunomodulation (TRIM) is another transfusion complication that can cause infectious harm to the recipient. In the past, allogeneic blood transfusions were found to increase survival in renal transplant recipients. However, blood transfusions have also been found to increase the incidence of postoperative bacterial infections not associated with the transfused products, activation of endogenous HIV and cytomegalovirus, increased recurrence rate of resected malignancies, and overall increased short-term (3-month) mortality rate. The pathophysiology of TRIM is still unclear at this point, but is thought to involve both immunosuppressive and proinflammatory mechanisms from donor white blood cells (WBCs), soluble WBC-derived mediators, and human leukocyte antigen peptides. Leukoreduction has improved but not solved this issue entirely.

Risk Assessment

Although the risks of TTIDs have decreased dramatically with improved blood banking practices, they are not zero. The risks today for three of the most common viral TTIDs are as follows:

- HIV: 1 in 2,000,000 transfusions
- Hepatitis B virus (HBV): 1 in 500,000 transfusions
- Hepatitis C virus (HCV): 1 in 2,000,000 transfusions

Incidences of other viral and parasitic transmissions are very difficult to accurately report. Of note, HIV, HBV, and HCV are inactivated in the preparation of blood-derived plasma products such as intravenous immunoglobulin and albumin and do not confer risk of transmission. TTIDs today are thought to occur through one of three mechanisms: donations collected during the "window period" of infection not able to be picked up during testing, inherent false negatives in the screening assays, and clerical errors during the blood banking process.

Bacterial contamination is said to range from 0.04% to 10% of platelet units, with risk of causing recipient bacteremia at 1 in 10,000

BOX 100.1 Infectious Agents Tested for in Donated Blood Products

Human immunodeficiency virus types 1 and 2
Human T-cell lymphotropic virus types 1 and 2
Hepatitis B virus
Hepatitis C virus
West Nile virus
Cytomegalovirus
Syphilis *(Treponema pallidum)*
Chagas disease *(Trypanosoma cruzi)*—only for first-time donors

Adapted from Goodnough LT: Blood management: transfusion medicine comes of age. *Lancet* 381(9880):1791-1792, 2013.

transfusions, and risk of sepsis-related mortality at 1 in 500,000 transfusions. The risk is dose dependent and therefore higher in pooled donors versus single-donor apheresis units. A study found that sepsis-related mortality was the third highest cause of transfusion-related death behind transfusion-related acute lung injury (TRALI) and acute hemolytic transfusion reaction (AHTR) (see Chapter 101).

Occupational Exposure

Blood-contaminated injuries (e.g., needle sticks) are an occupational health risk that can also cause infection. The risk of transmission after a needle stick with HIV-contaminated blood is 0.3% and HCV is 1.8%. The risk of HBV varies greatly from 23% to 62% depending on the source patient's HBeAg status. The true incidence of occupational exposures is unknown because they are often underreported.

Implications

After transfusion or other blood exposure, the implications of TTIDs can be profound. Recognition of symptoms and appropriate referral are of the utmost importance, although transmission of these illnesses is only retrospectively linked with a patient's history of blood product transfusion or a provider's history of occupational exposure.

The diagnosis of HIV or hepatitis depends on an index of suspicion and the development of viral symptoms weeks to months after exposure. Initial HIV infection is often asymptomatic, although roughly half of infected patients develop a viral syndrome (e.g., fever, pharyngitis, myalgia, lymphadenopathy) within 6 weeks of exposure. Subsequent antibody and nucleic acid testing confirms HIV infection. Similarly, initial infection with HBV or HCV may be asymptomatic or may involve a flulike syndrome weeks or even months after exposure. Clinical jaundice develops in less than one third of patients. The development of symptoms consistent with hepatitis (e.g., malaise, jaundice) several weeks after exposure to blood should prompt referral for appropriate hematologic studies. Those with a new diagnosis should be promptly referred for medical and psychological management.

MANAGEMENT

Bacterial Infections

The presentation of TTBI-related sepsis often varies on inoculum size, pathogen virulence, and recipient immune status, but the median time between completion of transfusion and onset of symptoms is 30 minutes (range of 0 to 5 hours). The timing of symptoms can be clinically indistinguishable from an AHTR (see Chapter 101).

When a serious transfusion reaction occurs, initial management includes stopping the transfusion; supportive treatment and resuscitation; blood collection (from the opposite arm) for a repeat type and cross, direct antiglobulin, plasma-free hemoglobin, and cultures; alerting the blood bank; and checking for clerical errors. If there is a high clinical suspicion of infection (i.e., platelet transfusion), it is reasonable to consider adding empiric broad-spectrum antibiotics.

Occupational Exposure

Should an occupational exposure occur, it is important to follow your facility's local practices. Exposures should be reported to the appropriate office for documentation, counseling, and management. Typically, the affected area should be washed immediately with soap and water. Involved mucous membranes are flushed with water or an appropriate salt solution.

If the source patient is HIV infected, the initiation of postexposure chemoprophylaxis with antiretrovirals within 24 to 36 hours may be appropriate to reduce the risk of developing an infection. Postexposure prophylaxis for HBV includes checking for previous vaccination history, vaccinating where necessary, and passive immunization with hepatitis B immune globulin. There is no accepted postexposure prophylaxis available for HCV, and the management typically involves serologic follow-up.

PREVENTION

There are many methods to prevent TTIDs. As discussed, most viral and parasitic agents are screened for in the blood donation process with a thorough history and testing process. TTBIs can also be prevented with adequate donor screening, as well as sterile sample collection, platelet agitation during storage, leukoreduction, improved culture methods and timing, and bactericidal treatments.

Consent and Alternative Options

Given the emotional impact associated with the risk of TTIDs, this issue must be put in its proper perspective during the patient's preoperative visit. In the case of any procedure that might involve significant blood loss, consent for blood product transfusion should be obtained. Although every hospital has its own consent form, consent should include the potential risks and benefits of transfusion, alternatives to transfusion, and the opportunity to ask questions.

Blood products should not be administered as generic volume expanders but should be given only for specific indications, such as to increase oxygen-carrying capacity or increase clotting factor or platelet levels. The preoperative donation of autologous blood, the use of isovolumic hemodilution, and intraoperative blood salvage techniques may be useful in avoiding exposure to allogeneic blood products. However, preoperative donation of autologous blood still poses infectious risks to the patient, ranging from clerical errors in the blood bank to TTBIs from improper collection and storage. Furthermore, although using restrictive transfusion strategies would theoretically decrease infection risk, studies have only shown a marginal improvement.

Occupational Exposure

The primary defense in preventing an occupational exposure is the proper use of Standard Precautions (Box 100.2), which includes barrier precautions, techniques to avoid sharps injuries, and hand hygiene. Secondary defense includes preexposure prophylaxis such as vaccination where warranted. Although no vaccines are currently available for HIV or HCV, HBV vaccination is recommended for high-risk health care providers, including anesthesia personnel.

BOX 100.2 Highlights of Standard Precautions

- Barrier precautions with all patients to prevent blood and body fluid contact
  - Gloves when contacting blood or body fluids or nonintact skin (do not wash or disinfect gloves, because disinfectants can cause deterioration)
  - Gown, mask, eyewear if splash or spray is likely
- Avoid sharps injuries
  - Prompt disposal in appropriate container
  - Avoid recapping needles
- Hand washing after glove removal or any blood or body fluid contact
- Artificial mouthpieces and airways for cardiopulmonary resuscitation

Data from Siegel JD, Rhinehart E, Jackson M, et al.: 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control* 35(10 Suppl 2):S65-S164, 2007.

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Blood and Blood Products: Transfusion Reactions and Complications

101

Seth Perelman

Case Synopsis

A 33-year-old woman, G3P2002 at 34 weeks' gestation with a known history of placenta previa, undergoes ultrasound concerning for placenta accreta. The patient underwent a successful cesarean section under epidural anesthesia but required allogeneic blood transfusions that included 6 units of packed red blood cells (PRBCs), 2 units of fresh frozen plasma (FFP), and 6 units of platelets. The patient was hemodynamically stable at the conclusion of the procedure; but developed fever, acute respiratory distress, and hypotension in the postanesthesia care unit 5 hours after the procedure, requiring mechanical ventilation.

PROBLEM ANALYSIS

Definition

Transfusion reactions are any unfavorable reaction to the administration of an allogeneic blood component. They may occur acutely or may be delayed and may range from clinically benign to life-threatening reactions. This chapter discusses the various reactions and their management, with particular focus on the clinical case presented.

Recognition

A temporal relationship of an unfavorable reaction to an allogeneic transfusion implies a transfusion reaction. These reactions may encompass a range of signs and symptoms, including fever, chills, rash, flank pain, hemodynamic instability, bronchospasm, coagulopathy, hemoglobinuria, and dyspnea. The specific reaction may indicate an evolving transfusion reaction and may help delineate the type of reaction; however, patients receiving blood transfusions often have underlying comorbidities that may mimic the symptoms of a transfusion reaction. The difficulty in attributing these symptoms to the transfusion may be further complicated in the operating room where the symptoms may be masked or confounded by general anesthesia. It is therefore imperative that a suspected reaction be evaluated promptly to minimize its impact.

Types of Reactions (Table 101.1)

Acute Reactions

Allogeneic blood transfusion (ABT) reactions may be categorized as acute versus delayed and immune mediated versus non–immune mediated. Specific diagnostic and management strategies will be discussed, as well as strategies to reduce transfusion-related morbidity and mortality (Table 101.2).

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions (AHTRs) are life-threatening reactions caused by acute intravascular hemolysis resulting from the binding of donor red cell antigens with recipient antibodies to form immune complexes. These reactions are often caused by clerical error (incorrect blood component transfused). These Ag-Ab immune complexes cause complement fixation, leukocyte activation, intravascular hemolysis, and hemoglobinuria and induce the formation of cytokines, resulting in hemodynamic instability, flank pain, fever, chills, and disseminated intravascular coagulation (DIC). Severe reactions are usually the result of ABO incompatibility or possibly to other red blood cell (RBC) Abs from prior alloimmunization. The severity of the reaction depends on the recipient Ab titer, the volume transfused, and the rate of transfusion. Most fatalities have been associated with transfusions greater than 200 mL, and for transfusions greater than 1000 mL, the mortality rate approaches 44%. Improved administrative systems have reduced the number of ABO-incompatible AHTRs, with the Food and Drug Administration (FDA) reporting 131 ABO-incompatible AHTR fatalities in 1976 to 1985 compared with 13 in 2010 to 2014. Laboratory findings include hemoglobinemia, hemoglobinuria, positive direct Ab test (DAT), and findings of DIC (prolonged prothrombin time/partial thromboplastin time, thrombocytopenia, hypofibrinogenemia). Despite the presence of more than 250 RBC antigens, AHTRs are usually the result of ABO or RH D group incompatibility.

Febrile Nonhemolytic Transfusion Reactions

Febrile nonhemolytic transfusion reactions (FNTRs) are common reactions characterized by fever and may be associated with chills, rigors, and malaise occurring during a transfusion or a few hours after a transfusion. They are usually caused by recipient antibodies reacting to donor leukocyte antigens to form an antigen-antibody complex with the release of complement-mediated endogenous pyrogens (interleukin-1 [IL-1], IL-6, and tumor necrosis factor–alpha). Management is usually symptomatic with antipyretics, but FNTRs are a diagnosis of

TABLE 101.1 Rates of Transfusion Reactions

Transfusion Reaction Type	Prevalence (per 100,000 Units Transfused)
Allergic transfusion reaction	112.2
Anaphylactic transfusion reaction	8
Acute hemolytic transfusion reaction	2.5–7.9
Delayed hemolytic transfusion reaction	40
Delayed serologic transfusion reaction	48.9–75.7
Febrile nonhemolytic transfusion reaction	1000–3000
Hyperhemolytic transfusion reaction	Unknown
Hypotensive transfusion reaction	1.8–9.0
Massive transfusion associated reactions (citrate, potassium, cold toxicity)	Unknown
Posttransfusion purpura	Unknown
Septic transfusion reaction	0.03–3.3 (product dependent)
Transfusion-associated circulatory overload	10.9
Transfusion-associated graft-versus-host disease	Extremely rare (near 0%) with irradiation or pathogen reduction methods
Transfusion-associated necrotizing enterocolitis	Unknown
Transfusion-related acute lung injury	0.4–1.0 with mitigation (varies by component and postimplementation of risk-mitigation strategies)

From Delaney M, Wendel S, Bercovitz RS, et al.: Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* pii:S0140-6736(15)01313-6, 2016. [Epub before print.]

TABLE 101.2 Types of Transfusion Reactions

Acute Transfusion Reactions	Delayed Transfusion Reactions
Hemolytic	Hemolytic
Nonhemolytic	Thrombocytopenia
• Febrile	Graft-versus-host disease
• Urticaria	Infectious transmission—viral, bacterial, parasites, prions
• Allergic reactions—pruritus, urticarial, and fever	Transfusion-related immunomodulation
• IgA-mediated anaphylaxis	Iron overload
• Transfusion-related lung injury	
• Transfusion-associated sepsis	
• Transfusion-associated circulatory overload	
• Coagulopathy	

IgA, Immunoglobulin A.
Modified from Proctor LT: Blood and blood products: transfusion reaction. In Atlee JL: *Complications in anesthesia,* 2nd ed. Philadelphia, Saunders, 2006, pp. 202–203.

exclusion because febrile reactions may also accompany more serious reactions such as AHTR, transfusion-related acute lung injury, and sepsis. In most circumstances the transfusion rate can be decreased without abandoning the transfusion. In countries where universal leukoreduction has been implemented, there has been a reduction in FNTRs.

Allergic Reactions

Allergic reactions are common, are usually mild, and present with urticaria, pruritus, and possibly fever. The majority are caused by an antibody-antigen reaction to serum proteins present in donor plasma and are immunoglobulin E (IgE) mediated. The presence of an urticarial transfusion reaction (UTR) does not necessitate abandoning the transfusion. The transfusion should be stopped, antihistamines should be administered, and the transfusion may be resumed when the symptoms have diminished.

Anaphylactic transfusion reactions are rare, but serious reactions are often found in patients that have a hereditary immunoglobulin A (IgA) deficiency and have anti-IgA antibodies to IgA in the transfused product or antibodies to other donor plasma constituents. This anti-IgA IgA immune complex interaction occurs immediately and is not dose related. In addition to the urticaria, present in UTRs, clinical features include angioedema, bronchospasm, and hypotension. Management is the same as for other causes of anaphylaxis and includes fluid resuscitation, epinephrine, antihistamines, and corticosteroids, depending on the severity of the reaction.

BOX 101.1 Definition of Transfusion-Related Acute Lung Injury (TRALI)

Suspected TRALI
- Acute onset within 6 h of blood transfusion
- Pao_2/Fio_2 less than 300 mm Hg, or worsening of P:F ratio
- Bilateral infiltrative changes on chest radiograph
- No sign of hydrostatic pulmonary edema (pulmonary arterial occlusion pressure ≤18 mm Hg or central venous pressure ≤15 mm Hg)
- No other risk factor for acute lung injury

Possible TRALI
- Same as for suspected TRALI, but another risk factor present for acute lung injury

Delayed TRALI
- Same as for (possible) TRALI and onset within 6–72 h of blood transfusion

From Vlaar AP, Juffermans NP: Transfusion-related acute lung injury: a clinical review. *Lancet* 382(9896):984–994, 2013.

Transfusion-Related Acute Lung Injury (Box 101.1)

Transfusion-related acute lung injury (TRALI) is considered to be one of the leading causes of transfusion-related morbidity and mortality in developed countries. It presents as an acute respiratory distress syndrome within 6 hours of transfusion. Its incidence varies significantly from country to country and has been most likely underestimated due to a lack of a consensus definition before 2004. The fact that it is a clinical diagnosis of exclusion and the differing methods of reporting (active vs. passive hemovigilance) have been the main factors for its underestimation. Recent reviews have noted an incidence of up to 1.12% per unit of blood transfused, with an incidence of 8% per transfused high-risk recipient, corresponding to an increase in reporting. TRALI refers to the new onset of acute lung injury (ALI) within 6 hours of completion of a transfusion where there are no other risk factors for ALI and no other signs of acute pulmonary vascular overload. Clinical features include hypoxemia, dyspnea, cyanosis, and tachycardia and may be accompanied by fever and hypotension. It is important to differentiate TRALI from other forms of ALI, including circulatory overload (TACO; see later in this chapter) and myocardial or valvular heart disease. The acute hypoxemia is defined by a Pao_2/F_io_2 ratio less than 300 mm Hg associated with chest radiographic findings of bilateral pulmonary infiltrates without signs of cardiogenic pulmonary edema. Because patients with coexisting pulmonary disease who receive an ABT would be excluded from the diagnosis of TRALI, the Canadian consensus group in 2004 included the definition of "possible TRALI" in patients who have one or more risk factors for ALI who develop worsening ALI after a transfusion. In this high-risk population, the development of "delayed TRALI" has also been described up to 72 hours after transfusion and is associated with a high mortality rate.

TRALI has been reported as occurring with all types of blood components; however, most reactions have occurred with products containing more than 50 mL of plasma, and classically FFP has been the most frequently implicated component. Risk-mitigation strategies, including female parturient donor deferral for plasma and apheresis

platelets, have reduced the incidence of FFP-associated TRALI. Currently, RBC-associated TRALI has the highest incidence of TRALI-related deaths due to plasma donor deferral and the volume of RBCs transfused compared with other blood components.

The original proposed pathophysiologic mechanism for TRALI was attributed to an antibody-mediated model, where white blood cell (WBC) antibodies (human leukocyte antigen [HLA] classes I and III or neutrophil specific) in donor plasma directed against the recipient's WBC antigens interact in the microcirculation of the recipient's lungs, causing direct or indirect neutrophil activation. The Ab titer and the volume of Ab containing plasma are risk-modifying factors that may indicate that differing thresholds may be required to develop TRALI in a specific at-risk subgroup versus a low-risk recipient. In 65% to 90% of TRALI cases, Abs have been identified in the donor plasma, and multiparous women and donors with a recent history of previous transfusions are at a higher risk for HLA antigen alloimmunization. However, not all cases of TRALI are Ab mediated, and not all transfused products containing HLA Abs cause TRALI. This has led to an alternative hypothesis, the so-called two-hit model.

In the "first hit," activation of the pulmonary endothelium caused by underlying patient risk factors results in the release of cytokines and the expression of adhesion molecules, which primes polymorphonuclear leukocytes (PMNs) to sequester in the pulmonary endothelium. PMN priming usually occurs before the transfusion due to recipient risk factors. Critically ill patients are at the highest risk for developing TRALI, but various studies have revealed specific recipient risk factors: high APACHE score, shock, massive transfusion, positive fluid balance, smoking, high peak airway pressures with mechanical ventilation, sepsis, emergency cardiac surgery, liver disease, chronic alcohol abuse, and recent surgery. The "second hit" involves the interaction of the PMNs with leukocyte Abs and/or biologic response modifiers (BRMs) present in the plasma containing blood component that accumulate with storage (bioactive lipids and other soluble factors). The interaction of the Abs or BRMs with the PMNs results in the release of cytokines, oxidases, proteases, and reactive oxygen species that damage the pulmonary capillary endothelium resulting in leakage and subsequent noncardiac pulmonary edema. The treatment for TRALI is supportive and consists of aggressive respiratory support with supplemental oxygen and mechanical ventilation if required at low enough pressures and tidal volumes not to induce barotrauma.

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload (TACO) is another transfusion-associated cause of respiratory insufficiency; however, it is secondary to volume overload. It typically occurs in the elderly and infants or in patients with underlying myocardial disease who receive blood component therapy in a short time interval. It is often underreported and underrecognized and is the second most common cause of transfusion-related mortality reported to the FDA. A recent prospective analysis found that the rate of platelet-associated TACO was 1:167 transfused platelet units, much greater than is currently reported through passive reporting. A retrospective review of TACO-associated risk factors and infusion practices revealed a patient history of congestive heart failure, renal dysfunction, and age greater than 70 and found that inappropriate infusion practices and suboptimal fluid management strategies were often employed. Differentiating TACO and TRALI can be challenging, especially given that both can coexist, but TRALI is often associated with fever, hypotension, and exudative pulmonary infiltrates, whereas TACO is associated with findings of circulatory overload, elevated levels of N-terminal prohormone of brain natriuretic peptide, and/or myocardial dysfunction and usually responds to diuresis.

Transfusion-Associated Sepsis

Transfusion-associated sepsis (TAS) is caused by the transfusion of a bacterial-contaminated blood component. Initial symptoms may include fever, chills, hypotension, and cardiovascular collapse, usually occurring within 4 hours of transfusion. Contamination usually results from the introduction of skin flora from the donor phlebotomy site and less commonly from asymptomatic donor bacteremia or rarely during blood processing. The storage temperature of the units results in the propensity for different kinds of bacterial infections. RBCs are stored at 4°C, making contamination and proliferation with gram-negative bacteria such as *Yersinia enterocolitica* and *Psuedomonas* species more likely. Platelets are stored at room temperature (22°C), making contamination with gram-positive bacteria such as *Staphylococcus epidermidis, Staphylococcus aureus,* and *Bacillus* species more likely. Introduction of automated bacterial detection of apheresis (single-donor) platelets in 2004 has drastically reduced the incidence of TAS, as well as a shift from whole blood product pooled platelets to single-donor apheresis platelets, yet TAS still ranks third among transfusion-associated mortalities. Platelets still account for 70% of the TAS fatalities, because storage at 4°C allows for exponential bacterial proliferation and many of the recipients are immunocompromised. Despite optimal collection techniques and passive hemovigilance, low numbers of bacteria enter the blood component at the time of phlebotomy, and many septic reactions are not attributed to the transfusion because of underlying infections; thus the true incidence of TAS may be underestimated. In a recent study, Hong and colleagues identified an incidence of 1:2572 bacterial platelet–contaminated units. Treatment for TAS requires a high index of suspicion and includes broad-spectrum antibiotics and hemodynamic support. Although not currently used universally, pathogen-reduction systems for platelets are associated with a lower rate of septic events.

Coagulopathy

RBCs are devoid of coagulation factors, fibrinogen, and platelets; therefore the massive transfusion of RBCs may lead to a dilutional coagulopathy. Dilutional coagulopathy or resuscitation-associated coagulopathy may also be induced by large volumes of crystalloid or unbalanced blood component administration during hemorrhage. This coagulopathy may be in addition to the coagulopathy of trauma where there is delayed or inadequate perfusion resulting in activation and consumption of coagulation factors, in addition to the coagulopathy secondary to hypothermia, acidosis, and prolonged shock. Trauma-associated coagulopathy has led to the development of fixed-ratio blood component therapy protocols, also known as "damage control" therapy, based on clinical observational studies in massive trauma patients where improved survival was achieved with fixed-ratio administration of blood components. In massively transfused patients, dilutional coagulopathy should be confirmed with laboratory coagulation testing or viscoelastic testing while component therapy is being administered.

Delayed Reactions

Delayed Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reactions (DHTRs) are immune-mediated transfusion reactions due to an amnestic response from alloimunization developed during a previous transfusion, pregnancy, or transplant. The recipient antibody, usually Kidd or Rh, is often unidentifiable due to low Ab titers but on reexposure mounts an Ab-mediated response to the donor antigen, usually 3 to 30 days after transfusion. The incidence of DHTRs is 1:2500 transfusions, but rises to 11% in patients with sickle cell disease. After exposure, the Ab titer

rapidly increases, and a delayed hemolysis reaction usually occurs. The extravascular hemolysis is gradual and is less severe than an acute reaction and an unexpected decrease in hemoglobin, jaundice, or a positive direct antiglobulin test may be noted. The most common clinical feature is jaundice and hemoglobinuria, followed by fever, back pain, dyspnea, chills, and hypertension. No treatment is usually required, but the blood bank should be notified to identify the antigen to avoid future reactions.

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of allogeneic transfusion, which occurs when donor-derived T lymphocytes mount an immune response against host tissue. In most transfusions the donor lymphocytes are destroyed by the recipient's competent immune system before the lymphocytes can mount an immune response against the host. In patients who are immunocompromised or where there is partial HLA matching between the donor and recipient, an immune response is not mounted and the donor lymphocytes can mount a response against the host. Clinical features include a maculopapular rash, abdominal pain, diarrhea, abnormal liver function, and pancytopenia from donor lymphocyte destruction of the host bone marrow. TA-GVHD typically develops 4 to 30 days after transfusion and is universally fatal; therefore prevention is of primary importance. In immunocompromised patients, patients receiving blood components from a family donor, or patients who have had a hematopoietic cell transplant, prevention can be achieved by gamma irradiation inactivation of transfused lymphocytes.

Posttransfusion Purpura

Posttransfusion purpura (PTP) is a rare immune-mediated delayed transfusion reaction that can occur 5 to 10 days after the transfusion of any blood component that contains platelets (RBCs, platelets). Women are predominantly effected by PTP, and it involves an antibody-mediated reaction to the human platelet antigen 1a (HPA-1a) of the donor platelet. Women who are HPA-1a negative (<2% of Caucasians) are sensitized by pregnancy, and both men and women may be sensitized by prior transfusion. Although unclear, an immune complex–mediated reaction may lead to the destruction of the transfusion recipient's platelets. Diagnosis is confirmed by the detection of platelet specific alloantibodies. Therapy involves intravenous immune globulin, although responses to steroids have been reported.

Transfusion-Transmitted Infections

Awareness of transfusion-transmitted infections (TTIs) has grown substantially since their peak with the human immunodeficiency virus (HIV) epidemic in the 1980s, and the risk of transfusion-associated infections has decreased substantially. Strategies used to mitigate the infectious risks of transfusion therapy have included donor deferral, donor screening, antibody testing, nucleic acid testing, leukoreduction, and pathogen inactivation. Despite the implementation of these safeguards, we are still faced with the inherent limitations of testing, differing window periods of infectious organisms, and organisms that are not tested for, as well as the constant threat of new emerging infections. With every new and emerging infectious threat, there is a delay between identification of the transfusion-associated organism and the development of appropriate screening and testing modalities. Despite the fact that only 3 years elapsed between recognition of the HIV threat and the implementation of donor testing, approximately 12,000 cases of transfusion-associated HIV infection occurred. There was a longer interval between recognition and testing for hepatitis C virus (HCV) between 1970 and 1990, resulting in 4.8 million transfusion-associated HCV infections. Any infectious organism with an asymptomatic blood-borne phase has the potential for transfusion-associated transmission. The organism must be able to survive in the collected transfusion component and cause infection via the intravenous route. HIV and HCV have prolonged infectious phases, but West Nile virus and dengue virus have much shorter incubation periods. In 2009 a consensus panel identified 68 emerging infectious disease threats to the US blood supply, and among these, human variant Creutzfeldt-Jakob disease, dengue viruses, and *Babesia* species were given the highest priority. Since that publication, six additional agents have been added to that list, including yellow fever viruses, arboviruses, xenotropic murine leukemia–related virus, human parvoviruses/bocaviruses, and most recently, the Middle East respiratory syndrome coronavirus, MERS-CoV. Zika virus is the latest threat to our blood supply, and there have been documented cases of transfusion transmission in Brazil. The high rate of asymptomatic infection limits the effectiveness of donor deferral, and investigational testing of blood is being implemented in high endemic areas. Although the general risk of TTIs remains low in developed countries, a zero-risk blood supply remains elusive, and TTIs remain a "fixed and inevitable property of transfusion medicine."

Transfusion-Related Immunomodulation

The immunosuppressive effects of ABT have been known for greater than 40 years, with the beneficial effect of improved renal allograft survival in transfusion recipients. The deleterious effects of transfusion-related immunomodulation (TRIM), namely, postoperative bacterial infection, cancer recurrence, and increased risk of activation of latent infections, have been debated since the 1980s. The pathogenesis of TRIM is thought to be related to the vast introduction of a multitude of antigens, particularly on the leukocyte, presented to the recipient during ABT, resulting in immune aberrations that may result in clinical deleterious effects. Although TRIM is a real biologic event, confirmed by laboratory immune aberrations of T-helper cell, natural killer cell, monocyte and macrophage function, and decreased cytokine production, the magnitude of its clinical effect is still debated. Although the observational evidence is compelling for postoperative infection associated with ABT, it is not absolute, and observational studies are prone to the effects of confounding factors, making their interpretation difficult. ABT may be a surrogate marker for other adverse prognostic factors that may have led to adverse clinical outcomes. The cardiac surgery population may be unique in that there is more consistent randomized clinical trial evidence to support increased short-term risk associated with WBC-containing ABT. Although nosocomial and hospital-acquired infections associated with transfusion therapy are not transfusion transmitted, they are transfusion associated, and have had a leading impact on clinical outcome. Despite the association of TRIM with allogeneic WBC transfusion, it would be premature at this point to implement universal leukocyte reduction for the specific reduction of TRIM effects.

Transfusional Iron Overload

There is no physiologic mechanism for the active elimination of excess iron, so total body iron is primarily regulated by iron absorption and iron loss and excess iron can be extremely toxic. A healthy individual absorbs approximately 1 to 2 mg/day, whereas 300 mL of blood contains approximately 200 mg of heme iron. Transfusional iron overload (TIO) is primarily a problem of chronic transfusion therapy seen in transfusion-dependent anemia. When the binding capacity of transferrin is exceeded and the non–transferrin-bound iron is deposited in tissues, parenchymal iron overload develops leading to end-organ dysfunction, particularly in the liver, heart,

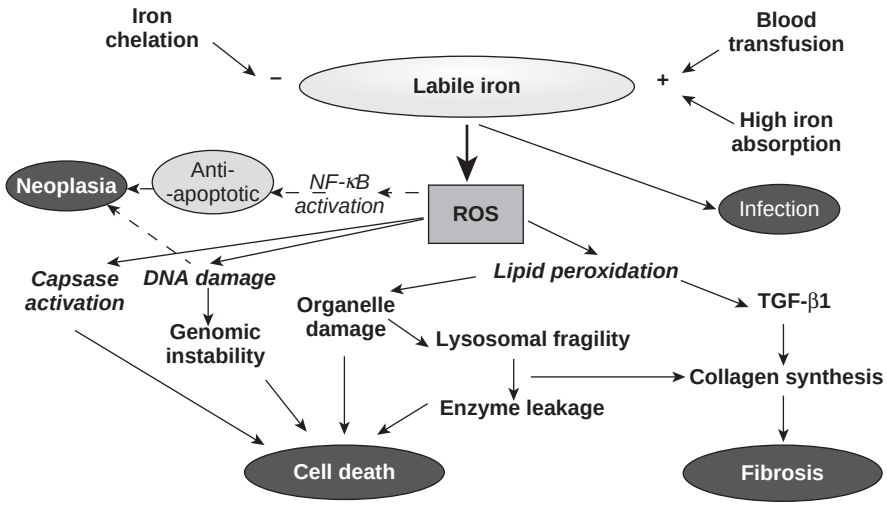

Fig. 101.1 Pathologic mechanisms and consequences of iron overload. In iron overload resulting from repeated blood transfusions or long-term increased iron absorption, iron that is not liganded to naturally occurring molecules, such as transferrin or ferritin or to therapeutic iron chelators, generates a variety of reactive oxygen species (ROS), most notably hydroxyl radicals. This occurs in cells where storage iron is accumulated (especially liver, endocrine tissues, and myocardium) thereby increasing levels of both storage and labile cellular iron. ROS increase lipid peroxidation and organelle damage, leading to cell death and fibrogenesis mediated by transforming growth factor (TGF) β1. ROS also damage DNA, risking genomic instability, mutagenesis, and cell death or neoplasia. ROS directly activates caspases thereby accelerating apoptotic death. Paradoxically, ROS may also have antiapoptotic effects by activating NF-kB *(dashed lines),* which may contribute to myelodysplastic syndrome transformation and to iron-mediated neoplasia such as hepatoma. (From Porter JB, Garbowski M: The pathophysiology of transfusional iron overload. *Hematol Oncol Clin North Am* 28[4]:683-701, 2014. Adapted from Porter JB: Pathophysiology of iron overhead. *Hematol Oncol Clin North Am* 19[Suppl 1]:7-12, 2005.)

pancreas, and other endocrine organs. The deposited free iron can participate in oxidative reactions leading to the formation of reactive oxygen species and subsequent toxicity. Additionally, TIO has been associated with insulin resistance, neoplasia, and infection (Fig. 101.1). The mainstay of treatment for TIO is iron chelation, and iron overload should be suspected with serum ferritin levels greater than 1000 ng/mL, a level that might be seen after 20 units of PRBCs in an 80-kg adult. Although the risks of TIO are usually manifested in the chronic transfusion-dependent population, the infectious risks attributable to iron-dependent support of bacterial growth may be seen after only a few units.

MANAGEMENT

Perioperative management of a transfusion reaction varies with type of reaction involved, and although the reactions that may arise in the perioperative setting are of an acute nature, it is important to be aware of the frequency and implications of both acute and delayed reactions. Mortality associated with an acute reaction is very rare, estimated at approximately 1 in 2 million, but often symptoms of a mild reaction may be an indication of a more severe reaction, and many of the signs and symptoms may be masked under general anesthesia. TRALI, TACO, AHTR, sepsis, and anaphylaxis are the acute reactions most likely to be associated with major morbidity and mortality. An algorithm for the management of various transfusion reactions is presented in Fig. 101.2.

When an acute transfusion reaction is suspected, certain immediate steps should be taken. The transfusion should be stopped immediately, and the transfusion service should be contacted. A patent intravenous line should be maintained, and supportive and symptomatic therapy should be initiated. Continuing the transfusion or abandoning the transfusion will depend on elucidating the etiology of the reaction and the association of other symptoms. Isolated fever may be a sign of an AHTR, TRALI, sepsis, a less serious FNTR, or part of the patient's underlying condition. At this point, confirmation should be made that the intended product was given to the correct patient. The patient should be reassessed for additional signs and symptoms, such as fever, respiratory distress, cardiovascular stability, angioedema, urticaria, hemoglobinuria, bronchospasm, and coagulopathy. If the patient is awake, additional signs and symptoms may include chills, back pain, chest pain, and pruritus. Depending on the constellation of signs, symptoms, and other supportive data, the clinician may be able to determine whether the reaction is life threatening and what resuscitative efforts may be warranted at that time. If the reaction is deemed life threatening, the remaining product or tubing should be saved and sent to the blood bank in addition to transfusion service–recommended laboratory tests (DAT, complete blood count, urinary assay, lactate dehydrogenase [LDH]). Additional transfusions are usually deferred until the preliminary evaluation is complete, unless additional products are required to treat the underlying disorder, such as hemorrhage.

Preliminary Evaluation of Transfusion-Related Clinical History

Fever/Chills

Most commonly, fever and chills are due to an FNHTR; however, potentially fatal reactions such as AHTR, sepsis, and TRALI must be ruled out first. If an AHTR is suspected, the correct product for the intended recipient needs to be confirmed, and laboratory tests should be ordered to rule out the presence of an immune-mediated hemolytic

All transfusions must be stopped when a patient is experiencing a reaction and assessed by a provider
Provide supportive therapy to support vital organ function (cardiac, pulmonary, renal)
For questions regarding transfusion reaction diagnosis or management, call the transfusion service, or other appropriate physician

Reaction	Symptoms	Interventions
Increase in temperature		
Possible febrile non-haemolytic reaction	Incremental increase <1°C above baseline and no other new symptoms	• Close observation, frequent vital signs • If stable and no other new symptoms, then continue with transfusion
Possible bacterial contamination Possible haemolysis	Incremental increase ≥1°C above baseline, or incremental increase <1°C with any other new symptoms (chills or rigors, hypotension, nausea or vomiting)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antipyretic drug • Consider blood cultures (patient); empirical antibiotics if neutropenic • Do not resume transfusion • Strongly consider culturing blood product if ≥2°C increase in temperature or if high clinical suspicion of sepsis • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
	For consistently febrile patient due to underlying disease or treatment, when possible: • Avoid starting transfusion if patient's temperature is increasing • Treat fever with antipyretic drug before starting transfusion • If incremental increase in temperature ≥1°C above baseline, treat as per above (stop and do not resume transfusion, cultures if indicated) • Notify blood transfusion laboratory, return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory	
Allergic symptoms		
Urticaria	Mild hives, rash, or skin itching only	• Stop transfusion, keep intravenous line open, and assess patient • Antihistamines • Notify patient clinician and blood transfusion laboratory; sample not required • If symptoms resolve, then can resume transfusion • If symptoms do not improve or worsen or recur, then discontinue transfusion; return unit (with administration set) to blood transfusion laboratory
Possible allergic reaction	Hives, rash, itching, and or any other new symptoms (throat, eye, and tongue swelling, etc.)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antihistamines • Do not resume transfusion • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
Respiratory symptoms		
Possible anaphylaxis, transfusion-associated circulatory overload, septic transfusion reaction, or transfusion-related acute lung injury	Bronchospasm, dyspnoea, tachypnoea and hypoxaemia, copious frothy pink-tinged fluid (from endotrachel tube)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and patient compatibility • Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support) • Chest radiograph for presence of bilateral interstitial infiltrate, if suggestive of transfusion-related acute lung injury • Blood cultures (patient and product), if high clinical suspicion of sepsis • Do not resume transfusion • Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quaratined
All other symptoms		
Possible anaphylaxis, haemolytic transfusion reaction, fluid overload, or transfusion-related acute lung injury	Chills, rigors, hypotension, nausea or vomiting, feeling of impending doom, back or chest pain, intravenous site pain, cough, dyspnoea, hypoxia	• Stop transfusion, keep intravenous line open, assess unit, check patient ID and unit ID and patient compatibility • Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support) • Blood cultures (patient and product) if high clinical suspicion of sepsis • Do not resume transfusion • Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quaratined

Fig. 101.2 Tranfusion reaction algorithm. (From Delaney M, Wendel S, Bercovitz RS, et al.: Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* pii:S0140-6736(15)01313-6, 2016. [Epub before print.])

reaction (DAT, repeat crossmatch, coagulation tests, LDH, unconjugated bilirubin, serum haptoglobin, serial hemoglobins). Sepsis would be accompanied by hemodynamic instability, and the blood product should be examined for discoloration and the presence of gas bubbles; the patient and donor product should be cultured if sepsis is suspected. TRALI may be accompanied by fever or chills but would require additional findings of respiratory involvement. An FNHTR is a less serious reaction, but it is a diagnosis of exclusion that is not accompanied by any systemic involvement and usually involves non–leukocyte-reduced products.

Dyspnea

Respiratory distress may be a result of TRALI, anaphylaxis, or TACO. Anaphylaxis may be accompanied by bronchospasm, urticaria, and angioedema, and the rapidity of onset is a salient feature. TRALI and TACO may be difficult to differentiate, especially because both may occur simultaneously. Distinguishing features may include larger infusion volumes, prior cardiac history, and supportive tests that confirm cardiogenic pulmonary edema in patients with TACO. TRALI may be associated with transient leukopenia and is often accompanied by fever.

Urticaria

Isolated episodes of urticaria are usually benign as long as they are not associated with symptoms suggestive of anaphylaxis. They usually occur within 4 hours of a transfusion and are most frequently associated with platelet transfusions. The transfusion should be paused, antihistamines may be administered, and the transfusion may be resumed if no other symptoms develop. No laboratory testing is required.

Hypotension

Hypotension in the perioperative setting may be due to hypovolemia, but a transfusion reaction should be suspected if the hypotension is not related to surgical hemorrhage and is temporally related to a transfusion. Hypotension may be secondary to anaphylaxis, AHTR, TRALI, and sepsis. Anaphylaxis is usually accompanied by the acute onset of angioedema, rash, and bronchospasm, in addition to hypotension. The predominant feature of TRALI is respiratory distress, whereas sepsis may be accompanied by other findings of shock, in addition to fever and laboratory evidence of an infectious etiology. AHTR usually involves findings of hemolysis, fever, and coagulopathy, in addition to hemodynamic instability. Another uncommon cause of hypotension is through activation of the intrinsic contact activation pathway of the coagulation cascade with bradykinin (or its metabolites)–mediated hypotension. This uncommon manifestation is more likely to occur in hypertensive patients treated with angiotensin-converting enzyme inhibitors, which decrease the metabolism of bradykinin, and receiving blood products through a negatively charged leukocyte reduction filter. The hypotension is usually transient, but supportive therapy may be needed, and other causes of hypotension should be ruled out. Many of these filters have been removed from the market, but this uncommon cause of hypotension should be considered in the differential diagnosis.

PREVENTION

Allogeneic transfusion is an essential part of perioperative patient care and can be lifesaving in certain populations, but is associated with substantial risks, known and unknown, and costs to society. A thorough understanding of transfusion risks, their management, and prevention is an obligate component of optimal patient care. Despite successful risk-mitigating strategies, a zero-risk blood supply is unattainable, and with ongoing globalization the risk of new emerging threats, especially infectious, will continue to threaten our blood supply. All of this will come at an increased cost to society, which will continue to widen the gap between developed and developing countries. Although transfusion can be lifesaving, it should be never be considered inherently safe, and evidence of its benefit should outweigh its risks. It is not always obvious, but minimizing allogeneic exposure is an effective way to minimize the risks associated with transfusion therapy. Numerous observational studies have documented large variations in transfusion practices among similar clinical settings, indicating that there are many unindicated transfusions. The American Association of Blood Banks has recommended as the first statement in its *Choosing Wisely* campaign, "Don't transfuse more units of blood than absolutely necessary." Patient blood management strategies rely on evidence-based use of blood components and include optimizing erythropoiesis, minimizing blood loss, and managing anemia, along with laboratory-guided transfusion algorithms that have been shown to reduce allogeneic exposure, decrease transfusion risks, and improve clinical outcomes. Minimizing the risks of transfusion reactions requires a multifaceted approach that addresses the safety of the blood supply from the point of donor selection through the storage period and minimizes risks through donor selection and deferral, screening, pathogen reduction, and inactivation. During the peritransfusion period it is incumbent on the health care team to be acutely vigilant of any untoward reaction, identify it, and manage the complication with the involvement of the transfusion service or blood bank. Delayed reactions whether immune mediated or infectious require recognition that the reaction may have been transfusion mediated and may require look-back schemes to identify and track the donor unit.

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Epidural Anesthesia: Unintended Intrathecal Injection

102

Thomas McCutchen • J.C. Gerancher

Case Synopsis

A frail, 55-kg, 79-year-old woman is admitted for elective hip replacement as the first surgery of the day in a specialty orthopedic surgery center. An epidural catheter is placed for surgical anesthesia and postoperative analgesia. With the patient sitting on the operating room table, catheter placement is uneventful. Fifteen milliliters of local anesthetic (2% lidocaine with 5 μg/mL of epinephrine) is administered via the catheter in three 5-mL doses over 3 minutes. Pain in the arthritic hip is immediately relieved, and the patient's lower extremities become insensate. Five minutes later, she complains of weakness and experiences difficulty breathing. She then becomes apneic and unconscious, with subsequent oxygen desaturation and hypotension. She is ventilated with a mask and then intubated. Blood pressure is maintained with ephedrine and intravenous fluid.

PROBLEM ANALYSIS

Definition

When local anesthetic in volumes typically used for epidural analgesia or anesthesia is unintentionally administered into the subarachnoid (intrathecal) space, morbidity and mortality may result due to high spinal anesthesia. Such injection may occur if local anesthetic is delivered through a needle or catheter that has fully or partially penetrated the dura and arachnoid membranes.

Recognition

The clinical consequences of unintended intrathecal injection depend on the amount of local anesthetic introduced into the cerebrospinal fluid (CSF). Small amounts result in numbness of the lower extremities; larger amounts result in extensive spread and possibly unconsciousness and respiratory arrest secondary to brainstem anesthesia.

Risk Assessment: Anatomic Considerations

The epidural space lies outside the dura mater. This tough outer layer of the meninges fuses with periosteum at the foramen magnum. The epidural space extends laterally to the spinal nerve roots, where it fuses with epineurium in the intervertebral foramina, caudad to the sacrococcygeal ligament and anterior to the posterior longitudinal ligament, ligamentum flavum, and laminae. It communicates with the paravertebral space via intervertebral foramina. The contents of the epidural space consist of fat, which is found predominantly posteriorly and laterally. Valveless veins are found predominantly in the lateral and anterior epidural space.

The arachnoid membrane is a delicate membrane that abuts the inner surface of the dura mater. It consists of layers of flattened cells with connective tissue fibers running between these layers. The cells are interconnected by tight junctions, which likely accounts for the fact that the arachnoid is the principal physiologic barrier for drugs diffusing from the epidural space to the intrathecal space. In the region of the foramina, where spinal nerve roots traverse both the arachnoid and the dura mater, the arachnoid membrane herniates through the dura to form granulations. Both spinal and intracranial arachnoid granulations serve as portals for CSF and its constituents to exit the central nervous system.

The pia mater is an even more delicate layer of the meninges that is adherent to the spinal cord. The intrathecal space lies between the arachnoid membrane and the pia mater and contains CSF. Spinal CSF directly communicates with intracranial CSF.

Implications

The epidural space is a potential space, as the majority of the dura is in contact with the walls of the vertebral canal. It is also a discontinuous series of compartments that become continuous only when liquid or air is injected. Thus a larger dose of local anesthetic is required for epidural anesthesia or analgesia compared with spinal anesthesia. This anatomy also explains the bandlike block that develops in dermatomes just above and below the level of epidural local anesthetic injection, with further spread directly related to the volume of local anesthetic injected. In contrast, when local anesthetic is introduced into and diffuses throughout CSF within the intrathecal space to produce spinal anesthesia, it can produce block well above and below the level of injection. In addition to the volume of drug delivered and its concentration, spread of an intrathecally administered local anesthetic is related to the patient's position in combination with the baricity of its solution. If the solution is isobaric, spread of the block is more dependent on the volume and concentration of the local anesthetic injected intrathecally, whereas spread of hypobaric and hyperbaric solutions is more dependent on patient position.

The C3–C5 spinal nerve roots, which contribute to the phrenic nerves, may be anesthetized when large volumes of local anesthetic intended for the epidural space are delivered spinally. Thus bilateral phrenic nerve paralysis leading to respiratory paralysis with awareness may result. Additionally, because the intracranial and vertebral spinal fluid spaces are continuous, local anesthetics can reach and anesthetize the brainstem.

MANAGEMENT

Early recognition of unintentional spinal injection is paramount to prevent further injections and limit the potential for morbidity. If the patient is in pain as the epidural is being dosed (e.g., an obstetric patient in active labor), the first sign of an unintended intrathecal injection may be almost immediate cessation of all pain after injection of a small test dose. This may be followed by motor and sensory block that develops more rapidly and extensively than would be expected after epidural injection.

Treatment for unintended spinal injection is supportive and consists of ensuring a patent airway, oxygenating and ventilating the patient, and supporting blood pressure with fluids (volume) and vasopressors (if needed) until the high block resolves. In any setting where neuraxial anesthesia is used, basic airway equipment must be readily available along with a well-thought-out plan for managing unconscious and apneic patients with possible complete cardiovascular collapse.

PREVENTION

Prevention requires a high index of suspicion during epidural needle and catheter placement, with careful aspiration and appropriate test dosing of the needle and catheter before the administration of the planned epidural volume of local anesthetic. With obvious free flow of CSF via the epidural needle or catheter during attempts to locate the epidural space, epidural doses and volumes of local anesthetic should not be administered. Often, unintended intrathecal needle or catheter placement is not obvious. For example, a dural tear may be made by the tip of the needle intended for epidural placement. There may be no CSF return from the needle if its tip resides mostly in the epidural space, but the epidural catheter may enter the spinal space via the tear. In this case slow, deliberate aspiration of the catheter before injection might identify CSF.

If saline is used for the loss-of-resistance technique or an epidural catheter is being replaced after recent dosing of a previously placed epidural catheter, it may be difficult to determine whether the clear fluid aspirated is previously injected saline or local anesthetic in the epidural space or CSF. Several maneuvers have been suggested to distinguish CSF from other fluids, including measurement of pH, temperature, or glucose. Unfortunately, none of these methods has broad clinical utility. If bubbles are aspirated along with the clear fluid and the total amount of clear fluid that can be aspirated is less than 3 to 5 mL, the catheter is *not* likely to be in the intrathecal space. However, one orifice of a multiple-orifice catheter may be intrathecal, and the catheter could either be replaced or not dosed as if epidurally placed until it has been adequately tested.

Epidural test doses consist of a small amount of local anesthetic. The rationale is that such small amounts injected into the intrathecal space would produce an easily recognizable motor and sensory spinal block without producing unacceptably high spinal anesthesia; if the same test dose were injected epidurally, it should produce minimal or no obvious effects. A typical test dose might be 40 to 60 mg of lidocaine, which would quickly produce signs and symptoms of relatively low-level spinal block if injected intrathecally. One must also keep in mind that if combined spinal-epidural anesthesia is performed and the patient has received sufficient spinal local anesthetic for surgical anesthesia, any test dose intended to rule out spinal catheter placement might result in a high level of spinal anesthesia.

In every instance, repeat dosing of an in situ epidural catheter should be incremental. Case reports have noted catheter migration into the intrathecal space. Providing an appropriate time interval between incremental dosing to assess for intrathecal injection should allow for the detection of migrated catheters. Intrathecal catheters left in place intentionally should be clearly labeled as such, to prevent accidental dosing of the subarachnoid space, with epidural volumes of local anesthetic intended for the epidural space.

Local anesthetics are not the only substances used during epidural injection. As a commonsense rule, most clinicians aim to avoid epidural medications thought to be harmful if injected spinally. In fact, several medications that are not marketed for intrathecal injection have a record of clinical safety when used routinely for both spinal and epidural injection. These include fentanyl, epinephrine, and the non–dextrose-containing local anesthetic solutions labeled "not for spinal use." Controversy continues over two potential exceptions to this rule: the local anesthetic chloroprocaine and preparations containing the preservative sodium metabisulphite. Although outside the scope of this chapter, both of these substances have been associated with neurotoxicity after unintended spinal injection of large volumes intended for the epidural space.

Blood is also routinely injected into the epidural space during epidural blood patch. Although the consequences of subarachnoid injection of blood are not known, unintended subarachnoid injection has been given consideration as a complication limited to a few case reports. Signs and symptoms after the injection of subarachnoid blood have been attributed to presumed irritation or even arachnoiditis and meningitis. Symptoms range from none to permanent pain and neurologic deficit. Distribution and severity of symptoms most likely correlate with the amount and spread of blood unintentionally injected into the subarachnoid space. Case reports in the literature suggest that most patients experience gradual onset of back, leg, and buttock pain that gradually improves without intervention other than analgesics. When performing an epidural blood patch, great care is taken to verify that the tip of the needle is in the epidural rather than the subarachnoid space before the injection of autologous blood. This might include gentle aspiration before injection and observation for CSF dripping from the hub of the epidural needle while keeping in mind that the incidence of CSF in the epidural space after spinal puncture remains unknown. The use of air rather than saline for loss of resistance should eliminate one potential source of clear fluid. The injection of a subarachnoid test dose of local anesthetic before the injection of autologous blood has been advocated in some situations. Should unintended subarachnoid injection of blood be suspected, management is expectant. Magnetic resonance imaging may rule out the presence of a significant subarachnoid hematoma. A discussion with the patient about what to expect regarding signs and symptoms should ensue, analgesics should be used to treat pain, and the patient's neurologic status should be monitored.

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103 Local Anesthetic Systemic Toxicity

Craig E. Cummings

Case Synopsis

A 76-year-old man (184 cm, 58 kg, American Society of Anesthesiologists [ASA] status 3) was scheduled for a total shoulder arthroplasty. His medical history was significant for coronary artery disease with remote bare metal stent placement and atrial fibrillation. A continuous interscalene block was planned for postoperative analgesia. The patient was sedated with intravenous midazolam and fentanyl before the insertion of a perineural interscalene catheter placed under ultrasound guidance. After negative aspiration of the catheter, bupivacaine 0.5% with epinephrine 5 μg/mL (20 mL) was injected incrementally through the catheter over approximately 1 minute. At completion of the injection, the patient was noted to have muscle twitching and electrocardiogram changes consistent with ventricular tachycardia.

PROBLEM ANALYSIS

Definition

Local anesthetics inhibit the ability to generate and propagate electrical impulses in excitable tissues via binding of voltage-gated sodium channels. Interaction of local anesthetics with a specific region of the alpha subunit on the inner pore of these channels acts to prevent conformational changes of channel activation and results in physical occlusion of the channel. This impedes the sodium influx normally associated with membrane depolarization. Local anesthetics differ from medications given via parenteral or enteral administration, as they are deposited in close proximity to their intended site of action and removed via systemic absorption into the circulation. Local anesthetics may be injected directly into perineural tissues or joint spaces, infiltrated into subcutaneous tissues, or applied topically to the skin and mucosal surfaces to provide anesthesia and analgesia. They are administered intravenously to produce regional anesthesia, to attenuate the rise in intracranial pressure that may be seen with intubation, and to treat cardiac dysrhythmias.

The toxic effects of local anesthetics have been described since cocaine was introduced into clinical practice in 1884, and the search for compounds with an improved safety profile has had a significant impact on the evolution of this class of drugs. Adverse reactions to local anesthetics can be localized or systemic. Local anesthetic–induced myotoxicity and neurotoxicity will not be discussed. Local anesthetic systemic toxicity (LAST) results from excessive plasma concentrations of local anesthetics and predominantly involves the central nervous system (CNS) and the cardiovascular system (CVS). The potential for toxicity parallels the intrinsic anesthetic potency of the local anesthetic, with more potent, more lipid-soluble compounds posing the greatest risk. Decreased protein binding and reduced drug clearance also increase the potential for toxicity. The clinical presentation of LAST is highly variable and ranges on a spectrum from mild symptoms caused by the systemic absorption of local anesthetic from the site of administration to catastrophic cardiovascular collapse (CC) after inadvertent intravascular injection. Less common systemic toxicities include allergic reactions and methemoglobinemia.

Recognition

Central Nervous System Toxicity

The CNS is more susceptible to the toxic effects of local anesthetics than the CVS. Local anesthetics readily cross the blood-brain barrier and produce a stereotypical pattern of symptoms in a dose-dependent manner (Fig. 103.1). As plasma concentrations of local anesthetics rise, primary symptoms of circumoral numbness, tinnitus, lightheadedness, and visual disturbances progress to altered mental status, tremors, and tonic-clonic seizures. This initial CNS excitation is thought to be related to early blockade of inhibitory neurons in the cerebral cortex, allowing for unopposed activity of facilitative neurons. With further increases in plasma and CNS concentrations of local anesthetics, neuronal activity is inhibited in an unbiased manner. This leads to global CNS depression presenting as unconsciousness and respiratory arrest.

Although the systemic toxic effects of local anesthetics are dose dependent, the rate of change in plasma levels is also an important factor. Toxicity secondary to slow intravenous injection or systemic absorption of local anesthetics is more likely to present with premonitory CNS symptoms and progress slowly in the conventional manner. Toxicity secondary to inadvertent intravascular injection of a large amount of local anesthetic would be expected to progress rapidly, and may present initially with generalized tonic-clonic seizures or CVS toxicity in the absence of premonitory symptoms.

External factors also have a significant impact on the potential for CNS toxicity. Acidosis exacerbates toxicity through a decrease in protein binding, increasing the fraction of free drug available to cross cell membranes. Increased arterial carbon dioxide tension ($Paco_2$) will increase cerebral blood flow via cerebral vasodilation, enhancing delivery of local anesthetic to the brain. The addition of epinephrine to local anesthetic solutions may augment CNS toxicity via increased cerebral perfusion and by increasing the fraction of pharmacologically active local anesthetic. Administration of benzodiazepines does raise the seizure threshold, but oversedation can lead to hypoventilation,

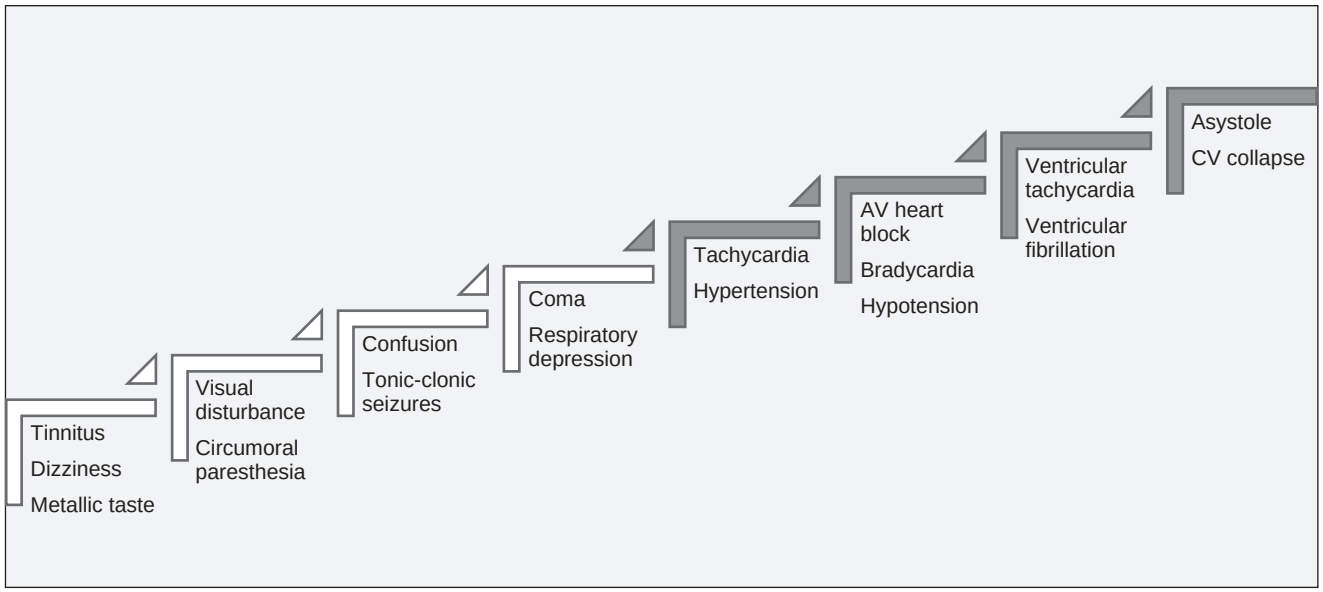

Fig. 103.1 **The classic progression of clinical signs and symptoms of local anesthetic systemic toxicity (LAST) related to slow intravascular injection or gradual systemic absorption of local anesthetic from the site of administration.**

hypercarbia, and hypoxia. Altered mental status produced by sedatives can also attenuate predictive signs of toxicity.

Cardiovascular System Toxicity

A combination of direct cardiac effects and neural mechanisms contributes to the cardiovascular toxicity induced by local anesthetics. Local anesthetics directly interfere with the normal electrophysiology and contractility of the heart via blockade of cardiac sodium channels, calcium channels, and mitochondrial metabolism. Initial signs and symptoms of cardiac toxicity include tachycardia and hypertension, often coinciding with the preliminary excitation of CNS toxicity. Escalating plasma concentrations of local anesthetics lead to the following:

- Atrioventricular heart block
- Bradycardia
- Left ventricular depression
- Lethal arrhythmias such as ventricular tachycardia and ventricular fibrillation

Direct cardiac depressive effects are compounded by vasodilatory effects in the periphery where high levels of local anesthetics produce smooth muscle relaxation. Increased plasma concentrations of local anesthetics can also contribute to hypotension through inhibition of autonomic vasoconstriction and other CNS-mediated vasoregulatory mechanisms.

The plasma concentration of bupivacaine required to evoke CC is merely three times higher than the concentration needed to induce a seizure (CC/CNS ratio), resulting in a narrow margin of safety and a rapid progression from CNS to CVS toxicity when plasma concentrations of bupivacaine reach toxic levels. This ratio is not equivalent among commonly used local anesthetics, and increased ratios seen with less potent local anesthetics such as lidocaine and mepivacaine offer a greater margin of safety. Compared with lidocaine, bupivacaine exhibits a more robust binding affinity for resting and inactivated cardiac sodium channels and remains tightly bound to these channels during diastole. Slow dissociation of bupivacaine from the sodium channels reduces ventricular conduction velocity and prolongs the refractory period, augmenting its cardiotoxicity through encouragement of reentrant ventricular arrhythmias. Cardiac dysrhythmia or circulatory collapse is the usual presenting sign of LAST during general anesthesia or in patients heavily sedated with benzodiazepines or other drugs that raise the seizure threshold. Additionally, the propensity for bupivacaine to induce malignant ventricular arrhythmias leads to CC without premonitory symptoms as the primary sign of toxicity in patients who have received a large intravascular dose of bupivacaine.

Allergic Reactions

True immunologically mediated reactions to preservative-free amide local anesthetics are exceedingly rare. Adverse reactions to local anesthetics are often related to unintentional intravascular injection or systemic absorption of local anesthetics leading to mild symptoms of toxicity. Systemic effects from additives such as epinephrine are also commonly reported as a hypersensitivity to the local anesthetic. True allergic reactions caused by immunoglobulin G (IgG) or IgE antibodies are primarily induced by ester local anesthetics, predominantly related to the metabolite para-aminobenzoic acid (PABA), a known allergen commonly found in cosmetic products. Commercial multidose preparations of amide local anesthetics frequently contain the preservative methylparaben, whose chemical structure shares similarities with PABA and can also trigger an immunologically mediated reaction.

Methemoglobinemia

Methemoglobinemia occurs when the ferrous form (Fe^{2+}) of hemoglobin is oxidized to the ferric form (Fe^{3+}), which is unable to bind or transport oxygen. Benzocaine and a metabolite of prilocaine, *o*-toluidine, can act as oxidizing compounds leading to the formation of methemoglobin. Prilocaine is available clinically as a eutectic mixture of prilocaine 2.5% and lidocaine 2.5% (EMLA cream). It is frequently used as a topical anesthetic in pediatric patients who may be at an increased risk of methemoglobinemia compared with adults due to immature reductase enzyme pathways. Benzocaine is also used clinically as a topical anesthetic on mucosal

BOX 103.1 Individual Patient Characteristics and Comorbidities That Increase the Likelihood of Developing Local Anesthetic Systemic Toxicity

Extremes of age (<4 months or >70 years)
Cardiac conduction defects
Ischemic heart disease
Liver disease
Mitochondrial disease
Acidosis

membranes before bronchoscopy, endoscopy, and transesophageal echocardiogram. Methemoglobinemia is characterized by central cyanosis refractory to oxygen therapy and typically occurs when levels of methemoglobin reach greater than 15%. Symptoms range in severity from anxiety, dyspnea, headaches, and nausea to altered mental status and hemodynamic instability. The severity of symptoms is proportional to the level of methemoglobin present in the blood. Methemoglobin levels greater than 50% to 70% are severe and often fatal. Diagnosis requires clinical vigilance and is suggested by the presence of chocolate-colored blood, as well as a discrepancy between oxygen saturation as analyzed by pulse oximetry and arterial blood gas. Diagnosis is confirmed by qualitative measurement of methemoglobin by cooximetry. Treatment of symptomatic methemoglobinemia is with intravenous methylene blue (1 to 2 mg/kg).

Risk Assessment

A number of variables influence the likelihood of developing LAST, including individual patient characteristics (Box 103.1) and regional anesthetic technique. Patients with severe liver disease are particularly vulnerable to LAST with amide local anesthetics secondary to decreased protein synthesis in conjunction with a reduced capacity for hepatic degradation. Preexisting ischemic heart disease or cardiac conduction abnormalities may sensitize patients to the cardiotoxic effects of local anesthetics. Acid-base status plays an important role in the development of LAST because increased Paco2 or decreased pH from metabolic derangement can lower the seizure threshold while simultaneously enhancing cerebral blood flow. The net effect of an acidotic state is an increase in the delivery of additional local anesthetic to the CNS.

Local anesthetics are absorbed into the systemic circulation by uptake and distribution from the site of administration. In the absence of inadvertent intravascular injection, plasma levels of local anesthetics are dependent on the following:

- Tissue blood flow at the site of injection
- Total dose of local anesthetic administered
- Physiochemical properties of the individual local anesthetic
- Associated use of vasoconstrictors

It is well established that systemic absorption of local anesthetics correlates positively with tissue perfusion at the site of injection. Peak plasma concentrations of local anesthetics are highest after intercostal nerve blockade, followed in order of decreasing concentration by injection into the caudal epidural space, brachial plexus, sciatic groove, and subcutaneous tissue. An increase in the total dose (volume × concentration) of local anesthetic administered leads to enhanced systemic absorption and elevated peak plasma concentrations, whereas the addition of epinephrine causes a reduction in peak plasma levels during epidural anesthesia and peripheral nerve blockade. The beneficial effects of vasoconstriction are most pronounced when epinephrine is added to local anesthetics that possess intrinsic vasodilatory properties such as lidocaine.

MANAGEMENT

LAST can occur despite our best efforts, and the severity of toxicity is dependent on the timeliness of detection and the adequacy of treatment. Clinical presentation of LAST is inconsistent with regard to the timing of onset, initial manifestations, and duration. Diagnosis requires an appreciation of this variability in addition to clinical vigilance. Manifestation of uncharacteristic signs and symptoms in patients who have received potentially toxic doses of local anesthetics should raise suspicion for LAST. Prompt recognition and treatment may halt the progression of toxicity to CC and facilitate resuscitation.

Cardiopulmonary resuscitation after bupivacaine-induced malignant arrhythmia is particularly challenging, and often refractory to standard advanced cardiac life support pharmacotherapies and techniques. However, resuscitative strategies involving the use of intravenous lipid emulsion have shown reproducible success when used in combination with high-quality basic life support as demonstrated by both animal studies and human case reports. In suspected cases of LAST, emphasis should be placed on the primacy of airway management. Hypoxia and acidosis exacerbate LAST and may reduce the efficacy of lipid emulsion therapy, thus optimal oxygenation and ventilation must be ensured. Seizure activity should be abolished rapidly with benzodiazepines. Propofol or barbiturates should only be used in the absence of benzodiazepines and administered with caution in the setting of hemodynamic instability. Small doses of succinylcholine can be administered to eradicate muscular activity and prevent metabolic acidosis that can occur with prolonged tonic-clonic seizures.

Standard advanced cardiac life support should be performed for cardiac arrest with the following modifications to pharmacologic management in the setting of LAST:

- Epinephrine has been shown in animal models to lead to pulmonary edema and delayed hemodynamic compromise when used in high doses, thus standard resuscitation doses of epinephrine should be reduced, used only in small repeated doses of less than 1 μg/kg as needed for hemodynamic support.
- Raising peripheral vascular resistance with potent vasoconstrictors such as vasopressin in the setting of toxic cardiomyopathy can hinder resuscitation by further impairing cardiac output and should be avoided.
- Amiodarone is the antiarrhythmic agent of choice for ventricular arrhythmias, as treatment with lidocaine and procainamide can further potentiate LAST.
- Beta-blockers, calcium channel blockers, and other agents that decrease contractility should be avoided.
- Intravenous lipid emulsion therapy should be considered for signs of severe LAST.

Controversy remains with regard to the ideal timing of lipid emulsion administration in the setting of LAST, but the recommended initial therapy using 20% lipid emulsion should include the following:

- A bolus of 1.5 mL/kg followed by a 0.25 mL/kg per minute infusion, continued for at least 10 minutes after circulatory stability is achieved.
- The initial bolus may be repeated, and the infusion rate doubled to 0.5 mL/kg per minute for persistent CC.
- Maximum dose is approximately 10 to 12 mL/kg over the first 30 minutes.

Propofol should not be used as a substitute for lipid emulsion therapy secondary to its low lipid content (10%) and direct cardiac depressant effects. Cardiopulmonary bypass should be considered for cases of severe LAST that fail to respond to treatment with lipid emulsion infusion and vasopressor therapy.

BOX 103.2 Modifications to the Clinical Practice of Regional Anesthesia for the Prevention of Local Anesthetic Systemic Toxicity

Preprocedural checklist
American Society of Anesthesiologists standard monitors
Minimal or absent procedural sedation
Intravascular marker or "test dose"
Frequent aspiration of needle or catheter
Incremental injection of small aliquots of local anesthetic
Use of minimum effective local anesthetic dose
Ultrasound guidance

Severe coronary artery disease may impair the efficacy of intravenous lipid emulsion, as delivery to the coronary vascular bed is necessary for the rapid removal of local anesthetics from cardiac tissue. Partitioning of local anesthetic into a lipid compartment or "lipid sink" in the blood allows for partial recovery of cardiovascular parameters. Lipid emulsion also produces a cardiotonic effect through an increase in intravascular volume and direct inotropic effects, facilitated by lipid metabolism and mitochondrial processing. Increased cardiac output accelerates movement of local anesthetic to the liver for metabolism. A transient elevation in local anesthetic concentration within skeletal muscle is also observed. Deposits of local anesthetic can redistribute back into the circulation over time, thus it is recommended that any patient experiencing substantial LAST be observed for at least 12 hours after the event.

Despite an ever-growing number of case reports describing the effectiveness of lipid emulsion therapy, its antidotal use in the treatment of LAST and other lipophilic drug overdose may not be without unintended consequences. A temporal association between the administration of intravenous lipid emulsion and the occurrence of pancreatitis, acute respiratory distress syndrome, and lipemia-induced laboratory interference has been described, but no causative relationship has been established to date. The optimal formulation of intravenous lipid emulsion for the reversal of LAST has yet to be determined, though formulations of both standard long-chain triglyceride emulsions and mixed long- and medium-chain triglyceride emulsions have been administered with successful resuscitative outcomes.

PREVENTION

Although it is rare for serious adverse events to result from the administration of local anesthetics, severe LAST does have the potential to cause significant morbidity and mortality. In the most recent ASA closed claims analysis of complications associated with peripheral nerve blocks occurring in 1990 or later, the associated mechanism of injury in 5% of the total claims involved inadvertent intravascular injection or absorption of local anesthetic. Furthermore, nearly one-quarter of the claims associated with death or brain damage involved LAST.

Although there is no single intervention that can reliably eliminate the risk of LAST, an emphasis should be placed on the importance of prevention in decreasing the incidence and severity of toxicity. The use of a preprocedural checklist may help ensure that important patient characteristics are not overlooked before the administration of local anesthetics, and confirm that resuscitative equipment and medications are immediately available. Patients should be monitored with ASA standard monitors both during and after the administration of local anesthetics as delayed episodes of LAST have been reported. The use of minimal or no sedation should be considered during the performance of regional anesthesia. Sedatives such as benzodiazepines increase the seizure threshold, but diminish the patient's ability to communicate subjective symptoms of CNS toxicity.

Best clinical practice should include techniques that minimize the potential for unintended intravascular injection and limit the systemic absorption of excessive doses of local anesthetic from the site of administration (Box 103.2). Maximum recommended doses of local anesthetics based on extrapolation from animal models, clinical experience, and case reports of toxicity should be applied with caution. Clinicians should instead focus on utilization of the minimum effective dose necessary to achieve the desired outcome. Dosing regimens should be further adjusted for conditions or disease states that may predispose patients to the development of LAST (see Box 103.1). Substitution of a less potent levoenantiomer such as ropivacaine may also reduce the potential for cardiac toxicity. Injection of local anesthetics should occur in small, fractionated aliquots with the time between each injection encompassing one circulation time. Aspiration of the needle or catheter should occur before each injection, and frequently throughout the injection, to assess for intravascular placement. In the absence of contraindications, the use of an intravascular marker such as epinephrine is recommended when administering potentially toxic doses of local anesthetics. Epinephrine added to local anesthetic solutions at a concentration of 1:200,000 (5 μg/mL) can aid in the identification of intravascular injection and decrease systemic absorption into the circulation through local vasoconstriction. Providers using this technique should be familiar with the various criteria for a positive epinephrine test dose and understand its limitations during different clinical scenarios.

The use of ultrasound guidance has been shown to have a significant impact on the incidence of LAST. A large multicenter trial published in 2013 with a study population of 20,021 patients who received 25,336 peripheral nerve blocks confirmed that LAST is a rare event with a reported overall incidence of 0.87 per 1000 peripheral nerve blocks. The study also demonstrated that the use of ultrasound guidance is associated with a reduced risk of LAST (odds ratio 0.19 to 0.28), and concluded that the use of ultrasound guidance may improve patient safety because it is associated with a reduced risk of LAST after peripheral nerve blockade. Ultrasound guidance has previously been shown to reduce the risk of inadvertent vascular puncture and reduce the dose of local anesthetic used for peripheral nerve blockade, both of which should theoretically decrease the risk of LAST.

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Respiratory Depression After Spinal Anesthesia

104

Perumal Tamilselvan • Joanna David

Case Synopses

Case 1
A 75-year-old man underwent total knee replacement under spinal anesthesia with local anesthetic and 300 μg of diamorphine or 100 μg of morphine. Late that evening he appears extremely sleepy and has oxygen saturation of 94% on nasal oxygen.

Case 2
A 60-year-old woman underwent a total vaginal hysterectomy under spinal anesthesia with local anesthetic and 300 μg of diamorphine. In the recovery room the patient complains of severe itching and nausea with vomiting. Her oxygen saturation is 98% on room air.

PROBLEM ANALYSIS

Definition

Epidural and intrathecal administration of opioids has been in practice for decades. Neuraxial opioids produce profound segmental antinociception in doses much smaller than would be required if administered systematically. The addition of fentanyl to spinal anesthesia prolongs the duration of sensory blockade without increasing the time to discharge, making it a popular choice in the ambulatory setting. Intrathecal opioids for labor analgesia have made it possible to lower the amount of local anesthetic used so that the mother can ambulate while the epidural is running (walking epidural).

Recognition

Side effects of intrathecal and epidural opioids are listed in Box 104.1. The most common are as follows:

- Respiratory depression
- Sedation
- Pruritus
- Nausea and vomiting

In general the side effects associated with neuraxial opioids are similar to those seen with intravenous, intramuscular, or oral opioid use. However, the severity, incidence, and timing differ owing to the interaction of opioids with their receptors in the spinal cord and the brain. The most serious complication is respiratory depression, which can be early or delayed.

Risk Assessment

Respiratory Depression

The degree and rate of the opioid's rostral spread in the cerebrospinal fluid (CSF) determine the side-effect profile for respiratory depression. The natural circulation of CSF brings residual drug into direct contact with the brain's respiratory center, which lies on the floor of the fourth ventricle. Typically, lumbar CSF reaches the brain in about 4 to 6 hours. Thus factors that determine the amount of the drug reaching the rostral CSF include where the drug was placed (intrathecally vs. epidurally; thoracic vs. lumbar area), its dose, and its lipid solubility. When a highly lipophilic drug such as fentanyl or sufentanil is placed intrathecally, it rapidly penetrates the spinal cord tissues to directly act on the dorsal horn neurons. Low residual concentrations of the drug remain in the CSF; therefore such drugs have a more segmental analgesic effect. In contrast, morphine is not highly lipophilic and has a slower uptake into the spinal cord and efflux from the CSF (via arachnoid granulations). Therefore higher concentrations of the drug remain in the CSF for longer periods. As a result, morphine is much more likely to reach the brain's respiratory center and cause delayed respiratory depression than fentanyl or sufentanil.

If an opioid is placed epidurally, it can have spinal or supraspinal (systemic) effects, imparting a biphasic nature to respiratory depression. This may manifest early (<2 hours) due to vascular uptake and redistribution, similar to what occurs after intramuscular dosing, or late (6 to 12 hours) due to rostral migration of the drug in the CSF. The ratio of spinal to supraspinal effects depends on how much of the drug is absorbed into the epidural venous plexus, how much is deposited in epidural fat, and how much penetrates the meninges and passes into the CSF. The drug's lipid solubility and molecular weight and shape in large part determine dural penetration and the amount that remains in the CSF long enough to spread rostrally. This explains why hydrophilic morphine or hydromorphone has more dural penetration (and therefore spinal activity) than highly lipophilic drugs such as fentanyl or sufentanil. For the same reason, there is a much greater risk of respiratory depression when morphine or hydromorphone is placed in the high thoracic or cervical epidural space.

Patients considered to be at increased risk for respiratory depression include the elderly and debilitated, those with significant pulmonary disease (including sleep apnea), and those receiving concomitant opioids or central nervous system depressants. Patients receiving chronic opioid therapy are drug tolerant and thus are much less likely to experience centrally mediated, neuraxial opioid respiratory depression. Postpartum patients also demonstrate less respiratory depression, possibly because of their younger age and increased ventilatory drive due to pregnancy. Finally, the overall reported incidence of significant respiratory depression (i.e., that requiring treatment) from neuraxial opioids is 0.2% to 2%, which is not much different from that associated with more conventional use (about 1%). Box 104.2 lists risk factors for respiratory depression.

BOX 104.1 Complications of Neuraxial Anesthesia

Respiratory depression
Sedation
Pruritus
Nausea and vomiting
Urinary retention
Gastrointestinal dysfunction
Anaphylaxis
Hyperalgesia
Behavioral problems
Dizziness or hypotension
Thermoregulatory dysfunction

BOX 104.2 Factors That Increase the Risk of Respiratory Depression

Opioid Characteristics
Larger doses
Intrathecal administration
Hydrophilic morphine or hydromorphone
Repeated boluses versus continuous infusion

Patient Characteristics
Elderly
Debilitated
Significant pulmonary disease
Sleep apnea
Opioid naive
Concomitant opioids or central nervous system depressants

Sedation

Sedation correlates with respiratory depression for two reasons. First, the opioid may have a direct effect on the thalamus, limbic system, or cerebral cortex from rostral spread in the CSF. Second, if significant respiratory depression does occur, resultant hypercapnia may create carbon dioxide narcosis. Therefore when a patient becomes increasingly somnolent after neuraxial opioids, episodic hypoventilation and respiratory depression should be carefully considered, even when respiratory rate and oxygenation are within acceptable limits.

Pruritus

The most common side effect of neuraxial opioids is pruritus. This may be generalized but is more likely to be localized to the face, neck, or upper thorax. The incidence varies widely, from 0% to 100%, and it is often elicited only after direct questioning. Severe pruritus is rare, occurring in only about 1% of patients. The higher the dose of opioids, the larger the risk of pruritus. It is also more likely to occur in obstetric patients due to interaction of estrogen with opioid receptors. All opioids have been found to cause pruritus, even though it is more common with fentanyl and morphine. The possible mechanism for pruritus is due to rostral spread of opioids via the CSF and interaction with opioid receptors present in the trigeminal nucleus in the medulla (itch center). This may explain why pruritus is much more common in the facial area. Histamine release is not a cause of pruritus; on the contrary, antihistamine may relieve the symptoms.

Nausea and Vomiting

The incidence of nausea and vomiting after intrathecal and epidural opioid administration is approximately 30%. Although the underlying mechanism is not related to systematic absorption of the drug, the incidence of nausea and vomiting after intravenous opioid administration is the same. Nausea usually occurs within 4 hours of injection and vomiting soon thereafter. The incidence may or may not be related to the dose of opioids administrated and may be higher with intrathecal morphine. Nausea and vomiting are more frequent in women than men. Administration of intrathecal and epidural opioids is likely to result in cephalad migration of the drug in CSF and subsequent interaction with opioid receptors located in the area postrema. Sensitization of the vestibular system to motion and decreased gastric emptying produced by opioids may also play a role in nausea and vomiting induced by intrathecal and epidural opioids.

Urinary Retention

The incidence of urinary retention after intrathecal and epidural opioid administration varies widely, from 0% to 80%, and occurs most often in young male volunteers. The incidence is not related to the dose of opioid administered and may be higher when intrathecal morphine is used. The underlying mechanism is not related to systemic absorption of the drug. Urinary retention after intrathecal and epidural opioid administration is much more common than after intravenous or intramuscular administration of equivalent doses of opioid. Urinary retention induced by intrathecal and epidural opioids is likely related to interaction with opioid receptors located in the sacral spinal cord. This interaction promotes inhibition of sacral parasympathetic nervous system outflow, which causes detrusor muscle relaxation and an increase in maximal bladder capacity leading to urinary retention. In humans, epidural morphine causes marked detrusor muscle relaxation within 15 minutes of injection that persists for up to 16 hours and is readily reversed with naloxone. Endogenous opioid likely plays an important role in normal control of bladder function.

Gastrointestinal Dysfunction

Intravenous and intramuscular opioids are known for their ability to alter gastrointestinal motility. Intrathecal and epidural opioids may also delay gastric emptying and prolong intestinal transit time. The cause of decrease in gastrointestinal motility after intrathecal or epidural opioid administration is not related to systemic absorption of the drug and appears to be caused by interaction with opioid receptors located in the spinal cord. In human volunteers, administration of epidural morphine delays gastric emptying. In mice, intrathecal morphine causes dose-dependent gastrointestinal dysfunction and naloxone-reversible prolongation of small bowel transit time. Patients administrated intrathecal or epidural opioids may exhibit signs and symptoms of ileus, which may, in turn, lead to nausea and vomiting.

Implications

Appropriate patient selection and careful vigilance can reduce serious adverse effects from neuraxial opioid use, especially central respiratory depression. Vigilant postoperative care is required because the use of hydrophilic drugs (morphine, hydromorphone) can lead to a delayed onset and longer duration of respiratory depression. Monitoring is necessary for at least 24 hours after the administration of neuraxial morphine or hydromorphone. Excessive somnolence may be the first sign, which is why mental status assessments should be performed during postoperative observation. Concomitant administration of other narcotics or central nervous system depressants should be avoided, especially in opioid-naive patients.

Small doses of lipophilic drugs such as fentanyl can be safely used in ambulatory surgery settings. Studies have shown that the risk of respiratory depression is minimal with intrathecal doses of less than 25 μg of fentanyl, even in elderly patients. For patients receiving

postoperative epidural analgesia, no special monitoring is necessary if fentanyl is used in reasonable doses, even with thoracic epidural catheters.

Side effects such as pruritus, nausea and vomiting, and urinary retention may be viewed as nuisance or minor complications, but even so there can be undesirable consequences. If they are severe enough, there may be an unanticipated hospital admission or a delay in discharge, unpleasant side effects from the treatment medications, or unwanted procedures such as an indwelling bladder catheter for inability to void.

Use of intrathecal narcotics for labor and delivery has become increasingly popular. Complications such as prolonged early labor and severe fetal bradycardia have been reported, but a causal relationship is still debated in the obstetric literature. The incidence of fetal heart rate abnormalities, especially bradycardia, may be dose dependent. The presumed cause is uterine hyperactivity due to an imbalance in circulating catecholamines after the rapid onset of analgesia. It should be emphasized that such heart rate abnormalities respond to conservative measures and are not associated with poor neonatal outcomes.

MANAGEMENT

For serious adverse effects, including respiratory depression, the best reversal agent is a pure opioid antagonist such as naloxone. Although intravenous naloxone has a rapid onset, the duration of a single bolus may be insufficient, and infusions are often warranted. For less critical side effects (e.g., pruritus), naloxone may be hard to titrate to effect without the reversal of at least some analgesia. If so, a mixed agonist-antagonist such as nalbuphine may be more suitable. Studies have shown that nalbuphine can effectively treat pruritus, nausea, or vomiting without altering the level of pain control.

Other agents have been used to treat the side effects of neuraxial opioids (Table 104.1). Serotonin 5-HT_3 antagonists (e.g., ondansetron) are effective for the treatment of both pruritus and nausea. Droperidol, with its weak serotonin antagonist activity, may help treat pruritus but is more useful against nausea and vomiting. Propofol inhibits dorsal horn signal transmission and can effectively treat nausea and pruritus; however, the management and cost of a propofol infusion for this purpose probably outweigh the benefits. Although histamine release is not the mechanism for opioid-induced pruritus, the sedating effect of antihistamines such as diphenhydramine may be beneficial by breaking the itch-scratch cycle, but they do not directly reduce the itch.

These may reduce side effects such as pruritus and postoperative nausea and vomiting without affecting analgesia. Respiratory depression is less likely to be treated with such agents as it is a centrally mediated effect.

PREVENTION

Limiting the dose of a neuraxial opioid can reduce the incidence of side effects. Thus a multimodal approach to postoperative analgesia may be the best prophylactic regimen. Nonsteroidal antiinflammatory drugs can reduce opioid requirements, provide analgesia, and perhaps even prevent pruritus by inhibiting prostaglandin synthesis. Dexamethasone is also an effective prophylaxis against nausea and vomiting and, in higher doses, may enhance analgesia. Droperidol may help reduce postoperative nausea and vomiting. Prophylactic ondansetron has been shown to reduce nausea, vomiting, and pruritus. Nalbuphine, however, may be a better drug for treatment than for prophylaxis. Intraoperative propofol infusions do not prevent either pruritus or nausea in the postoperative period. For continuous epidural analgesia, adding a low concentration of local anesthetic to the infusion reduces the opioid dose via a synergistic effect.

TABLE 104.1 Managing Complications of Neuraxial Opioids

Complications	Management
Respiratory depression	• Respiratory rate of less than 8 breaths/min or difficult to arouse • Give oxygen 6–8 L/min • Naloxone 100–200 μg intravenously every 2–3 min until the respiratory rate is greater than 8 breaths/min; repeat doses will be required due to naloxone's short duration; alternatively consider a naloxone infusion 50–100 μg/h
Sedation	• If drowsy but arousable, administer oxygen via nasal speculum • Check the respiratory rate and saturation • If unarousable, get help
Pruritus	• Ondansetron (4 mg intravenous [IV] bolus) • Propofol low dose (10–20 mg IV bolus) • Chlorpheniramine (may be effective, but will increase risk of respiratory depression due to sedative effects and should not be considered as first line of management) • Low-dose naloxone (100 μg subcutaneously or intravenously); repeat every 30 min
Nausea and vomiting	• Administer antiemetics as prescribed (usually ondansetron, prochlorperazine, or metoclopramide) • If not relieved by regular antiemetics, consider low-dose naloxone (100 μg/h)
Urinary retention	• Urinary catheter

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105 Anesthesia Circuit

Michael R. Mathis • Satya Krishna Ramachandran

Case Synopsis

A 57-year-old woman who is a heavy smoker experiences a difficult endotracheal intubation during induction of anesthesia. Mask ventilation also is difficult, partly because of the high inspiratory pressures required and partly because of a poor mask fit, with a resulting considerable leak between the mask and face. The first and subsequent attempts at intubation are greeted with a stiff bag and a lack of a CO_2 waveform on the capnograph; each time, a tentative diagnosis of esophageal intubation is made, and the tube is quickly removed. After each intubation, mask ventilation becomes progressively more difficult. Throughout this episode, the patient also becomes intermittently hypotensive. About 30 minutes after induction, an observer notices that the expiratory check valve of the anesthesia breathing system remained seated during the entire breathing cycle. Replacement of the valve solves the problem; ventilation becomes possible, and the subsequent intubation is successful. Thus this "cannot ventilate, cannot intubate" scenario had an unexpected twist.

PROBLEM ANALYSIS

Definition

The anesthetic breathing system (ABS) has been formerly defined by the American Society for Testing and Materials in device standards as "a gas pathway in direct connection with the patient through which gas flows occur at respiratory pressures, in which directional valves may be present, and into which a mixture of controlled composition may be dispensed." A particular component of the ABS, the CO_2 absorber, is discussed in Chapter 106.

Almost every piece of medical equipment carries some risk for misuse or failure. Anesthetic breathing systems have multiple mechanical components and connections and variations in manufacture and design, thereby predisposing to critical incidents and patient injury. The most popular ABS employed in the United States is the circle system; circle system components are listed in Box 105.1, and failure modes are listed in Box 105.2.

Critical incidents involving the ABS can be broadly classified as provider error or equipment failure. The following definitions were used in the American Society of Anesthesiologists (ASA) closed claims analysis and accurately define the individual ABS related issues. *Provider error* refers to "fault or human error associated with the preparation, maintenance, or deployment of a device," whereas *equipment failure* refers to "unexpected malfunction of a device, despite routine maintenance and previous uneventful use." An example of equipment failure is a unidirectional valve on the ABS that suddenly failed to open. A *disconnect* is defined as the loss of attachment or continuity in a breathing circuit that was initially configured in a functional and conventional manner. A *misconnect* is defined as a nonfunctional and unconventional configuration of breathing circuit components or attachments.

This patient's difficulties represent one of the many potentially lethal or injurious complications related to the ABS. Although advances in anesthesia machine design and anesthetic monitoring have decreased the frequency of the ABS as a cause for general anesthesia claims over the past two decades, critical incidents involving the ABS continue to be life threatening. Among general anesthesia closed claims filed after 1990, 20% have been identified as caused by ABSs, half of which resulted in irreversible brain damage or death. Stuck unidirectional valves—such as occurred with the patient in the case synopsis—represented a majority of ABS closed claims. Such an event can be one of the most rapidly damaging anesthetic incidents; with a closed expiratory system, gases that enter the lungs cannot exit, and airway pressure builds rapidly to a level at which the lungs may rupture. Other claims included misconnects as well as failure to use a self-inflating manual ventilation device (SIMVD) despite being available, when mechanical ventilator failure existed.

Recognition

Recognition of ABS problems can be notoriously difficult, as shown by the case synopsis. Because they do not seem to be related to anything done by the anesthesiologist, such as turning a dial, injecting a drug, or inserting an endotracheal tube, these incidents are potentially elusive and catastrophic. Unless a high index of suspicion is present, the anesthesiologist may concentrate on more common causes—in this case, esophageal intubation. Current monitors on their own may offer little help with ABS problems; however, the anesthesia machine check continues to be one of the single most valuable prevention methods. Closed claims analysis reviewers judged that in a majority of breathing circuit claims, injury could have been prevented through performing a preanesthesia machine check (75%). Above all, the most important monitor is the vigilant anesthesiologist, who monitors breath sounds and chest wall excursions and continually observes the monitors.

Risk Assessment

Any patient undergoing general anesthesia is subject to the risk of ABS-related complications. Higher tidal volumes, respiratory rates, and fresh gas flows increase the risk, especially in smaller patients. Patients with lung disease, particularly those involving emphysematous bullae, are especially susceptible to damage produced by increased airway pressure *(barotrauma).* The state of anesthesia decreases protective cardiovascular response mechanisms and contributes to further cardiovascular compromise under positive pressure ventilation. Also at

BOX 105.1 Components of the Circle System

Fresh-gas flow inlet
Inspiratory limb
Expiratory limb
Respiratory check valves
CO_2 absorber
Y-piece
Ventilator/reservoir bag
Adjustable pressure limiting ("pop-off") valve
Anesthetic gas scavenging system

BOX 105.2 Anesthesia Breathing Circuit Failures

Disconnection
See Box 105.1 for possible disconnect sites

Blockage (Raised Airway Pressures)
Mechanical compression/distortion
Foreign body within circuit
Heated hoses
Improperly connected scavenging system
Water condensation
Slowly progressing block of microbial filters

Leak (Lowered Airway Pressures)
Inspiratory limb
Expiratory limb
Any other tube or small connection

Valve Malfunction
Obstruction
Incompetence
Reverse flow/rebreathing

CO_2 Absorber Failure
Exhausted soda lime
CO production
Dry soda lime
Overheating
Retained canister wrapping
Cracked canister

Contamination
Microbes, viruses
Particulate matter

greater risk in incidents such as that presented in the case synopsis are patients with decreased blood volume or cardiac function. The rapidly rising airway pressure quickly impedes venous return, which in turn decreases stroke volume and arterial pressure, even in healthy patients.

The causes or enablers of ABS problems include wear-and-tear, damaged components, design weakness, improper or infrequent maintenance, improper assembly, carelessness, and failure to check the anesthesia workstation before use. In the 1980s and 1990s, failure to check equipment had been a common factor in a large proportion of critical incidents. In the survey of Cooper and colleagues, 20.5% of incidents involved "failure to check." In an Australian survey, "failure to check equipment" was involved in 11.8% of all incidents. More recently, in an update to the Australian survey of 1000 critical anesthetic incidents, 395 were attributable to equipment problems, among which a reduced proportion (2.5%) were from a failure to perform an anesthesia machine check. Nonetheless, critical incidents stemming from ABS failures continue to be not only life threatening but also preventable in the majority, and as such, continued efforts at improving ABS design and safety checks are justified.

In the seminal reports by Cooper and colleagues, critical incidents related to the ABS ranked high on the list: breathing circuit disconnection during mechanical ventilation (5.2%), breathing circuit leak (1.7%), breathing circuit misconnection (1.7%), and breathing circuit control errors (1.4%). The total number of critical incidents related to the breathing circuit was 10% of all incidents. An update to the Australian survey of critical incidents revealed similar results; of 395 critical incidents related to equipment problems, 61 (15%) were from failure to ventilate/leak, 21 (5.3%) from circuit disconnection, 8 (2.0%) from unidirectional valve malfunction, and 7 (1.8%) from misconnection.

In the updated ASA closed claims analysis, an overall decrease in gas delivery equipment claims have been made since 1990; nonetheless, many continue to be deemed preventable as judged by expert review. Within the analysis, 85% of gas delivery equipment claims involved provider error, 41% of which were judged as preventable by preanesthesia machine check. The most frequently cited events involved stuck inspiratory/expiratory valves; other events included plastic from the circuit blocking the circuit lumen, positive end-expiratory pressure valves connected to incorrect (inspiratory) limb of a circle system, and incorrect placement of the reservoir bag.

Implications

The consequences of breathing circuit complications can be disastrous. During the past several decades, a few large-scale surveys of anesthetic outcome have been published looking at gas delivery equipment as cause of serious injury. These studies attribute approximately 5% to 23% of anesthesia-related death and brain damage to problems with gas delivery equipment. Within an update to the ASA Closed Claims Project, 6022 claims involving general anesthesia were noted since 1990, of which 40 (0.7%) were attributable to breathing circuit complications. Among the claims related to breathing circuit complications, 15 (38%) resulted in death or severe brain damage.

As demanded by the life-threatening consequences of breathing circuit complications, progress has been made to reduce incidents over the past two decades. Indeed, since 1990 a decrease in both the number and severity of injury in claims related to gas delivery equipment has been made. Improvements to anesthesia delivery systems—focused on safer machine, ventilator, and circuit designs, as well as improved implementation of safety checks and more robust algorithms triggering alarms—represent a possible explanation for the decreased incidence and severity of claims made. In contrast to previous closed claims analyses, no claims were made related to breathing circuit disconnects, and a reduced proportion of claims were made related to breathing circuit misconnections. Despite these improvements, however, tantamount to patient safety is a vigilant, well-trained anesthesia provider, as the vast majority (86%) of recent gas delivery claims continue to be associated with preventable provider errors.

In summary, human error plays a major role in initiation and propagation of ABS complications. Patient injury from ABS complications is characterized by high severity of injury and high cost. Although improvements in ABS design and improved implementation of safety checks may have been attributable to the decrease in ABS-related complications over the past two decades, claims have persisted, and half of these claims have resulted from stuck inspiratory or expiratory unidirectional valves.

MANAGEMENT

The management, especially if an ABS-related condition is recognized relatively early, is usually simple. Occasionally, another anesthesia machine will have to be brought in to replace the offending one; this is not a trivial or brief matter. While this is taking place or often while a diagnosis is being confirmed, a method should be used to independently supply oxygen and ventilation. In this regard, it is important to recognize the role of prompt use of an SIMVD within the troubleshooting algorithm for anesthetic breathing systems. Within the updated

BOX 105.3 FDA Recommendations for Anesthesia Workstation Checkout Pertinent to the ABS

Initial status of the breathing system:
- Set selector switch in "bag" mode.
- Check that *breathing circuit* is complete, undamaged, and unobstructed.
- Verify that *CO_2 absorbent* is adequate.
- Install breathing circuit *accessory equipment* (e.g., humidifier, positive end-expiratory pressure [PEEP] valve) to be used during the case.

Leak check of breathing system:
- Set all gas flows to zero (or minimum).
- Close *adjustable pressure limiting (APL; "pop-off") valve*, and occlude *Y-piece.*
- Pressurize breathing system to 30 cm H_2O with *O_2 flush.*
- Open APL valve, and ensure that pressure decreases.

Ventilation system and unidirectional valves:
- Place second breathing bag on Y-piece.
- Set appropriate ventilator parameters for next patient.
- Switch to automatic ventilation (ventilator) mode.
- Fill *bellows* and second breathing bag with O_2 flush, and then turn ventilator on.
- Set O_2 flow to minimum and other gas flows to zero.
- Verify that during inspiration, bellows delivers appropriate tidal volume, and that during exhalation, bellows fills completely.
- Set fresh gas flow to about 5 L/min.
- Verify that the ventilator bellows and simulated lungs fill and empty appropriately and without sustained pressure at end exhalation.
- Check for proper action of *unidirectional valves.*
- Examine *breathing circuit accessories* to ensure proper function.
- Turn ventilator off, and switch to manual ventilation (bag/APL) mode.
- Ventilate manually, and ensure inflation and deflation of artificial lungs and appropriate feel of system resistance and compliance.
- Remove second breathing bag from Y-piece.

ASA closed claims analysis, three low-severity claims noted successful use of an SIMVD; in contrast, death or severe brain damage occurred in two claims in which SIMVD was not attempted despite being available, as well as another instance in which SIMVD was unavailable, and one other instance in which an SIMVD was used too late during inadequate ventilation only after cardiac arrest had ensued. Interestingly, despite a recurrence of closed claims involving lack of appropriate SIMVD use, studies have shown that verification of an available SIMVD is among the most frequently missed steps of the ASA 2008 preanesthesia checkout.

PREVENTION

The optimal way to prevent most ABS-related incidents has been available for decades: the anesthesia workstation checkout. A formal list of this checkout, which was compiled by the Food and Drug Administration (FDA), has been available since 1986. Additionally, the ASA has formulated a list of checkout recommendations, available since 1993 and updated in 2008. Checkout protocols typically entail four basic activities: verification of backup equipment and supplies (e.g., pressurized gas cylinders); inspection of equipment configurations (e.g., breathing circuit connections); inspection of equipment mechanics (e.g., proper action of unidirectional valves); and preparation of monitors (e.g., calibration, verification of function, and activation of alarms). The ASA closed claims analysis revealed that better selection and use of monitoring could have prevented the vast majority of complications in gas delivery system claims.

We cannot present the entire FDA checkout routine, although the section pertinent to the ABS is given in Box 105.3. As drafted by the ASA, the preanesthesia checkout procedure is detailed in Table 105.1. In the scenario presented at the start of the chapter, the simple preanesthetic act of disconnecting the Y-piece from the inspiratory

TABLE 105.1 2008 ASA Recommendations for Preanesthesia Checkout Procedure

TO BE COMPLETED DAILY, OR AFTER A MACHINE IS MOVED OR VAPORIZERS CHANGED

Item To Be Completed		Responsible Party
Item #1:	Verify auxiliary oxygen cylinder and manual ventilation device (Ambu bag) are available and functioning.	Provider and technician
Item #2:	Verify patient suction is adequate to clear the airway.	Provider and technician
Item #3:	Turn on anesthesia delivery system, and confirm that AC power is available.	Provider or technician
Item #4:	Verify availability of required monitors, including alarms.	Provider or technician
Item #5:	Verify that pressure is adequate on the spare oxygen cylinder mounted on the anesthesia machine.	Provider and technician
Item #6:	Verify that the piped gas pressures are ≥50 psig.	Provider and technician
Item #7:	Verify that vaporizers are adequately filled and, if applicable, that the filler ports are tightly closed.	Provider or technician
Item #8:	Verify that there are no leaks in the gas supply lines between the flowmeters and the common gas outlet.	Provider or technician
Item #9:	Test scavenging system function.	Provider or technician
Item #10:	Calibrate, or verify calibration of, the oxygen monitor and check the low oxygen alarm.	Provider or technician
Item #11:	Verify carbon dioxide absorbent is fresh and not exhausted.	Provider or technician
Item #12:	Perform breathing system pressure and leak testing.	Provider and technician
Item #13:	Verify that gas flows properly through the breathing circuit during both inspiration and exhalation.	Provider and technician
Item #14:	Document completion of checkout procedures.	Provider and technician
Item #15:	Confirm ventilator settings, and evaluate readiness to deliver anesthesia care. (ANESTHESIA TIME-OUT)	Provider

TO BE COMPLETED *BEFORE* EACH PROCEDURE

Subset of Items to Be Completed ***Between*** Cases		Responsible Party
Item #2:	Verify patient suction is adequate to clear the airway.	Provider and technician
Item #4:	Verify availability of required monitors, including alarms.	Provider or technician
Item #7:	Verify that vaporizers are adequately filled and if applicable that the filler ports are tightly closed.	Provider
Item #11:	Verify carbon dioxide absorbent is not exhausted.	Provider or technician
Item #12:	Breathing system pressure and leak testing.	Provider and technician
Item #13:	Verify that gas flows properly through the breathing circuit during both inspiration and exhalation.	Provider and technician
Item #14:	Document completion of checkout procedures.	Provider and technician
Item #15:	Confirm ventilator settings, and evaluate readiness to deliver anesthesia care. (ANESTHESIA TIME-OUT)	Provider

From American Society of Anesthesiologists: ASA Library of Anesthesia Workstation Checkout Procedures (checkout procedure submission template), 2008. Available at http://www.asahq.org/resources/clinical-information/2008-asa-recommendations-for-pre-anesthesia-checkout/sample-procedures. Accessed August 19, 2016.

and expiratory limbs of the ABS and trying to breathe in and out through both of them individually would have considerably increased the chances of preventing this disaster.

Because of the serious implications of high airway pressures, device standards take into account the fact that an alarm by itself may not allow the clinician sufficient time for alarm recognition, diagnosis of the problem, and remediable action. For that reason, each anesthetic workstation must have a fixed breathing pressure limitation protection module, whose maximum pressure cannot exceed 125 cm H_2O (12.5 kPa). Further, it is required on modern anesthesia workstations to have an *adjustable* breathing pressure limitation protection module if the fixed breathing pressure limitation protection module is 80 cm H_2O or greater. If there is no ventilator or if the anesthesia workstation is in the manual or spontaneous mode, the reservoir bag may be considered an airway pressure limitation protection module. The protection module offers limited protection in our case, because expired gases cannot reach the bag or the ventilator due to the obstructed expiratory check valve.

In summary, suspicion, observation, and compulsiveness can contribute to the prevention, recognition, and management of ABS-related complications. The anesthesiologist's motto of "vigilance" is important everywhere, but with ABS complications, unremitting vigilance is required. Acute increases in airway pressure or complete loss of tidal volumes due to leaks are true emergencies that present during anesthesia, in which fatal or crippling patient injury can take place in a matter of seconds.

Further Reading

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106 Carbon Dioxide Absorbers

Marc Sherwin • James B. Eisenkraft

Case Synopsis

A 75-year-old woman with perforated diverticulitis is undergoing a laparoscopic hemicolectomy under general anesthesia. The patient's abdomen has been insufflated with CO_2 to a pressure of 15 to 20 mm Hg for 45 minutes. The end-tidal CO_2 is observed to rise to 50 mm Hg without any adjustment made in the minute ventilation during this time. Over the last 15 minutes, the end-tidal CO_2 has increased to 55 mm Hg, and the inspired CO_2, which had been zero, has gradually increased to 6 mm Hg. Examination of the CO_2 absorber canister shows no color change in the absorbent.

PROBLEM ANALYSIS

Definition

Carbon dioxide absorbents are essential for the elimination of CO_2 in closed and semiclosed breathing circuits. The absorbent's chemical reaction with CO_2 allows low fresh gas flows to be used without causing rebreathing. The patient's expired gas passes through the canister containing absorbent granules where a reaction occurs that results in production of carbonate, H_2O, and heat, to varying degrees, depending on the composition of the absorbent used.

The absorbents most commonly used in contemporary anesthesia systems include Sodasorb, Medisorb, Drägersorb 800 Plus, Amsorb Plus, Litholyme, and Spiralith. Each exploits the components of absorbents in various degrees, such as levels of calcium hydroxide, activators (NaOH or KOH), water content, and indicators (Table 106.1).

Sodasorb, Medisorb, and Drägersorb 800 Plus all use various amounts of activators that react with carbonic acid (H_2CO_3) to form carbonates (CO_3). The carbonic acid is initially produced when the CO_2 from the patient's expired gas reacts with H_2O in the absorbent. The carbonates formed then react with calcium hydroxide [Ca(OH)2] to yield insoluble calcium carbonate ($CaCO_3$) precipitate. Both NaOH and KOH are regenerated in this final reaction, and when all hydroxides have become carbonates, the absorbent is exhausted. These absorbents all contain ethyl violet, which acts as a pH indicator turning violet when the pH decreases and the absorbent is exhausted. The basic chemical reactions are as follows:

1. $CO_2 + H_2O = H_2CO_3$
2. $H_2CO_3 + 2NaOH$ (*or* KOH) = Na_2CO_3 (*or* K_2CO_3) + $2H_2O$ + Heat
3. Na_2CO_3 (*or* K_2CO_3) + Ca(OH)2 = $CaCO_3 + 2NaOH$ (*or* KOH) + Heat

Amsorb Plus differs from other absorbents by avoiding use of alkali hydroxides (NaOH and KOH). The latter are strong monovalent bases that are associated with the breakdown of potent inhaled volatile anesthetic agents into hazardous compounds, including fluoromethyl-2-2-difluoro-1-(trifluoromethyl) vinyl ether (compound A) and carbon monoxide (CO). Amsorb consists of calcium hydroxide, water, and calcium chloride, which serves to preserve moisture, as well as calcium sulfate and polyvinylpyrrolidine to improve hardness and porosity. The reaction is as follows:

1. $CO_2 + H_2O = H_2CO_3$
2. $H_2CO_3 + Ca(OH)2 = CaCO_3 + 2H_2O$ + Heat

Litholyme and Spiralith are more recently introduced absorbents that also do not use activators, thus avoiding formation of compound A and CO. Litholyme incorporates a lithium chloride catalyst that does not react with inhaled anesthetic agents to enable CO_2 absorption. The benefit of lack of NaOH or KOH is also that these compounds cannot be regenerated and cause pH indicators to become colorless. Although nonreactivity with volatile anesthetic agents and permanent color change are of benefit, other advantages to using lithium hydroxide are its lower exothermic reactivity, reducing risk of fire, and economic/environmental impact. Epstein and colleagues reported that replacing soda lime with Litholyme allowed anesthesia providers to use sevoflurane with lower (<2 L/min) fresh gas flows, thereby decreasing consumption of sevoflurane. The savings achieved essentially offset the increased cost of Litholyme.

Spiralith differs from Litholyme in several ways. Unlike all other absorbents that first react with H_2O, Spiralith uses anhydrous LiOH powder within a nongranular polymer matrix that is partially hydrated. This results in a large surface area for reaction and reduction in temperature, longer duration of use, and cost-effectiveness. Environmental impact may be a factor in considering choice of absorbent used, and the manufacturers of Spiralith claim that this is an advantage of the absorbent, because it is a recyclable polymer sheet encompassing a powder. Spiralith does not incorporate a color indicator to alert when it is exhausted. It is therefore imperative to regularly replace this absorbent and to strictly monitor the patient's inspired CO_2 concentration in the breathing circuit. The reaction of the lithium hydroxide compounds with CO_2 is as follows:

$$2LiOH * H_2O + CO_2 = Li_2CO_2 + 3H_2O - Heat$$

(* H_2O Indicates Hydrated LiOH)

Recognition

Signs of exhausted absorbent include increased end-tidal CO_2 and inspired CO_2, as well as excessive heat production in the absorber canister. If appropriate high and low CO_2 alarm limits have been set on the capnometer, an alarm will be triggered when the set limits are exceeded. An increase in $Paco_2$ may cause hypertension and tachycardia, which

TABLE 106.1 Comparison of Absorbent Compositions

Composition	Sodasorb	Medisorb	Drägersorb 800 Plus	Amsorb Plus	Litholyme	Spiralith
Ca(OH)2	76.5%	81%	82%	>75%	>75%	0%
NaOH	2.25%	1%–2%	2%	0%	0%	0%
KOH	2.25%	0.003%	0.003%	0%	0%	0%
LiOH	0%	0%	0%	0%	0%	95%
LiCl	0%	0%	0%	0%	<3%	0%
H2O	18.9%	18%	16%	14.5%	12%–19%	Chemically bound
Indicator	Yes	Yes	Yes	Yes	Yes	No

Data from Materials Safety Data Sheets, Occupational Safety and Health Administration, U.S. Department of Labor.

can also be clinical indicators of exhausted absorbent. The acute hypercapnia will increase cerebral blood flow and intracranial pressure, which may be detected during a neurosurgical procedure by increased bleeding in the operative field. An increase in $Paco_2$ will also increase the respiratory drive, and "overbreathing" of the ventilator may be observed.

Exhaustion of absorbent should be recognized before starting an anesthetic. All absorbent canisters are designed to be transparent so that the contents can be inspected for changes in color of the ethyl violet pH indicator. When the patient's expired gas passes through the absorbent canister, the upstream absorbent granules will show the color change first. Contemporary anesthesia workstations are designed to use preloaded disposable "quick-change" canisters. The breathing circuit incorporates an absorber mount that is self-sealing so that no leak is created if the canister is removed. This is important in situations where the absorbent must be replaced during the case. In older machine designs, the absorber canister in the breathing circuit must be opened to replace the absorbent, creating a large leak until the absorbent cartridges have been changed and the canister is closed. Seif and Olympio reported such a situation when an anesthesia provider exchanged a Medisorb absorbent in a GE Aestiva/5 anesthesia machine during ventilation of a paralyzed patient whose airway was not easily accessible for connection to an Ambu bag. The resulting huge leak in the open absorber made continued positive pressure ventilation with the circle breathing system impossible. In this case the expiratory limb of the circuit was disconnected from the machine and connected to an Ambu bag, which allowed ventilation via the expiratory limb.

Ethyl violet is the pH indicator used in absorbents. When the pH decreases from 13.5 to 10.3, the compound changes from colorless to violet due to the elimination of a hydroxyl ion. The issue arises when the absorbent is not replaced; the NaOH and KOH will regenerate in the exhausted canister, gradually increasing the pH above the threshold for color change, and the absorbent may be exhausted but will no longer be violet. Ethyl violet may be deactivated by other means resulting in no color change. This was reported by Andrews and colleagues when fluorescent light was found to decrease concentrations of pH indicator by 50% within 8 hours of exposure in Sodasorb, and even in the dark, deactivation occurred over time once opened. The newer absorbents, such as Litholyme and Spiralith, do not exhibit the problem of activator regeneration. The absence of the NaOH and KOH compounds in Litholyme causes it to remain violet permanently. Spiralith, which is 100% lithium based, has no pH indicator. The lack of visible color change requires that the anesthesia provider continuously monitor $Fico_2$ unless the absorbent is changed regularly.

Risk Assessment

During an anesthetic, an exhausted CO_2 absorbent will likely present with signs or alarms of hypercapnia, but it is important to consider other possible causes of hypercapnia. If ventilation is constant, hypercapnia may be due to increased production (or delivery) of CO_2 or decreased elimination of CO_2. Examples of increased production include hypermetabolic states (e.g., sepsis, fever, overwarming the patient), CO_2 diffusion from laparoscopic insufflation, light anesthesia resulting in catecholamine release, bicarbonate therapy in which reaction with H^+ yields H_2O and CO_2, thyroid storm, and malignant hyperthermia. It may also be iatrogenic in that some machines are designed to be able to deliver CO_2 and such delivery may occur inadvertently. Other causes include deliberate bypassing of the CO_2 absorber or its removal from the circuit; or a misconnection/crossed pipeline may result in CO_2 being delivered via the N_2O delivery system, as reported by Ellett and colleagues, in which the N_2O hose was connected to the CO_2 wall outlet. Decreased elimination most commonly occurs due to hypoventilation, likely from inadequate minute ventilation or, in the spontaneously breathing patient, from drug-induced depression of respiratory drive. Rebreathing of CO_2 will result in hypercapnia, whether from channeling of gas flow through the absorbent, incompetent or missing unidirectional valves, or exhausted absorbent combined with insufficient fresh gas flow to remove CO_2 via the waste gas scavenging system.

Implications

Exhausted absorbents can lead to a number of hazardous complications in addition to hypercapnia. Other, rarer, complications that may arise from desiccation of absorbent is the production of compound A and carbon monoxide. Compound A has been purported to cause nephrotoxicity in rat models when used at low fresh flows (<2 L/min), with barium hydroxide lime, at high concentrations of sevoflurane, at high temperatures, and in desiccated absorbers. These data have yet to be applied conclusively to humans. In fact, studies by Yamakage and colleagues showed that using sevoflurane at fresh gas flows of 1 L/min for 4 hours with Medisorb or Amsorb (both of which contain minimal [0.003%] KOH and no KOH, respectively) compared with Drägersorb 800 Plus (2% KOH) produced no increase or only trivial increase in compound A levels. Epstein and colleagues have also suggested that when a nonreactive lithium-based absorbent is used, lower flows of sevoflurane may be safely and more economically used. It is still recommended, however, to maintain fresh gas flows greater than 2 L/min and avoid the use of sevoflurane in patients with renal insufficiency.

Even rarer nowadays is CO poisoning resulting from desiccated absorbent reacting with potent inhaled volatile anesthetics, particularly desflurane. Studies in 2000 by Stabernack and colleagues demonstrated that lithium absorbers and Amsorb, both of which lack NaOH and KOH, decreased the production of CO, whereas barium hydroxide lime (Baralyme) yielded the highest CO levels. The prototypical scenario in which this occurs is the first case on a Monday morning after the circuit has been left over the weekend with high gas flows that desiccate the absorbent. By turning off the machine at the end of the day and using absorbents that lack NaOH and KOH, the risk of CO production may be diminished.

TABLE 106.2 Causes of Increased Carbon Dioxide Concentration

Inspired	Expired
Exhausted absorbent	Fever/sepsis
Channeling	Malignant hyperthermia
Incompetent unidirectional valve	Bicarbonate administration
CO_2 delivered through circuit	Thyroid storm
Pipeline switch	Hypoventilation
	Laparoscopy (carboperitoneum)
	Light anesthesia

Another reported but fortunately rare complication of CO_2 absorbers is fires and explosions from excessive heat production. Malignant hyperthermia must also be considered when signs of increased CO_2 are associated with increasing temperature. The neutralization reaction of CO_2 generates water and heat, as described earlier, due to the exothermic reaction. The heat produced in this reaction varies with the composition of the absorbent. The very widely used absorbent Baralyme was associated with several cases of fires and in 2005 was withdrawn from the US market. Laster and Eger reported that soda lime reacted with varying levels of volatile anesthetics. The reaction resulted in temperatures as high as 90°C with sevoflurane, although though no fires ensued. In the event that a canister feels markedly hot, it is recommended to disconnect the patient from the breathing circuit and replace the absorbent.

MANAGEMENT

The most important measure in the management of exhausted CO_2 absorbents and potential complications is to ensure adequate oxygenation and ventilation of the patient. This may require switching to an alternate means of ventilation (e.g., Ambu bag and O_2) if needed. If absorbent exhaustion is the culprit, increasing fresh gas flows to essentially create a nonrebreathing system will effectively wash out CO_2 from the circuit, as well as minimize hazardous degradation products. Ultimately, however, management should involve replacing the absorbent, even if no color change is visible. It is preferable to change canisters in between uses of the breathing system for risk of being unable to replace the absorber.

When increased CO_2 is observed, it is important to consider causes other than absorbent exhaustion (Table 106.2). Being vigilant of the patient's temperature for signs of overheating or fever is key, and decreasing external warming may help. Keeping in mind that increased CO_2 may be a byproduct of the CO_2 being delivered by laparoscopy is another important consideration, while still bearing in mind malignant hyperthermia and ruling out the diagnosis through other corresponding clinical signs. Taking note of the minute ventilation and any changes from baseline may also provide a clue to the cause of increased CO_2 and appropriately increasing tidal volume or respiratory rate to eliminate CO_2. Finally, checking the anesthesia machine for faulty inspiratory or expiratory unidirectional valves or exhausted absorbent may reveal the cause of increased inspired CO_2, and having a low threshold to replace the absorbent with fresh absorbent will help determine whether it is the cause.

PREVENTION

The preuse checkout of the anesthesia workstation requires the anesthesia provider to check that an absorber is present and the absorbent is not exhausted. The breathing system is also checked for correct assembly and normal function of unidirectional valves. These inspections presently cannot be automated and so must be performed by the anesthesia provider. To prevent use of desiccated absorbent, it is recommended to institute a regular schedule of replacing absorbent canisters. As discussed earlier, the pH indicator is not a reliable guide as to whether it is time to replace the absorbent, as the NaOH and KOH can regenerate and cause ethyl violet to revert to its colorless form. Spiralith does not contain a pH indicator. As the most common result of exhausted CO_2 absorbent is hypercapnia, being vigilant for clinical signs of increased CO_2 is vital. It is critical that the anesthesia workstation/capnometer is measuring levels of $FiCO_2$, and when this value begins to exceed 2 to 3 mm Hg, the absorbent should be replaced.

In 2005 the Anesthesia Patient Safety Foundation published recommendations that, if followed, will reduce the risk of complications from CO_2 absorbents. The recommendations are as follows:

- Use absorbents that will not result in substantial degradation when exposed to volatile anesthetics.
- Establish policies to prevent desiccation and management strategies for when it occurs, such as turning off gas flow when the machine is not in use.
- Change the absorbent regularly, especially on Monday morning before the first case of the day.
- Change the absorbent whenever color change indicates exhaustion or when there is uncertainty of exhaustion.
- Change all absorbent cartridges when using a multicartridge system.

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Central Venous Pressure Monitoring

107

John T. Lemm • Jonathan B. Mark

Case Synopsis

A 65-year-old man is taken to the operating room for coronary artery bypass grafting. After induction of anesthesia, a right internal jugular triple-lumen central venous catheter (CVC) is placed. The operation proceeds without complications, and the patient is taken to the intensive care unit at the conclusion of the case. As the patient recovers from surgery, his care team decides to leave his CVC in place because peripheral intravenous (IV) access attempts have proved difficult. On the fourth postoperative day, the patient develops fever and chills, followed by tachycardia and hypotension.

PROBLEM ANALYSIS

Definition

Insertion of CVCs using the technique first pioneered by Sven-Ivar Seldinger has revolutionized the field of medicine. CVC insertion was transformed into a relatively straightforward and safe practice, and now in the United States alone, over 15 million CVC days are recorded annually. Although complications of CVC insertion are uncommon, the astute clinician should understand potential risks, as many can lead to serious injury if left unrecognized. Complications are generally organized into two categories: immediate problems associated with CVC insertion, and delayed effects stemming from prolonged catheter residence. These complications are listed in Tables 107.1 and 107.2, respectively. Strategies such as mandatory supervision of inexperienced operators and the use of ultrasound guidance have been widely adopted and likely reduce immediate adverse events such as arterial puncture and pneumothorax. Even with these preventive measures, clinicians should always closely monitor their patients during CVC insertion, as arrhythmias, hypotension, mental status changes, or oxygen desaturation are all signs of a potential problem.

One particularly devastating complication of central venous catheterization is a catheter-related bloodstream infection (CRBSI). Fever, hemodynamic instability, inflammation at the insertion site, and mental status changes all suggest a CVC-related sepsis syndrome, especially when there is no other apparent source of infection. Diagnosis of a CRBSI starts with clinical suspicion, followed by microbiologic confirmation. CRBSI is most stringently defined as isolation of the same organism from the catheter tip and peripheral blood sample, or from the catheter hub and peripheral blood in a patient without another obvious source of infection.

Recognition

CRBSI is recognized by the following:

- Fever in a patient with an IV catheter or CVC
- Inflammation or purulence at the IV catheter or CVC insertion site
- Positive catheter culture and peripheral blood cultures
- No other obvious source of infection

The most sensitive marker of a CRBSI is a febrile episode, and the differential diagnosis of fever in any patient with an indwelling IV catheter must include CRBSI until proven otherwise. A systematic approach is then implemented to rule out other sources of infection, including sputum and urine cultures, inspection of surgical wounds and skin integrity, and a thorough physical examination. Finally, all catheter insertion sites should be inspected for inflammation and purulence.

To obtain culture samples of catheter segments, the CVC or peripheral IV catheter must be removed. When removing a CVC, it is likely that the patient will require continued central venous access. If this is the case, a new CVC should preferably be placed at a different site rather than exchanging the catheter over a guidewire, because the risk of bloodstream infection increases dramatically with this technique, particularly when the CVC has been in place longer than 3 days. Certainly, if obvious signs of local infection exist, one should never attempt a "guidewire" exchange. Blood samples for culture should be obtained from a peripheral site at or near the time of CVC or IV catheter exchange for comparison with the catheter culture tip results. Isolation of the same organism from cultures of both the catheter segment and peripheral blood confirms the diagnosis of a CRBSI.

Semiquantitative and quantitative catheter cultures have greater specificity for infection diagnosis than do traditional broth cultures; however, one must realize that not every positive culture represents a CRBSI. A positive blood culture in the absence of signs of infection simply represents catheter colonization rather than a CRBSI, although catheter colonization is presumed to represent a major step in the progression toward overt infection. When using a semiquantitative culture technique, growth of more than 15 colony-forming units from the catheter segment of the same microbe cultured from the peripheral blood supports the diagnosis of catheter colonization. When a patient then manifests signs of infection, the diagnosis of CRBSI is made. Quantitative cultures represent an even more sensitive technique for diagnosing a catheter-related infection. Growth of more than 10,000 colony-forming units in a sample from a catheter segment is indicative of catheter colonization. The same results with evidence of systemic infection lead to the diagnosis of CRBSI.

In certain clinical situations such as a patient with challenging vascular access, it may be unwise to remove a catheter until after the

TABLE 107.1 Complications of Central Venous Pressure Monitoring During Catheter Insertion

Complication	Prevention	Recognition	Management
Air embolism	Use of Trendelenburg position during placement	Dyspnea Hemoglobin desaturation	Supplement with 100% O_2 Cardiovascular support as indicated
	Occlusion of open needles and catheter hubs in spontaneously breathing patients	Hypotension	
Pneumothorax	More common with subclavian approach	Cough during needle insertion Hemoglobin desaturation Dyspnea	Closed chest tube thoracostomy Observation if small (<15%)
	Use of small "finder" needle	Hypotension	Supplemental O_2
	Continuous aspiration with syringe during needle insertion More common with positive-pressure ventilation	Chest radiographic findings Decreased breath sounds	Cardiovascular support as indicated
Arrhythmias	Avoidance of guidewire insertion >15 cm	Electrocardiographic findings Audible change in pulse regularity	Withdraw guidewire Rarely, antiarrhythmic drug or external cardioversion
Arterial puncture	Careful attention to landmarks Palpation of arterial pulse	Bright red blood Pulsatile flow	Withdraw needle, and hold direct pressure ≥10 min
	Use of small "finder" needle	Expanding hematoma	With dilator or introducer placement, obtain vascular surgeon consultation
	Use of manometer (extension tubing) or pressure transducer to confirm venous access Use of portable ultrasound guidance	Airway compromise (with carotid puncture)	Airway support; intubation if indicated
Cardiac tamponade	Avoid forceful manipulation of catheter guidewire and dilator Confirmation of proper placement by chest radiograph	Cardiovascular decompensation Temporal association with catheter placement Echocardiogram	Surgical evacuation

TABLE 107.2 Complications of Central Venous Pressure Monitoring During Catheter Residence

Complication	Prevention	Recognition	Management
Vascular erosion	Confirmation of correct catheter tip placement with chest radiograph (junction of superior vena cava and right atrium) More common in left subclavian and internal jugular than right	Hydrothorax Cardiovascular decompensation (hemothorax, tamponade) Respiratory insufficiency	Surgical repair
Thrombosis	Heparin-bonded catheters may reduce risk Use of catheter only as long as absolutely indicated	May be "silent" Upper limb or shoulder edema or tenderness Pulmonary embolism may occur	Consider thrombolytic drug or heparin Surgical thrombectomy if severe
Infection	Strict aseptic techniques Maximal barrier precautions Use of catheter only as long as absolutely indicated Consider antimicrobial catheters Daily inspection of insertion site	Fever without other source of infection Local redness, tenderness, purulence Positive cultures of both catheter segment and blood samples from separate venipuncture with same organism	Removal of infected catheter Antimicrobial therapy
Misinterpretation	Appropriate "zeroing" and leveling of transducers Education and training	Correlation with clinical status Frequent zeroing and level checks of transducer	

diagnosis of CRBSI is finalized. In these situations, quantitative blood culturing and differential time to positivity (DTP) techniques are viable diagnostic alternatives. Quantitative culturing relies on comparing paired blood samples obtained from a CVC port and one peripheral venipuncture site. A colony count obtained from a catheter that is ≥ threefold higher than the colony count obtained from a peripheral blood culture supports the diagnosis of a CRBSI. When quantitative cultures are not available, as is the case in many laboratories, DTP is a useful substitute. DTP refers to microbe growth in the catheter hub sample at least 2 hours before growth is detected from the peripheral blood sample. As with quantitative cultures, DTP is also very highly sensitive and specific for CRBSI diagnosis.

Risk Assessment

The incidence of nosocomial bloodstream infection is estimated to be approximately 250,000 cases per year, and the majority of infections are associated with the use of an indwelling intravascular device. CVCs account for an estimated 90% of all CRBSIs. This is particularly troubling as the number of patients requiring these catheters for long-term vascular access, both as inpatients and outpatients, is steadily rising. Since the early 1990s the rates of CRBSIs have steadily declined, largely due to improved education, compliance with sterile insertion technique, and improved catheter management. Where many institutions once reported rates up to 8.5 bloodstream infections per 1000 catheter days, emerging data suggest that rates as low as 0.73 bloodstream infections per 1000 catheter days are easily achievable. Variability is common, however, as many factors influence infection rates, including hospital size, higher-risk patient populations, frequency of catheter use, and CRBSI diagnosis protocols.

Repeatedly demonstrated in the literature, the risk of CRBSI increases with the duration of central venous catheterization. Armed with this knowledge, many institutions adopted routine CVC replacement protocols, assuming it would lower infection rates. In 1992 a randomized controlled trial by Cobb and colleagues demonstrated that this practice was ineffective at reducing CRBSIs. In addition to providing no infection risk benefit, routine catheter changes increase the risk for mechanical complications, cause patient discomfort, and dramatically increase the use of nurse and physician time.

Any patient with a CVC is at risk for infection, but there are several host factors that significantly increase the risk of a CRBSI. These include patients with severe burns or other loss of skin integrity, bone

marrow transplant recipients, neutropenic patients, those receiving total parenteral nutrition, and those with a previous CRBSI. The most common sources of infection are the microbes colonizing the skin at the insertion site, and a strong correlation exists between patients with heavy skin colonization and CRBSIs. These organisms migrate from the skin along the transcutaneous tract of the catheter wound, eventually colonizing both the external and internal surfaces of the catheter.

Implications

CRBSIs are associated with mortality rates ranging from 12% to 25%, as well as significant patient morbidity, prolonged hospitalizations, and excess health care costs of up to $16,500. In the subset of patients with prosthetic implants (e.g., heart valves, vascular graft material), these infections are particularly devastating. Prosthetic materials are easily compromised once exposed to bloodstream bacteria, and once infected commonly require the risky process of explanting and subsequently replacing these devices.

MANAGEMENT

Once a CRBSI is suspected, the first step in management is the prompt removal of the infected catheter. If the patient still requires vascular access, a new IV catheter should be placed, preferably at a new location. One should only consider a guidewire-assisted exchange of an infected catheter if, after careful analysis, the risk of mechanical injury from a new insertion clearly outweighs the infectious risk of such an exchange (e.g., challenging vascular access patients). Once removed, the old catheter tip and intradermal segment should be sent for semiquantitative or quantitative culture. Simultaneously, two sets of blood cultures should be obtained for comparative analysis, ideally both from different peripheral sites.

Early implementation of broad-spectrum antimicrobial therapy is a mainstay for treating CRBSIs; however, it should be instituted only after catheter exchange and blood cultures have been obtained. Antibiotic choices should provide coverage for gram-positive and gram-negative bacteria with antifungal coverage an option for particularly high-risk patients. Once culture results are reported and sensitivities are known, antibiotic therapies must be tailored to the specific organism to prevent antimicrobial resistance.

Flowcharts for diagnosing acute fever in a patient suspected of having nontunneled CVC infection and approaches to managing patients with nontunneled CVC-related bloodstream infections are provided in Figs. 107.1 and 107.2, respectively.

PREVENTION

Strict adherence to the guidelines for the prevention of intravascular catheter-related infections as set forth by the Centers for Disease Control and Prevention (CDC) is critical to prevention of CRBSIs. Highlights of these recommendations include the following:

- Use a CVC only when a true indication exists, and remove it as soon as the indication no longer applies.
- Educate and train health care providers who insert and maintain CVCs.
- Practice strict adherence to hand washing and maximal sterile barrier precautions during CVC placement insertion.
- Use 2% chlorhexidine preparation for skin antisepsis.
- Avoid routine replacement of CVCs as a strategy to prevent infections.
- Use antiseptic- or antibiotic-impregnated CVC devices.

Any intravascular device provides a portal for microorganisms to enter the bloodstream (Fig. 107.3). The patient's skin and the person inserting the catheter are the most likely sources of infecting microorganisms. As previously mentioned, heavy skin colonization at the insertion site appears to be a predictor of increased risk of CVC infection. Strict adherence to hand washing and cutaneous antisepsis are the cornerstones of reducing CRBSIs. The use of 2% chlorhexidine for skin antisepsis is associated with a lower incidence of CVC-related local infection and CVC-related bacteremia compared with 10% povidone-iodine or 70% alcohol, and is therefore recommended for skin preparation by the CDC. Catheter location also plays a role in the risk of CVC infections. Whenever possible, femoral venous cannulation should be avoided as it is associated with significantly higher rates of infection than subclavian or internal jugular venous cannulation. Compared with the internal jugular vein, the subclavian vein may be associated with a lower infection risk, but these benefits must be weighed against the risk of mechanical injury to the patient during placement, especially by an inexperienced operator.

Maximal barrier precautions, including the use of a long-sleeved surgical gown, surgical mask, and large surgical sheet, have been shown to significantly reduce the risk of CRBSIs compared with less stringent precautions (sterile gloves and small drape). In fact, Raad and colleagues demonstrated over a sixfold reduction in the incidence of catheter-related septicemia when these maximal barrier precautions were implemented. Given the overwhelming data supporting the use of maximal sterile barrier precautions to prevent CRBSIs, the CDC recommends maximal barrier precautions for all central line insertions except in emergency situations.

Insertion sites for all intravascular devices must be inspected and palpated daily, as early recognition of local catheter-related infection may help prevent progression to bloodstream infection. Dressing care is a controversial aspect of CVC maintenance. Although most institutions use transparent CVC dressings for reasons of patient comfort and convenience, studies have repeatedly demonstrated higher rates of colonization and infection when transparent dressings are used compared with gauze dressings. More recently, the use of transparent dressings with chlorhexidine gluconate–impregnated sponges has become widespread, although there exists only weak data that they significantly reduce rates of infection. Current guidelines suggest the replacement of gauze CVC dressings every 2 days, and the replacement of transparent dressings every 7 days, to effectively reduce colonization and CRBSI.

The use of antimicrobial-impregnated catheters has been shown to significantly reduce the risk of CRBSIs. Currently, there are two main types of these antimicrobial catheters: chlorhexidine–silver sulfadiazine–coated catheters and minocycline-rifampin–coated catheters. The largest meta-analysis reviewed 11 studies with 2611 total CVCs and demonstrated summary odds ratios of 0.44 and 0.56 for catheter colonization and catheter-related infections, respectively, compared with uncoated CVCs. Although both classes clearly reduce CRBSIs compared with traditional uncoated catheters, the minocycline-rifampin catheters may provide a superior antimicrobial benefit compared with the chlorhexidine–silver sulfadiazine, although the evidence remains weak.

As the use of CVCs continues to rise, clinicians will continue to see complications from their placement. Although proper management of central line complications, including CRBSIs, is critical, institutions must focus chiefly on risk prevention. Continuing education for providers who insert these catheters, as well as those providing daily catheter management, is a cornerstone of effective risk reduction. Protocols such as central line bundles effectively limit adverse events, including infection, but total compliance remains elusive. The astute clinician must recognize the risks of complacency and strive to observe these important quality measures on a daily basis.

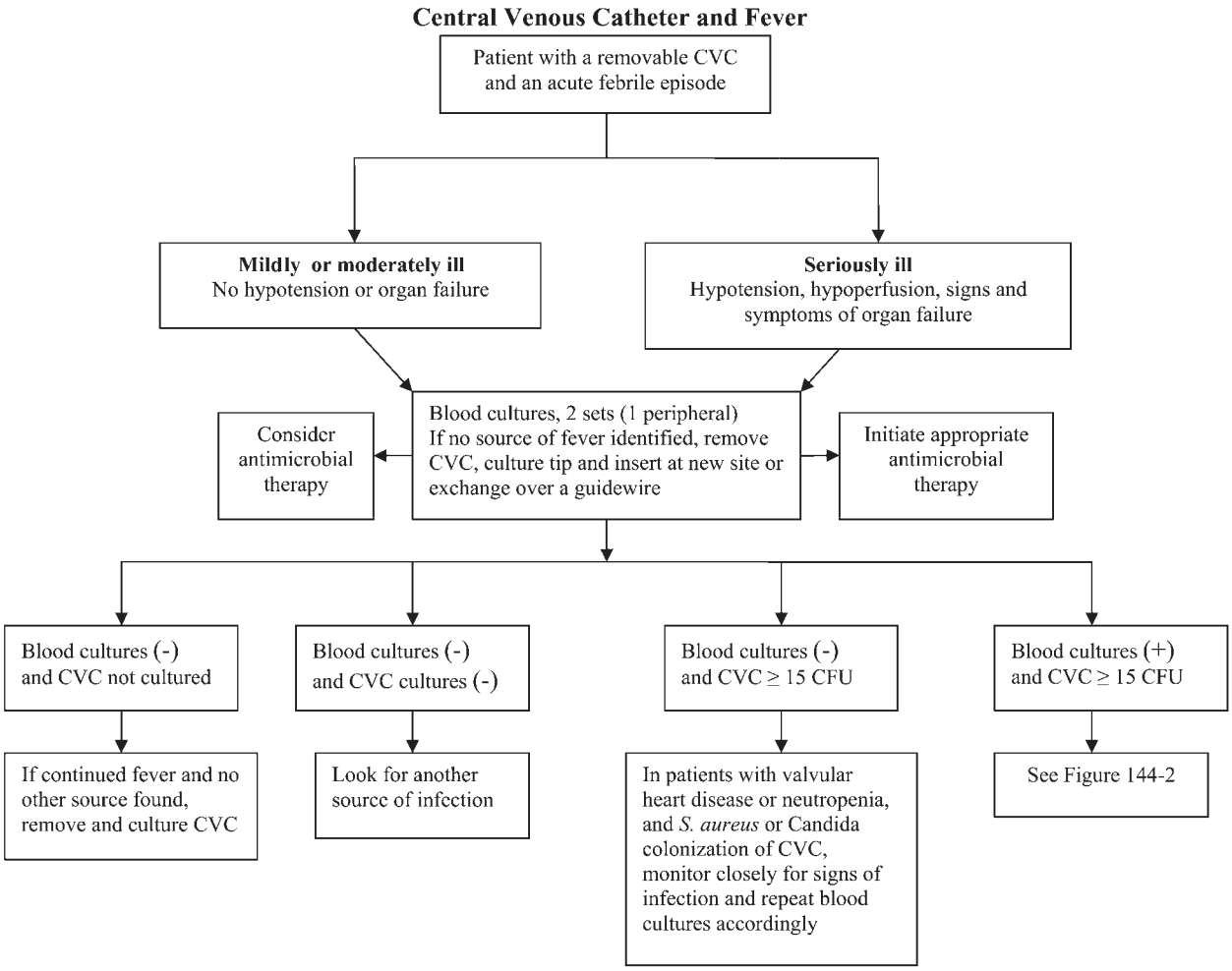

Fig. 107.1 Diagnosis of acute fever in a patient with suspected nontunneled central venous catheter (CVC) infections. *CFU,* Colony-forming unit. (Adapted from Mermel LA, Farr BM, Sheretz RJ, et al.: Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 32[9]:1249-1272, 2001.)

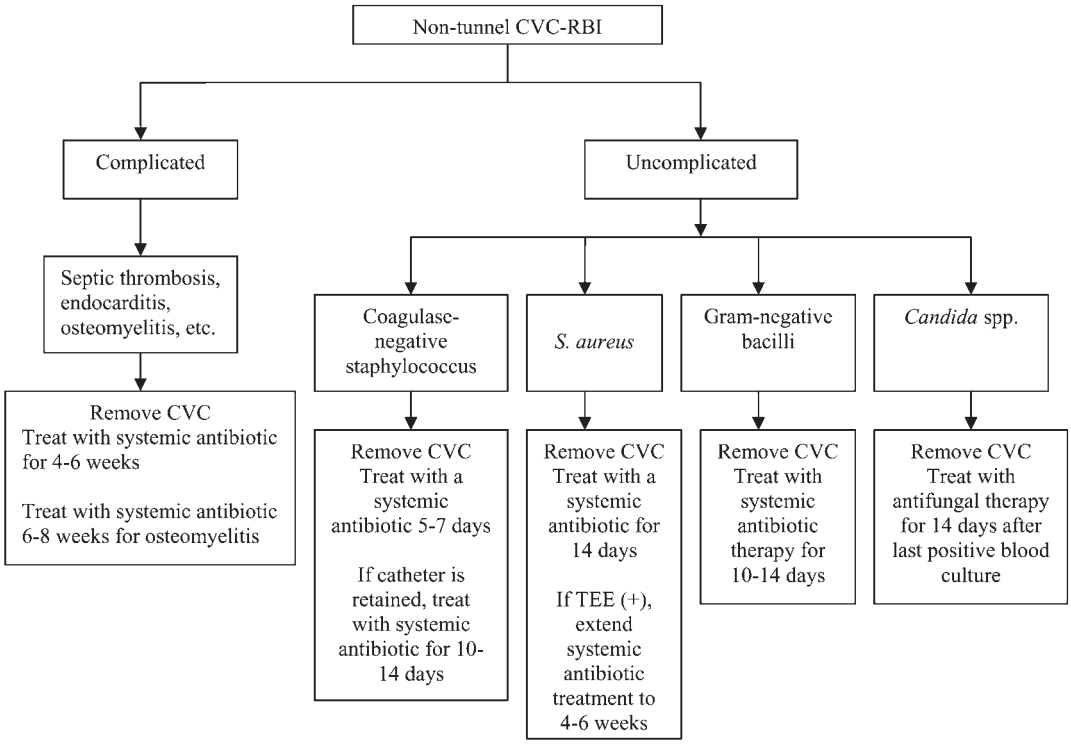

Fig. 107.2 Management of patients with nontunneled central venous catheter–related bloodstream infection (CVC-RBI). *TEE,* Transesophageal echocardiography. (Adapted from Mermel LA, Farr BM, Sheretz RJ, et al.: Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 32[9]:1249-1272, 2001.)

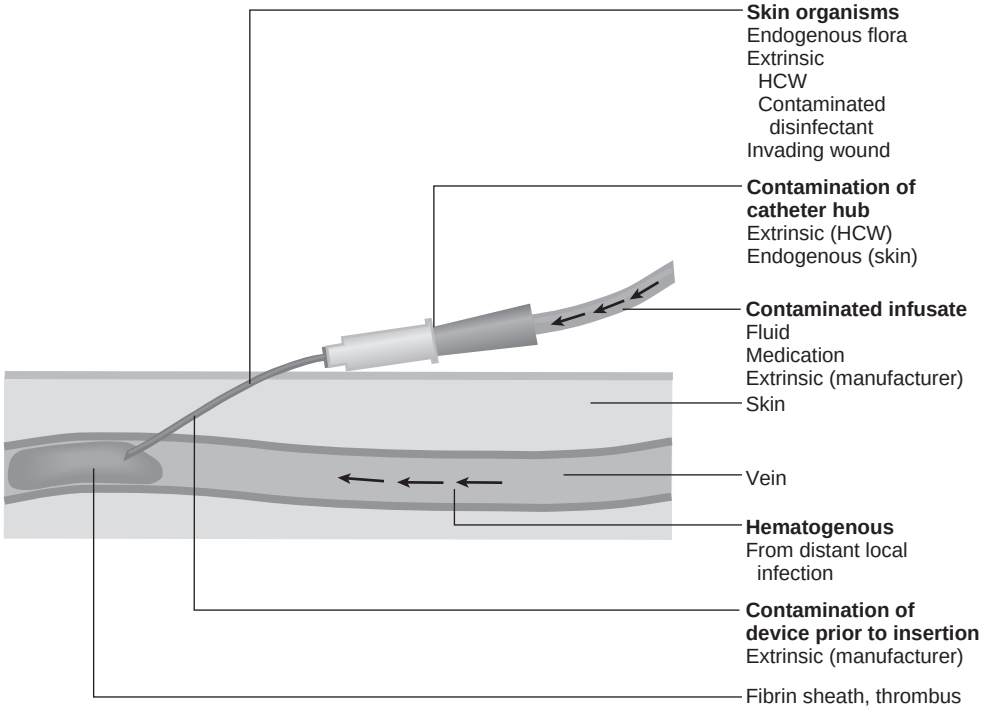

Fig. 107.3 Sources of intravascular cannula–related infection. The major sources are skin flora, contamination of the catheter hub, contamination of infusate, and hematogenous colonization of the intravascular device and its fibronectin-fibrin sheath. *HCW,* Health care worker. (From Maki DG: Infections due to infusion therapy. In Bennett JV, Brachman PS, editors: *Hospital infections,* 3rd ed. Boston, Little, Brown, 1992, pp 849–898.)

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108 Electrical Safety

Jeffrey J. Schwartz • Jan Ehrenwerth

Case Synopses

Macroshock
A 50-year-old man in good general health is undergoing laparoscopic cholecystectomy under general anesthesia. In the middle of the procedure, the anesthesiologist feels a tingle, and the patient develops ventricular fibrillation. Immediate resuscitation and defibrillation restore normal sinus rhythm. The case continues uneventfully after a faulty monitor is removed from service.

Microshock
In an adjacent room, a 60-year-old man with a temporary pacemaker is undergoing lower-extremity vascular bypass surgery. While the anesthesiologist is adjusting the pacemaker leads, the patient develops ventricular fibrillation. Immediate resuscitation and defibrillation restore normal sinus rhythm.

PROBLEM ANALYSIS

Definition

Electric shock occurs when a person becomes part of, or completes, an electrical circuit. To become part of the circuit, a patient must contact it at two points of different voltage. The contact need not be to a wire. Saline-soaked drapes conduct electricity, metal chassis can be energized due to faulty wiring, and leakage currents can flow between any two conductors.

The mechanism of electric shock can be divided into two categories:

- *Macroshock* refers to large amounts of current flowing through intact skin: 5 milliamperes (mA) is accepted as the maximum harmless current; 10 to 20 mA causes sustained muscle contraction; 100 to 300 mA causes ventricular fibrillation.
- *Microshock* refers to relatively small currents applied directly to the myocardium. The current density is very high, and as little as 100 microamperes (μA) can cause ventricular fibrillation. This current is too small to be sensed as a tingle by the operator.

Recognition

Recognition of an electrical problem involves not only the realization that an electric shock has occurred but also the awareness that the potential for electric shock exists. Electric shock frequently manifests in the operating room (OR) as sudden-onset ventricular fibrillation (VF) or ventricular tachycardia (VT). The anesthesiologist generally considers a cardiac origin for VF or VT, but the possibility of electric shock must always be kept in mind. Any perception of tingling represents a dangerous situation and must be investigated immediately. Microshock can be recognized only in an appropriate clinical setting, as there are often no premonitory findings.

Risk Assessment

All patients and personnel exposed to an environment with electrical equipment are at risk for macroshock. The OR is an especially hazardous place owing to the common use of saline solutions and the mechanical abuse to which electrical equipment is often subjected. Patients with an electrical connection to the heart, such as a saline-filled central venous catheter or pacemaker wires, are at increased risk for microshock.

The most common cause of macroshock is damaged or faulty wiring in electrical equipment. Line voltages (110 to 220 V) provided by the utility company are kept out of contact by insulated wires. Insulation can wear down and come into contact with a metal chassis or directly with the patient. The use of numerous safeguards (see later) means that for an electric shock to occur, the safeguards must have failed, been ignored, or been absent.

Implications

The implications of electric shock depend on the following:

- Amount of current
- Frequency of current
- Duration of current
- Whether current is applied directly to myocardium

The voltage used in most OR equipment is 110 or 220 volts (V). By Ohm's law, the current that flows (amperes) when 120 V is applied is 120 V/resistance measured in Ohms (Ω). The resistance of dry skin, about 120,000 Ω, allows 1 mA to flow. The resistance of wet skin, about 1200 Ω, allows 100 mA to flow, which is a potentially fatal shock. The frequency of electric power in the United States is 60 Hz, which, by coincidence, is the most dangerous frequency.

Electric current affects electrically excitable tissue. Electric current flowing through a nerve or muscle causes pain and contraction, much as a peripheral nerve stimulator does. Electric current flowing through the heart can cause VT or VF and death.

MANAGEMENT

Management of electric shock itself consists of appropriate resuscitation, including cardiopulmonary resuscitation and defibrillation. If it can be identified, the source of current and faulty equipment must be removed. Electric shock, however, is often a diagnosis of exclusion.

Line Isolation Monitor

In ORs that use isolated power (i.e., line isolation circuits), the line isolation monitor (LIM) gauges the integrity of such isolation. If the

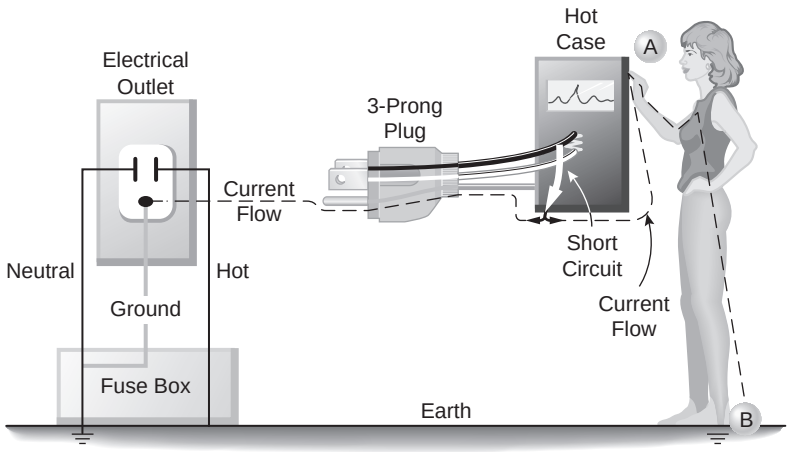

Fig. 108.1 When a faulty piece of equipment with an equipment ground wire is properly connected to an electrical outlet with a grounding connection, the current *(dashed line)* will preferentially flow down the low-resistance ground wire. An individual touching the case *(point A)* while standing on the ground *(point B)* will still complete the circuit; however, only a small part of the current will go through the individual. (From Ehrenwerth J, Seifert HA: Electrical and fire safety. In Barash PG, Cullen BF, Stoelting RK, et al., editors: *Clinical anesthesia,* ed 7. Philadelphia, Wolters Kluwer, 2013, pp 189–218.)

LIM alarm sounds, the power is no longer isolated, and electric current could flow in the event of another fault. The OR, however, is still safe, and all equipment will function normally. The usual cause of an LIM alarm is that faulty equipment has been plugged into an electrical outlet. Nonessential electrical equipment should be unplugged, one piece at a time, until the faulty one is identified. Less commonly, many pieces of apparently flawless equipment, but all with small leakage currents, may be simultaneously connected to the same circuit. Because of concerns with false alarms, the LIM threshold was changed from 2 to 5 mA.

Ground Fault Circuit Interrupters

In ORs that use ground fault circuit interrupters (GFCIs), faulty equipment may cause the GFCI to interrupt current to all devices serviced by it. The GFCI has a reset button to restore current, but the faulty piece of equipment must be identified and removed, or the GFCI will trigger again.

PREVENTION

Electric shock is an extraordinarily rare complication owing to the various safeguards undertaken by anesthesiologists, equipment manufacturers, and OR construction engineers.

Grounding

Most electrical equipment in the OR is grounded. This means that the chassis, metal case, and other internal components are all connected to a common earth ground via the third prong on the device's plug. This connection tends to shunt fault current safely to the ground rather than to a person in contact with the equipment (Fig. 108.1).

Power Isolation

Many ORs use isolated power to decrease risk. The utility company supplies grounded power, which means that one of the wires that carries electricity is also connected to the earth via a large, buried conducting rod. This provides additional safety in the distribution of electric power. However, it also means that, to one degree or another, all patients are already directly connected to one part of an electrical circuit. Only one additional connection, due to faulty wiring, is necessary for the patient to complete the circuit. An isolation transformer can convert the grounded power from the utility company to isolated power that has no direct connection to the ground (Fig. 108.2). Two contacts with faulty equipment, which is an unlikely situation, would now be necessary to cause electric shock.

Line Isolation Monitor

If isolated power is used, the integrity of the isolation must be monitored, or the system might accidentally become grounded without warning. The LIM continually measures the impedance between the power lines in the OR and the ground. The impedance should be (near) infinity. If it senses that the impedance is reduced and that the power is no longer isolated, an alarm sounds.

Ground Fault Circuit Interrupter

Some ORs use GFCIs to decrease risk. GFCIs continually monitor the difference in current going to and returning from an appliance. If the difference exceeds a certain threshold (typically 5 mA), presumably because some current is being shunted through a patient or OR personnel, the GFCI cuts off the power before any injury can occur. If the GFCI outlets were set up in a so-called daisy chain, one faulty piece of equipment could interrupt the power to several other normally functioning pieces of equipment. This would be potentially dangerous in an OR. Therefore the latest NFPA-99 code will require any GFCI in an OR to control only one outlet and not permit the "daisy chaining" of outlets.

Pacing Leads and Saline Monitoring Lines

Central venous catheters and pacemaker wires should be manipulated only with gloved hands and while touching nothing else to minimize the likelihood of the flow of small leakage currents.

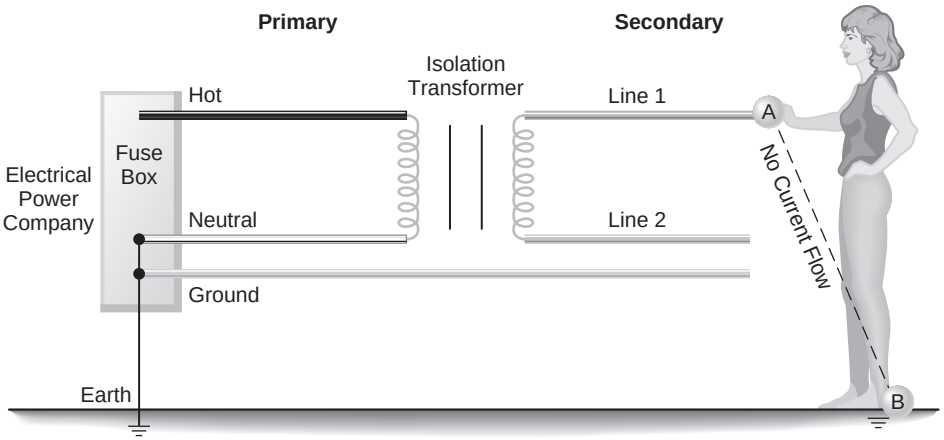

Fig. 108.2 A safety feature of the isolated power system (IPS). An individual in contact with one side of the IPS *(point A)* and standing on the ground *(point B)* will not receive a shock. In this instance the individual is not contacting the circuit at two points and thus is not completing the circuit. Point A is part of the IPS, and point B is part of the primary or grounded side of the circuit. (From Ehrenwerth J, Seifert HA: Electrical and fire safety. In Barash PG, Cullen BF, Stoelting RK, et al., editors: *Clinical anesthesia,* ed 7. Philadelphia, Wolters Kluwer, 2013, pp 189–218.)

Inspection

A program must be in place for regular inspection and testing of equipment by the biomedical engineering department so that faulty wiring, broken equipment ground wire, or excessive leakage currents can be detected before they pose a hazard.

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Fires in the Operating Room

109

Herodotos Ellinas

Case Synopsis

A 35-year-old man is brought to the operating room for an emergent awake tracheostomy after a gunshot wound to the face with facial and neck expanding hematomas. Chlorhexidine gluconate was used as antiseptic for the procedure, and the patient was draped with surgical towels while receiving 100% oxygen for preoxygenation.

PROBLEM ANALYSIS

Definition

A fire is a rapid, persistent, exothermic oxidation of a combustible substance (fuel) that releases heat and light energy; fire is usually accompanied by flame. Surgical fires are rare events with an incidence of 550 to 650 per year, defined as the burning of materials on or in a surgical patient. This is in contrast to an operating room (OR) fire, which is defined as any fire that occurs in the OR and does not necessarily involve the patient. Examples of fires that occur *in* the patient include airway fires, such as ignition of an endotracheal tube by a laser, and intraabdominal fires caused by sparks igniting bowel gas. An example of a fire occurring *on* the patient includes ignition of drapes, sponges, and other fuels by an electrosurgical instrument. Approximately 62% of surgical fires are located in the airway or on the face; 24% of surgical fires occur elsewhere *on* the patient, and 14% occur elsewhere *in* the patient. Though rare, surgical fires can cause serious injury or death, and in most cases they are preventable.

Despite the use of nonflammable anesthetics, fires still occur in the OR, and they are caused by the presence of the "fire triad": an ignition source, an oxidizer, and a fuel (Fig. 109.1). Contributing factors include ineffective communication, lack of training, misconception, and the improper use of medical devices. Common ignition sources are electrosurgical equipment (59%), lasers (32%), and other heat sources, including electrocautery, hot wire cautery, fiberoptic light sources, defibrillators, and high-speed burs. Oxidizers are substances that support the combustion of fuels and cause fires to burn more intensely and vigorously than they would in the absence of an oxidizer. Although not explosive, air, oxygen (O_2), and nitrous oxide (N_2O) are the common oxidizers found in the OR environment. There are a number of potential fuels in the OR, including surgical drapes, gowns, sponges, endotracheal tubes, skin-preparation solutions, hair, and skin. Some fuels are more likely to burn than others, and some fuels ignite only in the presence of an oxidizer.

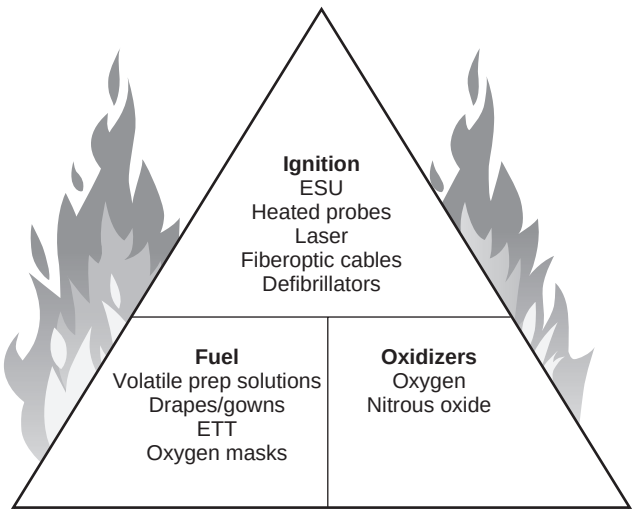


Fig. 109.1 Fire triad.

Fires in the OR are commonly associated with laser surgery of the airway. They usually result from ignition of an inadequately protected endotracheal tube (Fig. 109.2) or excessively long exposure of any combustible material placed in the airway (e.g., wet cotton pledgets) to a direct hit from the laser beam. The incidence of such fires is thought to be from 0.5% to 1%. Initially, most fires are located only on the external surface of the endotracheal tube; if unrecognized, they may lead to a blowtorch-like flame if the lumen of the tube is reached, allowing the O_2-rich contents of the tube to enhance the combustion process.

Based on a closed claims analysis, electrocautery was involved in 90% of fire claims and oxygen-enriched environment during monitored anesthesia care cases was a critical part in fires during operations of the head, neck, and upper chest. The risk of fire during surgery of the head, neck, and airway is increased because of the O_2-enriched atmosphere created by the O_2 and N_2O building up beneath the surgical drapes or in the oropharyngeal cavity. Depending on the procedure, the O_2-enriched atmosphere may be immediately adjacent to or encompass the operative site. There are several scenarios that can lead to the development of an O_2-enriched atmosphere. During head and neck surgery that is performed under local anesthesia, a mask, nasal cannula, or other open breathing system can spill O_2 near the patient's mouth, nose, or airway, and O_2 can collect under the drapes. O_2 leaking from an uncuffed endotracheal tube (ETT) can saturate the oropharynx during tonsillar surgery and similar procedures. Entering the trachea with an electrocautery device introduces an ignition source into the O_2-enriched atmosphere of the patient's tracheal airway, providing two of the three components of the fire triad, the ETT cuff providing the other one.

Fires can also result from a misdirected or reflected laser (laser light is reflected off metal surfaces) impinging any flammable material, such as the surgical drapes covering the patient. Many liquids

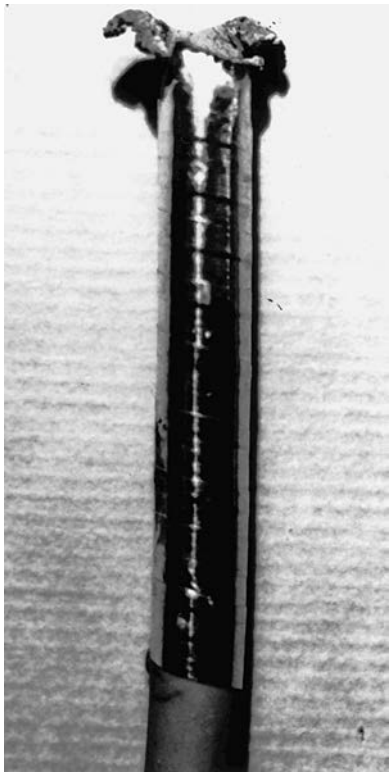


Fig. 109.2 Endotracheal tube damaged by a laser-induced airway fire. (Courtesy Dr. Allan Brown, University of Michigan Medical Center.)

BOX 109.1 Causes of Fires and Explosions in the Operating Room

- Electrocautery during head, neck, and upper chest surgery in an awake patient receiving supplemental O_2
- Electrocautery or laser use in the area of an endotracheal tube, particularly during tracheostomy formation
- Laser surgery of the esophagus or trachea
- Ignition of flammable skin-preparation solutions or bowel gas
- Exothermic reactions between potent inhaled anesthetics (e.g., sevoflurane) and desiccated CO_2 absorbent (Baralyme)

used in the OR (e.g., skin preparations, tinctures, degreasers, solutions in suture packs) contain flammable, volatile organic chemicals. Skin preparations may contain alcohol or acetone, and they are flammable until all the liquid has evaporated. Careless application may allow the solution to wick into the patient's hair, pool on the patient's skin, pool under the patient's body, or soak into linens. If the patient is draped before the solution is completely dry, vapors can be trapped and channeled to the operative field, where they may be exposed to a heat source and ignite. Likewise, bowel gas may be ignited by surgical diathermy. Intestinal gases contain varying concentrations of nitrogen, CO_2, hydrogen, methane, and O_2 and can be flammable in certain proportions. In addition, N_2O, and its exothermic breakdown components, O_2 and nitrogen, can make these gases even more flammable.

Fires and explosions resulting from the interaction of an ignition source, such as static electricity, and flammable or explosive anesthetic gases (e.g., ether, cyclopropane) are of historical interest only. However, the interaction of potent inhaled anesthetics with desiccated CO_2 absorbent can result in the production of carbon monoxide, extreme heat, smoke, fires, and explosions (Box 109.1).

Recognition

Sparks, pops, and flashes may indicate a situation conducive to ignition, combustion, or explosion. Most frank fires in the OR are heralded by flame and smoke. Anesthetists should monitor the CO_2 absorber for signs of excessive heat production and also monitor the relationship between the inspired sevoflurane concentration and the vaporizer setting. An unusually delayed rise or unexpected decline in the inspired sevoflurane concentration compared with the vaporizer setting may indicate exothermic sevoflurane degradation (see Box 109.3).

Risk Assessment

Whenever there is a high-energy source of ignition (e.g., electrosurgical unit [ESU] or laser), a potentially combustible material (e.g., endotracheal tube, alcohol-containing skin preparation, surgical drapes), and an oxidizer (O_2, N_2O, or both), there is the potential for combustion. The risk of fire is greater if the concentration of oxidizer is higher, so it is advisable to keep the inspired O_2 concentration as low as possible.

Any patient undergoing airway surgery is at risk of the consequences of an airway fire, regardless of whether a laser is used. The Silverstein Fire Risk Assessment Score can be used to ascertain the risk for a fire during an operation and allow for better communication to prevent unforeseeable outcomes. This assessment assigns points based on three factors (1 to 3 points): surgical site, open oxygen source, and ignition source presence. A high index of suspicion should be maintained at all times when anesthesia is being provided for laser surgery or during any airway surgery involving the use of electrocautery (e.g., tonsillectomy, tracheostomy). Risk of fire is also greater when surgery on the head and neck is performed under local anesthesia using an open breathing system (e.g., nasal cannula, facemask).

Exothermic reactions between CO_2 absorbents and sevoflurane are most likely to occur when the absorbent is desiccated. Most absorber fires occur during the first case on a Monday morning after a period of nonuse.

Implications

Most surgical fires, if appropriately handled, result in little or no harm to the patient. However, inappropriate handling can have catastrophic consequences, including death or a prolonged period of ventilation in the intensive care unit consequent to pulmonary edema, sepsis, or multiple organ failure syndrome. A late complication of airway fire is tracheal stenosis.

MANAGEMENT

OR staff should be educated about the nature, prevention, and extinguishing of surgical fires. Training, simulations, and drills should be used to familiarize staff with reactions and responses to surgical fires. Comprehensive training includes instruction in the rescue, alert, containment, and evacuation (RACE) response to large fires. Carbon dioxide fire extinguishers are recommended for this purpose and should be available in close proximity to the OR suites. Staff should be familiar with the location and operation of such firefighting equipment, medical gas supply shut-off valves, battery-powered portable lighting systems, ventilation systems, building alarms, and electrical systems.

A small fire can often be extinguished safely and simply by patting the flame with a gloved hand or towel. The area should be carefully

inspected to make sure that all the burning material has been extinguished. The OR team should assess the conditions that led to the fire and make efforts to prevent a recurrence.

Large fires on the patient demand immediate action to extinguish the fire, protect the patient from (additional) thermal injury, and treat the patient, if injured. A comprehensive response requires the collaboration of the anesthesiologist, surgeon, and OR nursing staff. The anesthesiologist should stop the flow of O_2 to the patient and be prepared to resume or assist ventilation with air. The surgeon or nurses should remove burning materials from the patient and extinguish them. This is especially important for paper drapes, which are impervious to water; dousing them with water may not extinguish a fire burning on the underside. It is also important to remove burned material from the patient, even if it is extinguished, to prevent further burn injury from the hot material. The surgeon should assess and treat the patient's injuries. If the fire is large enough, the extreme heat and smoke may force the OR team to evacuate the area. The team should attempt to rescue and evacuate the patient, but this may not be possible.

In the event of an airway fire or explosion, the anesthesiologist, surgeon, and nursing staff must act quickly and decisively to reduce injury to the patient. The ETT or other source of ignition or fire should be removed immediately from the patient, and ventilation must be stopped to stem the supply of O_2 to the flames. The ETT should be extinguished in a bucket of water, which should always be available during laser surgery. It should be inspected for missing parts that might have been left behind in the airway. The patient should be mask ventilated with 100% O_2 while anesthesia is continued. Bronchoscopy should be considered to evaluate damage to the lower airways if the fire was of the interior blowtorch type. The latter results from a transluminal burn in an ETT during the inspiratory part of the respiratory cycle. If airway damage is detected, the patient should be reintubated; if there is appreciable upper airway damage, low tracheostomy may be indicated. Appreciable lower airway damage caused by smoke inhalation and heat damage may require prolonged intubation and ventilation.

PREVENTION

The American Society of Anesthesiologists (ASA) OR fires algorithm (Fig. 109.3) outlines four measures in preventing OR fires:

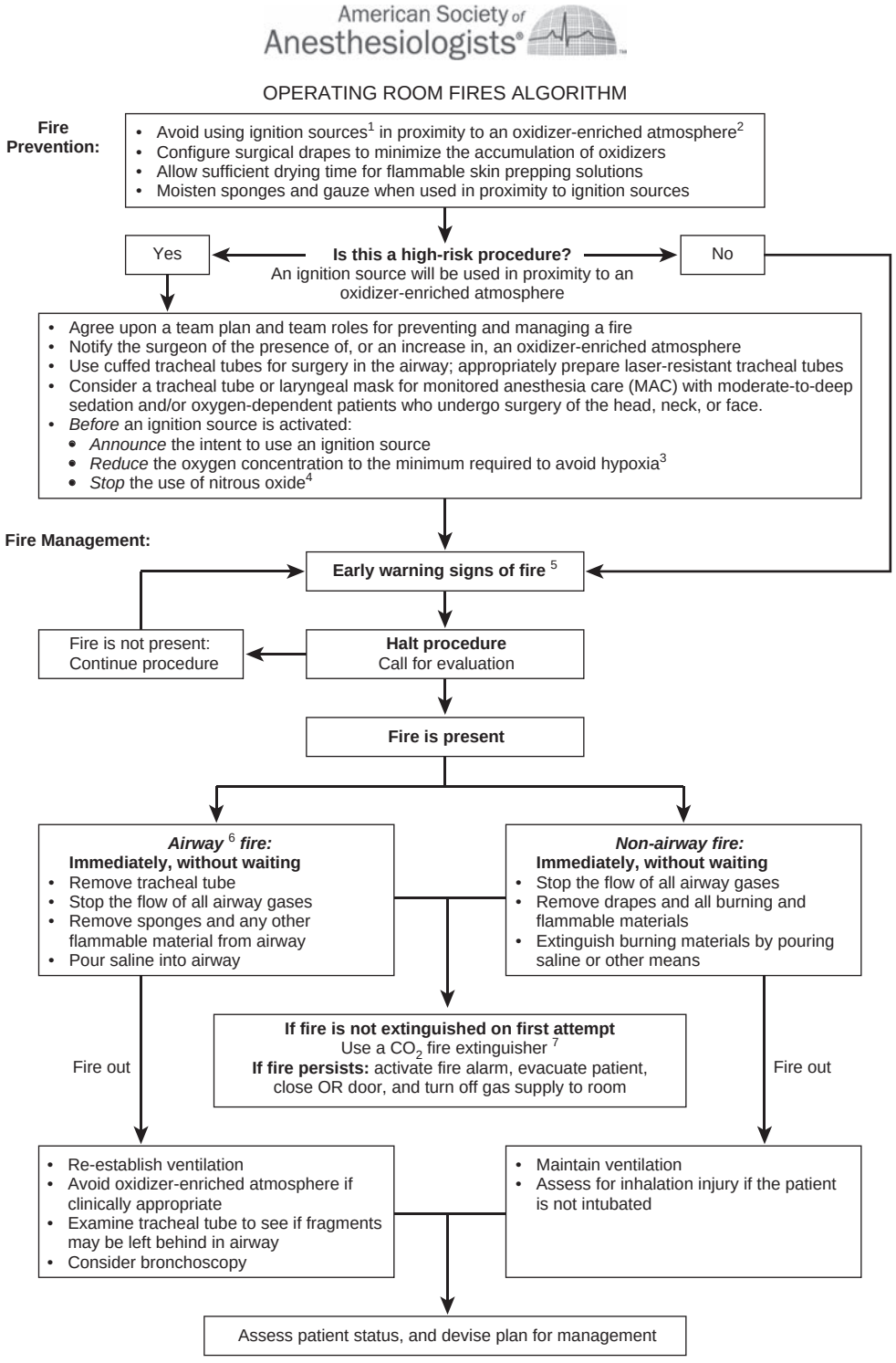
- Avoidance of ignition sources near oxidizers
- Placement of surgical drapes strategically to avoid trapping and accumulation of oxygen
- Use of adequate drying time for flammable skin preparations
- Use of moistened sponges and gauze near ignition sources

Anesthesiologists and other health care providers must consider the risk-benefit ratio of supplemental O_2 during monitored anesthesia care cases, particularly during surgical procedures involving the head and neck. Additional O_2 should be delivered as determined by clinical judgment, considering the patient's preoperative O_2 saturation as measured by room-air pulse oximetry. When higher concentrations of O_2 are necessary to maintain O_2 saturation, the OR team should be prepared for the potential for ignition and fire. Supplemental O2 needs to be discontinued for at least 1 minute before the use of an ignition source near the patient's head, neck, or airway. If an O_2-enriched atmosphere is unavoidable, the use of electrosurgical units should be minimized, and careful application of nonflammable drapes should be considered.

Skin preparations vary in alcohol content with the most recent recommendations for excellent antiseptic coverage using chlorhexidine gluconate with 70% isopropyl alcohol content, a highly flammable substance. Adequate drying time (per product insert—more than 3 minutes on hairless skin and up to 1 hour in wet hair) should be mandated in elective procedures and alternative products should be used in urgent/emergent procedures (e.g., Hibiclens, Betadine). In addition, modified draping techniques to avoid pooling of the preparation solution, careful placement of expiratory hoses, and use of an active scavenging system are warranted for high-risk procedures.

The risk of airway fires resulting from use of the surgical laser can be reduced by avoiding misdirection of the laser, both within and outside the operative field, and accidental operation when directed at the drapes or the patient's face (Box 109.2). The patient's eyes should be covered with wet gauze pads and not taped closed, because tape is combustible. During laser airway surgery, cuffed laser ETTs should be used. Although there are many commercially available ETTs for use with laser surgery, none is completely impervious to ignition.

OR fires require vigilance and thoughtful preparation by all involved. Precautionary measures regarding the use of ignition sources (e.g., ESU, electrocautery) are summarized in Table 109.1, and those of oxidizers (e.g., O_2, N_2O), fuels, and CO_2 absorbers are listed in Box 109.3, Table 109.2, and Box 109.4, respectively.



[1] Ignition sources include but are not limited to electrosurgery or electrocautery units and lasers.
[2] An oxidizer-enriched atmosphere occurs when there is any increase in oxygen concentration above room air level, and/or the presence of any concentration of nitrous oxide.
[3] After minimizing delivered oxygen, wait a period of time *(e.g.,* 1–3 min) before using an ignition source. For oxygen-dependent patients, *reduce* supplemental oxygen delivery to the minimum required to avoid hypoxia. Monitor oxygenation with pulse oximetry, and if feasible, inspired, exhaled, and/or delivered oxygen concentration.
[4] After stopping the delivery of nitrous oxide, wait a period of time *(e.g.,* 1–3 min) before using an ignition source.
[5] Unexpected flash, flame, smoke or heat, unusual sounds (*e.g.,* a "pop," snap or "foomp") or odors, unexpected movement of drapes, discoloration of drapes or breathing circuit, unexpected patient movement or complaint.
[6] In this algorithm, airway fire refers to a fire in the airway or breathing circuit.
[7] A CO_2 fire extinguisher may be used on the patient if necessary.

Fig. 109.3 ASA operating room fires algorithm. (From Apfelbaum JL, Caplan RA, Barker SJ, et al.: Practice advisory for the prevention and management of operating room fires. An updated report by the American Society of Anesthesiologists Task Force on Operating Room Fires. *Anesthesiology* 118[2]:271–290, 2013.)

BOX 109.2 Recommendations for Avoiding Laser-Induced Fires in the Operating Room

- Discuss plan of action for fire prevention during a time-out of a high-risk procedure
- Minimize Fio_2 (<0.3) and avoid N_2O
- Use a laser-resistant ETT with high-risk procedures
- Place the ETT cuff as far distally as possible in the trachea when performing oropharyngeal surgery (e.g., tonsillectomy)
- Use dyed saline in the cuff to allow early detection of ETT cuff rupture
- Use wet pledgets above the ETT cuff, but replace any string with wire
- Use jet ventilation or intermittent apnea

ETT, Endotracheal tube; *Fio_2,* fraction of inspired oxygen; *N_2O,* nitrous oxide.

TABLE 109.1 Precautions Regarding Ignition Sources in the Operating Room

Source	Management Guidelines
Electrosurgical unit (ESU)/ electrocautery	Use bipolar cautery to limit ignition potential Minimize supplemental O_2 concentration Place ESU electrode probes in holster or away from patient and surgical drapes when not in use Exercise caution when using ESU near locations where O_2 concentration is elevated (throat, mouth) Use appropriate ESU modes for cutting; avoid arcing coagulation modes Soak gauze/pledgets in saline when used near cautery Avoid eschar buildup on electrode tip; clean buildup off as needed
Surgical lasers	Limit laser output to lowest acceptable power density and pulse duration Test-fire laser onto a safe surface Place laser in standby mode when not in use Activate laser only when tip is under surgeon's direct vision Allow only the person using the laser to activate it Deactivate laser and place it in standby mode before removing it from the surgical site Pass the laser fiber through the endoscope, when performing endoscopic laser surgery, before introducing it into the patient Use appropriate laser-resistant tubes during upper-airway surgery
Fiberoptic cables and light sources	Ensure fiberoptic connections are complete before activating the light source Deactivate the light source before disconnecting the scope from the light cable
Defibrillators	Use according to the manufacturer's instructions Avoid discharging in O_2-enriched atmosphere Train operators in the use of defibrillation equipment Use disposable adhesive defibrillator pads instead of nondisposable paddles whenever possible Maximize contact between the patient and the surface of the pad or paddle Use the appropriate conduction gel, when using paddles

BOX 109.3 Precautions Regarding Oxidizers (Oxygen and Nitrous Oxide)

- Use air or O_2 with an Fio_2 less than 30% in open breathing systems
- Identify and ameliorate O_2-enriched environments
- Tent drapes around the patient's head and neck when supplying supplemental O_2 in an open breathing system
- Discontinue supplemental O_2 for 1 min before using ESU near the head and neck
- Use wet gauze or sponges with uncuffed endotracheal tubes to minimize leak of O_2 into oropharynx, during oropharyngeal surgery
- Turn O_2 off when not in use
- Avoid use of nitrous oxide (N_2O); a mixture of N_2O and O_2 is not less dangerous than pure O_2; N_2O diffusion into bowel gas introduces additional oxidizer to support combustion of hydrogen and methane

ESU, Electrosurgical unit; *Fio_2,* fraction of inspired oxygen.

TABLE 109.2 Precautions Regarding Fuel Sources in the Operating Room

Source	Management Guidelines
Flammable skin preparations (degreasers, acetone, alcohol) and ointments (collodion, petroleum jelly, tincture of benzoin, aerosols, paraffin)	Minimize use of high alcohol content skin preparations Apply skin preparations carefully; do not allow them to soak into hair or linens; avoid pooling on or under patient Wait for skin preparations to dry completely before draping patient
Linens, drapes, gowns, masks, hoods, caps	All are flammable, even if labeled "flame resistant" Use wet drapes and towels adjacent to laser site Use incise drapes to isolate surgical field from fuels and oxidizers Use wet gauze sponges when possible
Anesthesia components (endotracheal tubes, masks, nasal cannulae, tape, blood pressure cuffs)	Use cuffed endotracheal tubes when possible Use laser-resistant tubes for upper-airway laser cases Fill cuff with methylene blue-dyed saline for airway laser cases (to indicate breach in cuff) Protect cuff with wet pledgets for airway laser cases
Patient hair	Cover hair near the operative site with sterile surgical water-based jelly to prevent it from igniting
Intestinal gases	Avoid nitrous oxide Avoid mannitol-based bowel preparations Dilute intestinal gases with an inert gas, if indicated

BOX 109.4 Precautions Regarding Carbon Dioxide Absorbents and Halogenated Anesthetics in the Operating Room

- Alert anesthesia personnel, including technicians and providers, to the nature of this hazard
- Develop anesthesia machine setup and maintenance protocols that ensure absorbents do not become desiccated and are replaced regularly
- Minimize or eliminate gas flow through absorbent between uses, and turn anesthesia machine off at day's end, to avoid desiccation
- Replace absorbent if its hydration status is in question
- Periodically monitor temperature of CO_2-absorbent canisters
- Monitor relation between inspired sevoflurane concentration and vaporizer setting; an unusually delayed rise or unexpected decline in inspired sevoflurane concentration compared with the vaporizer setting may indicate exothermic sevoflurane degradation
- Consider using alternative absorbents that are free of strong alkali compounds (e.g., Amsorb)

ACKNOWLEDGMENT

The author wishes to thank Dr. Paul E. Kazanjian and Dr. Anthony R. Doyle for their contributions to the previous edition of this chapter.

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Flowmeters

110

Robert G. Loeb

Case Synopsis

Anesthesia induction has just been completed on a healthy 20-year-old man undergoing inguinal herniorrhaphy. Gas flows are set to 1 L/min of oxygen (O_2) and 2 L/min of nitrous oxide (N_2O). The O_2 saturation begins to fall as the O_2 analyzer alarms (Fig. 110.1). Actuating the O_2 flush valve resolves the problem temporarily.

PROBLEM ANALYSIS

Definition

Flowmeter malfunction is a rare cause of anesthesia machine failure, because modern anesthesia machines are designed to prevent many flowmeter problems. Although the last flowmeter incident was published in 2004, flowmeter malfunctions are still occasionally reported to the U.S. Food and Drug Administration (FDA).

Patients have died from breathing hypoxic gas mixtures administered from erroneously set flowmeters. Poor flowmeter design was sometimes a contributing factor because, in the past, anesthesia machines were designed with two flowmeter assemblies connected in parallel for each gas. Improved flowmeter design now decreases the chance of user error. Additionally, since the 1980s all anesthesia machines have a proportioning device that restricts the relative flow rates of O_2 and N_2O to prevent erroneous administration of hypoxic gas mixtures (see Chapter 117). For example, anesthesia machines manufactured by Dräger are equipped with an O_2-proportioning regulator called the Oxygen Ratio Controller, and those manufactured by GE Healthcare are fitted with a mechanical linkage called the Link-25. Both are generally reliable, but occasional malfunctions of the Link-25 have been reported.

Flowmeter assemblies consist of a flow control valve with an associated flowmeter (Fig. 110.2). A *traditional* flowmeter assembly consists of a mechanical flow control valve and one or two glass flowmeter tubes, connected in series, for each compressed gas. *Electronic* flowmeter systems have an electronically controlled valve and an electronic flowmeter for each gas, and the user controls gas flow via a computer interface. In anesthesia machines with *hybrid* flowmeters, each gas has a mechanical flow control valve and an electronic flowmeter.

Mechanical flow control valves are variable resistance needle valves. Turning the valve in a counterclockwise direction increases gas flow by decreasing the resistance across the valve. The resultant flow depends on the valve resistance and the pressure differential between valve inlet and outlet; therefore upstream or downstream pressure fluctuations will cause variations in flow. Flow is manually adjusted based on readings of the associated flowmeter.

Electronic flow control valves are variable-resistance valves that are electrically powered and electronically controlled. The user turns an electronic knob in a clockwise direction, or uses another onscreen control, to increase the desired gas flow rate. A microprocessor then decreases the resistance of the valve and continuously adjusts it so that the difference between the measured flow rate and set flow rate is zero. Some systems can be configured to control the total flow rate and set O_2 concentration.

Patients have died when a flowmeter has been connected directly to an endotracheal tube without an interposed gas outlet path. In an analysis of equipment-related closed claims, misuse of supplemental oxygen delivery tubing outside of the operating room accounted for 9 of 40 cases, each of which resulted in pneumothorax. This can happen, for instance, if oxygen-delivery tubing is directly connected to the endotracheal tube, or if a T-piece outlet is intentionally or accidentally blocked. It is critical that all clinicians understand that the maximum outlet pressure of a flowmeter is equal to its inlet pressure, which is nominally 50 PSI. Although this number may seem small, remember that it equates to about 3500 cm H_2O because 1 PSI is equal to about 70 cm H_2O.

Anesthesia machine glass flowmeter tubes, and wall-mounted oxygen or air flowmeters, consist of a float within a tapered glass tube whose inner diameter is larger at the top than at the bottom. To be

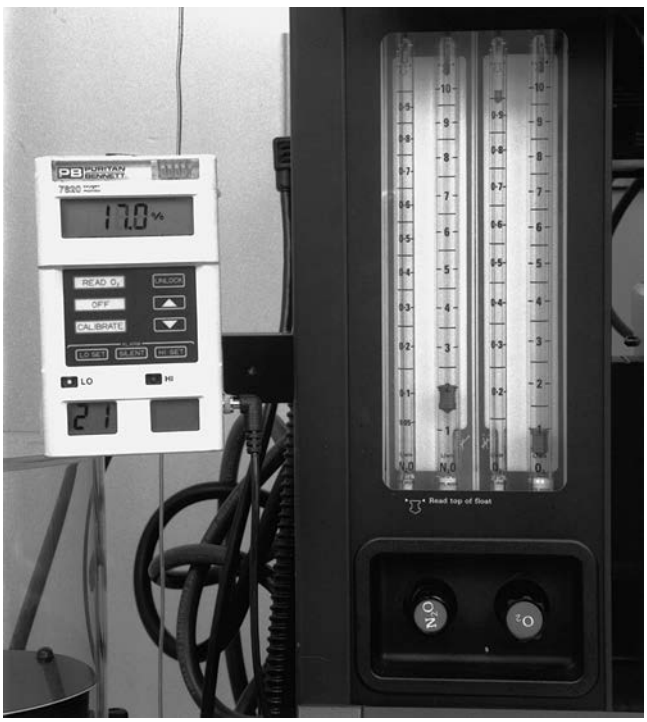

Fig. 110.1 The inspired oxygen concentration is dangerously low and is not consistent with the flowmeter settings.

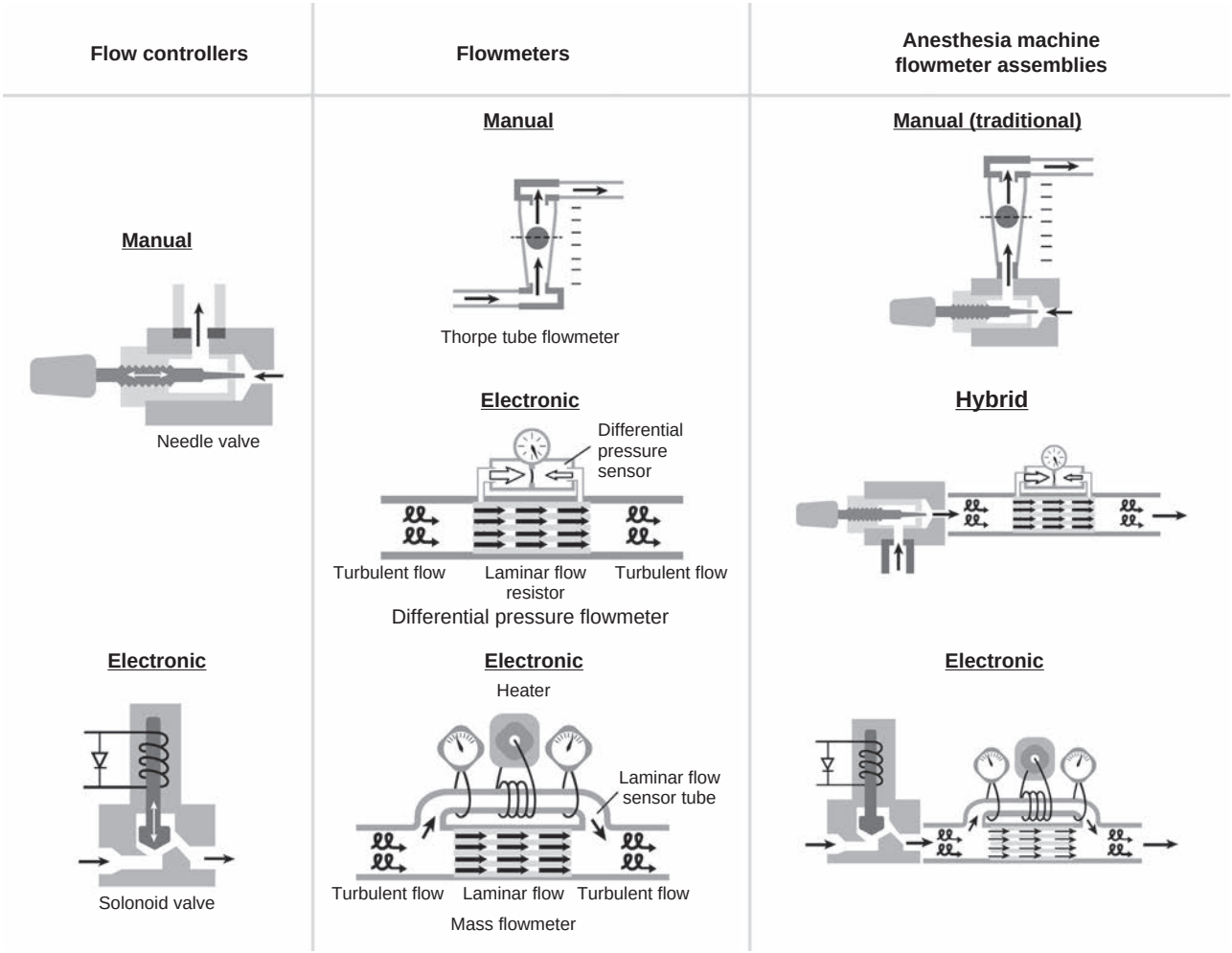

Fig. 110.2 Three types of anesthesia machine flowmeter assemblies: traditional (manual), hybrid, and electronic. Traditional flowmeter assemblies consist of a manual needle valve and a downstream Thorpe tube flowmeter. Some new anesthesia machines have completely electronic flowmeter assemblies, each consisting of an electrically powered and electronically controlled valve coupled with an electronic flowmeter. Other modern anesthesia machines have hybrid flowmeter assemblies where gas flow is controlled using manual needle valves, but the flows are measured and displayed electronically. There are various types of electronic gas flowmeters, such as differential pressure flowmeters that measure the pressure drop of the gas as it passes across a flow resistor and mass flowmeters that measure the convective heat transfer of a gas.

accurate, the flowmeter tube must be in a vertical position, and the movement of the float must not be restricted by static electricity, water, or dirt within the tube. Flowmeters are calibrated as a matched tube and float set; replacement of either component can result in significant inaccuracy. Modern glass flowmeters are permanently sealed to prevent mistakes in matching the float and tube during maintenance. Each flowmeter is calibrated for a specific gas, and is not accurate for measuring the flow of any other gas. To prevent mistakes during anesthesia machine maintenance, modern flowmeters are indexed so that they fit only into the housing for the appropriate gas. To protect flowmeter tubes from breakage, they are housed behind a plastic shield.

Increasingly, anesthesia machines have electronic flowmeters instead of glass flow tubes. Advantages of electronic flowmeters include improved reliability and reduced maintenance, improved precision and accuracy at low flows, and the ability to transmit flow data to an electronic record and automatically control gas flows. A number of technologies can be used to electronically measure flow, including mass flow and differential pressure. Mass flow sensors operate on the principle of heat transfer, measuring the energy required to maintain the temperature of a heated element in the gas-flow pathway. Each sensor is calibrated for a particular gas, because every gas has a different specific heat index. Differential pressure flowmeters measure the pressure difference across a fixed-flow resistor. Again, each sensor is calibrated for a particular gas, because every gas has a different density and viscosity. Gas flows are shown on dedicated LED displays or on the main anesthesia machine's flat-panel display. Displays on the anesthesia machine's flat panel can be configured as numeric or graphic and may also be configured to show individual flow rates or calculated total flow rate and set O_2 concentration. There have been no reported problems with the electronic flowmeters, except for the loss of calibration factors due to RAM battery failure.

Recognition

A malfunctioning flowmeter is most easily detected during the anesthesia machine preuse checkout. The American Society of Anesthesiologists (ASA) has developed a checkout procedure (which can be downloaded from http://asahq.org/resources/clinical-information/2008-asa-recommendations-for-pre-anesthesia-checkout) that detects

most serious anesthesia machine malfunctions. *Item #8: Verify that there are no leaks in the gas supply lines between the flowmeters and the common gas outlet* detects a missing, leaking, cracked, or broken flowmeter. Visual inspection of the flow tubes may reveal a cracked or broken flowmeter. A float that sticks to the tube can be detected by adjusting the flow of all gases through their full range, while checking for smooth operation of the floats. It should be noted, however, that it is unlikely that an improperly calibrated flowmeter would be detected by the ASA anesthesia apparatus checkout.

During intraoperative use, a malfunctioning flowmeter results in different-than-expected gas concentrations in the breathing circuit (e.g., higher or lower concentrations of O_2 than dialed) or unexpected flow rates from the anesthesia machine to the breathing circuit. There is no monitor of the gas flow emanating from the anesthesia machine, although in extreme cases the practitioner may notice that the reservoir bag or ventilator bellows is not filling normally. The respiratory gas analyzer at the Y-piece and the O_2 analyzer in the breathing circuit are the closest downstream monitors of the gas concentrations coming from the anesthesia machine. The readings on these monitors, however, rarely match the settings on the anesthesia machine, because of rebreathing. The discrepancy between dialed concentrations and breathing circuit gas concentrations is especially apparent during low gas flows. If a flowmeter problem is suspected, the anesthesia practitioner can sample gas from the fresh gas hose to check the composition of gases flowing from the anesthesia machine; if this is not possible, the gas concentrations in the breathing circuit can be checked at high flow rates.

Risk Assessment

Anesthesia machine malfunction is an uncommon cause of critical events. For instance, only 4 of the first 2000 incidents reported to the Australian Incident Monitoring Study involved anesthesia machine failures. Two of these incidents, however, resulted from flowmeter problems and were considered potentially life threatening. The FDA database of medical device reports contains occasional reports of flowmeter malfunctions. Most of these consist of tubing disconnections between the flowmeter and the gas outlet, or cracked flowmeter tubes, typically in older stand-alone or auxiliary oxygen flowmeters.

Regular maintenance of the anesthesia machine is necessary to prevent malfunction due to wear. Ironically, some anesthesia machine failures have been attributed to mistakes made during maintenance. The clinician should therefore be vigilant for equipment problems when using a machine that has recently been serviced. Old anesthesia machines may pose the greatest safety hazard. A survey of anesthesia machines in Iowa found that machines ranged from 1 to 28 years old (average, 8 years). Although older machines did not malfunction more often than newer ones, they often lacked safety features and essential monitoring (e.g., O_2/N_2O flow ratio alarms, O_2 analyzers). Thus clinicians should be wary of older machines without these features.

Implications

Flowmeter malfunction can present as a breathing circuit leak or an inappropriate gas composition within the breathing circuit. Although gas cannot flow retrograde from the breathing circuit to a broken flowmeter, leakage of gas from a broken or missing flowmeter can quickly lead to insufficient gas volume in the breathing circuit. This manifests as an empty breathing bag or ventilator bellows and can lead to a misdiagnosis of the malfunction as a breathing circuit leak or disconnection, because these malfunctions occur more commonly. A large leak from the flowmeter assembly is a serious problem because it prevents effective ventilation of the patient.

Flowmeter inaccuracy or a small leak from a cracked O_2 flowmeter can cause the anesthesia machine to dispense a hypoxic gas mixture into the breathing circuit. The O_2 analyzer is designed to detect such an occurrence. Other flowmeter problems are not liable to lead to patient injury. Leakage of a gas other than O_2 should not result in a hypoxic mixture, because flowmeters are arranged to prevent the preferential loss of O_2 in such a situation.

MANAGEMENT

An O_2 flush should temporarily rectify loss of circuit volume or hypoxia due to a flowmeter problem. The O_2 flush bypasses many internal components of the anesthesia machine, including the flowmeter assembly. Also, retrograde leakage of O_2 after a flush is prevented on most anesthesia machines by a one-way valve (or a vaporizer that incorporates a one-way valve).

When serious flowmeter malfunction is detected intraoperatively the patient should be ventilated with an alternative system, such as an Ambu bag, while the defective anesthesia machine is replaced. The defective machine should be removed from service until it has been repaired and thoroughly inspected by a trained technician.

PREVENTION

Most flowmeter failures are preexisting. If so, a thorough preuse check of the anesthesia machine should prevent most critical events due to flowmeter malfunction. Many problems, including a missing, leaking, cracked, or broken flowmeter, can be detected with the ASA-recommended anesthesia machine checkout procedure. Flowmeter calibration, however, is not verified during this checkout procedure.

Although many equipment-related malfunctions are prevented by routine preuse inspection, anesthesia practitioners are not proficient in detecting anesthesia machine faults. For instance, anesthesiologists and certified registered nurse anesthetists detected an average of only 44% of intentionally created anesthesia machine faults at a conference exhibit. Only 15% of participants detected that the O_2 flowmeter was miscalibrated to deliver 10% of the indicated flow. Checklists do not necessarily improve performance either. Anesthesiologists detected 26% of anesthesia machine faults when they used their own checkout methods, and 29% of the faults when they used the FDA checkout procedure (1986 version). However, they were not instructed in the use of the FDA checklist, and intensive instruction can improve the performance of apparatus checkout procedures.

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Intracranial Pressure Monitoring

111

Adrian Pichurko • Paul Smythe

Case Synopsis

An 18-year-old man has open long bone fractures and severe traumatic brain injury due to a motor vehicle accident. His Glasgow Coma Scale score is 6, and a computed tomography scan of the head reveals diffuse cerebral edema. An intraventricular monitor reveals a pressure of 30 mm Hg. Treatment for increased intracranial pressure is initiated, and the patient is transferred to the operating room for treatment of the long bone fractures.

PROBLEM ANALYSIS

Definition

Intracranial pressure (ICP) is the pressure or force exerted within the rigid cranial vault by the intracranial contents. In normal adults the intracranial contents comprise brain, 80%; blood, 10%; and cerebrospinal fluid (CSF), 10% of volume.

Normal ICP is approximately 5 to 13 mm Hg (7 to 18 cm H_2O). In patients who do not have intracranial pathology, the intracranial contents are considered to have normal elastance. This means that small increases in intracranial volume do not result in increased ICP. According to the Monro-Kellie hypothesis, this occurs because when the volume of one compartment increases, the volume of another compartment decreases by an equal amount, leaving the total volume unchanged. This type of compensation is necessary because all three elements of the intracranial contents are almost incompressible. Reduced elastance occurs when the intracranial volume approaches that of the intracranial space. In this case a small increase in intracranial volume creates a dramatic and possibly life-threatening increase in ICP.

The diagnostic and therapeutic use of ICP monitors has not changed appreciably in the last 5 years. Most centers consider 20 mm Hg the upper limit of normal for ICP, although others use 15 mm Hg for this cutoff. ICP above 15 to 20 mm Hg is considered intracranial hypertension (ICH; see Chapter 150). Treatment for ICH is often initiated at 20 to 25 mm Hg. Cerebral perfusion pressure (CPP) should be considered when managing patients with ICH. CPP is defined as mean arterial blood pressure minus ICP, and it is the physiologic variable that defines the pressure gradient driving cerebral blood flow and delivery of oxygen and metabolites. It is therefore closely related to cerebral ischemia. The optimal level at which CPP should be maintained is unclear, but several clinical studies suggest that keeping CPP greater than 70 mm Hg is associated with a substantial reduction in death rates and improved quality of survival. Further, it is likely to enhance ischemic brain perfusion after severe traumatic brain injury (TBI). In most cases of TBI, CPP is manipulated by normalizing intravascular volume or inducing systemic hypertension.

Recognition

ICP monitoring can assist in the diagnosis and treatment of ICH. All ICP monitoring systems have certain characteristics in common, beginning with physical attachment to the system being monitored. This connection requires a watertight fluid interface between the ICP monitor and the intracranial compartment and consists of rigid tubing leading to a flexible membrane. Because ICP is being monitored, the compartment must be sealed. Any leakage would be indicative of serious underlying pathology that must be addressed. This could range from CSF leakage (best-case scenario) to cerebral herniation (worst-case scenario). With no leakage, any change in ICP leads to some degree of deformation of the flexible membrane contiguous with this space.

Construction

The deformed membrane is coupled to a transducer. Regardless of the coupling interface (i.e., rigid tubing), its role is to accurately transmit any membrane deformations occurring with each ICP pulsation. A transducer converts these coupled or transmitted pulsations to an electrical signal, which is then amplified to enhance the signal generated by the transducer for display purposes. The display is essentially a voltmeter. It may be connected to an oscilloscope or stylus recorder to display the ICP waveform and pressure changes. ICP monitoring systems differ mainly according to the type of coupling between the deformed membrane and transducer, and according to the anatomic location at which each system is placed.

Zeroing

All ICP monitoring devices must convert ICP to some voltage for electronic display. This relationship is expressed as the equation $y = mx + b$, where y is the voltage, x is the pressure, and m is the ICP curve slope. The characteristics of the transducer are such that there is a linear relationship between voltage and pressure, or m (discussed further under "Calibration"). It would be optimal for a monitor to read zero voltage when the pressure applied to the transducer is equal to zero. Adjusting the b term of the equation to zero so that

the relation becomes $y = mx$ accomplishes this and is called *zeroing*. Zeroing means that if the transducer produces a voltage when the pressure being measured is zero, it must be balanced or offset by an internally applied voltage of the opposite sign. The zero pressure of biologic pressure monitoring systems is always the ambient atmospheric pressure. Zeroing is achieved by opening a stopcock or valve on the transducer to sense the ambient or room air pressure as zero. Modern systems require pushing a zeroing button, and this setting is automatically remembered. Zeroing the transducer (ICP or any other pressure transducers) is important because an error in this step affects all subsequent pressure readings.

Transducer Location

With ICP monitoring devices, the transducer can be located either externally or at the catheter tip inside the cranium. External transducers can be rezeroed at any time after placement of the ICP monitor. Monitors that have catheter-tip pressure transducers must be zeroed before placing the catheter into the intracranial compartment. Once placed, most catheter-tip pressure transducers cannot be rezeroed, with the exception of emerging Air Pouch transducing technology that allows automatic rezeroing.

Calibration

Calibration is accomplished by adjusting the m term, or slope, of the equation $y = mx + b$. The control on ICP amplifier systems that adjusts the slope is labeled "calibration," "gain," "amplification factor," or "slope." Most contemporary transducers have a small microprocessor incorporated within the transducer that is precalibrated. They produce a small constant voltage proportional to the degree of compression, termed the *calibration factor.* The most common calibration factor is 200. At 200 mm Hg, this means that the transducer may put out more or less voltage at a given pressure than it should. The calibration can be checked by applying a known pressure to the transducer and adjusting the monitor display to read the same as the known pressure applied. It is advised that calibration of all transducers be periodically cross-checked.

Drift

When zero and gain settings change across time, this is referred to as *drift.* Because no transducer can be perfect, all transducer-amplifiers drift to some extent.

Transducer Types

Two different types of transducers are used in contemporary ICP monitors. The first, the *strain-gauge transducer,* consists of a membrane physically attached to a magnet that moves with pulsations within a series of coils. As the magnetic flux changes across the coils, a current is induced that is proportional to the degree and frequency of magnet movement. This current is proportional to the pressure applied to the strain-gauge transducer. However, the most commonly used transducer is a highly specialized version of the strain-gauge transducer referred to as a *piezoelectric transducer.* This is a highly standardized ceramic crystal that generates voltage when a force is applied. In most piezoelectric systems, the transducer structure, analogous to the deformable membrane, is the crystal itself. The preset calibration factor is generally 200.

The second class of transducers is the *fiberoptic transducer.* It uses a laser beam to couple membrane movement with the electrical component of the transducer. This system still depends on a membrane being distorted by intracranial compartment pressure variations. The transducer side of the membrane is reflective (mirrored), with the laser beam directed to this side of the membrane. When the membrane moves, it reflects the laser light beam at an angle that diverges from that of any incident light. This reflected light signal is related to the incident light signal to generate a quantitative estimate of the membrane distortion caused by altered ICP. A signal is generated for amplification and is proportional to the movement of the membrane.

TABLE 111.1 Intracranial Spaces Used to Monitor Intracranial Pressure

Space	Method of Pressure Transduction	Cerebrospinal Fluid Drainage	Recalibration
Intraventricular	Fluid-coupled external strain gauge	+	+
	Fluid-coupled strain-gauge catheter tip	+	+
	Fluid-coupled fiberoptic catheter tip	+	+
Parenchymal	Strain-gauge catheter tip	–	–
Subarachnoid	Fluid-coupled external strain gauge	–	+
Subdural	Strain-gauge catheter tip	–	–
	Fiberoptic catheter tip	–	–
	Fluid-coupled external strain gauge	–	+
Epidural	Fluid-coupled external strain gauge	–	+
	Pneumatic	–	+

+, Possible or necessary; –, not possible or not necessary.

Sources of Error

External transducers are accurate and can be recalibrated. They must be maintained at a fixed reference point relative to the patient's head to avoid measurement error. Internal transducers (catheter-tip strain-gauge or fiberoptic devices) are calibrated before intracranial insertion and cannot be recalibrated once they are placed (i.e., without a separate intraventricular catheter). Therefore if the device measures drift, there is the potential for inaccurate ICP measurements, especially if the ICP monitor is used for several days.

Ventricular Intracranial Pressure Monitoring

The intracranial spaces most frequently monitored are intraventricular, intraparenchymal, subarachnoid, subdural, and epidural (Table 111.1). Ventricular ICP monitoring is considered the gold standard for comparing the accuracy of ICP monitors in other intracranial compartments. It also has the therapeutic benefit of draining CSF for the treatment of ICH. ICP monitoring devices have been ranked based on their accuracy, stability, and ability to drain CSF. A ventricular catheter connected to an external strain-gauge transducer or catheter-tip pressure transducer device is the most accurate and reliable method of monitoring ICP and allows for therapeutic CSF drainage. Parenchymal catheter-tip pressure transducer devices measure ICP similar to ventricular ICP pressure. Subarachnoid or subdural fluid-coupled devices and epidural ICP devices are less accurate.

Continuous Intracranial Pressure Monitoring

With continuous ICP monitoring, three types of waveforms may be observed: A, B, and C. B and C waves are of limited clinical significance and correspond to changes in respiration and arterial blood

TABLE 111.2 Advantages and Disadvantages of Intracranial Pressure Monitoring by Device Location

Device Location	Advantages	Disadvantages	Waveform Quality
Intraventricular	Gold standard Accurate measurement of ICP Allows drainage or sampling of CSF Allows instillation of drugs or dyes directly into CSF Determines $\delta P/\delta V$	Catheter can become occluded by blood or tissue Risk of infection or hemorrhage May require frequent zeroing	Excellent
Parenchymal	Useful when unable to obtain ventricular access Accurate Requires zeroing only once No need to adjust transducer to patient position	Potential for significant drift Breakage of fiberoptic cable Cannot be recalibrated once placed Does not provide for CSF sampling	Good
Subarachnoid	Ability to leave cerebral parenchyma undisturbed Quick to insert Useful to insert when unable to obtain ventricular access	Lumen may be occluded by blood or tissue Tendency for dampened waveforms Less accurate at high ICPs Must be zeroed frequently CSF leakage a concern	Fair
Subdural	Useful after craniotomy Ease of placement Best when ICP relatively low	Risk for waveform dampening Underestimates ICP when high	Poor
Epidural	Dura not penetrated Low risk of infection Ease of insertion	Sensing membrane must remain coplanar to dura Risk of false or misleading readings Least understood of all ICP monitors	Poor

CSF, Cerebrospinal fluid; *ICP,* intracranial pressure; *$\delta P/\delta V$,* change in pressure as a function of change in volume.
Modified from Guidelines for the Management of Severe Head Injury. Brain Trauma Foundation, 1995.

pressure, respectively. A waves, referred to as plateau waves, are of clinical significance. These waves arise from an elevated baseline ICP and can reach magnitudes of 50 to 120 mm Hg for 2 to 20 minutes. These waves result from cerebral blood volume increases in response to CPP fluctuations and occur in vascular beds with overall intact autoregulation. These waves may signify impending limitation of the ICP volume compensation system.

Methods exist to measure ICP noninvasively, with varying degrees of accuracy. Morphologic modalities include magnetic resonance imaging, computed tomography, ultrasound, and fundoscopy to detect signs of decreased intracranial compliance. Among other signs, ophthalmic nerve sheath diameter can be assessed with such imaging by comparing its diameter to that of the ophthalmic nerve. Physiologic modalities of assessment include transcranial and ophthalmic Doppler, tympanometry, and near-infrared spectroscopy, as well as neurophysiologic tools such as electroencephalography and visual evoked potentials. None of these modalities is reliable enough to be used alone in ICP assessment.

Risk Assessment

ICP monitoring has been used most extensively in patients with TBI (see also Chapter 150). In the TBI patient population, ICP monitoring may accomplish the following:

- Help in the early detection of intracranial mass lesions
- Limit the indiscriminate use of therapy to control ICP, which is potentially harmful
- Reduce ICP by CSF drainage and thus improve cerebral perfusion
- Help in determining prognosis
- Improve outcomes

Comatose head-injured patients (Glasgow Coma Scale score 3 to 8) with abnormal computed tomography scans should have ICP monitoring. Comatose patients with normal scans should also have ICP monitoring if they have two or more of the following risk factors:

- Age older than 40 years
- Unilateral or bilateral motor posturing
- Systolic blood pressure less than 90 mm Hg

ICP monitoring is also indicated in patients with TBI who have a Glasgow Coma Scale score greater than 9 with a mass lesion and in pediatric patients who cannot participate in serial monitoring by examination.

Routine ICP monitoring is not indicated for patients with mild or moderate head injury. The mortality rate for patients with an intracranial process associated with ICH increases twofold to tenfold when patients have a disturbance in consciousness and are unable to follow commands. ICP monitoring may be recommended in these situations, which include subarachnoid hemorrhage (with and without hydrocephalus), intracerebral hemorrhage, hydrocephalus, encephalitis, meningitis, venous sinus thrombosis, ischemic infarct with swelling, and hepatic encephalopathy. Table 111.2 lists the advantages and disadvantages of ICP monitoring by device location.

Implications

The evidence for routinely measuring ICP in at-risk patients is not entirely clear. Studies have shown mixed results, including no effect and even worse mortality rate. Current consensus guidelines recommend its use as part of a protocol in at-risk patients nonetheless, citing moderate evidence. ICP and CPP measurement are also recommended to detect life-threatening herniations, where more significant evidence exists.

ICP monitoring complications include infection, hemorrhage, neural injury, inadvertent injection, malfunction, obstruction, and malposition. *Bacterial colonization* is a more accurate term than *infection* because there have been no reports in large prospective studies of clinically significant intracranial infections associated with ICP monitoring devices. Colonization of the ICP monitor increases significantly after 5 days of insertion. Irrigation of fluid-coupled ICP monitors significantly increases bacterial colonization. The average rate of bacterial colonization is 5% for ventricular, 5% for subarachnoid, 4% for subdural, and 14% for intraparenchymal devices, either catheter-tip strain-gauge or fiberoptic. However, clinically significant intracranial infections are uncommon. The overall incidence of hematomas associated with ICP devices is 1.4%. The incidence of malfunction or obstruction in fluid-coupled ventricular catheters, subarachnoid bolts, or subdural catheters has been reported as 6.3%, 16%, and 10.5%, respectively. When ICP measurements are greater than 50 mm Hg, obstruction and loss of signal and waveform can occur. Malfunction with parenchymal and ventricular pressure fiberoptic catheter-tip transduction devices ranges from 9% to 40%. This requires reinsertion of a new fiberoptic device.

External ventricular drains also pose the risk of CSF overdrainage resulting from apparatus disconnection or inappropriate leveling during a change in patient positioning. This can result in rebleeding of an aneurysm, subdural hemorrhage from disruption of bridging veins, and reverse brain herniation. Guidelines released in 2017 by the Society for Neuroscience in Anesthesia and Critical Care recommend, in cases of accidental disconnection, clamping the EVD immediately and replacing all parts distal to any contamination. They also recommend clamping EVDs prior to any change in patient positioning. However, with prolonged (intrahospital) patient transport, that decision should be individualized to avoid the risk of intracranial hypertension.

MANAGEMENT

Treatment of ICH is recommended when ICP is 20 mm Hg or greater or if there is significant brain swelling (see also Chapter 150). Treatments are generally classified according to the intracranial contents targeted for therapy and include the following:

- Brain tissue volume
- CSF volume
- Cerebral blood flow
- Mass lesion

Brain tissue water content is 75% to 80%, and treatments designed to decrease brain tissue volume are aimed at decreasing brain tissue water. Hyperosmolar agents such as mannitol are used for this purpose. The administration of mannitol creates an osmolar gradient between cerebral blood and brain tissue, which favors the movement of water from the tissue space into the vascular space. Mannitol may also act initially to decrease cerebral blood volume by decreasing blood viscosity secondary to free water movement. Decreased blood viscosity results in increased cerebral blood flow, which prompts vasoconstriction in normally autoregulating brain areas. This decreases cerebral blood volume and, secondarily, ICP. Effective doses range from 0.25 to 1 g/kg of body weight. Euvolemia should be maintained, and serum osmolarity should not exceed 320 mOsm. Furosemide and other diuretics can be used to decrease brain tissue water by increasing blood osmolarity. This favors the movement of water from the brain tissue space into the cerebrovascular space. Corticosteroids have been reported to decrease brain tissue water content when vasogenic edema is the chief cause of increased water; however, they are not consistently helpful in the treatment of other forms of cerebral edema or in clinical conditions in which both vasogenic edema and other forms of edema are present. Corticosteroids are not recommended for the treatment of increased ICP in the management of acute head injury, because associated side effects may worsen outcomes. Adverse effects include decreased immune response in areas of the body other than the brain, suppression of intrinsic steroid production, and hyperglycemia.

Reduction in CSF volume may directly improve elevated ICP and increase the clearance of brain tissue water from edematous areas. The most direct means of decreasing CSF volume is through CSF drainage. This is usually accomplished via an intraventricular catheter or lumbar subarachnoid catheter. However, caution is advised when using the latter in patients with ICH, owing to the risk of acute brainstem herniation. CSF volume can also be reduced by promoting its movement from the intracranial space to the spinal subarachnoid space. Head elevation and repositioning relative to the subarachnoid space favor such movement.

Methods to reduce cerebral blood volume include hyperventilation, the use of drugs known to cause cerebral vasoconstriction and the restriction of those that impair cerebral autoregulation, head elevation above the level of the heart, suppression of cerebral metabolism, and the minimizing of increased intrathoracic pressure with airway manipulation or mechanical ventilation. Hypocapnia with hyperventilation reduces cerebral blood flow and volume via cerebral vasoconstriction. The latter is mediated by acute increases in perivascular pH. However, hypocapnia may compromise cerebral perfusion due to cerebral vasoconstriction, especially in patients with severe TBI. In the absence of increased ICP, chronic prolonged hyperventilation therapy (to an arterial carbon dioxide tension of 25 mm Hg) should be avoided after severe TBI. Also, use of prophylactic hyperventilation therapy during the first 24 hours after severe TBI should be avoided because it may compromise cerebral perfusion at a time when cerebral blood flow is already reduced. Hyperventilation therapy may be required for short periods with acute neurologic deterioration or for extended periods if ICH is refractory to sedation, paralysis, CSF drainage, and osmotic diuretics. Sedative-hypnotic drugs (e.g., barbiturates, etomidate, propofol) are cerebral vasoconstrictors and decrease ICP. In extreme cases, barbiturate-induced coma may be necessary to control ICP.

Drugs that impair cerebral autoregulation can increase cerebral blood volume and ICP. These include inhalation anesthetics and direct-acting vasodilators (e.g., nitroprusside, nitroglycerin, calcium channel blockers, prostacyclin, adenosine). Control of blood pressure with indirect-acting agents (e.g., labetalol, trimethaphan) prevents the increase in cerebral blood volume and ICP. Head elevation above the heart reduces cerebral blood volume by increasing cerebral venous outflow. Suppression of cerebral metabolism is accomplished by the use of hypothermia and barbiturate-induced coma.

Space-occupying masses increase total intracerebral volume and therefore ICP. Treatment for mass lesions includes removal, chemotherapy or radiation therapy, and creation of additional space for normal intracranial contents, such as decompression or craniectomy.

PREVENTION

There is no medical treatment for the prevention of increased ICP that is not part of the management of ICP covered in the previous section. Short of surgical intervention (in the case of intracranial hemorrhage, increasing tumor size, or hydrocephalus, for example), one prevents an increase in ICP by addressing the same three contents of the cranium, namely brain tissue volume, CSF volume, and cerebral blood volume. In summary:

- Brain tissue volume
  - Diuretics (mannitol)
  - Corticosteroids (for vasogenic edema)
- CSF volume
  - Ventriculostomy
  - Lumbar drain
- Cerebral blood flow
  - Hyperventilation
  - Head elevation and repositioning
  - Discontinuation of inhalational anesthetics (and other cerebral vasoconstrictors)
  - Barbiturate administration
  - Sedation and paralyzing agents

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112 Intravenous Drug Delivery Systems

Rajamani Sethuraman

Case Synopsis

A 35-year-old man weighing 90 kg undergoes mandibular fracture fixation. He receives total intravenous anesthesia with propofol and remifentanil infusion, oxygen, and air for 4 hours. Twenty minutes before the end of surgery the patient has a heart rate of 130 beats per minute and a blood pressure of 170/100 mm Hg. At the conclusion of the operation, he wakes up restless and combative and requires 15 mg of morphine to relieve his pain and make him comfortable. He complains of being aware and could recall the conversations in the operating room. On removing the drapes at the end of the procedure, the propofol line was discovered to be leaking.

PROBLEM ANALYSIS

Definition

The patient described in the case synopsis awoke with significant pain due to the redistribution and elimination of remifentanil and propofol. These two factors play an important role in the declining plasma concentration of a drug, which in turn is affected by the duration of infusion. He complained of being aware during anesthesia due to the disconnected propofol infusion line. However, the redistribution is not so important with remifentanil, which is quickly eliminated by plasma esterases. The bolus dose before initiation of an infusion to produce a given drug plasma concentration is calculated by the following formula:

$$\text{Bolus dose} = \text{Ct} \times \text{VD}$$

where Ct is the target concentration and VD is the volume of distribution for a given drug. VD is an apparent volume that includes central (where the drug is injected) and peripheral compartments where the drug is distributed. As time progresses with infusion, a steady-state concentration is reached between the compartments leading to steady-state volume of distribution. Calculating a bolus dose according to initial VD would be too low, just as the dose would be too high if calculated using the final VD. Hence this introduces the concept of VD at the drug's peak effect, which can be calculated due to the fact that plasma and effector site concentrations are similar at the time of peak effect. Maintenance infusion rate (MIR) is calculated as follows:

$$\text{MIR} = \text{Ct} \times \text{Cls}$$

where Ct is the target concentration and Cls is the rate of clearance.

The context-sensitive half-time is the time taken for the plasma concentration of a drug to decrease by 50% after stopping a continuous infusion that maintained a constant concentration in plasma. The concept of context-sensitive half-time needs to be understood when using a continuous infusion of anesthetic drugs that exhibit multicompartmental kinetics. In this setting, the net distribution of the drug in and out of the peripheral compartments varies according to the duration of the infusion. The "context" in this instance is the duration of the infusion (Fig. 112.1). In certain situations, decreases in plasma concentration other than 50% may be more clinically relevant. A more general term, *context-sensitive decrement time,* applies to this situation. Here a decrease in the effector site concentration occurs, as noted by a falling plasma concentration, which is presumed to model the decrease at the effector site. The context-sensitive decrement time provides a clinically useful framework for understanding the relationship between the duration of the infusion and the time before recovery occurs (Fig. 112.2).

Automated drug delivery systems can provide precise predictions of the time required for the plasma (or effector site) concentration to change, based on the actual dosing regimen. These predictions can help clinicians terminate the infusion at the appropriate time. However, the postinfusion kinetics do not correlate with the elimination half-life. This is clearly demonstrated by a remifentanil infusion, because even after 3 hours the context-sensitive half-time is shorter than its terminal half-life. Hence we can say that remifentanil is a context-insensitive drug.

Recognition

Excessive opioid administration is characterized by slow respirations, bradycardia, and pinpoint pupils. With the advent of shorter-acting opioids (e.g., remifentanil), an opposite response may be noted if the infusion is terminated too early and further analgesia is not instituted in time, as happened in this case.

Although it is important to understand the pharmacokinetics of the drugs used, one should not overlook practical errors in the setup of the system. The most common problems are as follows:

- Disconnected intravenous (IV) line
- Air in the IV line
- Line occlusion
- Low battery
- Syringe or cassette disengagement
- Tubing disconnection
- Empty carrier fluid

Another factor that may influence the onset of anesthesia and subsequent dose adjustment is the proximity of the infusion's connection

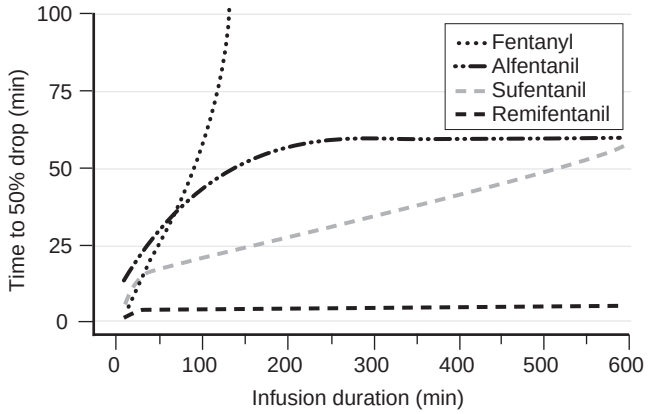

Fig. 112.1 Context-sensitive half-times as a function of infusion duration for each of the pharmacokinetic models simulated. *Solid* and *dashed lines* are used only to permit overlapping lines to be distinguished. (From Glass PA, Shafer SL, Reves JG: Intravenous drug delivery systems. In Miller RD, editor: *Anesthesia,* 5th ed. New York, Churchill Livingstone, 2000.)

to the patient. When an infusion is connected in a piggyback fashion, the rate at which the drug reaches the circulation is directly related to the IV flow rate and inversely to the volume of IV dead space between the infusion connection and the IV cannula. Therefore the connection should be as close to the IV catheter as possible to minimize the effect of carrier IV fluid rate on drug delivery. Because of all these issues, vigilance with regard to the IV drug delivery device is very important. Additionally, newer infusion pumps are installed with audible alarms for an idle pump, battery failure, empty syringe, and 3 minutes before the syringe becomes empty.

Risk Assessment

The context-sensitive half-time and context-sensitive decrement time play an important role in running IV drug infusions safely. For most IV anesthetic agents, a 50% reduction in concentration is required before the patient returns to an awake state, and an 80% to 90% decrease is required before a patient can be safely discharged in an outpatient setting. Drug elimination half-lives are usually consistent. However, this is not true for context-sensitive half-times and context-sensitive

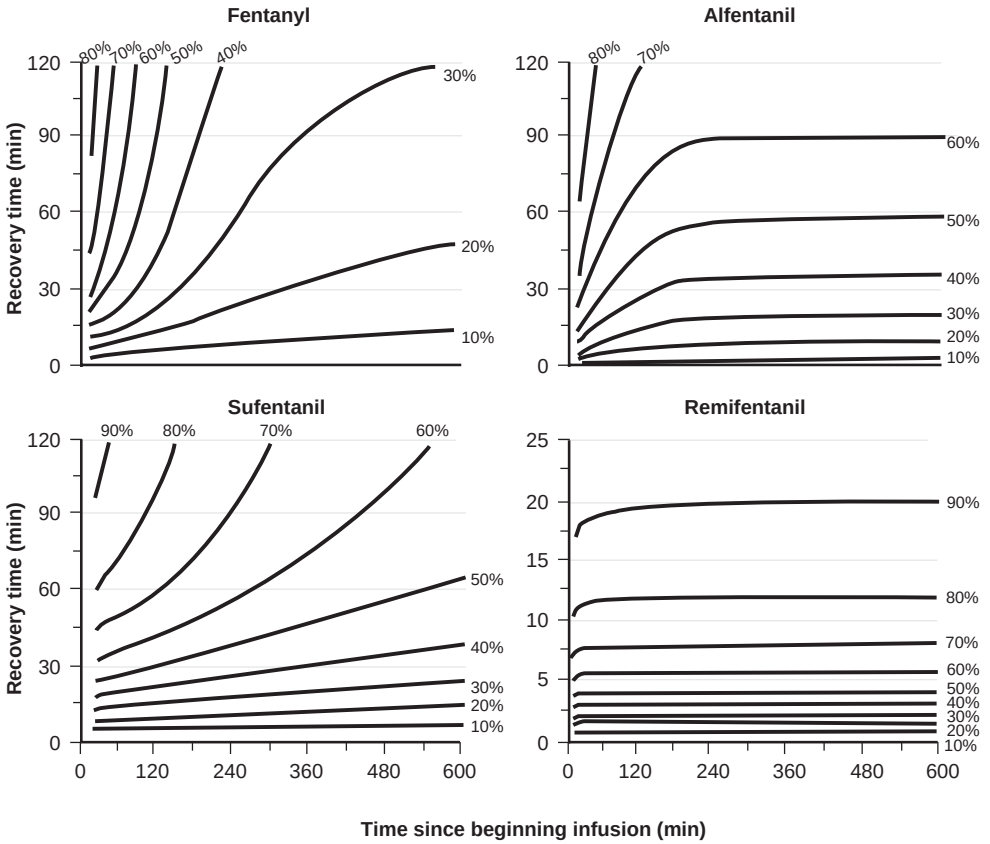

Fig. 112.2 Recovery (decrement time) curves for fentanyl, alfentanil, sufentanil, and remifentanil showing the time required for decreases of a given percentage (labeled for each curve) from the maintained intraoperative effector site concentration after termination of the infusion. After the loading dose, an initially high infusion rate should be used to account for the redistribution and then titrated to the lowest infusion rate that will maintain adequate anesthesia or sedation. For sedation, the loading dose is given over 5 to 10 minutes and adjusted according to the patient's response. For anesthesia, midazolam is administered with an opiate. (From Glass PA, Shafer SL, Reves JG: Intravenous drug delivery systems. In Miller RD, editor: *Anesthesia,* 5th ed. New York, Churchill Livingstone, 2000.)

TABLE 112.1 Common Problems With Intravenous Drug Delivery Systems and Recommended Preventive Measures

Problem	Reason	Prevention
Pump setup errors	Error in concentration or rate	Two-person check Use prefilled syringes or bags
	Drawing up and pump-setting errors	Double-check units and rates (e.g., mg/h or mL/h)
Underinfusion	Faulty device	Check service date Check that clamp and delivery mechanism movement is smooth
	Delayed onset because of mechanical slack	Normally, alarms sound when switched on, performing self-check
	Air in line	Purge and prime the line
	Occlusion	Check the IV line Check the need to increase the occlusion pressure limit
Overinfusion	Faulty device	As above
	Siphonage	Check for cracked syringe; check that syringe barrel and plunger are firmly engaged Position the device at the same level as the patient Use an antisiphon valve
	Postocclusion bolus	Release the line pressure before relieving the obstruction Add an antireflux valve in the second line
	Bolus drug treatment	Place the pump at the level of the patient Disconnect the infusion line whenever the syringe is removed from the pump
Communication	Absent or incorrect label	Use correct labeling, color coding
	Absent or incorrect record	Check that the volume infused matches the dose and duration of infusion
	Absent or incorrect information during patient transfer or handover of care	Provide complete and accurate information regarding patient's course before transfer of care

IV, Intravenous.
Modified from Keay S, Callander C: The safe use of infusion devices. *BJA Contin Educ Anaesth Crit Care Pain* 3:81-85, 2004.

decrement times. As in the case synopsis, the context-sensitive decrement time is shorter for remifentanil compared with other opioids, owing to its rapid metabolism and its minimal distribution to peripheral compartments.

Complications related to the use of IV drug delivery systems are often due to human error. If a routine checklist is followed, these errors can be minimized (Table 112.1). Use of AC power, use of a dedicated IV cannula, removal of all air from the tubing and syringes, and constant vigilance should prevent interruptions in flow.

Implications

Commercial target-controlled infusion systems are available now. Target-controlled infusion systems are total IV anesthesia systems that can be set to achieve a desired plasma and effector site concentration of IV agents. The pumps can be programmed to deliver a desired concentration by the clinician using demographic data of the patient, which include age, ideal weight, height, and sex. These systems can also predict recovery time once the infusion is terminated.

There are also newer closed-loop systems that can adjust the rate of infusion according to feedback from auditory-evoked potentials and bispectral index. In the near future, these systems will be part of everyday anesthesia practice. Their pumps are driven by pharmacokinetic models using software algorithms, and pharmacokinetic parameters for various drugs can be programmed into the devices. Fig. 112.3 illustrates the potential sources of error in pharmacokinetic model drug delivery systems to prevent awareness under anesthesia (AUA).

An understanding of pharmacokinetics is important when using any drug, and this is especially true with IV drugs. For example, remifentanil has a different elimination profile compared with fentanyl, alfentanil, and sufentanil. Because this difference was not considered for the patient in the case synopsis, the result was poor analgesia on recovery. Inadvertent disconnection led to awareness.

MANAGEMENT

Drug delivery failure is investigated by asking the following questions:
- Is the pump working?
- Is the drug physically moving?

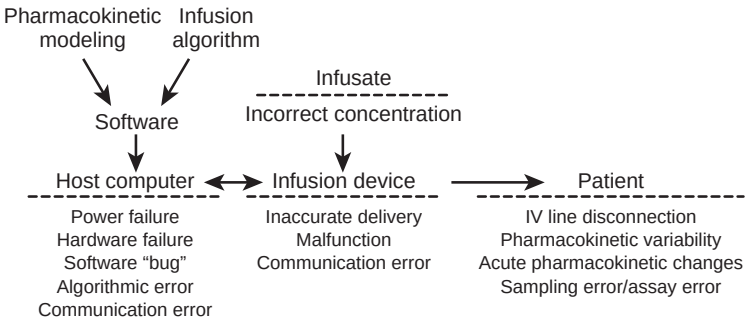

Fig. 112.3 Commercially available target-controlled infusion systems have computer functions incorporated into the device itself. Potential sources of error in drug delivery systems based on pharmacokinetic models are shown. (From Glass PA, Shafer SL, Reves JG: Intravenous drug delivery systems. In Miller RD, editor: *Anesthesia,* 5th ed. New York, Churchill Livingstone, 2000.)

TABLE 112.2 Manual Infusion Schemes When Combined With 66% Nitrous Oxide and Oxygen

	ANESTHESIA		SEDATION OR ANALGESIA	
Drug	Loading Dose (μg/kg)	Maintenance Dose (μg/kg/min)	Loading Dose (μg/kg)	Maintenance Dose (μg/kg/min)
Alfentanil	50–150	0.5–3	10–25	0.25–1
Fentanyl	5–15	0.03–0.1	1–3	0.01–0.03
Sufentanil	0.25–2	0.01–0.05	0.1–0.5	0.005–0.01
Remifentanil	0.5–1	0.1–0.4	[a]	0.025–0.1
Ketamine	1500–2500	25–75	500–1000	10–20
Propofol	1000–2000	50–150	250–1000	10–50
Midazolam	50–150	0.25–1.5	25–100	0.25–1
Methohexital	1000–1500	50–150	250–1000	10–50

[a]No loading dose necessary if used for intravenous sedation.

- Is the carrier fluid moving?
- Are connections secure and not leaking?
- Is the vascular access patent?

If the cause of a failure cannot be identified and corrected quickly, one should switch to an alternative anesthesia technique to minimize the risk of awareness as happened with this patient. If the patient is in pain because the infusion was turned off too early, supplemental analgesia and anesthesia should be instituted as appropriate. Use of tagged and prefilled syringes avoids incompatibility with commercial target-controlled infusion systems. Target-controlled infusion systems need to be reset in between patients; otherwise, the wrong patient information will be used by the infusion pump. Total IV anesthesia infusion pumps are associated with a median absolute performance error, which represents overinfusion or underinfusion. Adequate depth of anesthesia must be maintained while using total IV anesthesia, especially when the patient is paralyzed. Use of depth-of-anesthesia monitors such as bispectral index, auditory evoked potentials, and entropy along with clinical parameters could avoid AUA. Knowledge of the potential problems listed in Table 112.1 will help avoid most errors.

PREVENTION

If one bases the loading dose on the initial volume of distribution, an incorrect dose may be given. Equilibration with other compartments and clearance should be taken into account when calculating the infusion rate. Titration of doses and infusion rates should be modified according to clinical requirements. Over time, as the peripheral compartments equilibrate with the plasma concentration, the infusion rate must decrease in order to maintain the desired concentration at the effector site. This is achieved by understanding the pharmacokinetic and dynamic characteristics of individual drugs and patients and by titrating the infusion to specific effects, similar to using an inhalation anesthetic end-tidal concentration analyzer. Unfortunately, unlike with the latter, there is no in-line plasma drug concentration analyzer. Constant vigilance on delivery line, syringe, pump and clinical parameters would help avoid the problems of overdosing and underdosing. Examples of some dosing regimens are given in Table 112.2. Familiarity with IV drug delivery systems will avoid the peaks and troughs of intermittent IV bolus dosing, ultimately improving the patient's hemodynamic stability and recovery time, reducing IV drug usage and increasing patient satisfaction.

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113 Laser Complications

Arul Prakash Pandian James

Case Synopsis

A 75-year-old man with metastatic non–small cell carcinoma of the lung is scheduled for bronchoscopic tumor ablation using laser, under general anesthesia. He has a chronic nonproductive cough, and a computed tomography scan reveals tumor encroachment on the right bronchus.

PROBLEM ANALYSIS

Definition

Improved technology, better reliability, and reduced cost have led to an increase in the applications for medical lasers over the past decade. Lasers deliver sterile, intense energy in the form of a beam of coherent monochromatic light by stimulated emission of photons from excited atoms. Patients and operating room (OR) personnel are exposed to certain hazards with medical lasers, including atmospheric contamination, inadvertent perforation of a tissue structure or vessel, ignition of flammable material, and embolism.

Although there are no federal safety requirements for medical lasers, there are national safety standards. The latter exist to decrease or prevent laser mishaps. Laser hazards are classified into four general risk categories, ranging from no risk to substantial risk. Medical lasers fall into the highest risk level. Therefore proper use requires trained personnel and protective equipment for the operation of medical lasers.

Recognition

There are several types of medical lasers. Their differences are based on the medium used and the wavelength produced (Table 113.1). In addition to laser hazards in general, different types of lasers have their own unique risks. For example, the wavelength of the carbon dioxide (CO_2) laser is in the far-infrared region and is absorbed by the first surface it encounters, necessitating eye protection for both patient and OR personnel to prevent corneal damage.

Argon, KTP:YAG, and Nd:YAG in both the visible and near-infrared range are transmitted through clear material but absorbed by pigmented tissue. Therefore they pass through the cornea but could damage retinal tissue.

Laser hazards can be divided into beam-related and non–beam-related hazards. Non–beam-related hazards include electric shock and laser-generated air contaminants. Beam-related hazards include perforation of a vessel, pilot balloon of an endotracheal tube, and thermal injury. Delayed complications may appear after the use of certain lasers. In particular, the Nd:YAG laser can penetrate deeper than anticipated, causing bleeding or perforation to appear several hours to days later, when necrosis and edema are maximal.

Risk Assessment

Both patients and OR staff must be protected from laser hazards while the laser beam is being used. Reflected beams can be aimed at an unintended site, causing eye damage, ignition of flammable material, or burns.

During laser airway surgery, airway fires are the most common serious complication and can cause severe morbidity and death. Should contact with a flammable endotracheal tube result in a fire, the blow-torch-like nature of the ignited fumes in an oxygen (O_2)-rich environment can result in immense damage. If inhaled, smoke produced by the vaporizing of 1 g of tissue is equivalent to smoking six unfiltered cigarettes. This smoke, or the "laser plume," can potentially be a vector for viral transmission, although there has been no documentation of a health care provider contracting a disease in this manner.

Implications

Laser use has increased tremendously in the past few years. Lower cost and increased reliability have made medical lasers attractive for a variety of surgical applications. In addition to removing tumors, lasers are used to treat conditions such as benign prostatic hypertrophy and macular degeneration, to perform coronary angioplasty, and to treat various dermatologic and ophthalmic problems. Their increased utilization, however, results in the increased potential for complications. Lasers require a highly skilled staff trained in their use. They must be vigilant and able to anticipate associated risks and take measures to protect the patient and other medical personnel. If properly and promptly managed, complications are generally minor and treatable.

MANAGEMENT

Airway fire is the most serious complication of laser use. To minimize damage, the OR team must act quickly and in a coordinated fashion, taking the following actions:

- Disconnect the O_2 source, and remove the endotracheal tube or other object on fire.
- Douse any flames with normal saline.
- Resume anesthesia with mask ventilation, using l00% O_2.
- Perform diagnostic laryngoscopy and rigid bronchoscopy to inspect the extent of damage.
- Remove any debris.
- Reintubate if airway damage is present.
- Consider a low tracheostomy if the damage is severe or if reintubation is unsuccessful.
- Use mechanical ventilation if required.
- Administer systemic steroids if necessary.
- Obtain and check the chest radiograph.

TABLE 113.1 Commonly Used Lasers and Associated Hazards

Medium	Wavelength (nm)	Color	Features	Potential Hazard
CO_2	10,600	Far infrared	Readily absorbed by all biologic tissue; very precise, superficial penetration; not fiberoptically transmitted	Corneal damage
Holmium:YAG	2060 2140 (pulsed)	Infrared	Precise cutting ability; minimal diffusion of thermal energy; good hemostasis; transmitted fiberoptically	Corneal damage; can pierce metal
Nd:YAG	1064	Near infrared	Can be transmitted fiberoptically; uses photocoagulation plus thermal necrosis; highest tissue penetration	More prone to late complications, delayed edema, tissue sloughing, retinal damage
Ruby	694	Red	Absorbed by pigments except hemoglobin	Retinal damage
Helium-neon	632	Red	Used as an aiming beam for CO_2 plus Nd:YAG lasers	Harmless, unless directed toward eyes
KTP:Nd:YAG	532	Green	Fiberoptic transmission possible; some scatter and necrosis (less than Nd:YAG)	Similar to Nd:YAG (less retinal damage or tissue penetration)
Argon	488,514	Blue/green	Can be transmitted fiberoptically; absorbed by hemoglobin and pigmented tissue	Retinal damage

Surgical drapes are fire resistant, but if they are ignited, the flames are difficult to extinguish because the drapes are also water resistant. A fire extinguisher should be available when surgical drapes are in use. If any OR personnel are injured, they must be appropriately treated, and an incident report should be generated. The event should be investigated to prevent recurrences.

PREVENTION

Prevention depends on the particular complication to be avoided. Only personnel with the proper training and credentials in laser use and safety precautions should be allowed to operate the laser. While it is in use, everyone in the OR should be protected from known laser hazards.

Eye Protection

Because the eye is most vulnerable to injury, all personnel must wear proper eye protection. Wraparound goggles with side protectors are advised, because standard eyeglasses do not protect the eyes from reflected beams that may glance off the side. Contact lenses are not protective. The protective lens must absorb the particular laser wavelength being used. Clear lenses are adequate for CO_2 lasers, but for all other lasers the lenses must be tinted.

The patient's eyes must be protected. Patients who are awake should also wear laser-safe goggles. If they are not the operative site, the eyes of anesthetized patients should be closed and covered with saline-soaked gauze or a nonshiny metal shield.

Because all lasers other than CO_2 lasers penetrate clear glass, windows must be protected. Signs must be placed prominently at all entrances to the OR warning of laser use, and spare goggles should be available at all entrances.

Perforation Risk

When not directed at the target tissue, the laser beam should be turned off or set in a standby mode. Misdirected laser beams can cause inadvertent perforation of a vessel or viscus.

Coronary arteries have been perforated during laser angioplasty, resulting in severe complications (e.g., tamponade, acute myocardial infarction, urgent coronary artery bypass surgery). Currently, the risk for such perforation approaches l%.

Complications from perforation may not develop until several days postoperatively. Systemic air embolism with serious complications has also been reported with laser use.

Skin Damage

Avoid prolonged laser exposure to nontargeted skin. All nearby skin should be protected with moist drapes. Compared with the cornea, the skin has a layer of dead cells that makes damage less likely.

Environmental Hazards

Laser plume (described earlier) can produce an unpleasant odor, may cause tearing and bronchial irritation, and may be a viral vector. Inhalation of this plume can be minimized with the use of a high-efficiency smoke evacuator and the use of special laser surgical masks. However, such masks require periodic replacement when moist. Moreover, some laser plume facemasks may not provide complete protection from all laser-induced airborne debris.

Airway Fire

No preventive measure guarantees that a fire will not occur. An insufflation technique or jet ventilation could be used for airway surgery, if possible, but the patient must be monitored for barotrauma and gastric dilation.

The flammability of endotracheal tubes can be decreased by using laser-resistant endotracheal tubes, a conventional endotracheal tube wrapped in metal foil, or a commercially made metal tube. Foil-wrapped tubes can have rough edges that abrade tracheal tissue, and they may have gaps that expose flammable portions. Cuffs of metal tubes are flammable. Metal tubes are less flexible and have a reduced internal diameter that makes ventilation more difficult; they are also expensive. If a cuff is in the airway, it should be inflated with dyed saline to indicate when cuff rupture occurs. Use of moistened pledgets around the tracheal tube is also helpful.

Keep the fraction of inspired O_2 as low as possible to maintain adequate O_2 saturation. Do not use nitrous oxide, because it can support combustion.

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The author wishes to thank Dr. Pattricia Klarr for her contribution to the previous edition of this chapter.

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114 Mechanical Ventilators

Brian J. Woodcock

Case Synopsis

A 100-kg, 68-year-old man is anesthetized and intubated. Bilateral breath sounds are verified. The ventilator is turned on and set to a tidal volume of 600 mL, respiratory rate of 10, and inspiratory-expiratory ratio of 1:2. Two minutes later, the lowering tone of the pulse oximeter alerts the anesthesiologist, who notices an absence of chest wall movement. The ventilator appears to be cycling normally, so the anesthesiologist picks up a stethoscope and reaches to adjust the switch-over valve to manual, but it is already in the manual position.

PROBLEM ANALYSIS

Definition

Failure to change the ventilator-manual switch to the ventilator position after a period of manual ventilation is the source of many mechanical ventilator complications that can cause serious harm to patients. In the American Society of Anesthesiologists (ASA) closed claim analysis of adverse anesthetic outcomes, there were threefold more claims related to misuse of equipment or operator error compared with equipment failure.

Examples of ventilator misuse or operator error include the following:

- Failure to turn the ventilator on after a period of manual ventilation
- Inappropriate set rate or tidal volume for patient size
- Maximum pressure limit set too high for patient size
- Maximum pressure limit set too low, causing low tidal volume
- Inappropriate inspiratory-expiratory ratio
- High fresh gas flow causing increased tidal volume
- Oxygen (O_2) flush during ventilator inspiration
- Alarms for pressure, volume, or fraction of inspired oxygen (Fio_2) inactivated by the operator, causing a delay in noticing other malfunctions

Equipment failure or incorrect assembly can include the following problems:

- Hole in the bellows
- Bellows mounted incorrectly, so no seal is formed between the bellows and the casing
- Electrical or mechanical failure, stalling the mechanism
- Failure of the alarms for pressure, apnea, or Fio_2

Other causes of ventilator failure actually arise elsewhere on the anesthesia machine. These complications, covered in other chapters, include failure of driving gas pressure (see Chapter 116); circuit disconnection, sticking valves, and misconnections of the circuit hoses (see Chapter 105); and scavenger errors (see Chapter 120).

Recognition

The failure to recognize and promptly rectify problems with ventilators can have catastrophic consequences. In the ASA closed claim analysis, 12 cases were associated with ventilator problems; 7 resulted in death, and 5 resulted in brain injury. There is only a small window of opportunity to correct the malfunction of the ventilator before adverse physiologic events take place as a result of it.

Turning the Ventilator On

Failure to actually turn the ventilator on is common. This usually occurs soon after induction and may be unnoticed for many minutes. If the ventilator-manual switch has not been turned to the ventilator position, the signs are as follows:

- Loss of the end-tidal carbon dioxide ($ETCO_2$) waveform
- Activation of the $ETCO_2$ apnea alarm
- Distention of the reservoir bag and rising airway pressure on the manometer if the pop-off valve is closed

If the ventilator has not been turned on but the ventilator-manual switch has been turned to the ventilator position, the signs are as follows:

- Loss of the $ETCO_2$ waveform
- No airway pressure perceived by the manometer
- Activation of the apnea pressure and $ETCO_2$ apnea alarms

Ventilator Rate and Tidal Volume

Inappropriate settings for tidal volume or respiratory rate may cause either inappropriate tidal volume size and hyperventilation or hypoventilation leading to falling or rising $ETCO_2$. In the case of a child or small adult, hypotension may result from the decrease in venous return due to large tidal volumes and increased intrathoracic pressures. Barotrauma may also occur, with consequent pneumothorax or subcutaneous emphysema. In the case of an adult with ventilator settings for a small child, the most notable feature would be hypoventilation, including a low peak airway pressure, a rising $ETCO_2$, and O_2 desaturation if hypoventilation is severe.

Pressure Limit

An inappropriately high pressure limit setting may allow excessive tidal volumes and pressures, leading to barotrauma. A low pressure limit setting may lead to inadequate tidal volume and hypercarbia.

Inspiratory-Expiratory Ratio

An inappropriate inspiratory-expiratory ratio may be set when unusual ventilator rates are used—for example, at the end of a case when the

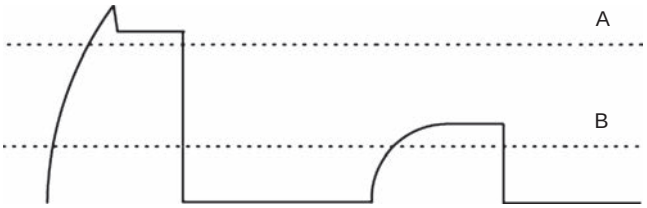

Fig. 114.1 The threshold pressure alarm limit (TPAL; *dashed lines*) delineates the airway pressure level at which inspiration is detected. When the TPAL is adjustable, it should be set at less than 5 cm H_2O below the peak inspiratory pressure (setting A). With a correct TPAL setting, a reduced peak airway pressure breath, such as that occurring in the presence of an airway breathing system leak (second breath), will be sensed as being absent, and the apnea alarm will sound if the condition continues. However, if the TPAL is too low (setting B), the reduced breath will be detected, but the ventilator alarm will not sound. Appropriately high TPAL settings allow the alarm to be triggered when a leak in the system causes a reduction in peak inspiratory pressure, even with an airway pressure waveform.

rate is set very low to allow arterial CO_2 tension to rise. At low rates, an inspiratory-expiratory ratio of 1:2 might result in very prolonged inspiratory times.

Fresh Gas Flow

Failure to reset the fresh gas flow to a lower rate after intubation of a patient may lead to hyperventilation. The set tidal volume on the bellows is supplemented by the amount of fresh gas entry into the circuit during the inspiratory period. For example, with a fresh gas flow of 10 L/min, a respiratory rate of 10, and an inspiratory-expiratory ratio of 1:2, each tidal volume is increased by 333 mL above that set by the bellows. This may cause significant hyperventilation or barotrauma in a small patient if the maximum pressure limit is set too high.

Pressing the O_2 flush during ventilator inspiration can lead to large volumes of gas entering the patient, leading to the development of pneumothoraces due to barotrauma.

Ventilator Alarms

Ventilators have two alarms, the *ventilator alarm* and the *threshold pressure alarm limit (TPAL) alarm.* The ventilator alarm has two buttons, the "silence alarm" button and the "alarm off" button. Pressing the "silence alarm" button during a period of manual ventilation can prevent the ventilator alarm from sounding when a period of apnea ensues. When the intent is to use manual ventilation or to hold ventilation for a limited period, the "silence alarm" button should be pressed to cancel that alarm for a period of 60 or 120 seconds. Pressing the ventilator "alarm off" button, which indefinitely cancels the ventilator alarm, removes the ability of the ventilator alarm to automatically be rearmed if the operator fails to turn the ventilator back on.

The TPAL alarm delineates the airway pressure level at which inspiration is detected. When this is adjustable, it should be set at less than 5 cm H_2O below the peak inspiratory pressure. This allows the alarm to be triggered when a leak in the system causes a reduction in peak inspiratory pressure but not a complete loss of the waveform (Fig. 114.1). The Narkomed 2B anesthesia machine gives a (silent) advisory notice when the pressure is set too low for the current peak pressure.

The ventilator alarm should be considered the most important alarm in the operating room. A vigilant anesthesia provider should feel uncomfortable whenever this alarm sounds. Even if the reason for the alarm is known and anticipated (e.g., after switching to spontaneous ventilation after reversal of muscle relaxation at the end of a case), the alarm should not be allowed to continue unattended. Any ventilator alarm condition should be corrected, or the alarm should be reset to the appropriate level for the new status of the patient. Similarly, when leaving the operating room at the end of a case, the ventilator alarms should not be left sounding.

Ventilator Bellows

Development of a hole in the bellows can be recognized by the following:

- Decreasing concentration of the inhaled anesthetic gas
- Rising Fio_2 if the driving gas is O_2
- Falling Fio_2 if the driving gas is air or an O_2-air mixture
- Hyperventilation or hypoventilation

If the bellows is mismounted or a hole develops in it, the O_2 used to power the bellows is directly connected to the circuit gases. Because the driving gas is at a higher pressure, it enters the bellows and mixes with the circuit gases. It therefore dilutes the anesthetic gases in the circuit and raises the Fio_2, unless air is used as the driving gas, in which case the Fio_2 would fall (see also Chapter 116). The main result of a leaking bellows is its inability to hold volume after the O_2 flush valve is used to fill it. Although such a malfunction could cause hypoventilation, it is more likely that the driving gas will hyperventilate the patient. This occurs because the bellows moves inadequately to operate the sensing mechanism, and large tidal volumes are delivered. Also, a hanging bellows can entrain room air during expiration if there is a circuit disconnection or leak.

A leak caused by a hole is more likely in an old, worn-out bellows. A hole in a new bellows might result from inadequate inspection at the factory. Mismounting may occur if the person mounting the bellows is not familiar with the equipment. Because the bellows may be changed when an adult case follows a pediatric case, or vice versa, this is a time to be especially vigilant for problems related to mismounted bellows.

Ventilator Failure

The ventilator control assembly can be the cause of ventilator failure due to electrical or mechanical problems. Total electrical failure is easily recognized, but partial mechanical problems due to internal leaks or faulty valves may be more difficult to discern.

Risk Assessment

Some circumstances are associated with greater risk of ventilator problems. Failure to correctly set the ventilator on-off switch or the changeover valve may occur in the following circumstances:

- Soon after induction
- After a period of manual ventilation
- When the anesthetist is distracted
- When multiple providers are present

The period of greatest risk is immediately after induction, after bilateral breath sounds have been confirmed and the anesthetist is distracted by placing other monitors or by the patient's hemodynamic instability. Resuming ventilation after coronary artery bypass is another period of high risk, because the ventilator has been off for a lengthy period. The "inverse anesthetist ratio" states that the care given to the patient is inversely related to the number of anesthetists present. When multiple anesthesia personnel are present, each may assume that someone else turned on the ventilator.

Inappropriate ventilator settings often occur when beginning a pediatric case after an adult case or when beginning an adult case after

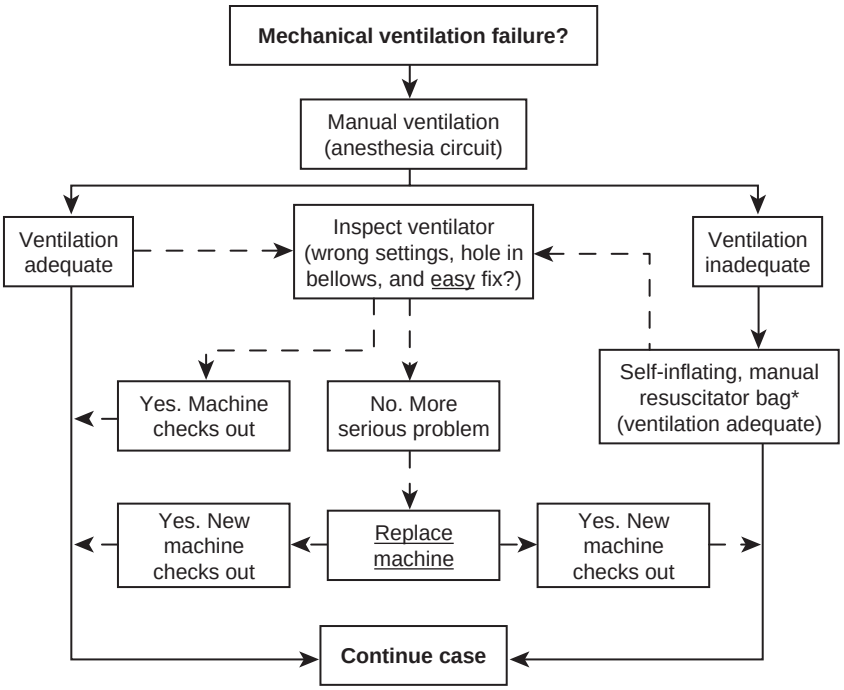

Fig. 114.2 Suggested algorithm for responding to a problem with mechanical ventilation. *If a manual resuscitator bag is not immediately available, use mouth–to–tracheal tube ventilation. *Solid lines,* Immediate action; *dashed lines,* remedial action. Under no circumstances should a machine be repaired while in use.

a pediatric case. Wrong settings for the tidal volume or respiratory rate produce a minute ventilation that is inappropriate for that patient. At high risk is a very small pediatric patient placed on a ventilator set for a full-sized adult. The pediatric patient is put at very high risk for barotrauma, secondary to high inspiratory pressure, and hyperventilation. Conversely, an adult placed on a ventilator set for a child is at risk for severe hypoventilation.

Implications

Most of the problems discussed here eventually cause a ventilatory abnormality, such as hypercarbia or hypocarbia. Prolonged absence of ventilation may lead to hypoxia. The length of time before hypoxia occurs is variable, depending on the Fio_2 before apnea and the respiratory status of the patient. Other complications include severe hypotension secondary to reduced venous return and significant barotrauma from hyperinflation.

MANAGEMENT

The initial response to any problem with mechanical ventilation is to immediately switch to manual ventilation (Fig. 114.2). First, this is done using the anesthesia circuit. If the patient is still inadequately ventilated, a self-inflating manual resuscitator bag or mouth–to–tracheal tube ventilation is used. Once manual ventilation is established, the ventilator can be thoroughly inspected for the source of the error. The settings should be verified as correct for that patient; if not, they should be reset. If there is a hole in the bellows, it should be replaced immediately, or the anesthesia machine should be exchanged. It is never appropriate to repair a machine while it is in use in the operating room.

PREVENTION

Preventing problems related to mechanical ventilators depends on the following:

- Operator vigilance
- Monitoring of airway pressures and expiratory volume, and appropriately set alarms
- Skilled routine maintenance
- Thorough checkout procedure performed before each case, following Food and Drug Administration guidelines:
  - If a switching valve is present, test its function in both bag and ventilator mode.
  - Close the pop-off valve (airway pressure leak) if necessary, and occlude the system at the patient's end.
  - Test for leaks and pressure relief by appropriate cycling (exact procedure varies with the type of ventilator).
  - Attach the reservoir bag at the mask fitting, fill the system, and cycle the ventilator. Ensure that the bag is properly filling and emptying.

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Patient Warming Systems 115

Michael P. Eaton

Case Synopsis

A 76-year-old man is brought to the operating room emergently for open repair of a right ileac artery injury. The patient is placed on an under-body blanket that is connected to a properly functioning forced-air warming system, and the unit is turned on to the maximum setting (43°C). Postoperatively, the patient is noted to have partial- and full-thickness burns to the posteromedial aspect of the right leg.

PROBLEM ANALYSIS

Definition

Perioperative hypothermia is known to be associated with significant increases in morbidity. Thus the prevention of hypothermia is an important goal of anesthetic care, but the use of devices to prevent hypothermia is not without risk. The primary complication resulting from these devices is tissue burns. Other complications include hyperthermia, hypothermia (from incorrectly set or malfunctioning devices), electrocution, and possibly infection.

Patient warming devices can be divided into two main categories: (1) items not designed for patient warming that are nonetheless used for that purpose, and (2) devices specifically designed and manufactured for the purpose of preventing and treating hypothermia. In the American Society of Anesthesiologists (ASA) closed claims analysis of injuries caused by patient warming devices, the former category accounted for the majority of claims. Included in this category are the following:

- Heated intravenous (IV) solution bags
- Heated bottles of irrigating or other fluids
- Reheated "hot packs"

Devices specifically designed and manufactured for the prevention and treatment of hypothermia include the following:

- Circulating water blankets
- Electrical resistive heating pads/blankets
- Forced-air warming blankets
- Radiant heaters
- Regular or reflective blankets
- Breathing circuit heated humidifiers
- Intravenous fluid warmers

The last device is discussed in Chapter 119. Table 115.1 provides further details about the mechanism of injury, risk factors, and preventive measures for some of the listed devices.

Recognition

Intraoperative hyperthermia and hypothermia are recognized by continuous monitoring of the patient's core temperature. The existing ASA standards require temperature monitoring whenever temperature instability is expected.

Unfortunately, recognition of burns usually occurs postoperatively, when it is too late to prevent the injury. Typically, patients complain of pain in the burn-injured area. Analgesics given to treat pain related to surgery may mask pain due to a burn injury and delay the diagnosis. Inspection of the patient's back or other area of contact at the end of the procedure is important whenever a warming device has been used. This is typically accomplished by operating room nurses when patients are moved, but should be a team activity recognized for its importance by all members of the team. Early recognition may allow aggressive treatment to prevent infection, which has the potential to be life threatening.

Risk Assessment

Risk from the two categories of warming devices seems to accrue to different patient groups. In the closed claims analysis of burns from heated IV solution bags, the average patient was a female, age 38 years, having surgery for which significant hypothermia would not be expected. The primary risk factor for these patients was the use of a device that was not intended for the warming of patients. Frequently the bags were kept in blanket warmers or ovens whose temperature was poorly regulated. Alternatively, they were heated in microwave ovens with no temperature control. A survey of hospitals using heated IV bags perioperatively found that several institutions allowed these bags to be heated to more than 50°C. Two hospitals kept bags at temperatures higher than 70°C, which would produce burns within only a few seconds of exposure (Fig. 115.1).

Injury from devices designed for patient warming is more likely to be related to patient factors or to device malfunction or misuse. A previous search of the Food and Drug Administration's Manufacturer and User-Facility Device Experience (MAUDE) database for reports of injuries from one company's forced-air warming device found that in 24 of 30 cases in which the cause of injury could be determined with some certainty, the device was used without the blanket (so-called hosing) or otherwise contrary to the manufacturer's recommendations.

A common patient factor is the likelihood of poor local tissue perfusion at the site of contact with the warming device. These injuries are usually most severe in areas overlying bony prominences (pressure points). Patients undergoing vascular surgery (as for our index patient), diabetic patients, and those having procedures involving cardiopulmonary bypass are at increased risk for thermal injury related to warming devices. These patients have poor regional tissue perfusion related to their disease state, surgery, or cardiopulmonary bypass, which allows local temperature to increase to the point of injury because blood flow is inadequate to redistribute applied heat. Pressure

TABLE 115.1 Injury from Patient Warming Devices

Device	Mechanism of Injury	Risk Factors	Preventive Measures
Heated IV solution bags	Conduction heat transfer	Overly heated solutions	Do not use
Electrical resistance heating pads	Conduction heat transfer	High settings	Use only for awake, alert patients
	Electrocution	Device malfunction	Use lowest effective settings
Conductive fabric blankets/mattresses	Conduction heat transfer	Worn/improperly maintained equipment	Check before each use
			Perform routine maintenance
			Check before each use
			Perform routine maintenance
Circulating water blankets	Conduction heat transfer	Patients with poor tissue perfusion	Use on top of patient, rather than beneath (to eliminate pressure component of injury)
		High heat output from machine	Use lowest effective settings
		Machine malfunction	Check before each use
			Perform routine maintenance
Heat lamps	Radiant heat transfer	Too close to patient	Maintain proper distance from patient as per manufacturer's recommendations
		Lamp modified	Use recommended diffuser or lens
Forced-air warmers	Convective heat transfer	No blanket or wrong blanket used	Use blanket only from the same manufacturer
		PACU machine or high settings used	Use only operating room–approved machine on lowest effective setting
		Patients with poor (or no) tissue perfusion	Use lower settings on patients with vascular insufficiency
			Do not use distal to tourniquet or cross-clamp

IV, Intravenous; *PACU,* postanesthesia care unit.

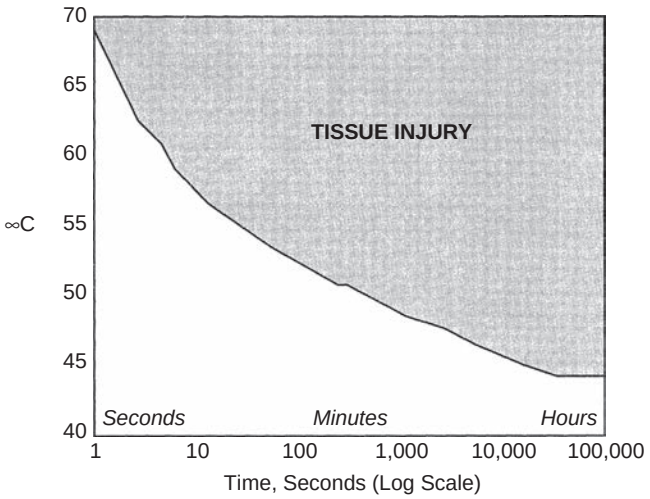

Fig. 115.1 Time required for contact with an object at various temperatures to produce burn injury. (Data from Moritz AR, Henriques FC Jr: Studies of thermal injury. II. The relative importance of time and surface temperature in the causation of cutaneous burns. *Am J Pathol* 23[5]:695–720, 1947.)

applied to the skin at the site of contact with the warming device also compromises perfusion and increases the likelihood of injury. Reports of injury caused by a circulating water system typically include pressure at the contact point as a contributing factor.

Patients at the extremes of age also appear to be at higher risk for thermal injury, both because they are at increased risk for the development of hypothermia and are therefore more likely to have heating devices applied during surgery and because they may suffer from poor tissue perfusion.

Device malfunction may cause injury if proper routine maintenance has not been performed or if the equipment is not used according to the manufacturer's directions. Even properly used and maintained machines may produce injury if tolerances allowed by the device exceed the ability of tissue to safely absorb and transfer the energy. This is especially likely when high temperature gradients exist between the device and the patient. Some commonly used circulating water blankets allow water temperatures as high as 48°C, even when properly calibrated and maintained. Temperatures greater than 45°C may predictably produce thermal injury, depending in part on the time of exposure (see Fig. 115.1).

Patient warming systems draw high levels of electrical current, and poorly maintained devices or those contaminated with fluids may overheat and cause a fire, presenting a hazard to the caregivers as well as to the patient. Electrocution is another risk of faulty electrical equipment, albeit less likely with isolated power systems.

Recently there have been a number of allegations that forced-air warming (FAW) increases the risk of infection, particularly for joint replacement surgery. All 34 of the current MAUDE database reports for one manufacturer of FAW devices consist of surgical site infections (SSIs) that have resulted in litigation against the device manufacturer. Despite the assertions of malpractice attorneys and some manufacturers of competing products, the link between FAW and SSIs is far from proven. Although it does appear that the use of FAW may disrupt the laminar flow of clean high-efficiency particulate air–filtered air in operating rooms, two recent reviews have concluded that there is insufficient evidence linking FAW and SSIs. Two important conclusions were reached: (1) The quality of research in this area is poor, and (2) maintenance of normothermia, currently most often accomplished by FAW, has been shown to decrease the incidence of SSIs, and should not be simply abandoned due to concerns about wound contamination.

Implications

Patients having major vascular procedures or those involving cardiopulmonary bypass often have such diminished cardiovascular reserve that major burns can be a fatal complication. Less severe burns can also cause major morbidity. Permanently disfiguring scars that result from well-intended but ill-advised warming methods can put practitioners at significant medicolegal risk.

Hyperthermia may cause an increase in cardiac and respiratory work and oxygen demand that produces undue stress on patients with limited physiologic reserves. Vasodilation and sweating may produce relative or absolute hypovolemia and acidosis, and a hypermetabolic state may cause hypoglycemia. Iatrogenic hyperthermia may be misdiagnosed as malignant hyperthermia, resulting in a whole cascade of unnecessary treatment. Extreme hyperthermia may result in central nervous system damage and death.

Surgical site infections are a major source of perioperative morbidity and mortality. Patients with SSIs have significantly increased length of stay and greatly increased cost. It has been estimated that the total cost to U.S. health care for SSIs is $3.4 billion to $10 billion.

MANAGEMENT

On recognition that a burn injury has occurred, prompt referral to a physician skilled in the treatment of burns is essential. The proper management of burns is the subject of many textbooks and is not discussed further.

Management of hyperthermia includes turning off or removing the warming device from the patient and uncovering as much of the patient as is practical under the circumstances. Active cooling is rarely necessary if overzealous warming is the sole reason for the elevated temperature; however, many temperature management devices are capable of active cooling as well as warming. If the temperature elevation is severe or refractory to passive cooling, other causes, such as infection, sepsis, or malignant hyperthermia, should be sought.

PREVENTION

The best management for injury related to patient warming devices is prevention. The ASA closed claims analysis of such injuries found that in 17 of 28 cases, care was judged to be substandard. This was the finding in all but one case of burns resulting from the application of heated IV solution bags or bottles. These devices should never be used for patient warming; they are not intended for that purpose, they are inefficient, and they are associated with an unacceptably high risk of patient injury.

Injuries from approved patient warming devices are more difficult to prevent, but attention to a few important details should make injury unlikely:

- All devices should be maintained as recommended by the manufacturer.
- Any machine that fails safety testing during routine maintenance should be removed from service immediately.
- The anesthesia provider responsible for the patient's care should personally check the settings of the machine used.
- The provider should be familiar with and adhere to the manufacturer's recommendations for use of the device. No alterations in the device should be made unless they are approved by the manufacturer.
- Intraoperatively, constant vigilance must be maintained to ensure that portions of the heating devices not intended for direct patient contact, such as the tubing for a water blanket or the hose of a forced-air mattress, do not touch the patient.
- When possible, water blanket devices should be used on top of the patient rather than beneath. This should minimize the risk of poorly perfused tissue being in contact with the device. This should also enhance the efficacy of the device, because operating table mattresses already provide adequate insulation, and the primary loss of a patient's heat is into the room. In fact, warming devices generally act by decreasing or eliminating the loss of the patient's own metabolic heat rather than by adding extrinsic heat.
- Pressure (e.g., from positioning aids) should not be put on parts of the body in contact with conductive warming devices. That is, water or electrical resistance blankets should not be applied until the patient has been properly positioned for the planned procedure.
- Warming devices should not be placed on any part of the body that is distal to a tourniquet or cross-clamp, because large device-tissue temperature gradients can develop, with resultant injury.

ACKNOWLEDGMENT

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116 Pipeline Source Failure

James F. Szocik

Case Synopsis

It is the first day of operation of the hospital's new outpatient surgery wing. The anesthesiologist reports to work looking forward to a day of easy cases consisting of healthy American Society of Anesthesiologists class I outpatients. During the first case, however, a tiny chirp is heard, accompanied by an advisory stating that the oxygen (O_2) supply is low. Several seconds later, the anesthesiologist notices that the ventilator bellows is not filling, the comforting sound of the cycling ventilator is absent, and a cacophony of alarms is sounding, including apnea pressure and volume alarms and minute volume alarms.

PROBLEM ANALYSIS

Definition

A pipeline failure can be one of two types: a quantitative problem, with too little or too much pressure, or a qualitative error, indicating that a contaminant is present (Box 116.1). In the extreme case of switched pipelines, the contamination consists of 100% undesired gas. The pipeline is made up of a large number of components (Fig. 116.1), any of which can fail.

Recognition

Quantitative errors in pipeline supply can be detected via a pressure-sensing device. A machine checkout using guidelines recommended by the Food and Drug Administration will detect a lack of pipeline pressure or an excess of pressure. During a procedure, modern anesthesia machines are equipped with a low-O_2 pressure alarm that sounds to alert the operator that the O_2 supply is failing. A nitrous oxide (N_2O) pipeline failure does not sound an alarm on the anesthesia machine. However, supply pipelines for the other gases may have central pressure alarms.

Qualitative errors are more difficult to detect. Gross contamination of O_2 can be detected by using an O_2 sensor, which is calibrated to read 21% in room air, and confirming that the sensor reads greater than 90% with 100% pipeline O_2. A properly calibrated O_2 sensor will advise if a different gas has been switched into the O_2 pipeline. However, no currently available monitor or analyzer can detect the entire spectrum of potential contaminants in a pipeline system (e.g., carbon monoxide, trilene, solvents), especially at low concentrations. One's olfactory sense may detect some contamination, but this exposes the tester to potentially dangerous contaminants.

Risk Assessment

All patients receiving gas other than room air are at risk. Most pipeline problems involve the quantitative aspect of pressure (either too high or too low). A case reported in 2004 involving a triply redundant system (i.e., primary, secondary, and reserve tanks) highlighted the resiliency of such a system. Despite a shutdown of the primary and secondary tanks due to a massive spill of liquid oxygen from a failed connection, the reserve tank was able to supply the demands of multiple operating rooms and intensive care unit beds. In a survey of more than 200 anesthesia departments at academic institutions, 37 of 76 reported mishaps involved low pressure in the O_2 pipeline. These can be detected during the standard anesthesia machine checkout. More serious is a crossover in the pipeline supply, which can result in hypoxia. Crossover errors involving the O_2 source are detected when verifying that the O_2 analyzer reads greater than 90%, using pipeline gas as part of the standard anesthesia machine checkout. Contaminated gases are more insidious. They can occur as part of the manufacturing or refining of gases, from the improper use of cleaning solutions in the pipeline, or from improper welding techniques. Detailed analysis of the gas at the patient end is the only way to detect this kind of failure. Many failures and instances of contamination are associated with construction and modification of the pipeline system. Greater vigilance is needed whenever construction is ongoing in the vicinity of the pipeline.

Implications

Pipeline pressure that is too low can result in inadequate delivery of gases to the patient. In the case of N_2O, inadequate anesthetic depth and patient awareness may occur. Lack of O_2 is far more serious and can result in hypoxia and organ damage. Pipeline pressure that is too high can damage the anesthesia machine, resulting in broken flowmeters, inaccurate readings, or internal rupture of components. If this occurs, the anesthesia machine must be replaced immediately intraoperatively.

Qualitative problems with gas delivery can asphyxiate the patient if a non–life-sustaining gas is substituted for O_2 or poison the patient if the contaminant is toxic. As reported by Moss and Evans, trichloroethylene contamination was implicated in four deaths in Texas. Hospital workers initially detected the problem when they noticed an odor in the delivered O_2.

In summary, quantitative errors are easily detected. No patient should be harmed by lack of O_2 or N_2O. In contrast, except for pipeline crossover, qualitative errors are more insidious. Aside from detailed gas analysis, there is no fail-proof method to detect contamination of piped gases.

MANAGEMENT

One strategy can accommodate all permutations of pipeline failure, including contaminations (Fig. 116.2). In all cases of pipeline failure,

BOX 116.1 Pipeline Problem List

A. Quantitative Problems

I. Low pipeline pressure
   1. Kinked hose to machine
   2. Leak in hose to machine
   3. Leak in coupling hose to machine
   4. Obstruction in pipeline
   5. Valve in hall turned off
   6. Leak in pipeline
   7. O_2 supply empty
   8. Failure of reserve supply to activate
   9. Regulator frozen in closed position

II. High pipeline pressure
   1. Regulator frozen in open position
   2. Liquid gas in line expanding

B. Qualitative Problems

I. Contamination in piping
   1. Error in indexed safety system allowing cross-connection
   2. Piping crossover
   3. Foreign body in pipeline
   4. Cleaning solution in pipeline

II. Contamination at source
   1. Wrong gas filled in tank
   2. Cleaning solution in tank
   3. Wrong connection at source

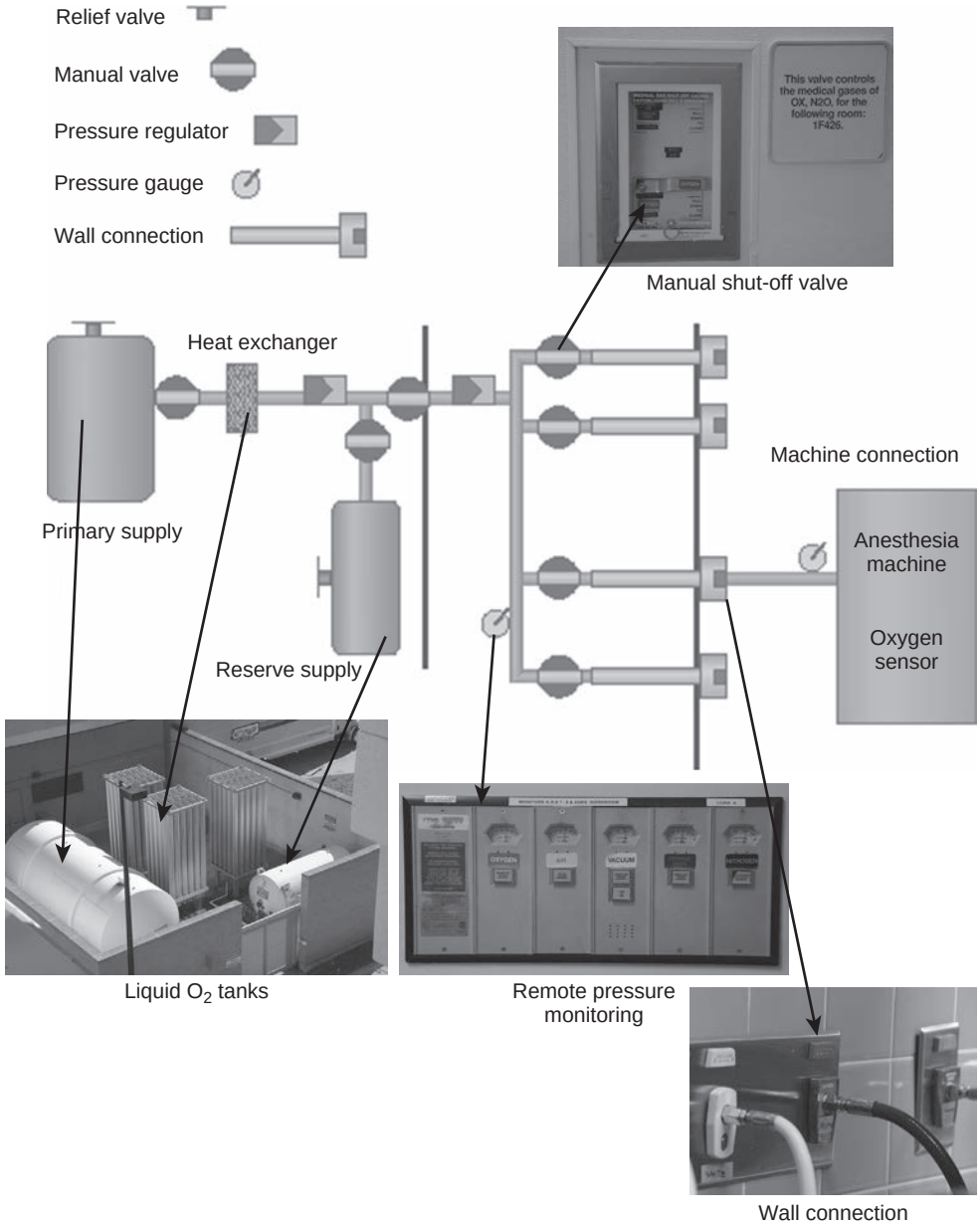

Fig. 116.1 Schematic diagram of a piped-gas delivery system. The primary supply may be liquid, large cylinders, or on-site compression. For the anesthesiologist, detection of pipeline problems occurs at the anesthesia machine (either pressure gauge or oxygen sensor), which is the final common pathway for the large number of components constituting the piped-gas supply.

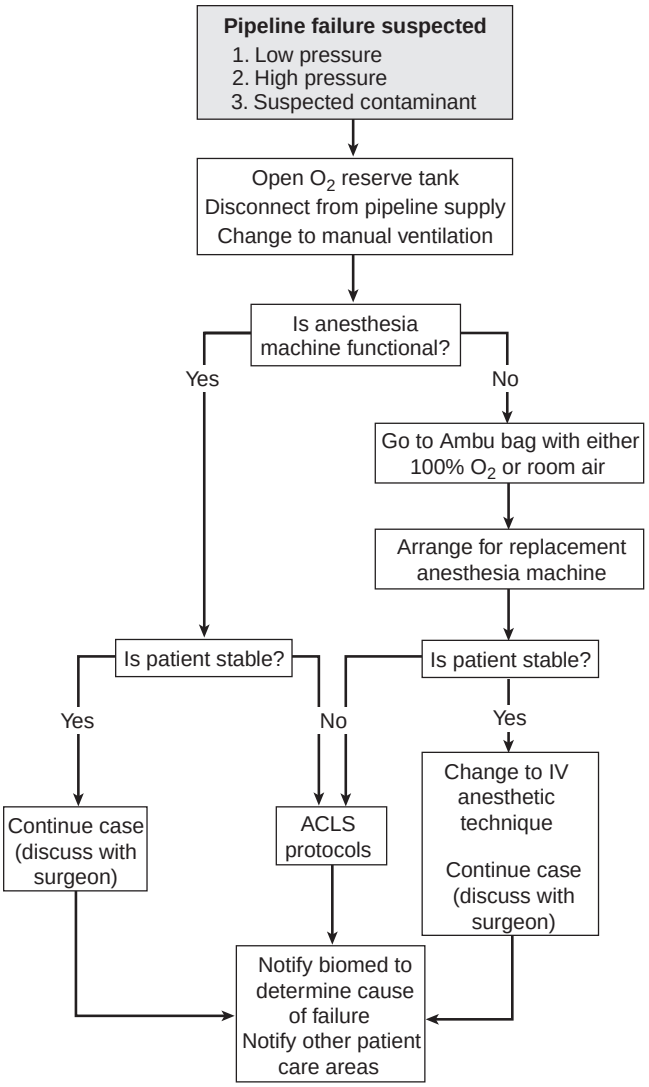

Fig. 116.2 Simple algorithm for dealing with pipeline failure. *ACLS,* Advanced cardiovascular life support; *biomed,* hospital biomedical engineering department.

O_2 and ventilation must be provided to the patient. If the anesthesia machine is functional, O_2 and ventilation are most easily provided by changing to the anesthesia machine O_2 tank supply and disconnecting from the wall O_2 supply. Because the anesthesia machine preferentially draws from the wall (pipeline) O_2 source, the pipeline should be disconnected from the anesthesia machine to prevent additional contamination from entering the system. Because most ventilators are driven by pressure from the O_2 supply, changing to manual ventilation will conserve O_2 in an emergency. However, if the anesthesia machine has been damaged by high pressure, or if both the pipeline supply and the tank supply have failed or are suspected of being contaminated, a self-inflating Ambu bag with room air will keep most patients alive until reserve equipment becomes available. Anesthetic needs can be met by total intravenous anesthesia. Vital time should not be wasted trying to troubleshoot and fix a potentially damaged anesthesia machine. Finally, notice of a failure needs to be communicated quickly to other patient care areas, so that more global failures or contaminations can be dealt with properly.

At this point, the hospital's biomedical engineering department should be asked to determine the nature and origin of the failed component. Analogous to the low-pressure strategy, the source of the failed component (most likely a regulator) can be identified by determining whether the entire system or only a portion of the system is affected.

If a contaminant is suspected, the tank supply should be activated, the machine disconnected from the pipeline source, and the biomedical engineers notified to take a sample of the gas for analysis. Construction or maintenance records are helpful to determine when any work was done on the pipeline.

PREVENTION

Prevention of pipeline catastrophes has both mechanical and human elements. Pipeline gas supplies are mechanical constructions, and all mechanical constructions have a failure rate. Given enough time, a valve, regulator, or other pipeline component will fail. Automatic systems to activate reserve and secondary supplies, pressure relief valves, and other mechanical safety devices help prevent patient injury. Proper inspection and maintenance carried out by trained personnel will help prevent mechanical failures. Computer-controlled systems, however, can fail catastrophically without warning. If so, the human element becomes most important.

Prevention of patient injury involves all the mechanical safeguards mentioned earlier plus a more important human element. Because all mechanical safeguards can fail, it is up to a vigilant anesthetist to detect malfunctions and activate appropriate secondary systems. In the operating room environment, this means that a properly checked-out anesthesia machine must be available for every anesthetic administration.

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Proportioning Systems

117

Stewart J. Lustik • Keith M. Franklin

Case Synopsis

A healthy 45-year-old woman presents for total abdominal hysterectomy to be done under general anesthesia. After denitrogenation with 100% oxygen (O_2), anesthesia is induced with propofol. The patient is paralyzed with succinylcholine and easily intubated. Nitrous oxide (N_2O) and isoflurane are added. Desaturation occurs quickly, despite a normal end-tidal carbon dioxide tracing, clear bilateral breath sounds, and normal blood pressure. The O_2 analyzer reads 14%. The flowmeters reveal the delivery of 5 L/min of N_2O and 0.8 L/min of O_2.

PROBLEM ANALYSIS

Definition

A hypoxic mixture was delivered to this patient due to a faulty proportioning system. The proportioning system is one of several safety devices designed to prevent the delivery of hypoxic gas mixtures to the patient. A properly functioning proportioning system does not allow the delivery of a mixture of more than 75% N_2O with 25% O_2.

A Link-25 proportion-limiting control system was used on the previously manufactured Modulus, Modulus II, and Excel series, as well as the current Aestiva and Aespire anesthesia machines produced by GE Healthcare (previously Datex-Ohmeda). The delivery of more than a 3:1 ratio of N_2O to O_2 is prevented by the combination of an interlocking gear mechanism and regulation of the gas inlet pressures. The N_2O control valve has a 24-tooth sprocket, which is connected by a chain to the freewheeling 48-tooth sprocket of the O_2 control valve (Fig. 117.1). N_2O and O_2 control valves may be moved independently to deliver up to 75% N_2O; however, when the ratio of N_2O to O_2 rises to 3:1, the kick-in tab on the O_2 gear engages with the stop screw on the O_2 control knob. Thus the N_2O and O_2 control valves become linked. Any further increase in N_2O proportionally increases the O_2 flow to prevent a more than 3:1 ratio. Similarly, an attempt to decrease the O_2 flow would proportionally decrease the N_2O flow to maintain a 3:1 ratio. When the N_2O and O_2 control valves are linked, the 2:1 sprocket ratio results in the final 3:1 ratio of gases delivered due to the adjustment of gas inlet pressures. The second-stage N_2O regulator reduces the inlet pressure to 38 ± 0.5 pounds per square inch gauge, and the O_2 regulator is adjusted to 20.75 ± 3.75 pounds per square inch gauge.

The proportioning system of the anesthesia machines previously manufactured by North American Dräger is called the Sensitive–Oxygen Ratio Controller (S-ORC) (Fig. 117.2). Supplied O_2 and N_2O are modulated through respective resistors to exert a backpressure on the upper (O_2) and lower (N_2O) diaphragms. This backpressure, in conjunction with the differing spring constants of the upper and lower springs, causes movement of a piston attached to the proportioning valve. An increase in N_2O flow beyond 72% to 78% moves the piston, which raises the proportioning valve and limits further N_2O flow. For example, if the O_2 flowmeter is set at 1 L/min, the S-ORC will not allow more than 3 L/min of N_2O. If the N_2O control knob is turned to increase the flow to more than 3 L/min, the pressure of N_2O on the diaphragm will move the piston to prevent a further increase in N_2O flow. Similarly, if the O_2 flow is reduced to less than 22% to 28%, the N_2O flow will be reduced proportionally to maintain the O_2 percentage required.

Many recently designed anesthesia machines, such as the GE Healthcare Aisys CS2, Dräger Perseus 500, and Mindray A7 (Fig. 117.3), use an electronic proportioning system. The O_2 and N_2O flows are electronically measured, and if the N_2O flow is too high, a current-driven proportional valve limits N_2O flow to allow a minimum of 25% or 26% O_2. The proportional valve must be checked for calibration every 12 months. These machines also allow the user to set the desired fresh gas flow and O_2:N_2O ratio with digital inputs.

Recognition

Diagnosis of a faulty proportioning system requires recognition of the signs of mechanical failure, delivery of a hypoxic mixture, receipt of a hypoxic mixture, or all of these:

- Mechanical failure
  - Absence of the audible and palpable "clink" of the Link-25 system when the increase in N_2O flow results in a mixture of more than 75% N_2O.
  - Heights of the N_2O and O_2 flowmeter bobbins or bar graphs indicate a ratio of more than 3:1. A stuck flowmeter bobbin may also be the cause.
- Delivery of a hypoxic mixture
  - Low reading of the O_2 analyzer.
- Receipt of a hypoxic mixture
  - Hypoxia enhances adrenergic tone, leading to tachycardia and hypertension. If uncorrected, it will ultimately lead to bradycardia, hypotension, and asystole.
  - Peripheral hemoglobin oxygen desaturation is indicated by pulse oximetry measurements.
  - The patient appears cyanotic.

Risk Assessment

Although delivery of a hypoxic mixture due to a broken proportioning system is rare, there are several potential causes of proportioning system failure. First, defective mechanics in the proportioning system may result in the delivery of a hypoxic mixture. There have been case reports of malfunctions of the Link-25 proportioning system

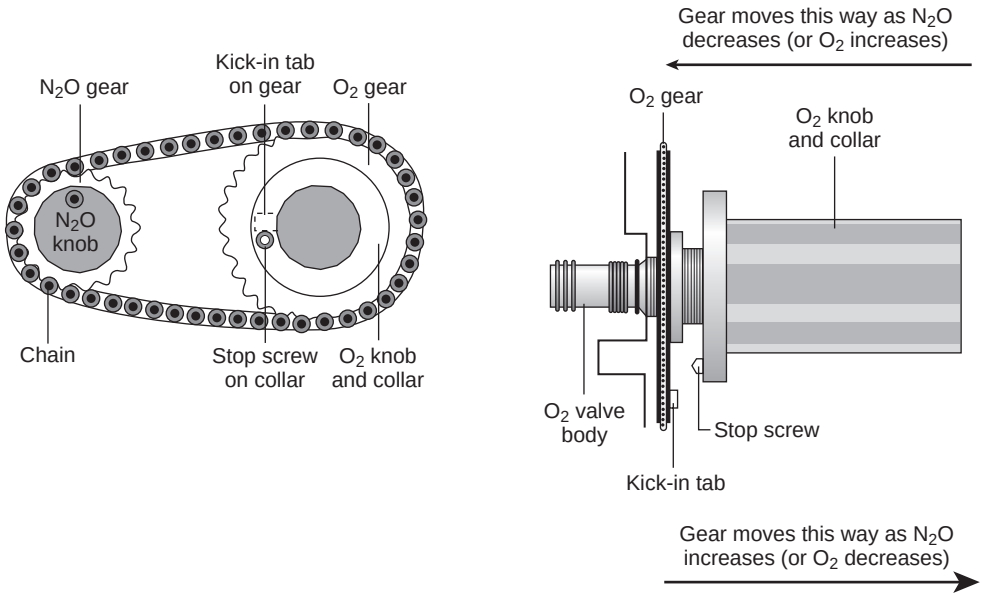

Fig. 117.1 Ohmeda Link-25 proportioning system. As the nitrous oxide–to–oxygen (N_2O-to-O_2) ratio increases, the O_2 gear moves toward the O_2 knob. When the N_2O-to-O_2 ratio reaches 3:1, the O_2 gear interfaces with the O_2 knob, and the O_2 and N_2O knobs become linked. (Courtesy Ohmeda.)

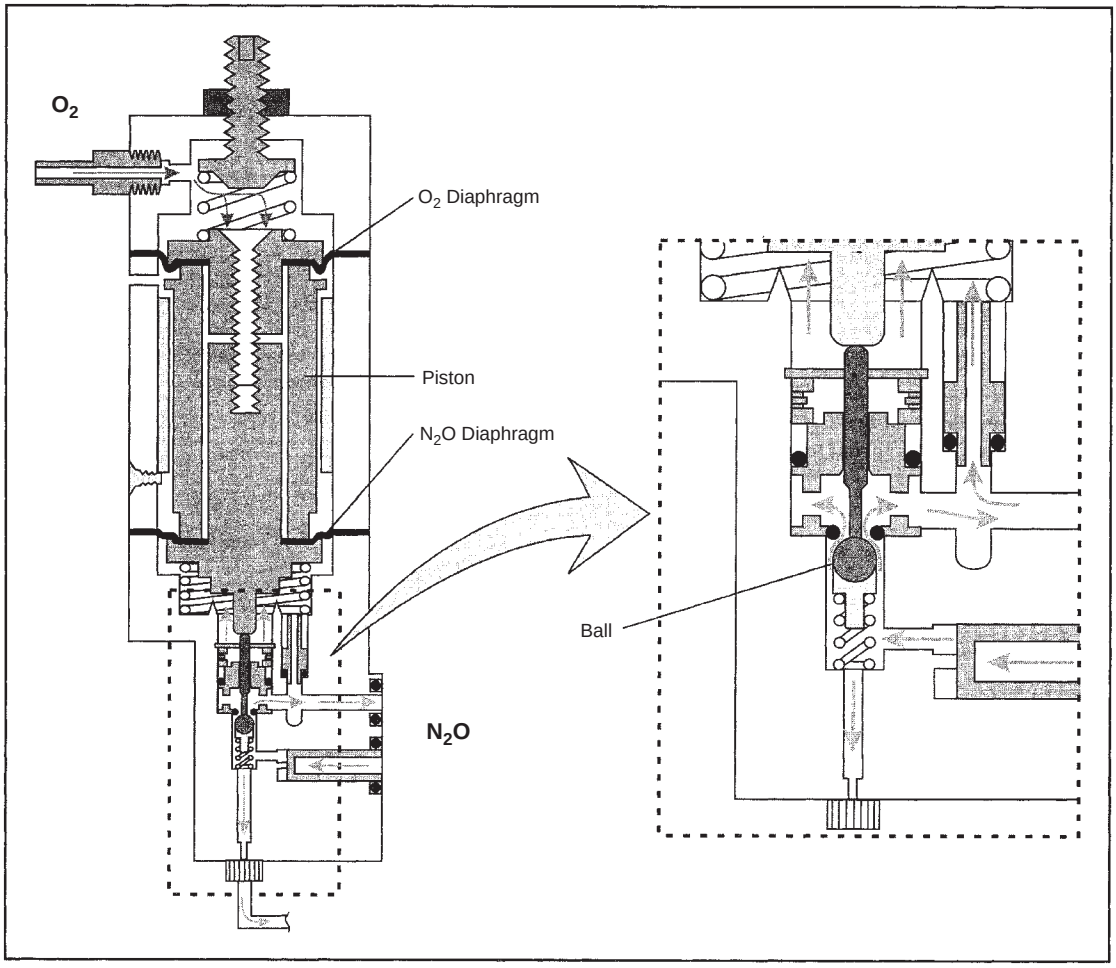

Fig. 117.2 Narkomed oxygen ratio controller. When oxygen (O_2) flow is reduced below 25% ± 3%, O_2 pressure on the upper rolling diaphragm becomes less than nitrous oxide (N_2O) pressure on the lower diaphragm, and the piston moves upward. This allows the spring beneath the ball valve to force the ball valve up, partially occluding the flow of N_2O until a new equilibrium is reached. Increasing the O_2 flow until it is more than 25% ± 3% pushes the piston and ball valve downward to reduce the obstruction to N_2O flow. (Courtesy North American Dräger.)

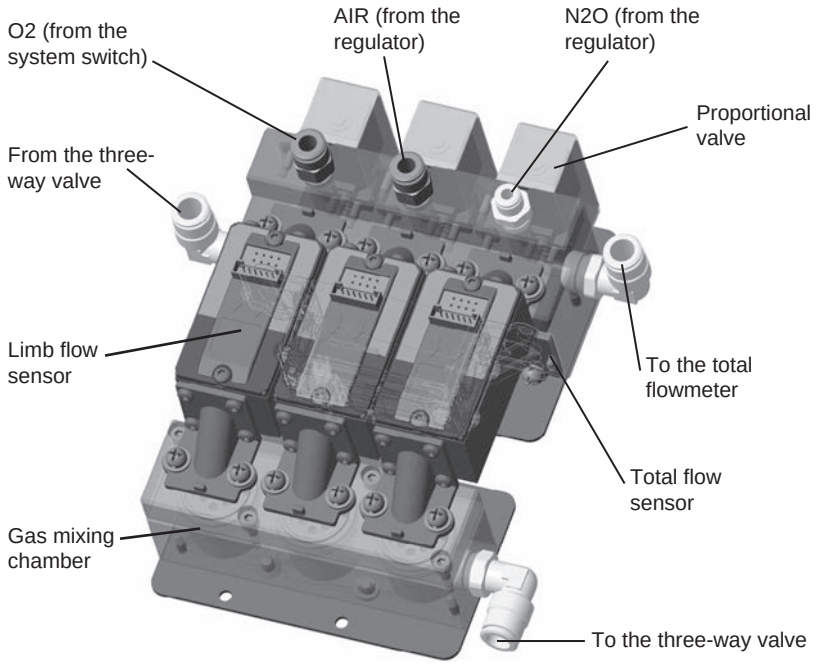

Fig. 117.3 Mindray A7 electronic flow control system. Three electronic flow sensors give feedback to the proportional valves; these valves control fresh gas flow of oxygen, air, and nitrous oxide. Oxygen cannot be set below 26% when nitrous oxide is used. (Courtesy Mindray North America. From *A7 anesthesia system service manual.* Mahwah, NJ, Mindray, Inc., 2015.)

on Ohmeda machines. In one case, a broken chain connecting the sprockets allowed N_2O to increase to hypoxic concentrations. The chain on later models was made of stainless steel as opposed to plastic, which increased its tensile strength. However, this did not prevent the chain from coming off of the O_2 knob in a subsequent instance. In another case, malposition of the O_2 control knob on its stud caused failure of the knob to engage, despite delivery of 100% N_2O. In addition, loosening the stop screw on the collar of the O_2 control knob has led to the delivery of a hypoxic mixture in at least three cases. Another case of failure of the Link-25 system involved the sprocket becoming disengaged from the knob. Although there are no reports to date of failure of any of the electronic proportioning systems, a valve failure could lead to delivery of a hypoxic mixture. Mechanical failure on the North American Dräger machine is also rare, although defects in any of the S-ORC components (e.g., diaphragm, spring, piston, adjusting screw, resistor) could lead to the delivery of a hypoxic mixture.

Second, pneumatic components of the GE machine may fail. If the second-stage O_2 or N_2O regulators on Ohmeda machines lose calibration, delivery of more than 75% N_2O oxide may result. The North American Dräger machines do not use second-stage regulators.

Third, electronic components of the proportioning systems of modern anesthesia machines (Aisys CS2, Perseus, and Mindray A7) may fail, although the N_2O flow is automatically shut off if the total gas flow to the patient is more than the set flows for N_2O plus O_2.

Fourth, a hypoxic mixture or inadvertent N_2O may be delivered to the patient despite a properly functioning proportioning system. This could occur as follows:

- Proportioning systems control only the ratio of O_2 and N_2O; thus a hypoxic mixture could be delivered if another gas (e.g., helium) is added to the mixture. It is possible to deliver less than 21% O_2 when desflurane is mixed only with air, even with the Aisys, which compensates for desflurane when used with N_2O.
- A gas other than O_2 is in the O_2 pipeline or cylinder.
- There is a leak downstream from the proportioning system, including the O_2 flowmeter.
- The S-ORC (North American Dräger) may result in the inadvertent delivery of N_2O. If the flow of O_2 is reduced while N_2O is delivered at a 3:1 ratio, N_2O will be reduced proportionally. If it is later desired to increase the O_2 concentration, increasing the flow of O_2 will cause N_2O to rise in a 3:1 ratio until the initial N_2O flow is achieved.

Implications

The delivery of a hypoxic mixture may result in arterial O_2 desaturation, organ ischemia, cardiovascular collapse, and eventually death if not corrected.

MANAGEMENT

If delivery of a hypoxic mixture is due to a malfunctioning proportioning system, the N_2O control knob should be shut off. The proportioning system can be bypassed by using the O_2 flush valve or a separate O_2 tank. The anesthesia machine should be removed from use until a service representative can inspect and replace the proportioning system, if necessary.

PREVENTION

The proportioning system should be included in the routine anesthesia machine check before the initiation of anesthesia. The Food and Drug Administration's anesthesia apparatus checkout guidelines recommend, "Attempt to create hypoxic O_2/N_2O mixture, and verify correct change in gas flows and/or alarm." On Ohmeda machines, attempts to increase the N_2O flow to more than a 3:1 ratio with O_2 should proportionally increase the flow of O_2; likewise, attempts to decrease the O_2 flow to less than a 1:3 ratio with N_2O should proportionally decrease N_2O. On the North American Dräger and newer GE

Healthcare anesthesia machines, it should not be possible to increase the N_2O-to-O_2 flow ratio to more than 3:1, and decreasing O_2 below a 1:3 ratio should proportionally decrease the N_2O flow.

Measurement of the fraction of inspired O_2 during anesthesia is required by American Society of Anesthesiologists guidelines. The O_2 analyzer must be calibrated before the administration of anesthesia, because this is the most reliable method of detecting the delivery of a hypoxic mixture. A positive-pressure leak test in the North American Dräger machine, and a negative-pressure leak test with Ohmeda machines, must be performed preoperatively to detect a leak downstream from the proportioning system that could lead to the delivery of a hypoxic mixture.

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Pulmonary Artery Pressure Monitoring

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Yuriy S. Bronshteyn • Jonathan B. Mark

Case Synopsis

A 73-year-old woman with known severe mitral regurgitation and a permanent pacemaker is admitted to the surgical intensive care unit with urosepsis and refractory hypotension. Because of her lack of hemodynamic response to fluid boluses, a pulmonary artery catheter (PAC) is placed through her right internal jugular vein and advanced to 53 cm. The recorded pulmonary artery (PA) pressure is 90/30 mm Hg. The next morning, her pulmonary artery pressure is noted to be 76/20 mm Hg, and the waveform display at that time is shown in Fig. 118.1. The intensivist inflates the balloon of the PAC to record PA occlusion pressure. Within seconds, the patient becomes anxious and tachypneic and coughs bright red blood. Suspecting that the hemoptysis is the result of PA rupture, the intensivist inserts an endotracheal tube. A chest x-ray confirms that the PAC tip is positioned in the distal right PA, and the right lung shows a new infiltrate. A bronchial blocker is inserted into the right mainstem bronchus under fluoroscopic guidance to isolate the right lung and allow unilateral left lung ventilation. As a result of ongoing hypoxemia, venoarterial extracorporeal membrane oxygenation is initiated and results in improved gas exchange and blood pressure. The following day, the patient undergoes successful coil embolization of a proximal branch of the right pulmonary artery.

PROBLEM ANALYSIS

Definition

PACs are commonly used by anesthesiologists and intensivists to guide hemodynamic management of circulatory shock and monitor surgical patients with severe pulmonary hypertension and/or severe ventricular dysfunction. PAC placement requires the insertion of an introducer sheath into a large vein such as the internal jugular, subclavian, or femoral, but may also be achieved via the axillary vein. The PAC is then placed through the sheath into the lumen of a vein, its balloon is then inflated, and the catheter is advanced with the assistance of the blood flow to and through the right atrium (RA), right ventricle (RV), and proximal PA. Continuous pressure monitoring is used as the PAC is advanced to identify catheter tip location and confirm proper placement. Fluoroscopic guidance can also be used to assist PAC placement. More recently, a technique for transesophageal echocardiography–guided PA catheterization has been described.

Complications of PAC monitoring may occur during or after catheter placement. Insertion-related complications include those that occur during all central venous catheterizations, except that the larger size of the dilator and sheath used for PAC insertion can result in more serious vascular injury (complications related to central venous catheterization are discussed in Chapter 105). In addition to central vascular injury, other mechanical injuries described during PAC insertion and monitoring include arrhythmias, tricuspid or pulmonic valve injury, and pulmonary artery perforation. Beyond mechanical complications, PAC monitoring has been associated with central line bloodstream infection, infectious endocarditis, and pulmonary thromboembolism. Finally, and perhaps most importantly, misuse of the pulmonary artery catheter and misinterpretation of catheter-derived data remain important, and perhaps the most common, clinical complications.

Arrhythmias or Bundle Branch Block

As the PAC passes through the RA and RV, both atrial and ventricular arrhythmias are commonly observed. Atrial or ventricular ectopic beats and nonsustained ventricular tachycardia occur commonly (estimates range from 13% to 70% of all PAC placements). Ventricular ectopy can also occur in patients with a PAC in situ and during removal of the catheter. Most atrial and ventricular arrhythmias caused by catheter manipulation are benign and self-limited. However, onset of a supraventricular tachycardia such as atrial fibrillation in some patients may cause severe hypotension and require treatment. Hemodynamically significant sustained ventricular tachycardia or ventricular fibrillation is very infrequent but can develop and may require complete withdrawal of the PAC from the heart.

New right bundle branch block (RBBB) can occur during or shortly after PAC insertion in up to 5% of patients. This is of little consequence except in patients with preexisting left bundle branch block (LBBB). In these patients, complete heart block may ensue, resulting in severe hemodynamic instability requiring emergency cardiac pacing or other standard treatment of severe bradycardia or asystole. Studies suggest that this is uncommon, occurring in fewer than 1% of patients.

Malposition of the Catheter Tip

Obtaining accurate hemodynamic data from a PAC depends on positioning the catheter tip in the main pulmonary trunk or in one

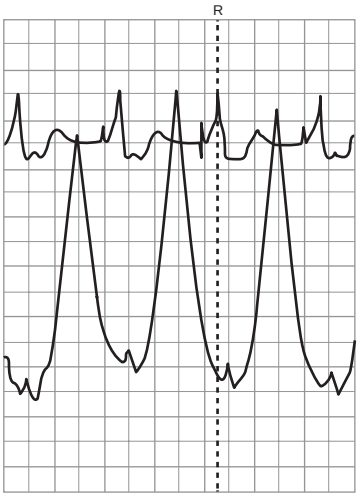

Fig. 118.1 The patient's pulmonary artery catheter waveform just before balloon inflation. The digital display on the monitor records a pressure of 76/20 mm Hg. Note that the electrocardiogram shows ventricular pacing with the R wave highlighted by the dotted vertical line. (Modified from Mark JB: *Atlas of cardiovascular monitoring.* New York, 1998, Churchill Livingstone.)

of the proximal pulmonary arteries (3 to 5 cm beyond pulmonic valve). Errant catheter tip position can generate erroneous data and contribute to PAC-induced vascular injury. When the PAC tip is unintentionally located in the RV rather than the PA, not only will the displayed "diastolic" pressure be erroneous (RV diastolic as opposed to PA diastolic pressure) (Fig. 118.2), but measurements of cardiac output and mixed venous oxygen saturation will also be inaccurate.

After initial PAC insertion, the catheter tip may migrate distally as the catheter softens and blood flow propels it into a more distal and smaller pulmonary artery branch. A catheter with its tip located in a permanent "wedge" position can lead to pulmonary infarction or pulmonary artery rupture, particularly if there is an attempt to inflate the balloon in this position. Alternatively, misidentification of "wedge" pressure as pulmonary artery systolic pressure might lead to inappropriate therapy. Notably, in patients with significant mitral regurgitation, the two pressure tracings can be difficult to distinguish (Fig. 118.3).

Pulmonary Thromboembolism

Autopsy studies reveal an extremely high incidence (approximately 60%) of catheter-related thrombosis in patients with PACs. The thrombus is often attached to the catheter at or near the site of insertion of the introducer sheath. Thrombus also occurs on endothelium or endocardial surfaces that have been traumatized by PAC placement or residence. Thromboses are usually small, but they can be massive and cause clinically important pulmonary embolism. In addition, thrombi can distort hemodynamic measurements by occluding the catheter measurement ports in the RA and PA and the catheter tip thermister used for measuring cardiac output. Heparin bonding may reduce catheter thrombus formation, but increases the risk of heparin-induced thrombocytopenia.

Balloon Rupture

Repeated inflation/deflation of the PAC balloon and multiple reinsertions through the introducer sheath and its external hemostatic valve can damage the PAC balloon. Balloon rupture is recognized when an attempt to inflate the balloon with air (1.5 mL) is met without resistance, and gentle aspiration of the balloon lumen returns blood, rather than air.

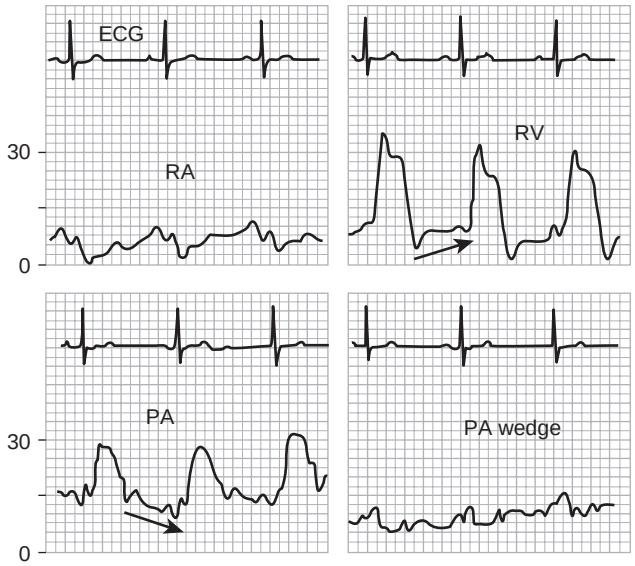

Fig. 118.2 *Upper left,* Right atrial (RA) tracing showing normal central venous or RA pressure waveform. *Upper right,* Right ventricular (RV) tracing showing an increased systolic pressure compared with the RA pressure. *Lower left,* Pulmonary artery (PA) tracing showing increased diastolic pressures compared with the RV tracing. *Lower right,* PA wedge tracing showing a venous pressure waveform, similar to that seen in the RA, but representing an indirect measurement of the downstream left atrial pressure. Note that the absolute values for RV and PA pressures are similar in this example (approximately 30/10 mm Hg) and may not be recognized by examining the monitor digital display. However, the RV and PA waveforms have distinctly different morphologies. The RV pressure *increases during diastole* owing to RV filling whereas the PA pressure *decreases during diastole* owing to PA runoff toward the lung and left side of the heart (see *arrows*). (Modified from Mark JB: *Atlas of cardiovascular monitoring.* New York, 1998, Churchill Livingstone.)

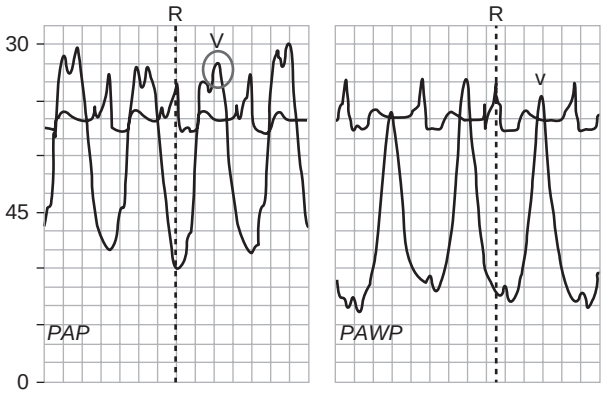

Fig. 118.3 *Left,* Pulmonary artery pressure *(PAP)* tracing in a patient with severe mitral regurgitation. Note that the initial pressure peak precedes the electrocardiogram (ECG) T wave. *Right,* Pulmonary artery wedge pressure *(PAWP)* tracing in the same patient. Note the tall regurgitant V wave with a pressure peak that follows the ECG T wave. This same regurgitant V wave may be seen distorting the PAP tracing, giving it a notched or bifid appearance. As noted in Fig. 118.2, the monitor digital display values may not clearly distinguish the PAP from the PAWP. (Modified from Mark JB: *Atlas of cardiovascular monitoring.* New York, 1998, Churchill Livingstone.)

TABLE 118.1 Signs and Symptoms of PAC Complications

Complication	Associated Signs/Symptoms
Catheter coiling or knotting	1. Resistance to advancement or withdrawal of catheter 2. RV waveform that persists when the catheter is advanced 20 cm beyond the depth of initial RV pressure waveform appearance or at an absolute insertion depth of 60 cm from a right internal jugular site 3. Diagnosis confirmed with chest x-ray
PAC infection	Erythema or pus at insertion site coupled with systemic signs of infection (fever, leukocytosis, etc.)
PAC tip position in RV	Increasing rather than decreasing pressure during diastole on pressure tracing (see Fig. 118.2)
PAC tip unintentionally in wedge position	1. PA tracing shows wedge waveform without balloon inflation (see Fig. 118.2) 2. Chest x-ray showing PAC tip >5 cm right or left of midline 3. Blood sampled from PAC tip shows typical arterial hemoglobin saturation (≥85%) and Pa_{O_2} (≥55 mm Hg) values rather than typical mixed venous values (<80% and <50 mm Hg, respectively)
PA rupture	Anxiety, dyspnea, hemoptysis, hemothorax, hypotension, hypoxemia

PA, Pulmonary artery; *PAC,* pulmonary artery catheter; *RV,* right ventricle.

BOX 118.1 Risk Factors for Pulmonary Artery Rupture

Age >60
Pulmonary hypertension
Distal pulmonary artery catheter migration
Cardiopulmonary bypass
Anticoagulation
Hypothermia
Pulmonary artery catheter balloon overinflation

Pulmonary Artery Perforation or Rupture

Pulmonary artery injuries, including pseudoaneurysm, perforation, or rupture, are among the most serious and life-threatening complications of PACs. Their exact incidence is unknown, but estimates range between 0.03% and 0.2%, with a mortality rate estimated at 41% to 70%. Barash and associates proposed possible mechanisms for PAC-related perforation or rupture based on postmortem study of isolated whole lung preparations:

- A PAC tip that has been advanced too far distally can perforate the vessel.
- Eccentric balloon inflation can propel the tip of the catheter through the vessel wall.
- Balloon overinflation can result in intraballoon pressures of 250 mm Hg, which can be partially or fully transmitted to the pulmonary artery walls, causing overdistention and rupture.

Additionally, attempts to inflate the balloon in a catheter already in a "wedged" position are likely to cause vessel injury and perforation (see Case Synopsis).

Catheter Knotting or Entanglement

PACs can become entangled around cardiac structures or knotted inside the patient. Similarly, PACs have been entrapped by cardiac sutures during open-heart surgery and have become entangled with cardiac papillary muscles and chordae tendineae, pacing and defibrillator leads, and other central vascular access catheters. Knotted or entangled PACs are often discovered during attempts to withdraw or advance the catheter. A number of techniques are described to allow safe nonoperative catheter removal, often with the assistance of an interventional radiologist.

Catheter Colonization and Sepsis

Approximately 1% to 2% of PACs are implicated in bloodstream infections. Further, the PAC itself can injure the endocardial surface of the tricuspid and pulmonic valves, predisposing to infective endocarditis, especially in patients with prosthetic heart valves. Thus strict sterile technique and full barrier precautions should be used when placing PACs.

Inappropriate Use and Data Misinterpretation

PACs are diagnostic tools that require proper interpretation to appropriately guide therapy. Studies in Europe and the United States conducted in the 1990s revealed that intensivists and critical care nurses had multiple gaps in knowledge regarding basic aspects of PAC data interpretation. Roughly half of physicians were unable to do the following:

- Identify the pulmonary artery "wedge" pressure from a clear tracing (see Fig. 118.2)
- Identify the determinants of oxygen transport
- Recognize a blood gas consistent with arterial cannulation

Notably, all of these are fundamental to the safe and effective use of PACs.

Recognition

Signs and symptoms associated with specific PAC complications are summarized in Table 118.1. Differences in morphology between RV, PA, and wedge tracings are summarized in Fig. 118.2.

Risk Assessment

Risk factors for the development of arrhythmias during or after PAC insertion include the following:

- Total time spent passing the PAC through the RA and RV
- Presence of previous myocardial infarction or ischemia, particularly RV ischemia, or LBBB (risk of complete heart block)
- Presence of hypoxemia or acidosis
- Electrolyte imbalance (especially hypokalemia or hypomagnesemia)

Factors associated with increased risk of PA rupture, infarction, or pseudoaneurysm are listed in Box 118.1. During cardiac surgery, manipulation of the heart or distal migration of a cold and stiff PAC when the right-sided heart chambers are emptied during cardiopulmonary bypass predisposes to PA perforation. Risk of PAC-related infection increases with duration of catheterization. The incidence of thrombus formation increases with the duration of catheterization and the severity of the illness.

Implications

As with all invasive procedures, PACs have associated risks and benefits. The incidence of serious complications is estimated to be 0.1% to 5%. This risk must be weighed against the potential benefit of rapidly identifying and managing hemodynamic disturbances. A recent Cochrane review concluded that in critically ill patients, PAC placement does not improve mortality, intensive care unit or hospital length of stay, or cost. However, the authors acknowledge that PACs may benefit subsets of patients in select situations that have not been studied thus far.

TABLE 118.2 Proposed Management Strategies for PAC Complications

Complication	Management Strategies
Atrial or ventricular arrhythmia	Advancement of catheter into pulmonary artery or withdrawal into superior or inferior vena cava
Complete heart block	Transcutaneous or transvenous pacing
Catheter kinking	Careful catheter repositioning with or without fluoroscopy
Catheter knotting	1. Chest x-ray and/or echocardiography to confirm diagnosis 2. Removal by interventional radiology and/or surgery
Catheter-associated infection	Removal of catheter and initiation of systemic antibiotics
Catheter-associated thrombosis	Anticoagulation and consideration for early removal of catheter
Balloon rupture	Careful removal of PAC

PAC, Pulmonary artery catheter.

BOX 118.2 Algorithm for Management of PAC-Related Pulmonary Artery Rupture

Step 1: Reposition PAC tip proximal to site of bleeding, and reinflate the PAC balloon
Step 2: Secure the airway with a single-lumen or double-lumen endotracheal tube
Step 3: Determine laterality of bleeding (e.g., using chest x-ray or transesophageal echocardiography to look for laterality of PAC); place patient in lateral position with the bleeding side down if feasible
Step 4: Achieve lung isolation using any of the following:
1. Using double-lumen endotracheal tube
   a. Inflate both cuffs and ventilate unaffected lung
   b. Consider applying PEEP to the affected lung
2. Using single-lumen endotracheal tube (SLETT)
   a. Right-sided pulmonary artery rupture: insert bronchial blocker, and verify position of blocker in right mainstem bronchus using fluoroscopy or bronchoscopy
   b. Left-sided pulmonary artery rupture: advance SLETT, and confirm its position into right mainstem bronchus using fluoroscopy or bronchoscopy

Step 5: Initiate venoarterial extracorporeal membrane oxygenation

PAC, Pulmonary artery catheter; *PEEP,* positive end-expiratory pressure.

The American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization recommends considering the patient, the surgical procedure, and the practice setting when deciding on the appropriateness of placing a PAC. Recent large retrospective studies suggest that PAC use may improve outcomes for elderly and/or severely injured trauma patients and decrease transfusion requirements in cardiac surgery patients. Further, clinicians currently rely on PACs to guide therapy of patients with complex heart failure states, including patients undergoing cardiac surgery and those requiring mechanical circulatory support. Finally, PACs are more likely to help patient care in practice settings where physicians and nurses have a sufficient level of training and familiarity with their use.

MANAGEMENT

Proposed management for complications of PAC are listed in Table 118.2. Addante and colleagues have proposed an algorithm for management of pulmonary artery rupture caused by PACs. We present our modified version of this algorithm in Box 118.2. Venoarterial extracorporeal membrane oxygenation not only stabilizes gas exchange, but also directs blood flow away from the site of pulmonary hemorrhage. Other potential therapies include the following:

- Coil embolization of pulmonary artery
- Direct surgical PA repair
- Surgical ligation of PA with or without lung resection

PREVENTION

Prevention of PAC complications begins with careful consideration of risks, potential benefits, and alternatives for individual patients. Notably, PAC placement is an elective, invasive procedure whose clinical value remains debated. For instance, in a patient with significant tricuspid regurgitation, thermodilution may overestimate or underestimate the cardiac output, limiting the value of the PAC as a hemodynamic monitoring tool. Alternatives to PAC should always be considered, especially in patients at high risk of PAC-related complications (see Risk Assessment earlier in this chapter). For example, cardiac function can also be assessed using echocardiography and any number of cardiac output monitors utilizing arterial pulse contour or thoracic electrical bioimpedance and bioreactance principles.

Only avoidance of PAC placement can fully prevent PAC complications, but adherence to safety principles may reduce some PAC-related risks. Vascular access–related complications of PAC may be reduced by routine use of ultrasound to guide venipuncture and pressure transduction to confirm intravenous cannulation before dilation of the target vessel. In patients with LBBB who require a PAC, clinicians can make preparations to institute rapid transcutaneous pacing during PAC placement if complete heart block were to occur. However, this precaution remains debated because of the low incidence of complete heart block even in patients with LBBB undergoing PAC placement. Risk of balloon rupture may be decreased by limiting the number of times the balloon is inflated.

Prevention of PA rupture requires careful technique during PAC insertion and manipulation and prompt removal of catheters that are no longer needed. During initial insertion, once a PA wedge pressure tracing is obtained, the balloon should be deflated and the catheter withdrawn 2 to 3 cm while still recording a PA pressure waveform. Ideally, a PAC should be left with its tip 3 to 5 cm beyond the pulmonic valve. Typically, this translates to an insertion depth of 40 to 50 cm when it is introduced into the right internal jugular vein, but the depth varies widely depending on the insertion site and the patient's height. In addition, measurement of "wedge" pressure (1) may increase the risk of PA perforation, (2) can be estimated from the pulmonary artery diastolic pressure (except in patients with severe pulmonary arterial hypertension and increased pulmonary vascular resistance), and (3) is not needed for routine guidance of fluid therapy. Radiographic or echocardiographic confirmation of proper PAC position should be obtained whenever possible. Routine chest radiography may alert the operator to inadvertent distal PAC migration or other technical complications. For instance, on chest x-ray, the PAC tip should lie no more than 2 cm from the lung hilum and no more than 5 cm from the midline. Any provider who places PACs ought to have in mind a plan for management of pulmonary artery rupture (e.g., see Box 118.2). Additionally, any patient with a PAC in situ should have the need for the catheter reassessed at least daily to encourage prompt removal of unnecessary PACs.

Competence in the placement and interpretation of data from PACs is mandatory. This requires formal training in right-sided heart catheterization, along with supervised PAC placement. The minimum number of PAC placement procedures to ensure competence is debatable, but ongoing maintenance of skills is mandatory. Given the decline in use of PACs over the past two decades, such training may need to occur partly in a simulation setting.

ACKNOWLEDGMENT

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119 Rapid Fluid and Blood Delivery Systems

S. Devi Chiravuri • L. Kareen Porter

Case Synopsis

A 65-year-old man is brought to the operating room for emergent repair of a ruptured abdominal aortic aneurysm. The patient is intubated, hypothermic (34.5°C), and hypotensive (blood pressure 85/60 mm Hg). Volume resuscitation is instituted with warmed intravenous (IV) fluids under pressure using a Level 1H-1200 IV fluid warmer. Before skin incision, the blood pressure drops to 60/30 mm Hg, and the end-tidal carbon dioxide ($ETCO_2$) drops precipitously from 35 to 10 mm Hg, suggesting a massive venous air embolus.

PROBLEM ANALYSIS

Definition

Rapid fluid and blood delivery (RFBD) devices are used when IV fluid or blood must be delivered at rates greater than those attainable with free-flow or IV pressure bag devices. Contemporary RFBD devices allow for flows of 1000 mL/min, with the ability to "dial in" flow rates. In addition to high flow, they allow one to select or set the temperature of the infusate.

High flows are provided by pressure. RFBD pressurization can be achieved by two methods: external pneumatic pressurization and occlusive roller pumps. Heating is provided by either water bath conduction heat exchange or a magnetic induction heater.

In addition to delivering high-volume flow rates and heating the fluids, RFBD devices must be able to detect or vent air. Air traps are able to extract small volumes of entrained air, but larger volumes may exceed the capacity of the trap. Many commercially available RFBD devices include safety mechanisms to prevent delivery of air to the patient by shutting off flow if air is detected.

Potential complications associated with the use or malfunction of RFBD devices include the following:

- Air embolism
- Hypervolemia or overtransfusion (transfusion-associated circulatory overload)
- Overheating of fluids
- Hypothermia
- Hemolysis
- Electrical shock

Recognition

Venous Air Embolism

Venous air embolism is a condition that is well described in anesthesia (see also Chapters 127 and 186). It occurs when air enters the venous system, either via entrainment at the operative site or inadvertently via IV catheters; this is more likely with central than with peripheral access. This air travels to the heart and can significantly decrease cardiac output. It can also travel via a patent foramen ovale to the left side of the heart (paradoxic air embolism [PAE]) and potentially lead to coronary or cerebral ischemia. Detection of air can be via echocardiogram, precordial Doppler, or a sudden drop in $ETCO_2$. Signs of a venous air embolus include the following:

- Systemic hypotension
- Increased central venous or pulmonary artery pressures
- Arrhythmia
- Hypoxemia
- Acute decrease in $ETCO_2$
- Decrease in pulmonary compliance
- Cardiovascular collapse

Hypervolemia

Hypervolemia can cause initial hypertension, but this may be followed by hypotension as left ventricular preload and end-diastolic volume increase and eventually drop off the Frank-Starling curve (forward left ventricular failure). If central monitoring is in place, elevated pulmonary artery pressures and pulmonary capillary wedge pressures are seen.

Hypothermia or Hyperthermia

Hypothermia may occur when transfusion is conducted without vigilant temperature monitoring or if the heating mechanism is faulty. This can cause coagulopathy, arrhythmias, peripheral vasoconstriction, and prolonged neuromuscular blockade.

Hyperthermia can be as detrimental as hypothermia. Elevated temperature is detected with temperature monitoring. Core monitoring is more accurate than skin temperature monitoring. Hyperthermia can cause denaturing of molecules such as hemoglobin and cause hemoglobinemia and hemolysis. Clinically, it can manifest as sweating, vasodilation, acidosis, and hemoglobinuria.

Electrical Shock

Electrical shock is not unique to RFBD devices. It can occur with any electrical device that comes in contact with patients. Electrical shock may cause pain, tetanus, thermal injury, or transient arrhythmias.

Risk Assessment and Implications

Vigilance is imperative, as with any medical device. Fatal complications can result from machine malfunction or operator error.

MANAGEMENT

Management of a venous air embolism includes prevention of further entry of air and treatment of air embolism. In the past, anesthesiologists were taught to prevent PAE by decreasing the right atrial to left atrial pressure gradient with positive end-expiratory pressure or Valsalva maneuver. However, these have since been shown to increase the risk of PAE and have largely been abandoned for the relatively superior practice of jugular venous compression.

If a venous air embolus is suspected:

- Alert the surgeon in the event that the air is being entrained at the operative site.
- Stop the rapid infusion device.
- Lower the patient's head, and place the patient in left lateral decubitus position (if possible). Perform jugular compression.
- Discontinue nitrous oxide; place patient on 100% Fio_2.
- If a central venous line is in place, attempt to aspirate air.
- Provide hemodynamic support, including pressors and chest compressions if necessary.

If hypothermia is present, normothermia may be reestablished by increasing the room temperature, use of heating mattresses and forced-air warming blankets, and warming of IV fluids (see Chapter 115). Hyperthermia is treated by switching off any heating devices and may necessitate active cooling through exposure or forced-air convection.

Hemolysis has several causes: shear stresses from overpressurized infusion, overheating of blood and blood products, or transfusion reactions or mismatch. Treatment includes the following:

- Discontinue the transfusion.
- Notify the blood bank, and recheck the crossmatch.
- Maintain the urine output.
- Alkalinize the urine.
- Monitor for signs of disseminated intravascular coagulation.
- Treat signs of hyperkalemia.

Hypervolemia can present as pulmonary or circulatory collapse. Treatment includes the following:

- Circulatory support
- Diuretics
- Vasodilator therapy
- Assisted ventilation or positive-pressure ventilation
- In extreme cases, phlebotomy

PREVENTION

Vigilance is key to minimizing risk in the operating room. Meticulous venting of air before connecting IV lines and infusion devices is an important step. Careful monitoring of $ETCO_2$ is a necessary precaution.

Hyperthermia and hypothermia can be prevented by aggressive treatment and core body temperature monitoring. Skin temperature monitoring can give false information, especially when there is vasoconstriction.

It is also important to pay close attention to the patient's volume status. Urine output, central venous pressure, pulse pressure variation, and transesophageal echocardiogram can provide useful information if available.

The risk of electrical shock can be minimized with vigilance and proper maintenance of all electrical devices in the operating room. Quick checks of the insulation and ground fault detection alarms are a good start.

Finally, the importance of familiarity with and proper use and maintenance of RFBD devices cannot be stressed enough. Attending in-service training programs related to such equipment and maintaining competency in its use should be a priority. Users must be familiar with the capabilities and limitations of these devices under different circumstances, such as battery versus AC power. To avoid the risk of incompatibility and clotting, medications should not be administered through RFBD devices. RFBD devices should be serviced regularly per manufacturer recommendations to prevent malfunction or contamination of water bath heating units. RFBD systems may play a key role in surgery that requires large-volume resuscitation (e.g., major trauma, cardiovascular surgery, liver transplantation), but only when used properly and with good judgment.

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120 Scavenging Systems

Marc Sherwin • James B. Eisenkraft

Case Synopsis

A 25-year-old man with no significant medical history presents for tonsillectomy. After induction of anesthesia and tracheal intubation, anesthesia was maintained using a mixture of O_2/N_2O/isoflurane at a total fresh gas flow (FGF) of 6 L/min. The patient was breathing spontaneously from a circle breathing system. At the request of the surgeon, the anesthesia machine was moved a little to the side, after which the breathing circuit reservoir bag became increasingly distended. Opening of the adjustable pressure limit (APL or "popoff") valve maximally failed to decrease the pressure in the bag. The breathing circuit needed to be intermittently disconnected from the anesthesia machine to relieve the pressure. When the FGF was decreased to 2 L/min, intermittent disconnections of the circuit became necessary less frequently. A hissing sound was audible arising from the closed reservoir waste gas scavenging system interface, and the interface reservoir bag was noted to be completely collapsed.

PROBLEM ANALYSIS

Definition

Fresh gas flows continuously from the anesthesia machine into the circle breathing system; therefore a similar volume must leave to prevent a potentially dangerous increase in the breathing circuit pressure. The waste gas scavenging system is designed to collect the waste gas that leaves the breathing circuit at end-exhalation via the APL valve if the patient is breathing spontaneously, or via the ventilator pressure relief valve (PRV) if the lungs are being ventilated mechanically, and remove it from the operating room. The goal is to decrease contamination of the operating room atmosphere by the anesthetic gas mixture in the breathing circuit.

The basic components of a waste gas scavenging system are the gas collection assembly, transfer tubing, scavenging interface, gas disposal tubing, and disposal assembly (Fig. 120.1). The waste gas is first vented through the APL valve and the ventilator PRV to hoses, called transfer tubing, and conducted to the scavenging interface. The waste gas leaves the interface via disposal tubing, which is usually a separate hospital vacuum system that uses purple-colored hoses to distinguish it from the white-colored hoses used by the hospital main vacuum system.

The scavenging interface design can be either a *closed* reservoir that has positive and negative PRVs and a reservoir bag that provides a means to assess the system's function, or an *open* reservoir that communicates with the atmosphere via (valveless) ports.

In the closed reservoir design, the positive pressure relief valve has an opening pressure of 5 cm H_2O (10 cm H_2O in some new workstations) above which waste gas is released into the room (Fig. 120.2). This scenario is possible if the vacuum flow rate is inadequate (e.g., purple vacuum hose not connected) or there is downstream occlusion of the disposal system. In this case a positive pressure of 5 (or 10) cm H_2O is transmitted back to the breathing system and appears on the breathing system pressure monitor as positive end-expiratory pressure (PEEP). The negative PRVs open at –0.5 cm H_2O (and –1.8 cm H_2O). This scenario occurs when the vacuum flow rate exceeds the rate at which waste gas enters the closed reservoir interface. Entrainment of room air at a high flow rate through the negative PRVs may generate a hissing sound. In the open system, the fixed ports in the reservoir chamber allow room air in or gas out depending on the pressure inside the interface.

The disposal assembly can be described as active or passive. An active system involves the application of suction (vacuum) to remove waste gas from the interface, whereas a passive system allows gas to flow passively through the tubing to the exhaust grill of the operating room. The active system's vacuum should draw 25 L/min of gas to allow for sufficient disposal during induction and emergence when FGFs are high. The disposal tubing, like the transfer tubing, should be designed to prevent occlusion and should not run along the floor to minimize the likelihood of compression or obstruction.

Recognition

Malfunction of the waste gas scavenging system may lead to dangerous conditions for the patient. Increases in breathing system pressure that exceed appropriately set limits will cause an alarm to be annunciated. Pressure monitoring systems provide alarms for high peak pressure, high PEEP, continuing pressure, low pressure, and negative pressure. If the patient is breathing spontaneously, the breathing system reservoir bag status provides a simple means to assess pressure. If pressure is increasing in the breathing circuit this indicates that gas is entering the system faster than it is leaving, therefore the gas flow pathway must be traced from upstream to downstream to determine the site of the resistance or obstruction. If the gas collecting assembly components (APL valve and ventilator PRV) are functioning correctly, gas is released into the transfer tubing to be conducted to the scavenging interface. If the transfer tubing is obstructed, then the waste gas cannot flow to the scavenging interface. When assessing the interface, it is important to recognize the type of system (closed vs. open reservoir) used. In a closed interface that has an active disposal assembly, the reservoir bag should be surveyed for overdistention or underdistention. A collapsed bag indicates that gas removal exceeds inflow. This would occur if the transfer tubing becomes occluded (such as by a wheel of the anesthesia workstation rolling over it when the workstation is moved). With no gas arriving to the interface, continuous negative pressure from the hospital vacuum connected to the interface causes room air to be entrained through the negative PRVs, causing a hissing noise.

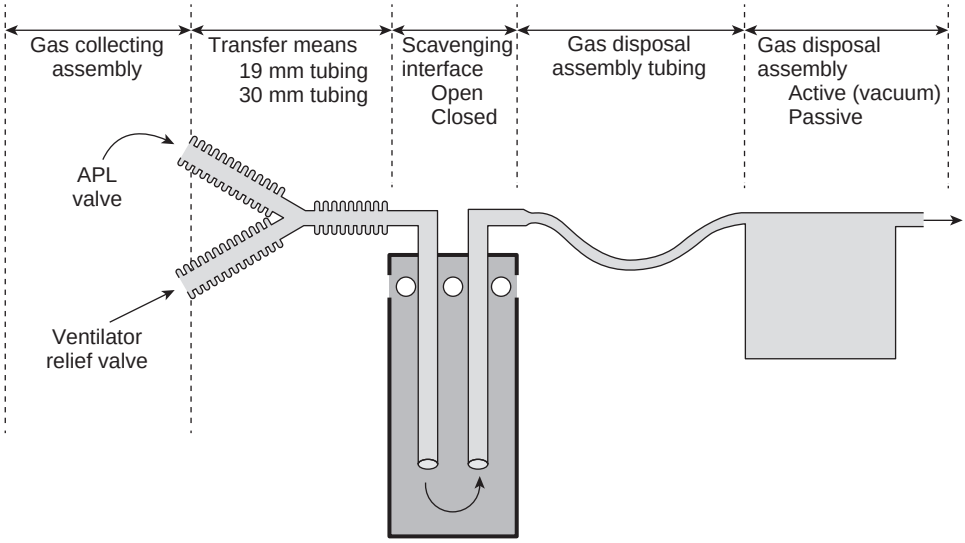

Fig. 120.1 Components of an anesthetic waste gas scavenging system. The interface shown in the diagram is of the open reservoir design. Open ports allow air to enter the interface when the rate of removal of gas by the vacuum exceeds the rate of inflow from the transfer tubing.

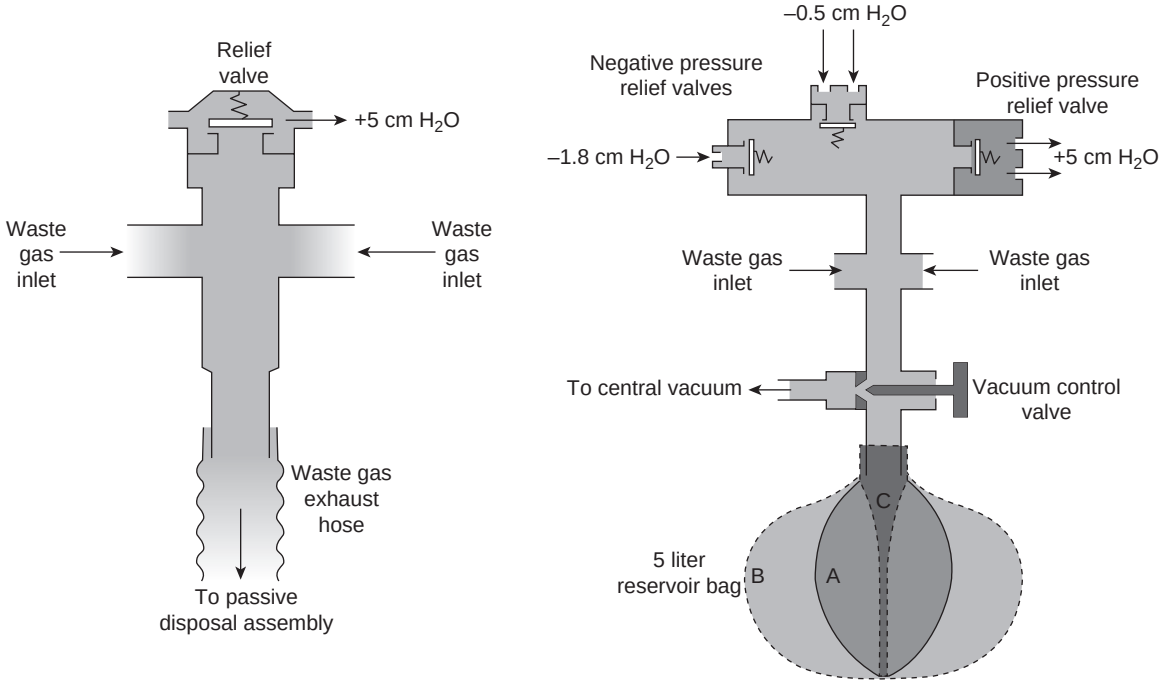

Fig. 120.2 Closed reservoir scavenging interfaces. *Left,* Interface used with a passive disposal system. *Right,* Interface used with an active system. (Courtesy Dräger Medical, Inc., Telford, PA.)

Risk Assessment

Contamination of the operating room atmosphere by waste anesthetic gas can occur due to the practice of the anesthesia provider or by equipment malfunction. Examples of techniques that will increase contamination include the following:

- Turning on anesthetic gas flow before connecting the breathing circuit to the patient
- Disconnecting the breathing circuit from the patient while anesthetic gas is flowing
- Uncuffed tracheal tubes or uninflated cuffed tracheal tubes
- Leak from the mask during induction or maintenance with an anesthetic gas
- Spilling of a liquid anesthetic gas agent such as during vaporizer filling
- Flushing the breathing circuit

Besides provider error, mechanical issues may arise that can lead to operating room contamination. Leaks in the anesthesia machine, the circle system, and the waste gas system may lead to contamination of the atmosphere.

The gas collecting assembly will capture the overflow anesthetic gas through either the APL or ventilator PRV whence it is conducted through two separate tubes that merge into the transfer tube. If the gas cannot move into the scavenging interface, as there is an obstruction in any part of the gas collecting assembly or transfer tubing, the pressure within the breathing circuit will increase. High pressures can lead to barotrauma and possibly even tension pneumothorax.

The scavenging interface can also have issues that can lead to endangerment if the valve system is faulty. In a closed system, if the pressure relief valves are malfunctioning, the negative or positive

TABLE 120.1 National Institute for Occupational Safety and Health Recommendations for Trace Gas Levels

Anesthetic Gas	Maximum Time-Weighted Average Concentration (parts per million)
Halogenated agent alone:	2
Nitrous oxide alone:	25
Combination of halogenated agent plus nitrous oxide:	
Halogenated agent:	0.5
Nitrous oxide:	25
Dental facilities (nitrous oxide alone):	50

From U.S. Department of Health, Education and Welfare: *Criteria for a recommended standard: occupational exposure to waste anesthetic gases and vapors*. Washington, DC, U.S. Department of Health, Education and Welfare, 1977.

pressure in the scavenging system will be transmitted to the breathing circuit. The interface pressure relief valves can become blocked, particularly the negative pressure relief valves. In an open system, if the ports are accidentally obstructed and the gas cannot leave through the disposal system, the resulting pressure will be transmitted to the breathing circuit.

Implications

Problems with the scavenging system are potentially dangerous to the patient. Extreme negative pressures will restrict ventilation, cause alveolar collapse, and may even cause negative pressure pulmonary edema. Positive pressures could interfere with ventilation and cause barotrauma and tension pneumothorax. Although in most cases the PRVs should prevent complications of the scavenging system, the rate of waste gas inflow, the vacuum flow rate, and the size of the reservoir bag will affect a closed reservoir system regardless of the valve functionality.

The contamination of the operating room with waste gas was once thought to be hazardous to the anesthesia provider and operating room personnel. In 1977 the National Institute for Occupational Safety and Health published recommendations for maximal allowable levels of trace anesthetic gases in the atmosphere, averaged over an 8-hour period (time-weighted average) (Table 120.1). These recommended levels have never been promulgated into law and therefore are not enforceable by the Occupational Safety and Health Administration. To date, no study has proven conclusively that trace concentrations of waste anesthetic gases in the operating room atmosphere represent a health hazard to personnel.

Allen and Lees reported a case of fire in an engineering equipment room that was the disposal site of the vacuum pumps for one hospital. The waste gas that is disposed of often contains highly combustible levels of oxygen and, if directed to areas where conditions are right, dangerous fires will be produced.

MANAGEMENT

If there is concern that the waste gas scavenging system is malfunctioning, the patient should be disconnected from the anesthesia breathing system. The patient's lungs may be ventilated using an Ambu bag, and, if continued anesthesia is necessary, it should be maintained using intravenous agents. It is important to examine the system for obvious signs of a problem, such as occluded tubing or an obstructed valve. If the cause of the malfunction cannot be determined, the equipment should be replaced. If the patient has sustained a negative pressure injury, such as atelectasis or pulmonary edema, he or she should be treated with positive-pressure ventilation and 100% oxygen. If positive pressure has resulted in tension pneumothorax, appropriate treatment should follow with chest tube insertion.

PREVENTION

Whenever N_2O and potent inhaled anesthetic agents are being administered, the anesthesia machine should be equipped with a functioning waste gas scavenging system. The preuse checkout of the anesthesia workstation includes a check of the waste gas scavenging system. The transfer tubing should be 30 mm in diameter, or, if 22 mm, color-coded yellow to distinguish it from the 22-mm diameter breathing circuit tubing. The tubing should be as short and rigid as possible to prevent occlusion, as this part of the system is proximal to the PRVs of the scavenging interface and can lead to a dangerous situation when kinked. The interface should be inspected for any loose objects nearby that could interfere with the valves or ports. The disposal tubing should be overhead to prevent accidental obstruction, and if it is on the floor, no equipment should be placed on the line. The waste gas must be disposed from the hospital in an area where it will not recirculate.

To prevent leaks and avoid contamination of the operating room atmosphere, regular checkout procedures of the anesthesia equipment should be followed, including checking the oxygen and N_2O supply for leaks when the cylinder valve is open. Appropriate leak tests should also be utilized. The risk of operating room contamination is higher in cases where uncuffed tracheal tubes are used.

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Surgical Electrocautery

121

Jeffrey J. Schwartz • Jan Ehrenwerth

Case Synopsis

A 59-year-old man is having an open resection of the right colon for cancer. The surgeon is having a difficult time getting exposure, due to adhesions from a previous surgery. On several occasions, he complains that the electrosurgical unit (ESU) is not working properly and wants the energy increased. The circulating nurse complies with his requests. Eventually a new ESU is obtained, but this does not solve the problem. The operation is completed after 3 hours, and the patient is transferred to the postanesthesia care unit (PACU). When the PACU nurse replaces the electrocardiogram (ECG) electrodes, she notes second-degree burns under two of the pads.

PROBLEM ANALYSIS

Definition

The electrosurgical unit (also referred to as the *ESU* or the *Bovie*) is used by surgeons to coagulate blood vessels or to cut tissue. The ESU uses high-frequency AC electrical energy in the range of 500,000 to 1,000,000 Hertz (cycles per second). Electrical current at this frequency does not excite cardiac tissue, but instead passes through the tissue without creating an electrical shock or causing ventricular fibrillation.

The surgeon uses a handheld device that has an active electrode with a small surface area. This small area allows for a very high current density that then produces a cut or coagulates the tissue. This energy must then be returned to the machine. This is done via a large surface area gelled electrode, called a return plate or dispersive electrode. This is placed on the patient and connected to the ESU machine. This dispersive electrode has a very high surface area so that there is a low current density, which safely conducts the energy (Fig. 121.1). It should be noted that this dispersive electrode is frequently referred to as a ground plate. This is absolutely incorrect, as the patient would never be intentionally grounded in the operating room (OR) because this increases the risk of electrical shock.

In the event that the dispersive electrode is not properly applied to the patient, or the gel on the plate has dried out or not properly applied, the high-frequency energy will seek alternate return pathways. Most frequently the ECG electrodes are the alternative pathway. However, because the contact area of the ECG electrodes is relatively small compared with the return plate, the current density will be high and the patient will frequently get a burn at the site where the ECG electrode contacts the patient's skin or at the site of the improperly placed dispersive electrode (Fig. 121.2). Temperature probes and bispectral index monitor electrodes can also be routes for return current and sites of burns. Metal jewelry, if in contact with the OR table, can also create an alternative path for the current and cause a burn.

Recognition

Recognition of problems with the ESU can be very difficult. Because the ESU operates at very high frequencies, the energy can easily return to the unit even when the return plate is not properly applied. In many cases the ESU can appear to be operating normally. Modern units have safety features that will alert the user to some of the problems. For instance, an alarm will sound if the wire from the return plate is not plugged into the unit.

Other signs of potential problems include the surgeon asking for the power to be increased on several occasions, the surgeon having trouble cutting tissue or coagulating blood vessels, and an awake patient feeling a hot or burning sensation.

Several other problems have been associated with the use of the ESU. One of the major problems is electromagnetic interference (EMI). EMI can interfere with pacemakers, causing arrhythmias; interfere with monitoring devices; and simulate ventricular fibrillation with an automated implantable cardioverter-defibrillator (AICD).

Patients with implanted pacemakers can either experience tachyarrhythmias or inhibition of the generator. Monitoring problems are mainly seen as electrical interference or electrical noise. ESU noise can cause the AICD to accidentally shock a patient who is in sinus rhythm, which could cause ventricular fibrillation.

Other ESU problems include vaporization of various chemicals and viral particles. Also, the ESU has been implicated as the heat source in a majority of OR fires.

Risk Assessment

Assessing the risk from ESU usage is dependent on the type and age of the ESU. Newer models have several safeguards built in that can alarm when a problem occurs. Most ESU problems involve the common unipolar ESU, where the surgeon holds the active electrode and there is a large surface area return electrode. The bipolar ESU is an electrically wired forceps, and the two blades of the forceps serve as the positive and negative electrodes. No return plate is required, and the power is relatively low. This device poses a low risk of problems.

Another device that has a minimal risk is the electrocautery. This is a battery-powered, handheld device that is literally a hot wire used to coagulate tissue or blood vessels. It can be used in ophthalmologic or other minor surgery cases.

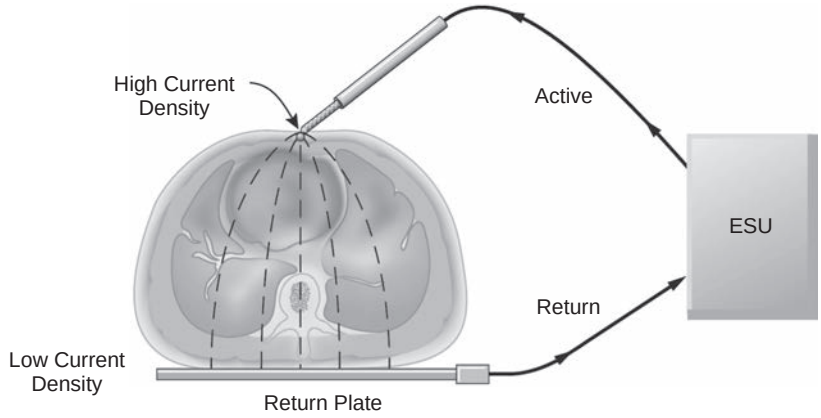

Fig. 121.1 A properly applied electrosurgical unit (ESU) return plate. The current density at the return plate is low, resulting in no danger to the patient. (From Ehrenwerth J, Seifert HA: Electrical and fire safety. In Barash PG, Cullen BF, Stoelting RK, et al., editors: *Clinical anesthesia,* 7th ed. Philadelphia, Wolters Kluwer, 2013, pp 189–218.)

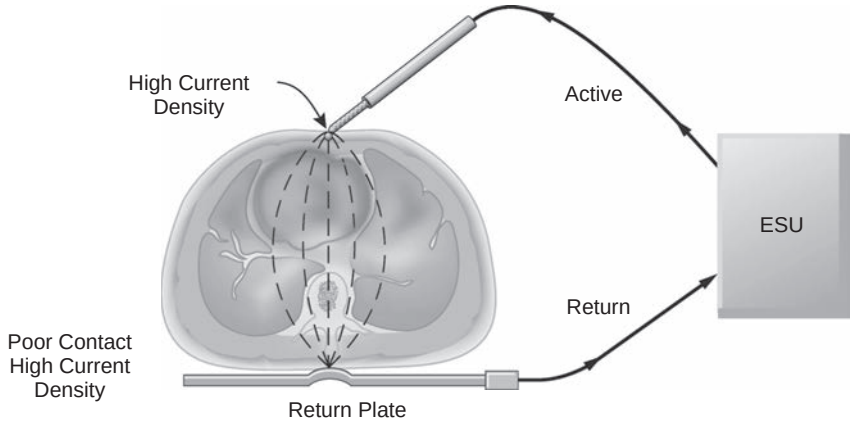

Fig. 121.2 An improperly applied electrosurgical unit (ESU) return plate. Poor contact with the return plate results in a high current density and a possible burn to the patient. (From Ehrenwerth J, Seifert HA: Electrical and fire safety. In Barash PG, Cullen BF, Stoelting RK, et al., editors: *Clinical anesthesia,* 7th ed. Philadelphia, Wolters Kluwer, 2013, pp 189–218.)

MANAGEMENT AND PREVENTION

Safety Precautions

Prevention of burns from a malfunctioning ESU is achieved by careful attention to ensuring that the ESU and all its components are functioning properly before being used. It is generally the OR circulating nurse who is responsible for checking the safety of the ESU; but anesthesiologists, surgeons, and all OR team members have a responsibility.

The Association of periOperative Registered Nurses (AORN) has published practice recommendations on the use of ESU. These include the following:

- Checking the expiration date of the dispersive electrode, opening the package immediately before use, and inspecting the dispersive electrode for damage. In particular, the conductive gel surface should not be dried out.
- The conductive side of the dispersive electrode should be placed on clean, dry, hairless skin covering a well-vascularized muscle mass as close to the surgical site as possible. The dispersive electrode should not be placed over an implanted metal prosthesis or even tattoos if it can be avoided, as these tend to concentrate the electric current and can cause localized heating. The dispersive electrode should not be placed over bony prominences because the irregular surface may cause loss of contact between the gel and the skin. The dispersive electrode should not be placed distal to tourniquets or over scar tissue because these do not conduct electricity well. If the position of the patient is changed intraoperatively, the position of the dispersive electrode should be rechecked.

Modern ESUs monitor the impedance of the entire electric circuit and can alarm or disable if increased impedance such as might be seen with a disconnect or poor application of the dispersive electrode occurs. However, this is not foolproof. As indicated previously, loss of contact may be indicated by less heating at the active electrode and the surgeon requesting a higher power output. Such a request should prompt an evaluation of the dispersive pad and its connections.

Laparoscopic procedures present an additional risk of ESU burns that are not related to poor placement of the dispersive electrode. Damage to the insulation surrounding an active electrode in the abdomen can lead to stray electrical energy going somewhere other than desired. Even with intact insulation, it is possible to have capacitive coupling between the handle of the active electrode and nontarget tissue.

If a burn does occur, the ESU should be removed from use pending testing by biomedical engineering, though the likelihood is that the failure was in the dispersive electrode. The patient should be treated for the burn injury. Small first-degree burns generally require only topical therapy with aloe or other moisturizer. More serious burns will

require a plastic surgery consultation and possible excision with skin grafting. Because the heating occurs from within the body, there may be more tissue damage than is visible superficially.

Other Electrosurgical Unit Risks

In patients with a cardiac implantable electronic device (CIED), the dispersive electrode should be placed as far as possible from the device to minimize electrical interference with the device. When it is necessary to use the active electrode within 15 cm of a CIED, consideration should be given to altering the function of the CIED for the duration of the surgery. There are various published guidelines for the management of this situation. In summary, the safest strategy is that patients with an AICD should have the antitachycardic function suspended for the duration of surgery. Patients with a pacemaker who are pacemaker dependent should have the pacemaker switched to an asynchronous mode.

To prevent the ESU from causing fires, all alcohol-based prep solutions should be allowed to thoroughly dry for the manufacturer-recommended amount of time, generally 3 minutes, before draping the patient. In head and neck procedures where the airway is not secured, careful attention must be paid to limit or eliminate the use of supplemental oxygen. An oxygen-enriched environment will markedly increase the flammability of all OR materials.

Further Reading

American Society of Anesthesiologists: Practice advisory for the perioperative management of patients with cardiac implantable electronic devices: pacemakers and implantable cardioverter-defibrillators: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Cardiac Implantable Electronic Devices, *Anesthesiology* 114(2):247–261, 2011.

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122 Transesophageal Echocardiography

Jack S. Shanewise

Case Synopsis

A 75-year-old woman undergoing emergency coronary artery bypass graft surgery for unstable angina has incomplete revascularization due to lack of a suitable conduit. Insertion of a transesophageal echocardiography (TEE) probe during cardiopulmonary bypass is difficult. After several attempts, the probe suddenly advances; however, its tip appears in the surgical field anterior to the heart, after perforating the pharynx. Subsequent discussion with the patient's husband reveals that she has a 20-year history of dysphagia.

PROBLEM ANALYSIS

Definition

As regular users of TEE, anesthesiologists need to be aware of potential complications and their prevention. Most TEE complications are minor and are due to trauma to the oropharynx during probe insertion. More serious problems, such as pharyngeal perforation, esophageal perforation, and gastrointestinal bleeding, occur on rare occasions.

A TEE complication unique to the operating room is laryngeal injury with vocal cord dysfunction. This can occur in patients having TEE monitoring during sitting craniotomy with prolonged periods of extreme neck flexion. TEE probe placement and manipulation can compress the bronchi or cause displacement of the endotracheal tube, especially in small children. In patients who are not intubated, the TEE probe may inadvertently be inserted into the trachea instead of the esophagus. Also, the tip of the TEE probe sometimes buckles back on itself in the esophagus, making its removal difficult and hazardous.

Although esophageal burns due to transducer heat formation are theoretically possible, this complication has not been reported. Most TEE systems automatically shut down when the probe temperature exceeds a safe level. During TEE monitoring, anesthesiologists may be distracted from noticing more acute and important changes in vital signs. Also, without proper training and knowledge, TEE monitoring may be erroneously interpreted, leading to inappropriate management decisions.

Recognition

Oropharyngeal trauma may be seen directly or may manifest as bleeding from the mouth. Gastrointestinal hemorrhage may be occult and present as hypovolemic shock or unexplained anemia. Insertion of a gastric tube should confirm the diagnosis. Perforation of the esophagus may be apparent in the surgical field, or it may present later with sepsis or severe chest pain in a conscious patient. The diagnosis of esophageal perforation after TEE is often delayed, especially in the setting of other complications, and should be kept in mind for patients not doing well after heart surgery. Buckling of the probe tip results in an inability to withdraw the probe from the esophagus. It is also associated with unusual imaging (upside-down orientation) and reduced control-knob mobility.

Risk Assessment

When possible, all patients should be asked about esophageal symptoms and diseases before insertion of the TEE probe. Three questions should always be asked:

1. Have you ever had any trouble with your esophagus?
2. Do you have any difficulty swallowing food?
3. Have you ever vomited blood?

If the patient answers "no" to all three questions, it is safe to proceed. When the patient cannot be interviewed directly, a family member should be questioned. At a minimum, the medical record should be reviewed for esophageal problems.

Contraindications to TEE are listed in Box 122.1. However, if TEE might provide important information and there is a history of esophageal disease, a preprocedure gastroenterologic evaluation with fiberoptic esophagoscopy is one option to consider. The mouth should be inspected before TEE probe insertion to look for loose teeth and preexisting injuries. TEE probes with stretched and loose steering cables may be more prone to buckle back on themselves in the esophagus and should be repaired before use.

In most settings in which intraoperative TEE is used, other monitoring and interventional devices occupy the same pathway as the TEE probe or a nearby one. These devices include endotracheal tubes, temperature-monitoring devices, gastrointestinal drainage tubes, and feeding tubes. Given the size and rigidity of TEE probes, displacement of any one of these devices is a distinct possibility. Potential complications from device dislodgment range from minor annoyances (e.g., improperly functioning gastric tube) to potentially life-threatening situations (e.g., displacement of the endotracheal tube into a mainstem bronchus, impairing the ability to ventilate the patient).

Implications

Although rare, fatal complications from TEE can occur. As with all medical procedures, a risk-benefit analysis must be made before proceeding with the TEE examination. There is, however, a large experience with this procedure, indicating that the risk is very small when performed on properly screened patients and using the proper technique.

BOX 122.1 Contraindications to Transesophageal Echocardiography

Absolute Contraindications

Esophageal obstruction
- Stricture
- Tumor

Upper or lower sphincter hypertrophy
Esophageal injury
Perforation
Recent esophageal surgery
Fistula
Esophageal diverticulum
Unstable cervical spine

Relative Contraindications

Undiagnosed dysphagia
Esophageal varices
Upper gastrointestinal tract bleeding

MANAGEMENT

Bleeding from the mouth after TEE should prompt careful, direct inspection of the mouth and pharynx to identify the location and extent of the injury. Minor trauma to the oropharynx often requires no specific treatment, but antibiotics may be indicated for more extensive injuries. Significant, persistent gastrointestinal bleeding after TEE should be evaluated with endoscopy. Besides identifying the site of bleeding, endoscopy can provide treatment, such as electrocautery and/or infiltration of a vasoconstrictor. If perforation of the esophagus is suspected, it can be diagnosed by fluoroscopy with water-soluble contrast swallow. Perforation is usually treated as a surgical emergency. Pharyngeal perforation can be diagnosed by direct inspection and, if significant, warrants emergency consultation with an otolaryngologist for surgical drainage. Airway patency always takes precedence over TEE monitoring, and the probe should be removed immediately if airway problems occur. A TEE probe with its tip buckled back on itself in the esophagus should be advanced into the stomach to allow room for it to unflex before any attempt is made to remove it.

PREVENTION

The two cornerstones for preventing TEE complications are preprocedure assessment for esophageal disease and careful and gentle probe insertion and manipulation. Other devices occupying the same pathway must be carefully watched during placement and removal of the TEE probe. Excessive force should *never* be used to pass an apparent obstruction to TEE probe advancement. The probe should not be locked in a flexed position for prolonged periods, and it should never be advanced or withdrawn when the wheel locks are engaged.

Patients with gastric pathology can safely undergo TEE examination, but the operator must not advance the TEE probe beyond the esophagus to avoid any potential problems with gastric insertion. Although not strictly a complication, damage to the TEE machinery is an extremely undesirable consequence of careless use. Typically, TEE systems are among the most expensive operating room devices, and repairs are extremely costly. This fact, along with the fragile nature of these complex electronic devices, underscores the need for gentle handling of TEE probes.

ACKNOWLEDGMENT

The author wishes to thank Dr. Patrick Benedict for his contribution to the previous edition of this chapter.

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123 Vaporizers

Christopher J. Curatolo • James B. Eisenkraft

Case Synopsis

A 54-year-old man, American Society of Anesthesiologists (ASA) physical status 2, undergoes general anesthesia for a laparoscopic ventral hernia repair. His baseline blood pressure is 120/70 mm Hg. After an uneventful intravenous induction and tracheal intubation, the sevoflurane vaporizer concentration dial is set to deliver 3% sevoflurane in oxygen at a fresh gas flow of 6 L/min. Mechanical ventilation is begun, and the patient's next blood pressure measurement is 50/30 mm Hg. The breathing circuit gas analyzer shows isoflurane with an inspired concentration of 4.4 vols%.

PROBLEM ANALYSIS

Definition

Assuming that the agent analyzer reading is correct, the patient is receiving isoflurane instead of the intended sevoflurane, and at a concentration much greater than that set on the vaporizer concentration dial. The difference in anesthetic may be due to the unintentional or deliberate filling of the agent-specific sevoflurane vaporizer with a different anesthetic (in this case, isoflurane). Situations that result in delivery of increased anesthetic vapor concentration include vaporizer misfilling, malfunction, tipping, overfilling, and gas flow reversal through the vaporizer.

Recognition

The end result of these situations is an anesthetic agent and/or concentration that differs from that intended. This manifests as clinical and hemodynamic signs of anesthetic overdose, including profound hypotension, as occurred in this case. Identification of the agent and measurement of its concentration in the breathing circuit are critical to making a correct diagnosis. Before attempting to troubleshoot the cause of the excess and incorrect agent, the clinician should immediately discontinue use of the vaporizer in question and purge the breathing system with oxygen to rapidly decrease the anesthetic concentration. The cardiovascular depression must be corrected. The anesthesiologist might also consider disconnecting the patient from the anesthesia machine's breathing circuit and ventilating the patient's lungs using an alternative system, such as a self-inflating manual ventilation device (e.g., Ambu bag) or a different anesthesia circuit (e.g., Bain) connected to an O_2 source.

Some investigative work is required to determine whether the anesthetic overdose is due to a vaporizer or a breathing circuit problem. Because modern potent inhaled volatile anesthetics are delivered using machine-mounted, calibrated, agent-specific vaporizers, the vaporizer concentration dial is set to a certain value (e.g., 1%), and the concentration of agent in the gas flowing from the common gas outlet (CGO) of the anesthesia machine is sampled and analyzed. The CGO is where the gas mixture created by the anesthesia machine flowmeters and vaporizer leaves the machine to be conducted to the fresh gas inlet of the breathing system. The CGO is therefore the sampling location in the delivery system that is closest to the vaporizer outlet. With the fresh gas flow set to 5 L/min of the carrier gas with which the vaporizer is calibrated by the manufacturer (air for Dräger vaporizers; O_2 for GE, Datex-Ohmeda, and Penlon vaporizers), the concentration dial is set to 1%, and the concentration of agent in the gas flowing from the CGO is measured using a calibrated anesthetic agent analyzer. The measured concentration should be within 10% to 15% of the vapor concentration dial setting (e.g., if the dial is set to 1%, the concentration measured should be between 0.85% and 1.15%) if the vaporizer is in calibration (according to the manufacturers' specifications).

If a different anesthetic is detected, the agent-specific vaporizer does not contain the agent for which it is labeled. The vaporizer (and if necessary the anesthesia machine) should be removed from service until it has been inspected and tested in a nonclinical environment. If a higher-than-expected concentration is detected, it is likely that the problem is with the vaporizer and not the breathing circuit. If the measured agent concentration agrees with the dialed-in concentration, a possible problem is liquid agent in the anesthesia circuit. In the event that a freestanding vaporizer is being used (i.e., one placed in series between the fresh gas source and the breathing circuit [and one used by perfusionists during cardiopulmonary bypass]), it should be inspected to ensure that the direction of fresh gas flow through the vaporizer is correct (i.e., the fresh gas enters via the vaporizer inflow, not the outflow, connection).

Risk Assessment

Vaporizer Malfunction

Most contemporary anesthesia vaporizers other than for desflurane are of the variable-bypass design. The incoming fresh gas is split into two pathways. Most of the gas flows through a bypass and is not exposed to anesthetic vapor, while a lesser flow enters the vaporizing chamber and emerges with the anesthetic agent at its saturated vapor concentration. When the two flows mix at the vaporizer outlet, the bypass flow mixes with the vaporizing chamber outflow to produce the desired (dialed-in) concentration. Although rare, vaporizers themselves may fail. For example, it has been reported that the agent level indicator on the vaporizer may fail and not indicate that the vaporizer is empty of any inhalation anesthetic. This would not be noticed until a vigilant provider noted the inspired or end-tidal anesthetic agent to be much lower than the vaporizer concentration dial setting. Some anesthesia machines, in addition to high anesthetic agent concentration alarms,

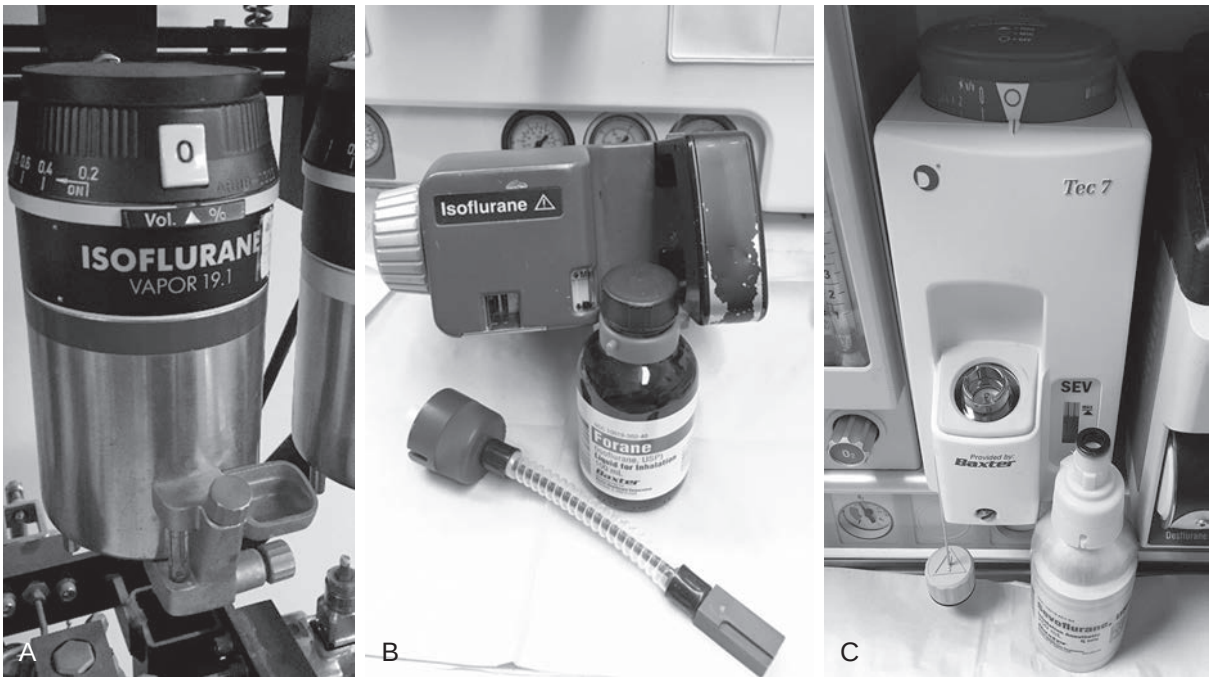

Fig. 123.1 Filling systems for agent-specific vaporizers. A, Funnel-fill. **B,** Key-fill. **C,** Easy-fill.

also have low concentration alarms, which may be helpful in this scenario. Closed-claims analyses continue to report the occurrence of awareness secondary to insufficient inhaled anesthetic.

Agent-Specific Vaporizer Misfilling

There are several scenarios in which filling an agent-specific vaporizer with the wrong agent may occur. In certain practice settings, a vaporizer may be drained to conserve liquid anesthetic agent or to properly store a vaporizer that will not be used for some time. During any vaporizer drainage process there exists the possibility to mismatch agents (i.e., drain one agent into an empty bottle labeled for a different agent). In some parts of the world, anesthesia providers must make do with only one or two vaporizers that may not always match the available inhaled anesthetics. Adler and colleagues have described how to do this as safely as possible when on a medical mission and have published mathematical and experimental models of vaporizer output based on different scenarios of vaporizer and agent mismatch. Finally, despite advances in filling design (e.g., Key-Fill and Quik-fil bottle adapters), there are reports of providers overcoming these safety features and misfilling vaporizers. Fig. 123.1 shows examples of vaporizer filling systems.

Overfilling and Tipping

Overfilling or tipping of a vaporizer can cause liquid agent from the vaporizing chamber (or sump) to enter the bypass, which is designed for gases (e.g., O_2, nitrous oxide, air) only. A very small amount of liquid agent introduced into the bypass can lead to the delivery of potentially lethal concentrations of anesthetic agent to the patient circuit. This is because saturated vapor concentrations of potent inhaled agents (at 20°C and 1 atmosphere pressure) range from 21 vols% for sevoflurane to 88 vols% for desflurane. Under these conditions, 1 mL of liquid agent evaporates to produce approximately 200 mL of vapor (Table 123.1). If the volume of a circle breathing circuit is approximately 5 L, 1 mL of liquid agent entering that circuit could result in a concentration of approximately ([200/5000] × 100) = 4% with complete mixing; with incomplete mixing far greater concentrations may result.

In the United States, vaporizer filling mechanisms may be of various designs (e.g., funnel-fill, key-fill). Funnel-fill vaporizers lack an agent-specific filling system (see Fig. 123.1). They must be carefully inspected during filling to ensure that the level of liquid in the sump chamber does not exceed the maximum fill line indicated on the sight glass. Overfilling of key-fill vaporizers has been extensively described. Key-fill systems are designed for use with an airtight joint between the bottle containing the anesthetic liquid and the matching vaporizer, with the vaporizer dial turned to the OFF position. Correct use prevents overfilling by two mechanisms. First, intake of air into the bottle of anesthetic agent is interrupted when filling has reached the maximum safe level of liquid in the vaporizing chamber. Second, when the vaporizer is in the OFF position, the air space at the top of the vaporizing chamber is sealed, thereby preventing overfilling. Because filling of a key-fill vaporizer is slow, this has led to improper practices to expedite the process. Such practices include loosening the seal between the key fill device and the vaporizer, which allows direct entry of room air into the bottle, and turning the concentration dial to the ON position. This double-fault condition allows an excessive amount of air to enter the agent bottle and therefore an excessive amount of liquid agent to enter the vaporizer. Such vaporizer overfilling has led to anesthetic overdose and neurologic injury.

Tipping also remains a concern with many vaporizers. If a vaporizer is removed from the anesthesia machine and is tipped on its side, liquid agent in the vaporizer sump may enter the gas inlet and outlet pathways of the vaporizing chamber. The Dräger Vapor 2000 and 3000 series vaporizers incorporate a transport setting (selected by turning the agent dial concentration to "T"), which allows the vaporizer to be removed from its mount on the anesthesia machine and isolates the liquid agent compartment, thereby preventing tipping issues. The GE Aladin vaporizing system uses agent-specific cassettes that are designed such that tipping has no effect on vaporizer output (see Fig. 123.1, *B*).

Freestanding Vaporizers and Reversal of Flow

Although modern delivery systems use vaporizers that are securely mounted to a manifold on the anesthesia machine, freestanding vaporizers continue to be used on cardiopulmonary bypass machines,

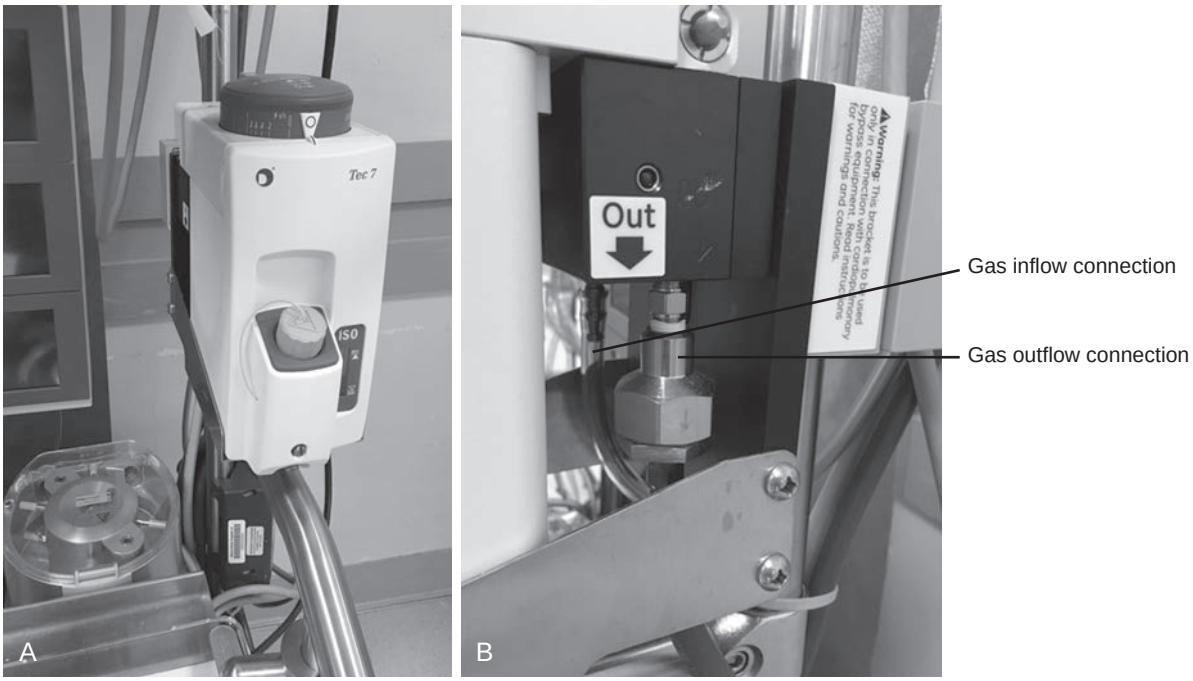

Fig. 123.2 A, A freestanding vaporizer mounted on a cardiopulmonary bypass machine. **B,** A side view shows the inlet and outlet hoses, which, if reversed, could result in dangerously increased anesthetic vapor concentrations.

TABLE 123.1 Volume of Anesthetic Vapor per Milliliter of Liquid Anesthetic at 20°C

Anesthetic	Vapor/Liquid (mL/mL)
Desflurane	182
Enflurane	195
Halothane	226
Isoflurane	196
Sevoflurane	182

From Eisenkraft JB: Anesthesia vaporizers. In Ehrenwerth J, Eisenkraft JB, Berry JM, editors: *Anesthesia equipment: principles and applications,* 2nd ed. Philadelphia, Elsevier, 2013, p 67.

TABLE 123.2 Bypass Flow–to–Vaporizing Chamber Outflow Dilution Ratios at 20°C

Concentration	Halothane	Isoflurane	Sevoflurane
1%	32:1	30:1	20:1
2%	10.6:1	14.5:1	9.5:1
3%	7:1	9.3:1	6:1

Adapted from Eisenkraft JB: Anesthesia vaporizers. In Ehrenwerth J, Eisenkraft JB, Berry JM, editors: *Anesthesia equipment: principles and applications,* 2nd ed. Philadelphia, Elsevier, 2013, p 67.

in veterinary facilities, and in laboratories. Freestanding vaporizers are especially hazardous for several reasons. Because they are freestanding, they may be more prone to tipping, which as mentioned may result in dramatically increased vaporizer concentration outputs compared with the concentration dial setting. Additionally, reversal of the direction of gas flow through a variable-bypass, concentration-calibrated, agent-specific vaporizer can profoundly affect its performance, depending on the model. Fig. 123.2 shows a freestanding vaporizer mounted on a cardiopulmonary bypass machine. Note the manufacturer's explicit labeling of the outflow connection ("OUT") as a means to help prevent flow reversal accidents. Such incidents of flow reversal have been reported to result in dangerously high concentrations of inhalation anesthetics. Finally, unauthorized tampering with an anesthesia machine could result in reversed gas flow connections to the vaporizer manifold.

Implications

Anesthetic agent concentrations that exceed those set on the vaporizer concentration dial may result in complications ranging from mild hemodynamic instability to total cardiovascular collapse. All potent inhaled agents are myocardial depressants and peripheral vasodilators. Delivering an overdose of isoflurane when sevoflurane was intended can have disastrous consequences. The higher saturated vapor pressure (SVP) of isoflurane (238 mm Hg at 20°C) compared with sevoflurane (160 mm Hg at 20°C) means a much greater vapor output concentration will result. Furthermore, because isoflurane (minimum alveolar concentration [MAC] 1.2%) is more potent than sevoflurane (MAC 2%), this error is compounded and the vaporizer potency (MAC equivalent) output that much more clinically significant. In the situation described in the case synopsis, rather than the intended sevoflurane concentration of 3% (1.5 MAC), the misfilled vaporizer delivered isoflurane in a concentration of 4.4% (3.7 MAC).

Agent-specific variable bypass vaporizers create the dialed-in concentration of anesthetic by adjusting a flow ratio between the bypass and vaporizing chamber outflow. This ratio depends on the physical properties of the anesthetic agent, as well as the temperature and dialed-in concentration. It is inherently agent specific due to the different saturated vapor pressure versus temperature curves of each volatile agent (see Table 123.1). Table 123.2 shows the ratios of bypass flow to vaporizing chamber outflow created by variable bypass agent-specific vaporizers to achieve the desired dialed-in concentrations. In the present case, for example, sevoflurane has a saturated vapor pressure of 160 mm Hg at 20°C; thus at 1 atmosphere pressure sevoflurane will represent 21% of the atmosphere in the vaporizing chamber (because SVP/P_{atm} = 160/760 = 21%). Therefore if 100 mL/min of gas emerges from the vaporizing chamber, 21 mL of this is sevoflurane vapor (because 21/100 = 21%). To produce a concentration of 1%, this 21 mL of sevoflurane must be diluted in a total volume of 2100 mL (because 21/2100 = 1%). For a total volume of 2100 mL, a total flow of 2079 mL/min entering the vaporizer would have split such that 79 mL flowed to the vaporizing chamber and 2000 mL flowed through the bypass (2100 – 79 – 21). Finally, the outflow dilution

TABLE 123.3 Predicted Vapor Concentrations and Potencies of Misfilled Vaporizers

Vaporizer	Agent in Vaporizer	Dial Setting (%)	Dilution Ratio	Output (%)	Output MAC
Isoflurane	Isoflurane	1	30:1	1.00	0.83
	Sevoflurane	1		0.68	0.34
	Isoflurane	2	14.5:1	2.00	1.67
	Sevoflurane	2		1.35	0.68
	Isoflurane	3	9.3:1	3.01	2.51
	Sevoflurane	3		2.04	1.02
Sevoflurane	Sevoflurane	1	20:1	1.00	0.50
	Isoflurane	1		1.48	1.23
	Sevoflurane	2	9.5:1	2.00	1.00
	Isoflurane	2		2.95	2.46
	Sevoflurane	3	6:1	3.00	1.50
	Isoflurane	3		4.43	3.69

ratio is the ratio of the bypass flow to the vaporizing chamber outflow. In this case the ratio is 2000:100 or 20:1.

If 3% sevoflurane were dialed-in (to achieve 1.5 MAC equivalents), an outflow dilution ratio of 6:1 would be created between bypass flow and vaporizing chamber outflow. This is because 21/(100 + 600) = 3%. When the sevoflurane vaporizer set to 3% is misfilled with isoflurane (SVP = 238 mm Hg at 20°C), the vaporizing chamber contains isoflurane vapor in a concentration of 31% (238/760). Now, when 100 mL/min of gas flows from the vaporizing chamber, the 31 mL isoflurane vapor is diluted in a total volume of 700 mL (100 + 600), resulting in an isoflurane concentration of 31/700 = 4.4% (or 3.7 MAC equivalents).

Table 123.3 shows the predicted agent concentrations and anesthetic potency (MAC equivalents) resulting from misfiling sevoflurane and isoflurane vaporizers.

The ASA Closed Claims Project has provided many valuable insights into adverse outcomes in anesthesiology. In 1997 Caplan and colleagues reported an analysis of adverse anesthetic outcomes arising from gas delivery equipment. The analysis revealed breathing circuits followed by vaporizers as the most common causes of adverse outcomes arising from anesthetic equipment. In an updated (2013) similar analysis by Mehta and colleagues, vaporizer problems (underdose and overdose) were the most common cause of anesthesia gas delivery equipment claims since 1990. Despite the rare occurrence of these complications, the consequences of many of these events were disastrous, with significant morbidity and mortality rates.

MANAGEMENT

An anesthetic agent analyzer with the appropriate high-concentration alarm limits set, although not currently an ASA standard of basic anesthetic monitoring, is critical because this is the most sensitive way to detect excessive concentrations or the unintended delivery of a different agent, as occurred in our case synopsis. Although many providers rely on the accurate calibration of individual vaporizers, the lack of an agent analyzer considerably increases the chances of an inhaled anesthetic agent overdose or underdose and does not prevent the unintended delivery of a different agent. Standard monitors, including electrocardiogram and blood pressure monitor, are critical for detecting the hemodynamic consequences of such potential overdoses. If the patient is breathing spontaneously, changes in the respiratory pattern may be noted. When vapor concentrations greatly exceed the concentration dial setting, an alternative means of ventilating the patient's lungs should be immediately available for use (as recommended by the Food and Drug Administration in 1993 and ASA in 2008). The source or mechanism of the excess anesthetic agent should be investigated, as described earlier.

PREVENTION

Overfilling a vaporizer can be avoided by not exceeding the maximum fill line in the sight glass and, in the case of key-fill vaporizers, by following the manufacturer's instructions (i.e., filling the vaporizer with the vaporizer dial set to the "off" position and ensuring an airtight seal between the key-filling nozzle and the vaporizer).

If a vaporizer has been tipped or tilted excessively, it should be purged with a high fresh gas flow from the machine's flowmeters (i.e., not the oxygen flush, which bypasses the vaporizers) with the vaporizer concentration dial set to the *maximum* concentration until no trace of the agent is detectable. This setting maximizes flow through the inlet and outlet pathways of the vaporizing chamber, as well as through the bypass. The vaporizer is then refilled, and the calibration is checked as previously described before the vaporizer is put back into clinical service.

Freestanding vaporizers are potentially more hazardous than machine-mounted ones. GE-Ohmeda vaporizers may be mounted on cardiopulmonary bypass machines using a specially designed bracket. When such freestanding vaporizers are used, care should be taken to avoid tipping during both transport and use. Fresh gas inflow and outflow connections to the vaporizer should be checked to ensure that they are not reversed, because reversal of these connections may result in increased vapor concentration output.

The manufacturer-recommended specific anesthesia machine checkout should be performed daily, as well as an abbreviated checkout before starting each subsequent case. Hemodynamic supportive measures should be employed as appropriate. Low as well as high anesthetic agent concentration alarms are helpful in detecting underdose and overdose situations, both of which were found as causes of adverse outcomes in the closed claims analyses. The proper use of a vaporizer limits the potential for malfunctions that may result in an unintended dose or even type of anesthetic agent. If such a malfunction occurs, analysis of the gas in the breathing circuit should lead to prompt recognition and appropriate action to prevent harm to the patient. As always, a vigilant anesthesiologist can make the difference between a near miss and significant morbidity or mortality.

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124 Adverse Neurologic Sequelae: Central Neurologic Impairment

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Case Synopsis

A 68-year-old man with a history of insulin-dependent diabetes mellitus, hypertension, and an 80 pack-year smoking history is scheduled for four-vessel coronary artery bypass grafting (CABG). After uneventful induction of anesthesia, severe aortic atheromatous disease is observed via transesophageal echocardiography in the aortic arch, so epiaortic ultrasound scanning is performed before aortic cannulation to ascertain the optimal location. The patient is maintained during cardiopulmonary bypass at a temperature of 32°C with a mean arterial pressure of 50 to 60 mm Hg. No transfusion is necessary to maintain the hemoglobin above 7 mg/dL. Despite technical success of the surgery, the postoperative course is complicated by significant short-term memory loss and impaired manual dexterity. The patient is discharged first to a skilled nursing facility and eventually to an assisted-living home.

PROBLEM ANALYSIS

Definition

Many patients, particularly the elderly and those undergoing major surgery, suffer a global decline in neurologic capacity after surgery not attributable to a discrete ischemic event (stroke) or as a consequence of acute illness or drug effect (delirium). This decline may be temporary, lasting weeks to months, or may result in permanent disability and alteration of functional capacity. The syndrome of central neurologic impairment after surgery is diagnosed by a drop in cognitive performance measured on postoperative neuropsychological testing compared with preoperative baseline testing. However, neuropsychological testing is labor intensive and not routinely performed as a preoperative baseline, so many patients are not formally diagnosed with postoperative cognitive dysfunction (POCD), even when it is clinically suspected. Unlike the diagnosis of delirium, there is no DSM-V definition of POCD, nor is there a defined degree of decline on neuropsychological testing required to make the diagnosis. The spectrum of central neurologic dysfunction after anesthesia is broad, and this chapter will focus on the subject of POCD; the subjects of postoperative delirium (see Chapter 166), delayed emergence from anesthesia (see Chapter 137), emergence agitation (see Chapter 189), and thromboembolic complications (see Chapter 183) are discussed elsewhere in this text.

Recognition

The first sign that a patient has suffered some neurologic decline may be a report of "not feeling right" or the patient's family members noting that their loved one has "slowed down" or become more forgetful. Historically, because this decline was most frequently observed after cardiac surgery, it was thought to be related entirely to cardiopulmonary bypass (e.g., "pump head"). It is now recognized that this phenomenon can occur after any major surgery, though it is still most common after cardiac surgery. The prevalence of POCD at hospital discharge after major noncardiac and cardiac surgery is surprisingly high, with 30% to 40% of patients after noncardiac and greater than 50% of cardiac surgery patients affected. This decreases 3 months after major noncardiac surgery to approximately 5% for young and middle-aged patients, while still affecting greater than 12% of elderly patients. Months after cardiac surgery, the prevalence of patients affected remains approximately 30%.

Neurocognitive testing used to diagnose POCD may evaluate several domains of cognitive function, including global, executive function, learning and memory, visuospatial functioning, and/or psychomotor function (Table 124.1). The Mini Mental Status Examination (MMSE) is a bedside questionnaire that can easily be used to assess global neurocognitive function and covers many areas of cognition (Table 124.2). Although designed as a screening tool for dementia, the MMSE is a screening tool that can be used postoperatively to detect changes in cognition and improvement over time. It requires 5 to 10 minutes to administer and is scored out of 30 possible points. The test requires basic literacy and is susceptible to a learning effect over time, possibly confounding the results. The MMSE is less likely to distinguish specific areas of dysfunction than performing a wider range of neurocognitive testing.

The number of cognitive domains that should be included in testing is unknown, but a minimum of four is recommended. Even when a complete battery of tests is performed, the threshold drop required to diagnose POCD has not been established. The implications of a significant drop in only one domain are also undefined. Testing is usually performed after the acute effects of surgery have resolved (generally after 1 week).

TABLE 124.1 Neurocognitive Testing Used in the Diagnosis of Postoperative Cognitive Dysfunction

Core Domain	Cognitive Process	Measure	Administration Time
Global	Multiple	Montreal Cognitive Assessment (MoCA)	Approximately 15 min
Executive function	Simple attention	Digit Span Forward Subtest from Wechsler Adult Intelligence Scale–3rd revision (WAIS-III)	Approximately 5–10 min
	Complex attention (working memory)	Digit Span Backward Subtest (WAIS-III)	Approximately 5–10 min
	Response inhibition	Stroop Color Word Test	3–4 min
	Mental flexibility	Trail Making A and B Test	5 min per subtest
	Verbal fluency	Controlled Oral Word Associate test (COWA)	3 min
Learning and memory	Auditory-verbal learning and memory	Hopkins Verbal Learning Test–Revised (HVLT-R)	35 min
	Visual learning and memory	Brief Visuospatial Learning Test–Revised	45 min
Visuospatial functioning	Visuomotor integration	Digit Symbol Coding Test (WAIS-III)	5 min
	Complex visuospatial perception	Hooper Visual Organization Test (HVOT)	Approximately 10–12 min
Psychomotor function	Manual dexterity and motor speed	Lafayette Grooved Pegboard Test	Approximately 5 min

Modified from Berger M, Nadler JW, Browndyke J, et al.: Postoperative cognitive dysfunction: minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiol Clin* 33(3):517–550, 2015.

TABLE 124.2 Cognitive Abilities Tested in the Mini Mental Status Examination (MMSE)

Cognitive Ability	Points	Tests
Orientation	10	Accurately report time and place
Registration	3	Repeat names of objects
Attention and calculation	5	Perform simple arithmetic or spelling
Recall	3	Recall earlier named objects
Language	9	Name an object, repeat a simple phrase, follow a three-stage command and a simple written command, write a simple sentence, copy a simple drawing

Risk Assessment

Although the exact mechanism of POCD is unknown, it likely results from a combination of pathways including cerebral micoemboli and a central neuroinflammatory response to surgery or anesthesia. Specific risk factors have been identified, both patient related and procedure related, but many of these risk factors are nonmodifiable. Advanced age has repeatedly been identified as a risk factor for POCD, and given the advancing age of surgical populations, it becomes even more important to seek out modifiable risk factors.

Nonmodifiable risk factors:

- Advanced age
- Baseline neurocognitive reserve (education level, genetic risk, hippocampal volume)
- Previous stroke
- Preexisting neurologic disease
- Postoperative delirium

Potentially modifiable risk factors:

- Cigarette abuse
- Postoperative infection
- Postoperative respiratory complication or baseline pulmonary disease
- Duration of anesthesia, surgery, or hospital stay
- Peripheral vascular disease
- Diabetes mellitus
- Hypertension, particularly systolic hypertension greater than 180 mm Hg on admission
- Excessive alcohol consumption
- General anesthesia versus regional (controversial)
- Relative anesthesia overdose (controversial)

Note that although conflicting data exist, several studies have suggested that excess exposure to general anesthetic drugs may contribute to POCD and that bispectral index (BIS) monitor-guided titration of anesthetics may minimize that risk. Further research is required to conclusively establish this relationship.

Risk factors specific to cardiac surgery:

- Proximal aortic atherosclerosis or previous CABG
- Postoperative atrial fibrillation
- Low perfusion pressure during cardiopulmonary bypass
- Hemodilution during cardiopulmonary bypass
- Hyperglycemia
- Rapid rewarming from hypothermia
- On-pump (versus off-pump) CABG

Certain technical maneuvers by surgeons increase the microembolic load to the brain, which has been implicated in POCD, including manipulation of the aorta by cannulation, cross-clamping, side-clamping, unclamping, or lifting of the heart. Manipulation of the cardiopulmonary bypass circuit and prolonged time spent on bypass have also been implicated as risk factors for central nervous system (CNS) injury by increasing the embolic load of air and microthrombi.

Implications

Perioperative CNS injury can be devastating in terms of quality of life and resource utilization. Even subtle neurocognitive changes may have significant implications for returning to baseline function and independence in patients with limited neurocognitive reserve. In one Danish prospective study, patients with POCD at 3 months had significantly increased mortality (hazard ratio 1.63 [1.11–2.38], adjusted for sex, age, and cancer). Patients with POCD at 1 week were more likely to leave the labor market prematurely due to disability or early retirement (hazard ratio 2.26 [1.24–4.12], adjusted for sex and age). The need for social transfer payments for a higher proportion of time was also significantly greater in those with POCD at 1 week (60% vs. 41.2%). As the age of surgical patients is ever increasing, preventing and treating POCD is a significant public health issue.

MANAGEMENT

Many unanswered questions exist surrounding the etiology, risk factors, and management of POCD (Table 124.3). Once POCD has occurred, very little is known about the optimal treatment, other than to provide supportive therapy for cognitive rehabilitation. As many cases will resolve spontaneously, little research in this area has been conducted. Because postoperative delirium and inflammatory states are risk factors for POCD, attempts to optimize these conditions are warranted. This includes treatment of critical illness or infections and avoidance of prolonged untreated postoperative pain.

TABLE 124.3 Unanswered Questions Surrounding Postoperative Cognitive Dysfunction (POCD)

Factor of Interest	Question
Age	How does aging affect POCD risk?
Type of anesthesia	For which patients does general versus regional anesthesia influence risk of POCD?
Dementia	Is POCD associated with an increased long-term risk of dementia?
Coexisting degenerative disease	How are degenerative diseases resulting in central neuroinflammation, such as Alzheimer's disease, related to POCD?
Risk assessment	Are there CSF biomarkers of POCD?
Role of SSRIs	Are SSRIs an effective treatment option for prevention or improvement in the course of POCD?
Ischemic preconditioning	Does ischemic preconditioning prevent POCD?
Prehabilitation	Is physical or cognitive prehabilitation effective for reducing the severity of POCD?

CSF, Cerebrospinal fluid; *SSRI,* selective serotonin reuptake inhibitor.
Adapted from Berger M, Nadler JW, Browndyke J, et al.: Postoperative cognitive dysfunction: minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiol Clin* 33(3):517–550, 2015.

PREVENTION

Despite considerable interest in the pharmacologic prevention of cognitive decline perioperatively, no superior drug regimen or consensus management has been established. Several drugs have been associated with some benefit on early cognitive function, thought to be related to antiinflammatory properties. Ketamine (0.5 mg/kg) given as an intravenous bolus at anesthetic induction improved cognitive performance 1 week after cardiac surgery in a randomized study of 51 patients. Similarly, in two randomized trials, magnesium sulfate administration improved cognitive function during the first several days after cardiac or vascular surgery. However, the short duration of benefit with these drugs makes them of limited clinical effect. Randomized trials examining thiopental, propofol, nimodipine, glutamine/aspartate, lexipafant, rivastigmine, xenon, erythropoietin, and remacemide have failed to demonstrate any benefit on POCD rates.

Optimizing the cerebral outcome after cardiac surgery has been the subject of many clinical trials in the last decade. Currently, the use of monitoring tools for detecting poor cerebral perfusion shows promise for improving cognitive outcomes (e.g., near-infrared spectroscopy [NIRS]). Cerebral oximetry is frequently used in cardiac surgery to monitor the oxygen saturation of blood in the brain. Using an interventional strategy to optimize brain oxygenation if oximetry drops below 20% of baseline has so far not resulted in a decrease in POCD, but an association between prolonged cerebral desaturation less than 50% and risk of neurocognitive decline has been established. A multimodality monitoring strategy adopted for high-risk patients, including hemodynamic monitoring, temperature monitoring, NIRS, and possibly BIS monitoring, is the most promising strategy for improving cognitive outcomes after major surgery. It remains to be established how, when, and for whom this monitoring is indicated and which interventions are most effective in response.

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Adverse Neurologic Sequelae: Peripheral Nerve Injury

125

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Case Synopsis

A 62-year-old man underwent coronary artery bypass graft surgery via a median sternotomy, with harvesting of the internal mammary artery. During a routine postoperative visit, the patient complains of a "tingling" sensation in the fourth and fifth fingers of his left hand. On physical examination, he has decreased sensation over those fingers, with minimally reduced muscular function in the ulnar distribution. A neurology consultation is obtained, and the patient is diagnosed with a brachial plexus injury.

PROBLEM ANALYSIS

Definition

A significant source of perioperative morbidity, peripheral nerve injuries (PNIs) are a well-described complication of anesthesia. Despite the usually transient nature of the lesions, this injury is one of the most litigious. In the most recent closed claims analysis from the American Society of Anesthesiologists (ASA), PNI comprised 16% of all claims. The stability of that percentage over the 10 years between analyses (15% previously) is striking. This implies a lack of understanding of the pathophysiology of the injury and ineffectiveness of our current preventive strategies. Ulnar neuropathies are the most commonly noted lesion, followed by brachial plexus injury, lumbosacral nerve root injury, and spinal cord injury. In more recent years the proportion of claims for ulnar neuropathy have been declining, but claims for spinal cord injury have been increasing.

Further demonstrating the incomplete understanding and likely multifactorial nature of the complication is that anesthesia care was deemed to be appropriate in 66% of cases. Commonly proposed mechanisms of injury include the following:

- Direct trauma/laceration (i.e., with internal jugular vein cannulation, first rib fracture penetrating the plexus)
- Compression/stretch (mechanical compression leading to a conduction block or ischemia)
- Toxins (i.e., direct injection of local anesthetic)
- Double crush—preexisting nerve lesion (diabetes mellitus or rheumatoid arthritis) leaves the nerve at risk if the same or nearby area is compromised

The true incidence of PNI has proven difficult to determine, in part due to the retrospective nature of many of the studies, which suffer from underreporting. Overall incidence has been reported at 0.03% to 0.14%. In cardiac surgery, quoted incidence ranges from 0.2% to 38%. Despite the overwhelming prevalence in cardiac surgery, PNIs have been reported in a wide variety of surgical subspecialties: neurosurgery, orthopedics, general, colorectal, obstetric, and gynecologic. In fact, one study looking at greater than 380,000 cases over 10 years found the highest incidence in neurosurgery, cardiac, general, and orthopedic surgery. Whereas much of the literature discusses brachial plexus injury, a wide variety of PNIs can be seen (i.e., peroneal, phrenic, and sympathetic). The same study also noted an association of PNI with epidural and general anesthesia compared with peripheral nerve blocks, monitored anesthesia care, and spinals. Neuraxial techniques were more commonly associated with lower extremity injuries.

Recognition

The majority of all PNIs are detected in the immediate postoperative period. Fewer cases are not detected for days to weeks after the initial operation. Variability in the temporal relationship from surgical procedure to symptom presentation suggests that a triggering event may occur postoperatively. It has also been suggested that preexisting peripheral neuropathies may manifest at this time.

PNI can present with sensory deficits, motor deficits, or both. Some authors suggest that in brachial plexus injuries, the deficit displayed is a progression of the disease process—sensory and motor fibers differing in the timing of cell loss. In patients undergoing median sternotomy, it has been suggested that the lower roots are more likely to suffer from sensory loss, and the upper and middle roots will suffer from motor loss. After cardiac surgery, brachial plexus injuries tend to be found in lower roots and therefore present as sensory deficits. Injury associated with noncardiac cases tends to affect the upper/middle trunk.

Controversy exists surrounding the use of somatosensory evoked potentials (SSEPs) to detect the development of PNIs intraoperatively. The use of SSEPs to detect potential nerve injury has been described in the neurosurgical literature. Hickey and colleagues attempted to apply this concept to cardiac surgery. Their study noted that significant changes in SSEP waveforms were present with sternal retractor placement. However, these changes did not correlate with postoperative neuropathies, leaving their ability to predict PNI intraoperatively

BOX 125.1 Preexisting Anatomic and Pathophysiologic Risk Factors for Perioperative Nerve Injury

- Diabetes
- Neuropathy
- Alcoholism
- Herpes zoster
- Polyarteritis nodosa
- Peripheral vascular disease
- Coagulopathies
- Hypertension
- Hypothyroidism
- Cervical rib
- Deformities in shoulder or derivation of brachial plexus

BOX 125.2 Risk Factors for Perioperative Nerve Injury During Cardiac Surgery

- Sternal retraction
  - Positioning of sternal retractors
  - Asymmetric sternal retraction
- Internal mammary artery harvesting
- Duration of surgery
- Duration of cardiopulmonary bypass
- Hypothermia
- Penetration injury due to first rib fracture during sternotomy
- Injury during cannulation of internal jugular vein
  - Direct, needle-related injury
  - Hematoma formation resulting in compression of brachial plexus

in question. Changes detected in SSEPs at the conclusion of surgery may be able to better predict peripheral lesions.

Nerve injuries occurring secondary to positioning are usually unilateral and affect only one nerve. They should be distinguished from other potential causes of neurologic dysfunction such as cervical spine injuries, musculoskeletal injuries, an autoimmune neurologic disorder, or acute brachial plexitis (Parsonage-Turner syndrome). Acute brachial plexitis (1.6 per 100,000 cases annually) is a condition characterized by a fast onset of severe bilateral shoulder pain that can radiate down the arms. The pain does not typically follow a nerve root distribution and is ultimately replaced by muscle weakness and signs of muscle wasting. It is caused by a stress reaction to surgery and therefore can occur associated with procedures that are not typically characterized as high risk for PNI. The treatment is supportive, and the condition typically self-resolves over a few months.

Risk Assessment

It is clear from the literature that certain nerves are at greater risk of injury during anesthesia. Consistently demonstrating the highest incidence of injury are the ulnar nerve and brachial plexus. This is most likely due to their anatomic positions. The ulnar nerve takes a superficial course as it wraps around the condyle and can be compressed in the medial epicondylar groove. The brachial plexus is particularly susceptible to injury as it is fixed at two points: superiorly, where the roots exit from the vertebral canal, and distally by the axillary fascia. Augmenting its susceptibility to compressive injury, this plexus is in close proximity to multiple bony prominences: the clavicle, first fib, head of the humerus, and coracoid.

These anatomic relationships are thought to play a significant role in the mechanism of injury with median sternotomy. Vander Salm and colleagues, in a cadaveric study, were able to show an increased incidence of first rib fractures with median sternotomy. They described a physical displacement of the rib into the plexus in 11 of 15 cases. In another 15 cadavers, the sternal retractor was placed two interspaces more caudal and no rib fractures were noted. Subsequently, the same authors noted no correlation between rib fractures and brachial plexus injuries but did find a significant difference in brachial plexus injury when the retractor was placed caudally.

The placement of sternal retractors has repeatedly been shown to contribute to nerve injury, but the mechanism has never been conclusively determined. One possibility is that compression/ischemia of the plexus occurs with the cephalad and posterior rotation of the first rib. Lederman and colleagues suggest that internal jugular vein cannulation may contribute to injury either by direct needle trauma or subsequent hematoma formation.

Among cardiac surgeries, the asymmetric sternal retraction required with coronary artery bypass graft (CABG) has been implicated as a major risk factor. CABGs requiring internal mammary artery (IMA) harvest have an incidence of PNI approaching 10%; without it the incidence is closer to 1%. Jellish and colleagues used SSEPs to confirm this finding, demonstrating a significant decrease in the amplitude in both arms when asymmetric sternal retractors were used. Some authors have postulated that a "hands-up" position can help relieve tension on the brachial plexus and could help to reduce neural injury. Jellish and colleagues demonstrated that fewer SSEP changes were associated with hands-up positioning compared with arms positioned at the sides. However, they concluded that the changes seen were more likely due to ulnar nerve compromise, and the position did not afford any significant reduction in brachial plexus injury.

Many authors have sought to identify the patient or operating room characteristic that increase the risk for PNIs. The most commonly cited risk factors include extremes of weight, male gender (particularly for ulnar neuropathy), and preexisting neuropathies such as from diabetes or peripheral vascular disease (Box 125.1). In cardiac surgery, notable risk factors include hypothermia, asymmetric sternal retraction, and IMA harvest for CABG (Box 125.2).

Implications

The majority of PNIs recover spontaneously over about 1 month. Neurapraxia, the mildest form of injury, with the best prognosis, causes a conduction block without physical discontinuity leading to a temporary loss of function. Axonotmesis, the next level of injury, also carries an excellent prognosis. Damage in this injury is to the axon and surrounding myelin, but the mesenchymal framework is maintained allowing for regeneration. Neurotmesis is the most severe form of injury resulting in complete transection of the nerve. This type of injury results in complete functional loss and usually does not recover without surgical intervention. Preexisting conditions such as diabetes have been implicated in prolonged recovery from PNIs.

MANAGEMENT

When confronted with a possible PNI, the first step in management is a detailed neurologic examination. If a lesion is detected, a neurologic consultation may be warranted. Electromyography (EMG) may be considered in the immediate postoperative period, especially if previous neurologic dysfunction is suspected. The study can detect changes in conduction velocities of both sensory and motor nerves. Most nerve injuries will take 2 to 3 weeks to develop changes that can be detected by EMG. Any positive findings in the immediate postoperative period suggest the presence of a preexisting neuropathy. A repeat study at 3 to 4 weeks is warranted if symptoms persist, in an effort to determine whether any neural changes have taken place.

Treatment of peripheral nerve lesions is supportive and depends to a great degree on the severity of the lesion. In the acute phase,

BOX 125.3 ASA Task Force Recommendations for Prevention of Peripheral Nerve Injuries

Test ability of patient to tolerate anticipated surgical position preoperatively
Limit abduction of arms to less than 90 degrees in supine position
Maintain neutral position of forearm (whether tucked or abducted)
Supination may help to relieve pressure on ulnar groove
Maintain intraoperative vigilance of desired position
Appropriate padding of extremities (excessively tight padding may increase risk of neuropathy)
Use of chest roll in laterally placed patient may reduce risk of peripheral nerve injury
Inappropriately placed shoulder braces in Trendelenburg surgery may increase risk

analgesics such as opioids or neuropathic medications (e.g., gabapentin) may be necessary. Physical therapy is the cornerstone of treatment for motor deficits. Depending on the degree of physical limitation, splinting may be necessary to help prevent further injury and assist in activities of daily living. For severe injuries that do not heal, referral to surgery may be indicated. Surgical intervention is usually limited to conditions that involve anatomic abnormalities such as thoracic outlet syndrome, fracture of the first rib, or compression by bony prominences. Some authors suggest that early surgical intervention can improve the regenerative capacity of the nerve.

PREVENTION

The incompletely understood and multifactorial nature of PNI makes prevention of the complication difficult. A thorough understanding of the anatomy of the brachial plexus and other commonly injured nerves is of primary importance to ensure proper positioning. Very little evidence exists to guide anesthetic management in these cases. In 2011 an ASA task force on preventing PNIs put forth recommendations that are largely based on consensus opinion. The recommendations focus primarily on appropriate patient position; the conclusions are summarized in Box 125.3. The ASA also advocates for a postoperative assessment of neurologic function to increase the likelihood of early detection of a lesion.

As mentioned, cardiac surgery has unique risk factors that predispose to brachial plexus injury. In addition to the steps noted previously, most practitioners would recommend the following:

- Minimizing sternal retraction, especially during IMA harvest
- Caudal placement of sternal retractors
- Maintaining neutral head position to minimize countertraction on brachial plexus
- True median sternotomy (avoid asymmetric sternal retraction)

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126 Adverse Events and Unanticipated Outcomes: Comprehensive Disclosure

Scott A. Falk • Dale W. Lanks

Case Synopsis

A 38-year-old woman with a history of hypertension and obesity (body mass index 32) is scheduled to undergo a laparoscopic cholecystectomy for chronic recurrent cholecystitis. In the preoperative assessment, she discusses her allergy to penicillin with the anesthesiologist. They explore this a bit more, and the patient explains that it was a reaction from childhood that she does not recall but one her mother told her about.

The patient is brought to the operating room and has a routine induction of general anesthesia. An oral endotracheal tube is placed without difficulty. The anesthesiologist discusses antibiotic choice with the surgeon, and cefazolin is chosen as providing the best prophylaxis against postoperative surgical site infections. The anesthesiologist administers the cefazolin, noting that the patient's prior reaction to penicillin was probably minor, and there is a low cross-reactivity of allergens between cephalosporins and penicillins.

Three minutes after the cefazolin is administered, the patient becomes difficult to ventilate and profoundly hypotensive. Resuscitation is initiated, and treatment for an anaphylactic reaction is started. The patient is stabilized but remains on an epinephrine infusion. The anesthesiologist and surgeon decide to postpone the surgery and bring the patient to the intensive care unit (ICU) intubated.

INTRODUCTION

Unfortunately, adverse events and unanticipated outcomes occur during the course of the delivery of health care. Up to 13.5% of Medicare beneficiaries experienced an adverse event during a health care episode. However, such events do not necessarily mean that the clinician made a mistake, was negligent, or deviated from the standard of care. What such events do mean is that something, for whatever reason, did not go as anticipated or planned. Whenever an adverse event or unanticipated outcome occurs, patients and their families not only want but are entitled to a full explanation about what has happened to them during the course of their care, and why. Knowing how to effectively disclose an adverse event or unanticipated outcome, regardless of its etiology, can have a significant and beneficial impact on all aspects of the eventual outcome of the disclosure, including maintaining a trusting patient-physician relationship and helping to reduce any potential professional liability exposure. Adverse events or unanticipated outcomes compounded by poor patient-physician relationships pose the greatest professional liability risks.

The practice of anesthesiology has long been at the forefront of efforts to improve patient safety, but special challenges exist when adverse events or unanticipated outcomes involve anesthesia providers. Whereas patients can pick their surgeon and often the hospital or outpatient facility in which to have their procedure, in most cases they do not pick their anesthesiologist and often do not meet this provider until shortly before the procedure. As a result, there is essentially no preprocedure relationship during which a rapport or trust can be established. However, the anesthesia provider must be actively involved in the disclosure of an anesthesia-related event, and how this, along with the documentation, are handled can often make the difference between an understanding patient and one that becomes litigious.

In addition to being the right and ethical thing to do, full disclosure of an adverse event or unanticipated outcome has been a requirement of The Joint Commission since 2001. It requires that any unanticipated event that has significant clinical implications for the patient, whether temporary or permanent, be disclosed. Full disclosure is also encouraged by other organizations, such as the National Quality Forum, which considers full disclosure one of its safe practices for health care. In addition, in several states, disclosure is also a statutory requirement.

Why disclose?

- The Joint Commission requires disclosure.
- State law may require disclosure.
- It is what patients expect.
- It provides an opportunity for an apology and lessens anger.
- It improves patient and physician trust.
- It promotes patient safety and quality improvement.
- It sets the stage for early intervention.
- It helps minimize potential professional liability risk exposure.
- It is the right thing to do regardless.

PREPARING FOR DISCLOSURE

A full and open disclosure should occur whenever something does not go quite right or as planned, even if the event was not related to

a deviation from the standard of care and did not cause a permanent injury. Although timely disclosure is essential, it must be done in a coordinated, thoughtful, and empathic manner. Each institution should actively assess its disclosure culture to facilitate best practices. Preparation for disclosure is an important first step and involves a team, not just the involved clinician. The prep team may include individuals who will not be involved in the actual disclosure but can be helpful in the necessary debriefing session to understand the event and its implications; in determining what should be disclosed, who should do the disclosure, and how it should be disclosed; and in preparing an anticipated course of action after the disclosure. All members of the prep team, including the clinicians that will be performing the disclosure, as well as the individual who will remain the primary contact person for the patient and family, need to be aware of and understand what the disclosed information will be. This allows for consistent messaging and conveys that we are all working together.

DISCLOSURE

In most cases, disclosure should be done as soon as possible, even if all the facts and circumstances of the event are not yet known. Optimally, disclosure should occur face-to-face with the patient and/or family/substitute decision maker. Disclosure should only include factual and objective information as it is known at the time of the disclosure. It is never appropriate to speculate, assign blame, criticize other clinicians, or editorialize about the circumstances surrounding the event or the facts that have yet to be determined. Timely disclosure helps to avoid the patient and family questioning why you waited so long to disclose the event and helps eliminate the misconception that you were hesitant to inform them of its occurrence or are attempting to hide or withhold information. Full disclosure often is not achieved in the initial disclosure discussion and can at times be an ongoing process. Although it is important to have at least the preliminary facts at the time of the initial disclosure, it is not necessary to have all the answers, and it is impossible to predict what a patient's and/or family member's questions might be. It is imperative to let the patient and their family know that as more information and facts become known, they will be shared with them. If, during the course of disclosure, questions are asked that do not currently have an answer, it is always appropriate to say, "I don't know, but I will find out more information and return to discuss this with you."

Whenever possible and if appropriate, disclosure should be performed by a small disclosure team that includes the anesthesia provider who was involved in the event, as this demonstrates accountability and responsibility. In most cases, especially in situations where the patient may not have previously met the involved anesthesiologist, it is helpful to have the patient's surgeon or primary care provider also present for the disclosure. This not only provides the patient with the familiar face of a clinician with whom the patient already has a trusting and ongoing patient-physician relationship, it also provides the attendance of the clinician best qualified to answer the patient's questions (e.g., "What does this mean for my health?" or "Does this change my prognosis?"). In addition, because the information that is disclosed to the patient has the potential to be overwhelming, the presence of the clinician who will remain involved in the patient's follow-up care will allow that individual to be helpful to the patient in his or her subsequent attempts to recall the disclosure discussion accurately.

Another key member of the disclosure team is the nurse manager on the unit where the patient will be after the event. Involvement of the nurse manager in the disclosure discussion will ensure that this individual is aware of exactly what the patient and family were told and what their reaction was to the disclosed information. The nurse manager can then share this information with the nursing staff on the unit. The nursing staff will have much more ongoing and frequent contact with the patient and family and will often be the ones that the patient or family will initially approach with subsequent questions about the event. It is important that the nursing staff be aware of the event and know to whom they can refer any questions that the patient or family may have. By being part of the disclosure team, the nurse manager can serve not only as the contact person for the patient and family but also for the nursing staff.

Likewise, it is important to have a family member present for the disclosure whenever possible, as this allows for someone else to not only hear and remember the facts but also provide emotional support to the patient. However, it is essential to understand that family members may also be affected by the information, and just as it is important to care for the patient after disclosure of an adverse event, it is equally important to care for the family. This may involve requesting other departments such as patient and guest services, pastoral care, or social work to assist in providing support and helping both the patient and the family cope.

Depending on the nature of the event, it may be helpful to also have that facility's chief medical officer or patient safety officer present for the disclosure as well. This will help to demonstrate that such events, regardless of the circumstances, are taken seriously by administration and will be used to evaluate the care provided and subsequently institute change if needed. It is important for patients and their families to know that the health care facility will use the adverse event or unanticipated outcome as a learning experience in its efforts to prevent similar occurrences in the future.

DISCUSSING POTENTIAL COMPENSATION

If the patient or family unexpectedly raises the issue of compensation during the initial disclosure discussion, the most appropriate response is to inform them that their concerns about compensation will be shared with the appropriate administrators and that someone will get back to them. Do not make any promises regarding potential compensation. However, there may be situations in which the adverse event or unanticipated outcome to be disclosed does involve a deviation from the standard of care that has resulted in a significant and/or permanent injury. In these situations, and after a discussion with hospital administration and appropriate members of senior management during the disclosure prep meeting, it may be appropriate to initiate a compensation discussion by tactfully assuring the patient and family that the hospital/facility will work with them to address their potential future economic needs. Although most often it is best to leave any discussion of compensation for a future meeting, after the patient's immediate medical needs are met, it is important for the patient and family to know that this will be eventually discussed. There is precedent for significant economic compensation in litigation cases related to anesthetics.

EXPRESSING REGRET OR AN APOLOGY

There has long been a hesitancy to express regret for an adverse event or unanticipated outcome or, when appropriate, offer an apology. Clinicians have often been concerned that to do so will be perceived as an admission of guilt, contribute to patient or family anger, and increase the likelihood of litigation. Many patients may not initially be angry that an adverse event or unanticipated outcome occurred,

BOX 126.1 Disclosure Tips

- DO include the involved anesthesiologist.
- DO include the patient's surgeon or primary care provider.
- DO include the nurse manager.
- DO explain in lay terms the nature, severity, and cause of the adverse event or unanticipated outcome factually, objectively, and in a nonjudgmental manner based on the facts known at the time.
- DO describe the potential impact the event has, will have, or may have on the patient's clinical course and prognosis.
- DO express regret and, when appropriate, offer an apology.
- DO allow time for questions.
- DO establish a follow-up plan.
- DO keep all channels of communication open.
- DON'T discuss any potential deviations from the standard of care.
- DON'T discuss the clinical competency of involved personnel.
- DON'T make promises regarding potential compensation.

but they will become angry if they feel dismissed, and lingering anger is a major contributor to seeking legal action. Thus far, concerns that expressing regret or offering an apology would increase litigation have been unfounded, and it is becoming increasingly apparent that apologies and full disclosure may actually reduce the chances that a patient will subsequently pursue litigation. Expressing regret or offering an apology can be difficult or awkward, but doing so in a genuine and heartfelt manner humanizes the disclosure experience and provides tremendous emotional benefits to all involved, including the clinicians. Determining how and who should offer the apology is part of the preparation for disclosure based on the nature of the adverse event or unanticipated outcome and those involved (Box 126.1).

DOCUMENTATION

Equally important to disclosure is documentation. This includes not only documentation about the actual adverse event or unanticipated outcome but also documentation of the disclosure discussion. Just as medical record documentation regarding a patient's clinical status should be thorough, factual, and objective, so too should documentation of a disclosure discussion.

Disclosure documentation should include the following:

- Date and time
- What was disclosed
- Who was present for the disclosure
- The patient's and family's reaction to the disclosure
- What questions were asked and the answers given
- What the next follow-up plan will be

If you are uncertain about how or what to document, seek guidance from your risk management department.

FOLLOW-UP

It is unrealistic to think that on hearing the news of an adverse event or unanticipated outcome, the patient and his or her family will able to think of all of their possible questions or concerns. They need time to digest and reflect on the information that they just received. The full range of effects that an adverse event or unanticipated outcome has on a patient may not be known at the time of the disclosure and may not be known for quite some time. Therefore it is key to stay connected with both the patient and the family as they deal with the ramifications of such an event or outcome. Let them know that you will return to see them and answer any future questions that they may have. Provide them with contact information to let them know that you will remain accessible to them. During this time, the health care team needs to not only provide the necessary medical care to the patient but also provide care to the family. This may include making arrangements for family members to stay with the patient in the hospital or nearby, covering expenses such as hotel, meals, and parking. An effective disclosure provides an excellent opportunity for service recovery and improves the patient and family experience after an adverse event or unanticipated outcome. Work with your risk management or guest services department to determine what service recovery interventions would be appropriate, including interventions that may need to be customized for the particular situation. It is impossible to know what a particular family's immediate needs are, so it is always beneficial to ask them what can be done for them to meet these needs.

CASE SYNOPSIS ANALYSIS

Disclosure Prep Team

- Involved anesthesiologist
- Surgeon
- Perioperative nurse manager
- ICU nurse manager
- Risk management
- Patient and guest services representative

Disclosure Team

- Involved anesthesiologist
- Surgeon
- ICU nurse manager

Information Disclosed

Because the patient is intubated and in the ICU, the event will initially be disclosed to her husband.

- After your wife was given general anesthesia, an antibiotic known as cefazolin was given to her to help prevent a postoperative infection.
- Shortly after the cefazolin was given, she experienced an apparent anaphylactic reaction to this medication.
- Rather than proceeding with the surgery once she was stabilized, it was felt that it would be best to postpone the procedure, and she was transferred to the ICU.
- Her previous childhood allergic reaction to penicillin was known and discussed with her. However, the specific type of reaction she experienced as a child was unknown.
- After discussion with her surgeon, the decision was made to administer cefazolin because it is the most effective prophylactic antibiotic against postoperative surgical site infections, and there is a low incidence of an allergic reaction to cefazolin in patients with a known or potential allergy to penicillin.
- After she was given the cefazolin, she experienced a significant drop in her blood pressure and continues to require epinephrine to support her blood pressure.
- She will be monitored closely in the ICU, and it is anticipated that she will be able to have the breathing tube removed once she is more awake and her blood pressure does not require the epinephrine for support.
- We very much regret that this happened, and once she is awake and off the breathing machine, we will be back to explain all of this to her too. In the meantime, do you have any questions, or is there anything that we can do for you?

Anesthesia Documentation

9/1/16 10:30 AM

38 yo female scheduled for laparoscopic cholecystectomy evaluated preoperatively and reported allergy to PCN as a child. She did not recall what type of reaction she experienced, as it was told to her by her mother. After a discussion with the surgeon, Dr. X, regarding pt's childhood PCN allergy, the decision was made to administer cefazolin due to its effectiveness at providing infection prophylaxis and the low cross-reactivity of allergens between cephalosporins and penicillins. After uneventful induction of GA and placement of ETT, pt given cefazolin. Three minutes later, pt became difficult to ventilate and hypotensive. Resuscitation was initiated and treatment of anaphylactic reaction started. Epinephrine infusion started and pt stabilized. Surgery canceled and pt transported to the ICU intubated. Along with Dr. X and ICU nurse manager, met with pt's husband and fully explained events, including the decision-making process used before giving cefazolin. Husband appropriately upset and asking questions about when will the pt wake up and how long will she be ventilated. Informed him that it is anticipated that she will gradually wake up and will be extubated once she is awake enough to breathe on her own. Also informed him that the events will be fully explained to the pt once she is awake and alert. I explained to him that we all regret that this occurred and informed him that I will return to see them later this afternoon. My contact information was also provided to him.

Follow-Up Plan

- Involved anesthesiologist and surgeon will remain connected to the patient and her husband.
- The ICU nurse manager will be the designated contact person for the patient and her husband to facilitate getting all their questions answered and their immediate needs met.
- Depending on the immediate needs of the patient and her husband, patient and guest services should be involved to facilitate service recovery efforts such as arranging accommodations for the patient's husband to stay nearby and providing cafeteria meal vouchers or parking coupons.

DISCUSSION

Being proactive, accountable, responsible, forthright, straightforward, and caring for both the patient and the patient's family is an essential step in helping to minimize risk and reduce liability exposure after an anesthesia-related adverse event or unanticipated outcome. Although a patient and/or family members may be angry that the event occurred, if they feel they are being treated with respect and kindness, their anger will not be fueled by feeling like they are being avoided or that the truth is being withheld.

Although it is impossible to ensure that everything will always go right in the delivery of health care, how we handle the times when things do not go as planned will have a significant impact on the future direction the adverse event or unanticipated outcome will take. The benefits of an open, honest, transparent, timely, caring, and empathetic full disclosure will be immeasurable in restoring trust and can go a long way in lessening the impact that an adverse event or unanticipated outcome may have on the patient, the family, the involved clinicians, and the health care facility.

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127 Air Emboli

Lisa Wise-Faberowski • Michael I. Chen

Case Synopsis

An 8-week-old infant is undergoing a craniectomy for sagittal craniosynostosis. As the surgeon is excising the cranial bone segment, precordial Doppler sounds change, and the blood pressure rapidly declines (Fig. 127.1).

PROBLEM ANALYSIS

Definition

Gas bubbles within the vascular system are termed *gas emboli* or *air emboli.* When venous air emboli enter the arterial circulation, they are termed *paradoxic air emboli.* Venous air emboli or paradoxic air emboli from gases dissolved in solution are released through *effervescence,* or they may enter the bloodstream from outside through *insufflation* or *entrainment.*

The amount of gas dissolved in a liquid is a function of temperature and pressure. A sudden increase in the temperature of a gas-containing liquid can release gas bubbles from solution through effervescence. This can occur during rapid rewarming after hypothermic cardiopulmonary bypass or by rapidly warming cold intravenous fluids or blood products. It also happens in divers who experience a too-rapid decompression (the "bends").

More commonly, gas is introduced into the bloodstream by insufflation (e.g., during laparoscopy, thoracoscopy, arthroscopy) or delivered with fluids or blood products by pressurized delivery systems. Veins that do not easily collapse can also entrain air—for example, venous sinuses in bone; open, large central veins; and open veins that are well above the level of the heart. For entrainment to occur, the vein opening must be sufficiently above the level of the heart to exceed central venous pressure (e.g., sitting craniotomy). Venous and paradoxic air emboli can occur in the supine, prone, or lateral position. The risk of such entrainment is increased by low venous pressure or negative intrathoracic pressure, as occurs during spontaneous respiration.

Small children are at special risk for venous air emboli. Significant blood loss may occur rapidly, and a small amount of blood may constitute a large portion of a child's blood volume. This is a particular concern during craniotomies, because the calvaria is very thin. Further, the head is relatively large in proportion to body size, frequently resulting in the surgical site's being elevated above the heart level during a supine or prone craniotomy. Finally, owing to the high prevalence of intracardiac shunts (patent foramen ovale), amounts of venous air emboli that might be insignificant in an adult can result in paradoxic air emboli and be disastrous for a neonate.

Recognition

Awake patients may experience dyspnea and coughing as a result of venous air emboli. During anesthesia, changes in vital signs occur late and usually only after the entrainment of large amounts of air. Monitoring methods to detect venous air embolism, in decreasing order of sensitivity, include the following:

- Echocardiography or Doppler ultrasonography
- End-tidal carbon dioxide ($ETCO_2$) decrease or new appearance of end-tidal nitrogen (ETN_2)
- Pulmonary artery pressure elevation
- Central venous pressure elevation
- Blood pressure reduction
- Electrocardiogram (ECG) changes (e.g., right ventricular strain, ischemia, arrhythmias)
- Audible cardiac or "mill-wheel" murmur

Echocardiography and Doppler monitoring are exquisitely sensitive. They can detect even microbubbles from routine intravenous injections and minor entrainment of air. Air emboli detected with echocardiography and Doppler monitoring should alert the clinical team but must be interpreted cautiously, taking into account the severity of detected air (amount, duration, and associated clinical signs) and the clinical situation (e.g., craniotomy). ECG changes are more ominous, and an audible cardiac or "mill-wheel" murmur is least sensitive; however, when associated with echocardiographic or Doppler evidence of venous air embolism, they suggest that a significant amount of air has been entrained.

Echocardiography

Transthoracic or transesophageal echocardiography (TEE) enables the recognition of discrete air bubbles and the relative quantification of larger volumes (i.e., the density of snowstorm pattern). Further, TEE localizes emboli to the right or left side of the heart and detects cardiac anomalies (septal defects) that increase the risk of paradoxic air emboli (Fig. 127.2). TEE has been used in neonates who weigh as little as 2.5 kg. Limitations to its widespread use include the following:

- High cost
- Requirement for a separate, highly trained observer during anesthesia and surgery
- Risk of injury to the pharynx, larynx, and esophagus
- Possible displacement of the endotracheal tube, especially during manipulation in small infants

Consequently, although TEE is a very sensitive technique for detecting venous air emboli, it is currently not practical in many institutions and may not be necessary as a routine monitor.

Doppler Ultrasonography

Precordial Doppler ultrasonography is as sensitive as TEE for the detection of venous air emboli. It enables semiquantitative assessment of air emboli but does not permit localization of air to the right or left side of

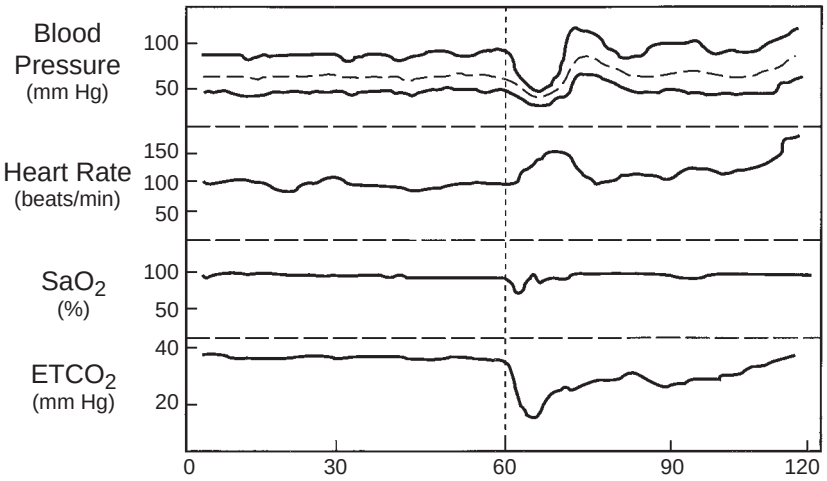

Fig. 127.1 Schematic trend recording of blood pressure, heart rate, oxygen saturation (Sa_{O_2}), and end-tidal carbon dioxide ($ETCO_2$) concentration in an 8-week-old infant during sagittal craniosynostosis repair. The *dotted line* marks the time at which Doppler sounds changed dramatically. Note the sudden decrease in blood pressure and $ETCO_2$, tachycardia, but little change in Sa_{O_2}.

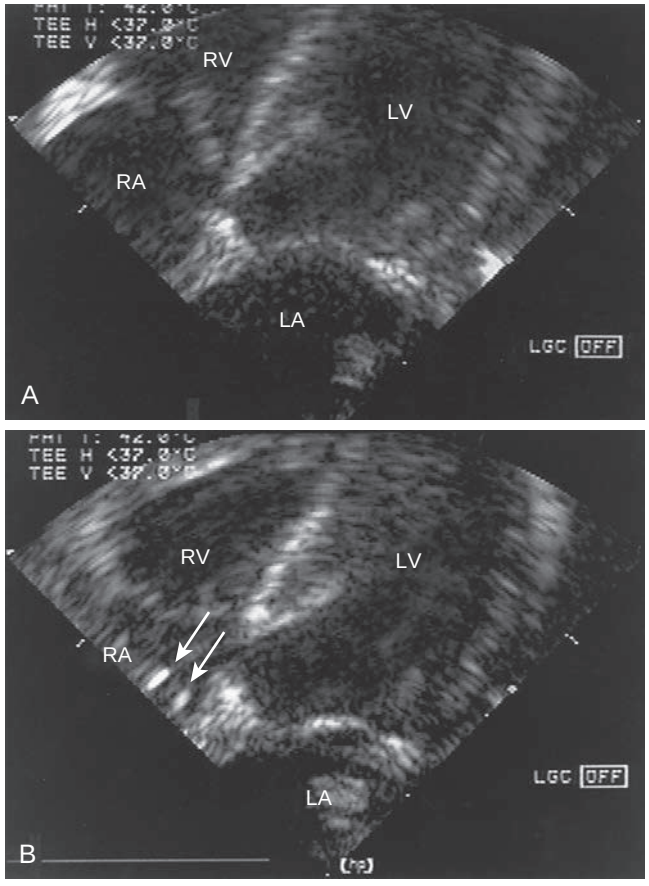

Fig. 127.2 Transesophageal echocardiographic four-chamber view of the left atrium (LA), right atrium (RA), left ventricle (LV), and right ventricle (RV). A, View of the heart without venous air embolism (VAE). **B,** *Arrows* indicate the reflections produced by air bubbles in the RA during VAE.

the heart. The smaller distance between the heart and chest wall increases the sensitivity of Doppler ultrasonography in infants. The probe needs to be placed over the right side of the heart, generally at the nipple line, just to the right of the sternum. Minor movement may dislodge the probe, so it should be securely fastened to the chest. Correct positioning is confirmed by injecting a few milliliters of intravenous solution into an intravenous catheter while listening for a characteristic loud change in Doppler sounds. Doppler probes are easily dislodged and can cause pressure necrosis in prone patients. This can be avoided in small infants by placing the Doppler probe on the patient's back. Electrocautery and echocardiography can interfere with Doppler ultrasonography.

End-Tidal Carbon Dioxide

Significant venous air emboli reduce the end-tidal carbon dioxide ($ETCO_2$) concentration owing to increased dead-space ventilation. However, $ETCO_2$ can also be decreased because of reduced pulmonary blood flow from pulmonary thromboembolism, sudden large blood loss, decreased venous return, or reduced cardiac output due to cardiac dysfunction, bradycardia, or arrhythmia. A falsely low $ETCO_2$ may occur with gas leakage or air entrainment around an uncuffed endotracheal tube or dilution of small tidal volumes with fresh gas flows, unless sampling occurs near the endotracheal tube tip. Even so, a sudden change in $ETCO_2$ from a previously stable baseline is usually significant.

Exhaled Nitrogen

Unless air is added to the inspired gases, nitrogen (N_2) disappears from expired gas. Reappearance of N_2 indicates a circuit leak or alveolar diffusion from venous air emboli. Without an air leak, the sudden reappearance of ETN_2 is quite specific for venous air emboli but not very sensitive; even large venous air emboli increase ETN_2 by only 1% to 2%.

Pulmonary Artery Catheter

Pulmonary artery catheters reveal increased pulmonary artery pressure due to pulmonary vascular obstruction by air. Similar to low central venous pressure, low pulmonary artery wedge pressure may predispose to venous air emboli and paradoxic air emboli. However, pulmonary artery catheters in infants and small children are not practical or necessary in most situations.

Central Venous Catheter

Central venous catheter placement is justified for high-risk procedures, such as craniotomy in the sitting position, even in a small child.

It is rarely necessary for a healthy child when the bed is flat. A central venous catheter is useful for administering fluids and medications if peripheral venous access is difficult, as well as for monitoring central venous pressure. Low central venous pressure may indicate the need for fluid replacement to reduce the risk of venous air emboli; a sudden increase may signal major venous air emboli. A central venous catheter is sometimes effective for retrieving large venous air emboli, especially if the catheter has multiple orifices and the tip is near the junction of the superior vena cava and right atrium. This position is confirmed by radiograph or by recording a unipolar ECG with a right atrial ECG adapter. To do so, substitute the catheter lead for the V lead, and observe the characteristic P-wave changes (increased amplitude leading to tall, spiked P waves that may exceed R- or S-wave amplitudes) as the catheter is advanced into the right atrium.

Arterial Blood Pressure

An arterial catheter allows continuous assessment of blood pressure and arterial blood gas determinations. Its use is justified in any procedure with a significant risk for bleeding or venous air emboli, especially in young children.

Pulse Oximetry

With significant venous air emboli, oxygen desaturation may be detected by pulse oximetry. Arterial blood gas analyses may reveal hypercarbia and an increased arterial-alveolar oxygen gradient.

Risk Assessment

Pediatric patients are at increased risk for venous air emboli during the following procedures:

- Any surgical procedure in which the operative site is sufficiently above the heart, especially when sudden and severe blood loss is possible
- Craniotomy with a large craniectomy (e.g., craniosynostosis repair)
- Craniotomy with an operative site directly over large dural venous sinuses (e.g., posterior fossa exploration)
- Craniofacial procedures (e.g., frontal or midface advancement) with large bony excision and elevation of the head to minimize bleeding
- Certain orthopedic procedures (e.g., scoliosis surgery)
- General surgical procedures (e.g., liver surgery) with a high risk of entering large venous structures (e.g., hepatic veins, inferior vena cava)
- Liver transplantation surgery
- Any open-heart surgery
- Angiography and cardiac catheterization
- Placement, use, and discontinuation of circuits for cardiopulmonary bypass or extracorporeal membrane oxygenation
- Hemodialysis, plasmapheresis, or central venous catheter insertion
- Barotrauma during positive-pressure ventilation
- Use of air to identify epidural space through loss of resistance

Implications

Significant pulmonary air emboli can result in decreased cardiac output, arterial hypotension, and cardiovascular collapse as a result of one or more of the following:

- Obstruction of peripheral pulmonary vessels by gas bubbles
- Air lock from gas in large pulmonary vessels or the heart
- Reflex pulmonary vasoconstriction
- Right ventricular failure secondary to pulmonary hypertension
- Electromechanical dissociation or arrhythmias
- Myocardial ischemia from reduced coronary perfusion pressure, coronary paradoxic air emboli, or hypoxemia

Impaired pulmonary function with carbon dioxide retention and arterial oxygen desaturation can result from the following:

- Ventilation-perfusion mismatch from pulmonary vascular obstruction with increased dead-space ventilation
- Reactive bronchoconstriction with increased airway resistance
- Interstitial pulmonary edema

Gas bubbles enter the arterial circulation directly or through intracardiac communications. Most neonates have a patent foramen ovale, usually with left-to-right shunting. Although the foramen ovale may be probe-patent in 25% to 50% of infants and in 20% to 30% of adults, rarely is shunting demonstrated. However, increased right-sided pressures with venous air emboli may facilitate paradoxic air emboli across a patent foramen ovale. Paradoxic air emboli can result in myocardial or cerebral ischemia.

MANAGEMENT

Key to the successful management of venous air emboli during surgery is close communication between the anesthesiologist and surgeon. In addition, the following guidelines should be considered:

- Doppler sounds should be audible to everyone. Intravenous injections likely to cause Doppler sound changes should be announced beforehand.
- If Doppler ultrasonography indicates venous air emboli unrelated to injections, the surgeon should use indicated measures (e.g., apply bone wax, flood the surgical field with saline, cover it with saline-saturated gauze) to reduce air entry.
- When venous air embolism is suspected, look for an associated decrease in $ETCO_2$ or blood pressure, indicating a significant venous air embolus or blood loss. Reappearance of ETN_2, if monitored, confirms the diagnosis of venous air emboli.
- Nitrous oxide, though not contraindicated for these procedures, should be promptly discontinued in the presence of venous air emboli. The patient is then ventilated with 100% oxygen to avoid further enlargement of gas bubbles and to treat hypoxemia.
- Change the table position so that the surgical site is below the level of the heart. Be sure that the patient is securely fastened to the operating table.
- Gentle compression of the jugular veins has been recommended to reduce air entry and to unmask possible entry sites, but care must be taken to avoid carotid artery compression.
- Although air may be aspirated through a central venous or pulmonary artery catheter, it does not usually allow removal of a significant amount of entrained air.
- Positioning the patient in the left lateral decubitus position has been suggested to aid in resuscitation, but it may not be practical during some procedures.
- Support cardiovascular function with additional intravenous fluids or inotropic agents (ephedrine, epinephrine) as indicated. Cardiopulmonary resuscitation is rarely required, especially if the embolus is detected quickly and appropriate measures are instituted.

PREVENTION

A careful history and physical examination, as well as familiarity with the planned surgery, are essential to assess the risk for venous air emboli or paradoxic air emboli. Use precordial Doppler ultrasonography as a

sensitive and noninvasive monitor to detect venous air emboli early. Consider the use of filters or bubble traps when significant or rapid fluid or blood replacement is anticipated. For high-risk procedures, be prepared to use measures to reduce air entrainment and venous air emboli (e.g., positioning, use of bone wax, flooding the surgical field).

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128 Alleged Malpractice

David S. Smith • Mary Ellen Nepps

Case Synopsis

A 23-year-old woman undergoes emergency cesarean section under general anesthesia for fetal bradycardia and placental abruption. She is hypotensive (blood pressure 70/30 mm Hg) and tachycardic (heart rate 150 beats per minute) as the procedure begins. After delivery, the baby has poor Apgar scores, with evidence of fetal acidosis (cord pH 7.01). Postoperatively, the patient complains of awareness during surgery. The baby develops cerebral palsy, seizures, and developmental delay. Two years later, a malpractice action is brought alleging that the anesthesiologist was negligent.

PROBLEM ANALYSIS

Elements of a Malpractice Claim

A lawsuit is a civil case seeking monetary damages to compensate for injury. In this particular case, the lawsuit is based on a claim of professional negligence. Other legal theories that can underlie a professional liability lawsuit include abandonment (the practitioner had an obligation to be present but was not) or lack of informed consent. To prevail in a claim of negligence, the plaintiff (person who is suing) must establish the following: (1) a duty to the patient, (2) breach of that duty, (3) causation of injury, and (4) damages. The plaintiff has the burden to prove each of these elements. Typically, in civil cases, the burden of proof is by the greater weight of the evidence, not beyond a reasonable doubt as is the case in criminal cases. In most instances, the issue of duty is not contested, as it is established by virtue of the physician-patient relationship. To establish breach of that duty, the plaintiff typically must present competent expert testimony to show that there was failure to comply with the applicable standard of care by the defendant (person being sued). A poor outcome in itself is not evidence of negligence. The question for the jury is whether the practitioner exercised the degree of skill and care ordinarily exercised by practitioners under the same or similar circumstances. A practitioner holding himself or herself out as a specialist may be held to a higher standard than a generalist. With respect to causation, typically the plaintiff must establish that the alleged deviation from the standard of care was the proximate cause of the claimed injury. In some states, however, that standard has been relaxed in certain types of cases to permit the plaintiff to meet his or her burden by establishing that the deviation increased the risk of harm. Finally, the plaintiff must prove the damages claimed. These typically include economic (lost earnings, medical expenses, etc.) and noneconomic damages (pain and suffering, loss of life's pleasures, etc.). Depending on the state, there may or may not be caps on how much a jury may award for noneconomic damages.

Notice of a Potential Claim

There are several ways that an anesthesiologist may become aware of a potential malpractice lawsuit. Dissatisfaction with care on the part of the patient or the patient's family is a significant driver of lawsuits. Thus a complaint to a nurse by the patient or a relative of the patient may be the first indication that a lawsuit may be pursued. Patients also may complain to the surgeon or his or her assistants during the episode of acute care or during a postoperative office visit. Another possibility is that a patient lodges a formal complaint with the hospital administration concerning the practice of a particular anesthesiologist. Often, however, the first indication of a patient's or family member's intent to pursue litigation comes when the anesthesiologist receives notice of the lawsuit.

Formally, a lawsuit begins with the filing of a legal document in court. In most instances, the initial filing is called a *complaint.* In some states, the lawsuit can be initiated by a summons, which simply provides notice that a lawsuit has been filed, and then a complaint with more detailed information subsequently is filed. No action is required until the anesthesiologist is served with the complaint or summons. The complaint typically sets forth the basis of the lawsuit: how the plaintiff was injured by the alleged substandard care and the particulars on which the claim is based. When such a complaint is received, the physician's malpractice carrier should be notified immediately and sent a copy of all documents received. Particularly once there is notice of a lawsuit, it is critical that all records be preserved and that there is no destruction or alteration of records or other pertinent documents. If discovered, attempts to alter or destroy documents create the impression of culpability and can greatly complicate and, in fact, compromise the defense.

Risk Assessment

The incidence of anesthesia malpractice lawsuits has decreased over the past 20 years. Increased use of pulse oximetry and capnography may be partially responsible for a lower incidence of unrecognized esophageal intubation, cardiac arrest, and brain damage that led to many earlier lawsuits. Box 128.1 lists many causes of alleged malpractice related to anesthesia care.

The majority of anesthesia-related obstetric claims involve cesarean delivery, with maternal death (21%) and newborn brain damage (17%) being the most common. Reviewers in the American Society of Anesthesiologists (ASA) Closed Claims Project found improper anesthetic care to be a contributing factor in less than half of newborn brain-damage suits. Half of all obstetric anesthesia claims are filed for minor injuries (e.g., headache, backache, pain during surgery, emotional distress). In approximately 40% of all lawsuits in the ASA Closed Claims Project, payment was made to the plaintiff despite the reviewers' findings of appropriate anesthesia care.

BOX 128.1 Some Causes of Alleged Malpractice

- Failure to supply adequate oxygenation
  - Intubation error
  - Oxygen supply failure
  - Obstructed airway
- Failure to maintain adequate circulation
  - Hypotension
  - Arrhythmias
  - Cardiac arrest
- Aspiration
- Awareness
- Neurologic injury
  - Peripheral nerve injury
  - Spinal cord damage
  - Extradural foreign body
- Dental injury
- Corneal injury
- Physical injury to airway, arytenoid cartilage, vocal cords, trachea
- Physical injury related to positioning, including fracture dislocations, pressure ulcers, infection
- Postoperative visual loss
- Failure to diagnose
- Failure to adequately communicate to the patient or other members of the care team

BOX 128.2 Stages in a Malpractice Lawsuit

- Summons/complaint
- Response to complaint
- Discovery
- Expert reports/depositions
- Motions
- Pretrial conference/settlement conference/mediation
- Settlement or jury trial

Preparing a Defense

There is a sequence of events that ensues after initiation of a malpractice lawsuit (Box 128.2). Once the formal complaint has been filed, a response must be forthcoming within a stipulated time period. Failure to meet deadlines can have adverse effects on the ability to defend against the lawsuit and could result in a default judgment being taken against the physician. The professional liability carrier assigns an attorney to defend the anesthesiologist and prepare the response to the complaint. The anesthesiologist may request a specific attorney, which the insurer typically will honor as long as that attorney is on a list of attorneys approved by the malpractice carrier. The anesthesiologist also may retain a personal attorney at his or her own expense. Usually this is not necessary unless the case potentially could lead to licensure problems or grave economic hardships. If personal counsel is retained, he or she will work with the attorney assigned by the malpractice insurer; however, the assigned attorney will continue to handle the physician's defense of the lawsuit.

During the early planning stages, it is imperative that the anesthesiologist be completely candid with his or her attorney and share all information, both positive and negative. Although attorneys who handle malpractice claims frequently have familiarity with medicine, the anesthesiologist must educate the attorney on the specific medical aspects of the case and help the attorney prepare the defense. Providing key literature, guidelines, and so on will assist the preparation of a strong defense. Confidentiality is an important consideration. Communications between an attorney and the attorney's client typically are privileged and confidential and not subject to disclosure. Discussions the anesthesiologist has with a colleague concerning the substance of a case are not privileged and are fully discoverable (the discovery process is discussed under Management). Any document concerning the care at issue that an anesthesiologist includes in the patient's medical chart is discoverable, as is any statement written about the events. It therefore is advisable not to create documents about the care at issue outside of the documentation in the medical record. Email and text messages also are discoverable. It is now fairly routine for plaintiff attorneys to request relevant electronic communication including emails, text messages, social media postings, and medical record audit trails. Backup policies vary among different email providers, and email messages can have surprisingly long lives. Social media such as Facebook or Twitter is no place for clinical, patient-specific discussions, and anything placed there is discoverable. Documents involved in a malpractice case need to be kept in a secure location.

TABLE 128.1 The Discovery Process

Method	Description
Interrogatories	Written requests consisting of a long list of questions that the defendant is required to answer.
Requests to produce medical information	Requests for copies of pertinent medical records; most hospitals have mechanisms in place to secure paper and electronic medical charts involved in malpractice actions.
Requests to produce documents	These can involve any document the plaintiff or defendant believes is important to the case (e.g., a plaintiff might request a copy of a board certification certificate). Letters, emails, text messages, transcripts of telephone conversations, etc., also can be requested.
Deposition of witnesses	Testimony taken under oath in a format similar to that used in court.

LITIGATION PROCESS

Discovery

This is the exchange of information among all the participants in a lawsuit. Plaintiffs have a right to all relevant, nonconfidential material related to the care of the patient. Table 128.1 lists the main methods of discovery.

The deposition perhaps is the most familiar method of discovery. Under oath, the defendant is asked questions that he or she must answer. The format of a deposition is similar to that used in court. The attorneys for both sides are present. There is no judge. There is a court reporter who makes a transcript of the questions and answers. What the anesthesiologist says at a deposition carries as much weight as what he or she says in court. Significant deviations between testimony during deposition and testimony during trial can be used against the defendant. This potential use of the deposition makes review and correction of the transcript very important. A professional attitude, appearance, and demeanor are important during a deposition, for two reasons. First, the deposition typically is the initial opportunity for the plaintiff's attorney to meet the defendant. In addition to the information provided by the answers to the questions, the plaintiff's attorney views this encounter as an opportunity to assess what kind of witness the anesthesiologist would be before a jury. Second, it has become an increasingly common practice for plaintiff attorneys to videotape depositions and then play back portions in the courtroom. It is essential that there be no discrepancy between the demeanor presented at deposition and that presented at trial.

Before the deposition, the anesthesiologist and his or her attorney should meet to go over what to expect, what questions to anticipate, how to answer specific queries, and how to behave. The anesthesiologist should be guided by his or her attorney's advice; however, the following are some useful guidelines: Be respectful of the process and

BOX 128.3 The Course of a Trial

- Jury selection.
- Opening statements by the lawyers for both sides.
- Plaintiff lawyers attempt to prove that the defendant was negligent and caused injury. In furtherance of this objective, the plaintiff's team presents and examines witnesses (both fact and expert), introduces demonstrative evidence, etc. There also is cross-examination of any witnesses by the defense team.
- Defendant's lawyers attempt to establish that the defendant's care of the patient was appropriate and proper and/or did not result in injury, using the same techniques noted above.
- Closing arguments. Both sides summarize the case from their respective points of view.
- Jury instruction by presiding judge. The judge explains the law as it applies to the case and provides instruction to the jury on how to conduct their deliberations.
- Jury deliberation. The jury discusses the case, reviews the testimony, and examines the evidence in an attempt to arrive at a decision for or against the defendant.
- Verdict. A public statement of the jury's decision, including the amount of damages, if any, awarded.

those present. Questions should be answered directly and factually. Do not volunteer any information. Do not show anger, boredom, or frustration. Avoid the use of slang, sarcasm, or humor. Disparaging comments about the plaintiff are clearly to be avoided. Do not begin an answer until the question is completely stated. Let a second or two elapse before answering to give the defense attorney the opportunity to object. Speak in a clear voice that is easy to hear and understand. Avoid excessively rapid or slow delivery. Avoid excessive use of medical terminology. One can express compassion for what has happened to the plaintiff without accepting blame. The goal, both during deposition and during trial testimony, is to come across as a competent, caring physician who did his or her very best for the patient.

Experts

As noted, to establish a claim of medical negligence, the plaintiff must present competent medical expert testimony that the anesthesiologist deviated from the standard of care and that the deviation was the proximate cause of the patient's injury. Typically, during the course of the litigation the plaintiff will be required to provide expert reports in support of the claim, and the defense attorney will provide reports from experts supportive of the defense. In some states, experts may be subject to deposition before trial; in others, trial will be the first opportunity to question the expert witness about his or her opinions.

Motions

Motions are requests to the court for an order on a particular issue in the case. Among the types of motions are motions to compel certain discovery to which objection may be made, motions to preclude or limit certain types of discovery, and motions to limit or dismiss certain claims or to dismiss certain parties. Motions do not usually require the physician's presence in court. The attorney will advise the client of any motions that require his or her involvement.

Pretrial Conference

Before a trial begins, all attorneys involved in the case typically are required to participate in a hearing held by the court. The anesthesiologist does not attend this conference. At the pretrial conference, matters such as setting a trial date, deadlines for filing pretrial motions, and submitting proposed jury instructions may be discussed. In some jurisdictions, the court also will conduct a conference at the outset of the case to set deadlines for completion of pretrial discovery, disclosure times for expert witnesses, and the filing of certain types of motions. Some states have a mandatory pretrial mediation or a mandatory settlement conference to attempt to settle the case before the trial.

Trial Testimony

The testimony during a trial is similar to that at a deposition, with certain differences. There is a presiding judge to rule on objections as to the substance and form of the questions posed. There is a lay jury that typically is not as medically sophisticated as the attorneys who conducted the depositions may have been. Because it is the jury that decides for or against the defendant, it is important for the physician to make a connection with the jury when presenting testimony as opposed to engaging the attorneys or the judge. As noted earlier, testimony should be presented in a slow, clear manner with a minimum of jargon or complex medical terms. At the same time, care should be taken to avoid "talking down" to the jury. The jury may not understand the medical terminology and may be unclear as to the details of the medical procedure but likely will be more inclined to find for the defense if they are satisfied that the defendant is a caring, conscientious doctor who did his or her best for the patient. The course of a trial is briefly outlined in Box 128.3.

Witnesses are usually called to testify during the trial. Most of these witnesses have knowledge of the events that took place, and they testify to what they saw, heard, and so on. In virtually all cases, the plaintiff and defendant(s) will testify. The defendant physician may not only be called during the defense case but also in the plaintiff's case, during which he or she can be questioned as a presumed hostile witness. There also are "expert" witnesses who, because of specialized knowledge, are permitted to provide opinions about the standard of care, whether the care at issue met the applicable standard of care, and whether any breach of the standard of care caused injury. The court decides whether or not to accept a witness as an expert, and either side can challenge the qualifications of an expert to testify. When warranted, parties typically also are entitled to preliminarily challenge the scientific basis for an expert's opinion.

Though there has been an extensive discussion about the trial process, most malpractice lawsuits are settled before trial. There are a number of reasons for this: the outcome of a trial is far from predictable for either side and can result in lengthy appeals regardless of which party prevails; settlement achieves certainty and finality; going to trial involves considerable cost for both sides; and sometimes there are concerns about the strength of the claim or the defense or about how a jury may respond to certain aspects of the case.

Insurance coverage considerations also are important in determining whether to pursue trial or settlement. Many physicians worry that a malpractice award will be higher than the limits of their insurance policy. The typical anesthesia malpractice policy has a per occurrence limit of $1 million. Only 4% of the payments in the ASA Closed Claims Project exceeded this amount. The percentage of malpractice awards greater than $1 million has not increased since the beginning of data collection by the ASA. The risk of an excess award, however, can vary greatly depending on the jurisdiction in which the case is pending. Malpractice policies do not reimburse physicians for time away from practice or the loss of income associated with a lawsuit. Policies typically have a clause that specifically excludes coverage for intentional acts of wrongdoing. Most policies have a clause requiring reasonable cooperation by the physician with the assigned attorney and the insurance company. A practitioner who refuses to comply with discovery requests, meet with his or her attorney, give a deposition, or be present at trial could compromise his or her insurance coverage.

BOX 128.4 Behaviors That May Help One Reduce the Risk of a Lawsuit

- Engage in ongoing education both on one's own and via lectures and courses.
- Work with one's associates and institution to develop ongoing patient safety and quality improvement programs. Identify and address areas of risk.
- Do a preoperative patient interview and chart review.
- Provide a clear explanation of risks and alternatives; be friendly, smile, and do not rush the patient or family.
- Obtain informed consent. Make sure the patient and the family understand what is being proposed, the risks, and that expectations are appropriate.
- Adhere to the ASA monitoring recommendations.
- Correctly label medications.
- Perform accurate and legible anesthesia record keeping; document adverse or unexpected events, and provide ongoing care after any adverse event.
- Be familiar with one's anesthesia and other equipment.
- Appropriately request assistance; avoid delaying assistance requests.
- Be familiar with the procedure being performed.
- Exercise care while positioning anesthetized patients.
- Avoid distractions while providing anesthesia care.
- Maintain good relationships with the surgeons, nurses, and other personnel.
- Provide a postoperative follow-up visit in person or by telephone.

Another consideration is that malpractice settlements and awards are reportable to the National Practitioner Data Bank (NPDB). Established by Congress in 1986, the NPDB receives the following reports: medical malpractice payments regardless of amount, adverse actions (e.g., denied or restricted licensure, denial or restriction of hospital privileges, exclusion from state or federal health care programs, adverse professional society actions), and health care–related civil judgments or criminal convictions. This information is typically queried when a physician applies for or renews hospital privileges. There is an understandable concern that NPDB entries may adversely affect employment, licensure, or privileges. State boards and credentialing bodies typically are focused on identifying troubling patterns in terms of the clinical issues involved and the size of the payments made on behalf of the physician. A small number of malpractice reports typically do not suggest such a pattern and likely would not be of concern. Adverse action reports involving clinical privileges or licensure could be of greater concern.

PREVENTION

The prevention of malpractice starts with following the applicable standard of care at all times. Box 128.4 lists several strategies that may decrease the risk of being sued. Visiting the patient preoperatively and postoperatively is important as it enhances communication and allows patient concerns to be addressed. Patient or family dissatisfaction with care may increase the likelihood of litigation. Therefore maintaining good relationships with patients not only is good practice but good risk management.

In recent years there have been efforts to break down "barriers" and improve communication after an adverse event by allowing expressions of empathy, apology, or condolence without these gestures being admissible in subsequent litigation. Proponents suggest that these may be cathartic for both the patient and the physician and may decrease the desire to punish. Many states now have statutes that allow for these gestures without the risk that they subsequently will be used against the physician in court. Although the scope of the protection varies from state to state, it is advisable to make these gestures before any litigation, and they should not include an admission of fault.

Being sued appears to be an occupational hazard for all physicians. According to Jena and colleagues, by age 65, 75% of physicians in low-risk specialties and 99% of physicians in high-risk specialties will have been named in a malpractice claim. In this data set, anesthesiology was considered a low-risk specialty.

PSYCHOLOGIC RESPONSE TO BEING SUED

The psychologic response to being sued both during the litigation and after the case is over has not been adequately discussed or considered in the literature. According to Charles' concise summary, at least 95% of physicians react to being sued by experiencing periods of emotional distress. In some cases, the anxiety can lead to major depressive disorders, substance abuse, or physical manifestations such as atrial fibrillation. Recognizing the potential emotional toll is the first step in developing appropriate coping mechanisms.

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129 Anaphylaxis and Anaphylactoid Reactions

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Case Synopsis

A 54-year-old woman presents for a hysterectomy and oophorectomy for ovarian mass. She is induced with propofol, fentanyl, and vecuronium. Sevoflurane in air/oxygen is delivered for maintenance. She receives 2 g of cefotetan shortly after intubation. Within the next 20 minutes, she develops hypotension refractory to phenylephrine and ephedrine. End-tidal CO_2 is 22 mm Hg. Epinephrine in doses of 100 μg are repeatedly given, and she requires an epinephrine infusion to maintain a mean arterial pressure greater than 60 mm Hg. The case is canceled, and she is transferred to the intensive care unit. One week later she is rescheduled for the surgery.

PROBLEM ANALYSIS

Definition

Patients under anesthesia are exposed to a large number of medications given intravenously: anesthetics, antibiotics, volume expanders, blood products, analgesics, antiseptics, dyes, and contrast material. Thus anesthesiologists are likely to experience a patient developing anaphylaxis during their career. Anaphylaxis is a rapid-onset systemic life-threatening allergic reaction. However, it can present with only a single sign (bronchospasm or hypotension) and thus can be misdiagnosed, because many disorders may present similarly. In mild cases with recovery without specific treatment, lack of recognition of anaphylaxis can lead to fatal consequences on reexposure. Reactions have classically been described as anaphylactic (immunoglobulin E [IgE] mediated) or anaphylactoid (not IgE mediated). The European Academy for Allergy and Clinical Immunology has proposed to define the clinical reaction as anaphylaxis and subclassify it as allergic or nonallergic after laboratory diagnosis reveals the exact mechanism. However, the American Academy of Allergy, Asthma and Immunology still defines the reactions as anaphylactic and anaphylactoid in its most current practice parameters of 2015. Regardless of how it is classified, for the anesthesiologist it does not matter, as anaphylaxis treatment remains the same no matter what the etiology. The majority of reactions during anesthesia are mediated by IgE to an antigen, which results in mast cell (tissues) and basophil (blood) degranulation. Up to 50% of patients with type I hypersensitivity to a neuromuscular blocking drug (NMBD) deny having had prior contact with the medication. IgE specific to an NMBD can be detected by skin test even if it was the first encounter for a patient.

Although this theory has not been proven, it is thought that prior exposure to a compound with similar quaternary ammonium groups sensitized the patient to form specific IgE molecules. Food, cosmetics, disinfectants, and other medications often contain such ammonium groups. Thus when exposed to a NMBD for the first time, these preformed IgE molecules cross-react to the ammonium group of the NMBD.

Recognition

Epidemiology

In most of the European series including France, the United Kingdom, and Scandinavia, NMBDs are the most common anesthetic medication to induce perioperative anaphylaxis (30% to 50%) (Figs. 129.1 and 129.2). In the United States, there is only a single-center study of 38 patients that reported the incidence as 11%. Latex remains in second place and may have decreased in the United States, due to intensified prevention policies. Antibiotics continue in third place despite an increase in incidence over 30 years, likely due to the increased adherence to antibiotic prophylaxis. Perioperative anaphylaxis has an estimated incidence of 1:3500 to 1:20,000 during anesthesia and a mortality rate of 1.4% to 9%, which is greater than non–anesthesia-related anaphylaxis. Despite the prompt action of an anesthesiologist, this increase in mortality rate is postulated to be due to the patient's underlying conditions, short reaction time due to the huge antigen load given intravenously, the already cardiodepressive effects of the anesthetics, and the fact that most are IgE mediated, which is the more severe form of anaphylaxis. It is 3 times more common in women than in men. Emerging allergens include nonsteroidal antiinflammatory drugs (NSAIDs), dyes, radiocontrast material, and chlorhexidine.

Pathogenesis

Drug-induced anaphylaxis is mediated by both IgE- and non–IgE-dependent pathways. The independent pathways include complement and kallikrein activation. The typical syndrome is uniphasic where the reaction occurs immediately to within 3 hours. In biphasic anaphylaxis, it stops for at least 1 hour before restarting within 72 hours without reexposure to the triggering agent. In the protracted variant, the immediate reaction continues for hours.

In the IgE-mediated pathway, preexisting IgE antibodies bound to mast cells and basophils cross-link on exposure to an antigen. Cell activation occurs with a massive release of preformed mediators (histamine, prostaglandin D2, leukotriene D4, platelet-activating factor)

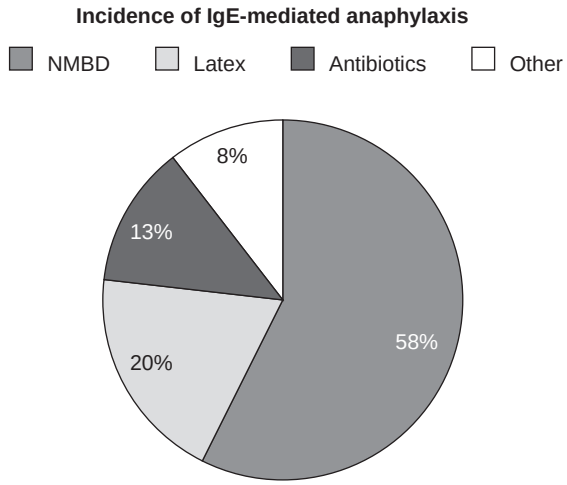

Fig. 129.1 Most common causes of anaphylaxis. (Data from Mertes PM, Alla F, Trechot P, et al.: Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 128[2]:366–373, 2011.)

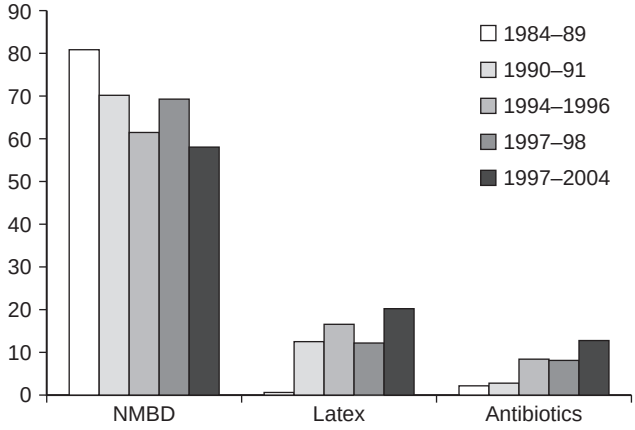

Fig. 129.2 Comparison of incidence of anaphylaxis in France over 30-year period of study. (Data from Mertes PM, Laxenaire MC, Alla F, et al.: Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 99[3]:536-545, 2003; and Mertes PM, Alla F, Trechot P, et al.: Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 128[2]:366–373, 2011.)

TABLE 129.1 Severity Scale of Perioperative Hypersensitivity Reaction

Grade		Clinical Signs
I	Cutaneous reaction	Erythema, urticaria, angioedema
II	Non–life-threatening reaction	Cutaneous ± hypotension ± tachycardia ± dyspnea ± gastrointestinal
III	Life-threatening reaction, single organ or multiorgan	Shock and/or bronchospasm
IV	Cardiac arrest	

From Dewachter P, Mouton-Faivre C, Emala CW: Anaphylaxis and anesthesia, *Anesthesiology* 111:1141–1150, 2009.

that contribute to vasodilation and smooth muscle contraction. Mast and basophils can also be directly activated by complement (non-IgE pathway). Another mechanism is the activation of tissue and plasma kallikreins, which liberate vasoactive kinins (bradykinin and kallidin) that contribute to vasodilation, contraction of airway smooth muscle, and vascular permeability. Although tryptase is released, it is unclear how it contributes to the anaphylactic process.

Ring and Messmer (1977) developed a perioperative severity scale (Table 129.1). During anesthesia, anaphylaxis typically manifests as distributive shock and/or bronchospasm, to full-blown cardiac arrest. Angioedema of tongue and lips can occur; however, if the patient is already intubated, asphyxiation is averted. Cardiac ischemia may not only be consequential to the severe hypotension, but may also be secondary to activation of mast cells located in coronary arteries themselves (Kounis syndrome). Urticaria may not initially be present during severe hypotension but may appear with restoration of the blood pressure.

Risk Assessment

Atopy is a risk factor for anaphylaxis triggered by latex, but it is not considered a risk factor for most drug-induced anaphylaxis. Comorbidities such as coronary artery disease, asthma, or emphysema may contribute to worsened outcome: (1) ischemia from anaphylaxis (or the treatment with epinephrine) or (2) from severe bronchospasm (or inability to ventilate). Patients who are on β-blockers or angiotensin-converting enzyme (ACE) inhibitors seem to have more profound hypotension and also remain more resistant to therapy.

- It is important to realize that there is a 60% to 70% cross-reactivity from one class of NMBD to another. However, a negative skin-tested NMBD can be safely substituted.
- Penicillin- or amoxicillin-allergic patients have a higher incidence of allergy to first-generation cephalosporins due to their shared β-lactam ring, but not to second- or third-generation cephalosporins.
- Egg and soy allergies do not predispose to anaphylaxis with propofol. Propofol is an oil-water emulsion that contains soybean oil and egg lecithin found in egg yolk. These compounds are not the causative allergen. In egg-allergic patients, it is the egg white protein that is the causative allergen. Soy-allergic patients can receive propofol, because the allergenic proteins are removed during the refining process. The responsible allergens in propofol are the isopropyl and phenol groups.
- Local anesthetics are subdivided into esters and amides. The skin reaction that esters cause is often due to the metabolism to para-aminobenzoic acid (PABA). When administered with epinephrine to increase the duration of action, systemic absorption can lead to symptoms attributable to an allergy: anxiety, tremor, tachycardia, and headache. The prevalence of a true IgE-mediated allergic reaction was reported to be 0.97% in about 3000 patients. Reactions to the preservatives in local anesthetics, methyl paraben, have also been described.

Emerging Allergens in Anesthetic Practice

- NSAIDs are increasingly employed for multimodal analgesia. If needed for ongoing pain treatment, skin testing to determine safe alternative NSAIDs may be warranted.
- Chlorhexidine is increasingly used as a disinfectant during surgery. It can be bound to central venous catheters, which should not be overlooked as a possible culprit if protracted anaphylaxis occurs.
- Dyes such as isosulfan blue used during lymphatic mapping for sentinel node biopsy and other dyes used intraoperatively have increasingly led to hypersensitivity reactions. Methylene blue has been used to virus-inactivate fresh frozen plasma (FFP).
- Blood products: IgA-deficient patients who have IgA antibodies can react to FFP or platelets containing IgA antigens. Methylene blue must be thought of in addition to a reaction to the blood product itself.

Clinical Manifestations of Anaphylaxis

Manifestations of drug-induced anaphylaxis include cutaneous reactions (urticarial and angioedema), respiratory (bronchospasm), and cardiovascular effects (hypotension and tachycardia or bradycardia). When massive hypovolemia allows an empty ventricle to contract, the Bezold-Jarisch reflex is thought to induce bradycardia for improved ventricular

BOX 129.1 Suggested Protocol if Urgent Surgery Is Needed

1. Be prepared for an anaphylactic reaction: epinephrine 10–20 μg/mL syringes, 2 large-bore intravenous lines, arterial line
2. Avoid latex
3. Avoid the previous antibiotic, penicillins, and first-generation cephalosporins
4. Use alternative antiseptic: povidone versus chlorhexidine
5. Send specific serum IgEs (only positive tests are valid)
6. Use a different technique: avoid all previously used drugs
   a. Regional technique
   b. Inhalation agents
7. If alternative technique is not possible, send for early skin testing:
   a. Positive: avoid these medications and use skin test–negative drugs
   b. Negative: caution as high cross-reactivity between classes of neuromuscular blocking drugs; prophylaxis with antihistamine and steroids may help in cases of anaphylactoid reactions

Adapted from Soetens F, Rose M, Fisher M: Timing of skin testing after a suspected anaphylactic reaction during anaesthesia. *Acta Anaesthesiol Scand* 56(8):1042–1046, 2012.

filling. In the face of this bradycardia, atropine can result in immediate cardiac arrest. Asthmatic patients are more likely to develop severe bronchospasm; however, anyone who develops severe bronchospasm after induction associated with hypotension and need for epinephrine should have a tryptase level checked. Cardiac patients or those taking β-blockers or ACE inhibitors are more likely to develop severe hypotension. Biphasic or protracted presentations are seen in up to 10% of the cases. The *presumptive* diagnosis is made perioperatively on a *clinical* basis and supportive *biomarkers,* whereas the diagnosis relies on allergologic evidence. If not clinically considered, misdiagnosis or delayed diagnosis occurs because hypotension can be a side effect of many of the anesthetic drugs, blood loss, or attributable to a comorbidity. Colloids used to treat hypotension from other causes (deep anesthesia or sympathectomy from an epidural) may erroneously not be considered as the cause of anaphylaxis. Urticaria and angioedema may also be missed due to the fact that the patient is draped or intubated.

Diagnosis

Histamine is not a good diagnostic marker as it is transiently elevated (half-life of 10 to 20 minutes) and may during the time of resuscitation return to baseline. However, it still should be sent. Urine *N*-methylhistamine stays around longer and may be detected up to 6 hours, but may not be available in all hospitals. A tryptase concentration level of greater than 25 μg/L is deemed a highly sensitive marker. It peaks around 60 minutes and has a 2-hour half-life. With a level of greater than 11.4 μg/L, an anaphylaxis diagnosis should be considered. A recent study showed that patients with cardiac arrest or severe hypotension do not have elevated histamine or tryptase levels when not associated with anaphylaxis. However, postmortem analysis has shown that other causes of death can lead to elevations greater than 11.4 μg/L, presumably as blood can be hemolyzed and basophils disrupted. Tryptase should be sent as soon as feasible after resuscitation (or death) and repeated at 1- to 2-, 6-, and 24-hour intervals. All guidelines share the recommendation to measure a tryptase level. The 24-hour level is considered the baseline level, and twice the basal level is considered diagnostic of anaphylaxis.

The patient should be referred to an allergist for a skin prick test (SPT) or an intradermal test (IDT) for identification of the culprit drug, typically 4 to 6 weeks after the reaction. It is thought that mast cells may be depleted of their stored allergic mediators if the patient undergoes immediate testing. Nevertheless, immediate testing (within days) can be helpful if positive. If the surgery is urgent, Box 129.1 suggests a protocol to be used. The SPT is positive when the wheal diameter is equal to half of that produced by a positive control such as histamine and at least 3 mm larger than a negative control (saline). Other NMBDs, opioids, and induction agents should also be evaluated to offer options for future surgeries by IDT. In vitro tests such as the radioallergosorbent test, enzyme-linked immunosorbent assay, or fluorescent enzyme immunoassay testing of the patient's serum IgE (sIgE) to the presumed offending agent with a secondary anti-IgE antibody will detect the amount of sIgE bound. These tests are usually done to look for allergies to NMBDs, latex, β-lactams, chlorhexidine, and ethylene oxide, a sterilizing agent for operating instruments. Newer diagnostic tests are being studied, such as the basophil activation test whereby flow cytometry detects basophil activation markers expressed after basophils are exposed to a specific allergen.

MANAGEMENT

As 50% of the fluids can quickly exit extravascularly leading to hypotension, 1 to 2 L of crystalloid and/or colloid (unless considered the culprit medication) are given rapidly and epinephrine must be immediately administered. It reverses the vasodilation, bronchoconstriction, and mucosal edema. The key reason to initially use epinephrine over norepinephrine or vasopressin is its ability to increase cAMP thereby directly inhibiting further degranulation of mediators. It is important to keep the patient's underlying condition such as coronary artery disease, advanced age, or stroke risk in mind, especially during the crisis, so as not to overdose the patient with epinephrine. Doses should start at 10 to 50 μg and then titrated up to 100 to 300 μg. Repeat dosing should prompt initiation of an epinephrine infusion. This can be quickly made up by adding 1 mg (1:1000) to a 250-mL fluid bag (4 μg/mL) infused at 1 to 4 μg/min. When epinephrine is not adequate to restore blood pressure, other vasopressors should be added. Antihistamines cannot abort anaphylaxis and are slow acting, but can aid in improving skin manifestations. Mindful administration of antihistamines is required because both H_1 and H_2 blockers, if rapidly infused, can cause hypotension. Steroids might prevent the biphasic phase. Glucagon can be considered in patients on β-blockers. It directly activates adenyl cyclase and may alleviate refractory hypotension and bronchospasm. Methylene blue, through its blockade of nitric oxide–induced vasodilation, has been shown in case reports to be an effective treatment in patients with refractory shock to catecholamines and vasopressin.

Table 129.2 outlines management of anaphylaxis.

PREVENTION

The only way to prevent anaphylaxis during anesthesia is to avoid known causative medications or suspected agents given with a prior anesthetic. However, unless one cannot avoid agents within the same class, the patient should be tested (including skin testing) before exposing the patient to further anesthesia. A collaboration between the anesthesiologist and allergist is essential to identify the culprit medication and alternative safe anesthetics to be used in the future. In the case scenario, the delay of surgery was discussed with the surgeon. A delay was not ideal, but chemotherapy could have been given during the 4 to 6 weeks while awaiting the allergy testing. However, given her cancer diagnosis, her surgery was considered urgent. All suspected agents were avoided, and no NMBD was used. A thoracic epidural with 1% ropivacaine resulted in adequate muscle relaxation. She was maintained with sevoflurane in air/oxygen. The patient did well with the surgery. The decision to proceed was wisdom in hindsight as the ovarian mass turned out to be an appendiceal cancer and she would have received the wrong chemotherapy. In addition, the anesthesiologist and allergist were able to identify safe anesthetic medications for future surgeries. In fact, she safely underwent a hyperthermic intraperitoneal chemotherapy surgery several months later.

TABLE 129.2 Management of Anaphylaxis

	Rationale
Intraoperative	
Medication	
Stop all current infusions and giving any previously administered drugs	
Crystalloids rapidly 1–2 L	35%–75% of fluid can extravasate within 15 minutes
Epinephrine	Shuts down release of mediators
β_2 agonists (albuterol)	Longer acting than epinephrine for bronchospasm
100% oxygen	
Steroids	No longer indicated emergently, secondary management to prevent biphasic response
Antihistamines	No longer indicated emergently, indicated to treat urticaria, pruritus, angioedema
Diagnosis	
Serum tryptase (immediate)	Elevation >11 ng/mL
Serum histamine (immediate)	May remain elevated up to 1 hour
Urine histamine or *N*-methylhistamine	May no longer be available in most hospitals
Perioperative	
Serum tryptase (1, 3, 6, and 12 hours)	Diagnosis, detects peak level and return to baseline
Serum IgE for specific drug	Succinylcholine, propofol, antibiotics, latex, etc.
Allergy consultation for skin testing	To identify culprit antigen

Further Reading

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130 Angioedema and Urticaria

Catherine Drexler

Case Synopsis

A 57-year-old hypertensive African American woman with recent initiation of angiotensin-converting enzyme (ACE) inhibitor undergoes laparoscopic cholecystectomy under general endotracheal anesthesia. After 1 hour in the recovery room, the patient complains that her tongue feels "thick." On examination the tongue is grossly swollen and protruding from the patient's mouth; she is able to speak and denies dyspnea or pruritus; no urticaria or wheezing is noted. There has been no response to 25 mg of diphenhydramine administered intravenously 15 minutes ago.

PROBLEM ANALYSIS

Definition

Angioedema and urticaria result from diverse causes, both immune mediated and non–immune mediated. They often occur together, along a spectrum ranging from benign and self-limited to life threatening.

Urticaria is defined by erythematous, pruritic wheals of cutaneous edema. Angioedema is a similar process, occurring in the deep dermis, subcutaneous, and submucosal tissues, with more diffuse edema. As a result of dermal sparing, angioedema tends to be nonpruritic.

Sites of angioedema involvement include the face, tongue, larynx, extremities, genitalia, and gastrointestinal tract. The latter may present with symptoms suggesting an acute intraabdominal process. Life-threatening airway obstruction may result from laryngeal involvement.

Urticaria and angioedema can be acute or chronic. Often the cause remains unknown. Inherited conditions such as hereditary angioedema (HAE) and C1 esterase inhibitor (C1-INH) deficiency may be suggested by family history. Angioedema due to deficient C1-INH may also be acquired, often in the context of an underlying autoimmune or malignant condition. A deficiency of C1-INH allows activation of the complement cascade due to cleavage of C1 by its esterase, with resultant vasodilation and angioedema.

Acute urticaria or angioedema result from activation and degranulation or degradation of mast cells and basophils, which can be mediated by immunoglobulin E (IgE) or other triggers (e.g., complement-mediated or direct mast cell–releasing agents). These cells release or generate various mediators causing vasodilation and increased vascular permeability. The extensive list of agents includes histamine, histamine-releasing factors, prostaglandin D, leukotrienes C4 and D4, platelet-activating factor, anaphylatoxins (C3a, C4a, C5a), bradykinin, kallikrein, cytokines such as interleukin (IL)–4 and IL-5, and interferon-γ. The clinical features of mast cell degradation are similar, regardless of the classification and underlying cause (Box 130.1).

Recognition

Prompt recognition of urticaria or angioedema is crucial to optimizing outcomes.

In this case the problem is easily recognized because it is reported by an alert patient. However, intraoperative diagnosis of urticaria or angioedema may be difficult for several reasons. Surgical drapes, warming blankets, and surgical "prep" solutions may obscure and limit cutaneous exposure, delaying recognition. Bronchospasm associated with histamine release may be incorrectly attributed to airway manipulation or asthma. Hypotension due to vasodilation from systemic reactions may be wrongly presumed to be evidence of myocardial depression, anesthetic effects, or hypovolemia. Finally, multiple drugs capable of immunologic or nonimmunologic mast cell activation and degranulation may be administered over a brief period; these include antibiotics, induction and neuromuscular blocking agents, and opioids. Therefore even on noting a reaction, it may be difficult to discern the cause, and whether it represents a true "allergic" (IgE-mediated) event.

Once urticaria or angioedema is recognized, it is important to note the temporal relation between administration of drugs and onset of the reaction. Responses may be delayed, causing erroneous conclusions about the causative agent.

Risk Assessment

About 15% to 20% of the population will experience an episode of angioedema or urticaria during their lifetime; angioedema is more prevalent in middle-aged women. African Americans have higher rates of ACE-inhibitor–associated angioedema compared with Caucasians, which may relate to genetic variants resulting in lower levels of other (non-ACE) enzymes involved in the cleavage of bradykinin. Without prior patient or family history, it is difficult to prospectively identify patients at risk because of the wide range of potential causes. In this scenario the patient takes an ACE inhibitor, which has recognized association with angioedema. Although generally occurring within weeks to months after initiation of the medication, ACE-inhibitor–associated angioedema has been reported after exposure for years. Further, there are cases in which angioedema episodes have continued after discontinuation of the ACE inhibitor. Airway instrumentation (e.g., endotracheal intubation) and dental procedures have been reported as angioedema triggers. Also, it is common for patients to receive nonsteroidal antiinflammatory drugs (NSAIDs) perioperatively; genetic polymorphisms associated with susceptibility to NSAID-associated urticaria and/or angioedema have been described.

Risk assessment begins with a thorough history, physical examination, and identification of medications and treatments administered. Key to proper diagnosis and treatment of angioedema is noting

BOX 130.1 Classification of Angioedema

Idiopathic
Immune-mediated angioedema
- Immunoglobulin E mediated
- Physical urticaria
- Contact reactions

Complement Mediated
C1 esterase inhibitor (C1-INH) deficiency
- Hereditary angioedema
- Acquired C1-INH deficiency

Serum sickness
Urticarial vasculitis
Systemic lupus erythematosus
Transfusion reactions

Non–Immune Mediated
Direct mast cell or histamine release
Angiotensin-converting enzyme inhibitor related

Other Rare Syndromes
Systemic mastocytosis
C3b inactivator deficiency
Infection
- Helminthic
- Fungal
- Viral

Systemic diseases
- Hyperthyroidism
- Collagen vascular diseases

Malignancies (especially B-cell malignancies)

whether there is coexisting urticaria. The presence of urticaria and pruritus suggests that the process is "allergic," or IgE mediated, and thus histaminergic. As such, favorable response to antihistamine medications and epinephrine would be anticipated. In the absence of urticaria, other mediators, such as bradykinin or complement, may be driving the reaction; recognizing the distinction is necessary for properly directed therapy. The angioedema related to ACE inhibitor use is nonimmunologic and thus is unlikely to respond adequately to antihistamines, epinephrine, or corticosteroids.

Risk assessment must include appraisal the airway, considering the possibility of laryngeal involvement, which is suggested by dyspnea or voice change. If intubation is required, fiberoptic bronchoscopy may be the best option. Tracheostomy may be required. The airway should also be examined before extubation after an angioedema event.

Implications

The primary concern is that perioperative urticaria or angioedema can progress quickly to loss of airway patency and/or anaphylaxis. Enhanced monitoring is required, as well as the presence of a practitioner capable of managing the compromised airway. Large volumes of intravenous fluids may be required in the event of a systemic reaction with hemodynamic collapse. If there is no response to antihistamines, epinephrine, and corticosteroids, nonhistaminergic angioedema should be suspected, which will require a different management strategy. Large doses (up to 4× typical allergy dosing) of antihistamines should be tried before considering a reaction to be antihistamine unresponsive.

MANAGEMENT

Angioedema is broadly categorized as histaminergic or nonhistaminergic in terms of its presentation, etiology (causative agent and chemical mediator(s), and treatment.

After assessment and management of the airway and hemodynamic status, the patient's medications should be reviewed and possible causative agents discontinued. Fluid resuscitation should be started if the patient shows evidence of intravascular volume depletion. Epinephrine is used in the presence of cardiovascular collapse, anaphylaxis, or severe respiratory compromise associated with bronchospasm.

Some reactions are mild and self-limited, resolving over hours to days, and do not require treatment beyond appropriate intensive monitoring, laboratory work if indicated, and elimination of the causative agent.

Laboratory work indicated for acute angioedema without urticaria includes complete blood count with differential and thyroid-stimulating hormone. In the presence of urticaria, serum IgE and tryptase support an allergic mechanism. Measurement of complement proteins C1-INH and C4 may be done if there is suspicion of inherited or acquired C1-INH deficiency or qualitative abnormality. Low levels of complement proteins would support a diagnosis of HAE or C1-INH deficiency; normal values are seen in ACE-inhibitor angioedema. Based on results of initial testing and evidence of underlying systemic causes, further testing for other conditions such as autoimmune disease or malignancy may be performed.

A number of drugs have recently been approved for treatment of acute nonhistaminergic angioedema and long-term treatment in the HAE population. Given the common use of ACE inhibitors in the United States following new guidelines for treatment of hypertension, a practitioner may be more likely to encounter ACE-inhibitor angioedema than HAE. There are many reports of successful use of these drugs to treat ACE-inhibitor angioedema.

Plasma-derived C1-INH (pdC1-INH, Berinert) was approved in 2009 for acute HAE attacks. The dose for acute attack is 20 U/kg intravenously. Patients with HAE receive training in self-administration of the drug. Plasma-derived C1-INH in patients with ACE-inhibitor–induced angioedema resulted in a shorter time to resolution of symptoms and fewer intubations or tracheostomies compared with historical controls who received then-standard treatment with antihistamines and steroids, though large-scale studies in this population are lacking.

Recombinant human C1-INH (rhC1-INH, Rhuconest in the United States) at 50 IU/kg intravenously was approved in 2014 for HAE. It inhibits C1, along with plasma kallikrein, FXIa, and FXIIa, which are also inhibited by C1-INH. Like pdC1-INH, it would be expected to be useful in treatment of ACE-inhibitor–induced angioedema. The half-life for rhC1-INH is shorter than that for pdC1-INH, though there is less concern for transmission of infectious agents.

Icatibant (Firazyr) is a selective bradykinin B2 receptor blocker approved in 2011 for acute HAE attacks in adults. It was recently reported in a randomized trial involving ACE-inhibitor–induced angioedema to be superior to symptomatic treatment with antihistamines and glucocorticoids, with faster onset of symptom relief, as well as shorter time to complete resolution of symptoms. After a dose of 30 mg subcutaneously, the median time to lessening of symptoms was 2 hours, and 8 hours to complete response.

A kallikrein inhibitor, ecallantide (Kalbitor), which also blocks bradykinin from kallikrein breakdown, was approved in the United States in 2009 for acute HAE attacks, at a dose of 30 mg subcutaneously. Onset of symptom relief is reported as 2 hours. Unlike icatibant, this drug is not approved for self-administration due to 3% risk of anaphylaxis.

All of the selective agents share the drawbacks of high cost ($5000–$10,000 per treatment) and lack of universal availability.

Before approval of newer agents, fresh frozen plasma (FFP), usually 2 units, has been used to treat ACE-inhibitor–induced angioedema because it contains kininase, which acts to break down

excessive bradykinin. There is theoretical risk of worsening symptoms in complement-mediated forms of angioedema, because FFP also contains complement components. Though more cost-effective than the more expensive agents discussed previously, there are also potential risks associated with infectious disease transmission, volume overload, and other transfusion-related complications.

PREVENTION

In ACE-inhibitor–induced angioedema, discontinuation of the drug is the only form of prevention. Some patients will experience angioedema while taking angiotensin receptor blockers, although the incidence is less than that with ACE inhibitors.

Preventive treatment is often used in the HAE population and is categorized as preprocedure prophylaxis and long-term prophylaxis. Dental procedures are considered especially high risk, warranting preprocedure prophylaxis. Attenuated androgens are effective for acute and long-term prevention, but have many unwanted effects (notably virilization), making them potentially unsuitable for female patients, as well as children. Plasma-derived C1-INH has been shown to be effective for acute prophylaxis, as well as long-term prevention of attacks in selected patients. The antifibrinolytic tranexamic acid was used, but other agents have proven to be more effective.

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Autonomic Dysreflexia

131

David L. McDonagh • Catherine B. Barden

Case Synopsis

A 35-year-old man with T1 spinal cord transection 3 years ago, sustained in a motorcycle accident, is scheduled for elective cystoscopy with removal of a bladder stone. In the preoperative holding area, he feels anxious and has a pounding headache, facial flushing, and hypertension (168/100 mm Hg). His admission blood pressure was 92/58 mm Hg.

PROBLEM ANALYSIS

Definition

Autonomic dysreflexia (AD) or hyperreflexia is a syndrome of episodic autonomic hyperactivity in the setting of spinal cord injury (SCI). The syndrome is more common in complete SCI, where there is no sensation or motor function below the level of the lesion. Lesions at or above T6 (above the splanchnic sympathetic outflow) put a patient at risk for AD; lesions below T6 rarely cause the syndrome. Noxious stimuli below the level of the SCI can result in an afferent volley of neural input to the spinal cord and unchecked reflex efferent sympathetic outflow. This sympathetic outflow would normally be suppressed by supraspinal (descending) inhibition, but that connection to the brain no longer exists. Animal studies suggest that increased α-adrenoreceptor expression in the vasculature after prolonged denervation may also be involved in the pathophysiology of AD. The resulting unchecked vasopressor response causes hypertension and can lead to end-organ damage.

Recognition

In 1860 Hilton first described a quadriplegic patient with episodes of AD. Symptoms include anxiety, throbbing headache, facial flushing, blurred vision, nausea, and nasal congestion. Muscle spasms can also occur. Physical examination signs include hypertension and often reflex bradycardia (Box 131.1). Below the level of the SCI, where sympathetic outflow predominates, the skin is typically cool, and there is piloerection. Above the level of the injury, where a parasympathetic counterregulatory response predominates, the skin is warm, flushed, and profusely diaphoretic. Hypertension is invariably present but is not necessarily extreme. These patients may have low normal blood pressure (≤120/80 mm Hg) at rest. With noxious stimulation, blood pressure may increase into the high normal range (>120/80 mm Hg) or stage 1 hypertension (>140/90 but <160/110 mm Hg), although severe (stage 2) hypertension (≥160/110 mm Hg) can occur (see Chobanian and colleagues in Further Reading).

Risk Assessment

All patients with SCI at or above T6 should be considered at risk for AD. The overall incidence is greater than 50%, and men are more commonly affected than women. Those with complete SCI are at the highest risk. The syndrome is seen in the subacute to chronic phase of SCI, beyond the initial injury and after spinal shock resolves. Patients with a history of previously diagnosed AD or a history of compatible symptoms should be managed with great vigilance. Recent symptoms should prompt a search for any inciting causes (Box 131.2). The most common causes are bladder distention, urinary retention, and fecal impaction. A variety of noxious stimuli below the level of the spinal cord lesion (i.e., in the area of sensory loss) can provoke AD, such as labor and delivery. Keep in mind that any surgical procedures or other stimulation below the spinal cord lesion may provoke AD, even though the patient may not have sensation in that body part.

Implications

Severe hypertension is the primary insult in AD. If uncontrolled, sustained hypertension can result in end-organ injury—a hypertensive emergency. (Note: Hypertensive crises include urgencies and emergencies. Both generally require an acute blood pressure elevation to 160/110 mm Hg or higher. With *urgency* there is no evidence of end-organ damage; there is with hypertensive *emergency*.) The main concerns are seizure, hemorrhagic stroke, subarachnoid hemorrhage from occult aneurysmal rupture, intraocular hemorrhage, dysrhythmias, and myocardial strain leading to myocardial ischemia. The syndrome of AD can be fatal on rare occasions (see Wan and Krassioukov in Further Reading).

MANAGEMENT

Anesthetic management includes the following:

- Search for and treat the inciting cause (e.g., urinary catheter placement)
- Upright or reverse Trendelenburg positioning
- Choice of anesthetic (general vs. neuraxial vs. regional)
- Appropriate intraoperative and postoperative monitoring
- Vasodilator drugs (e.g., nitroglycerin, nicardipine, hydralazine)
- Vasopressors and intravenous fluids (to treat excess hypotension)
- Deepening of general anesthesia (such as with propofol or remifentanil)
- Postponement of elective cases if hemodynamic control cannot be accomplished

Urinary retention or fecal impaction frequently precipitate AD. Intraoperatively, surgical stimulation below the level of the spinal cord lesion may also be responsible. Be sure to consider and rule out similar

BOX 131.1 Signs and Symptoms of Autonomic Dysreflexia

Hypertension
Bradycardia
Arrhythmias
Visceral and muscular spasms
Piloerection
Pallor or flushing
Severe headache
Anxiety
Convulsions
Loss of consciousness
Profuse sweating
Blurred vision
Shortness of breath
Nausea and vomiting

BOX 131.2 Potential Inciting Causes of Autonomic Dysreflexia

Bladder distention or urinary retention
Fecal impaction or rectal examination
Surgery below level of spinal cord lesion
Uterine contraction, labor
Urologic procedures
Intramuscular injection
Decubitus ulcers
Hemorrhoids
Acute abdominal processes
Skin irritation or restrictive clothing

syndromes, such as preeclampsia or eclampsia in a parturient. Sitting the patient upright causes some orthostatic hypotension and should be the initial maneuver to correct hypertension. Initial treatment for the underlying cause includes pausing the surgical procedure, bladder catheterization (or flushing of an indwelling catheter), and rectal examination with fecal disimpaction if necessary.

The choice of anesthetic (regional or general) should be tailored to the surgical procedure and the needs of the patient. Spinal, epidural, or regional anesthesia is very effective for ablating the afferent neural activity that results in AD and should be used when appropriate (such as epidural or spinal anesthesia during labor and delivery). The possibility of provoking AD with injection of a local anesthetic for peripheral nerve block or skin infiltration should be kept in mind. Also, remember that succinylcholine should generally be avoided in SCI patients due to risk for hyperkalemia.

For intraoperative and postoperative monitoring, consider arterial line placement or continuous noninvasive arterial pressure monitoring in addition to standard monitors. Have vasodilator drugs immediately available. Acute blood pressure reduction can be accomplished with a variety of agents. Intravenous labetalol, nicardipine, nitroglycerin, and nitroprusside are acceptable and can be given as a bolus or by continuous infusion. Have additional intravenous fluids and vasopressors ready to treat iatrogenic hypotension. Be prepared to quickly deepen the level of anesthesia if using a general anesthetic. In a study of patients undergoing transurethral litholapaxy, target-controlled remifentanil infusion was an effective method to decrease AD in addition to inhalation anesthetics. The use of bolus remifentanil in this setting has not been reported, although it has proven efficacy in blocking autonomic responses to noxious stimuli in other settings. Finally, postpone an elective case if preoperative AD cannot be promptly evaluated and treated.

PREVENTION

Preventive measures are tailored to the inciting factor in an individual patient. Regular urinary catheterization and laxative use to ensure regular bowel activity are important in the inpatient or outpatient setting. Patients should be taught to recognize the symptoms, correct the problem if possible, and request emergency medical care if needed. In the perioperative setting, identify at-risk patients, craft an appropriate anesthetic (general vs. neuraxial vs. regional), consider preemptive bladder catheterization, and have medications (vasodilators and bolus anesthetics) immediately available to treat acute hypertension.

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Awareness Under Anesthesia

132

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Case Synopsis

"I thought I was about to die. [One minute] I was wheeled into a fairly routine orthodontic operation. … Suddenly, I was aware something had gone very wrong. I could hear what was going on around me, and I realised with horror that I had woken up in the middle of the operation, but couldn't move a muscle. … I lay there, frantically trying to decide whether I was about to die … [it was] as though the anaesthetist had removed everything from me apart from my soul."

—Patient story from the NAP5 report

PROBLEM ANALYSIS

Definition

Accidental awareness during general anesthesia (AAGA) is the spontaneous report by a patient that he or she has been aware at a time during anesthesia and surgery when the patient expected to be unconscious. This definition, taken from the *5th National Audit Project* (NAP5) in the United Kingdom, better reflects patient experiences than some older definitions. For example, whereas previous definitions were more concerned only with reports of AAGA during surgery, the newer definition encompasses patient experiences during induction (e.g., where the induction dose may have been insufficient yet the patient is paralyzed, as in a rapid-sequence induction), and during emergence (e.g., where the anesthetic agent is allowed to wear off before reversal of neuromuscular blockade, the ensuing unintended paralysis being correctly interpreted by the patient as "accidental awareness"). The overall incidence of AAGA based on spontaneous reports is approximately 1:19,000, but with striking differences between the use of neuromuscular blockade (approximately 1:8000) and the nonparalyzed (approximately 1:136,000). The incidence in cesarean section is extremely high (approximately 1:670).

In addition to spontaneous reports, many research investigations employ the Brice interview. This is a set of direct questions to the patient, the key ones asking what is the last thing the patient recalls before "falling asleep" and what is the next thing the patient remembers. From the answers the interrogator surmises whether or not AAGA may have occurred (even in the absence of a spontaneous or direct report). The incidence of a "positive" response to a Brice interview is surprisingly high at approximately 1:600, and it is debated as to whether this is significant AAGA, or merely a triggered or prompted implicit recall. A third aspect to "awareness" is the possibility of retention of implicit memory. Explicit memory concerns recall of things or events; implicit memory is evidence of association for things or words that may have been encountered when unconscious. A famous example of this is the "Robinson Crusoe" experiment. Very rarely, if ever, does anyone spontaneously associate the word "Friday" with "Robinson Crusoe"—unless, that is, if they are played a tape of the story during anesthesia, when approximately 63% of patients will do so. Again, the clinical implications of evidence for such implicit memories after anesthesia remain unclear.

RECOGNITION, MANAGEMENT, AND PREVENTION

In AAGA, issues of recognition, management, and prevention all overlap. Our practical approach to AAGA has been greatly changed by the results of NAP5. By far the largest study into AAGA ever published (its number of cases exceeds the total number ever reported in the literature), it offers 64 recommendations for clinical practice (and over 100 suggestions for research). It is now clear that undetected AAGA cannot happen in an unparalyzed patient—a patient with only light anesthesia may move or sit up, but this will not go undetected. The key message of NAP5 is that neuromuscular blockade is the prime risk factor for all cases of AAGA. NAP5 also discovered that the rates of monitoring neuromuscular blockade were very low, as were rates of neuromuscular blockade reversal. Thus the majority of cases arose because neuromuscular blockers were used inappropriately, in excessive and unmonitored doses, and not reversed at the end of surgery. The main recommendations were therefore that (1) neuromuscular blockers should only be used when strictly necessary and at suitable doses; (2) whenever used, they should be monitored with a nerve stimulator; and (3) this should guide reversal of neuromuscular blockade at the end of surgery, before anesthesia is lightened to allow the patient to awaken. In this way, the degree of paralysis is kept to a level sufficient for surgery yet also sufficient to allow the patient to move, if perchance the patient is accidentally aware. This guidance is now the minimum mandatory requirement in the United Kingdom.

Perhaps surprising to some, NAP5 did not recommend the universal use of processed electroencephalogram (pEEG) monitors such

as the Bispectral Index or E-Entropy. The utility of these monitors remains controversial, with some clinical trials (based on Brice interviews) suggesting they reduce the incidence of AAGA, but other trials failing to reproduce these findings. At a more fundamental level, the utility of pEEG monitors as diagnostic tools has been questioned, especially as their numeric outputs are not consistent across anesthetic agents for apparently similar depths of anesthesia. It is well established that pEEG readings do not correlate with the gold standard "isolated forearm technique," and even in completely awake but paralyzed volunteers, pEEG readings are falsely very low. Although some authoritative guidelines suggest that pEEG readings should be less than 60 to avoid AAGA, NAP5 found several reports where despite outputs less than 60, traumatic AAGA occurred. Even more worryingly, NAP5 discovered several cases where the concentration of anesthetic had been reduced to 0.2 to 0.3 minimum alveolar concentration (MAC), with resultant AAGA, because the pEEG readings had been very low (approximately 40) falsely suggestive of very deep anesthesia. The suggestion of some authorities that MAC should be maintained greater than 0.7, with appropriate alarms, seems reasonable.

However, NAP5 does recommend use of pEEG (or isolated forearm) monitoring when total intravenous anesthesia (TIVA) is used with neuromuscular blockade. This is for the logical and pragmatic reason that there is no other way to monitor whether the intravenous agent is actually in the body. There have been several examples of unnoticed line disconnections causing AAGA. This advice is now the minimum monitoring guidance in the United Kingdom.

Psychological Implications

It is well recognized that AAGA can lead to posttraumatic stress disorder (PTSD), or serious symptoms short of PTSD. Adverse psychological sequelae can include anxiety, depression, sleep disturbance with nightmares, panic attacks, and several other long-term psychiatric disorders. Psychological trauma is compounded by disbelief of the patient, which delays intervention. NAP5 discovered that, much more than pain, it was the feeling of paralysis that was especially traumatic. An AAGA Support Pathway described in NAP5 now includes, first, admission to the patient that his or her experience may well be real and is being taken seriously. Honest discussion (in the United Kingdom termed a doctor's *duty of candor*) should include the possible reasons as focus for any investigation. Contact should then be maintained with follow-up and, if there are any signs of psychological disturbance, early referral for psychological support.

Causality and Medicolegal Aspects

The occurrence of AAGA does not always indicate that the anesthesiologist is at fault. Of course, some situations may be extremely difficult to explain: drug error (e.g., neuromuscular blockade before any hypnotic agent, TIVA line disconnection, failure to turn on a volatile agent, failure to adhere to now-published standards on monitoring or reversing neuromuscular blockade). Even where machine failures result in interruptions to anesthetic delivery, it may be argued that a fundamental cause is failure to monitor or respond to falling end-tidal volatile levels (or to rising pEEG readings in TIVA). The result of NAP5, that AAGA occurs mainly at induction and emergence rather than during maintenance of anesthesia, helps guide improved consent and consequently helps manage patient expectations. Providing detailed written information before surgery can help explain some of the complex statistics around AAGA. At the preoperative visit, the anesthesiologist should explain that very brief and vague awareness of instrumentation of the mouth or the sensation of tubes is not uncommon during induction or emergence, or that there may be short-lived periods of muscular weakness that will resolve. This can all help prepare and reassure the patient of rare situations when anesthetic or neuromuscular dosing is imbalanced. In other words, guaranteeing complete loss of consciousness (except perhaps when neuromuscular blockers are not used) is not an accurate promise to make, in the context of AAGA.

However, a minority of patients may be inherently resistant to anesthetic agents. NAP5 found that in approximately 5% of cases there was a family history of anesthesia or repeated AAGA experiences, suggestive of greater-than-expected anesthetic requirements. In approximately 20% of cases, the NAP5 review panels could find no deficiency in the conduct of anesthetic or the dosing or monitoring strategies employed. Like all other drugs, anesthetics work directly on specific protein receptors and channels (and not nonspecifically on the lipid membrane), which may exhibit natural variation (polymorphisms). Therefore it is incumbent on the practitioner to demonstrate good adherence to published guidance, especially with respect to managing neuromuscular blockers, but to be aware that resistance is a possibility. These aspects are drivers for research.

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Bradyarrhythmias

133

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Case Synopsis

During an open abdominal aortic aneurysm repair, a 71-year-old man suddenly becomes profoundly hypotensive after acute blood loss. The mean arterial blood pressure is 40 mm Hg, and the electrocardiogram (ECG) shows a wide complex rhythm of 35 beats per minute. The patient's preoperative ECG showed a first-degree heart block with a bifascicular bundle branch block pattern.

PROBLEM ANALYSIS

Definition

Bradyarrhythmias include cardiac rhythm abnormalities associated with a slow ventricular depolarization rate (<60 beats per minute). Such rhythm disturbances are clinically significant when associated with abnormalities of vital organ function, such as central nervous system impairment (syncope, altered mental status), postural hypotension, heart failure, or other major organ system dysfunction (especially renal, hepatic, or gastrointestinal).

Bradyarrhythmias are caused by failure of impulse formation, failure of impulse conduction, or both (Box 133.1). Anatomic structures involved in the generation and propagation of electrical impulses within the heart (i.e., its specialized conduction system) are depicted in Fig. 133.1.

The maximum diastolic potential of the sinoatrial (SA) node is between −50 and −60 mV. When maximum diastolic potential is reached, SA node cells immediately begin to depolarize. Spontaneous phase 4 depolarization is due to an imbalance between slowly decaying delayed rectifier (an outward potassium current) and slowly recovering inward calcium currents. The latter cause the cell interior to become progressively less negative with respect to the exterior. A pacemaker current is involved only when the cell interior is less negative than −50 mV. In SA node cells, this current is probably subserved by L-type calcium channels. However, T-type current may be activated during the latter half of spontaneous phase 4 depolarization (i.e., normal automaticity). Cells of the SA node depolarize to +10 mV, their maximum action potential overshoot. Thus maximum amplitudes are 60 to 70 mV. Once these are reached, SA node cells repolarize. During early repolarization, especially in atrial or ventricular muscle or Purkinje fibers (i.e., "fast-response" fibers), sodium "window" and calcium currents contribute, along with several different potassium repolarizing (outward) currents. (*Note:* Fast-response fibers have higher action potential maximum amplitudes and overshoots and faster rates of conduction than do SA or atrioventricular [AV] node cells. They also have more prominent early rapid [phase 1] repolarization.) Regardless, in all fiber types, net ionic movements during repolarization favor net outward movement of positive charges (mainly potassium), in addition to a variable contribution of reduced inward calcium and sodium current. During the action potential upstroke (depolarization), net ionic movements favor the net inward movement of positive charges. These are carried mainly by sodium and calcium, but there is also reduced outward movement of potassium.

The normal SA firing rate is 60 to 100 beats per minute. Drugs, neural input (both sympathetic and parasympathetic), temperature, and hormones influence the rate of sinus node depolarization by affecting either the rate of spontaneous (phase 4) depolarization or the threshold for a regenerative (self-sufficient) action potential upstroke.

In addition to sinus bradycardia (sinus rhythm with a rate less than 60 beats per minute; Fig. 133.2), there may be bradycardic (slow) escape rhythms arising in lower pacemakers. Such escape pacemaker rhythms (i.e., originating below the AV junction) are often associated with advanced second- and third-degree AV heart block. (Advanced

BOX 133.1 Causes of Bradyarrhythmias

Intrinsic Myocardial Causes

Failure of Impulse Formation

Sinus bradycardia
- Slow sinus node automatic rate
- Sinoatrial conduction block

Carotid sinus hypersensitivity
- Neurocardiogenic syncope (with decrease in sympathetic outflow)

Failure of Impulse Conduction

Atrioventricular node heart block
- First-degree block
- Second-degree block
  - Type I
  - Type II
- Third-degree block

External Factors

Anesthetics

Deep inhaled anesthetics (sevoflurane, halothane)
Sedatives (opiates, dexmedetomidine)
Regional blockade of cardiac acceleratory fibers (T1–T4)

Surgery

Oculocardiac reflex
Peritoneal stimulation
Carotid body stimulation

Drugs

β-Blockers, nondihydropyridine calcium channel blockers, amiodarone, digoxin
Reflex bradycardia from alpha blockade (phenylephrine)

Metabolic Causes

Hypothermia
Endocrine (hypothyroidism, Addison disease)
Electrolytes (hyperkalemia, hypermagnesemia)

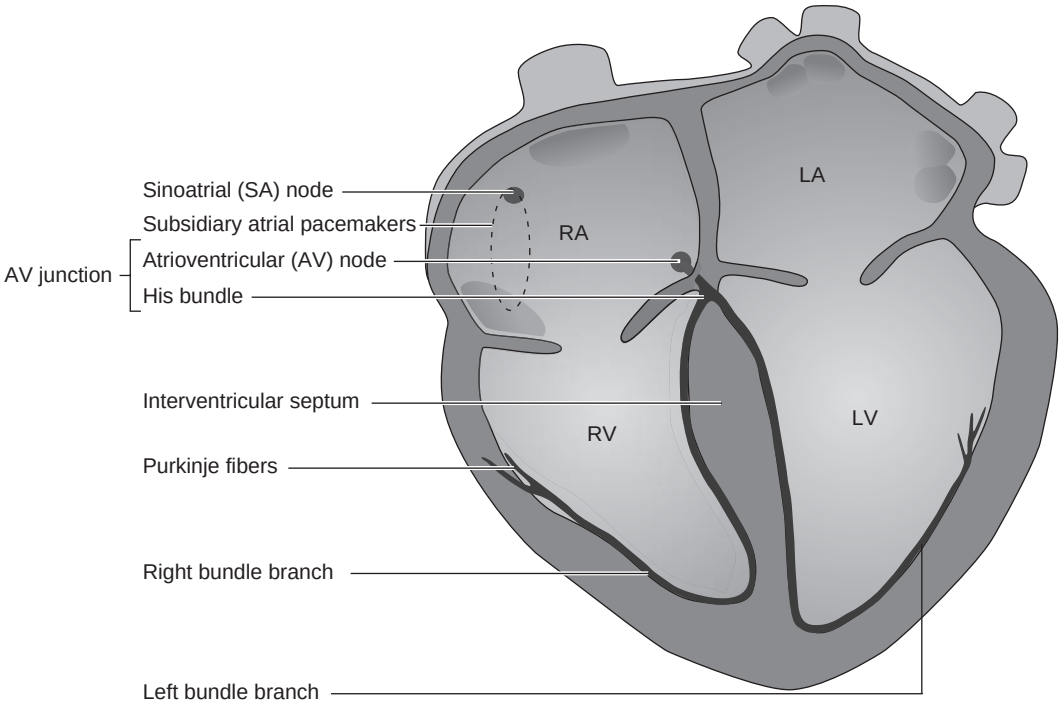

Fig. 133.1 Anatomic structures involved in the generation and propagation of electrical impulses within the heart (i.e., its specialized conduction system). *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

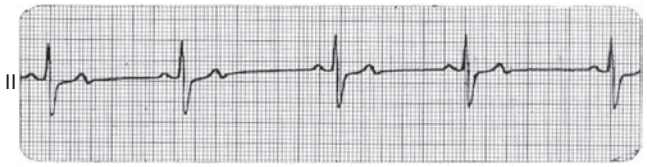

Fig. 133.2 In sinus bradycardia, there is a regular relationship between the P waves and QRS complexes. The rate is less than 60 beats per minute.

second-degree AV heart block is defined as two or more successive, blocked P waves, but with some that are conducted. With third-degree [complete] AV heart block, no P waves are conducted to the ventricles.)

Subsidiary Atrial Pacemakers

These pacemakers are found along the sulcus (crista) terminalis and around the coronary sinus orifice. Subsidiary atrial pacemaker rhythms are identified by flattened, biphasic, or negative P waves (e.g., wandering atrial pacemaker) in leads with normally upright P waves (leads II, III, and aVF). Both lower- and upper-rate cutoffs for subsidiary atrial pacemakers appear to be similar to those for the SA node. The P-R interval may be the same as or slightly less than that of the SA node (<0.10 second).

Atrioventricular Junctional Pacemakers

With AV junctional bradycardia, there may be no apparent P waves, or they may be inverted in ECG leads with normally upright P waves during sinus rhythm. Associated, inverted P (retrograde) waves may occur just before the QRS complex (P-R interval less than 0.10 second) or, less commonly, after the QRS complex.

Purkinje Fibers

Typically (e.g., during escape rhythms associated with advanced second-degree or complete [third-degree] AV heart block), escape rates are less than 50 beats per minute (may be lower in adults). Commonly, there are no associated P waves; however, there may be dissociated, upright P waves. These originate in the SA node or subsidiary atrial pacemakers but are blocked and bear no relationship to QRS complexes. However, even with advanced second- or third-degree AV heart block, retrograde (ventriculoatrial) conduction may be intact, so that associated P waves may be possible. If so, these will be inverted in leads with normally positive P waves. (*Note:* During advanced second- or third-degree AV heart block, the sinus node beats independently of the ventricles, and its rate is faster than that of the pacemaker controlling the ventricles. This is because sinus nodes are under autonomic control, blood pressure is lower with ventricular escape rhythm, and there is a baroreflex-mediated increase in sympathetic efferent activity.)

Ventricular Muscle Fibers

Rarely, ventricular fibers exhibit automaticity. When this occurs, it is due to loss of resting membrane potential. The partial depolarization of these fibers may be the result of disease, usually in association with myocardial ischemia or infarction. Ventricular rates are generally less than 40 beats per minute, and retrograde P waves are uncommon. Not uncommonly, the atria beat independently of the ventricles (AV dissociation).

After SA node depolarization, the impulse is conducted via specialized atrial conducting tissue. SA conduction block is failure of conduction within the atrial tissue; it is characterized by the absence of P waves on the ECG. When this occurs (or the SA node fails to depolarize), lower pacemaker fibers must assume control of the ventricles. Finally, as alluded to earlier, the SA node is most influenced by altered parasympathetic or sympathetic (autonomic) control. Often, this is mediated by baroreceptors and cardiac mechanoreceptors.

Recognition

ECG features of sinus bradycardia and lower pacemaker escape rhythms were already discussed. In addition, bradycardia may also be

due to AV conduction delay or block. First-degree AV block is simply delayed AV impulse transmission (P-R interval >0.12 second), with no dropped ventricular beats (QRS complexes). Second-degree AV block is block of some impulses between the atria and ventricles. It is further subdivided into Mobitz type I, Mobitz type II, and advanced second-degree AV block. With Mobitz type I (Wenckebach) AV block (Fig. 133.3), some but not all atrial beats are blocked in a recurring pattern, with progressively prolonged P-R intervals before dropped beats. The ratio of conducted to dropped beats may be fixed (e.g., 3:2, 4:3) or variable (e.g., 4:3 and 3:2). With Mobitz type II block, there are no progressively prolonged P-R intervals before dropped beats, but the block may also be variable (Fig. 133.4). With advanced second-degree AV block, there are two or more dropped beats between conducted beats; again, the ratio between the two can vary. Finally, with third-degree (complete) AV block, there are no conducted atrial beats (Fig. 133.5). The atria and ventricles are controlled by different pacemakers, and the QRS complexes may be narrow (if the pacemaker that controls the ventricles is above the bifurcation of the bundle of His) or widened (if below the bifurcation). Thus in third-degree AV heart block, there is complete AV dissociation (independent beating of the atria and ventricles).

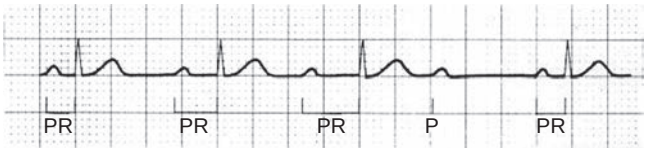

Fig. 133.3 With Mobitz type I (Wenckebach) second-degree atrioventricular (AV) block, there is progressive P-R interval prolongation before blocked P waves (i.e., the fourth P wave). As with first-degree AV block, the P-R interval is greater than 0.12 second, but there are no dropped ventricular beats. In this example, block would be variable (not shown) if the ratio of conducted to nonconducted atrial beats varied (e.g., 3:2, 4:3), as commonly occurs with Mobitz type I second-degree AV block. Block usually occurs within the AV node or at its margins.

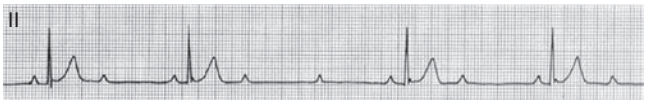

Fig. 133.4 With Mobitz type II second-degree atrioventricular (AV) block, there may be no P-R interval variability (fixed block), or block may be variable (as shown) or intermittent. If fixed, block is constant at some fixed ratio of atrial to conducted beats (e.g., 2:1, 3:1, 4:1). If variable, block varies on a recurring basis (e.g., 2:1 and 3:1). If block is intermittent, periods of normal AV conduction are interrupted by occasional dropped beats, but not on a recurring basis. Type II second-degree AV block most commonly occurs at or below the bundle of His.

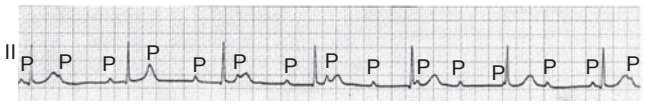

Fig. 133.5 With third-degree atrioventricular (AV) heart block (almost always at or below the bundle of His), P waves are independent of the QRS complexes (i.e., complete AV dissociation, as with ventricular-origin bradyarrhythmias or tachyarrhythmias). With third-degree AV heart block, the QRS complexes can be narrow (as shown) if the pacemaker that controls the ventricles is within or above the bifurcation of the bundle of His, or widened if the pacemaker controlling the ventricles is more distal.

Risk Assessment

Bradyarrhythmias can arise from either intrinsic myocardial causes or external influences, such as increased vagal tone or electrolyte imbalance. Implanted artificial pacemakers (see Chapter 16) are indicated for patients with symptomatic bradyarrhythmias (e.g., easy fatigability, near or true syncope) without reversible causes.

General Anesthesia and Surgery

Bradyarrhythmias that occur during general anesthesia can have many causes. Deep inhalation anesthesia (especially with older volatile agents) and opiates are well-known causes of significant bradycardia during anesthesia. Surgical stimulation may be associated with a relative increase in vagal tone, leading to slowing of SA node automaticity, AV node conduction, or both. Well-known examples are the oculocardiac reflex, peritoneal stimulation, and stimulation of the carotid body; such responses terminate when the stimulation is discontinued. Although both drug- and surgery-induced bradyarrhythmias usually respond to drugs—either anticholinergics (atropine, glycopyrrolate) or sympathomimetics (epinephrine, isoproterenol)—if temporary transvenous or pacing wires are available (e.g., during cardiac surgery), pacing is always preferable to drugs. Drugs have the potential to cause excessive tachycardia, are not easily reversed, and may cause arrhythmias. If AV conduction is intact and transesophageal or transvenous pacing is available, it is preferred over drugs as treatment for sinus bradycardia and AV junctional rhythms. Drug-resistant, clinically significant bradyarrhythmias should always be treated with external (transcutaneous) or internal (transvenous or epicardial) pacing to improve hemodynamics.

Neuraxial Blockade

Neuraxial blockade, involving the high thoracic level, may lead to vagal dominance (bradycardia) by blocking sympathetic outflow from the cardiac accelerator fibers that originate in the upper thoracic spinal cord. This bradycardia usually responds well to treatment with anticholinergic agents.

Drug-Induced Bradycardia

Many patients undergoing surgery are taking medications that slow the sinus heart rate or AV node conduction (e.g., β-blockers, nondihydropyridine calcium channel blockers). The combination of these medications, anesthesia, and surgery may result in significant bradyarrhythmias. Again, bradycardia is usually reversed with either anticholinergic or sympathomimetic agents. However, caution is advised, because excess tachycardia can put patients with ischemic heart disease or arrhythmias at further risk. In the case of elective surgery, one should consider a preoperative dose reduction of any drugs that may cause untoward bradycardia due to reduced heart rate or AV conduction block.

Metabolic Causes

Metabolic conditions may cause significant preoperative or intraoperative bradyarrhythmias. These include hypothermia (now rare with the widespread use of forced air warming blankets), endocrine disorders, and electrolyte abnormalities. With severe hypothermia, there may be sinus bradycardia or escape rhythms, with or without associated Osborne or J waves (Osborne or J waves consist of prominent notching of the terminal QRS complex with ST segment elevation). Patients with hypothyroidism and Addison disease often have preoperative bradycardia that may become more clinically significant during surgery and anesthesia due to effects of anesthetic drugs. Hyperkalemia (which hyperpolarizes cells of the SA and AV nodes) can also

cause significant sinus bradycardia or slow AV node conduction. The ECG may show a slow, wide-complex rhythm. Severe hyperkalemia can result in AV heart block or asystole. Hypermagnesemia may also cause sinus bradycardia by reducing the slow, inward, depolarizing calcium current. Both hyperkalemia and hypermagnesemia should be corrected before elective surgery to prevent bradyarrhythmias.

Implications

Because cardiac output is often reduced with bradyarrhythmias, especially with impaired or loss of atrial transport function (e.g., slow atrial fibrillation or escape rhythms), bradyarrhythmias may be poorly tolerated during anesthesia. Moreover, any vasodilation, hypovolemia, or myocardial depression is even more poorly tolerated with significant bradycardia. For example, the normal physiologic response to acute hypotension is impaired if there can be no increase in heart rate or cardiac output to maintain tissue perfusion. It is important to remember that cardiac output is the product of both heart rate and stroke volume. Whereas stroke volume is altered by contractility and preload, in addition to the effects of increased heart rate (except for the Treppe or Bowditch effect, whereby an increase in heart rate increases cardiac contractile force), cardiac output is reduced by bradycardia and bradyarrhythmias, especially if the latter are associated with loss of atrial transport function. Properly timed atrial contractions are critical for left ventricular filling in patients with impaired ventricular relaxation (diastolic dysfunction). These include elderly patients and those with chronic hypertension, aortic stenosis, or hypertrophic cardiomyopathy. Patients with impaired ventricular systolic function may also tolerate slow heart rates poorly. In this case stroke volume is reduced by increased end-systolic volume; forward flow must be increased by higher heart rates. Valvular regurgitation, such as mitral regurgitation, is more severe at slower heart rates, possibly due to an increase in mitral annular size.

MANAGEMENT

Failure of Impulse Formation

Sinus Bradycardia

Clinically significant sinus bradycardia is treated according to the severity of any physiologic impairment. Conservative management includes removing or reducing the dose of drugs known to inhibit the SA node or removing the surgical stimulus (e.g., oculocardiac reflex). If this is not effective or possible, use of anticholinergics (e.g., atropine) or sympathomimetics (e.g., ephedrine, epinephrine, isoproterenol) is considered. If this is ineffective, or if sinus bradycardia results in severe hemodynamic compromise or collapse, artificial pacing (transcutaneous, transvenous, or transesophageal) should be instituted.

Atrioventricular Junctional Escape Rhythm

AV junctional rhythms, whether bradycardia or tachycardia (rate >100 beats per minute), abolish any atrial transport function and may also be associated with tricuspid or mitral regurgitation. In patients dependent on atrial transport function (those with severe diastolic dysfunction), restoration of sinus rhythm is highly desirable. Anticholinergics or sympathomimetics are often ineffective or only increase the rate of AV junctional rhythm. Use of a β-adrenergic blocker (e.g., esmolol) may restore dominance of the SA node during general anesthesia. However, use of a drug that may exacerbate bradycardia is risky and should be attempted only when the AV junctional rhythm is greater than 60 beats per minute. Other measures include changing to an intravenous anesthetic that may have less impact on the SA node compared with volatile anesthetics. Transesophageal atrial pacing restores atrial transport function and improve preload.

Sick Sinus Syndrome

Sick sinus syndrome includes sinus bradycardia, sinus arrest, and chronotropic incompetence; it also may be associated with supraventricular tachyarrhythmias (bradycardia-tachycardia, or "brady-tachy" syndrome), the most common of which is atrial flutter or fibrillation. Regardless, treatment for bradycardia is as described earlier for sinus bradycardia. Management of associated tachycardia is discussed in Chapter 161. Always keep in mind, especially in patients with sick sinus syndrome and a history of tachyarrhythmias, that excessive tachycardia or tachyarrhythmias are a distinct possibility with any positive chronotropic treatment. Often, patients with symptomatic sick sinus syndrome have had dual-chamber pacemakers implanted, as well as drug treatment to prevent tachyarrhythmias and to slow AV node conduction.

Failure of Impulse Propagation

First-Degree Atrioventricular Block

No treatment is indicated for first-degree AV block, unless it is associated with symptomatic or hemodynamically significant bradycardia or escape rhythms. There are, however, rare exceptions. For example, after cardiac surgery, shorter P-R intervals may improve diastolic filling (preload), especially after hypertrophic cardiomyopathy repair. Thus dual-chamber sequential (AV) pacing with surgically placed temporary pacing wires to shorten the P-R interval may result in improved ventricular filling. Also, if hemodynamic insufficiency is due to P-R interval prolongation, both perioperative and long-term (if symptomatic) dual-chamber pacing should be considered.

Second-Degree Atrioventricular Block

Mobitz type I AV block is usually due to impaired AV node conduction. It rarely progresses to complete heart block. Pacing (temporary or permanent) is indicated only when any associated bradycardia is hemodynamically significant or severely symptomatic. Mobitz type II AV block can be treated conservatively in the absence of preoperative symptoms. It is likely due to intra- or infra-Hisian disease and frequently progresses to advanced second- or third-degree heart block. Symptomatic, hemodynamically disadvantageous bradycardia is an indication for temporary pacing (surgery) and, if persistent, permanent pacing.

Third-Degree Atrioventricular Block

Some children with congenital complete AV heart block are asymptomatic, and permanent pacemaker implantation can be postponed until adolescence. However, pacing is indicated for all adult patients with third-degree block unless it has a reversible cause (e.g., digoxin intoxication, β-blocker overdose).

Treatment of Symptomatic Bradycardia

The 2015 advanced cardiac life support (ACLS) guidelines outline the emergent management of symptomatic bradycardia with pulses

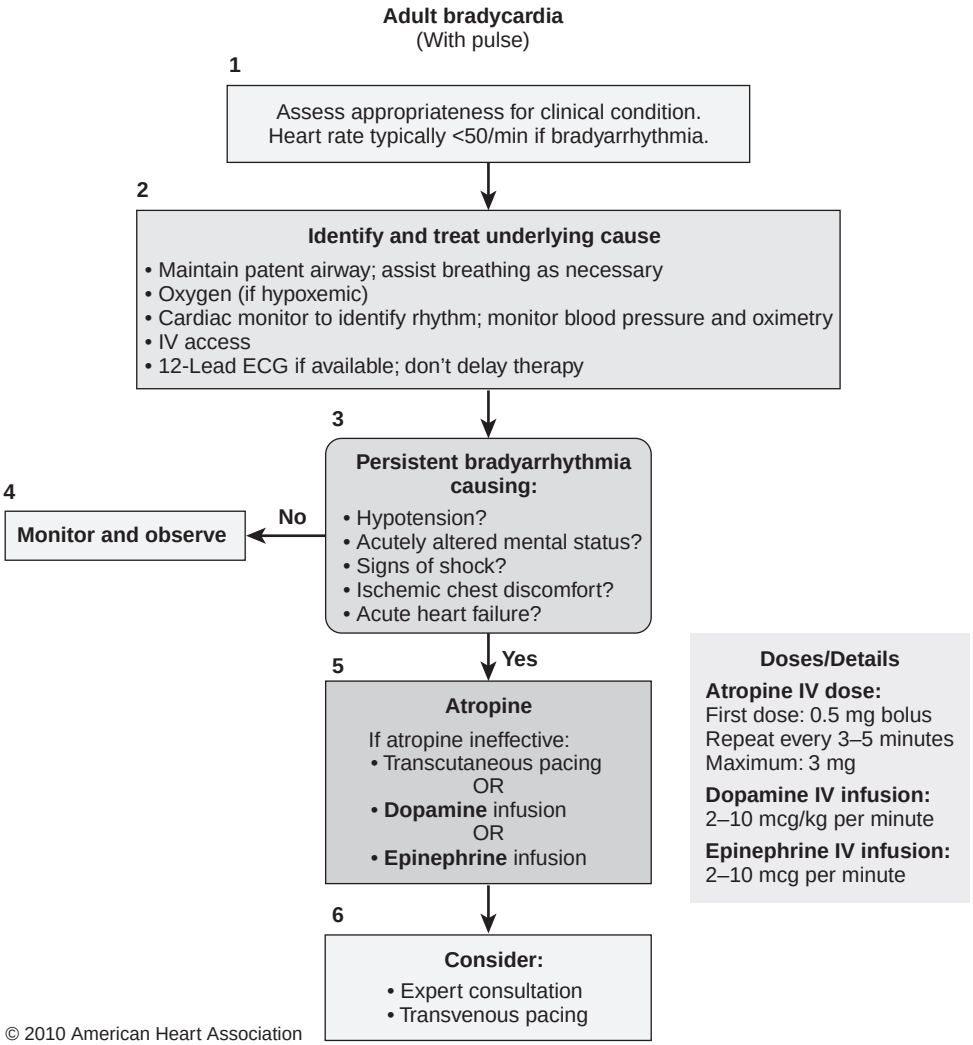

Fig. 133.6 Advanced cardiac life support (ACLS) management of bradycardia algorithm. (Copyright by ACLS Training Center. This is current with respect to 2015 American Heart Association Guidelines for CPR and ECC. These guidelines are current until they are replaced in October 2020. After that date, please contact ACLS Training Center at support@acls.net for an updated document.)

(Fig. 133.6). Note that "symptomatic bradycardia" is directly responsible for development of syncope or presyncope, dizziness, or confusion resulting from cerebral hypoperfusion. Provided that the airway is patient and the patient's minute ventilation and oxygenation are adequate, the initial treatment of bradycardia is atropine. If ineffective, the patient may be started on an infusion of a β-agonist such as epinephrine or dopamine. Transcutaneous pacing should be available in case the infusion is ineffective. Arrangements for transvenous pacing should be made if needed, as transcutaneous pacing is uncomfortable and often requires sedation.

PREVENTION

Patients undergoing surgery have similar indications for permanent pacemaker placement as the general population. The American Heart Association, American College of Cardiology, and North American Society for Pacing and Cardiac Electrophysiology (now the Heart Rhythm Society) have published guidelines for the implantation of permanent pacemakers (see Further Reading). Indications for temporary perioperative pacing are less well established. However, temporary pacing should be strongly considered for patients without an implanted cardiac rhythm management device and with debilitating symptoms or documented disadvantageous bradycardia, escape rhythms, or AV heart block and facing intermediate or high-risk surgery.

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Bronchospasm

134

Joan Benca

Case Synopsis

A 6-year-old boy with a history of mild intermittent asthma is scheduled for urgent laparoscopic appendectomy. After preoxygenation and a rapid-sequence induction, the patient is easily intubated. There is no sign of aspiration. After intubation, peak inspiratory pressure increases from 18 to 35 cm H_2O, accompanied by a decrease in oxygen saturation from 100% to 82%, a decrease in blood pressure from 98/64 to 68/34 mm Hg, and an increase in heart rate from 80 to 130 beats per minute. Chest auscultation reveals diffuse bilateral expiratory wheezes. The carbon dioxide trace on the capnogram is sharply upsloping.

PROBLEM ANALYSIS

In asthmatics, bronchospasm is caused by the spasmodic contraction of the bronchial smooth muscle. Bronchospasm is a rare event during general anesthesia, occurring in only 1% to 2% of general anesthetics. Data from the American Society of Anesthesiologists (ASA) closed claims study indicate that, though uncommon, severe bronchospasm can result in death or brain injury.

Bronchospasm is a diagnosis of exclusion, and occurs most commonly after induction and airway placement or on airway removal. Many things occurring at the time of induction and intubation can precipitate bronchospasm. The medications administered can cause histamine release. Airway placement can stimulate the parasympathetic nervous system causing reflex bronchoconstriction. Administered medications can cause immediate hypersensitivity reactions, either immunoglobulin E (IgE) mediated or non–IgE mediated.

To determine which of these things is occurring, the patient should immediately be hand ventilated with 100% oxygen to quickly determine lung compliance, while auscultating the chest to confirm wheezing (Box 134.1). If airflow is critically low, breath sounds may be severely diminished or absent. It is important to immediately confirm correct endotracheal tube position and patency of the endotracheal tube. It is important to rule out signs of pulmonary edema, mucous plugging, and tension pneumothorax on physical examination. Kinking or plugging of the endotracheal tube should be ruled out. Aspiration of a foreign body or stomach contents can also elicit bronchospasm. Inadequate depth of anesthesia can also precipitate or contribute to bronchospasm.

MANAGEMENT

This patient exhibits signs of airway obstruction that are consistent with bronchospasm, including wheezing, prolonged expiration, reduced breath sounds, increased airway pressure during positive-pressure ventilation, decreased oxygen saturation, and hypotension. The end-tidal carbon dioxide trace appears upsloping, but this alone is not specific for bronchospasm; it indicates only obstruction to exhalation somewhere along the expiration pathway. In severe bronchospasm, the CO_2 waveform may be diminished or absent, despite elevated arterial P_{CO_2} because of airflow obstruction.

Immediate treatment is critical, including hand ventilation with 100% oxygen, deepening the anesthetic with intravenous and inhalation anesthetics, and administration of a short-acting selective β_2-agonist via either nebulizer or metered-dose inhaler through the endotracheal tube. Intravenous epinephrine 0.1–1 μg/kg as a bolus followed by an infusion starting at 0.01 μg/kg/min should be administered if there is no immediate response to the β_2-agonist and deepening the anesthetic. The inhalation anesthetics sevoflurane and isoflurane are both excellent bronchodilators, and one of these should be administered. Desflurane is an airway irritant and should not be used in a patient exhibiting bronchospasm. Another medication that may be helpful with acute, severe bronchospasm is intravenous magnesium (40 mg/kg).

Inhaled magnesium has not been shown to be beneficial in this setting. High-dose intravenous steroids should be considered, methylprednisolone 2 mg/kg as a loading dose and then 0.5 to 1 mg/kg every 6 hours. Subcutaneous terbutaline (0.01 mg/kg up to a maximum of 0.3 mg) may be administered and repeated every 20 minutes. Terbutaline is helpful when a patient's airway is so tight that it is difficult to treat with inhaled bronchodilators or anesthetic vapor. During the acute event, it may be very difficult to differentiate anaphylaxis from bronchospasm, and a tryptase level can be sent within the first 2 hours to help make the diagnosis. If anaphylaxis is possible, the patient also needs to be referred to an allergist for skin prick testing at least 1 month after the acute event. Most, but not all, patients with anaphylaxis exhibit a skin rash or flushing.

If a patient exhibits signs of bronchospasm and hypotension, intravenous epinephrine as described previously should be administered. If a patient who cannot tolerate tachycardia exhibits bronchospasm (e.g., idiopathic hypertrophic subaortic stenosis), ipratroprium, an anticholinergic agent, can be administered via nebulizer or metered-dose inhaler. Because ipratropium is a quaternary amine, there is no systemic absorption and no systemic side effects. Ipratroprium is considered a second-line agent after β-agonists but may be indicated in select patients.

PREVENTION

Acute bronchospasm is not limited to patients with asthma, but asthmatics do exhibit a slightly higher incidence of bronchospasm in the

BOX 134.1 Other Causes of Wheezing in Anesthetized Patients (Not Bronchospasm)

Mechanical obstruction of endotracheal tube or other airway device
Tension pneumothorax
Pulmonary edema
Aspiration of gastric contents
Pulmonary embolism
Foreign body aspiration (e.g., tooth)

BOX 134.2 Causes of Bronchospasm in Anesthetized Patients

Nonspecific bronchial hyperresponsiveness
Anaphylactic or anaphylactoid reaction to medication, blood, latex
Succinylcholine, atracurium, rocuronium
Exacerbation of asthma
Medication administration: β-blockers, prostaglandin inhibitors, anticholinesterases
Stimulation of parasympathetic fibers and M2 and M3 muscarinic receptors
Tracheal irritation from intubation or extubation

BOX 134.3 Therapy for Acute Bronchospasm

Deepen anesthesia with potent inhalational anesthetics (sevoflurane, isoflurane) or intravenous anesthetics (propofol, ketamine, or dexmedetomidine)
β-Agonist
Albuterol metered-dose inhaler through an aerosolization chamber (2 puffs)
  Nebulizer in anesthesia circuit (2.5 mg in 3 mL 0.9% normal saline)
  Metered-dose inhaler through Bush adapter (8–10 puffs)
Epinephrine intravenous 0.1–1 μg/kg bolus followed by 0.01 μg/kg/min
  Intratracheal 10 μg/kg
  Intramuscular 10 μg/kg
Terbutaline 0.01 μg/kg subcutaneous, maximum 0.3 μg
Anticholinergics
  Ipratroprium metered-dose inhaler (18 μg/puff) 4–8 puffs q 20 min × 3 hours
  Ipratroprium nebulizer 250–500 μg q 20 min × 3 doses
  Glycopyrrolate 4 μg/kg IV
  Atropine 20 μg/kg IV
Steroids
  Methylprednisolone 1–2 mg/kg IV, maximum 125 mg
  Hydrocortisone 2 mg/kg IV
  Dexamethasone 0.1–0.5 mg/kg IV, maximum 10 mg
Magnesium sulfate
  40 mg/kg over 20 min IV

IV, Intravenously.

perioperative period. In pediatric patients, other risk factors for bronchospasm include history of eczema or hay fever, family history of eczema or smoking, younger age, and presence of upper respiratory tract infection within 2 weeks before the anesthetic. Nocturnal dry cough in children, history of wheezing with exercise, or more than three episodes of wheezing in the past 12 months is associated with increased risk of perioperative bronchospasm. A review of prior anesthetic records and asthma exacerbations requiring hospitalization may be helpful in planning the anesthetic.

Preoperative assessment to determine severity of disease and degree of control should include a history of the patient's respiratory illnesses or asthma, how well controlled the symptoms are on the current regimen, the medications that the patient is taking, how frequently rescue medications are required, whether the patient has been hospitalized or intubated, and how the patient has responded to anesthesia and airway management in the past.

After identifying patients who are at risk for perioperative respiratory events, it is important to optimize their preoperative preparation. Children with poorly controlled asthma may benefit from a pulmonary consultation before anesthesia. Inhaled bronchodilators and inhaled steroids should be continued on the morning of surgery. For asthmatics, readiness for anesthesia means the patient is compliant with medications and is at baseline respiratory status, delaying surgery until at least 2 weeks symptom free after an upper respiratory infection or 6 weeks after pneumonia. For emergency surgery, administration of inhaled β_2-selective agents before administering an anesthetic may be helpful.

Preoperative physical examination on the day of surgery must include chest auscultation, noting the type of breath sounds and length of the expiratory phase, examination of the chest for retractions or use of accessory muscles, and evaluation of the patient's vital signs, looking for increased respiratory rate or decreased oxygen saturation. Active wheezing, any signs of increased work of breathing, retractions, coughing, fever, or low arterial oxygen saturation are all reasons to delay an elective anesthetic.

The anesthetic needs to be carefully planned, including induction agents, airway management, and use of muscle relaxants and reversal agents.

Intravenous induction is preferable to inhalation induction to decrease risk of bronchospasm. Airway management using facemask anesthesia or a laryngeal mask airway, instead of an endotracheal tube, decreases the incidence of bronchospasm. Regional anesthesia is another option that avoids the problems associated with airway instrumentation, but is not an option for most children. Propofol and ketamine have bronchodilating effects and are better for preventing bronchospasm on induction than etomidate and barbiturates. Sevoflurane and isoflurane are better bronchodilators than desflurane. Spraying lidocaine on the vocal cords before intubation is associated with an increased incidence of bronchospasm, most likely because of mechanical irritation. However, lubricating a laryngeal mask airway with lidocaine gel before placement decreases the incidence of bronchospasm compared with water-soluble gel. Use of intravenous lidocaine is controversial, but more likely to be beneficial than intratracheal lidocaine. Many pediatric anesthesiologists avoid muscle relaxants because they are the commonest agents associated with immediate hypersensitivity reactions. Also, administration of neostigmine for reversal of muscle relaxants can stimulate airway reactivity via acetylcholine receptor activation.

Anticholinergic medications cause bronchodilation, including nebulized ipratroprium, intravenous glycopyrrolate, and intravenous atropine. Onset of bronchodilation after intravenous glycopyrrolate and atropine is at least 20 minutes, and bronchodilation from glycopyrrolate is longer than with atropine.

Bronchospasm may still occur despite careful patient preparation and choice of an appropriate anesthetic technique (Box 134.2). Treating bronchospasm in an anesthetized patient can be difficult. Using an inhalational anesthetic and/or intravenous propofol, ketamine, or dexmedetomidine are all good choices. However, it can be difficult to deepen anesthesia with an inhalation agent if ventilation is severely compromised. Adjunctive measures to deepen the anesthetic and treat bronchospasm include intravenous epinephrine, subcutaneous terbutaline, intravenous magnesium, anticholinergics, and nebulized β-agonists. Administration of β-agonists via a breathing circuit using a metered-dose inhaler and a Bush adapter is not as effective as using a nebulizer or aerosol-enhancing chamber. Because of this, it is recommended to administer 8 to 10 puffs from a metered-dose inhaler when using a Bush adapter. With severely impaired ventilation due to bronchospasm, epinephrine should be administered, and the anesthetic should be deepened using an intravenous agent until effective ventilation is possible. Box 134.3 lists therapeutic steps for acute bronchospasm.

Ketamine is an intravenous anesthetic with good bronchodilating properties that may be considered. Corticosteroids do not have an immediate beneficial effect in acute bronchospasm. However, they should be administered to patients with acute bronchospasm to help

reduce ongoing inflammatory changes that contribute to the airway irritability. If a patient exhibits bronchospasm with a laryngeal mask airway in place, the laryngeal mask airway should be removed and ventilation by mask attempted. If unsuccessful, intubation is indicated. Removal of an airway device is another potential trigger for bronchospasm. If a patient has been treated for bronchospasm while under anesthesia, there is not uniform agreement about whether the patient should be extubated deep or awake. The argument for awake extubation is that if the patient becomes bronchospastic on emergence, an airway is in place to facilitate treatment. Others prefer deep extubation to avoid airway irritation on emergence. Finally, the most important factor in preventing bronchospasm during general anesthesia is to provide an adequate depth of anesthesia before and during airway manipulation and/or tracheal intubation, as well as during the surgical procedure itself. It is important to ensure adequate depth of anesthesia and to match the depth of the anesthetic to the degree of stimulation by the surgeon or anesthesiologist.

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135 Celiac Plexus Block: Side Effects and Complications

Ignacio Badiola

Case Synopsis

A 71-year-old man is referred to the pain management center for abdominal pain secondary to a diagnosis of metastatic pancreatic cancer. The patient recently underwent a local anesthetic block of the celiac plexus with 80% relief of his abdominal pain. He presents today for a neurolytic block using phenol. The procedure seems uneventful until he is ready to be transferred to the recovery area, where he complains of numbness and weakness in his legs.

PROBLEM ANALYSIS

Definition

The first celiac plexus block was performed in 1914, and since then many indications for, and techniques of, celiac plexus block have been described. Complications, although rare, can be severe and catastrophic. The celiac plexus is a neural structure that innervates the gastrointestinal (GI) tract from the distal third of the esophagus to the transverse colon. It also innervates the kidneys, adrenals, spleen, liver, and biliary tract. Thus this block has been successfully used for analgesia in patients with multiple types of GI malignancies, including pancreatic cancer and upper GI malignancies, as well as nonmalignant pain conditions such as chronic pancreatitis. In most cases a diagnostic block is done first with local anesthetic followed by a neurolytic block with either phenol or alcohol with the goal of providing longer-term relief.

The celiac plexus is primarily a sympathetic nervous system structure, and blocking it with local anesthetic or ablating it with phenol/alcohol tends to produce symptoms due to sympatholysis with a resulting increase in parasympathetic tone. This causes vasodilation of the splanchnic circulation leading to a decrease in venous return and cardiac preload with a resultant decrease in blood pressure. This will usually present as orthostatic hypotension. The increase in parasympathetic tone to the GI viscera can lead to an increase in bowel motility and diarrhea.

Severe complications are rare; however, neurologic complications can be catastrophic. Nerve damage, paraplegia, and aortic dissection are uncommon but possible complications. A meta-analysis reported serious adverse events in 2% (13 of 628) patients. These events included lower extremity weakness, paresthesia, epidural anesthesia, lumbar puncture, hematuria, pneumothorax, and pleuritic chest pain. Paraplegia is also a described complication, especially with phenol/alcohol, possibly from spasm of the artery of Adamkiewicz.

Other complications that can occur after a celiac plexus block include kidney injury, retroperitoneal hematoma, pneumothorax, chylothorax, intervertebral disc penetration, abscess formation, worsening pain, and ejaculatory failure (Box 135.1).

Recognition

Orthostatic hypotension is usually seen after completion of the procedure when the patient attempts to sit up from the supine position. The decrease in blood pressure is often accompanied by dizziness, hyperhidrosis, and possible syncope. This may be marked in patients with malignancy due to volume depletion from decreased oral intake commonly seen in these patients. Recognition includes awareness of these symptoms along with blood pressure measurements. Blood pressure should be measured at baseline, throughout the procedure, and after the procedure, especially as the patient moves from prone to supine and finally from supine to an upright position. The patient should be gradually—rather than abruptly—returned to a sitting position.

Bowel hypermotility with accompanying diarrhea is common after celiac plexus block. Many patients with malignancy have baseline constipation due to opioid consumption and may consider bowel hypermotility somewhat beneficial. Patients should be counseled that this should be expected and that they should take measures to stay hydrated.

Pneumothorax is an uncommon complication; however, because the pleura can reflect down to T12/L1, this should always be considered as a complication in any patient complaining of shortness of breath or hypoxemia after a celiac plexus block.

Complications related to sensory and motor changes are usually seen almost immediately after local anesthetic or neurolytic injection. Recognition involves multiple checks before injecting local anesthetic or neurolytic agent. This includes using image guidance (computed tomography [CT] or fluoroscopy) for needle placement, aspirating for blood or cerebrospinal fluid before injection, and injecting contrast to help exclude vascular uptake. A small amount of local anesthetic should also be injected before injection of neurolytic to help rule out incorrect needle placement. Weakness or sensory changes after this local anesthetic test dose would confirm incorrect needle placement into the epidural/intrathecal space or nerve roots prompting needle repositioning.

Risk Assessment

Like any other interventional procedure, the benefits must outweigh the risks of the procedure. A meta-analysis from 1995 looked at 24

BOX 135.1 Complications of Celiac Plexus Neurolysis

- Local pain
- Orthostatic hypotension
- Diarrhea
- Nerve injury
- Paresthesia
- Epidural anesthesia
- Lumbar puncture
- Kidney injury
- Hematuria
- Pneumothorax
- Retroperitoneal hematoma
- Chylothorax
- Ejaculatory failure
- Worsening pain
- Intervertebral disc penetration
- Infection

studies with over 1000 patients with cancer (63% pancreatic, 37% nonpancreatic) and showed good to excellent pain relief in 89% of patients during the first 2 weeks after the neurolysis. These benefits persisted at 3 months. Those with pancreatic cancer responded similarly to those with other types of cancers. The study authors noted that neurolytic celiac plexus blocks provided long-lasting benefits in patients with various GI malignancies with common adverse events that were considered transient and mild. These included local pain (96%), diarrhea (44%), and hypotension (38%). Serious adverse events were noted to be 1% for neurologic complications (i.e., lower extremity weakness, paresthesia, epidural anesthesia, and lumbar puncture). They also noted a 1% complication rate for nonneurologic events such as pneumothorax and hematuria.

Implications

Common side effects are usually self-limited and should be expected. They should be discussed with the patient and caregivers before the procedure. Bowel hypermotility is usually beneficial in cancer patients and in patients with severe pain as they are usually constipated from opioid use. Orthostatic hypotension usually improves after intravascular volume equilibration.

Although many pneumothoraxes will require only patient monitoring, a more severe pneumothorax may require an invasive placement of a tube thoracostomy and admission to the hospital. Although uncommon, this should be discussed with the patient before the procedure.

Fortunately, neurologic complications such as paraplegia from injection of a neurolytic are uncommon. However, the implications of this occurring need to be stressed with the patient as it can be permanent.

MANAGEMENT

Management depends on the complication present. Orthostatic hypotension should be treated by having the patient remain supine, possibly in a Trendelenburg position. Because the cause is vasodilation and increased venous capacitance, oral or intravenous fluids can be provided. Pharmacologic therapy with α1-agonists such as phenylephrine can be used as well in refractory cases.

Bowel hypermotility is most commonly due to unopposed parasympathetic activity. It is self-limiting and can be treated symptomatically with fluid repletion and antihypermotility agents such as loperamide. A literature review (see Yang and colleagues in Further Reading) noted two case reports of persistent diarrhea. One case was treated successfully with octreotide.

Pneumothorax management depends on the size of the pneumothorax and clinical symptoms. A small pneumothorax without symptoms can usually be managed with observation, whereas a large symptomatic pneumothorax may require tube thoracostomy.

Management of neurologic complications is more complicated. If neurologic symptoms are present during test dose injection, the needle should be repositioned. If symptoms occur during injection of a neurolytic, the procedure should be aborted immediately. Aspiration of the neurolytic agent can be attempted but is unlikely to be effective. Neurology/neurosurgery and possibly interventional radiology should be consulted immediately, although options to reverse damage already done are limited.

PREVENTION

Common side effects of hypotension and bowel hypermotility are expected for a correctly performed celiac plexus block/neurolysis.

Radiologic guidance is usually cited as a way to prevent complications, especially neurologic complications. Current imaging techniques include CT, fluoroscopy, and endoscopic ultrasound. A meta-analysis looking at 1145 patients with malignancy noted that 246 (32%) of the blocks were performed without radiologic guidance, 214 were performed using CT, radiograph was used in 271, fluoroscopy in 36, and ultrasound in 7 patients. Analyzing outcomes based on radiologic technique failed to show a lower incidence of adverse effects for radiologically versus nonradiologically guided procedures. However, the authors note that most of the studies analyzed were retrospective studies. It should also be noted that the use of endoscopic ultrasound was used in only 7 of the 1145 patients analyzed and thus not adequately powered to detect any difference in adverse event outcomes.

A retrospective look (using a questionnaire sent to pain clinics) of 2730 neurolytic celiac plexus blocks was performed, with four cases reporting permanent paraplegia and three of those cases also reporting loss of anal and bladder sphincter tone. All four of the cases noted use of radiographic screening with a contrast agent. However, it was not specifically stated what kind of radiographic imaging was performed.

ACKNOWLEDGMENT

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136 Corneal Injury

Katharine H. Zentner • Luis L. Llamas • Lois L. Bready

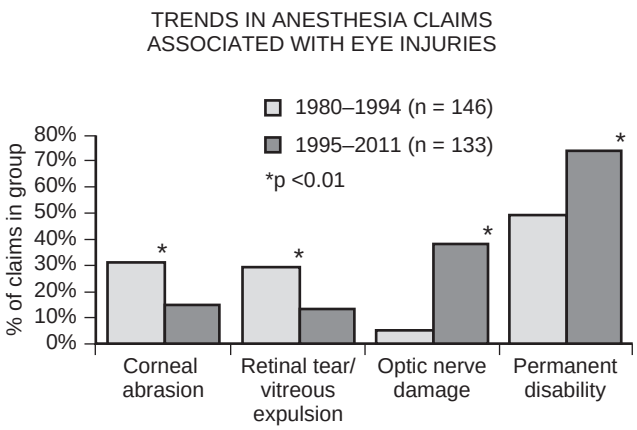
Case Synopsis

A 25-year-old woman in the postanesthesia care unit (PACU) complains of pain and a foreign body sensation in her right eye. Earlier that day, she underwent nasal polypectomy under general endotracheal anesthesia. Physical examination reveals residual petroleum-based ointment containing mascara particles around both eyes, right-sided conjunctival erythema, marked tearing, photophobia, and diminished visual acuity. A pulse oximeter probe is attached to her right index finger.

PROBLEM ANALYSIS

Definition

Corneal injuries (CIs) occur infrequently during the perioperative period, but are painful, decrease patient satisfaction, and may delay PACU or hospital discharge. There are three main types of perioperative CIs: (1) corneal abrasions (CAs), caused by mechanical trauma; (2) exposure keratopathies, due to inadequate eyelid closure during anesthesia; and (3) chemical burns, usually secondary to inadvertent exposure to skin antiseptic solutions. CAs are the most common ophthalmic injury in the perioperative period, with published incidence ranges of 0.013% to 0.17%. Long-term sequelae are uncommon, but may include corneal ulceration or erosion, with loss of visual acuity. Chemical burns frequently cause subsequent scarring. Fortunately, in recent years the percent of anesthesia claims associated with CAs has decreased significantly (Fig. 136.1).



Claims associated with eye blocks for eye surgery were excluded from this analysis. Permanent injury and claims for optic nerve injury have increased over time while claims for corneal abrasion and retinal tear or vitreous expulsion have decreased.

Fig. 136.1 Trends in anesthesia claims associated with eye injuries. (From Posner KL, Lee LL: Anesthesia malpractice claims associated with eye surgery and eye injury: highlights from the anesthesia closed claims project data request service. *ASA Newsletter* 78[11]:28–30, 2014.)

Recognition

Symptoms of corneal trauma are generally recognized within 1 to 3 hours of conclusion of anesthesia and may include eye pain, tearing, foreign body sensation, photophobia, and diminished visual acuity. Bedside examination may reveal an abraded site (Fig. 136.2), particularly with the use of oblique lighting. Abrasions may be visualized by the installation of fluorescein dye, which fills in the corneal defect and makes it visible with a cobalt-blue light.

Examination may reveal a thin band of denuded cornea within the interpalpebral area, corresponding to the area of exposure (Fig. 136.3A) or linear defects from mechanical abrasion (Fig. 136.3B). Chemical corneal toxicity usually leads to chemosis (i.e., marked swelling of the conjunctiva), with various corneal epithelial defects, including punctate keratitis (Fig. 136.4).

Risk Assessment

A number of risk factors associated with anesthesia, taken together with the proximity of ophthalmic tissues to airway and other manipulations (Fig. 136.5), may predispose to corneal trauma. The corneal epithelium is delicate; even gentle tactile contact may cause trauma. Advanced patient age and general anesthesia have been the most

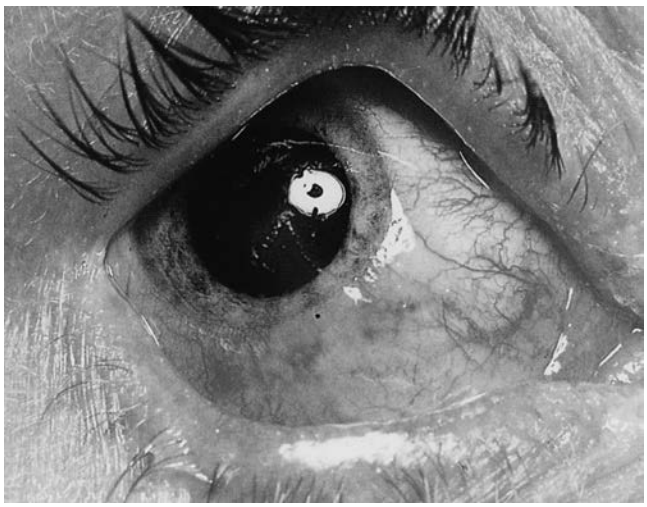


Fig. 136.2 Corneal abrasion.

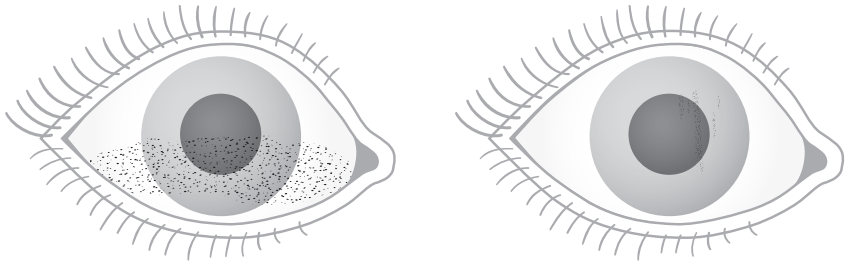


Fig. 136.3 Staining patterns of the cornea and conjunctiva. A, Interpalpebral abrasion (indicating exposure due to incomplete eyelid closure). **B,** Linear defects (suggesting mechanical abrasion).

Fig. 136.4 Grade I chemical burn with punctate keratitis (the mildest form).

consistently cited risk factors, but corneal injuries may also occur during conscious sedation when patients become too sedated to react to incidental trauma or eyelid closure is incomplete. During general anesthesia, protective corneal reflexes are inhibited, tear production is diminished, and suppression of the blink reflex inhibits the redistribution of lubricant over the ocular surface. Foreign bodies (i.e., contact lenses, mascara particles) may be present. Oxygen use during transport/recovery and intraoperative patient positioning, particularly Trendelenburg, are additional risk factors. In the Trendelenburg position, the corneal thickness is increased as a result of elevated intravascular, episcleral venous, and intraocular pressures, which leads to greater ocular dehydration and an increased risk of sloughing and abrasion.

Chemical Injury

When antiseptic solutions are applied to the skin near the eyes (i.e., during head and neck procedures), inadvertent contact with the cornea can occur. Most skin antiseptics are toxic to the cornea and exposure may cause chemical burns, with the potential to cause blindness (Box 136.1). If the solution accidentally splashes or runs into the tear film (e.g., during preparation for surgery on the head and neck), intense toxic effects may result. Hibiclens (chlorhexidine gluconate 4% and detergent) has been reported to cause permanent corneal scarring. The solution least toxic to the cornea is 10% povidone-iodine. Because both the concentration of the solution and the contact time are critical factors in corneal toxicity, if exposure to a chemical disinfectant occurs, it is prudent to immediately irrigate the conjunctival sac with saline, balanced salt solution, or water. The great majority of reported cases of severe keratitis due to exposure to surgical preparation solutions occur during operations performed by nonophthalmologists on or around the head and neck. This suggests that failure to recognize the exposure and the consequent lack of irrigation may have played a role in the adverse outcomes. Be aware that surgical preparation solutions can flow in a retrograde fashion from the nasal cavity into the conjunctival sac via a patent nasolacrimal duct.

Exposure to acidic gastric secretions can also cause a chemical burn to the cornea. If such exposure is recognized or suspected, once again, irrigation of the conjunctival sac is advised.

Manecke and colleagues reported a case in which severe bilateral corneal injuries were attributed to the use of preservative-containing eye lubricant. The preservative chlorambutanol and benzalkonium chloride have been demonstrated to cause corneal epithelial cell exfoliation. If ophthalmic ointment is used, a preservative-free preparation should be chosen.

Corneal Abrasion

Direct pressure on the eye by the facemask, head strap, hand, arm, elbow, ID badge of the anesthesiologist or surgeon, or other nearby objects can abrade the corneal surface. Corneal abrasion may occur during the induction of anesthesia, during mask airway management or instrumentation of the airway, on application of ophthalmic lubrication (if the tip of the eye lubricant tube contacts the cornea), during the procedure (pressure on the eye by the surgeon's or anesthesiologist's hands, elbows or instruments), or at emergence (due to causes similar to those during induction or if the patient rubs his or her eye to clear secretions or lubricant).

MANAGEMENT

The painful nature of corneal injuries generally leads to early patient complaints. A bedside examination with fluorescein dye, as detailed earlier, may be sufficient for diagnosis. Obtain an ophthalmology evaluation as soon as possible; however, initiation of treatment should not be delayed while waiting for ophthalmologic evaluation, as this may lead to unnecessary prolongation of the patient's pain.

Recent reports point to the success of anesthesiologist-led management protocols for minor perioperative corneal abrasions. For all patients reporting postoperative eye discomfort or pain, Segal and colleagues recommend prompt treatment in the PACU by anesthesiology staff with ophthalmic antibiotic ointment and simultaneous ophthalmologic consultation. Alternatively, Chelly and colleagues recommend installation of artificial tears in the affected eye every 30 minutes for 2 to 3 hours until symptoms subside. If symptoms persist after 2 to 3 hours, 0.5% erythromycin ophthalmic ointment should be applied to the affected eye every

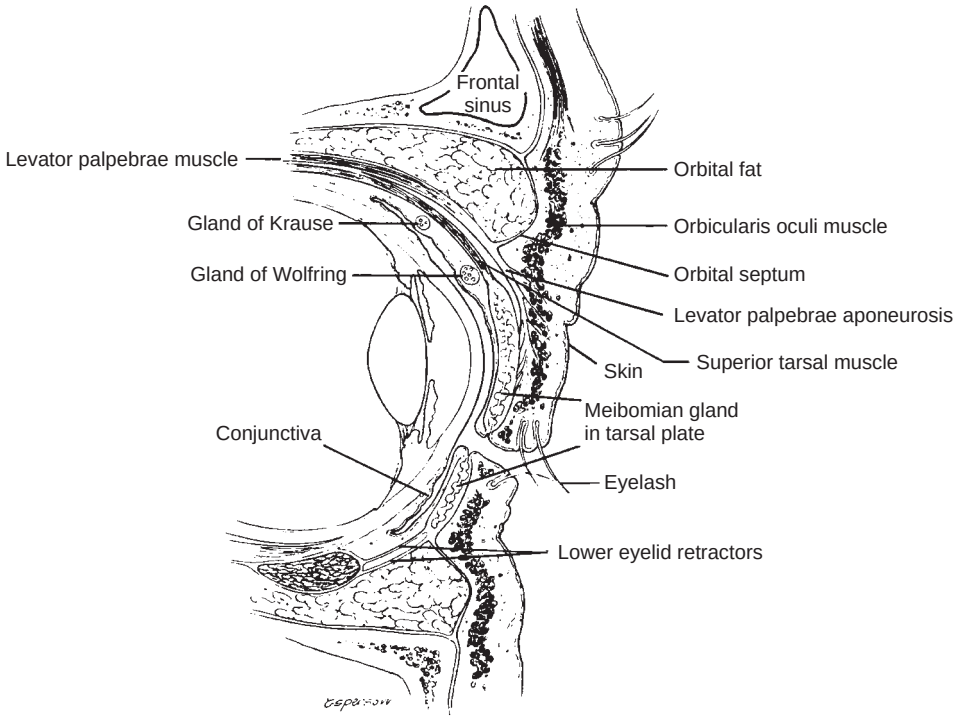


Fig. 136.5 Schematic cross section of the orbit and eyeball.

BOX 136.1 Corneal Toxicity of Skin Antiseptics

Hibiclens (chlorhexidine gluconate, 4% isopropyl alcohol with a detergent)
pHisoHex (3% hexachlorophene and a detergent)
Lavacol (70% ethanol)
Betadine surgical scrub (7.5% povidone-iodine scrub with a detergent)
Tincture of iodine (2% iodine, 2.35% sodium iodate, 46% ethanol)
Detergent-containing iodine-based products

From MacRae SM, Brown B, Edelhauser HF: The corneal toxicity of presurgical skin antiseptics. *Am J Ophthalmol* 97:221–232, 1984.

6 hours. In the event of patient allergy to erythromycin, an alternative treatment should be chosen (e.g., ciprofloxacin, tobramycin, bacitracin). In Chelly's study, an ophthalmologic consultation was only obtained if symptoms did not improve by the next morning.

PREVENTION

Awareness of the risk for ophthalmic injury is paramount to prevent such occurrences. With proper planning, it is possible to eliminate most manipulations and potentially damaging objects that may be injurious to the eyes.

The application of tape to close the eyelid can protect the cornea from trauma, chemical injury, and dehydration. Horizontal lid taping is advised over vertical lid taping and should be performed as soon as the eyelid reflex disappears, before airway management, unless a rapid-sequence intubation is performed. Intraoperatively, eye checks should be performed as tape displacement has been reported, leading the ocular surface to come into contact with the adhesive. At the conclusion of anesthesia, tape should be removed in a downward fashion (so that the eyelids remain closed during tape removal), to avoid the risk of stripping off the corneal epithelium and abrasion.

Gauze eye pads or protective eye goggles are indicated if the head is not supine and visible to the anesthesiologist (e.g., lateral or prone positioning, head or neck surgery with drapes covering the head, use of a head wrap, upper airway surgery). Although some clinicians advocate the routine use of eye goggles, a good fit can be challenging owing to interpatient variability in head size, interpupillary distance, and so forth.

Preservative-free ophthalmic lubricants can be used to prevent dehydration, which reduces one risk, but may introduce another when the patient rubs his or her eyes to clear the lubricant.

Patients should not use mascara on the morning of surgery or should be assisted in its removal before the induction of general anesthesia. Contact lenses must be removed to avoid damage to the cornea or lenses. Finally, placement of the pulse oximeter probe on a finger other than the index finger (e.g., the fourth or fifth digit) is recommended to prevent self-inflicted corneal abrasion during the patient's emergence from anesthesia.

ACKNOWLEDGMENT

The authors wish to thank Dr. Stacey Allen for her contribution to the previous edition of this chapter.

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Delayed Emergence

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Somi R. Desikan

Case Synopsis 1

A 65-year-old man undergoes open reduction and internal fixation of a tibial fracture under general anesthesia (GA). He has a history of hypertension and diabetes mellitus. He was on ramipril and metformin. GA drugs included midazolam 2 mg, total intravenous anesthesia with propofol and remifentanil, and he was ventilated on i-gel. Morphine 20 mg was given toward the end of the operation. After 150 minutes of surgery and 20 minutes of removal of i-gel in the postanesthesia care unit (PACU), the patient was still unresponsive to verbal stimuli.

Case Synopsis 2

An 80-year-old woman had a laparoscopic appendectomy under GA. She had a body mass index (BMI) of 35 (weight 95 kg) and mild chronic kidney disease (estimated glomerular filtration rate 55). She had modified rapid-sequence induction with fentanyl 100 μg, propofol 200 mg, rocuronium 50 mg, and anesthesia maintained with sevoflurane in oxygen and air. After 90 minutes of surgery, neuromuscular blockade was reversed, and the patient was extubated. Immediately after that, the patient became unconscious, had shallow respiratory efforts, and had difficulty maintaining oxygenation.

Case Synopsis 3

An 86-year-old woman had fixation of a fractured neck of the femur under GA plus fascia iliaca block. She had hypertension and atrial fibrillation, and was on amlodipine and warfarin. She had a fall at home, and her Glasgow Coma Scale (GCS) score was 14 preoperatively. GA drugs included propofol 100 mg, fentanyl 75 μg, and breathing spontaneously on oxygen/air and sevoflurane through a laryngeal mask airway. After a 45-minute procedure and 30 minutes in the PACU, the patient had not regained consciousness.

PROBLEM ANALYSIS

Definition

There is no universally accepted definition of delayed emergence/recovery after anesthesia. In clinical practice, it is thought to be the failure of the patient to regain the expected level of consciousness within 20 to 30 minutes of the end of anesthetic administration. It may also include abnormal emergence such as severe agitation. The time it takes for full consciousness to recover after anesthesia is influenced by patient factors, anesthetic drugs used, duration of surgery, and interaction between various medications used during the perioperative period. In many patients, it is probably multifactorial with a predominant contribution from one factor.

Common causes of delayed recovery include the following:

- Interactions and potentiation of drugs between preoperative medications and anesthetic drugs
- Absolute or relative overdose of sedative and anesthetic drugs
- Concomitant administration of benzodiazepines and opioids
- Sensitivity of patients to drugs (e.g., opioid-naive patients)

Uncommon causes include the following:

- Metabolic disorders
- Electrolyte disorders
- Postoperative delirium
- Sepsis

Rare causes include the following:

- Serotonin syndrome
- Central anticholinergic syndrome
- Psychiatric disorders
- Stroke and other neurologic complications

Recognition

Recognition of delayed emergence is usually made by simple neurologic assessments such as AVPU (**a**lert, responds only to **v**erbal stimuli, responds only to **p**ain, **u**nresponsive) or the GCS score. It is a diagnosis of exclusion; hence the anesthesiologist must promptly evaluate these patients to diagnose and rule out airway obstruction, respiratory failure, and hypoglycemia to differentiate delayed emergence from life-threatening problems that may falsely manifest as delayed emergence.

The patient should be evaluated immediately with assessment of vital signs after an airway, breathing, circulation (ABC) approach (especially the rate and the character of spontaneous breathing and

oxygen saturation) and a physical examination. ABC should be reevaluated throughout the course of delayed emergence. An aid to assessing and managing an unconscious patient is outlined in Fig. 137.1.

Risk Assessment

In modern anesthesia with short-acting anesthetic drugs, a majority of the patients recover very quickly after surgery, and most patients are ready to be discharged from the PACU within the first hour. Although delayed emergence has many causes, its predictability and the rate at which it will occur have not been studied well so far. Most case reports are purely anecdotal, and thus no incidence rate has been determined. Though incidence due to long-acting anesthetic drugs may be coming down, actual incidence of delayed recovery may not be, because of patients with complex medical problems on multiple medications having major operations. The cause may also be multifactorial, such as an elderly patient with dementia or renal impairment who has a lengthy procedure under GA. Pharmacologic causes are more likely, especially in the first hour. After the first hour, metabolic, neurologic, and other rare causes are more likely.

Risk factors for delayed recovery include the following:

- Elderly
- Patients with dementia
- Preexisting cognitive or psychiatric disorders
- Patients with hepatic and renal impairment
- Long operation and anesthesia duration
- Longer-acting anesthetic medications
- Absolute and relative overdose of anesthetic drugs
- Patients on sedative and antipsychotic medications
- Intoxicated patients having emergency surgery
- Patients physically exhausted before surgery

Implications

A majority of patients with delayed emergence recover well. Provided life-threatening problems are rapidly diagnosed and treated, close observation and monitoring will be enough for most patients. Some patients may need unplanned inpatient, high-dependency/intensive care management. Very rarely patients may require surgical

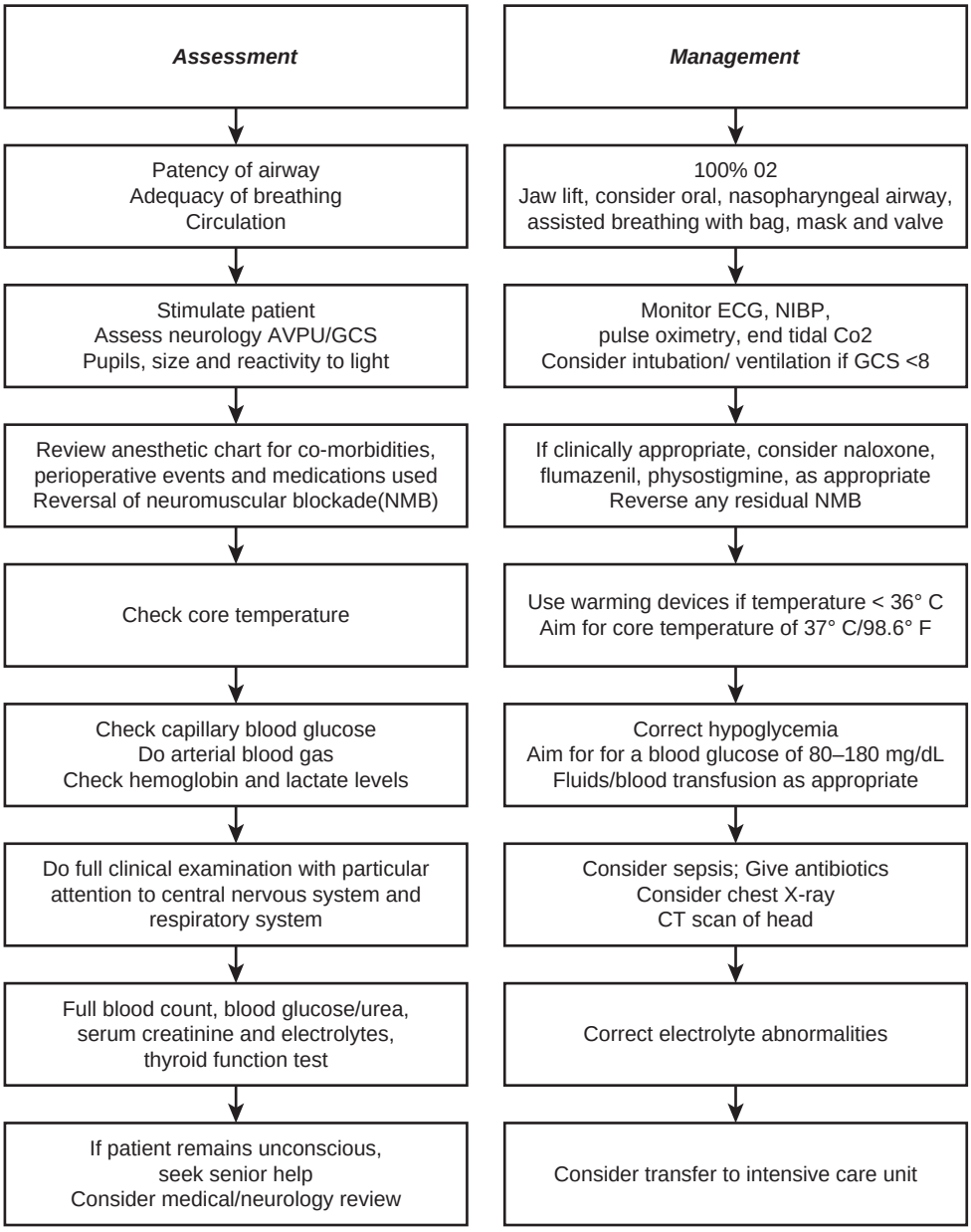

Fig. 137.1 Approach to a patient with delayed emergence from anesthesia.

intervention, such as evacuation of subdural hematoma, which may initially present as delayed emergence.

MANAGEMENT

Assessment and Investigation

Delayed emergence is a clinical diagnosis. A systematic approach such as the one presented in Fig. 137.1 will help identify and treat life-threatening problems early. Once problems such as airway obstruction, respiratory failure, and hypoglycemia are ruled out, management is usually close observation on a one-to-one basis and monitoring. Routine monitoring of continuous electrocardiogram, pulse oximetry, noninvasive blood pressure, and temperature should be done in all patients.

Further investigation may become necessary either to diagnose or to rule out specific clinical conditions. Access to blood sugar and neuromuscular monitoring should be readily available in the PACU. Arterial blood gas (ABG) analysis and radiologic tests such as chest x-ray or computed tomography (CT) of the head may become necessary. There should be plans in place to use such testing or plans to transfer to a facility to do so.

Treatment

Once serious problems are ruled out, with continued close monitoring most patients recover with time, especially if the delayed emergence was due to drugs. Reversal agents (naloxone, flumazenil, physostigmine, and neostigmine [Sugammadex]) may be used for treatment as well as diagnosis of prolonged effects of narcotics, benzodiazepines, inhalation anesthetics, and muscle relaxants.

Appropriate reversal dosages are as follows:

- Naloxone, 40-μg doses every 2 minutes intravenously to a total of 200 μg
- Flumazenil, 0.2 mg/min intravenously to a total of 1.0 mg
- Physostigmine, 1.25 mg intravenously
- Neostigmine 50 μg/kg along with glycopyrronium 10 μg/kg
- Sugammadex 2 to 4 mg/kg

Electrolyte and metabolic abnormalities should be corrected in symptomatic patients, but this must be done carefully to avoid serious undesired effects.

Pharmacologic Causes and Mechanisms

A number of factors including dose, metabolism, excretion, patient susceptibility, and drug interactions determine the residual effect of the drug in the recovery period. Biologic variation in central nervous system sensitivity follows the bell-shaped curve. Some patients require very small amounts of drugs for induction and maintenance, whereas others require larger quantities. The majority, of course, fall in the middle. The concentration of drug that reaches the brain receptor and the sensitivity of the receptor to that specific drug determine the response.

Decreased hepatic metabolism occurs in patients at the extremes of age, malnourishment, hypothermic patients, and in patients who simultaneously receive several drugs that are detoxified by the hepatic microsomal enzyme system (e.g., ethanol, barbiturates).

Although redistribution is responsible for the short action of some drugs (such as thiopental), it can contribute to delayed emergence as well, especially when given in repeated doses. Fat-soluble drugs, such as inhalation anesthetics, are distributed to fat stores. The result is a storage depot that releases anesthetic back into the circulation after the end of the procedure. This is especially true for long-acting anesthetics and particularly in obese patients.

Benzodiazepines such as midazolam and diazepam are commonly used for anxiolysis. In larger doses, especially combined with opioids in the elderly, it often causes delayed recovery. Opioids produce analgesia, sedation, and respiratory depression. Sensitivity of patients to opioids varies widely. Opioids also reduce the sensitivity of the brainstem chemoreceptors to carbon dioxide in a dose-dependent manner. This results in hypercarbia, with a further reduction in consciousness level. Neuromuscular blockade in the conscious patient can mimic unconsciousness.

Herbal supplements such as kava, St. John's wort, and valerian have the potential to cause excessive sedation and delayed emergence.

The duration of unconsciousness after intravenous anesthetic drugs is affected by context-sensitive half-life, dose, coadministration of other drugs, and patient factors. Delayed recovery is commonly observed in the intensive care unit after prolonged drug infusions lasting days. Emergence from volatile agent anesthesia depends on pulmonary elimination of the drug and minimum alveolar concentration (MAC) awake (the end-tidal concentration associated with eye opening to verbal command). MAC is consistently and approximately 30% of the MAC. Agents with higher blood gas solubility such as isoflurane and halothane (vs. sevoflaure or desflurane) take longer to be eliminated from the body and can cause delayed recovery, especially after long operations in obese patients.

Metabolic Causes and Mechanisms

Hypoglycemia can manifest as confusion, abnormal behavior, seizures, and coma. Long starvation times and diabetics on sulphonylureas and insulin are particularly prone to develop hypoglycemia. Severe hyperglycemia can also prolong unconsciousness. Hyponatremia, especially if acute, can cause lethargy, delayed awakening, and seizures. Fluid overload and hyponatremia particularly occur when large volumes of hypotonic irrigation solution have been used during transurethral resection of the prostrate (TURP), leading to TURP syndrome. Hyponatremia and pulmonary and cerebral edema in these patients lead to variable cerebral signs, including coma. Measuring electrolytes in an ABG will be the quickest way to confirm the diagnosis. Intensive resuscitation and management including intubation, ventilation, and cardiovascular support may be needed if patients develop seizure and coma. Slow correction of no more than 2 mEq/L per hour until serum sodium of 130 mEq/L is reached should be done. Hypernatremia and uremia may also present as or exacerbate confusion and coma in recovery. Hypothermia is common, especially in extremes of age and after long operations. Apart from its own effect on slowing down cerebral activity, hypothermia slows down the metabolism of drugs leading to prolonged effects of these drugs and delayed wakeup after anesthesia. Hypothermia and acidosis occur together in many patients, which potentiates the effect of drugs such as fentanyl because of decreased protein binding in acidotic patients. Respiratory failure due to a variety of causes leads to hypoxemia and hypercarbia, leading to a vicious cycle of unconsciousness that exacerbates respiratory failure.

Intracranial hemorrhage, thrombosis, and infarction can occur in association with intraoperative arrhythmias, hypotension, or hypertension, especially in patients with cerebrovascular disease. Spread of local anesthetic from blocks such as epidural or stellate ganglion block lead to unconsciousness.

Postoperative delirium occurs in 5.8% of patients after coronary artery bypass graft and can occur in up to 28% of patients undergoing emergency oncology surgery. Manifestations of delirium are varied and range from hypoactive to agitation. Hypoactive types can be particularly confused with residual effects of anesthetic drugs.

Uncommon Causes

Serotonin syndrome usually presents as a triad of neuromuscular abnormalities, autonomic hyperactivity, and mental status changes. Clinical manifestations can be mild to severe. It usually occurs when

two or more serotonergic agents are administered concomitantly. Anti-Parkinson drugs (levodopa) and antidepressants, such as selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, all increase synoptic serotonin levels.

Central anticholinergic syndrome (CAS), though much less common than in the past, may manifest as cerebral irritation, agitation, stupor, and coma. Drugs such as atropine, tricyclic antidepressants (amitriptyline), and neuroleptics (chlorpromazine) can precipitate CAS. It usually responds to physostigmine.

PREVENTION

Anesthesia for a Patient Who Has, or Claims to Have Had, Delayed Emergence

- Elicit a detailed history including whether the patient had to be admitted as unplanned inpatient care or high-dependency/intensive care unit care.
- Get the anesthetic chart and clinical notes from the previous procedure.
- Ask the patient/look for evidence of any investigations, specialist review.
- Look for evidence of administration of reversal agents such as flumazenil, naloxone, or physostigmine.
- Read about the drug interactions of medications the patient is currently taking.

Anesthesia Plan

- Consider local/regional anesthesia if possible for the planned procedure.
- Avoid sedative premedication.
- Use short-acting anesthetic drugs.
- Use age-adjusted MAC.
- In morbidly obese patients, use an adjusted formula such as IBW + 40% excess weight for target-controlled infusion of propofol. If in doubt, titrate to effect and monitor.
- Calculate IBW by using the Broca formula: *men,* height in cm – 100; *women,* height in cm – 105.
- Consider using depth-of-anesthesia monitoring such as bispectral index and entropy.

Discussion About the Case Synopses

Case 1

This patient never had a GA in the past. He had protective airway reflexes, breathing at a rate of 8 to 10 breaths per min, responding to painful stimuli. He also had small but responsive pupillary reflex. His blood sugar was normal. Opioid sensitivity was the cause of delayed awakening in this patient. Though use of naloxone was considered, it was decided not to administer it because the patient was safely maintaining oxygenation and had had a major painful procedure. After approximately 40 minutes in the PACU, the patient started responding to verbal stimuli. He remained drowsy for another hour and was discharged back to the ward after 2 hours.

Case 2

Though not strictly a case of delayed emergence, this case illustrates respiratory failure in the PACU due to inadequate reversal of neuromuscular blockade (NMB). This patient was given 100% oxygen, continuous positive airway pressure, and a repeat dose of neostigmine, but continued to deteriorate. This patient was about to be reintubated, but because of a high suspicion of residual NMB, it was decided to give Sugammadex, which rapidly reversed NMB and improved respiratory failure.

Case 3

During assessment in the PACU, it was noted that the patient's GCS score indicated unresponsiveness to painful stimuli, and the right pupil was dilated and not reacting. Her blood sugar was normal and international normalized ratio was 1.4. She was intubated and ventilated, and a CT scan of the head was performed that revealed an acute chronic subdural hematoma. The patient was then transferred to a neurosurgical center for surgical evacuation of a subdural hematoma.

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Dental Injuries

138

Myrna C. Newland

Case Synopsis

A 54-year-old woman is scheduled for a laparoscopic cholecystectomy under general anesthesia. Preoperative examination reveals a body mass index of 32, a short neck, and a Mallampati score of III. Dental examination reveals multiple caries, several crowns on molar teeth, and prominent upper incisors. She has been told in the past that she was "a difficult intubation." A videolaryngoscope was used successfully for endotracheal intubation under general anesthesia. There was no dental injury.

PROBLEM ANALYSIS

Definition

Dental injuries related to general anesthesia and tracheal intubation have been recognized as one of the most frequent complications associated with anesthesia and a source of medicolegal complaints. *Dental injuries* have been defined as any notable change to the patient's dentition during the perianesthetic period that may or may not have required dental consultation or treatment. In 1986, Lockhart and colleagues reported on a survey sent to all directors of anesthesia training programs in the United States asking for estimates of dental injuries in their programs. Dental injuries were estimated to occur at a rate of 1 per 1000 cases out of approximately 1 million anesthetics. A large study by Warner and colleagues reported in 1999 from the Mayo Clinic found an incidence of 1 per 2805 cases undergoing general anesthesia with tracheal intubation. They found no reports of dental injury in over 285,000 cases of regional anesthesia or monitored anesthesia care.

We analyzed all perianesthetic dental injuries in our practice at the University of Nebraska Medical Center from a database of adverse events associated with anesthesia in 161,687 anesthetics over 14 years. There were 78 cases of dental injury for a rate of 1 per 2073. The epidemiology of upper airway injury in patients undergoing major surgical procedures was reported in 2012 using data from the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) for the years 2005 to 2008. Data were collected prospectively from 251 participating hospitals for patients undergoing general anesthesia for major surgical procedures. Out of 563,190 patients, 1202 sustained an airway injury. Independent risk factors were a difficult airway and advanced age. The most common airway injury was lip laceration/hematoma followed by tooth injury. Dental injuries may occur outside of the operating room. A study reported in 2011 looked at 3423 emergency non–operating room airway management cases. There were 144 cases with airway-related complications and 6 cases of dental injury giving an incidence of 1 per 570 cases. Difficult intubations were noted in 10%. Predictors of complications included three or more attempts at intubation, emergency department location, grade III or IV view of the larynx, and general care floor location. Reasons for intubation were primarily respiratory distress or cardiac arrest.

Analysis of Quality Assurance Data and Closed Claims

An 8-year audit by Vallejo and colleagues of quality assurance data covering 816,690 anesthetics within a large university hospital system that included community, tertiary, and quaternary care centers found dental injury to be the most common cause of patient complaints among all complications of airway management with medicolegal consequences. There were 360 cases of dental injuries. Patients with general anesthesia had an incidence of dental injury of 1 per 1754 cases. Pediatric patients had a much lower incidence of 1 per 7692. Major risk factors for dental injury were general anesthesia with endotracheal intubation on preexisting poor dentition.

An analysis of patient injury from anesthesiology closed claims between 2007 and 2012 by a large national malpractice insurer, The Doctors Company, found a total of 607 claims. The most frequent injuries were tooth damage (20.8%) and death (18.3%). Tooth damage was related to intubation or extubation. Difficult intubation and poor condition of teeth were common factors. Broken crowns and dental implants needed replacement, veneers fell from teeth, and invasive procedures were occasionally needed to retrieve teeth, crowns, or bridges that were swallowed or aspirated. In many cases there was no evidence of preoperative assessment or documentation to note the condition of teeth or oral appliances. The average indemnity for tooth damage was $6174.

Recognition

Dental injuries may occur in the operating room, postanesthesia care unit, intensive care unit, or elsewhere in the hospital during emergency care and may be reported by the patient, nurses, or anesthesia providers. Dental injuries and their definitions include the following:

- Enamel fractures: a scratch or chip in the enamel of the tooth
- Subluxation: an injury to the tooth-supporting structures with abnormal loosening, but without displacement of the tooth
- Luxation: partial displacement of the tooth from its socket
- Avulsion: complete displacement of the tooth from its socket
- Fractures: crown fracture alone or both crown and root fractures
- Other injuries: damage to dental restorations, implants, prosthetic crowns, fixed partial dentures (bridges), and dislodgement of veneers

Risk factors for dental injury are general anesthesia with tracheal intubation, preexisting poor dentition, difficult laryngoscopy, and

intubation. Teeth most frequently injured are maxillary incisors. Children may be at increased risk for dental injury because of loose and easily dislodged primary teeth. A review by Tan and colleagues of 80,811 general anesthetics over a 12-year period at a tertiary pediatric center found 42 cases of dental injury in children 2 to 15 years of age, with 69% occurring in children 5 to 8 years. The incidence of dental injury was 1 per 1924 anesthetics. Sixty-two percent of the dental injuries occurred in patients with an inaccurate dental history. Two patients required a repeat anesthetic for tooth removal and reimplantation.

MANAGEMENT

Dental damage is commonly noted by the anesthesia provider at the time it occurs. Eighty-two percent of cases in our study had preexisting poor dentition or reconstructive work, and 86% of all dental injuries were discovered by the anesthesia provider in the operating room (68%) or in the postoperative care unit (14%). Those patients with preoperative poor dentition or reconstructive work and who were difficult to intubate were at approximately 20-fold greater risk of dental injury than those easy to intubate. Fig. 138.1 shows the standard method of tooth numbering beginning with the right maxillary molar tooth. The numbers of dental injuries per affected tooth in our study are reported by numbers placed within the teeth. Relative risk of injury is illustrated along the side. The teeth most frequently injured were the maxillary incisors. Examination of the mouth and teeth should be performed after tracheal intubation is completed and also at the end of the case after extubation of the trachea.

- Any dental damage should be documented in the chart.
- Any avulsed or broken teeth or appliances should be retrieved and accounted for.
- Any permanent tooth displaced from its socket should be stored in normal saline or cool fresh milk until it can be splinted or reimplanted.
- Dental consultation should be obtained as soon as possible if reimplantation is considered.
- If necessary, radiographs of the neck, chest, or abdomen may be taken to locate missing teeth or appliances.
- Aspiration of a tooth or tooth fragments is a serious complication, and if undetected may lead to pulmonary complications such as pneumonia.
- Discussion with the patient or family member should occur when the patient is fully awake.
- For less severe injuries such as enamel fracture, a dental consultation should be considered before the patient is discharged.

PREVENTION

A review of perioperative dental considerations for the anesthesiologist by Yasny strongly recommends a preoperative assessment of the patient's airway and dentition. Some patients present with evidence of chronic dental neglect with loose or missing teeth, evidence of multiple caries, and periodontal disease. In some cases a preoperative consultation with a dentist is indicated. The maxillary incisors are the teeth most commonly injured with intubation. If they have been restored with bonding, veneers, or crowns, they are not as strong as natural teeth and may be more prone to damage. Any loose teeth are vulnerable to loss. Documentation on the medical record should include the results of the preoperative dental assessment and notation of specific teeth at risk. Discussion with the patient of possible dental injury should be undertaken and documentation of this discussion

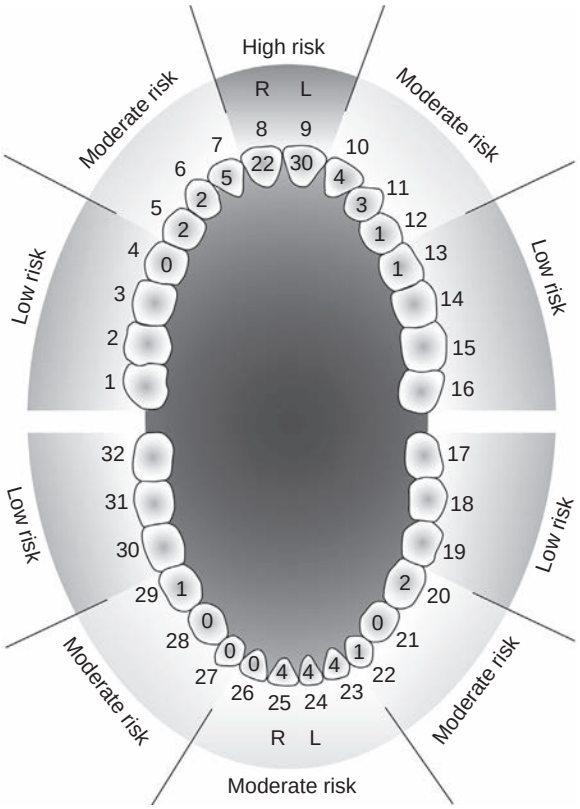

Fig. 138.1 Numerals outside the teeth in this figure show a standard method of tooth numbering beginning with the right maxillary molar tooth. Numerals placed within the individual tooth in the diagram depict the number of injuries to that tooth reported in the study by Newland and colleagues. The left maxillary central incisor (tooth no. 9) had the greatest number of injuries (30). Tooth number 8 had the next highest (22). Both maxillary incisors are in the area of high risk for dental injuries during tracheal intubation. (From Newland MC, Ellis SJ, Peters KR, et al.: Dental injury associated with anesthesia: a report of 161,687 anesthetics given over 14 years. *J Clin Anesth* 19[5]:339–345, 2007.)

should be placed in the chart. Vulnerable teeth, veneers, implants, and bridges or other appliances should be identified on a dental chart that is a part of the preoperative assessment form. Anesthesia providers should be aware of the Universal Numbering System used in the United States for the complete adult (permanent) dentition. Adult dentition includes 32 teeth in the upper and lower jaws. Teeth are numbered from 1 through 32 beginning at the maxillary right quadrant's third molar (no. 1) (see Fig. 138.1). The central maxillary incisors are number 8 on the right and number 9 on the left. Number 9 is the most commonly injured tooth with intubation, likely due to contact with the laryngoscope blade. Children have a maximum of 20 primary or deciduous teeth.

Plans for dealing with a possible difficult intubation should be considered. In addition to examining the patient's dentition preoperatively and documenting findings in the medical record, all patients at risk for a possible difficult intubation should be identified. Aziz and colleagues reported on the effectiveness of a video laryngoscope that was used in 2004 cases identified as possible difficult intubations out of a total of 71,570 intubations. Common predictors of difficult intubation were used, including Mallampati III/IV; thyromental distance less than 6 cm; mouth opening less than 3 cm; neck pathology from mass, surgical scar, or radiation; obese neck; or reduced cervical motion. A video laryngoscope was used successfully for intubation in

97% of cases. Complications occurred in 21 of 2004 cases. Most were minor soft tissue injuries. However, there were six major complications that consisted of vocal cord trauma, tracheal injury, hypopharynx trauma, tonsillar perforation, and two dental injuries: a chipped tooth and a tooth that was dislodged.

It is likely not possible to prevent all anesthesia-related dental injuries, but much can be done to keep them at a minimum. A thorough assessment of each patient's dentition at the preoperative evaluation and awareness of risk factors is necessary. Proper documentation in the record and communication with the patient as well as appropriate consultation with dental colleagues will do much to decrease the incidence of dental injury and mitigate the effects should injury occur.

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139 Difficult Airway and Failed Extubation

Mohammad El-Orbany

Case Synopsis

An obese man (body mass index 40) sustained closed head injury, lung contusions, and C-spine injury after a fall from a tree. Tracheal intubation was performed by paramedics at the scene, and the patient was transported to the hospital. Three days later, the patient had satisfactory neurologic and respiratory recovery, but the neck collar was still in place. After meeting extubation criteria, his trachea was extubated. The patient immediately developed severe respiratory difficulty, and his oxygen saturation started to drop. Attempts to ventilate the lungs with a facemask were unsuccessful. As the patient lost consciousness, laryngoscopy was performed after removing the neck collar and applying in-line head stabilization. No laryngeal structures could be visualized.

PROBLEM ANALYSIS

Definition

Failed Extubation

Extubation failure is the inability to maintain adequate respiratory functions after endotracheal tube removal due to airway obstruction or hypoventilation. Without proper and timely management, it eventually leads to oxygen desaturation, hypoxemia, and respiratory failure. Immediate reintubation is needed until the underlying cause is treated and the patient can tolerate extubation. A crisis/near-miss situation may develop if reintubation proves difficult or fails. The American Society of Anesthesiologists (ASA) task force on the management of the difficult airway recommended preformulating an extubation strategy in patients who may be at risk of extubation failure and are known to have a difficult airway. The guidelines recommended a "staged extubation" strategy that can be achieved by using an airway device that functions as a "bridge" to full extubation and ensures continuous airway access in case reintubation is needed after removing the endotracheal tube.

Difficult Airway

A difficult airway is defined as a clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation (FMV), difficulty with tracheal intubation, or both. Some patients with difficult FMV may be relatively easy to intubate, and vice versa. The common causes of airway management failures are listed in Box 139.1.

Difficult Facemask Ventilation

Difficult FMV occurs when positive-pressure ventilation, by an unassisted anesthesiologist, fails to maintain oxygen saturation above 90% (with an inspired oxygen concentration of 100%) or the ventilation effort fails to prevent or reverse signs of inadequate gas exchange. Inadequate FMV occurs secondary to inadequate facemask seal, excessive gas leak, or excessive resistance to the ingress or egress of gas. Signs of inadequate facemask ventilation are listed in Box 139.2.

Difficult Laryngoscopy and Intubation

Difficult laryngoscopy refers to the inability to visualize any portion of the vocal cords after multiple attempts using conventional rigid laryngoscopy. Difficult intubation occurs when endotracheal intubation requires multiple attempts, and failed intubation means failure to place the endotracheal tube after multiple attempts. The incidence of difficult laryngoscopy (more than two attempts) is between 0.5% and 2%. The first attempt must be optimized by providing an adequate depth of anesthesia, muscle relaxation, proper positioning of the head and neck, and application of external laryngeal manipulation if needed. Switching blades can sometimes improve visualization, and a straight laryngoscope blade may be more efficacious with an "anterior" larynx. Alternatively, a video laryngoscope can provide better visualization of the glottis. No more than two or three attempts should be made at direct laryngoscopy, because repeated attempts may worsen the patient's outcome (e.g., conversion of a can-ventilate to a cannot-ventilate situation, or laryngeal edema causing glottic airway obstruction after tracheal extubation). FMV should be performed between intubation attempts, and laryngoscopy must be stopped if

BOX 139.1 Underlying Causes of Airway Management Failures

- Inaccurate or incomplete preoperative airway assessment
- Failure to predict:
  - Ease/difficulty of mask ventilation
  - Ease/difficulty of direct laryngoscopy/ tracheal intubation
  - High-risk tracheal extubation
- Unwillingness to abandon failed airway management plan
- Failure to call for help early, when difficult airway is first apparent
- Incomplete preparation of backup plan
- Deterioration of performance under stress
- Failure in judgment

BOX 139.2 Signs of Inadequate Facemask Ventilation

Insufficient or absent chest movement
Absent or inadequate breath sounds
Audible signs of airway obstruction, gastric air insufflation, or gastric dilation
Inadequate or decreasing oxygen saturation (late)
Cyanosis (late)
Absent, inadequate, or elevated end-tidal carbon dioxide
Absent or inadequate exhaled gas flow (spirometry)
Hemodynamic consequences of hypercarbia or hypoxemia (e.g., tachycardia, hypertension, dysrhythmias)—occur late, should not wait for them to diagnose inadequate facemask ventilation

BOX 139.3 Predictors and Patient Factors Associated With Difficult Facemask Ventilation and Suggested Solutions

Facial Hair
Place adhesive plastic sheet, with mouth and naris openings, over facial hair to achieve better mask seal
Place oral, nasal, or laryngeal mask airway early

Edentulous
Consider leaving dentures in place until laryngoscopy to improve facemask seal
Place laryngeal mask airway early

Body Mass Index >30
Preoxygenate patient with continuous positive airway pressure, and use 20- to 30-degree reverse Trendelenburg position
Increases time interval to desaturation after onset of apnea or difficult mask ventilation
Reverse Trendelenburg "unloads" diaphragm, improving pulmonary compliance
Use laryngeal mask airway early for positive-pressure mask ventilation

Snoring and Obstructive Sleep Apnea
Place oral, nasal, or laryngeal mask airway early

Age >55 Years
History of Smoking
Supraglottic, Glottic, and Subglottic Pathology or Stridor
Strongly consider awake airway management
Avoid sedation if stridor is present

Bronchospasm (Active or At Risk For)
Nebulize with bronchodilator before induction

BOX 139.4 Predictors of Difficult Direct Laryngoscopy and Endotracheal Intubation

Interincisor Gap
If distance between upper and lower incisors is <3–4 cm, direct laryngoscopy may be difficult because of the following:
Insufficient space for blade insertion and blade "traction" without dental injury
Less room for endotracheal tube passage and direction
Possible obscured line of sight to glottic opening

Length of Upper Incisors
Long incisors impede alignment of oral and pharyngeal axes during direct laryngoscopy
Relatively long, protruding upper incisors are worrisome

Mallampati Oropharyngeal Classification
With Mallampati class I or II, tongue should be easily retracted from the line of site during direct laryngoscopy
Mallampati class >II is worrisome

Mandibular Space
With hyomental and thyromental distances (estimates of mandibular space) >6 and 7 cm, respectively, larynx should be sufficiently posterior for favorable line of sight with direct laryngoscopy

BOX 139.4 Predictors of Difficult Direct Laryngoscopy and Endotracheal Intubation—cont'd

Distance <3 ordinary fingerbreadths (5 cm) is worrisome

Length and Thickness of Neck
Short, thick neck reduces ability to align upper airway axes during direct laryngoscopy
In obese patients, large neck circumference and Mallampati class >II are worrisome

Head and Neck Range of Motion
Atlanto-occipital (AO) extension or neck flexion on chest of <35 degrees predicts difficult direct laryngoscopy; this amount of AO extension and neck flexion is required for proper alignment of oral, pharyngeal, and laryngeal axes
Obese body habitus may preclude optimal alignment of oral, pharyngeal, and laryngeal axes
Direct laryngoscopy in obese patients is facilitated when head, neck, and shoulders are elevated ("stacked"), bringing chin level with sternum; fiberoptic bronchoscopy intubation is rarely necessary with proper positioning
Higher Mallampati class and large neck circumference are reliable predictors of difficult intubation in obese patients
Inability to touch chin to chest is worrisome

Maxillary-Mandibular Overbite (Buck Teeth)
Buck teeth reduce the ability to align oral and pharyngeal axes during direct laryngoscopy

Mandibular Translation
Ability to protrude lower jaw by >1 cm often predicts good direct laryngoscopic view
Ability to touch bottom incisors to the upper lip–skin border is reassuring

Mandibular Space Compliance
Worrisome findings include stiffness, induration, and presence of mass

Palate Configuration
Narrow or highly arched palate reduces oropharyngeal volume and ability to visualize glottis with both laryngoscope blade and endotracheal tube in mouth

oxygen saturation drops below 90% to 92% (maintenance of oxygenation takes precedence). The most experienced anesthesiologist should perform the final attempt at direct laryngoscopy.

Recognition and Risk Assessment

Reviewing the patient's prior anesthetic history and previous records of airway management (if available) is extremely helpful when formulating the airway management plan. Preanesthetic airway evaluation should be performed in all cases (including emergencies and monitored anesthesia care cases) to elicit predictors of potential difficulty if any is present. Predictors of difficult FMV, as well as some suggestions for dealing with them, are listed in Box 139.3. Placing a laryngeal mask airway permits adequate ventilation in most of those patients and should be used early when a difficulty is encountered with FMV. Predictors of difficult laryngeal visualization with direct laryngoscopy are listed in Box 139.4. Unfortunately, airway examination findings have low and variable sensitivity and marginal specificity; however, worrisome findings, particularly in combination, suggest a difficult laryngoscopy/intubation. For example, a Mallampati class higher than II in association with other airway findings signifies a potential difficulty during traditional direct laryngoscopy.

Anesthesiologists must accurately document the ease or difficulty of FMV, laryngoscopy attempts and blades used, the laryngoscopic view obtained, how intubation was ultimately achieved, and any special maneuvers or devices used.

Difficult FMV and difficult intubation, along with other preoperative general conditions and specific intraoperative events, indicate a high possibility of difficult/failed extubation. Patients with a difficult airway

BOX 139.5 Predictors of High-Risk Tracheal Extubation

1. Airway Risk Factors

a. Preexisting airway difficulties:
   History or actual occurrence of difficult mask ventilation and/or difficult intubation
   Obstructive sleep apnea
   Neck scars, masses, contractures, or burns
   Prior neck dissection and radiation therapy
   Maxillofacial trauma
   Deep neck or pharyngeal infection
b. Perioperative airway deterioration:
   Hematoma or vocal cord dysfunction after thyroid surgery
   Edema or bleeding after anterior or posterior neck surgery (cervical spine or carotid endartrectomy)
   Airway edema/trauma from intubation or surgery
   Vocal cord and laryngeal surgery
   Uvulopalatopharyngoplasty
c. Restricted airway access:
   Halo fixation
   Maxillary-mandibular wiring
   Cervical spine fusion

2. General Risk Factors

a. Impaired respiratory function: Obstructive sleep apnea, laryngeal incompetence or vocal cord dysfunction, diaphragmatic splinting, recurrent laryngeal nerve palsy
b. Cardiovascular instability or excessive blood loss with massive fluid resuscitation
c. Neurologic diseases: may affect pharyngeal muscles or vocal cord functions (e.g., Parkinson disease, stroke patients, and demyelinating diseases)
d. Neuromuscular: preexisting neuromuscular disorder, residual neuromuscular block
e. Hypothermia: may affect neuromuscular function, prolong medication effects, result in shivering increasing oxygen delivery requirements
f. Acid-base and/or electrolyte derangement: affect neuromuscular functions and prolong duration of neuromuscular blocking drugs
g. Rheumatoid arthritis: cervical spine, temporomandibular joint, and cricoarytenoid joint can be affected, limiting mouth opening and range of neck motion

should meet the usual criteria for extubation and be fully awake. They also should cough and phonate during endotracheal tube cuff deflation. Predictors of difficult/failed extubation are shown in Box 139.5.

A preformulated extubation strategy should be planned before anesthesia induction in patients with a high risk of extubation failure. Factors to consider in formulating this strategy are listed in Box 139.6.

BOX 139.6 Factors to Consider When Formulating an Extubation Strategy

Relative advantages of awake extubation vs. tracheal extubation before return of consciousness
- Was intubation difficult?
- Was facemask ventilation difficult?
- Is risk for aspiration high?

Upper airway edema or bleeding may have adverse impact on effective ventilation after extubation
- Bleeding, tissue edema, or nerve injury can cause airway obstruction after neck surgery
- Edema risk may be higher with recent neck infection or prior irradiation

Direct or indirect trauma to peritracheal, laryngeal, and supraglottic structures
- Manipulation during surgery increases potential for airway obstruction
- Edema may occur after difficult or multiple laryngoscopies but not be apparent until after extubation

Recurrent laryngeal nerve injury

Predetermined plan for airway management if patient is unable to maintain adequate ventilation after removal of endotracheal tube

Extubation over previously inserted endotracheal tube exchange catheter
- Functions as a guide for rapid reintubation
- Can facilitate ventilation if tube exchanger has a lumen

Extubation over flexible fiberoptic bronchoscope
- Endotracheal tube can be readvanced into trachea if necessary
- Trachea and glottic and supraglottic structures can be examined for abnormalities as bronchoscope is slowly removed
- Bronchoscope removal can be stopped if significant airway concerns are identified
- Bronchoscope may be readvanced into trachea, with subsequent passage of "loaded" endotracheal tube
- Wire can be inserted through fiberoptic bronchoscope suction channel before bronchoscope's gradual removal to serve as guide for reintroduction of bronchoscope or airway exchange catheter into trachea

MANAGEMENT

The "cannot ventilate, cannot intubate" (CVCI) situation, once recognized, must be managed quickly and decisively. Emergency airway management options include the following.

Emergency Noninvasive Airway Ventilation

As per the ASA difficult airway algorithm, if the initial intubation attempts are unsuccessful and FMV is inadequate, a supraglottic airway device (SAD) should be considered/attempted if feasible. In most situations, ventilation can be adequately established unless the cause of airway obstruction is glottic or subglottic in nature or proper seating of the device cannot be achieved. The following discussion highlights rescue supraglottic airway devices that are most commonly used in a CVCI situation.

The laryngeal mask airway (LMA Classic or Unique) serves as an airway ventilating device, a conduit for intubation, or both. The incidence of morbidity and/or mortality resulting from CVCI situations has dramatically decreased after the adoption and widespread use of the LMA, which is now an integral part of the ASA difficult airway algorithm. Some of the limitations of LMA use are as follows:

- It is a supraglottic device and may be ineffective in the presence of glottic or subglottic pathology (like any other SAD).
- It does not protect the trachea against pulmonary aspiration of gastric contents.
- Gastric distention may occur when positive-pressure ventilation is employed.
- It may not be able to achieve adequate airway sealing pressures in patients with poor pulmonary compliance who require positive-pressure ventilation.
- It is not an option with limited mouth opening or when the mandible is wired, unless the wire is cut emergently.

The intubating LMA (ILMA) is designed to provide ventilation and to facilitate blind (as well as fiberoptic-assisted) endotracheal intubation.

The LMA Supreme (or the LMA ProSeal) may prove especially useful when ventilation is required and gastric distention or regurgitation is a major concern (e.g., CVCI in the obstetric patient). These devices are not as useful as a conduit for fiberoptic bronchoscope (because of their smaller lumen) as the classic or ILMAs, but can function as rescue ventilation devices in a crises situation in a patient at risk of aspiration.

The Air-Q laryngeal airway allows ventilation and provides a conduit for tracheal intubation whether blindly or fiberoptic assisted.

The laryngeal tube (LT) is an SAD consisting of an airway tube and two low-pressure balloons (cuffs). After blind oral insertion, its distal blind end lies in the upper esophagus. The distal (esophageal) balloon seals the airway distally, protecting from regurgitation, and the proximal (pharyngeal) balloon seals the upper pharynx to prevent the gas mixture from leaking backward. The two cuffs are inflated simultaneously through a single port. Ventilatory openings lie in the airway tube between the two cuffs and allow ventilation to occur. Fiberoptic

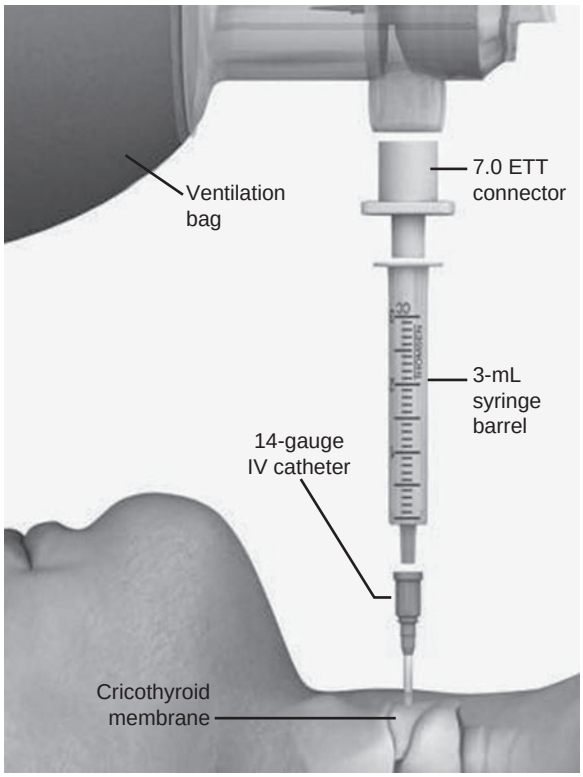

Fig. 139.1 Needle cricothyrotomy. A 14-gauge intravenous catheter is introduced through the cricothyroid membrane until air is aspirated and the catheter is threaded into the tracheal lumen. The catheter is then attached to a 3-mL syringe barrel and a 7.0 endotracheal tube adaptor preassembled together. Emergency ventilation can be established by using a self-inflating bag (as in the illustration) or by using a breathing circuit from the anesthesia machine.

tracheal intubation through the LT using an "exchange technique" is also possible. Recently the LT was fitted with a second lumen for suctioning and free gastric drainage in cases with "full" stomach.

The LMA CTrach resembles the intubating LMA but has a camera attached to its tip and a small monitor attached to the handle for displaying the laryngeal view. It can be used for ventilation and tracheal intubation with indirect visualization.

Emergency Invasive Airway Access

If ventilation cannot be established with an SAD (e.g., when placement is not feasible, inadequate seating with leakage, glottic or subglottic obstruction), rapid development of severe hypoxemia may occur. Immediate intervention with an invasive surgical technique is indicated, especially when the situation is associated with bradycardia. As per the algorithm, invasive airway access can be established with a surgical or percutaneous cricothyrotomy, jet ventilation, or retrograde intubation. The cricothyroid membrane is the most accessible airway entry area below the level of the glottis, and cricothyrotomy can be lifesaving in a CVCI situation when all other measures have failed. Needle cricothyrotomy can be easily performed with a 5-mL syringe filled with 3 mL of normal saline and attached to a 14-G intravenous catheter. The catheter is introduced through the cricothyroid membrane until air is aspirated. The syringe is removed, a 3-mL syringe (without the plunger) is attached to the catheter, and a 7.0 endotracheal tube adaptor is attached to the syringe, providing a fit to attach a self-inflating bag or an anesthesia breathing circuit (Fig. 139.1). Transtracheal jet ventilation can also be applied through the catheter, which will have to be fixed properly because if it is dislodged, air emphysema can occur, complicating the situation. Time should also be allowed for exhalation to avoid barotrauma. Once oxygenation improves and the critical period is over, a more definitive airway should be sought. Alternatively, emergency cricothyrotomy can be performed with any of the commercially available percutaneous dilational cricothyrotomy (PDC) kits (Fig. 139.2). PDC is a rapid, relatively straightforward procedure that is touted as having a decreased operative time and lower complication rate compared with surgical cricothyrotomy. A simplified cricothyrotomy technique (consisting of palpation, incision, insertion, and intubation) can be performed with some of these kits in approximately 30 seconds in experienced hands. It is important to ensure that experienced help is available to perform cricothyrotomy before attempting tracheal extubation of at-risk patients. Emergency cricothyrotomy is a temporary measure to restore oxygenation and tide the patient over a crisis situation. Definitive airway management, such as surgical tracheostomy or other attempts at tracheal intubation, should follow once the patient's condition is stabilized.

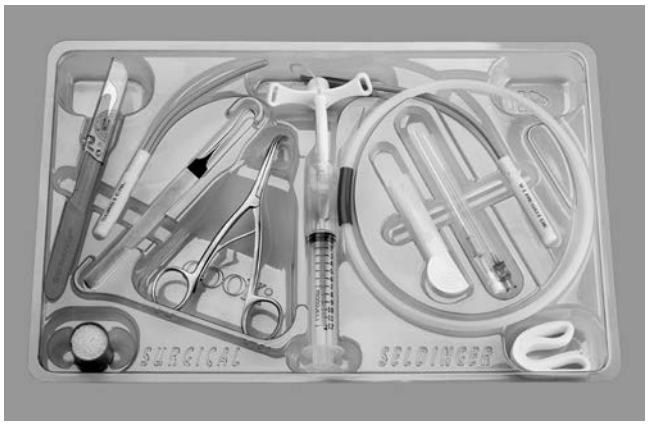

Fig. 139.2 A commercially available emergency cricothyrotomy kit. (Courtesy Cook Medical, Bloomington, IN.)

PREVENTION

Tracheal extubation is a high-risk phase of anesthesia management. According to the ASA closed claims analysis, the incidence of death and permanent neurologic injury due to difficult airway management during induction has dramatically decreased whereas the incidence of these grave complications is still the same for other phases of anesthesia, including the extubation and recovery phase. A clear strategy to prevent the morbidity and/or mortality associated with tracheal extubation should be in place before anesthesia induction, particularly in patients with a difficult airway. Identification of patients who are at increased risk of extubation failure and who may be difficult to reintubate is a first step. Based on the recommendation of the ASA difficult airway management task force and the guidelines of the Difficult Airway Society in the United Kingdom, a staged extubation strategy should be planned ahead, and an airway device should be left in the airway after tracheal extubation to provide continuous access in case reintubation is needed and to provide reversibility to the extubation procedure. An airway exchange catheter (Fig. 139.3), extubation over a fiberoptic bronchoscope, or inserting an LMA behind the existing tube (Fig. 139.4) before extubation (Bailey's technique), can serve this purpose. Boxes 139.7 and 139.8 describe in steps the procedure of using the airway exchange catheter and the LMA as bridging devices in high-risk extubation situations as recommended by the Difficult Airway Society in the United Kingdom.

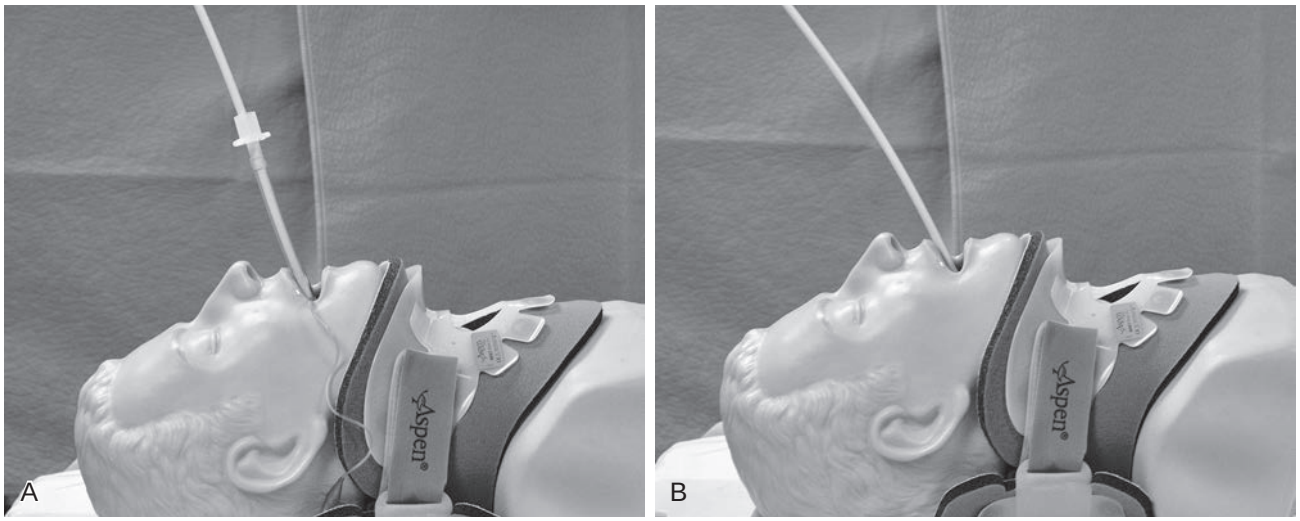

Fig. 139.3 The use of an airway exchange catheter as a bridge to tracheal extubation in difficult airway patients who are at risk of extubation failure. A, The catheter is introduced through the existing endotracheal tube. **B,** The tube is removed, and the catheter is kept in place as a continuous airway access device in case reintubation is needed later.

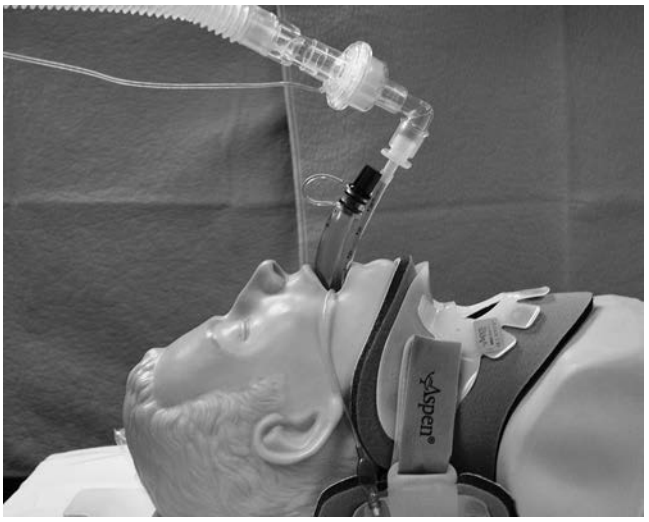

Fig. 139.4 The use of an LMA as a bridge to tracheal extubation in difficult airway patients at risk of extubation failure. The LMA is introduced behind the existing tube (Bailey's technique). The tube is then removed, and the LMA is kept for continuous airway access.

BOX 139.7 Sequence for Use of an Airway Exchange Catheter for "At-Risk" Extubation

1. Decide how far to insert the airway exchange catheter (AEC). It is essential that the distal tip remains above the carina. If there is any uncertainty about the position of the tracheal tube tip, its position relative to the carina should be checked with a fiberoptic bronchoscope before AEC insertion. An AEC should never be inserted beyond 25 cm in an adult patient.
2. When the patient is ready for extubation, insert the lubricated AEC through the tracheal tube to the predetermined depth. Never advance an AEC against resistance.
3. Employ pharyngeal suction before removal of the tracheal tube.

BOX 139.7 Sequence for Use of an Airway Exchange Catheter for "At-Risk" Extubation—cont'd

4. Remove the tracheal tube over the AEC while maintaining the AEC position (do not advance the AEC).
5. Secure AEC to the cheek or forehead with tape.
6. Record the depth at the teeth/lips/nose in the patient's notes.
7. Check that there is a leak around the AEC using an anesthetic circuit.
8. Clearly label the AEC to prevent confusion with a nasogastric tube.
9. The patient should be nursed in a high-dependency or critical care unit.
10. Supplemental oxygen can be given via a facemask, nasal cannula, or CPAP mask.
11. The patient should remain on nothing-by-mouth status until the AEC is removed.
12. If the presence of the AEC causes coughing, check that the tip is above the carina and inject lidocaine via the AEC.
13. Most patients remain able to cough and vocalize.
14. Remove the AEC when the airway is no longer at risk. AECs can be tolerated for up to 72 hours.

CPAP, Continuous positive airway pressure.

BOX 139.8 Sequence for Laryngeal Mask Airway Exchange in "At-Risk" Extubation

1. Administer 100% oxygen.
2. Avoid airway stimulation: either deep anesthesia or neuromuscular blockade is essential.
3. Perform laryngoscopy and suction under direct vision.
4. Insert deflated laryngeal mask airway (LMA) behind the tracheal tube.
5. Ensure LMA placement with the tip in its correct position.
6. Inflate cuff of LMA.
7. Deflate tracheal tube cuff and remove tube while maintaining positive pressure.
8. Continue oxygen delivery via LMA.
9. Insert a bite block.
10. Sit the patient upright.
11. Allow undisturbed emergence from anesthesia.

The "bridging" device should be kept in place until the risk of extubation failure and the need for reintubation is no longer an existing threat and it is felt safe to remove this device. Rescue reintubation over an exchange catheter, a bronchoscope, or through the lumen of an LMA has a high success rate and is a prudent approach to avoid a mishap or a near-miss in patients who may develop a CVCI situation after tracheal extubation. Last but not least, the availability of personnel who are experienced in establishing invasive airway access should be ascertained before performing high-risk extubation in a patient with a known difficult airway.

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140 Disorders of Water Homeostasis: Hyponatremia and Hypernatremia

Brenda G. Fahy • Arturo G. Torres

HYPONATREMIA

Case Synopsis 1

A 68-year-old man with a medical history of hypertension, chronic obstructive pulmonary disease, chronic renal insufficiency, and insulin-dependent diabetes mellitus presents for right total-knee replacement. His laboratory values are as follows: serum sodium, 130 mEq/L; serum osmolality, 260 mOsm/kg; urine sodium, 35 mEq/L; and normal glucose, blood urea nitrogen (BUN), and thyroid and adrenal function tests. The patient denies nausea, lethargy, and weakness.

PROBLEM ANALYSIS

Definition

Serum sodium concentration and osmolality are closely regulated by water homeostasis; this is mediated by thirst, arginine vasopressin, and the kidneys. A disruption in water homeostasis is manifested by an abnormal serum sodium concentration—hyponatremia or hypernatremia. The former is defined as a serum sodium concentration of less than 135 mEq/L, with severe hyponatremia occurring at values less than 120 mEq/L. Causes of hypotonic hyponatremia are listed in Box 140.1; causes of nonhypotonic hyponatremia (formerly known as pseudohyponatremia) are listed in Box 140.2.

BOX 140.1 Causes of True Hypotonic Hyponatremia

Decreased Expanded Extracellular Fluid (ECF) Volume

Extrarenal sodium loss
- Gastrointestinal diseases: vomiting, diarrhea
- Trauma: blood loss
- Skin: burns, sweating

Renal causes
- Cerebral salt wasting syndrome
- Diuretics
- Adrenal insufficiency
- Kidney disease

Normal ECF Volume

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Diuretics (e.g., thiazide)
Endocrine disorders (adrenal insufficiency and hypothyroidism)
Primary polydipsia

Increased ECF Volume

Congestive heart failure
Nephrotic syndrome
Cirrhosis

Recognition

Symptoms of hyponatremia are related to the serum sodium concentration and how rapidly the serum sodium decreases. The blood-brain barrier is virtually impermeable to sodium. Thus rapid decreases in serum sodium cause water entry into the cells of the brain and other tissues. This can lead to cerebral edema and progress to intracranial hypertension.

The magnitude and rapidity of water entry into brain cells explain the central nervous system (CNS) symptoms associated with hyponatremia and symptom severity. Early symptoms of hyponatremia-related CNS water entry include lethargy, weakness, and somnolence. If hyponatremia continues or worsens, symptoms may progress to seizures, coma, and death. Therefore hyponatremia must always be considered in the differential diagnosis of any mental status deterioration.

The diagnosis of hyponatremia is based on laboratory testing, time of development, and symptoms. Major steps in the initial evaluation of hyponatremia in the perioperative setting are outlined in Fig. 140.1. Plasma osmolality must be measured to exclude hyperglycemia and other causes of nonhypotonic hyponatremia. Normal values for plasma osmolality range from 274 to 290 mOsm/kg. Calculated plasma osmolality (P_{osm}) is determined by the following formula:

BOX 140.2 Causes of Nonhypotonic Hyponatremia

Normal Plasma Osmolarity

Hyperlipidemia
Hyperproteinemia
Transurethral resection of prostate or bladder tumor; hysteroscopy

Increased Plasma Osmolarity

Hyperglycemia
Hyperuricemia
Mannitol administration

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$P_{osm} = (2.0 \times [Na^+]) + \text{Glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$

The next step is to assess the severity of symptoms to determine whether any intervention is required. If treatment is not required, urine measurements are necessary. The urine osmolality and sodium concentration will identify whether the kidneys play a role. Kidney functionality is crucial for water homeostasis and vasopressin actions.

Prior recommendations focused on early volume assessment. Yet clinically our tools for determining volume status may often be inaccurate. Therefore once the urine sodium has been evaluated, assessing the effective arterial blood volume and extracellular fluid will further delineate the causes of hypotonic hyponatremia. Last, other electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia) are often connected with hyponatremia and need to be addressed.

Risk Assessment

Hyponatremia is a common clinical electrolyte disorder. From 15% to 22% of hospitalized patients have serum sodium values less than 135 mEq/L, and 1% to 4% have values less than 130 mEq/L. A recent study indicated higher postsurgical mortality rates in hyponatremic patients during the perioperative period. The causes of death were associated with thrombotic events, wound infections, and pneumonias. At this point, further studies are needed to clarify this alarming finding.

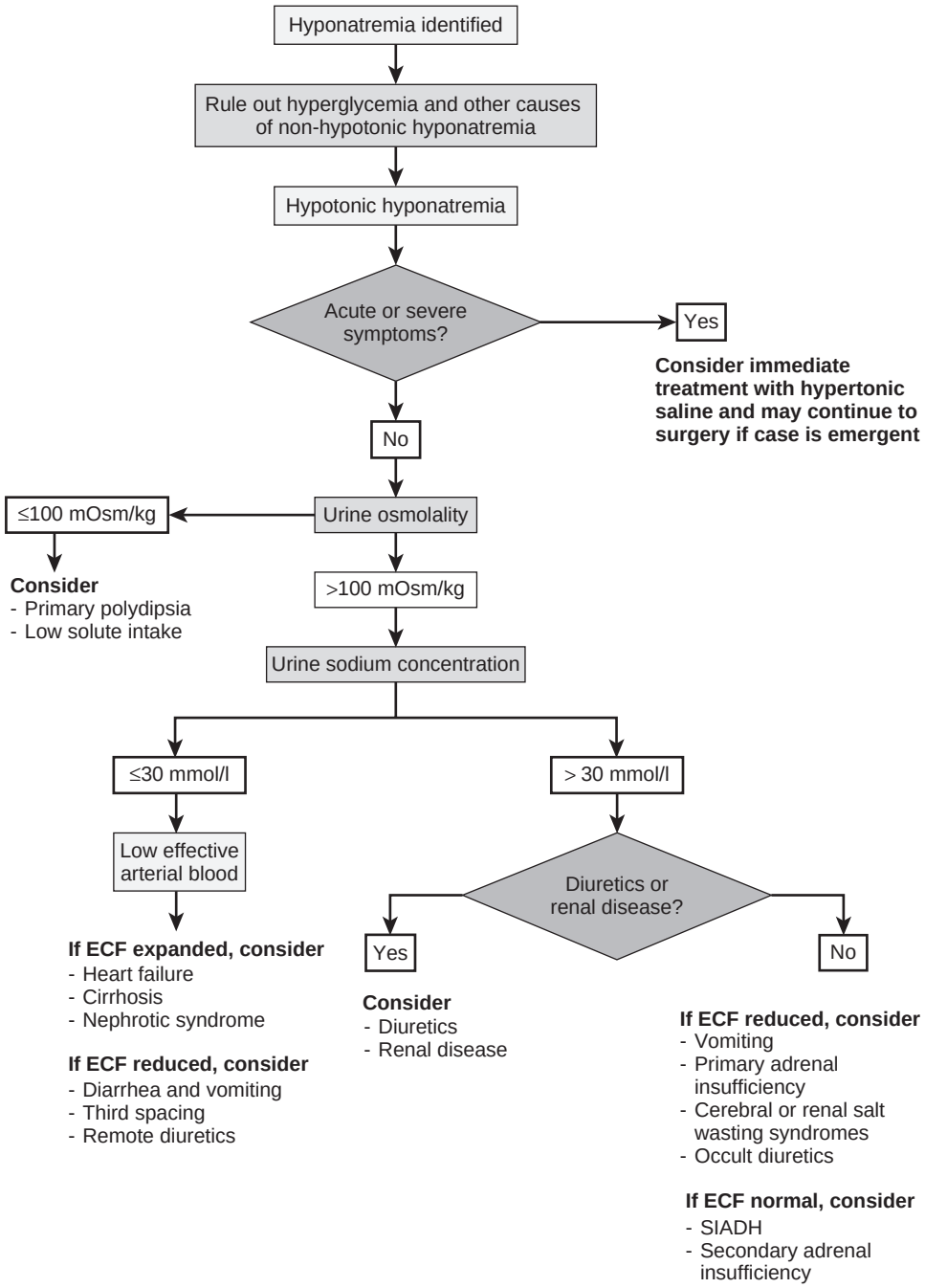

Fig. 140.1 Major steps in the initial evaluation of hyponatremia in the perioperative patient. (Adapted from Spasovski G, Vanholder R, Allolio B, et al.: Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 29[Suppl 2]:i1–i39, 2014.)

Hyponatremia often presents perioperatively as hypotonic hyponatremia. Acute causes of hyponatremia (<48 hours) associated with perioperative events include postoperative phase, endoscopic surgery of the prostate and uterus, fluid administration, colonoscopy bowel preparation, oxytocin, and vasopressin usage. General anesthesia alongside the sequelae of any surgery (pain, nausea, etc.) can contribute to syndrome of inappropriate antidiuretic hormone secretion (SIADH; Box 140.3). Intraoperative nonhypotonic hyponatremia can occur with transurethral resection of the prostate or bladder tumor, and hysteroscopy via intravascular translocation of irrigating solutions (e.g., glycine and sorbitol). The clinical manifestations may be due to accumulation of the solutions' metabolites (e.g., ammonia and serine) and not necessarily from hyponatremia.

Postoperative hyponatremia is primarily due to the increased effects of antidiuretic hormone (ADH) and, often combined with a liberal infusion of isotonic fluids intraoperatively, ADH will cause the kidneys to transform the infusion into a hypotonic one by excreting the sodium and retaining the free water. Under these circumstances, isotonic fluids (i.e., normal saline) during states of SIADH will cause increased free-water absorption and excretion of sodium. Another factor to consider is the association of positive fluid balances and reported worse in-patient outcomes. A goal-directed approach to fluid management in the perioperative period may help to avoid some of these complications.

Another consideration is the physiologic release of vasopressin based on osmoregulation and baroregulation. With circulatory hypovolemia or hypotension, baroregulation overrides the osmoregulatory system that would normally prevent hyponatremia and cause further release of vasopressin regardless of the sodium level. The tendency to bolus with fluids intraoperatively to treat hypotension can potentially aggravate the preexisting hyponatremia. Recent studies also indicate that prolonged periods of hypotension increase morbidity and mortality rates in the perioperative period. Under these circumstances, based on these physiologic principles, hypotension intraoperatively may benefit from treatment with vasopressors with adequate volume status instead of additional fluid administration.

BOX 140.3 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

Malignancy
Lung (especially small cell carcinoma)
Central nervous system
Pancreas

Pulmonary
Pneumonia
Tuberculosis
Fungal
Abscess

Neurologic
Infection
Trauma
Cerebrovascular accident

Drugs (Most Common)
Amitriptyline
Chlorpropamide
Cyclophosphamide
Desmopressin
Morphine
Nicotine
Nonsteroidal antiinflammatory drugs
Oxytocin
Selective serotonin reuptake inhibitors
Vincristine

The neurosurgical patient will invariably be at risk of hyponatremia. Most commonly, SIADH will be the culprit. Regardless of whether the cause is SIADH or cerebral salt wasting syndrome, treatment in the neurosurgical patient population will focus on gradual hyponatremia correction. Intraoperatively, fluid management and maintenance of cerebral perfusion pressure goals interact with the sodium imbalance. Careful fluid management, including the potential conversion of isotonic fluids into free water, is crucial, as this has the potential to further exacerbate the hyponatremia and lead to more cerebral edema.

Implications

The risk for hyponatremia is related to the absolute level of serum sodium. However, more critical is how rapidly the serum sodium falls due to accompanying fluid shifts. On exclusion of nonhypotonic causes of hyponatremia, it is necessary to determine the type of hyponatremia because therapy differs.

Whether correction of hyponatremia is required and how fast it should be accomplished depend on the severity of symptoms. With acute CNS symptoms, the risk of cerebral edema outweighs the risk of rapid correction; thus correction is undertaken quickly, while taking into consideration that too-rapid correction may cause excess morbidity or even mortality, including central pontine myelinolysis (discussed later).

MANAGEMENT

Treatment involves two basic principles: identifying and treating the underlying cause, and increasing serum sodium safely when indicated by symptomatology. With serious CNS symptoms or serum sodium of less than 110 mEq/L, rapid sodium replacement with hypertonic saline (3%) may be required to prevent death. Under these circumstances, the goal of hypertonic saline replacement should be to increase serum sodium 1 to 2 mEq/L per hour over a maximum of 3 hours. Careful monitoring is required throughout this process. Sodium replacement should not exceed 8 to 10 mEq/L over 24 hours. Despite the risks associated with acute, severe hyponatremia, too-rapid correction may cause demyelinating lesions in the pons, which can develop over several days. This disorder, termed *central pontine myelinolysis,* can lead to quadriparesis, coma, and death. Diagnostic confirmation is performed by computed tomography or magnetic resonance imaging. Risk factors for central pontine myelinolysis are presented in Box 140.4.

In asymptomatic cases of hypotonic hyponatremia when volume status is able to be determined, management is primarily focused on identification and treatment of the underlying cause. Rarely under these circumstances does the sodium concentration have to be increased. More important, the emphasis should be on avoiding anything that further contributes to the hyponatremia. In a patient with low effective arterial circulation, isotonic fluid infusion in a goal-directed approach is reasonable. However, hospitalized surgical patients tend to be fluid positive and this should be a consideration. If diuretics are the cause, these should be discontinued and appropriate fluids and electrolytes administered. Mineralocorticoids should be replaced if indicated.

Euvolemic hyponatremic patients require free-water restriction. Steroid or thyroid hormone replacement may also be required. Isotonic

BOX 140.4 Risk Factors for Central Pontine Myelinolysis

Sodium correction rate greater than 12 mEq/L in 24 hours or 25 mEq/L in 48 hours
Overcorrection of serum sodium greater than 140 mEq/L within 2 days
Hypoxic or anoxic episodes before therapy
Hypercatabolic states (e.g., burns) or malnutrition (e.g., chronic alcoholism)
Chronic rather than acute hyponatremia

fluids should not be used to treat hyponatremia due to SIADH (these can increase free-water retention). Reversible causes of SIADH (e.g., medications) should be sought and treated (see Box 140.3).

Expanded extracellular fluid (ECF) in hyponatremic patients is due to excessive secretion of ADH. This occurs when a disease process (e.g., cirrhosis, nephrotic syndrome, or congestive heart failure) results in increased total body fluids, but with an associated decrease in effective circulating intravascular volume and glomerular filtration rate. Therapy focuses on the underlying disease process and free-water restriction.

The patient presented in case synopsis 1 has hypotonic hyponatremia secondary to diuretic usage with underlying renal insufficiency. His hyponatremia is likely chronic, based on the absence of CNS symptoms. His anesthetic plans should include a goal-directed fluid-administration approach with early reliance on vasopressors when there is an adequate volume status to treat hypotensive periods to avoid worsening the preexisting hyponatremia. Vigilance should continue postoperatively to identify the potential contribution to the hyponatremia by ADH.

PREVENTION

Identifying high-risk patients and having a high index of suspicion for hyponatremia can help prevent hyponatremic complications. Therapy relies mostly on focusing and treating the underlying cause, and not treating hyponatremia per se. More important, for perioperative patients the aim is to avoid further exacerbation of the preexisting hyponatremia, and this requires one to exclude causes of nonhypotonic hyponatremia. Once the patient's pertinent laboratory values (serum and urine osmolality and urine sodium) are evaluated, the volume status can be considered to seek treatable causes of hypotonic hyponatremia.

HYPERNATREMIA

Case Synopsis 2

A 50-year-old man who suffered a traumatic brain injury 5 days ago after a motor-vehicle accident is scheduled for hip surgery to repair a right hip fracture after initial resuscitation in the intensive care unit (ICU). The patient remains intubated and, according to a nursing report, "stable." A plasma sample reveals sodium concentrations of 155 mEq/L. The patient's urinary catheter bag is full on arrival to the operating room.

PROBLEM ANALYSIS

Definition

Hypernatremia is defined as a serum sodium concentration greater than 145 mEq/L. The disorder is typically more common in critically ill and neurologic patients. Hypernatremia occurs in approximately 1% of hospitalized patients, and less frequently than hyponatremia. In children and adults, hypernatremia is seen primarily in individuals with restricted access to water (extremes of ages). Hypernatremia may be iatrogenic, resulting from excessive administration of high-sodium-containing fluids.

The body has two defense mechanisms to protect against hypernatremia: the ability to produce concentrated urine, and a powerful thirst mechanism. Release of ADH occurs when plasma osmolality exceeds 275 to 280 mOsm/kg, and the urine becomes maximally concentrated when plasma osmolality exceeds 290 to 295 mOsm/kg. If the thirst mechanism is intact and there is unrestricted access to free water, it is rare for an individual to develop sustained hypernatremia.

Recognition

The signs and symptoms of hypernatremia mostly reflect CNS dysfunction. They are more prominent when the increase in serum sodium concentration is large or occurs rapidly (i.e., over a few hours).

Presenting symptoms in the young include hyperpnea, agitation, irritability, insomnia, and a typically high-pitched cry. If unrecognized, these symptoms can further progress to muscle weakness, confusion, listlessness, lethargy, and coma. Unlike infants, elderly patients generally have few symptoms until the serum sodium concentration exceeds 160 mEq/L. The elderly are at high risk due to reduced thirst reflexes, impaired urinary concentrating power, and frailty (inability to access water). The level of consciousness can correlate with the severity of hypernatremia. Muscle weakness, confusion, and coma may be manifestations of coexisting disorders rather than of hypernatremia itself. Finally, unlike outpatient hypernatremia, the inpatient-acquired type affects patients of all ages. In addition, the clinical symptoms are even more elusive because these patients often have preexisting neurologic dysfunction.

Risk Assessment

Hypernatremia represents a deficit of water relative to whole-body sodium stores. This can result from a net water loss or a gain in hypertonic sodium (Box 140.5). Net water loss accounts for the majority of cases. Hypernatremia can occur only when the thirst sensation is impaired or access to water is limited. Hypernatremia in infants usually results from gastroenteritis (vomiting and diarrhea); in the elderly it is usually associated with thirst impairment, febrile illness, or infirmity. Another contributer is the use of diuretics (especially loop-type diuretics) in order to achieve a negative fluid balance in fluid-overloaded ICU patients.

In the majority of hypernatremic neurologic patients with low ECF, central diabetes insipidus (CDI) must be differentiated from dehydration. The incidence of CDI in the neurosurgical unit is approximately 4%. Traumatic brain injury patients are at high risk of developing CDI, as shown in case synopsis 2.

Implications

Hypernatremia results in the efflux of fluid from the intracellular space to the extracellular space to maintain osmotic equilibrium. This leads to transient cerebral dehydration and brain shrinkage. Brain-cell volume can decrease by as much as 10% to 15% acutely, but it adapts quickly. Within 1 hour, the brain significantly increases its intracellular content of sodium and potassium, amino acids, and unmeasured organic substances or idiogenic osmoles (i.e., rapid adaptation). Normalization of brain volume is completed by week 1 (slow adaptation), as the brain regains approximately 98% of its water content. When severe hypernatremia develops acutely, the brain may not be able to increase its

BOX 140.5 Common Causes of Hypernatremia

Decreased Expanded Extracellular Fluid (ECF) Volume

Reduced water intake
Intrarenal water loss
- Diabetes insipidus
  - Central
  - Nephrogenic

Extrarenal water loss
- From respiratory tract
- From gastrointestinal tract
- Fever

Increased ECF Volume

Iatrogenic: administration of sodium-containing fluids
Mineralocorticoid excess
- Primary hyperaldosteronism
- Cushing syndrome
- Exogenous

intracellular solute sufficiently to preserve its volume. If so, resulting cellular shrinkage can lead to structural changes. Venous sinus thrombosis progressing to cerebral infarction can also develop. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in animal models, as well as reports of humans. Patients with hepatic encephalopathy appear to be at higher risk for developing demyelinating lesions.

MANAGEMENT AND PREVENTION

Treatment for hypernatremia must correct the underlying cause, normalize the serum sodium concentration, and restore the normal circulatory volume. The therapeutic cornerstone is the provision and retention of free water to correct the serum sodium concentration. With CDI, fluid replacement with intravenous 5% dextrose or water via nasogastric tube with concomitant 1-deamino-8-D-arginine is recommended.

The calculated deficit does not account for insensible or ongoing urinary or gastrointestinal losses. Maintenance fluids, which include replacement of urine volume with hypotonic fluids, are given in addition to the deficit. If there are signs of severe hypovolemia or circulatory collapse, fluid resuscitation with normal saline, lactated Ringer's solution, or colloid should be instituted before correcting the free-water deficit. The type of therapy depends largely on the cause of hypernatremia and should be tailored to the pathophysiologic events involved in each patient (Table 140.1). Oral hydration should be started as soon as it can be safely tolerated. Plasma electrolytes should be measured every 2 to 3 hours until the patient is neurologically stable.

In patients with hypernatremia that has developed over hours (e.g., accidental sodium overloading), rapid correction improves the prognosis without increasing the risk of cerebral edema. This is because accumulated electrolytes are rapidly extruded from brain cells. In these particular patients, reducing the serum sodium concentration by 1 mEq/L per hour is appropriate. A slower pace of correction is advised for patients with chronic hypernatremia or for those of unknown duration, because full dissipation of brain solutes occurs over a period of days. In these patients, reducing the serum sodium concentration at a maximal rate of 0.5 mEq/L per hour prevents cerebral edema and convulsions. Consequently, some authorities (e.g., Adrogué and Madias) advise a target reduction in serum sodium concentration of 10 mEq/L per day for all patients with hypernatremia, except those in whom the disorder has developed over a period of hours. The goal of treatment is to reduce serum sodium concentration to 145 mEq/L.

TABLE 140.1 Management of Hypernatremia

Cause	Treatment
Sodium and water loss[a]; gastroenteritis	0.45% NaCl in 5% dextrose and water
Primary water loss[a]; ineffective breast feeding; hypodipsia	0.2% NaCl in 5% dextrose and water
Nephrogenic diabetes insipidus[a]	0.1% NaCl in 2.5% dextrose and water[b]
Central diabetes insipidus[a]	Desmopressin acetate
Sodium overload[a]	5% dextrose and water[c]

[a]See also Box 140.5.
[b]Acute management.
[c]Diuretics may be needed.
Adapted from Moritz ML, Ayus JC: Disorders of water metabolism in children. *Pediatr Rev* 23:371-380, 2002 and Adrogué HJ, Madias NE: Hypernatremia. *N Engl J Med* 342:1493–1499, 2000.

The preferred route for administering fluids is orally or via a feeding tube. If neither is feasible, fluids are given intravenously. The more hypotonic the fluid is, the lower the infusion rate should be. This reduces the risk for cerebral-edema formation. Finally, except in clear cases of circulatory compromise, 0.9% normal saline or lactated Ringer's solution is an unsuitable therapy for hypernatremia.

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Embolic Events of Pregnancy

141

Nolan McDonnell

Case Synopsis

A 34-year-old pregnant woman, gravida 3 para 2, presents at 29 weeks of gestation requiring an emergency cesarean delivery for preterm labor. After initiation of spinal anesthesia and delivery of the neonate and placenta, the parturient complains of nausea and promptly becomes unresponsive and apneic. She is intubated and rapidly becomes hemodynamically unstable and coagulopathic. After supportive treatment, she is able to be extubated and makes an otherwise uneventful recovery.

PROBLEM ANALYSIS

Definition

Embolic events during pregnancy are a leading cause of maternal morbidity and mortality throughout the developed world. They may present as an acute cardiovascular and respiratory collapse during pregnancy and in the early postpartum period. A variety of substances may result in an embolic phenomenon, with the majority being secondary to blood clots, air, and the condition known as "amniotic fluid embolism." The presentation may range from mild, subclinical signs and symptoms through to sudden cardiovascular collapse and require rapid, multidisciplinary support.

Recognition

Pulmonary Embolism

The symptoms of pulmonary embolism are listed in Box 141.1. In cases of massive pulmonary embolism, hypotension, syncope, or sudden cardiovascular collapse may be the presenting features.

The diagnosis of pulmonary embolism in pregnancy is potentially difficult. Chest radiographs, electrocardiogram, and arterial blood gas analysis may assist but are generally not diagnostic. Plasma D-dimer measurements are already elevated in pregnancy and therefore interpretation can be difficult. The two main imaging modalities employed are ventilation perfusion scintigraphy and computed tomography (CT) pulmonary angiography. Ventilation perfusion scintigraphy is a potentially useful initial test, although the positive and negative predictive values are dependent on the pretest probability of a pulmonary embolism. CT pulmonary angiography can potentially diagnose other pathology in addition to a pulmonary embolism (e.g., aortic disease) but at the expense of higher radiation exposure, particularly to the maternal breast tissue.

Amniotic Fluid Embolism

The term *amniotic fluid embolism* is somewhat of a misnomer. Whereas traditionally the condition was thought to result from the embolization of amniotic fluid and debris into the pulmonary circulation, current thinking suggests that the condition is more likely to be immune mediated and that the presence of amniotic fluid in the maternal circulation is a relatively common occurrence. The term *anaphylactoid syndrome of pregnancy* has been suggested as an alternative name for the constellation of signs and symptoms; however, this term has not been widely employed.

The signs and symptoms of amniotic fluid embolism can range from subtle symptoms through to the sudden onset of cardiorespiratory collapse (Box 141.2). The deterioration may be preceded by symptoms of anxiety and agitation, and electronic fetal monitoring may show decelerations, loss of variability, and prolonged bradycardia. Coagulation changes are prominent and may develop rapidly, and in rare circumstances they may be the presenting feature. The majority of cases occur in relation to labor and delivery.

The diagnosis of amniotic fluid embolism is clinical in nature and based on the presenting signs and symptoms while ruling out other potential causes of the presentation. There is no specific diagnostic test for the condition, although a mast cell tryptase may be useful to rule out anaphylaxis as a potential cause. The presence of amniotic fluid debris in the maternal pulmonary circulation at postmortem is potentially diagnostic but only if it is in keeping with the clinical

BOX 141.1 Signs and Symptoms of Pulmonary Embolism

- Sudden onset of tachypnea
- Dyspnea
- Pleuritic chest pain
- Apprehension
- Nonproductive cough
- Hemoptysis
- Cyanosis
- Accentuated second heart sound

BOX 141.2 Signs and Symptoms of Amniotic Fluid Embolism

- Dyspnea
- Cyanosis
- Hypotension
- Seizures
- Cardiovascular collapse
- Coagulopathy and profuse hemorrhage

BOX 141.3 Signs and Symptoms of Venous Air Embolism

- Gasping
- Dyspnea
- Chest pain
- Hypotension
- Mill-wheel murmur
- Cyanosis
- Increase in central venous pressure
- Reduction in end-tidal carbon dioxide
- Electrocardiographic changes
- Cardiac arrest

presentation. Echocardiography, either transesophageal or transthoracic, may be useful for assisting with the diagnosis and for guiding therapy. Reported cases have shown findings including acute right ventricular failure, severe pulmonary hypertension, and left ventricular failure.

Venous Air Embolism

The symptoms and signs of venous air embolism are listed in Box 141.3. The presentation of venous air embolism is variable and depends on the volume and speed that the air is entrained, the end location of the air embolism, and the underlying condition of the parturient. Air that becomes entrapped in the right ventricular outflow tract may result in an "air lock" and subsequently a rapid onset of hypotension and cardiac arrest. Air that embolizes into the coronary circulation may cause signs and symptoms consistent with acute myocardial infarction, including chest pain and arrhythmias. Cerebral air embolism may occur in conjunction with a persistent right-to-left shunt (e.g., a patent foramen ovale) and lead to visual disturbances, altered level of consciousness, seizures, and visual disturbances. Later changes may result from the interaction of the entrained air and endothelial and platelet surfaces, resulting in activation of the coagulation cascade, vasospasm, and microthrombi.

The detection of significant venous air embolism may be difficult. For parturients under general anesthesia, capnography is likely the most readily available and sensitive test. A sudden, sharp decline in end-tidal carbon dioxide concentration in conjunction with a decrease in oxygen saturation should alert the clinician to the potential diagnosis. Transesophageal echocardiography is likely to be even more sensitive, although it is unlikely to be in place at the onset of deterioration. Clinical signs that may assist with the diagnosis include the presence of a "wheel-mill" murmur, described as a splashing auscultatory murmur from intracardiac air. Blanching of arteriole segments in the nail beds and pallor of mucous membranes may also be seen.

Risk Assessment

Pulmonary Embolism

The majority of pregnancy-related pulmonary embolisms are associated with a venous thromboembolism. Pregnancy is a significant risk factor for thromboembolism, as all three components of Virchow's triad are present, and this risk extends into the first 6 weeks postpartum. For each pulmonary embolism that occurs, there are approximately 3 to 4 venous thromboembolisms. In the antenatal period, the risk of a thromboembolism is 7 to 10 times higher than in nonpregnant women and 15 to 35 times higher in the first 6 weeks postpartum; this is reflected in the majority of pulmonary embolisms occurring in the first 6 weeks postpartum.

Besides pregnancy, there may be preexisting or coexisting maternal and obstetric risk factors that increase the risk of venous thromboembolism and subsequent pulmonary embolism. In addition, these risk factors may change as the pregnancy progresses so that a parturient who begins a pregnancy in a low-risk cohort may end up as high risk secondary to the development of specific complications. Some of the major risk factors include maternal thrombophilia, a previous history of venous thromboembolism, increased maternal body mass index, advanced maternal age, nonelective cesarean delivery, and the development of hemorrhagic or infective complications.

Amniotic Fluid Embolism

Amniotic fluid embolism is a comparatively rare condition with a reported incidence that varies widely. Recent data suggest an incidence in developed countries on the order of 1:16,000 to 1:50,000 deliveries. Amniotic fluid embolism has been reported at all stages of pregnancy and into the early postpartum period, although the majority occur during labor. It has also been reported at other times where there may be a breach of the uteroplacental interface such as amniocentesis, termination of pregnancy, and trauma. A variety of risk factors have been described, including a male fetus, multiple gestation, placental abruption, cervical laceration, and polyhydramnios; and links to induction of labor as a risk factor have been inconsistently reported. Importantly, none of the described risk factors is readily modifiable.

Venous Air Embolism

Venous air embolism likely occurs more commonly than clinically recognized. Precordial Doppler studies have shown that approximately half of cesarean deliveries have evidence of venous air embolism, and more sensitive tests have shown nearly universal air entrainment. Only a small pressure gradient between exposed uterine vessels and the heart is required to entrain air, and most entrainment at cesarean delivery occurs between the time of uterine incision to the closure of the hysterotomy. Uterine exteriorization and the Trendelenburg position increase the pressure gradient between the heart and the uterus and predispose to air entrainment. In addition, sexual activity during pregnancy, particularly air insufflation during oral sex, is a recognized risk factor.

Implications

Pulmonary Embolism

Despite significant efforts to improve the prevention of venous thromboembolism in parturients, pulmonary embolism remains a leading cause of direct maternal mortality in many countries. In nonfatal episodes the parturient may be left with significant pulmonary hypertension and require prolonged periods of anticoagulation.

Amniotic Fluid Embolism

Though rare, amniotic fluid embolism is a leading cause of maternal mortality in many developed countries. Traditionally associated with a high mortality rate (over 80%), in recent series the mortality rate is lower (generally between 20% and 40%), and maternal outcomes appear good if the parturient survives the initial cardiovascular insult. The incidence of coagulopathy is high, and hence timely access to blood and blood products is often critical for survival. The neonatal outcomes depend on whether the fetus is in utero at the time of the collapse; if this occurs, the neonate has a potential mortality risk of over 50%. In mothers who do survive, a variety of potential complications may occur, including multiorgan failure requiring advanced intensive care resources.

Venous Air Embolism

Entrainment of air at delivery, although likely to be relatively common, only causes significant hemodynamic compromise in a small number of parturients. Small amounts of air may result in a ventilation-perfusion mismatch, hypoxemia, right ventricular failure, arrhythmias, and hypotension. Larger volumes (>3 mL/kg) may be fatal, usually secondary to right ventricular outflow tract obstruction.

MANAGEMENT

Pulmonary Embolism

Treatment for pulmonary embolism should focus on initial cardiovascular and respiratory support followed by immediate therapeutic anticoagulation if not contraindicated. Significant multidisciplinary planning is required to manage labor and delivery in women on therapeutic anticoagulation. In women who are hemodynamically unstable, thrombolysis (either systemic or catheter directed) may be indicated, although postprocedure bleeding is a significant risk. Additional treatment options that may be considered include the placement of an inferior vena caval filter or surgical embolectomy.

Amniotic Fluid Embolism

The treatment of a suspected case of amniotic fluid embolism is primarily supportive and aimed at restoring cardiac output, oxygenation, and prevention/management of any coagulopathy. If there is cardiopulmonary arrest, resuscitation should be commenced immediately, including endotracheal intubation, mechanical ventilation with 100% oxygen, and initiation of chest compressions. If the neonate is undelivered, uterine displacement to prevent aortocaval compression is essential. Early consideration should be given to the performance of a perimortem cesarean delivery if there has been no response to maternal resuscitation after 4 minutes. This will relieve aortocaval compression and potentially improve both maternal and neonatal survival and should be performed at the location of the cardiac arrest if it occurs in a health care facility.

Invasive monitoring and consideration of additional investigations such as echocardiography should be initiated as soon as the clinical condition allows. The rapid development of a coagulopathy should be anticipated, and hence notification of transfusion services that large volumes of blood and blood products may be required should be performed expeditiously. Clinical evidence of coagulopathy should trigger coagulation factor replacement, as the turnaround time for traditional coagulation investigations may delay appropriate care. Intensive care support is likely to be needed in most mothers who survive the initial episode.

Venous Air Embolism

Successful treatment of venous air embolism relies on early recognition and prompt measures to prevent further air entrainment. Communication between the obstetric and anesthesiology teams is essential. The patient should be positioned so that the heart is above the level of the surgical field (reverse Trendelenburg position) and in a left lateral position so as to promote migration of any intracardiac air bubbles into the distal pulmonary circulation. If the patient is receiving nitrous oxide, this must be stopped immediately because it may expand the size of any air bubbles present. One hundred percent oxygen should be administered to further help decrease the size of any air bubbles, and volume loading may be beneficial to increase right ventricular preload and further promote the migration of air bubbles into the distal pulmonary vasculature. Inotropic support may be required, and in severe cases the placement of a central venous catheter into the right atrium may allow partial aspiration of any air present. The definitive treatment of severe air embolism involves the administration of hyperbaric oxygen. This should be commenced within 5 hours of presentation to optimize outcomes.

PREVENTION

Pulmonary Embolism

The prevention of venous thromboembolism requires early pregnancy-specific risk assessment (and in some circumstances preconception counseling) with repeated risk assessment throughout the pregnancy and early postpartum period. Preventive measures should include general advice in relation to mobilization and hydration with consideration of mechanical and pharmacologic measures depending on the risk assessment. Some women will require both antenatal and postnatal measures, whereas others will require just postnatal prophylaxis. Postnatal prophylaxis may be required for 6 weeks or longer in women at high risk or with ongoing risk factors. Women should also be educated as to the signs and symptoms of venous thromboembolism so that they can seek early assessment.

Amniotic Fluid Embolism

Despite the recognition of several potential risk factors for amniotic fluid embolism, there are no readily modifiable risk factors that may allow prevention. Presently, an episode of amniotic fluid embolism in a preceding pregnancy does not appear to be a risk factor for subsequent presentations.

Venous Air Embolism

Avoiding a pressure gradient between the uterus and the heart through avoidance of a head-down position and exteriorization of the uterus may potentially prevent venous air entrainment. In addition, modest reverse Trendelenburg position from the time between uterine incision and closure may increase the venous pressure and help prevent entrainment. Early recognition, limitation of further entrainment, and appropriate management can potentially prevent further morbidity and mortality.

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142 Fat Embolism Syndrome

Jiabin Liu • Ignacio Badiola

Case Synopsis

A 29-year-old man who has suffered fractures of the femur and tibia in a motorcycle accident is brought to the operating room for intramedullary nailing of both injuries. Surgery is unremarkable, but the patient is noted to have persistent tachycardia in the recovery room, despite adequate fluid resuscitation and pain control. The following morning, he is tachypneic and complains of significant shortness of breath. On examination, his pulse oximeter reading is 88% on room air, and he has a petechial rash on his chest and neck. A chest radiograph shows diffuse bilateral infiltrates.

PROBLEM ANALYSIS

Definition

The essential feature of fat embolism syndrome (FES) is the presence of clinical signs and symptoms resulting from fat embolization. There is no gold standard definition of FES. Gurd's system was proposed in 1970 and is probably the most widely accepted system for clinical diagnosis. There are two major categories of symptoms: major and minor (Table 142.1). The diagnosis could be made if at least one major and four minor symptoms or signs are present in addition to the establishment of fat microglobulinemia. The major signs and symptoms include petechial rash, respiratory symptoms with bilateral signs of radiographic changes, and cerebral signs unrelated to head injury. The minor signs and symptoms include tachycardia, pyrexia, retinal fat or petechiae, urinary fat globules or oligoanuria, sudden drop in hemoglobin level, sudden thrombocytopenia, high erythrocyte sedimentation rate, and fat globules in sputum. There are other modifications based on Gurd's system, such as two major features, two major and two minor features, and so on. Although adopted clinically, there is no scientific justification for Gurd's diagnosis system.

Schonfeld and colleagues developed an index system that includes seven criteria, each with a different weighting. These criteria include diffuse petechiae, alveolar infiltrates, hypoxemia (less than 70 mm Hg), confusion, fever greater than 38°C, heart rate greater than 120 beats per minute, and respiratory rate greater than 30 breaths per minute. FES is diagnosed with a score of 5 or higher. However, the limitation of the Schonfeld index is that it is not valid for patients with cerebral, thoracic, or abdominal injury. Vedrinne and colleagues revised the scoring system for trauma patients with pulmonary infiltrates, neurologic changes, petechiae, platelet count, retinal changes, total blood lipids, and presence of long bone fractures. Weisz and Barzilai further modified the criteria for applicability to pediatric patients.

Future advance in FES diagnosis may come to fruition with imaging and laboratory advancement. Magnetic resonance imaging appearance, high-resolution computed tomography scans, cellular studies on bronchoalveolar lavage fluid, and other techniques may provide better diagnostic tools. However, these diagnostic modalities are not specific and are inconsistent for generalized clinical utilization.

Two main theories have been widely accepted because no single theory can explain all phenomena: the mechanical fat embolism theory and the biochemical free fatty acid theory.

Mechanical Fat Embolism Theory

The presence of fat microemboli can be visualized with ultrasonography. Manipulation and high-pressure reaming are all correlated with more microemboli events, whereas external fixation is associated with fewer events. The fat emboli are first released into the venous system and then travel to the pulmonary vasculature. This explains some of the pulmonary and cardiac symptoms. However, some patients can present with systemic signs without significant pulmonary symptoms, which is not well supported by the mechanical fat embolism theory. One theory is that the size and deformability of small fat emboli may allow pulmonary transit leading to a systemic presentation without clinically significant pulmonary symptoms.

Biochemical Free Fatty Acid Theory

Long bone surgery has been associated with elevated free fatty acids levels and lower oxygen tension. This could be attributed to the hydrolysis of neutral fats to free fatty acids after injury. Animal models have shown that free fatty acids can lead to severe vasculitis and disrupt pulmonary architecture with a resulting clinical presentation of hemorrhage and edema.

Recognition

Trauma with long bone fractures are the most common cause, with an estimated 90% of patients experiencing fat emboli. However, only 2% to 5% of all patients will be symptomatic and thus diagnosed with FES. The classical presentation is gradual onset at 12 to 36 hours after injury with pulmonary and neurologic symptoms. Early persistent

TABLE 142.1 Gurd's Diagnosis System

Major Features	Minor Features
Petechial rash	Tachycardia
Respiratory symptoms plus bilateral signs of positive radiographic changes	Pyrexia
Cerebral signs unrelated to head injury	Retinal fat or petechiae
	Urinary fat globules or oligoanuria
	Sudden drop in hemoglobin level
	Sudden thrombocytopenia
	High erythrocyte sedimentation rate
	Fat globules in sputum

tachycardia may be the first sign of impending problems. Patients could become progressively tachypneic, dyspneic, and hypoxemic, and may even deteriorate into full-blown acute respiratory distress syndrome (ARDS). Hematologic system and dermatologic system involvement are also common.

FES could be manifested intraoperatively under anesthesia. With any sudden change of vital signs during long bone procedures, FES should be considered in the differential diagnosis, especially with unexplained hypoxia and/or hypotension. A significant degree of fat emboli can occur over a short period of time. In patients with limited cardiac reserve, acute pulmonary hypertension may precipitate right ventricular failure with hypotension, tachycardia, hypoxemia, and cardiovascular collapse.

Risk Assessment

Fat embolism is common among trauma patients. The incidence is related to the nature of the injury and reported in 60% to 90% of patients. However, the incidence of patients who develop clinical signs and symptoms is much lower. Early reports from the 1970s indicated symptomatic FES in around 20% of these patients. This decreased by almost half over the next 20 years after improvement in surgical management. Bulger and colleagues identified 27 FES events in 3026 patients (0.9%). Fabian and colleagues reported at least 11% of FES among patients with femoral, tibia, and pelvic fractures. Pinney and colleagues reported the incidence of FES for femur fractures as 4%. Additional studies also reported incidences of around 2% to 5%.

Many risk factors have been identified, including general factors, injury-related factors, and surgery-related factors. General factors include male patient, age from 10 to 39 years, hypovolemic state, posttraumatic event, and reduced cardiopulmonary reserve. Injury-related factors include lower extremity fractures, especially femur shaft or bilateral femur fractures, multiple bone fractures, and fractures concomitant with pulmonary compromise. Surgical factors include reaming, nailing, arthroplasty after femur fracture, bilateral femur procedures, and arthroplasty with high-volume prosthesis.

Implications

The mortality rate of FES has decreased with modern intensive care unit (ICU) care. The major morbidity and mortality associated with FES is related to pulmonary dysfunction, acute lung injury (ALI), or ARDS. Because most patients with FES also have other coexisting injuries, it is very difficult to isolate FES-related mortality. The mortality rate is estimated around 5% to 15% among all symptomatic patients. FES has also been reported in bone marrow transplantation, pancreatitis, and fatty liver. The majority of patients would recover from the pulmonary sequelae of FES with supportive care. Acute neurologic changes may often present for several more days after the pulmonary issues have resolved. Long-term or permanent neurologic sequelae are occasionally seen in patients with visual disturbances or focal neurologic deficits.

MANAGEMENT

The management strategy for FES includes prophylaxis, early diagnosis, and supportive therapy. Early diagnosis is important because it may lead to earlier intervention and improved outcomes. Once FES is symptomatic, the mainstay of treatment is supportive. The focus is on ensuring oxygenation, ventilation, and hemodynamic stabilization. Heparin, corticosteroids, and dextran have failed to show benefit as a treatment for FES in reducing mortality and morbidity. However, prophylactic corticosteroids may have protective effects.

Respiratory failure from FES is comparable to ALI and ARDS. The management principles are the maintenance of effective gas exchange and oxygenation with positive end-expiratory pressure while avoiding ventilator-associated lung injury. FES could be manifested intraoperatively under anesthesia. In the case of this event, the management strategy should be open communication with the surgical team and maintenance of oxygenation, ventilation, and hemodynamic stability with volume and inotropic agents. Continuous ICU management should be implemented for improved outcomes.

PREVENTION

Early stabilization is effective in reducing fat embolism and FES by reducing recurrent fat embolization into the circulation. Early fixation within 24 hours has been shown to reduce the incidence of FES in both single-fracture and polytrauma patients. In addition, early mobilization and limiting sedation could potentially benefit patients by decreasing FES, among its other known benefits. Changes in surgical techniques, such as lavage of canal after reaming, may help reduce the extent and severity of fat embolism.

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Hypercoagulable States: Thrombosis and Embolism

143

Andrew Disque • Komal Patel • Mark A. Chaney

Case Synopsis

An obese 53-year-old woman with a history of congestive heart failure and ovarian cancer has an exploratory laparotomy under general anesthesia for tumor debulking. On postoperative day 1, she experiences sudden-onset shortness of breath.

PROBLEM ANALYSIS

Definition and Recognition

More than 150 years ago, Virchow suggested a triad that leads to intravascular coagulation: injury to blood vessels, venous stasis, and hypercoagulability. Injury to blood vessels, as might occur with direct trauma, major burns, surgical manipulation, or central venous access, causes endothelial damage, leading to the formation of local clot (thrombus) and subsequent propagation (thromboembolism). Venous stasis, as might occur in anesthetized surgical or immobilized patients, results in sluggish venous flow and a propensity for thrombus formation. An understanding of hypercoagulability requires a basic knowledge of the coagulation process.

Thrombus formation is triggered by endothelial injury, exposing subendothelial collagen to circulating platelets. These adhere and form a platelet plug. As this is forming, the clotting cascade is activated via one of two pathways. In the *intrinsic pathway,* subendothelial collagen is activated through activation of factor XII (which requires factors VIII, IX, and XI). In the *extrinsic pathway,* tissue thromboplastin (tissue factor) is released by injured tissue to activate factor VII. The final (common) pathway begins with activated factor X (Xa). Once factor X is activated, it binds with its cofactor, factor V, and platelet phospholipid, and this complex activates factor II (prothrombin) to form factor IIa (thrombin). Thrombin, bound to platelet phospholipid, cleaves fibrinogen into fibrin monomers. These aggregate to form a fibrin polymer that is loosely held together by hydrogen bonds (soluble fibrin, or fibrin S). Subsequently, factor XIII (fibrin stabilizing factor), which is activated by thrombin and calcium ions, mediates the formation of covalent peptide bonds between the fibrin monomers to yield a stable fibrin clot (insoluble fibrin, or fibrin I).

Normally, the clotting process is balanced by an endogenous anticoagulant and thrombolytic system that limits clot formation and eventually dissolves the clot. Thrombolysis is initiated by tissue-type plasminogen activator (t-PA) from injured cells near the fibrin clot. As t-PA cleaves circulating plasminogen into plasmin, this dissolves fibrin within the clot matrix.

Several physiologic mechanisms regulate the coagulation process, thus limiting clot formation to the injured area and preventing excessive clotting (i.e., disseminated intravascular coagulation [DIC]):

- Coagulation factors circulate in inactive form.
- Normal blood flow dilutes the concentration of activated factors and removes them from the site of injury. These are subsequently removed from the circulation by the liver and reticuloendothelial system.
- Some coagulation factors (e.g., factor Xa) require a phospholipid surface (tissue factor, platelet phospholipid) for proper interaction.
- Antithrombin (AT; formerly known as antithrombin III) complexes with and inactivates thrombin, as well as other circulating coagulation factors (with the exception of factor VII). AT molecules have two critical domains: one binds to thrombin and other activated clotting factors, and the other binds heparin. In the presence of heparin, the rate of AT binding to thrombin and other activated clotting factors is markedly accelerated.
- Thrombin binds to thrombomodulin (a protein located on the vascular endothelial surface), which activates protein C, thereby inactivating factors Va and VIIIa.
- Protein S is a cofactor (along with protein C) in the inactivation of factors Va and VIIIa.
- Tissue factor pathway inhibitor is synthesized by vascular endothelium and inhibits factor X in two ways: it directly inhibits factor Xa, and it complexes with factor Xa to inhibit tissue factor VIIIa, thereby inhibiting the extrinsic pathway.

Hypercoagulable states represent a spectrum of processes that increase the activation of coagulation, decrease endogenous anticoagulation, or decrease the activity of thrombolytic systems. These disorders may be qualitative or quantitative, and their clinical manifestations depend on the severity of the disorder. Hypercoagulable disorders are classified as inherited disorders (conditions for which specific defects of the endogenous anticoagulation system have been identified; Table 143.1) or acquired disorders (disease or states associated with increased risk of thrombotic complications compared with that in general population; Box 143.1).

Inherited Hypercoagulable Disorders

- *Factor V Leiden mutation and resistance to activated protein C.* Activated factor V serves as a cofactor in the conversion of prothrombin to thrombin. Factor Va is inactivated by activated protein C. A single point mutation in the factor V gene (R506Q [factor V Leiden]) makes the molecule resistant to degradation by activated protein C and thus leads to a hypercoagulable state by increasing the generation of thrombin. About 3% of the general population is heterozygous for this mutation. It accounts for 21% to 25% of patients with recurrent deep venous thrombosis (DVT).

TABLE 143.1 Inherited Disorders Causing Hypercoagulable States

Affected Component	Expression
Factor V gene mutation	Resistance to activated protein C by factor V
Prothrombin gene mutation	Increased prothrombin production
Antithrombin	Deficiency and dysfunction
Protein C	Deficiency and dysfunction
Protein S	Deficiency
Fibrinogenemia	Dysfunctional protein
Heparin cofactor II	Deficiency
Procoagulant factor	Deficiency
Plasminogen	Deficiency or dysfunctional protein
Plasminogen activator	Deficiency
Plasminogen activator inhibitor–1	Elevation

BOX 143.1 Acquired Disorders Predisposing to Thrombosis

Venous Stasis
Immobilization
Pregnancy
Congestive heart failure
Varicosities
Obesity

Coagulation Activation
Trauma
Surgery
Malignancies
Administration of factor concentrates
Lupus inhibitor
Myocardial infarction
Myeloproliferative disorders
Nephrotic syndrome
Oral contraceptives

Abnormal Vascular Surface
Atherosclerosis, hyperlipidemia
Diabetes
Homocysteinemia
Cigarette smoking
Estrogen therapy
Prosthetic cardiovascular device
Indwelling vascular catheters

Vascular Occlusive Disorders
Hyperviscosity, polycythemia
Sickle cell disease
Plasma cell dyscrasias

Increased Platelet Reactivity
Thrombocytosis
Surgery

- *Prothrombin gene mutation.* A specific point mutation in the prothrombin gene (G20210A) results in a 30% increase in the plasma prothrombin levels. Heterozygotes account for about 6% to 18% of patients with recurrent DVT.
- *Antithrombin deficiency.* AT is an α_2-globulin synthesized in the liver that inactivates thrombin; factors XIIa, XIa, Xa, and IXa; and kallikrein. AT deficiency was the first identified cause of hereditary hypercoagulable disorders. It is inherited in an autosomal dominant fashion and accounts for approximately 0.5% to 1% of patients with recurrent DVT.
- *Protein C and protein S deficiency.* Proteins C and S are vitamin K–dependent plasma proteins that inactivate factors Va and VIIIa. Their deficiency is transmitted in an autosomal dominant fashion and accounts for 5% to 10% of patients with recurrent DVT.

Acquired Hypercoagulable Disorders

- *Acquired protein C deficiency.* Acquired protein C deficiency has been observed in patients with DIC, acute leukemia, hepatic disease, and nephrotic syndrome; renal transplant patients; and patients taking warfarin or oral contraceptives.
- *Malignancy.* The incidence of clinical thromboembolic disease in patients with cancer has been estimated to be as high as 11%. Thrombotic episodes may precede the diagnosis of malignancy by months to years. It may present as migratory superficial thrombophlebitis (Trousseau syndrome), DVT, DIC, nonbacterial thrombotic endocarditis, or, rarely, arterial thrombosis. Tumors may secrete procoagulants (cysteine protease, tissue factor–like procoagulant). Tumors can also lead to venous thrombosis by external compression, vascular invasion (renal tumor), or hepatic involvement and dysfunction.
- *Pregnancy.* Pregnancy and the postpartum period are associated with the presence of all three components of Virchow's triad: venous stasis within the lower extremity veins (the gravid uterus impedes venous return), endothelial injury to the pelvic veins produced during delivery, and hypercoagulability. Pregnancy is also associated with increases in factors I, II, VII, VIII, IX, and X, along with decreases in protein S and AT activity. In addition, the activity of fibrinolytic inhibitors PAI-1 and PAI-2 is increased during pregnancy.
- *Surgery.* DVT and pulmonary emboli may occur postoperatively. Thrombosis in surgical patients appears to be related to surgical tissue trauma and the liberation of tissue factor, leading to thrombin formation. In addition, inflammation (leukocyte reactivity) and surgery-induced hemostatic changes may contribute to thromboembolism (Box 143.2). Hemostatic changes appear to correlate with the type of surgery and magnitude of surgical intervention and are maximal during the first 48 hours after surgery.
- *Immobilization.* It is postulated that venous stasis contributes to thrombosis by causing local hypoxia (with resulting endothelial injury) and inadequate clearance of activated procoagulant proteins.
- *Myeloproliferative disease.* Patients with myeloproliferative disorders (e.g., polycythemia rubra vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, agnogenic myeloid metaplasia, megakaryocytic myelosis, chronic myelocytic leukemia) have an increased incidence of thrombotic events. Both arterial and venous thrombosis may occur at unusual anatomic sites, including the mesenteric, renal, splenic, portal, and hepatic (Budd-Chiari syndrome) circulations.
- *Hyperviscosity syndrome.* Blood viscosity is increased when there is an elevated red cell mass (polycythemia), increased immature adherent leukocytes (aplastic anemia), deformed red cell membrane (sickle cell anemia), and increased globulin concentrations (plasma cell disorders). Sluggish flow associated with these conditions can result in vascular occlusion in any vascular bed. It is believed that immature white cells cause leukostasis; this in turn releases proteases, which promote thrombus formation.
- *Lupus anticoagulant.* Lupus anticoagulants are antiphospholipid antibodies (usually immunoglobulin [Ig] G and, rarely, IgM) directed against plasma proteins (e.g., β_2-glycoprotein I, prothrombin, annexin V) bound to anionic phospholipids. Lupus anticoagulants occur in about 5% to 10% of patients with systemic lupus erythematosus. They block the in vitro assembly of the prothrombinase complex, resulting in a prolongation of protein assays such as

BOX 143.2 Surgery-Induced Hemostatic Changes

Increased Platelet Reactivity
↑ Aggregation
↑ Dense granule release

Increased Leukocyte Reactivity
↑ Free radical release
↑ Surface adhesion molecules

Increased Coagulation Cascade Activation
↑ Fibrinogen
↑ Factor VIII
↑ Von Willebrand factor
↑ Thrombin formation

Decreased Endogenous Anticoagulants
↓ Antithrombin III
↓ Heparin cofactor II
↓ Tissue factor pathway inhibitor
↓ Protein C, protein S

Decreased Fibrinolysis
↑ Plasminogen activator inhibitor–1

activated partial thromboplastin time, dilute Russell viper venom time, kaolin plasma clotting time, and, rarely, prothrombin time. Although these changes suggest impaired coagulation, patients with lupus anticoagulants have a paradoxic increase in the frequency of arterial and venous thrombotic events. The mechanism for thrombosis is incompletely understood but may involve IgG binding to phospholipids that are essential for the normal activating and degrading effects of protein C and protein S, thus shifting the balance in favor of thrombus formation.

- *Hyperhomocysteinemia.* High levels of homocysteine are associated with both venous and arterial thrombosis. The mechanism by which hyperhomocysteinemia predisposes to thrombosis is unclear; however, potential mechanisms include endothelial activation, proliferation of smooth muscle cells, changes in endothelial nitric oxide production, or changes in endothelial sterol metabolism. The disorder can be congenital or acquired. Acquired forms are found in patients with dietary deficiencies of folate, vitamin B_{12}, or vitamin B_6. Congenital hyperhomocysteinemia is most commonly due to mutations affecting the cystathion β-synthase *(CBS)* gene or the methylenetetrahydrofolate reductase *(MTHFR)* gene.
- *Administration of factor concentrates.* For many decades, treatment of coagulopathy included administration of vitamin K, plasma, platelets, and cryoprecipitate. Given that warfarin reversal with plasma can take greater than 30 hours and requires significant volume administration, newer, more efficient options are becoming more available. These include prothrombin complex concentrates (PCCs), recombinant activated factor VIIa, factor IX concentrate, factor VIII concentrate, and fibrinogen concentrate. PCCs, which are available in 3- and 4-factor varieties, are solutions containing factors II, VII, IX, and X. Some of these newer treatments, particularly activated factor VIIa and PCCs, are associated with arterial and venous thrombotic events. As these products become more commonly used and studied, perhaps their risk of thrombosis can be limited; some studies have shown a similar efficacy and a much lower risk of thrombosis when doses are reduced.
- *Other factors.* Other factors that may be associated with hypercoagulable states are nephrotic syndrome, oral contraceptive use, hormone replacement therapy, prolonged travel, heavy smoking, hypertension, paroxysmal nocturnal hemoglobinuria, heparin-induced thrombocytopenia, thrombocytosis, and inflammatory bowel disease.

Thromboembolism

Arterial thromboembolism may lead to cerebral or other vital end-organ infarction. Venous thrombosis, which is 10 times more likely to occur in the leg than in the arm, can present acutely as a local thrombus in the extremity, or as a thromboembolism. For all intents and purposes, venous thromboembolism is pulmonary embolism, which has the following pathophysiologic effects:

- Increased pulmonary vascular resistance secondary to vascular obstruction, neurohumoral mediators, cytokines, and reflex vasoconstriction
- Impaired gas exchange secondary to increased alveolar dead space, ventilation-perfusion mismatch, and increased intrapulmonary right-to-left shunting
- Compensatory alveolar hyperventilation
- Right-sided heart dysfunction and dilation secondary to increased pulmonary artery pressure, wall tension, oxygen consumption, and ischemia
- Bronchoconstriction and increased airway resistance
- Reduced lung compliance secondary to edema, hemorrhage, and surfactant loss

Risk Assessment

Inherited Hypercoagulable States

The prevalence of factor V Leiden mutation and prothrombin gene mutation in patients with DVT is about 21% to 25% and 6% to 18%, respectively. However, patients with these mutations have a relatively low risk for thrombosis. By age 65 years, only about 6% of carriers of these mutations have experienced venous thrombosis, with most thrombotic events occurring during high-risk periods such as surgery. The frequency of factor V Leiden varies by ethnicity; it is common in people of European descent but rare in those of African or Asian descent.

AT deficiency accounts for only 0.5% to 1% of patients with DVT, but more than 50% of affected patients experience venous thrombotic events by age 60 years. Protein C and protein S deficiency accounts for 0.5% to 4% and 1% to 7% of patients with DVT, respectively.

Acquired Hypercoagulable States

- *Malignancy.* Intravascular thrombus formation can occur with any malignancy but is more common with neoplasms of the mucin-secreting organs (gastrointestinal and pulmonary). Migratory superficial thrombophlebitis occurs in up to 10% of patients with pancreatic carcinoma. Patients with malignancy also have other predisposing factors for venous thrombosis (e.g., surgery, immobilization).
- *Pregnancy.* Pregnancy is associated with an approximately sixfold increased risk of venous thromboembolism compared with nonpregnant patients (see also Chapter 141). Risk is greatest in the third trimester and first month postpartum. The incidence of DVT and pulmonary embolism has been estimated to be as high as 0.05% to 0.1%. Pulmonary embolism is estimated to account for 12% of fatalities during pregnancy. Risk factors for thrombosis in pregnancy include increasing age, cesarean delivery, prolonged immobilization, obesity, prior thromboembolism, and coexistent thrombophilia.
- *Surgery.* Orthopedic procedures on the hip and lower extremities are among the most thrombogenic surgical procedures. In the absence of prophylaxis, the risk of DVT after total knee replacement ranges from 45% to 70%, and fatal pulmonary embolism has been

reported to occur in 1% to 3% of patients undergoing hip surgery. Coronary artery bypass grafting surgery is associated with up to a 20% risk of DVT and a 4% risk of pulmonary embolism. Although the risk of thromboembolism is greatest during the first 2 postoperative days, embolic events may occur weeks to months after knee or hip surgery.

- *Immobilization.* Conditions leading to prolonged immobility (e.g., heart failure, stroke, spinal cord injury, old age, obesity, major trauma, surgery) increase the risk for hypercoagulability. DVT incidence rates of 58% in patients after major trauma and 33% in immobilized patients requiring medical intensive care have been reported.
- *Myeloproliferative disease.* There is a correlation between elevated hematocrit, blood viscosity, and occlusive vascular events.
- *Indwelling vascular catheters.* Thrombotic complications are common with central venous catheters and are often associated with catheter sepsis. Thrombosis can be due to fibrin deposition or vascular occlusion.

Implications

Because the heparin effect (anticoagulation) depends on adequate AT levels, patients with AT deficiency may not respond appropriately to heparin. The use of warfarin may produce a deficiency in protein C and protein S before anticoagulation, which is responsible for warfarin-induced skin necrosis. For patients with hypercoagulable states, heparin therapy may be indicated for conditions that significantly increase the risk of venous thrombosis and pulmonary embolism (e.g., surgery, major trauma, immobilization).

MANAGEMENT

Except for AT deficiency (see Prevention), there is no specific therapy for hypercoagulable states other than anticoagulation to prevent pulmonary embolism or to prevent extension of a current thrombosis and thrombolysis (streptokinase, urokinase, recombinant t-PA) to dissolve and treat formed thrombus. Anticoagulant options include heparin (standard unfractionated or low-molecular-weight heparin), fondaparinux, or warfarin. Fondaparinux (a synthetic heparin pentasaccharide) mediates its effect through antithrombin, but has the benefit of a substantially reduced risk of heparin-induced thrombocytopenia (HIT). In patients with HIT complicated by thrombosis, the American College of Chest Physicians (ACCP) recommends use of nonheparin anticoagulants, which are direct thrombin inhibitors (lepirudin, argatroban, bivalirudin, dabigatran) or direct Xa inhibitors (danaparoid, apixaban, rivaroxaban).

Treatment of pulmonary embolism may be primary or secondary. Primary treatment to remove clot includes thrombolysis, catheter embolectomy, clot fragmentation, or surgical embolectomy. Secondary treatment for the prevention of recurrences includes systemic anticoagulation (heparin, warfarin, direct thrombin inhibitors, direct Xa inhibitors) and inferior vena cava filters (e.g., bird's nest or Greenfield filters).

PREVENTION

Preventive measures for venous thrombosis and pulmonary embolism in high-risk patients include subcutaneous low-molecular-weight or unfractionated heparin, graduated compression stockings, and pneumatic compression devices. Fondaparinux has been approved by the Food and Drug Administration for the prophylaxis of DVT in patients undergoing surgery for hip fracture, hip or knee replacement, and abdominal surgery. Other alternatives recommended by the ACCP for DVT prophylaxis in patients undergoing hip fracture, hip replacement, or knee replacement surgery are apixaban, rivoroxaban, and dabigatran. Recombinant hirudin preparations (such as bivalirudin) have been used as prophylactic agents for DVT in European countries. In the United States they are currently approved for the treatment of heparin-induced thrombocytopenia and as anticoagulation for patients undergoing percutaneous coronary interventions. The following preventive measures should be considered for patients with acquired or inherited hypercoagulable states:

- *Antithrombin deficiency.* AT concentrations routinely decrease after surgery but can be increased with the administration of plasma. Recombinant human AT is also available, and its use should be considered perioperatively in patients with AT deficiency, keeping in mind that heparin can decrease AT concentrations.
- *Protein C and protein S deficiency.* Concentrations of protein C and protein S can be increased by the administration of plasma. Specific protein C concentrate is also available.
- *Myeloproliferative disease.* Because there is a correlation between occlusive vascular events and elevated hematocrit, blood viscosity, and leukocytosis, these three parameters should be returned to a more normal range with the appropriate use of phlebotomy, chemotherapy, or crystalloid solutions.

Further Reading

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Hyperglycemia and Diabetic Ketoacidosis 144

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Case Synopsis

A 75-year-old woman with type 2 diabetes mellitus, controlled by glyburide 5 mg twice a day, presents for scheduled coronary artery bypass grafting. She has diabetic nephropathy with a serum creatinine of 1.8 mg/dL. The patient did not take her oral antidiabetic medication before surgery, and her fasting plasma glucose was 130 mg/dL. After cardiopulmonary bypass, the intraoperative plasma glucose was 236 mg/dL. There was a brisk diuresis. The serum potassium was 5.8 mEq/L with a base deficit of –4.0 mEq/dL. The patient received furosemide and mannitol while on cardiopulmonary bypass and repeated doses of cardioplegia. Cardiopulmonary bypass took 130 minutes.

PROBLEM ANALYSIS

Definition

Hyperglycemia in adults is defined as a random plasma glucose level greater than 200 mg/dL. It is generally accepted that prevention of uncontrolled hyperglycemia is appropriate, although the optimal blood glucose range remains debated. Perioperative plasma glucose levels are determined by many factors, including preoperative glucose, nutritional status, and insulin levels and increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis.

At times of illness or acute severe stress, hyperglycemia may be present; this is referred to as *stress hyperglycemia* or *stress diabetes.* In some patients this may reflect the unmasking of an abnormality of glucose tolerance, which should be treated to reduce the risk of increased morbidity and mortality. The patient should subsequently be reevaluated and reclassified after recovering from surgery or acute illness. A similar approach is used in the management of gestational diabetes.

Diabetes mellitus (DM), the most common endocrine disease, is a chronic multisystem disease heralded by signs and symptoms of persistent hyperglycemia and confirmed by a random plasma glucose level greater than 200 mg/dL, a fasting plasma glucose level greater than 100 mg/dL, a plasma glucose level of 140 mg/dL or greater based on 2-hour postprandial testing or 2 hours after an oral glucose tolerance test, or a random glucose of greater than 200 mg/dL. Normal values for plasma glucose are given in Table 144.1. In the absence of acute metabolic decompensation or severe hyperglycemia, these criteria should be reconfirmed at least 24 hours apart. The diabetic patient population is heterogenous, and several diabetic syndromes have been defined. Hyperglycemia in diabetic patients is the result of either a relative or absolute deficiency of insulin and a relative or absolute excess of glucagon. In type 1 diabetes, there is an absolute deficiency in insulin production with an onset typically by adolescence and is thought to be a result of autoimmune destruction of islet cells in the pancreas. These patients become dependent on exogenous insulin to prevent lipolysis and eventually ketoacidosis. Type 2 diabetes is heralded by a relative deficiency in insulin and is more a manifestation of insulin resistance. Typical onset of type 2 diabetes is in adulthood, although data suggest the mean age is decreasing. Gestational diabetes is a third type that is defined by any degree of glucose intolerance with onset first recognized during pregnancy and complicates approximately 4% of all US pregnancies.

TABLE 144.1 Diagnostic Criteria for Prediabetes and Diabetes in Nonpregnant Adults

Normal	High Risk for Diabetes	Diabetes
Fasting plasma glucose (FPG) <100 mg/dL	FPG ≥100–125 mg/dL	FPG ≥126 mg/dL
2-h postprandial glucose (PG) <140 mg/dL	2-h PG ≥140–199 mg/dL	2-h PG ≥200 mg/dL Random plasma glucose ≥200 mg/dL + symptoms
HgbA1C <5.5%	5.5%–6.4%	≥6.5%

Diabetic ketoacidosis (DKA) is an emergent condition usually associated with type 1 DM. It generally occurs in the setting of absent insulin, poor glucose utilization, and often some pathologic stressor (e.g., illness, infection, trauma). The body attempts to preserve energy stores via gluconeogenesis, which is the mobilization of fats and amino acids into glucose-producing pathways, resulting in hyperglycemia and ketosis (Fig. 144.1).

Nonketotic hyperosmolar syndrome occurs in type 2 diabetics is often triggered by physiologic stress (e.g., illness, acute infection, pneumonia, stroke, myocardial infarction). Endogenous insulin is present in sufficient quantities to prevent these patients from developing ketoacidosis; however, they present with an anion gap metabolic acidosis secondary to lactic acidosis. This acid-base derangement occurs as a result of cellular hypoxia, likely due to hypovolemia, inadequate organ perfusion, or a shock state. Nonketotic hyperosmolar syndrome is characterized by severe hyperosmolarity (>320 mOsm/L), hyperglycemia (>600 mg/dL), and marked dehydration.

Recognition

Preoperatively, clinical symptoms and signs of hyperglycemia may be absent or vary widely. One-third of patients with DM are unaware that they have the condition. Symptoms and signs include the following:

- Polyphagia
- Polydipsia

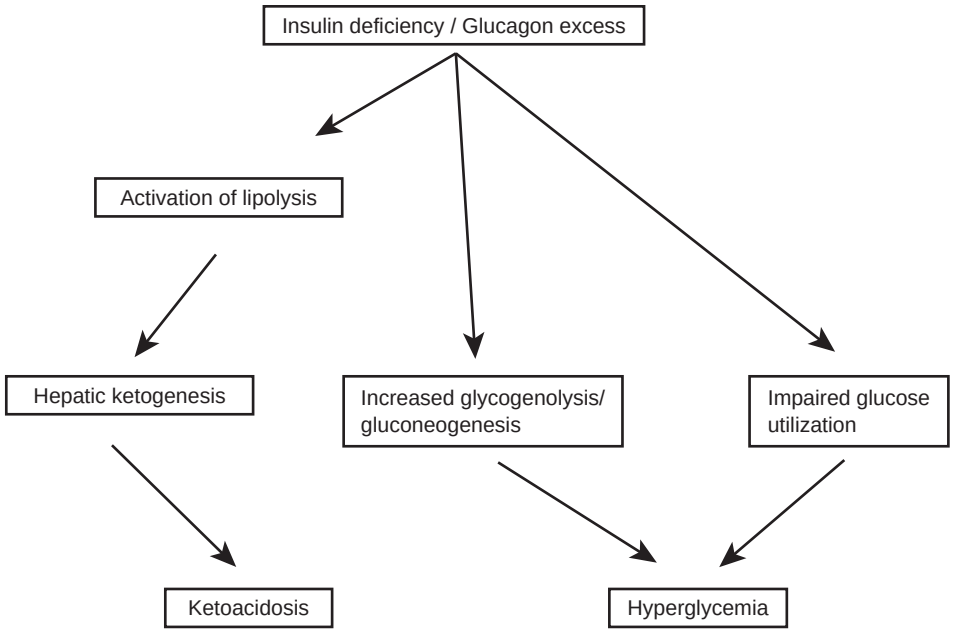

Fig. 144.1 Pathogenesis of diabetic ketoacidosis and hyperglycemia.

- Polyuria
- Confusion
- Coma

Intraoperative signs are as follows:

- Unexplained diuresis
- Tachycardia and hypotension
- Anion gap metabolic acidosis
- Hyponatremia and hyperkalemia

Frequently, hyperglycemia is first recognized by an increased plasma blood glucose level.

Risk Assessment

Causes of perioperative hyperglycemia are listed in Box 144.1. Emergency surgery increases the risk of type 1 diabetics developing DKA and type 2 diabetics developing nonketotic hyperosmolar syndrome. In emergency situations (e.g., trauma), patients may miss their usual insulin dose, interrupt their usual caloric intake, or encounter excessive pathologic stresses, which alter the normal counterregulatory hormone balance. The patient's inability to increase insulin production results in hyperglycemia.

Because DM affects multiple organ systems, it is associated with significant complications, including retinopathy, neuropathy, gastropathy, and nephropathy. Additionally, complications of diabetes that play a crucial role in anesthetic management include the effect of oxygen transport leading to decreased oxygen saturation in pregnant diabetic patients, autonomic dysfunction resulting in increased risk for intraoperative hypothermia, and orthostatic hypotension. DM also accelerates atherosclerosis leading to increased risk of coronary artery disease, cerebrovascular disease, and peripheral vascular disease.

Implications

There is a great deal of observational evidence from multiple patient populations demonstrating that hyperglycemia is associated with poor clinical outcomes in critically ill patients. However, it remains unclear if hyperglycemia causes poor outcomes or is merely a marker of severe illness.

BOX 144.1 Causes of Perioperative Hyperglycemia

- Diabetes mellitus (types 1 and 2)
- Dextrose-containing intravenous fluids
  - Maintenance solutions or parenteral nutrition
  - Medications
- Catecholamine-induced stress response
  - Burns
  - Trauma
  - Surgery
  - Sepsis
  - Stroke
  - Pain
  - Cardiopulmonary bypass
- Excess counterregulatory hormones
  - Cushing disease and Cushing syndrome
  - Pheochromocytoma
  - Acromegaly
  - Glucagonoma
- Drugs
  - Thiazide diuretics
  - Glucocorticosteroids
  - Phenytoin
  - Pentamidine
  - β-Adrenergic receptor blockers
  - Oral contraceptives
- Pancreatic disease
  - Pancreatitis or pancreatic trauma
  - Hemochromatosis
- Pregnancy

- *Trauma.* Patients who are hyperglycemic (blood glucose ≥200 mg/dL) after trauma have an increased mortality rate, hospital length of stay, intensive care unit (ICU) length of stay, and incidence of nosocomial infection.
- *Medical/surgical.* Critically ill medical and surgical patients who are hyperglycemic have a higher mortality rate than patients who are normoglycemic. A retrospective cohort study of 1826 medical and surgical ICU patients found a direct and proportional correlation between increasing blood glucose level and mortality with mortality rates of 10% in patients with mean blood glucose between 80

and 99 mg/dL and increasing to 43% in patients with a mean blood glucose greater than 300 mg/dL.

- *Cellular.* Hyperglcyemia leads to nonenzymatic glycosylation of immunoglobulins, granulocyte dysfunction, and reduction of both CD4 and CD8 lymphocyte populations. It also exaggerates ischemia-reperfusion cellular injury, induces cardiac cell death, and reduces coronary collateral blood flow. Hyperglycemia induces platelet hyperreactivity, which increases thrombosis, and it increases levels of interleukin-6, interleukin-8, and tumor necrosis factor–α, reflecting a proinflammatory action. Hyperglycemia and insulin resistance lead to endothelial cell dysfunction, inactivation of nitric oxide, decreased synthesis of prostacyclin, and increased synthesis of endothelin-1, which all lead to decreased local blood flow.
- *Renal.* Blood glucose levels in excess of 250 mg/dL overwhelm renal tubular absorption capabilities, which leads to hypovolemia secondary to an osmotic diuresis. A profound diuresis may result in prerenal azotemia, altered organ perfusion, cellular hypoxia, and lactic acidosis.
- *Cerebral.* Patients with DM or newly recognized hyperglycemia are at increased risk for severe strokes and increased mortality. Patients with severe traumatic brain injury (TBI) with blood glucose ≥170 mg/dL at the time of ICU admission was found to be an independent predictor of a poor Glasgow Coma Scale score 5 days later, worse neurologic outcomes, and increased intracranial pressure. Moreover, the association between hyperglycemia and adverse outcomes in TBI persisted throughout the hospitalization regardless of whether blood glucose was elevated at admission, increased during the ICU stay, or was highly variable during the ICU stay. Adverse outcomes included increased mortality rate, duration of mechanical ventilation, and ICU and hospital length of stay. Additionally, serum osmolarity greater than 330 mOsm/L is associated with central neurologic dysfunction and coma.
- *Cardiovascular.* A meta-analysis of patients admitted for acute myocardial infarction, with or without a prior diagnosis of DM, found that hyperglycemia was associated with increased hospital mortality and congestive heart failure.
- *Inpatients.* Newly noted hyperglycemia in medical and surgical patients resulted in an 18-fold increase in hospital mortality rate and longer hospital stays. DM represents the seventh-leading cause of death and is the second-leading comorbid condition among hospital discharges in the United States. The association between inpatient hyperglycemia and increased risk for complications and mortality is well established. Hyperglycemia is associated with prolonged hospital stay, increased incidence of infections, greater disability after hospital discharge, and death.
- *Major surgery.* From 30% to 40% of cardiac surgical patients have DM. Hyperglycemia is associated with increased mortality risk and deep-seated infection in cardiac surgical patients.

MANAGEMENT

It has been well established that correction of hyperglycemia with insulin administration reduces hospital complications and mortality rates in the critically ill, as well as in general medicine and surgery patients. Randomized control trials including the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study and meta-analyses have reported higher rates of severe hypoglycemia and increased mortality rate with intensive insulin therapy (glycemic targets of 80 to 110 mg/dL) versus more lenient glycemic targets. In 2009 the American Association of Clinical Endocrinologists/American Diabetes Association (AACE/ADA) formulated a consensus statement on inpatient glycemic control, outlining the argument in favor of more relaxed glycemic targets in the ICU, as high as 140 to 180 mg/dL. Of important note, however, is that glucose targets below 110 mg/dL are not recommended. Moreover, minimizing glycemic variability, independent of glucose levels, could result in lower rates of complications and cardiovascular mortality in critically ill patients, and in reduced hospital stays and mortality rates in non-ICU settings.

TABLE 144.2 Inpatient Glucose Targets for Nonpregnant Adults

Hospital Unit	Treatment Goal
Intensive/Critical Care	
Glucose range (mg/dL)	140–180
General Medicine and Surgery (Non-ICU)	
Premeal glucose (mg/dL)	<140
Random glucose (mg/dL)	<180

ICU, Intensive care unit.

Intraoperative Hyperglycemia

Significant evidence corroborates that hyperglycemia in the hospitalized patient with or without a history of DM increases both mortality and morbidity and that goal-directed insulin therapy may lead to improve outcomes. Treatment of hyperglycemia in the hospital setting and intraoperatively presents multiple challenges, including variable nutritional status and altered level of consciousness. With the overriding concern of patient safety, glucose targets should be set at moderately higher levels than targets for outpatients with DM. For most critically ill patients in the ICU, a glucose range of 140 to 180 mg/dL is recommended. For noncritically ill patients, the consensus premeal glucose target of less than 140 mg/dL and a random blood glucose below 180 mg/dL is recommended (Table 144.2).

Insulin therapy is the preferred method of glycemic control in most hospitalized patients. In the ICU and perioperatively, intravenous (IV) infusion of insulin is the preferred route. A variety of continuous insulin infusion protocols have been shown to be effective in achieving glycemic control, with a low rate of hypoglycemic events and improved hospital outcomes. No major clinical differences have been reported among different IV insulin algorithms as long as glucose levels are monitored with a prescribed frequency. Therefore most insulin algorithms appear to be appropriate, and the choice will depend on physician preference and cost considerations. Outside of the critical care setting, scheduled subcutaneous insulin regimens with a combination of basal, nutritional, and correctional components is recommended. Prolonged use of sliding-scale insulin as the sole method of glucose control is strongly discouraged. Randomized control trials have demonstrated improved glycemic control and lower rates of complications in general medicine and surgical patients treated with a basal prandial regimen using insulin analogs versus sliding scale regular insulin alone.

Diabetic Ketoacidosis

DKA is a medical emergency. Initial assessment includes the following:

- Identification of the precipitating event—infection, ischemia, missed insulin administration
- Volume status
  - Tachycardia, hypotension
  - Increased urea and creatinine
- Mental status—cerebral edema

- Hyperglycemia—increased plasma glucose and urine glucose
- Ketosis—increased serum ketones and β-hydroxybutyrate
- Increased anion gap acidosis
  - Increased respiratory rate (Kussmaul respiration)
  - Serum bicarbonate less than 15 mEq/dL; pH less than 7.3
- Potassium—initially increased secondary to metabolic acidosis, but decreased total potassium stores
- Sodium—laboratory measurement secondary to hyperglycemia

Fluid resuscitation, IV insulin administration, and correction of electrolytes are crucial.

- *Fluid resuscitation.* The fluid deficit is often between 4 and 8 L of sodium and free water. Initial resuscitation includes infusion of normal saline (0.9% NaCl) targeting that within the first 2 hours the patient should receive enough fluid to stabilize his or her hemodynamic parameters (usually 2 to 3 L of non–glucose-containing crystalloid solution). After intravascular volume is restored, subsequent administration of 0.45% saline should be started if the corrected serum sodium is normal or elevated; isotonic saline is continued if the corrected serum sodium is reduced. Once blood glucose levels have declined to less than 200 mg/dL, dextrose is added to the saline solution to maintain acceptable glucose levels and reduce the risk of cerebral edema. Infusion with hypotonic fluid may cause cerebral edema secondary to reverse osmotic shifts. Hypertonic solutions have no role because they may worsen the acidosis, dehydration, and hyperosmolar state.
- *Electrolytes.* Regardless of the initial measured serum potassium, patients with DKA have a large total body potassium deficit. Hyperglycemic osmotic diuresis causes systemic potassium wasting (up to 10 mEq/kg), whereas extracellular shift in potassium secondary to metabolic acidosis results in an elevated serum concentration. Provided the patient's urine output is adequate, acute renal failure is not evident, and a normal serum potassium level is documented, potassium should be repleted promptly. In general, replacement with potassium chloride at a rate of 20 to 30 mEq per hour is sufficient. Electrocardiographic monitoring is recommended during repletion of potassium. Measured hyponatremia is a laboratory phenomenon secondary to the dilutional effect of hyperglycemia. In general, for each 100 mg/dL increase in glucose above normal levels, serum sodium levels decrease by 1.6 to 2.0 mEq/L. No specific therapy is required other than correction of the hyperosmolar state. Phosphate levels may be depleted because this anion is excreted with osmotic diuresis. Routine replacement is controversial because rapid replacement can cause hypocalcemia. Phosphate replacement should be guided by periodic surveillance of magnesium, calcium, and phosphate levels.
- *Insulin therapy.* The only indication for delaying insulin therapy in patients with DKA is a serum potassium below 3.3 mEq/L, because insulin will worsen the hypokalemia by driving potassium intracellular. In moderate to severe DKA, treatment is initiated with an IV bolus of regular insulin (0.1 U/kg), followed by continuous IV insulin infusion (0.1 U/kg/h) and hourly determinations of blood glucose levels. Additional glucose supplementation may be necessary, but care must taken to avoid hypoglycemia.
- *Metabolic acidosis.* The administration of bicarbonate is controversial, with evidence of benefit lacking and the potential for harm present. However, it is generally agreed that in patients with an arterial pH ≤ 6.9 in whom decreased cardiac contractility and vasodilation can further impair tissue perfusion, and in patients with potentially life-threatening hyperkalemia, cautious alkali therapy may be beneficial.

PREVENTION

As of 2012 approximately 29.1 million Americans, 9.3% of the population, had diabetes, and 8.1 million of those were undiagnosed. Diabetic patients require a complete medical evaluation to detect diabetic complications and comorbidities. Oral agents need to be stopped before surgery. Long-acting sulfonylureas or chlorpropamide are stopped for at least 72 hours, whereas shorter-acting sulfonylureas and metformin are stopped the night before surgery.

For type 1 DM patients and patients with uncontrolled type 2 DM, it is essential to administer insulin. The aim of any regimen is to maintain good control without hypoglycemia. It also must be practical and easy to use as the patient is transferred from the ward to the operating room, to the recovery room, and back to the ward. It is important to monitor plasma glucose at frequent intervals. One regimen that fulfills all these criteria is the continuous IV administration of regular insulin. With an increasing number of type 1 DM patients on continuous subcutaneous insulin maintenance, the use of a continuous IV infusion perioperatively is advised. For stable type 2 DM patients having minor or moderately stressful surgery, oral therapy can resume postoperatively.

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Hyperthermia (Perioperative) 145

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Case Synopsis

A 23-year-old woman with a past medical history significant for bipolar disorder on a mood stabilizer requires emergent surgery for a ruptured appendix. The patient has no history of previous surgery and is unaware of any relevant family history. Preoperative vital signs are blood pressure 130/90 mm Hg, heart rate 105 beats per minute, temperature 38.5°C, and respiratory rate 15 breaths per minute. Thirty minutes after an uneventful rapid-sequence induction using succinylcholine and propofol for intubation and maintenance with sevoflurane and intravenous opioids, you notice that the temperature has increased to 40°C.

PROBLEM ANALYSIS

Definition

Hyperthermia is defined as a temperature above the normal core body temperature (generally 36.7°C–37.0°C ± 0.2°C–0.4°C). Elevated temperatures increase metabolic requirements, oxygen consumption, and insensible losses and can cause hypernatremia, seizures, and coagulopathy (Box 145.1). Although hypothermia is more commonly seen in the perioperative period, intraoperative hyperthermia is also a significant concern that has its own differential diagnosis, broader than simply fever due to infection and malignant hyperthermia.

Thermoregulation occurs via a feedback loop controlled by the hypothalamus, coordinating heat production and loss to maintain normothermia near the regulatory set point. This set point, the interthreshold range, and the hypothalamic regulatory reflexes are all affected by both general and regional anesthetics. Hyperthermia is distinct from fever, with fever being an elevation in core body temperature that occurs due to an *increased hypothalamic set point.* In fever, the elevated set point is due to circulating pyrogens (such as endotoxin from gram-negative bacteria) and cytokines (interleukin [IL]–1, IL-6, tumor necrosis factor, interferon-α); as such, fever responds to antipyretics (such as acetaminophen), whereas hyperthermia is not responsive to these pharmacologic agents.

Recognition

Recognizing a hyperthermic state requires accurate temperature monitoring. Intraoperative temperature measurements can be obtained via a variety of techniques with differing specificity. Skin surface temperatures, which vary with environmental influences much more than core temperatures, are the least invasive to obtain, and generally 2°C cooler than core temperatures in operative environments. Although forehead skin temperature is usually reflective of core temperatures after adjusting for the 2°C difference, transitional zone (rectal, bladder) and core temperature monitoring is preferred when feasible. Bladder temperatures are easily obtained using Foley catheterization systems with built-in thermistors; however, these temperatures are falsely low during low urine flow states. Other situations may require more reliable core temperature measurements using temperature probes within the pulmonary artery (as with a Swan-Ganz catheter) or distal esophagus.

BOX 145.1 Consequences of Hyperthermia

- Increased basal metabolic rate
- Increased oxygen consumption
- Increased evaporative water loss
- Electrolyte abnormalities (particularly hypernatremia)
- Seizures (and/or altered mental status)
- Coagulopathy (and DIC)

DIC, Disseminated intravascular coagulation.

Risk Assessment

Hyperthermia itself has a variety of physiologic implications. Although it may be iatrogenic and secondary to hypothermia prevention techniques, hyperthermia may also be an indicator of an underlying pathologic process (Box 145.2). It is often necessary to reevaluate all vital signs and monitors, and possibly obtain an arterial blood gas for analysis.

Iatrogenic/Passive Hyperthermia

The most common causes of intraoperative hyperthermia are iatrogenic, secondary to excessive insulation and active warming in

BOX 145.2 Differential Diagnosis of Intraoperative Hyperthermia

- Iatrogenic/passive hyperthermia (particularly in pediatrics)
- Neurologic injury
- Sepsis
- Malaria
- Malignant hyperthermia
- Severe thyrotoxicosis
- Hyperthermia during epidural analgesia
- Pheochromocytoma
- Neuroleptic malignant syndrome
- Adrenal crisis
- Serotonin syndrome
- Transfusion reaction
- Surgical conditions
- Drug hypersensitivity

attempts to limit hypothermia. This is particularly true in scenarios with limited exposed body surface area (such as ophthalmic surgery with full body drapes), thereby limiting evaporative and convective heat loss. Pediatric and neonatal patients may be more susceptible to thermal entrapment and iatrogenic hyperthermia due to their higher basal metabolic rate, immature sweat-production system, and larger proportion of body surface area in contact with rewarming devices.

Fever/Sepsis

As previously mentioned, during infection the hypothalamic set point is increased and results in fever. In fact, the majority of patients with infection in the intensive care unit present with fever. Although an infectious etiology of the intraoperative fever may be clear by the surgical indication (such as in the patient with the ruptured appendix in the case synopsis), this does not necessarily exclude other causes of hyperthermia that can work concomitantly to raise core body temperature.

Malignant Hyperthermia

Contrary to classical teaching, temperature elevation is a better early indicator of malignant hyperthermia (MH) than increased end-tidal carbon dioxide ($ETCO_2$). Furthermore, initial indicators of MH occurred greater than 30 minutes after anesthetic initiation (compared with popular assumptions that it is seen shortly after induction). MH is covered in depth in Chapter 195.

Neurologic Injury

During intracranial procedures, and even in nonintracranial procedures on patients with known intracranial pathology, hyperthermia may be the presenting sign of a neurologic complication. Neurogenic hyperthermia may be insidious, with a slow increase from 36°C to 40°C, and may be confused initially with passive hyperthermia due to limited exposed surface area. It may also be abrupt, with a rapid rise to 40+°C in less than 30 minutes. In either scenario, neurogenic hyperthermia is not accompanied by a concomitant rise in $ETCO_2$ (ruling out malignant hyperthermia) and has been linked to the following neurologic insults: acute hydrocephalus, intracerebral bleeding, and intraventricular hemorrhage (particularly into the third or fourth ventricle), and to hypothalamic injuries.

Epidural Analgesia

Prolonged epidural analgesia in laboring and nonlaboring patients has been associated with hyperthermia, with temperatures reaching 39.5°C. In these patients, the temperature rise is slow, developing after approximately 5 hours of epidural analgesia, and is an isolated finding with no other perturbations in vital signs. In laboring patients, the hyperpyrexia is believed to be the result of an increased metabolic rate and the inability to regulate heat loss due to sympathetic blockade, and is distinct from fever and inflammation (because antipyretics do not have an effect). However, these issues may be present in nonlaboring patients as well, and the underlying mechanism by which continuous neuraxial analgesia causes hyperpyrexia in these cases remains unclear.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a complication of antipsychotic drug therapy that can be confused with MH due to the presence of muscle rigidity, hyperthermia, rhabdomyolysis, autonomic instability, and altered mental status. The underlying pathophysiology of NMS is related to central dopaminergic blockade at the hypothalamus, and can be triggered by a variety of neuroleptics/antidopaminergics. It generally occurs within 2 weeks of initiating therapy but can present for the first time even after years of same-dose therapy. It can also be triggered by abrupt cessation of dopaminergic agents, such as those used in Parkinson treatment. In the perioperative arena, NMS has been noted to be triggered by chlorpromazine (Compazine), metoclopramide (Reglan), droperidol (Inapsine), and promethazine (Phenergan), both in patients already on neuroleptic therapy and as sole agents.

Serotonin Syndrome

Serotonin syndrome is associated with excess serotonin in the central nervous system and is classically described as having symptoms of mental status change, autonomic hyperactivity (including diaphoresis, tachycardia, hyperthermia, and hypertension), and neuromuscular abnormalities (ranging from tremor and hyperreflexia to muscle rigidity). The incidence of serotonin syndrome has increased in recent years due to the increasing use of proserotonergic agents in outpatient settings, particularly with antidepressants in the selective serotonin reuptake inhibitor class, as well as monoamine oxidase inhibitors, tricyclic antidepressants, amphetamines, and cocaine. It should be noted that the Food and Drug Administration and World Health Organization have released reports noting the possible interaction of $5\text{-}HT_3$ antagonists (such as ondansetron) with other serotonergic drugs leading to possible serotonin excess; however, there is no substantive evidence to support withholding $5\text{-}HT_3$ antagonists in treating postoperative nausea in patients on concomitant serotonergic therapy.

Endocrine Abnormalities

Specific endocrine entities, including severe thyrotoxicosis (thyroid storm), pheochromocytoma, and adrenergic crisis, are often associated with hyperthermia due to the increased metabolic rate created by the underlying pathology.

Transfusion Reaction

Transfusion reactions resulting in hyperthermia can also occur. These generally occur in close proximity to the initiation of the transfusion. With isolated hyperthermia, the most likely cause is a febrile nonhemolytic transfusion reaction. However, if other symptoms are present, such as rigors, increased respiratory rate, and/or hemodynamic instability, other transfusion reactions such as acute hemolytic transfusion reaction and transfusion-associated sepsis are more likely. See Chapter 101 for further discussion.

Malaria

Numerous case reports note that malaria can present similarly to malignant hyperthermia during an operation. Specifically, malaria typically presents with fever, tachycardia, and rigors while under general anesthesia; however, unlike MH, malaria should respond to muscle relaxants and would cause no rapid rise in $ETCO_2$.

Surgical Conditions

Certain surgeries are associated with intraoperative hyperthermia due to the equipment and/or techniques used. Hyperthermic intraperitoneal chemotherapy delivers chemotherapy heated to 42°C to 43°C into the peritoneum, which necessitates active cooling of the surgical-induced hyperthermia. Surgical cross-clamping of major vessels is

another situation with specific risks of hyperthermia due to stagnant blood distal to the cross-clamp: a warming device applied over the underperfused region beyond the cross-clamp can lead to thermal injuries.

Drug Hypersensitivity

"Drug fever," with increased temperature being the sole symptom, occurs in 3% to 5% of drug hypersensitivity cases, with HIV infections being linked to a higher risk of drug reactions. Drug fever is generally temporally related to drug administration but can also occur months later with the average onset time being 8 days. Drug fever is also associated with a rash in less than 20% of cases (rarely urticarial) and can be accompanied by nonspecific laboratory findings.

MANAGEMENT

Management of intraoperative hyperthermia is dependent on the underlying cause of the hyperthermia, and should also include interventions to mitigate the high temperature. As mentioned previously, coagulopathy and disseminated intravascular coagulation may result and should be treated appropriately.

Iatrogenic/Passive Hyperthermia

As the excessive insulation and active warming is the source of the hyperthermia, those should be addressed. This would entail removing excess blankets and disabling the active warming devices.

Fever/Sepsis

If the presumed cause of the hyperthermia is infection, antipyretics would be beneficial. In addition, appropriate antibiotic coverage and source control is indicated.

Malignant Hyperthermia

The resultant hyperthermia can be mitigated through the treatment of the MH: discontinuing triggering agents and administering dantrolene to interrupt the uncontrolled muscle contraction. In-depth MH management is covered in Chapter 195.

Neurologic Injury

Management of neurologic hyperthermia focuses on operative management of the neurologic insult. Hyperthermia may persist into the postoperative period as the pathologic process resolves (or as heme is absorbed and broken down in the case of intraventricular hemorrhage).

Epidural Analgesia

There is no need for specific interventions, aside from being aware that a temperature rise is a common occurrence. This does not, however, mean that other diagnoses need not be considered during an evaluation, such as chorioamnionitis in a laboring patient with an epidural and an elevated temperature.

Neuroleptic Malignant Syndrome

If considering NMS as the underlying cause of intraoperative hyperthermia, neuroleptic agents (and other potential triggering agents) should be avoided. Supportive care should focus on hemodynamic support and cooling. Second-line therapy, such as dantrolene, bromocriptine, or amantadine, is controversial, with limited evidence for their use, especially for first-line intraoperative management.

Serotonin Syndrome

Serotonin syndrome management begins with discontinuation/avoidance of triggering agents, as well as appropriate hemodynamic support. Avoid the use of indirect sympathomimetic agents, such as dopamine and ephedrine, which may worsen the serotonin syndrome. Neuromuscular blockade is beneficial and can help limit the rising body temperature. Active cooling may need to be employed. Antipyretics have no role and should be avoided. If increased depth of anesthesia and intravenous fluids do not improve the autonomic instability, a serotonin antagonist (cyproheptadine 12 mg crushed and given via an orogastric or nasogastric tube, followed by 2 mg every 2 hours until improvement in hemodynamic stability occurs) is warranted.

Endocrine Abnormalities

Management of endocrine pathology is focused on blunting the effects of the hormonal imbalance while providing general hemodynamic support. Specifically, in thyroid storm management involves immediate use of β-blockers (propranolol, or often esmolol due to easy titration) to blunt the sympathetic effects. Additionally, glucocorticoids have been shown to improve outcomes in thyroid storm. There may be utility to thionamide administration (such as propothiouracil or methimazole) and sodium iodine to limit further release of thyroid hormone and minimize peripheral conversion. See Chapter 11 for further reading.

Transfusion Reaction

If the hyperthermia is believed to be secondary to blood product transfusion, the severity of reaction determines the subsequent steps. For most scenarios, stopping the infusion is the first step. If it appears to be a febrile nonhemolytic transfusion reaction, transfusion may be resumed. With more serious transfusion reactions, additional hemodynamic support and management of any ensuing coagulopathy may be required. See Chapter 101 for more information.

Drug Hypersensitivity

Discontinuation of the drug in question is paramount. However, this is dependent on the severity of the reaction and indication for the drug's use intraoperatively.

Cooling Techniques

A variety of cooling techniques, both passive and active, can be employed to mitigate the hyperthermia. If the patient's temperature has risen above 39°C, active cooling should be employed. The easiest first step is to turn off any active warming devices (such as the forced air warmer), even turning them to ambient temperature to circulate cooler air. Other measures include exposing more surface area to increase convective and evaporative loss (although this can be difficult in the operative environment due to concerns for sterility). Active cooling can include the use of ice packs placed in the groin, axillae, and around the neck and head. More invasive active cooling involves the use of chilled intravenous fluids and/or iced peritoneal lavage (gastric and bladder lavage are less beneficial and have higher rates of complications).

PREVENTION

Prevention of intraoperative hyperthermia requires an understanding of the factors that contribute to its development, including which patients are at risk and adequate temperature monitoring to allow early detection and intervention.

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Hypothermia

146

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Case Synopsis

A 74-year-old woman with a history of dementia and osteoporosis is admitted after an unwitnessed fall in her house. She presents to the operating room and undergoes repair of a fractured hip under epidural anesthesia with general endotracheal intubation. She receives 4 units of packed red blood cells. In the postanesthesia care unit, she is confused and disoriented. Her heart rate is 110 beats per minute; blood pressure 160/90 mm Hg; temperature 33.8°C (oral); arterial oxygen tension (Pao_2) 63 mm Hg; and arterial carbon dioxide tension ($Paco_2$) 54 mm Hg (on nasal oxygen at a rate of 6 L/min).

PROBLEM ANALYSIS

Definition

Normal body temperature is regulated between 36°C and 38°C by central structures located primarily in the hypothalamus. Hypothermia is classified as mild to moderate (33°C to 36°C), severe (23°C to 33°C), or profound (<23°C). Inadvertent hypothermia is a preventable perioperative complication that occurs in 50% to 90% of anesthetics. Several major outcomes studies have shown that even modest hypothermia triples the odds of cardiac mortality, surgical wound infections, blood loss, and the need for allogeneic blood products. Accidental (Box 146.1) or iatrogenic (Box 146.2) causes may contribute to the development of hypothermia. These include patient, anesthetic, surgical, and environmental factors.

Recognition

During general anesthesia, hypothermia develops in a characteristic pattern. There is an initial rapid 0.5°C to 1.5°C decline in core body temperature within the first hour followed by a slow linear reduction in core temperature in the next 2 to 4 hours. The initial rapid decline is the result of heat redistribution from the core to the periphery as a result of anesthesia-induced vasodilation. The slower linear decline is the result of heat loss in excess of metabolic heat production. After 3 to 4 hours, core temperature plateaus, although peripheral temperature continues to decline.

The interthreshold range is the range of core temperatures within which no physiologic responses to temperature change are evoked. Normally, this is very narrow (about 0.5°C). However, from Fig. 146.1 it is apparent that anesthesia widens the interthreshold range to as much as 4°C. This implies, for example, that the central temperature could vary from 34°C to 38°C without any physiologic responses to conserve or eliminate heat. Within this range, the patient is poikilothermic (i.e., the central temperature varies directly with ambient temperature).

Heat transfer occurs by four different mechanisms: conduction, convection, evaporation, and radiation. Of these, radiation followed by convection are the most important factors in the development of perioperative hypothermia. All surfaces radiate heat, and there is a transfer of radiative heat if a temperature difference exists between two surfaces not in contact with one another. Convective heat loss is affected not only by temperature differences but also air speeds. It is purported that convective heat loss is significant in operating rooms because they are equipped with specialized ventilation systems designed to provide laminar air flow and high rates of air turnover. Evaporative heat loss occurs via sweating, via the respiratory tract, and through surgical wounds. This method of heat loss is only significant in premature infants and patients with large surgical wounds. Conduction is a method of heat transfer between two adjacent substances. Conductive heat transfer is negligible in the operating room due to the layer of thermal insulation (e.g., a foam pad) that separates the patient from the operating room table.

BOX 146.1 Accidental Causes of Hypothermia

Environmental
Wind chill
Cold water immersion

Impaired Thermoregulation
Extremes of age (neonates, elderly)
Prolonged immobilization
Drugs
- Alcohol
- Central nervous system depressants
- Drug overdose

Medical Conditions
Hypothyroidism
Large body surface area burns
Infection or sepsis
Malnutrition
Hypoglycemia
Hypothalamic stroke or tumor
Unconsciousness

BOX 146.2 Iatrogenic Causes of Hypothermia

Prolonged anesthesia and surgery
Prolonged cardiopulmonary resuscitation
Blood or blood product transfusions[a]
Large-volume fluid resuscitation[a]

[a]Without adequate warming.

General and regional anesthesia disrupts physiologic thermoregulatory responses (see Fig. 146.1). All general anesthetics slightly increase the sweating threshold while markedly decreasing the vasoconstriction and shivering thresholds; this response is even more pronounced in the elderly. The vasoconstriction threshold, which is normally 37°C, is decreased by about 2°C to 4°C. General anesthetics cause vasodilation through direct peripheral action. Nonshivering thermogenesis—an important thermoregulatory mechanism in infants—is also inhibited by volatile anesthetics. Anesthetics also reduce the metabolic rate by 20% to 30%; this serves to counteract somewhat the cutaneous heat loss caused by impaired peripheral vasoconstriction.

Core temperature typically decreases by 0.5°C to 1.0°C after initiation of regional or neuraxial anesthesia. As with general anesthesia, this initial decline in temperature is the result of heat transfer from core to periphery. Core temperature continues to decline rather than plateau, as under general anesthesia, due to impaired peripheral vasoconstriction. Regional and neuraxial anesthesia induce a sympathetic blockade that decreases the thresholds for vasoconstriction and shivering in affected dermatomes; furthermore, heat generation from muscle activity is reduced in proportion to the extent of segmental motor blockade. In addition, thermal input from affected segments is blocked, which may be interpreted as relative leg warming. This further blunts the vasoconstrictive and shivering response to cold. Paradoxically, patients may not endorse feeling cold during regional or neuraxial anesthesia. This is because the perception of cold is largely driven by peripheral skin rather than core temperature. This is one reason why it is important that patient temperature be monitored during regional and neuraxial as well as general anesthesia.

Risk Assessment and Implications

Even mild hypothermia induces platelet dysfunction, impairs the function of enzymes in the coagulation cascade, and increases the risk of intraoperative bleeding. This has been demonstrated in several randomized trials that have shown that even mild hypothermia is associated with increased surgical blood loss and allogeneic transfusion requirements. Quantitative laboratory assessment of coagulation function is misleading because blood samples are warmed to 37°C. There is now evidence that even mild intraoperative hypothermia may increase the risk of postoperative wound infection. This may be the result of vasoconstriction, which reduces tissue oxygen tension and impairs chemotaxis, both of which facilitate bacterial growth. Drug metabolism and anesthetic requirements are also markedly affected by hypothermia. Vecuronium-induced neuromuscular blockade is approximately doubled, with a 2°C decrease in core temperature. The minimum alveolar concentration (MAC) of volatile anesthetics decreases by about 5% for every 1°C drop in core temperature. During a constant infusion, plasma concentrations of propofol also increase above normal as body temperature decreases.

Emergence from anesthesia may be delayed by a number of cold-induced factors, including impairment of central nervous system function (e.g., obtundation, confusion, somnolence), slowed hepatic or renal clearance of anesthetic drugs and neuromuscular blocking agents, and impaired ventilatory response to hypoxemia and hypercarbia. As hypothermia becomes severe (<33°C), it has adverse effects on almost every organ system (Box 146.3; Fig. 146.2).

Cold-induced vasoconstriction and increased systemic vascular resistance may exacerbate postoperative hypertension (blood pressure of 160/90 mm Hg in the patient in the case synopsis is characteristic). Together with high norepinephrine concentrations, both may produce myocardial ischemia in susceptible patients. Furthermore, a prospective, randomized trial among patients with cardiac risk factors presenting for noncardiac surgery showed that the perioperative maintenance of normothermia was associated with a 55% reduction in morbid cardiac events. Moderate hypothermia is associated with an increased risk of cardiac dysrhythmias. As hypothermia becomes more severe, impulse conduction is impaired, and there is an increased risk for fatal ventricular rhythms. Postoperative shivering greatly increases oxygen demand and carbon dioxide production, leading to increased

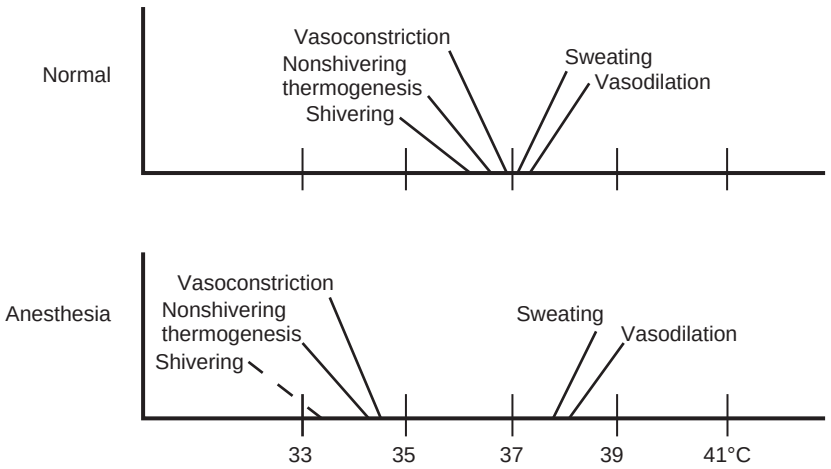

Fig. 146.1 Schematic illustration of thermoregulatory thresholds in nonanesthetized (normal) and anesthetized humans. The intersection of each regulatory response (e.g., shivering, sweating) with the temperature scale (core body temperature) is the threshold. The interthreshold range is shown as the distance between the first cold response (vasoconstriction) and the first warm response (sweating); temperatures within this range do not elicit autonomic thermoregulatory compensation. Because each thermoregulatory response has its own threshold and gain, there is an orderly progression of responses, and response intensities, in proportion to need. During general anesthesia (bottom), the thresholds for vasoconstriction and nonshivering thermogenesis are shifted down to about 34.5°C (depending on anesthetic type and dose). Similarly, thresholds for active precapillary vasodilation and sweating are increased about 1°C. Interthreshold range thus increases from 0.2°C to about 4°C. (From Sessler DI: Temperature monitoring. In Miller RD, editor: *Anesthesia,* 4th ed. New York, Churchill Livingstone, 1994, pp 1363-1382.)

minute ventilation, work of breathing, and oxygen consumption. If minute ventilation is fixed (mechanical ventilation) or suppressed (by anesthetic agents or opioids), hypercarbia and acute respiratory acidosis may result. When oxygen consumption is increased but cardiac output cannot compensate, oxygen extraction increases, setting the stage for hypoxemia and its sequelae. Shivering can also cause patient discomfort and other adverse sequelae, such as wound disruption and increased bleeding or intracranial and intraocular pressures. Overall, hypothermia and thermal discomfort contribute to longer stays in the postanesthesia care unit compared with normothermic patients.

Nevertheless, hypothermia may benefit some patients by providing organ protection against ischemia. Oxygen utilization is halved for each 10°C decrease in normal body temperature. Mild hypothermia (33°C to 36°C) provides important central nervous system protection. There is increasing evidence that it may play a protective role after cardiac arrest due to ventricular fibrillation. Induced hypothermia has been proposed as a method of brain protection in the management of traumatic brain injury (TBI) based on its potential to reduce cerebral metabolic rate and lower intracranial pressure. Clinical trials on the use of mild to moderate (33°C to 35°C) hypothermia after TBI have demonstrated mixed results. Hypothermia may also be beneficial in the management of neonatal asphyxia, where improved neurologic outcomes and reduced mortality rates have been demonstrated among neonates treated with therapeutic hypothermia. Finally, malignant hyperthermia is harder to induce in animals who are mildly hypothermic; therefore it is recommended that active warming be avoided in patients at risk of malignant hyperthermia.

BOX 146.3 Adverse Effects of Hypothermia on Organ System Function

Cardiovascular
Early: tachycardia, hypertension, increased cardiac output, vasoconstriction (catecholamine release)
Late: bradycardia, decreased cardiac output, hypotension
ECG: Generalized slow conduction, sinus bradycardia, T-wave inversion, QT prolongation, ventricular ectopy (32°C, Osborne waves; 30°C, ventricular fibrillation; see Fig. 146.2)

Respiratory
Early: increased respiratory rate
Late: reduced respiratory rate and tidal volume, diminished hypoxic pulmonary vasoconstriction and responsiveness to hypoxemia and hypercarbia, diminished mucociliary activity

Renal
Early: initial "cold" diuresis (increased central blood volume with increased renovascular resistance); diuresis continues due to impaired renal tubular sodium reabsorption
Late: oliguria and azotemia

Hematologic
Early: hemoconcentration, increased viscosity (sludging, poor tissue perfusion, ischemia), decreased oxygen availability (left shift of oxyhemoglobin dissociation curve)
Late: disseminated intravascular coagulation, thrombocytopenia

Metabolic
Early: hyponatremia, hyperkalemia, hyperglycemia (inhibition of insulin release and block of its cellular uptake)
Late: metabolic acidosis

Neurologic
Cerebral blood flow decreases 6% to 7% per 1°C decrease in temperature:
34°C: amnesia
30°C: obtundation
26°C: loss of pupillary and deep tendon reflexes
18°C: loss of brain activity (isoelectric electroencephalogram)

Gastrointestinal
Early: decreased intestinal motility (full stomach), diminished hepatic clearance
Late: ulceration of stomach, ileum, and colon; hemorrhagic pancreatitis

ECG, Electrocardiogram.

MANAGEMENT AND PREVENTION

Preoperative warming may help prevent redistribution hypothermia by minimizing the difference between the patient's peripheral and core body temperatures. This is usually achieved by applying a forced-air blanket in the preoperative holding area or preinduction room. Operating room temperature is the most important factor in determining the rate of heat loss by radiation and convection from the skin. Before anesthetic induction, the ambient temperature in the operating room should be increased to 23°C to 26°C to maintain normothermia. Once the patient is fully draped and protected, the temperature can be decreased so that it does not impair the performance of the surgeon or assistants. Ambient room temperature should be increased again at the end of the operation. A preoperative amino acid infusion augments thermogenesis and has also been used to reduce the occurrence of intraoperative hypothermia.

Temperature monitoring is mandatory for all procedures lasting 30 minutes or longer. However, "normal" temperature (like blood pressure) depends on where it is measured. Monitors for core body temperature include the tympanic membrane (susceptible to injury), nasopharynx (influenced by anesthetic gas temperature), esophagus (dependent on depth of insertion; note that if the thermistor is behind the trachea, core temperature will be less than 0.2°C below its true value), and pulmonary artery (if a thermistor-equipped pulmonary artery catheter is used). The rectum and bladder may reflect central core body temperature if the patient is warm and vasodilated,

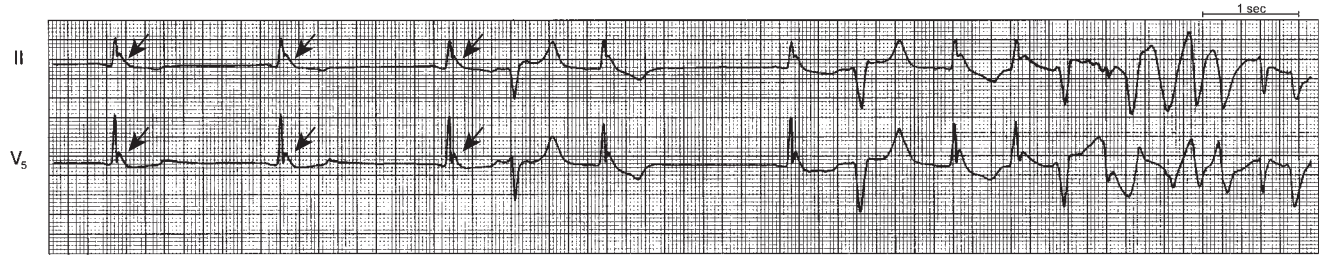

Fig. 146.2 Two electrocardiographic leads obtained during cooling with cardiopulmonary bypass. Sinus bradycardia (about 30 beats per minute) and prominent J (Osborne) waves *(arrows)* distinguish the first three complexes. Ventricular ectopy increases in frequency and progresses to fibrillation as the patient rapidly becomes hypothermic. Bladder and nasopharyngeal temperatures were 35.8°C and 31.4°C, respectively. (From Mark JB: *Atlas of cardiovascular monitoring.* New York, Churchill Livingstone, 1997, p 331.)

or peripheral body temperature if the patient is cold and vasoconstricted. Forehead skin temperature is approximately 2°C lower than core temperature but varies sufficiently to be a poor indicator of core temperature.

Roughly 90% of heat loss is through the skin surface; therefore the most effective heating methods are those that modulate cutaneous heat loss. Forced air warming is the most cost-effective method of maintaining normothermia in the perioperative period, typically increasing mean body temperature by 1°C per hour. Full-body or half-body blankets are available. One caveat is that it should not be used over the lower body during aortic cross-clamping because this will exacerbate the tissue oxygen demand-supply imbalance. Circulating water mattresses positioned underneath a patient cover relatively little surface area and do little to compensate for large anterior heat loss. In addition, they may cause pressure-induced thermal injury. Passive insulation (blankets, drapes) and electric heating pads are also not nearly as effective. Passive insulation works mainly by trapping a layer of air between the patient and the insulator. A single blanket provides an approximately 30% reduction in heat loss. Adding additional layers provides only modest benefit. Although an overhead radiant heater is frequently used for infants and small children, the patient's skin must be left exposed for heat transfer to occur. Heat transfer is blocked by interposed surgical or nursing personnel. Also, overhead heaters restrict access to the patient.

Routine use of heated and humidified anesthesia circuits is not warranted in adult patients except to reduce further heat loss in an already hypothermic patient or for extended, major surgical procedures. Such circuits do little to increase core temperature. After the induction of anesthesia, reduction of the total fresh gas flow to less than 2 L/min will help reduce heat and moisture loss from the airway, as will an "artificial nose" (i.e., a heat- and moisture-exchanging filter or hygroscopic condenser humidifier).

Whenever large volumes of crystalloid, colloid, or blood products are infused, a fluid warming device should be used. A unit of refrigerated blood at 4°C or 1 L of room-temperature crystalloid decreases mean body temperature in an adult by about 0.25°C. During massive blood transfusion, the use of a rapid infusion device (which can deliver up to 1 L/min) is essential to prevent potentially life-threatening hypothermia and irreversible hypothermic coagulopathy. However, it should be recognized that fluid warming does not actively warm patients; it only prevents fluid-induced cooling. In severe cases of hypothermia associated with acidosis and life-threatening coagulopathy, which usually occur in the context of trauma, active extracorporeal blood rewarming may be considered. This may be accomplished by cardiopulmonary bypass, arteriovenous rewarming, venovenous rewarming, or hemodialysis. These techniques increase core temperature by 1°C to 2°C every 3 to 5 minutes.

The most effective means of preventing postoperative shivering is to warm the skin (e.g., with a forced-air warming blanket). Impulses from skin thermoreceptors govern the hypothalamic response to cold; the warmer the skin, the lower the central temperature threshold for the onset of shivering. Premedication with α_2-adrenergic receptor agonists (clonidine, dexmedetomidine) may also suppress postoperative shivering. Postoperative shivering can be treated with cutaneous warming. It can also be treated with a variety of drugs. These include meperidine (12.5 to 25 mg), clonidine (75 μg), and tramadol (0.5 to 3.0 mg/kg).

Rewarming vasodilation begins variably after the patient's arrival in the postanesthesia care unit and depends on hypothermia severity. Increased muscle tone (i.e., subclinical shivering) initially generates heat during persistent peripheral vasoconstriction. As a result, core temperature climbs and may even "overshoot" to 38°C to 40°C, especially after hypothermic cardiopulmonary bypass. When peripheral vasodilation finally occurs, heat generation is balanced by heat loss, so that the central temperature reaches a plateau before returning to normal. If patients are hypovolemic, rewarming vasodilation can produce acute hypotension, reflex tachycardia, and myocardial ischemia. Thus in the early postoperative period, patients who are hypothermic, vasoconstricted, and hypertensive may benefit from vigorous fluid replacement, along with judicious use of vasodilator therapy (e.g., nitroprusside, nitroglycerin). Once rewarming vasodilation occurs, fluid replacement is essential, together with a vasopressor if needed.

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Inadequate Pain Relief

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Charles J. Lin • Michael L. Kentor • Brian A. Williams

Case Synopsis

A 30-year-old man, otherwise healthy, undergoes an ankle fusion as an outpatient procedure. The surgically uncomplicated procedure is performed under general anesthesia with endotracheal intubation. After emergence, the patient experiences severe, intractable pain, with subsequent postoperative nausea and vomiting (PONV) after opioids are used in the postanesthesia care unit (PACU). The patient eventually requires unplanned hospital admission for intractable pain, PONV, and somnolence. The patient is discharged 2 days later when he finally tolerates oral intake. The patient is readmitted to the emergency department 5 days later with constipation, episodic nausea, and wound dehiscence that cultures positively for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis.* One year later, he visits a chronic pain physician for persistent postoperative pain.

PROBLEM ANALYSIS

Definition

A national survey demonstrates that 80% of postoperative patients experience pain from discharge to 2 weeks postoperatively, and 86% of those patients experience uncontrolled pain. Inadequate postoperative analgesia has significant physiologic and emotional effects for the patient and increases the health care cost burden for the system at large. There are both short-term and long-term consequences (Table 147.1). Sympathetic activation in response to poor pain control increases cardiac demand and workload, which can heighten the risk of a postoperative cardiac event. Splinting and worsening ventilation/perfusion mismatch increase the risk for hypoxemia and respiratory distress. Excessive opiate use contributes to PONV and postoperative confusion. The net consequence of these risks is prolonged PACU stay, delayed discharge, lower patient satisfaction, and higher hospital admission rates.

Persistent postoperative pain, otherwise known as chronic postsurgical pain syndrome (CPSP), is an important consequence of inadequate postoperative pain relief. It is defined as pain that lasts for at least 2 months after a surgical procedure and after other pain diagnoses have been excluded. The procedures most likely to produce CPSP include limb amputation, thoracotomy, breast surgery, cholecystectomy, and inguinal hernia repair. The economic costs of both absenteeism and work performance decline are significant. A cross-sectional study of patients returning to work after a common chronic pain condition demonstrated a cost of $61.2 billion per year, mostly attributable to reduced performance.

TABLE 147.1 Systemic Effects of Inadequate Pain Relief

Neurologic	Persistent postsurgical pain
	Postoperative delirium and cognitive dysfunction
Psychological	Anxiety and depression
	Decreased patient satisfaction
Cardiovascular	Tachycardia
	Increased systemic vascular resistance causing hypertension
	Increased myocardial contractility
	Increased cardiac work
Pulmonary	Splinting and diaphragmatic impairment causing hypoventilation and diminished vital capacity
	Atelectasis and worsened ventilation/perfusion mismatch
	Poor cough and sputum clearance
	Hypoxemia
	Hypercarbia
Renal	Urinary retention from increased sympathetic tone
Gastrointestinal	Ileus from increased sympathetic tone
	Postoperative nausea and vomiting
Immunologic	Impaired immune system and immunosuppression
Global	Prolonged postanesthesia care unit stay
	Delayed recovery
	Decreased patient satisfaction
	Higher health care resource utilization and costs

Adapted from Joshi GP, Ogunnaike BO: Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin North Am* 23(1):21–36, 2005.

Risk Assessment

Formulating an adequate analgesic plan for each patient involves understanding the patient's risk for developing significant postoperative pain, for developing side effects from opiates, and assessing the risk of performing a peripheral nerve block (PNB). In addition to the procedures previously listed that are most inclined to cause CPSP, certain patient populations have a higher risk of complications related to opiates. For these groups, the best plan to optimize analgesia involves a multimodal regimen with narcotic-sparing techniques. These patient populations include the elderly, patients diagnosed with obstructive sleep apnea, and patients with preexisting pulmonary dysfunction.

The risks of the PNB need to be considered to appropriately select patients for this regimen. Absolute contraindications for PNB are as follows:

- Patient refusal. Of note, patient refusal should only occur after appropriate patient education by the anesthesiologist, which may take up to 10 to 15 minutes with some patients. It is common for some patients who initially refuse PNB to ultimately accept the block and appreciate its benefits compared with their prior general anesthesia experiences.
- Coagulopathy. Systemic anticoagulants such as warfarin should be converted to intravenous heparin injection preoperatively if PNB is indicated.

- Infection at the site of the needle placement.
- Systemic bacteremia or sepsis.

Practically speaking, all of these conditions are highly unlikely in outpatients presenting for same-day orthopedic surgery. Preexisting neurologic problems may sometimes be relative contraindications for PNB; careful documentation of the neurologic condition is mandatory when PNBs are performed in such a situation.

MANAGEMENT

Peripheral Nerve Block

The use of PNBs for anesthesia confers significant benefits including earlier discharge, fewer nursing interventions for pain or PONV, and fewer unplanned hospital admissions compared with general endotracheal anesthesia in patients undergoing ambulatory orthopedic surgery (Box 147.1). Williams and colleagues report in their review of 1200 consecutive cases for outpatient knee surgery that general anesthesia with a volatile agent is consistently associated with a twofold increase of the nursing intervention for pain in the same-day recovery unit and a threefold increase in unplanned hospital admissions, compared with the PNB technique using femoral and sciatic nerve blocks. Williams and colleagues also report the development of a Multimodal Perineural Anesthesia/Analgesia (MMPNA) program for orthopedic surgery, highlighted by the use of a combination of clonidine, buprenorphine, and dexamethasone with the local anesthetic bupivacaine in the nerve blocks. This combination provides a median block duration of greater than 30 hours for significant postoperative analgesia. This evidence is supported by a Cochrane review that concludes the use of adjuvant peripheral nerve blocks reduces pain in comparison to systemic analgesia for major knee surgery. Furthermore, continuous PNB techniques using indwelling catheters and portable infusion pumps offer excellent postoperative pain control for ambulatory surgery. In a prospective study of patients scheduled for outpatient arthroscopic rotator cuff repair, the group that receives an interscalene nerve block (continuous or single shot) is more likely to be fast-tracked and have a significantly shorter PACU stay compared with the group that does not receive a nerve block. Furthermore, the group that receives a continuous interscalene nerve block demonstrates the lowest pain scores and the longest sleep pattern postoperatively. Another study that retrospectively examined more than 20,000 patients undergoing rotator cuff repair demonstrates an 18% reduced risk for hospital admission in the group that receives a PNB with general anesthesia compared with general anesthesia without a nerve block. The study also notes that the hospital costs associated with admission were close to double.

BOX 147.1 Benefits of Regional Anesthesia Over General Anesthesia in Ambulatory Orthopedic Surgery

- Better analgesia over opiates
- Lower PACU pain scores
- Less postoperative nausea and vomiting
- Lower PACU analgesic consumption
- Faster PACU Phase 1 discharge
- Higher fast-track PACU Phase 1 bypass rate
- Shorter time to discharge home
- Increased operating room efficiency
- Higher patient satisfaction

PACU, Postanesthesia care unit.

There are two methods of PNB: (1) single-injection PNB techniques and (2) continuous PNB with an indwelling catheter. Although single-injection techniques have been shown to be effective, they can only offer postoperative analgesia ranging from a few hours up to 24 hours, depending on the local anesthetic and adjuncts used. As a result, the duration of these blocks may be too brief to provide sustained postoperative analgesia or effective analgesia to initiate active physical therapy. Early physical therapy is essential to optimize functional recovery after orthopedic surgery. Continuous PNB with an indwelling perineural catheter have the following advantages over single-injection and/or neuraxial techniques:

- Longer duration of postoperative analgesia
- Titratable dosing
- Preferential sensory block, when active physical therapy is required
- Avoidance of the neuraxis and its associated complications (especially in the context of systemic anticoagulation)

Other factors that need to be taken into consideration include the technique (ultrasound guidance, nerve stimulation) used to perform the PNB, the nerve to be blocked, and the site of the nerve block. The use of ultrasound-guided PNB is becoming widespread both because of the availability of the technology and the ease of learning this skill for basic blocks. The decision of which nerve to be blocked depends on the dermatome, myotome, and osteotome of the involved extremity. The location of the nerve block needs to account for tourniquet placement and surgical prep location. In this example, an ultrasound-guided sciatic nerve block with a catheter placement is appropriate (Fig. 147.1). The patient can then be discharged home with the

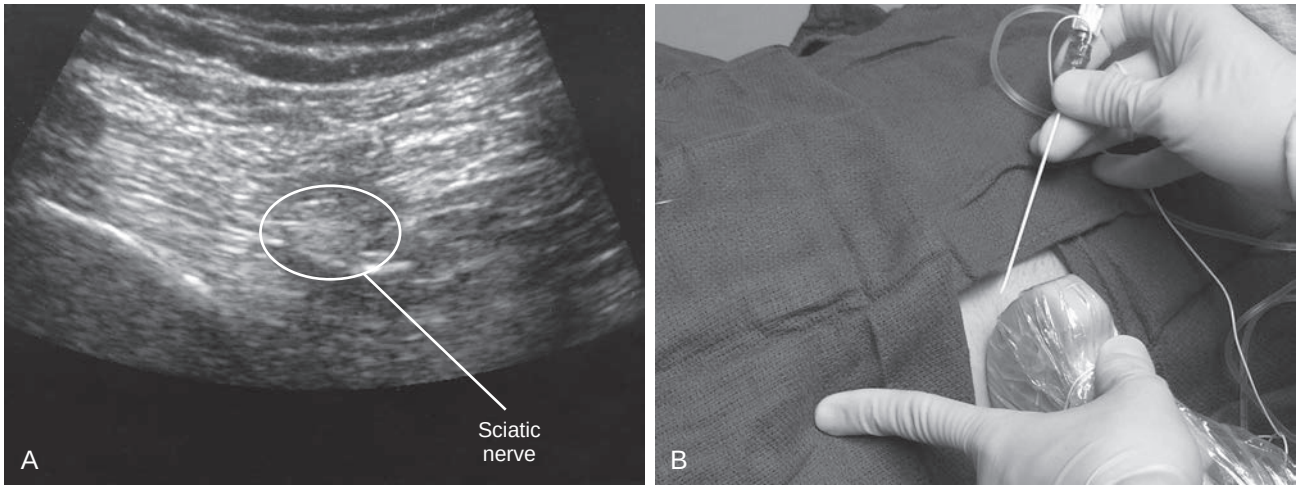

Fig. 147.1 Peripheral nerve block of sciatic nerve. A, Ultrasound image of the sciatic nerve during a peripheral nerve block. **B,** Image of the needle and ultrasound transducer during a peripheral nerve block.

indwelling PNB catheter and a portable infusion pump. Written instructions about catheter management are given and explained to the patient and a family member at the time of discharge, and the anesthesia care team makes daily phone calls with patients while the catheter is in situ. The anesthesia care team is immediately available by pager for questions. The nerve block catheter usually remains in place for 2 to 3 days, and it is removed by the patient or a family member.

PNB techniques can be safely used in patients who require postoperative anticoagulation for the prevention of deep venous thrombosis. Nevertheless, careful consideration is warranted when a patient is discharged to home with an indwelling PNB catheter and postoperative anticoagulation is a possibility. This situation may arise if the patient was on anticoagulation prior to surgery for indications such as atrial fibrillation, prosthetic heart valves, or coronary stents.

When intraoperative sedation or total intravenous anesthesia care is indicated, the use of propofol as a continuous infusion is beneficial for ambulatory surgery patients to minimize the risk of PONV. Often the use of PNB techniques can facilitate the use of intraoperative sedation in lieu of general anesthesia.

Multimodal Analgesia Regimen

The use of multimodal analgesia, which treats pain at different sites via different mechanisms, can reduce opiate consumption. These analgesics include nonsteroidal antiinflammatory drugs (NSAIDs, especially cyclooxygenase inhibitors specific to the type-II isoenzyme); *N*-methyl-D-aspartate (NMDA) antagonists such as ketamine; calcium channel antagonists such as gabapentin; and acetaminophen. The combination of these medications can provide synergistic analgesia and minimize the side effects of each.

PREVENTION

Peripheral Nerve Block as the Initial Choice

It is important to avoid *underutilization* of PNB techniques in outpatient orthopedic surgery populations, assuming the availability of anesthesiologists who are skilled with these techniques. Anesthesiologists should be proactive and educate patients and surgeons to welcome PNB techniques as "Plan A." Using PNB, either as the main anesthetic or as an adjunct to total intravenous anesthesia with propofol if indicated, facilitates rapid emergence and perioperative analgesia.

Preventive Measures for Postoperative Nausea and Vomiting

Developing a preoperative strategy that includes multiple agents such as a serotonin receptor blocker (e.g., ondansetron), an antidopaminergic agent (e.g., oral perphenazine 8 mg before and after surgery), and a corticosteroid (e.g., dexamethasone 5 mg intravenously) is important. Using a propofol infusion in conjunction with PNB is also beneficial. Minimizing the use of opioids, induction agents other than propofol (e.g., etomidate), volatile agents, and intravenous or perineural neostigmine during PNB are also helpful in decreasing the risk for PONV.

Constipation

This side effect can be a potential problem with the use of high-dose parenteral and oral opioids. Using the narcotic-sparing techniques listed previously can help in preventing this complication.

Nosocomial Wound Infection

Surgical site infections prolong hospital length of stay and are a source of increased health care costs. To prevent nosocomial wound infections associated with hospital admission, it is important to successfully discharge patients home the same day. This requires an organized, comprehensive symptom management plan as part of the total anesthesia and analgesia care plan.

Persistent Postoperative Pain

Early and effective analgesia is important for reducing the risk of persistent postoperative pain. A multimodal analgesic plan that involves NSAIDs, acetaminophen, PNBs, NMDA antagonists, and minimal opiates can help in avoiding this potentially debilitating complication.

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Infectious Complications of Central Neuraxial Block

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Stephanie Huang • Lu Fan Cai

Case Synopsis

A 58-year-old man with a history of insulin-dependent diabetes mellitus, rheumatoid arthritis, and bladder cancer status postneoadjuvant chemotherapy underwent a radical cystectomy and diversion. A lumbar epidural catheter was placed for perioperative analgesia, and the patient received an epidural infusion of ropivacaine and fentanyl for 3 days postoperatively. At the time of epidural catheter removal, the insertion site was surrounded by a small area of erythema, with a scant amount of serosanguineous drainage. The patient was followed by Acute Pain Service for an additional 2 days, at which time he reported progressively worsening thoracolumbar back pain, low-grade fever, and subjective lower extremity weakness. Examination of his back on postoperative day 5 revealed a dime-sized erythematous area at the previous epidural catheter insertion site with a small amount of purulent drainage when expressed. His neurologic examination was unremarkable. Laboratory studies demonstrated leukocytosis. A magnetic resonance imaging (MRI) scan with and without gadolinium contrast was obtained of the thoracic, lumbar, and sacral spine. MRI demonstrated an extensive posterior spinal epidural abscess from T12 to L4. The patient underwent an open laminotomy for drainage of the abscess and culture-directed antibiotic therapy for *Staphylococcus aureus*. The remainder of his hospital recovery was uneventful, and he was discharged home on postoperative day 8 without neurologic sequelae.

PROBLEM ANALYSIS

Definition

Infectious complications as a result of central neuraxial anesthetic and analgesic procedures are rare. However, when they do occur, they can result in significant patient morbidity, including epidural or paravertebral abscess formation and meningitis, leading to sepsis and paraplegia. A high index of suspicion, early diagnosis, and prompt therapeutic intervention are critical for achieving optimal outcomes.

There are a variety of infectious complications from central neuraxial block techniques ranging from superficial cellulitis at the subcutaneous puncture site to deep tissue infections, such as epidural abscess or meningitis. Most of these infectious complications are associated with percutaneous catheter techniques, but there are reports of epidural abscess and meningitis after single-injection neuraxial anesthesia or corticosteroid injections. Potential mechanisms for infection associated with central neuraxial block include (1) direct inoculation during needle or catheter placement; (2) infection at the catheter skin site, with spread along the catheter tract; (3) contamination of the injectate; and (4) hematogenous spread ("bacteremic seeding") from a distant source of infection.

Progressive neurologic impairment of bowel and bladder function or lower extremity sensory and motor deficits may result from epidural or paravertebral abscess with spinal cord or nerve root compression. The specific pathogenesis underlying spinal cord dysfunction with spinal epidural abscess is thought to be related to direct mechanical compression or vascular damage, with resultant spinal cord ischemia.

Recognition

Superficial infections usually present with localized erythema and drainage at the needle or catheter insertion site. Deep tissue infections may present with local symptoms concurrently with the following:

- Back pain
- Fever
- Localized tenderness to palpation
- Leukocytosis

Neurologic impairment due to deep tissue abscess and spinal cord or nerve root compression may present with the following:

- Radicular irritation
- Progressive sensory or motor deficits
- Bowel and bladder incontinence

The clinical features of meningitis include the following:

- Nuchal rigidity
- Headache
- Leukocytosis and pyrexia
- Photophobia

Patients with evidence of superficial infection should be evaluated and monitored for the development of symptoms associated with deep tissue infection. Culture of purulent drainage at the site of infection may be useful to direct appropriate antibiotic therapy. Before hospital discharge, patients must be instructed to notify appropriate health care personnel or to seek emergency medical evaluation in the event of any of the following:

- New onset of back pain
- Persistent fever
- Redness or soreness at the needle or catheter insertion site
- Any signs or symptoms of neurologic impairment

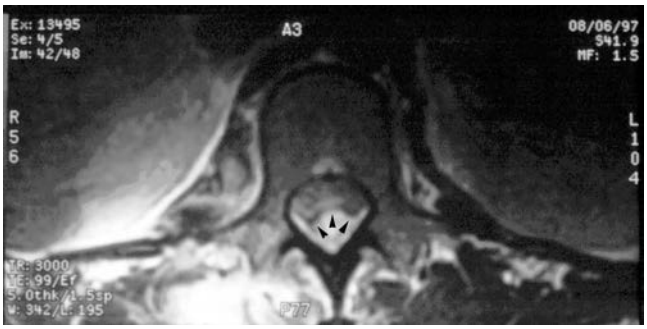

Fig. 148.1 Axial T2-weighted magnetic resonance image of the spine at the level of L1. There is a large, high-signal fluid collection in the posterior epidural space. The abscess is causing anterior displacement of the dural sac *(arrowheads),* producing approximately 30% reduction in the anteroposterior diameter of the spinal canal. (From Rathmell JP, Garahan MB, Alsofrom GF: Epidural abscess following epidural analgesia. *Reg Anesth Pain Med* 25[1]:79–82, 2000.)

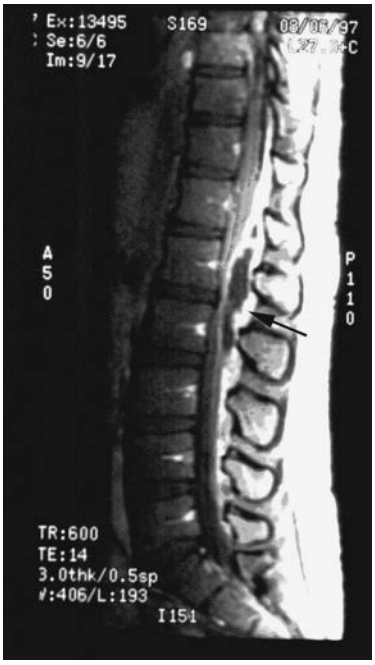

Fig. 148.2 Sagittal T1-weighted magnetic resonance image of the spine after intravenous administration of gadolinium. There is a large gadolinium-enhanced mass *(arrow)* in the posterior epidural space extending from T9 to L3. The area of low signal density within the abscess represents a poorly perfused area of liquefaction. (From Rathmell JP, Garahan MB, Alsofrom GF: Epidural abscess following epidural analgesia. *Reg Anesth Pain Med* 25[1]:79–82, 2000.)

Patients with signs or symptoms suggestive of spinal or epidural abscess should be urgently evaluated for any neurologic deficits both via a thorough neurologic examination and appropriate imaging studies. Radiographic diagnosis of spinal epidural abscess is best made by a gadolinium-enhanced MRI scan of the spine (Figs. 148.1 and 148.2). Diagnosis and treatment of epidural abscess should not be delayed until neurologic deficits become apparent.

Risk Assessment

In 2016 a nationwide database study of over 3.7 million epidural analgesia procedures performed in the United States from 1998 to 2010 found the incidence of epidural abscess in nonobstetric patients to be 7.2 per 100,000 catheterizations.

Similarly, a prospective audit on complications of central neuraxial block by the Third National Audit Project of the Royal College of Anaesthetists concluded an incidence of epidural abscess of 5.24 per 100,000 in nonobstetric epidural placements.

Furthermore, a retrospective study of 10,653 epidural catheters placed in the pediatric population from 1993 to 2010 identified 13 cases of infection—9 cellulitis, 2 paravertebral musculature infections, 1 epidural inflammation, and 1 epidural abscess.

Other recently published studies, including retrospective analyses and prospective clinical reviews, have reported epidural abscess rates in the range of 5 to 74 per 100,000. Although the specific incidence is yet to be elucidated, the presence of any of the following factors suggests a higher risk for infection after central neuraxial block:

- Immunocompromised state (e.g., acquired immunodeficiency syndrome [AIDS], cancer, chemotherapy, organ transplantation, chronic dialysis, intravenous drug abuse, malnutrition, chronic alcohol abuse)
- Diabetes mellitus
- Systemic steroid treatment
- Localized infection at insertion site
- Systemic infection, bacteremia, or sepsis
- Long-term catheter use

Implications

Both meningitis and epidural abscess can be life threatening or result in permanent neurologic sequelae if not treated in a timely fashion. Again, a high index of clinical suspicion, early diagnosis, and prompt medical or surgical treatment before the occurrence of irreversible neurologic deficits are key to optimizing patient outcomes.

MANAGEMENT

Patients with superficial infectious complications such as cellulitis can be managed by local drainage and antibiotic therapy. Patients with preexisting risk factors for infection should be carefully monitored for the development of any signs or symptoms of epidural abscess or meningitis. If discharged from an in-hospital setting, patients should be advised to seek immediate medical attention for new back pain or radicular pain, pyrexia, headache, photophobia, nucal rigidity, or other previously nonexistent neurologic deficits. This will facilitate timely detection, diagnosis, and therapy. Patients with a history of central neuraxial block who present with back pain and fever should undergo a thorough evaluation for serious infectious complications as part of the differential diagnosis. Epidural abscess after central neuraxial block has been diagnosed days, weeks, and even months after the intervention.

Although more conservative treatment approaches have been reported, early surgical decompression and drainage with concurrent antibiotic therapy for epidural abscess is still the definitive treatment. Epidural abscess with neurologic signs or symptoms requires urgent surgical intervention to prevent progressive and possibly permanent neurologic injury.

Intravenous antibiotic therapy should be initiated promptly. The initial agent used should be effective against *Staphylococcus* species, including methicillin-resistant *Staphylococcus aureus* (MRSA). Ultimately, antibiotic therapy should be directed by specific culture and sensitivity determinations, as well as by clinical or institutional considerations. Depending on the nature and severity of the infection, antibiotic therapy may be required for 4 to 6 weeks or longer.

PREVENTION

As with any invasive procedure, the risks associated with a planned central neuraxial block must be weighed against its potential benefits. Although infectious complications are rare, patients who might benefit most from such blocks are often those with associated comorbidities that increase the risk for serious infectious complications. A higher index of suspicion is required when evaluating these patients for potential infectious complications. The risk of complications, and the subsequent need for vigilance, also increases when indwelling catheters for postoperative or posttraumatic injury analgesia are used for an extended period of time.

Meticulous attention to sterile technique is vital for reducing infectious complications associated with central neuraxial blocks or catheters. Thorough hand washing, sterile gloves, surgical caps or hoods and masks, and sterile block techniques are all important considerations. A wide area of skin should be prepared with povidone-iodine, iodophor–in–isopropyl alcohol, or chlorhexidine. Adequate time must be given for the solution to dry before the central neuraxial block is performed. Also, use of a "no-touch" technique (i.e., landmarks identified and marked, if necessary, before skin preparation) helps reduce the risk of central neuraxial infectious complications. Compared with povidone-iodine, chlorhexidine and iodophor–in–isopropyl alcohol have been reported to provide superior antimicrobial skin disinfection and prevention of bacterial regrowth. Use of clear plastic surgical drapes offers the advantage of being able to visualize landmarks during the block procedure. Furthermore, covering epidural catheters with clear sterile dressings allows daily assessment of the insertion site without potential introduction of microbial contamination.

Sterile technique should be maintained for dosing catheters and when changing infusion connections for continuous epidural infusions. Maintaining a tightly closed infusion system throughout therapy should help reduce catheter contamination during line or infusate changes. Infusion solutions should be prepared by pharmacy personnel with sterile technique and under a laminar flow hood.

Central neuraxial block in patients with bacteremia remains controversial. If such blocks are deemed necessary or appropriate in patients with bacteremia, one should consider performing the block only after appropriate antibiotic coverage has been provided. For patients with indwelling epidural catheters who become bacteremic, one can consider removing the catheter, providing indicated antibiotic therapy, and then replacing the catheter at a different level if continuous epidural therapy is still desired. Routine culture of epidural catheter tips has low predictive value in identifying infection and contamination and is not advised. However, if the epidural catheter insertion site is surrounded by an area of localized inflammation or drainage, bacteriologic examination of the epidural catheter tip may suggest appropriate antibiotic therapy.

Although preventive measures are important, they cannot entirely eliminate the risk of infectious complications of central neuraxial block. A high index of suspicion for the development of infectious complications, prompt diagnosis, and immediate therapy are paramount for reducing patient morbidity and permanent neurologic injury.

ACKNOWLEDGMENT

The authors would like to thank Dr. James C. Crews for his contribution to the previous edition of this chapter.

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149 Interscalene Nerve Block: Potential Severe Complications

Alain Borgeat • Gina Votta-Velis

Case Synopsis

A 25-year-old man presents for rotator cuff repair and has an interscalene block and catheter placed. The block is performed using Winnie's landmarks and with the aid of a nerve stimulator. A triceps response is obtained at a depth of 2.5 cm. The catheter is threaded 6 cm past the tip of the stimulating needle. The procedure is uneventful, except for transient resistance encountered during catheter placement. After negative aspiration for blood and cerebrospinal fluid, 0.5% bupivacaine is slowly injected through the catheter. After 10 mL is injected, the patient becomes drowsy, then unresponsive and apneic, with loss of muscle tone in all extremities; his pupils are widely dilated. The patient is given oxygen with manual assisted ventilation, followed by tracheal intubation.

PROBLEM ANALYSIS

Definition

Total spinal anesthesia is one of the most severe complications that can occur during the performance of an interscalene block. Other severe complications include unintended intravascular (intraarterial/intravenous) injection of local anesthetic, high epidural anesthesia, subdural injection, pneumothorax, and neuropathy.

Recognition

The signs and symptoms of total spinal anesthesia result from blockade of the cervicothoracic segments of the central neuraxis. Symptoms of central nervous system involvement are virtually always present and range from the inability to phonate to unconsciousness and the rapid development of bilateral flaccid paralysis. Bilateral dilated, nonreactive pupils are frequently observed, consistent with a block of parasympathetic efferent activity from the Edinger-Westphal nucleus. The latter sign demonstrates that some amount of local anesthetic entered the cranium. Apnea is usually (but not always) present, due to the close proximity of the phrenic nerve roots (C3–C5) to the site of interscalene injection (C6–C7). The development of bradycardia and hypotension is explained by either cervicothoracic spinal block of the cardiac accelerator fiber (T1–T4) or penetration of local anesthetic into the medullary region of the central nervous system. The application of local anesthetic in this structure results in hypotension, bradycardia, and ventricular arrhythmias (Table 149.1).

The differential diagnosis includes injection of local anesthetic into the vertebral artery. When this occurs, seizures and unconsciousness are almost immediate. Hypotension and bradycardia may also be due to the cardiotoxic effects of local anesthetics. After epidural injection, such signs and space does not extend intracranially. Therefore signs and symptoms related to intracranial spread of local anesthetic are unlikely. Subdural injection is also part of the differential diagnosis. In this case the development of clinical block is even slower and usually asymmetric and incomplete. Intravascular injection or rapid reabsorption of the local symptoms develop more

TABLE 149.1 Signs of Inadvertent Injections of Local Anesthetics Following Interscalene Block

Intraarterial	Intravenous	Subarachnoid	Subdural
Central nervous system toxicity → **immediate** • Seizures • Unconsciousness	Systemic toxicity → **delayed** (5–15 min)	B/L anesthesia → **rapid** unconsciousness • Apnea • Dilated pupils • Flaccid paralysis	Comparable to subarachnoid → **delayed** • Apnea • Anesth asymmetric • Pupils asymmetric
Hemodynamic instability • Hypotension • Bradycardia	Hemodynamic instability • Hypotension • Bradycardia	Hemodynamic instability • Hypotension • Bradycardia • Ventricular arrhythmia	Hemodynamic instability • Hypotension • Bradycardia • Ventricular arrhythmia

B/L, Bilateral.

slowly. Moreover, the epidural anesthetic should always be considered with both central nervous system toxicity and hemodynamic instability. However, the presence of bilateral flaccid paralysis makes this diagnosis very unlikely.

Different mechanisms may be implicated in the occurrence of total spinal anesthesia after interscalene block (Box 149.1). Direct injection into the subdural or epidural space may be the consequence of incorrect needle placement through an intervertebral foramen. A perineural or intraneural injection may lead to secondary migration of the drug into the subdural space. Finally, long dural sleeves have been shown in autopsy studies, extending as far as 3 to 5 cm beyond the intervertebral foramen. Placement of a needle into an abnormally long dural root sleeve may explain the spread of local anesthetic into the intrathecal space.

Risk Assessment

Total spinal anesthesia after interscalene block, either with or without a perineural catheter, is a rare but serious complication. Such events are often documented as case reports. Thus there is no way to estimate the specific risk for this complication. The only identifiable factor that increases risk is the approach used to perform the block. Techniques used are the Winnie approach, the posterior approach, the modified lateral approach, and ultrasound-guided approaches. The relative advantages and disadvantages of each technique are given in Table 149.2.

Implications

Total spinal anesthesia is a rare complication after interscalene block. However, due to the proposed mechanisms mentioned in Table 149.1, it may occur even with appropriate needle placement, as in the case of long dural sleeves. Most important, its diagnosis should be prompt. The differential diagnoses of vertebral artery or intravenous injection should be rapidly ruled out so that the appropriate remedial measures can be instituted. Spontaneous breathing often eases promptly, so assisted manual or mechanical ventilation will be necessary. Bradycardia and hypotension may occur as a result of vasodilation and block of the cardiac acceleration fibers, which may lead to cardiac arrest if not treated urgently.

BOX 149.1 Proposed Mechanisms of Intrathecal Migration of Local Anesthetics

Injection through intervertebral foramen
Direct intraneural injection
Injection into dural root sleeve

TABLE 149.2 Interscalene Block Techniques: Relative Advantages and Disadvantages

Advantages/ Disadvantages	Winnie	Posterior	Modified Lateral	US
Spinal injection	++	++	–	–
Epidural injection	++	++	–	–
Vertebral artery injection	+	+/–	–	–
Intravenous injection	+	+	+	+
Pneumothorax	+	+	+	+
Discomfort	+/–	++	+/–	+
Ease of catheter placement	–	+	++	+

++, Most likely/easiest; +, less likely/easy; +/–, possible; –, unlikely/difficult.

MANAGEMENT

Immediate intervention is required:

1. Instantly cease the local anesthetic injection.
2. Provide assisted manual or mechanical ventilation with 100% oxygen. Tracheal intubation is often necessary but not always mandatory.
3. Consider the patient's mental status, drugs administered, and surgical procedure.
4. Volume expansion may be required to treat or prevent hemodynamic instability.
5. Vasopressors, positive chronotropic drugs, or temporary pacing may be required to treat bradycardia or hypotension. Monitor the patient in the intensive care unit or recovery room until the block wears off.

PREVENTION

The most important precaution is to administer the drug slowly, with repeated aspiration; however, intravenous, intraarterial, or intrathecal drug administration is still possible. The choice of approach for performing the interscalene block has implications in the occurrence of complications. The frequency of total spinals during interscalene block has been decreasing since the use of the lateral modified approach for the performance of the block, as well as ultrasound techniques.

Winnie's approach (Fig. 149.1) directs the needle more toward the spine and therefore increases the risk of injection through an intervertebral foramen, especially if the needle is directed too horizontally. The posterior approach is a paravertebral block. All paravertebral blocks carry at least some risk of puncturing the dural cuff (whether abnormally long or not) that accompanies spinal nerves distal to the intervertebral foramina. The modified lateral approach (Fig. 149.2) directs the needle away from spinal structures and is likely the safest technique for avoiding intervertebral or inadvertent dural puncture Advancing the catheter more than 2 to 3 cm past the tip of the stimulating needle carries no advantage. In fact, by threading it farther, the anesthesiologist loses control over its position (e.g., interscalene catheters have been placed within the pleura). Last, an important precaution is to perform the interscalene block only in awake or lightly sedated patients.

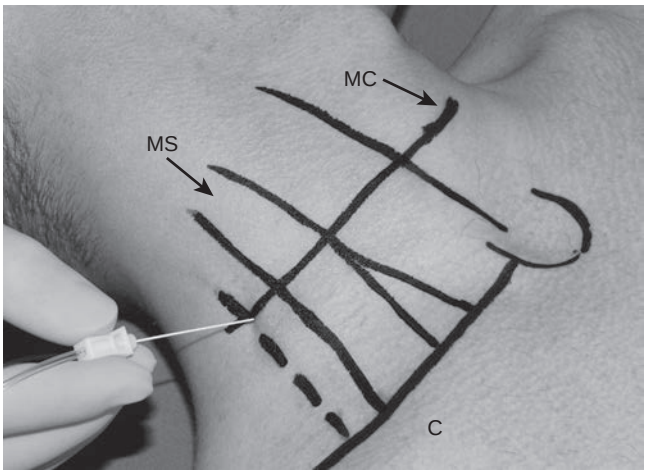

Fig. 149.1 Winnie's technique. The needle is directed medially, caudad, and slightly posteriorly toward the transverse process of C6. The needle is close to the spinal structures. *C,* Clavicle; *MC,* cricothyroid membrane; *MS,* clavicular head of sternocleidomastoid muscle; *dotted line,* interscalene groove.

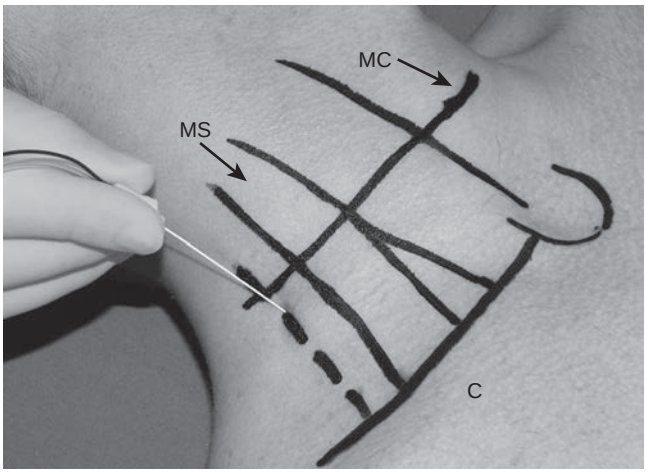

Fig. 149.2 Modified lateral approach. The needle is inserted toward the plane of the interscalene space at an angle between 45 and 60 degrees. The needle avoids the spinal structures. *C,* Clavicle; *MC,* cricothyroid membrane; *MS,* clavicular head of sternocleidomastoid muscle; *dotted line,* interscalene groove.

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Intracranial Hypertension 150

Rosemary Hickey

Case Synopsis

A 64-year-old man is scheduled for a craniotomy for resection of a brain tumor. He presented to the emergency department with progressive personality changes, memory disturbances, and urinary incontinence. Physical examination is remarkable for confusion, papilledema, and left hemiparesis. Computed tomography scan reveals a large mass with surrounding edema consistent with a glioblastoma. He has been started on dexamethasone (Decadron) 4 mg every 6 hours by the neurosurgical team. During the procedure, the surgeons ask for assistance in achieving brain relaxation, as the brain is bulging through the dura.

PROBLEM ANALYSIS

Definition

Intracranial hypertension exists when there is a sustained elevation in intracranial pressure (ICP) of more than 15 to 20 mm Hg. It results when the three intracranial components—blood, brain, and cerebrospinal fluid (CSF)—are no longer able to compensate for volume changes occurring within the cranium. CSF translocation from the head into the spinal subarachnoid space and its reabsorption via the arachnoid villi are the major compensatory means of accommodating intracranial volume increases. Spatial compensation can also be achieved through compression of the venous system and, ultimately, capillary collapse, leading to cerebral ischemia.

Changes in ICP that occur with changes in intracranial volume can be described by the intracranial elastance curve (Fig. 150.1). The first part of the curve is flat because compensatory reserves are adequate despite increases in intracranial volume. When these mechanisms are exhausted, the curve turns rapidly upward as compliance is critically reduced and small increases in intracranial volume create a substantial increase in ICP. The ICP waveform (Fig. 150.2) has three distinct peaks. The second peak (P2) is thought to be due to brain tissue compliance, and when it is elevated or exceeds the level of the P1 waveform, there is a marked decrease in compliance.

Recognition

The signs and symptoms most frequently associated with intracranial hypertension include headache, nausea, vomiting, papilledema, unilateral pupillary dilation, and oculomotor or abducens nerve palsies. Changes in consciousness and irregular ventilatory patterns indicate advanced stages of intracranial hypertension.

Headache is typically present on awakening, or it may awaken the patient from sleep. It is related to traction and distortion of pain-sensitive cerebral blood vessels and the dura mater. Vomiting may be due to direct stimulation of the vomiting centers by local compression. Papilledema is the most reliable sign of an increase in ICP, although intracranial hypertension may be present without it. Oculomotor palsies are secondary to herniation or compression of the nerve, and abducens palsies result from stretching of the nerve as the brainstem is displaced inferiorly by the increased pressure. A general slowing in mentation occurs from continuously increased ICP and a diffuse decrease in cerebral blood flow. Further deterioration in the level of consciousness indicates progressive transtentorial herniation. Alterations in vital signs (bradycardia, hypertension, alteration in respiration) also may occur from increased ICP and brainstem compression. Computed tomography scanning, magnetic resonance imaging, and angiography provide indirect evidence of elevated ICP. Indications of elevated ICP include a mass lesion accompanied by a midline shift of at least 0.5 cm, encroachment of the CSF cisterns by the expanding brain, or both.

Risk Assessment

The three major mechanisms of increased ICP are (1) increased intracranial volume due to an intracerebral mass lesion (e.g., tumor, massive infarction, trauma, hemorrhage, abscess), extracerebral mass lesion (e.g., tumor, hematoma, abscess), or acute brain swelling (e.g., anoxic states, acute hepatic failure, hypertensive encephalopathy, Reye syndrome); (2) high venous pressure resulting from heart failure, superior mediastinal obstruction, or cerebral or jugular venous obstruction, which increases blood volume in the pial veins and dural sinuses and may interfere with CSF absorption; and (3) obstruction to the flow (hydrocephalus) or absorption (pseudotumor cerebri) of CSF.

Implications

The danger of intracranial hypertension lies in the potential for cerebral ischemia and herniation of brain tissue. If ICP, either locally or globally, reaches levels exceeding mean arterial pressure (MAP), cerebral ischemia will develop. Effective cerebral oxygenation requires an adequate cerebral perfusion pressure (CPP), which depends on the resistance offered by ICP or cerebral venous pressure (CVP), whichever is higher. The relationship is summarized by CPP = MAP – (ICP or CVP). The likelihood of permanent tissue damage from cerebral ischemia depends on the severity and duration of the ischemia. If ICP is sufficiently high to obstruct venous outflow from the brain, arterial inflow also may be compromised.

Brain herniation can occur around any fixed structure in the skull. In open head trauma, injured brain may herniate through the fractured skull. In the intact skull, herniation can occur in three ways:

1. A hemisphere may be displaced medially through the falx, resulting in falcine herniation.

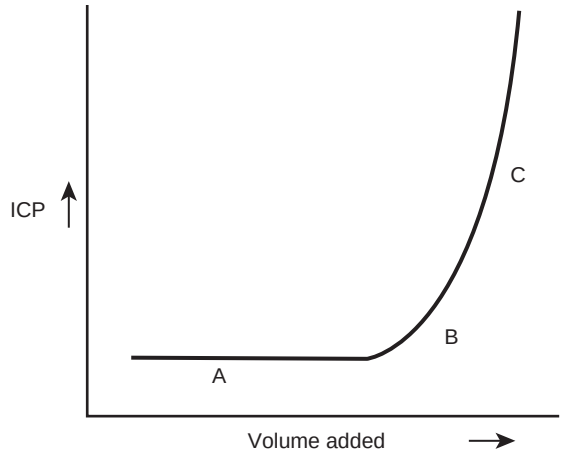

Fig. 150.1 Intracranial elastance curve. A, Normal elastance. **B,** Reduced elastance (small increase in intracranial pressure [ICP] with increasing intracranial volume). **C,** Poor elastance (large ICP increase with minimal increase in cerebral volume). (From Mahla ME: Neurologic surgery. In Kirby RR, Gravenstein N, editors: *Clinical anesthesia practice.* Philadelphia, WB Saunders, 1994, pp 1283–1311.)

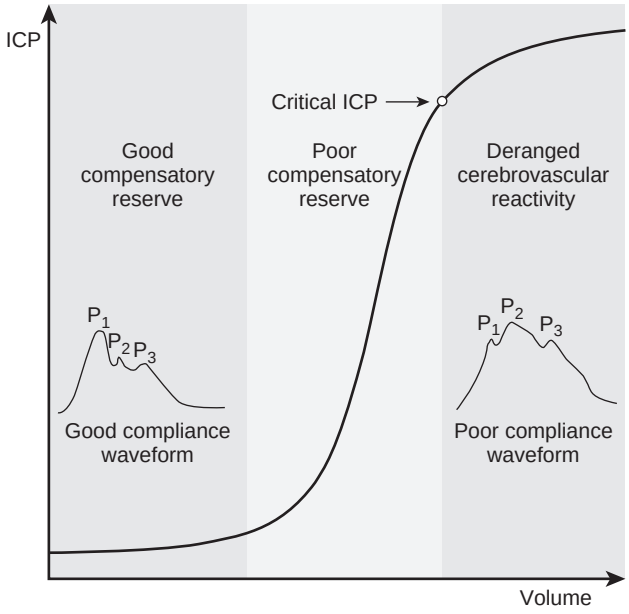

Fig. 150.2 Relationship between ICP and intracranial volume. (From Perez-Barcena J, Llompart-Pou JA, O'Phelan KH: Intracranial pressure monitoring and management of intracranial hypertension. *Crit Care Clin* 30[4]:735–750, 2014).

2. The medial edge of the temporal lobe (uncus) can herniate through the tentorial foramen, resulting in uncal herniation. The third cranial nerve is compressed, causing unilateral pupillary dilation and lack of reactivity to light. Impairment of consciousness results from brainstem compression.
3. Classic herniation of the cerebellum through the foramen magnum, compressing the medulla and resulting in cardiovascular and respiratory collapse, and bilateral pupillary abnormalities.

MANAGEMENT

Therapeutic interventions to lower elevated ICP have evolved toward standardized strategies that use an approach with an escalating treatment intensity, known as a "staircase" approach (Table 150.1).

TABLE 150.1 Staircase Approach to Treat Intracranial Hypertension and the Associated Risks

Level of Therapy	Therapy	Risks
Step1	Intubation Normocapnic ventilation	Ventilator-associated complications
Step 2	Increased sedation	Hypotension Obscuring of neurologic examination
Step 3	Ventricular CSF drainage	Infection
Step 4	Hyperosmolar therapy (mannitol or hypertonic saline)	Hypovolemia Electrolyte disturbances
Step 5	Hypocapnia	Cerebral ischemia
Step 6	Hypothermia	Infection Impaired coagulation
Step 7	Metabolic suppression (barbiturates)	Hypotension Prolonged awakening
Step 8	Decompressive craniectomy	Infection Hematoma Other surgical complications

CSF, Cerebrospinal fluid.

1. Initially, the patient is intubated with normocarbic ventilation. This is best accomplished by a practitioner experienced in intubation techniques after sedative and paralytic agents are given to minimize the ICP response to intubation. A videolaryngoscope is a helpful tool if intubation is deemed difficult or cervical spine precautions need to be maintained.
2. Additional sedation after intubation is used to prevent arterial hypertension and patient-ventilator dyssynchrony, as well as to minimize the risk of seizures. To avoid the risk of arterial hypotension from sedation, normovolemia must be maintained. A continuous infusion of propofol with or without narcotic is often chosen for sedation in the intensive care unit. In the operating room, propofol and remifentanil infusions are used with or without low doses of an inhalational agent. Venous drainage is maximized by keeping the head elevated 15 to 30 degrees, without excessive rotation or flexion.
3. Ventricular CSF drainage is accomplished with an external ventricular drain. Intermittent drainage may be performed when the ICP exceeds 20 mm Hg. This treatment carries the risk of infection.
4. Hyperosmolar therapy with mannitol or hypertonic saline is used to reduce brain volume and intracranial pressure. These agents create a gradient across the blood-brain barrier and extract water from the brain. Mannitol may also improve blood rheology and microcirculatory flow. As an osmotic diuretic, it has the risk of dehydration and hypovolemia. Serum osmolarity should be followed after treatment. Hypertonic saline may cause an abrupt increase in sodium concentrations and serum sodium levels should be followed. Loop diuretics (furosemide) provide intracranial decompression through a diuresis-mediated brain dehydration, reduced CSF formation, and resolution of cerebral edema via improved cellular water transport.
5. Hyperventilation reduces intracranial pressure by a reduction in cerebral blood flow, cerebral blood volume, and ICP. Because such a reduction in cerebral blood flow may be poorly tolerated, additional monitoring for cerebral ischemia is useful with either jugular bulb oxygen saturation or brain-tissue oxygenation ($pbtO_2$). With jugular venous oxygen saturation monitoring, values greater than 75% indicate hyperemia, so induced vasoconstriction associated with hyperventilation may be valuable; values less than 50% indicate cerebral ischemia, so attempts to induce further cerebral

vasoconstriction may be harmful. Measurement of $pbtO_2$ involves insertion of a mini Clark electrode into brain parenchyma. The threshold for critical ischemia is considered to be approximately 15 mm Hg.

6. Mild hypothermia is effective in decreasing ICP, but studies on its clinical benefit are variable, and it is associated with a number of adverse effects. Recent evidence does not support its use in patients with intracranial hypertension after traumatic brain injury.
7. Metabolic suppression with barbiturates has been used to reduce cerebral blood volume and ICP. Its use has been reserved for refractory intracranial hypertension after other therapies have failed. Electroencephalography (EEG) monitoring or monitors of anesthetic depth such as the bispectral index may be useful to guide therapy.
8. Surgical treatment of intracranial hypertension includes the evacuation of mass lesions, drainage of CSF, and decompressive craniotomy. Mass lesions most commonly include brain tumors or hematomas (epidural, subdural, intracerebral). Surgical excision reduces the volume of the intracranial space occupied by parenchymal components and thus improves intracranial elastance. Drainage of CSF is a simple and effective approach to reduce ICP. It is accomplished with intracranial ventricular catheters (as discussed earlier). Lumbar catheters are not recommended because of the risk of herniation in a patient with elevated ICP. CSF volume may also be reduced by the use of surgical shunt techniques, such as a ventricular-peritoneal shunt. Decompressive craniectomy is used to provide a larger reserve to compensate for increased intracranial volume. It may be performed prophylactically at the time of removal of mass lesions or as a rescue technique when maximal medical therapy has failed. Although ICP is reduced, its use has been controversial because of a lack of studies demonstrating improved clinical outcomes.

An additional treatment for reducing ICP is the use of corticosteroids in patients with brain tumors. They are effective for treating peritumor edema but are not effective for treatment of head trauma.

PREVENTION

Prevention of intracranial hypertension centers on avoiding factors that are known to increase ICP. Intravenous fluid management is directed toward achieving a euvolemic state. Therapy should avoid the use of intravenous solutions that decrease plasma osmolality (5% dextrose in water, 0.45% sodium chloride, lactated Ringer solution). The factor in administered fluid that most affects brain edema is the osmolality. An acute drop in osmolality affects brain water content and ICP more than an acute drop in oncotic pressure. Glucose-containing solutions are avoided because hyperglycemia may aggravate ischemic brain injury.

Other factors that increase ICP and should be avoided include compression of jugular veins by improper head positioning, coughing and straining on the endotracheal tube, seizure activity, hypercarbia, and hypoxia. Increased body temperature raises cerebral metabolic oxygen consumption and should be avoided. Volatile anesthetic agents may cause an increase in cerebral blood flow, cerebral blood volume, and ICP. In the presence of intracranial hypertension, these agents should be used in moderation and in combination with mild hyperventilation and intravenous anesthetics with favorable effects on ICP (e.g., etomidate, propofol, narcotics). Nitrous oxide is cerebrostimulatory and increases cerebral blood flow and cerebral metabolic oxygen consumption, especially when combined with volatile anesthetics. Use of nitrous oxide should be avoided with pneumocephalus (e.g., recent craniotomy) because of its potential to diffuse into and expand intracranial and other air-containing spaces.

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151 Intractable Nausea and Vomiting

Jennifer L. Stewart • David A. Nakata

Case Synopsis

A 28-year-old, 110-kg woman presents with intractable nausea and vomiting in the postanesthesia care unit after undergoing laparoscopic cholecystectomy under general anesthesia. The anesthesia was unremarkable except for preoperative anxiety and moderate postoperative upper airway obstruction, which was easily corrected by insertion of an oral airway. Past medical history was significant for unanticipated hospital admission for postoperative nausea and vomiting after previous inguinal hernia repair.

PROBLEM ANALYSIS

Definition

Postoperative nausea and vomiting (PONV) is an important cause of morbidity after all types of anesthesia. It typically occurs in the immediate postanesthesia period, with most cases lasting less than 24 hours. Nausea is a subjective sensation best evaluated by the patient and is mediated via unknown neural pathways. It often, but not always, arises as the antecedent event to retching or vomiting. Vomiting (emesis) is defined as the forceful retrograde oral expulsion of gastric contents. Retching differs from vomiting by the lack of expulsion of gastric contents. PONV has multiple causes that can be subdivided into patient-, surgical-, and anesthetic-related factors.

Recognition

The sensation of nausea is familiar to everyone, but because of its subjective nature, it is often difficult to appreciate, especially in a disoriented postoperative patient. Nausea is typically accompanied by decreased or inappropriate gastrointestinal activity and may include hypotonicity of muscular sphincters, hypoperistalsis or reverse peristalsis, and hyposecretion. The autonomic nervous system, especially the parasympathetic system, can also be affected, leading to manifestations such as skin pallor, diaphoresis, increased salivation, vasovagal reactions, and anorexia. If these symptoms persist, they invariably deteriorate to retching and vomiting.

Vomiting, unlike nausea, is virtually unmistakable in its presentation. The neuroanatomic pathways and mediators that produce vomiting are better understood than those associated with nausea. Two distinct areas in the brain are responsible for the initiation and coordination of vomiting: the chemoreceptor trigger zone in the fourth ventricle, and the vomiting center in the lateral reticular formation. The chemoreceptor trigger zone contains a high density of dopaminergic receptors and is connected by neural pathways to the vomiting center. Fig. 151.1 is a schematic representation of the factors that are known to interact with the areas responsible for vomiting. In addition, numerous physiologic changes occur, including relaxation of the gastric fundus and lower esophageal sphincter and the forceful contraction of the abdominal musculature, leading to the ejection of gastric contents.

Risk Assessment

The incidence of postoperative vomiting is typically reported to be between 20% and 40%. Box 151.1 presents factors that have been implicated in the development of PONV. A number of these factors are widespread throughout the general surgical population, making it common for individual patients to have multiple risk factors. These factors, in addition to specific patient characteristics, are useful in predicting which patients are at greatest risk of developing PONV. Unfortunately, there is no formal scheme that allows clinicians to predict which prophylactic maneuvers will yield the greatest success.

Some of the less obvious factors that influence the incidence of nausea and vomiting include anxiety, gender, obesity, experience of the anesthesiologist, and anesthetic agent. Anxiety may exacerbate PONV via the release of catecholamines. Experimental models exist in which vomiting can be induced by instilling catecholamines into the cerebral ventricles. This may also account for the increased incidence of nausea and vomiting associated with the use of anesthetic agents that increase circulating catecholamines. The increased incidence of PONV in women has traditionally been ascribed to a hormonal cause. This is supported by a decreased incidence of PONV in females at the extremes of age compared with age-matched males. However, a recent study postulates that the increased incidence of PONV in women may actually be due to a greater sensitivity to dopamine. Obesity may interfere with positive-pressure ventilation, leading to gastric distention.

The case synopsis provides examples of some of the common predisposing conditions that can increase a patient's risk for PONV, including female gender, obesity, previous history of PONV, anxiety, laparoscopic abdominal surgery, placement of an oral airway, and general anesthesia. Other factors may include increased gastric inflation or hypoxemia from difficult positive-pressure ventilation and increased arterial carbon dioxide tension from inadequate mask ventilation or abdominal insufflation of carbon dioxide during laparoscopy. Although contemporary volatile anesthetics are not known to promote nausea and vomiting, nitrous oxide has been incriminated. Possible mechanisms might be increased middle ear pressure with stimulation of the chemoreceptor trigger zone or distention of the gastrointestinal tract.

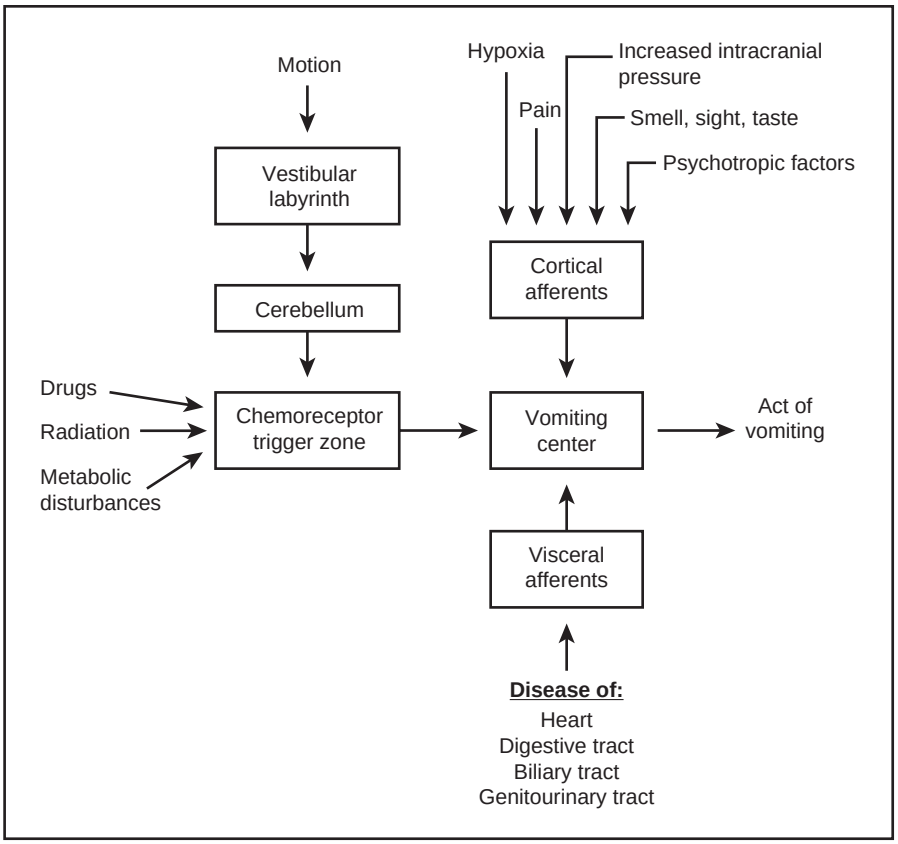

Fig. 151.1 Factors known to interact with the chemoreceptor trigger zone and the vomiting center to initiate vomiting.

BOX 151.1 Factors That May Influence the Risk of Postoperative Nausea and Vomiting

Age: children at greater risk than adults
Anesthetic technique
Anxiety
Concurrent illness
    Ethanol intoxication
    Increased intracranial pressure
    Metabolic disturbance
Experience of the anesthetist
Fasting
Female gender
    Day of the menstrual cycle
Gastric inflation
Hypercarbia
Hypotension
Inhalation anesthetics
Intravenous anesthetics
    Etomidate
    Methohexital
    Thiopental
Medications
Nasogastric tube
Nitrous oxide
Obesity
Opioids
Pain
Placement of airways
Previous history of postoperative nausea and vomiting
Prolonged operative procedure
Standing
Sympathetic stimulation
Transportation or movement of patient
Type of surgery
    Head and neck surgery
    Intraabdominal surgery
    Laparoscopic abdominal surgery
    Strabismus surgery

Implications

Box 151.2 lists a number of complications associated with nausea and vomiting. A number of coexisting diseases and certain surgical procedures may predispose a patient to the development of more serious sequelae of PONV, including increased intracranial pressure (leading to tentorial herniation) and esophageal disruption (Mallory-Weiss tear or Boerhaave syndrome). PONV can also cause wound dehiscence and disruption of complex surgical repairs. Retching or vomiting after procedures involving the head and neck is of special concern because of the fragile nature of these tissues. In addition, an especially risky situation may be created by procedures involving the oral cavity in which the mandible is fixed in the closed position. Under these circumstances, if a patient were to vomit, significant quantities of gastric contents could be aspirated.

MANAGEMENT

Box 151.3 lists antiemetic agents available for the prevention and treatment of nausea and vomiting. These drugs can be subdivided into

BOX 151.2 Complications Associated With Nausea and Vomiting

- Aspiration pneumonia
- Dehydration
- Delayed discharge from postanesthesia care unit
- Delayed discharge from hospital
  - Increased cost
  - Inconvenience
- Electrolyte imbalance
  - Hypokalemia
  - Hypochloremia
  - Hyonatremia
  - Alkalosis
- Esophageal rupture (Boerhaave syndrome)
- Increased postsurgical bleeding
- Increased intracranial pressure
- Mallory-Weiss tear

BOX 151.3 Antiemetics

- Anticholinergics
  - Scopolamine (intravenously or transdermal patch)
  - Atropine
- Antihistamines
  - Cyclizine (Marezine)
  - Dimenhydrinate (Dramamine)
  - Diphenhydramine (Benadryl)
- Butyrophenones
  - Droperidol (Inapsine)
  - Haloperidol (Haldol)
- NK_1 antagonists
  - Aprepitant (Emend)
- Phenothiazines
  - Promethazine (Phenergan)
  - Prochlorperazine (Compazine)
  - Perphenazine (Trilafon)
- Prokinetics
  - Metoclopramide (Reglan)
  - Domperidone (Motilium)
- Serotonin ($5\text{-}HT_3$) antagonist
  - Ondansetron (Zofran)
  - Dolasetron (Anzemet)
  - Granisetron (Kytril)
  - Palonosetron (Aloxi)
- Steroids
  - Dexamethasone (Decadron)

gastrointestinal prokinetic drugs, phenothiazines, butyrophenones, anticholinergics, antihistamines, NK_1-antagonists, serotonin ($5\text{-}HT_3$) receptor antagonists, and steroids. No single agent is universally effective for the prevention or treatment of PONV. Many of these drugs are associated with side effects, such as sedation and extrapyramidal reactions. This may cause some clinicians to restrict the use of these drugs, especially when one considers the typically negligible effect of PONV on overall outcome. In addition, when consideration is given to the large number of factors that can affect the development of PONV, choosing the most efficacious antiemetic can be difficult.

PREVENTION

Routine antiemetic prophylaxis is not warranted because fewer than 30% of patients experience postoperative emesis. When it occurs, it is often brief in duration. In addition, the sedation and delayed awakening caused by some of the commonly used antiemetic agents may hinder their usefulness. Even though antiemetic prophylaxis is not routinely advised, consideration must be given to the reality that the treatment of PONV is often less efficacious than its prevention. Therefore there may be specific instances when the prophylactic use of these agents is warranted for patients known to be at risk.

Given the multiple factors involved in the development of PONV, it is difficult to provide specific recommendations regarding prophylaxis. This is in contrast to the nausea and vomiting associated with radiation and chemotherapy, in which the inciting agents are more readily identifiable. Additionally, in refractory cases of PONV, a combination of drugs may be needed to increase efficacy. Unfortunately, combination therapy is markedly more expensive than single-drug therapy, and even with multidrug therapy success is not ensured.

Other factors aiding in the prevention of PONV include nonpharmacologic therapies such as decompressing the stomach with an orogastric or nasogastric tube. However, the presence of a gastric tube in the postoperative period may stimulate the gag reflex, thus mitigating the benefit of gastric decompression. Additionally, fluid hydration has been advocated to decrease the incidence of PONV. Given the relative low cost and safety associated with this therapy, it seems reasonable to consider it. Other, more exotic nonpharmacologic therapies include acupuncture, acupressure, and specific herbs. Finally, new drugs include tropisetron, a $5\text{-}HT_3$ antagonist now marketed in Europe that is currently in clinical trials in the United States, and casopitant, an NK_1 antagonist, also currently in clinical trials.

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Laryngeal and Tracheal Injury

152

Michael A. Hall • Andrew E. Ochroch

Case Synopsis

A 58-year-old, 50-kg woman presents to the operating room for total abdominal hysterectomy. After intravenous induction of general anesthesia, direct laryngoscopy is performed, yielding a view of only the arytenoids with the application of cricoid pressure. A single-use, coude-tip bougie is passed blindly until a positive hold-up sign is obtained, after which a 6.5-mm endotracheal tube is passed over the bougie into the trachea. Endotracheal placement of the tube is confirmed by capnometry. The surgery proceeds without incident. After taking down the drapes at the end of the surgery, diffuse subcutaneous emphysema is discovered over the torso with tracking up to the neck. Bronchoscopy performed before emergence from general anesthesia reveals a longitudinal tear in the membranous portion of the trachea extending into the right mainstem bronchus.

PROBLEM ANALYSIS

Definition

Injuries to the larynx and trachea can occur during laryngoscopy and endotracheal intubation, as well as after varying periods of time with an endotracheal tube in place; a selection of clinically relevant injuries is presented in Table 152.1. These conditions range in severity from self-limited to requiring extensive surgical repair. Acute injuries are most likely related to direct trauma during endotracheal intubation. Reported traumatic injuries have been attributed to the laryngoscope (both classic direct laryngoscopes and videolaryngoscopes), single-lumen and double-lumen endotracheal tubes, the endotracheal tube stylet, the intubating bougie, and laryngeal mask airways.

Injuries from prolonged intubation are more likely to be ischemic in nature and related to contact between the endotracheal tube, especially the cuff, and the tracheal mucosa. The trachea has a segmental blood supply, with perforating vessels feeding a submucosal plexus, which then perfuses the cartilaginous rings. Prolonged compression of the submucosal plexus causes ischemia to adjacent rings. Compression is most commonly attributed to an overinflated endotracheal tube cuff exerting a pressure of greater than 25 to 30 mm Hg on the tracheal mucosa. Ischemia will first lead to the development of edema and then progress to ulceration or granuloma formation. If allowed to continue unchecked, the ischemic damage will lead to the development of erosion through the trachea and the possible development of tracheoesophageal or tracheoinnominate fistulas. After removal of the endotracheal tube, severe injury may result in tracheomalacia, or less severe damage will heal by secondary intention, over the course of 3 to 6 weeks, and will lead to the formation of stricture, causing stenosis of the trachea.

Recognition

Given the diverse nature of possible injuries to the larynx and trachea, the signs and symptoms of injury during or after endotracheal intubation are best grouped by injury etiology.

Injury During Endotracheal Intubation

The majority of injuries sustained during the procedure of endotracheal intubation will be relatively minor, and include vocal cord hematoma, pharyngeal contusion, and luxation of the arytenoid cartilage. Patients will complain of sore throat shortly after extubation and may have some degree of voice change (hoarseness) or barking cough. More severe traumatic injury to the larynx may result in varying degrees of airway obstruction, leading to dyspnea, tachypnea, and stridor. Diagnosis is usually accomplished by nasopharyngolaryngoscopy in the awake patient, although this procedure is usually reserved for cases with airway compromise or cases where symptoms do not resolve spontaneously within 1 to 2 weeks. Perforation, laceration, or rupture of any portion of the airway or aerodigestive tract most commonly presents with mediastinal and subcutaneous emphysema and

TABLE 152.1 Examples of Clinically Relevant Injuries to the Larynx and Trachea Classified by Time Course

Injury During Placement of Endotracheal Tube	Injury During Short-Term (<24 Hours) Intubation	Injury During Long-Term (>24 Hours) Intubation
Vocal cord hematoma or laceration	Vocal cord and laryngeal edema	Vocal cord and laryngeal granuloma or ulceration
Luxation of arytenoid cartilage	Vocal cord paralysis	Laryngotracheal, subglottic, or tracheal stenosis
Hypopharyngeal perforation	Tapia syndrome (temporary palsy of ipsilateral recurrent laryngeal and hypoglossal nerves)	Laryngeal mucosal ulceration and submucosal hemorrhage
Tracheal laceration, perforation, or rupture	Tracheal edema or hyperemia	Tracheal ulceration
Carinal or bronchial laceration or perforation		Tracheomalacia
		Tracheoesophageal and tracheoarterial fistula

may also include pneumothorax or hemothorax. Rarely, severe traumatic injuries to the trachea or bronchi may result in airway hemorrhage with blood found within the endotracheal tube and suctioned from the airways. Evaluation will usually include chest radiography and fiberoptic bronchoscopy to evaluate the extent of injury.

Injury During Short-Term (<24 Hours) Intubation

Even during short-term placement of an endotracheal tube, a clinically significant amount of laryngeal and vocal cord edema can develop, manifesting as dyspnea, tachypnea, and stridor shortly after extubation and possibly progressing to partial or complete obstruction of the airway. In the setting of airway compromise, direct or indirect laryngoscopy will be required to assess the degree of obstruction and determine whether the airway can be resecured in a translaryngeal fashion or if a surgical airway will be required. Injury to cranial nerves has been reported with the use of the endotracheal tube, including to the recurrent laryngeal nerve. This is most likely caused by compression of the nerve by an overinflated endotracheal tube cuff where the nerve passes between the trachea and the thyroid cartilage. This will result in ipsilateral vocal cord paralysis, which is usually self-limited, and will require some form of laryngoscopy for evaluation.

Injury During Long-Term (>24 Hours) Intubation

Certain severe injuries, such as tracheoarterial fistulas and tracheomalacia, may become evident either while the endotracheal tube is still in place or shortly after extubation, but the more common complications of prolonged intubation, airway stricture, and stenosis, require weeks to months to fully develop and become symptomatic. This is partly because of the slow process of scarring that occurs within the trachea and partly because of the fact that the cross-sectional area of the trachea must be reduced by more than 70% to cause symptoms at rest. Patients will present with hoarse voice and cough progressing to dyspnea and tachypnea and finally stridor and use of accessory muscles of respiration. Whereas spirometry will demonstrate flow restriction consistent with airway obstruction, abnormalities in flow-volume loops will only be evident with severe stenosis. Given the clinical suspicion for airway stenosis, computed tomography with three-dimensional reconstruction is the imaging test of choice to reveal location and degree of airway narrowing, as well as assist with surgical planning.

Risk Assessment

Just as the complications of endotracheal intubation take a variety of forms, the patient factors that increase risk for complications are diverse. Minor laryngeal trauma, including hematoma and thickening with edema, is the most common injury incurred during laryngeal intubation, with reported incidence of up to 69% of patients undergoing intubation for short surgical procedures under general anesthesia. Risk factors include the following:

- Anatomic abnormality of larynx or upper airway
- Difficult intubation or need for multiple attempts at laryngoscopy
- Use of a double-lumen or oversized endotracheal tube

For the rare, life-threatening complications of intubation, true incidence is difficult to estimate; however, use of intubation adjuncts such as the bougie, as well as excessive movement or manipulation of the endotracheal tube, will increase risk for tracheobronchial trauma.

For patients requiring prolonged intubation, risk factors for developing ischemic injury to the trachea include the following:

- Overinflation of the endotracheal tube cuff
- Chronic disease compromising tracheal blood flow, including hypertension and diabetes mellitus
- Acute condition compromising tracheal blood flow, including anemia and hypotension

Implications

Complications of orotracheal intubation range from common and self-limited to rare and life threatening. The most common complication, postoperative hoarseness, has been shown to have a significant, negative effect on patient satisfaction after surgery and on patients' level of activity after discharge from the hospital. Perforation of any portion of the airway can lead to serious infections and the need for major surgery for repair. Tracheal stenosis commits patients to serial bronchoscopic procedures and major surgery for definitive repair. Any complication that threatens the patency of the airway may require tracheostomy placement, possibly in an emergent fashion.

MANAGEMENT

By far the most frequent injuries, together causing symptoms of sore throat and hoarse voice, incurred during airway manipulation are self-limited and will resolve within days of the event. However, more severe injuries, especially those causing airway obstruction, may require emergent intervention. For acute laryngeal or vocal cord edema causing stridor or dyspnea, inhaled nebulized racemic epinephrine may decrease edema and improve symptoms. Intravenous dexamethasone is also often used to decrease edema, although its use is not supported by randomized studies. Intravenous dexamethasone is also used to treat edema before extubation to improve the likelihood of a successful extubation; this has been well studied in the pediatric intensive care unit. Symptomatic luxation of the arytenoid cartilage may be treated by closed reduction by an otorhinolaryngologist, usually leading to resolution of voice changes and vocal cord movement abnormalities within 2 to 3 months.

Rare but potentially life-threatening injuries will often require surgical intervention. Tracheal or bronchial perforation or laceration will usually require right thoracotomy for repair, or a neck incision if the injury is extrathoracic. Nonoperative treatment, with broad-spectrum antibiotics to prevent the development of mediastinitis, has been reported for selected patients based on the severity of the injury or related findings. Fistulas from the trachea to adjacent structures will require surgical repair, potentially emergently in the case of fistulization to a blood vessel.

Treatment for airway stenosis depends on the severity and location of the injury. In patients with acute airway compromise, rigid bronchoscopy with serial dilation can be performed. However, given the transmural nature of the ischemic injury, this is usually only a temporizing measure before definitive surgical repair. For patients in whom surgical repair must be delayed or is not technically feasible, the use of a T-tube or intraluminal stent may palliate symptomatic airway obstruction. Definitive repair is defined by resection of the strictured segment and primary, single-stage reconstruction with careful attention paid to the tracheal blood supply and tension on the tracheal anastomosis.

PREVENTION

Prevention of laryngeal and tracheal injury focuses on decreasing trauma to the airway both during endotracheal intubation and while managing an intubated patient. Specific actions that can be taken to reduce the risk of these injuries are outlined in Table 152.2.

TABLE 152.2 Specific Strategies to Decrease Risk of Laryngeal and Tracheal Injury Related to Endotracheal Intubation

Performing Orotracheal Intubation	Managing an Intubated Patient
Conscious effort to minimize direct trauma to the vocal cords when performing laryngoscopy and when passing endotracheal tube through the glottis	Maintenance of appropriate endotracheal tube cuff positioning (depth) and inflation pressure
Effort made to optimize intubating conditions to increase the success rate of laryngoscopy and decrease the duration of time, as well as the number of attempts at laryngoscopy performed	Avoidance of advancing or withdrawing the endotracheal tube while cuff is inflated
Judicious use of the intubating bougie, feeling for tracheal rings instead of using hold-up technique	In ICU setting, appropriate pharmacologic treatment of gastroesophageal reflux as well as semirecumbent bed positioning (head of bed elevated 30 degrees)
Ensure endotracheal tube cuff is inflated with minimum pressure required to achieve adequate ventilation (ideally <20 mm Hg)	Appropriate antibiotic therapy for patients with perforation of the airway or aerodigestive tract
Secure endotracheal tube at an appropriate depth, avoiding placing cuff within the larynx or within a mainstem bronchus	
Avoid use of oversized endotracheal tubes	
Lubrication of distal end of endotracheal tube, especially double-lumen or oversized tubes	

ICU, Intensive care unit.

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153 Latex Reactions in Health Care Personnel

Kevin J. Kelly • Robert E. Kettler

Case Synopsis

A 44-year-old anesthesiologist notes a rash on his right middle finger that has recently progressed to urticaria. He has been in good general health all his life; however, he is allergic to fish and ragweed pollen, and he was treated for eczema as a child. The rash has been intermittently present for several years and is exacerbated by wearing gloves to perform medical procedures. In the past 2 weeks, he has experienced chest tightness and rhinoconjunctivitis on entering the operating room. His only medication is an antihistamine taken during autumn for hay fever.

PROBLEM ANALYSIS

Definition

Natural rubber latex allergy (see also Chapter 194) is an issue of clinical importance for health care workers in terms of both patient management and occupational health. Use of rubber gloves dates to the late 1800s, when Halsted apparently produced them to protect the hands of his scrub nurse from the disinfectant solution she used to wash her hands. Skin lesions on the hands caused by the wearing of rubber gloves were first described in the medical literature in the 1930s. The increasing prevalence of latex-induced reactions is due to a confluence in the late 1980s of a number of factors: the increasing prevalence of hepatitis and acquired immunodeficiency syndrome (AIDS) led to the need for universal precautions; this led to increased demand for and use of barrier devices, including gloves made from natural rubber latex.

The rubber industry responded to meet this demand, but final product quality may have been compromised by new entrants into the field, new geographic locations for rubber production, political turmoil in rubber-producing countries, and changes in the manufacturing process to increase output while complying with environmental and occupational health concerns. This increase in demand was associated with a greater number of medical gloves imported into the United States.

As the use of latex gloves increased, allergic reactions in patients and health care providers were reported, leading to greater awareness of the problem, which in turn led to efforts to recognize and report it. This growing medical awareness was reflected by an increase in MEDLINE citations of journal articles published with *latex* as a key word, as shown in Table 153.1. There was an increase in both the absolute number of these citations and the number of these citations relative to the entire database. By mid-2004, the number of latex citations had increased to 0.1% of the MEDLINE database.

Natural latex contains several polypeptides that bind immunoglobulin E (IgE) and that may be altered during denaturation, polymerization, or breakdown during the manufacturing process. Most latex gloves have a cornstarch powder to facilitate donning. This powder binds various latex antigens and can be dispersed in the atmosphere, readily facilitating exposure through the respiratory system.

Recognition

Three types of untoward latex reactions are recognized (Table 153.2): irritant dermatitis, type I IgE-mediated reactions, and type IV delayed contact hypersensitivity reactions.

Irritant Dermatitis

Irritant reactions occur because the glove creates a local environment that can cause physical or chemical irritation to the skin. Risk factors for irritant reactions include increased age, cold weather, and excessive sweating. The skin breaks down over several days, and erythema and fissures are noted on inspection of the affected area. These reactions are not immunologically mediated. However, by disrupting the cutaneous barrier to allergens, they may be risk factors for the development of immunologically mediated reactions.

Type I IgE-Mediated Reaction

Type I reactions are mediated by IgE and usually occur within minutes of contact with latex proteins. The allergen binds to IgE, resulting in the release of vasoactive substances from mast cells (i.e., histamine,

TABLE 153.1 Latex Citations in MEDLINE Database

Year	Number (%) of Latex Citations	Total Literature Citations (Millions)[a]
1966–1974	445 (0.02)	2.0
1975–1979	241 (0.02)	1.3
1980–1984	286 (0.02)	1.4
1985–1989	348 (0.02)	1.7
1990–1993	472 (0.03)	1.5
1994–1997	679 (0.07)	1.0
1966–1997	**2471 (0.03)**	**8.8**

[a]All entries are rounded to nearest 100,000. In August 2004, the MEDLINE database contained 14 million citations, of which 14,372 (10%) were about latex.

TABLE 153.2 Manifestations of Irritant, Immediate, and Delayed Reactions to Latex

Reaction Type	Time of Onset	Clinical Signs	Immune Mechanism
Irritant dermatitis	Often gradual (days)	Erythema; scalded or parched appearance; chapped, cracked, fissured, or scaling skin; possibly vesicles or blisters	None
IgE-mediated reaction (type I)	Within minutes; rarely >2 h	Swelling, pruritus, urticaria, rhinoconjunctivitis, asthma, hypotension, anaphylaxis	IgE release of mast cell mediators; antigens are natural latex proteins
Delayed contact hypersensitivity reaction (type IV)	6–48 h after contact	Acute: erythema, pruritus, vesicles, blisters, cracking, crusting, desquamation Chronic: dryness, scaling, fissures, thickening or darkening of skin	Delayed or cell-mediated immunity; T-cell response to small rubber chemicals acting as haptens

From Ownby DR: Manifestations of latex allergy. *Immunol Allergy Clin North Am* 15:34, 1995.

bradykinin, leukotrienes, prostanoids). There are several potential manifestations of IgE-mediated reactions, including urticaria, pruritus, bronchospasm, rhinoconjunctivitis, flushing, hypotension, angioedema, and anaphylaxis.

Type IV Delayed Hypersensitivity Reaction

Type IV reactions to latex gloves are cell-mediated reactions to chemicals retained in the glove. The symptoms are apparent within several days and include erythema, pruritus, vesicles, fissuring, scaling, and thickening. The rash usually extends beyond the site of contact. Natural rubber latex is usually not the cause of type IV reactions; additives from the manufacturing process, such as thiuram and mercaptobenzathiazole, are more likely causes.

Risk Assessment

There are few studies on the natural history and clinical course of natural rubber latex reactions; in addition, owing to differences in their methodology, there is variation in the reported prevalence. Even so, the prevalence of latex allergy in the general population has been consistently reported as less than 1%. Although a study of blood donors revealed detectable antibody in 6.5% of subjects, this does not indicate the presence of clinical allergy. The pediatric spina bifida population has been estimated to have a prevalence of 28% to 67%. The prevalence of latex allergy in health care workers is 5% to 17%, but its prevalence in health care workers with a history of atopy is 24% to 36%.

Latex reaction risk factors include a history of environmental allergy, food allergy (especially to banana, kiwi, or avocado), hay fever, eczema, asthma, and chronic latex exposure (either occupational or as a result of repeated therapeutic procedures, with both frequency and exposure intensity being factors). The skin is relatively impermeable to latex proteins. However, disruption of the skin by irritant or contact reactions may predispose subjects to the development of IgE-mediated disease and subsequent systemic reactions. Cornstarch powder lubricant, which binds latex protein, and any activity that disperses these particles in the atmosphere can increase the quantity of respiratory exposure. If a patient's history indicates a risk of latex allergy, a serum level of IgE reactive to latex allergens or skin testing from an allergist may be obtained. Further workup can be performed as outlined in Table 153.3.

Implications

The severity of a latex reaction can range from a minor annoyance to life-threatening anaphylaxis and can include disabling symptoms (e.g., asthma). In addition to these medical complications, there are social implications, such as the need to change responsibilities or careers and the cost of disability payments. Institutions and individuals may have to change aspects of their medical practice to reduce the risk of latex reactions in others.

TABLE 153.3 Manifestations of Irritant, Immediate, and Delayed Reactions to Latex

Negative	Positive
Patient at Risk of Latex Allergy[a]	
No symptoms; no latex allergy; no testing needed	Symptomatic; possible latex allergy; perform diagnostic tests
Serum Test	
Negative; do further testing	Positive; no further testing needed (latex allergy confirmed)
Latex Use Test	
Negative; do further testing	Positive; no further testing needed (latex allergy confirmed)
Skin Test	
Negative; no latex allergy	Positive; no further testing needed (latex allergy confirmed)

[a]Some investigators have advocated latex testing in all patients with spina bifida. This approach would identify asymptomatic patients who have positive serum test results. Until further studies are performed, this patient group should be considered to be allergic to latex.
From Kelly KJ, Kurup VP, Reijula KE, et al: The diagnosis of natural rubber latex allergy. *J Allergy Clin Immunol* 93:814, 1994.

MANAGEMENT

The mainstays of management are as follows:

- Avoidance of allergens
- Topical therapy
- Systemic therapy (see Chapter 129)

Antigen avoidance can be difficult because of the ubiquitous presence of natural rubber products, especially in the health care environment. However, steps can be taken, such as wearing nonlatex gloves or using some type of barrier between the latex gloves and the skin (e.g., vinyl gloves). Using gloves only when necessary can also reduce exposure. Individuals who suffer severe reactions and cannot avoid allergens may have to change their specialty or profession. Airborne exposure can be eliminated or reduced to levels that are clinically insignificant by the exclusive use of powder-free, low-allergen latex gloves or synthetic gloves. Topical therapy with steroids and moisturizers can relieve the symptoms of irritant

and type IV reactions. Therapy for systemic IgE-mediated reactions includes airway management, ventilatory and circulatory support if necessary (including the use of epinephrine), antihistamines, and bronchodilators.

PREVENTION

Susceptible individuals should be advised to avoid latex products, but as already noted, this can be difficult. They should wear allergy-alert identification and carry an autoinjectable device for the emergency administration of epinephrine. Institutions should consider managing prevention through a multidisciplinary committee that develops guidelines for patients, health care workers, and other employees. This committee should provide guidelines for the identification of latex-containing medical products, the identification and purchase of latex-free substitutes, the establishment of latex-free treatment areas for susceptible individuals, and the use of powder-free gloves.

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Local Anesthetic Neurotoxicity: Cauda Equina Syndrome

Christina M. Spofford

Case Synopsis

A 48-year-old man underwent right inguinal hernia repair under spinal anesthesia. With the patient in a sitting position, a 24-gauge pencil-point needle was inserted at the L4–L5 level. Spinal medications included 75 mg of 5% lidocaine hydrochloride with 7.5% glucose, 0.1 mg of epinephrine, and 25 μg of fentanyl, resulting in an L3 block after 5 minutes. The patient was then placed in the right lateral decubitus position, and an additional 50 mg of 5% lidocaine with glucose was administered intrathecally. A T10 block was achieved, and surgery proceeded uneventfully. Twelve hours postoperatively, perineal numbness persisted, and the patient was unable to void. Anal sphincter tone was diminished, and anal reflexes were absent. Lumbosacral magnetic resonance imaging results were within normal limits without evidence of abscess or hematoma. Six months postoperatively, the patient had to strain to urinate, was unable to have a spontaneous bowel movement, and continued to have diminished sensation in the S3–S5 region bilaterally.

PROBLEM ANALYSIS

Definition

As the term *cauda equina syndrome* (CES) implies, clinical manifestations are related to injury to the nerve roots below the conus medullaris. Consequently, CES results in varying degrees of bowel and bladder dysfunction, perineal sensory loss, and lower extremity motor weakness. Although there are multiple potential causes, two are of concern to anesthesiologists: (1) compressive injuries (e.g., epidural or spinal hematoma/abscess), and (2) direct toxicity of substances administered into the intrathecal space. Clinical experience and experimental data suggest that, under certain circumstances, local anesthetics in current clinical use have the potential to induce neurotoxic damage and CES. We review the problem in this chapter.

Recognition

The medical literature has the occasional report of significant neurologic injury associated with spinal and epidural anesthesia and has led to further understanding about local anesthetic neurotoxicity. Early reports of CES were associated with continuous spinal anesthesia (CSA) with microcatheters. These CSA-related cases shared two common elements: restricted sacral block that required repetitive doses of local anesthetic to achieve adequate surgical anesthesia, and the cumulative dose far exceeded that commonly used with single-injection spinal anesthesia. It was suggested that the combination of maldistribution and high dose of anesthetic led to neurotoxic concentrations in a restricted area of the subarachnoid space, a mechanism supported by subsequent in vitro and in vivo experimental data. Although most of the injuries involved the administration of 5% lidocaine through small-bore microcatheters, not all were associated with lidocaine, and some involved intrathecal delivery of anesthetic through an epidural catheter. Therefore withdrawal of microcatheters from clinical practice has not eliminated the risk of injury, as practitioners remain at liberty to use epidural equipment for CSA. Further, some clinicians routinely convert to a continuous spinal technique if dural puncture accidentally occurs during attempted epidural placement.

Factors that lead to neurotoxic injury with CSA are not unique to this technique; they also apply to single-injection spinal anesthesia. Specifically, inadequate sensory block with single-injection spinal anesthesia is often the result of maldistribution. Under such circumstances, there is the potential for repeat injections to distribute in the same pattern, resulting in neurotoxic concentrations of local anesthetic within a restricted area of the subarachnoid space. Case reports and review of the closed claims database appear to support this concern.

There is a third mechanism by which high doses of anesthetic may be administered into the subarachnoid space. If a practitioner is administering an epidural anesthetic and fails to appreciate that the needle or catheter has traversed the dura or arachnoid, the doses administered may achieve neurotoxic concentrations in the subarachnoid space. Such doses may be sufficient to induce injury even in the absence of maldistribution, as evidenced by case reports.

Reports of neurologic injury with CSA, repetitive injection after failed spinal anesthesia, and inadvertent intrathecal injection of anesthetic intended for the epidural space established the potential toxicity of anesthetics administered at a dose exceeding the usual clinical range for spinal anesthesia. More surprising, two reports raised the suspicion that neurologic deficits might occur with the administration of lidocaine at doses recommended for single-injection spinal anesthesia. One was a case report of CES after the intrathecal injection of 100 mg of lidocaine with epinephrine. The second was a prospective study of regional anesthesia from France. In both reports there were persistent

deficits after single injections of lidocaine that could not be otherwise explained. In all cases, relatively high doses (≥75 mg) were used, and cases of permanent injury occurred only after injection of the maximum recommended clinical dose (100 mg).

Risk Assessment

In prospective studies, retrospective reviews, and epidemiologic studies, the incidence of CES resulting from neurotoxic reactions to local anesthetic varies. Such information is potentially misleading, however, because the incidence depends on practice patterns. The roughly 1 in 5000 incidence of permanent deficits with single-injection lidocaine spinal anesthesia in the aforementioned report from France may overestimate the risk, because modifications have been made to reduce the risk of injury (see Prevention). Nonetheless, when assessing the likelihood that postoperative CES is the result of a neurotoxic reaction, one should consider the circumstances of the case relative to factors known to be associated with clinical toxicity (e.g., inadvertent intrathecal injection of an intended epidural dose of anesthetic).

In addition to the rare occurrence of CES after spinal or epidural anesthesia, transient neurologic symptoms (TNS)—defined as pain or dysesthesia in the buttocks and lower extremities—may occur in up to a third of individuals receiving lidocaine for spinal anesthesia. Known risk factors for TNS include outpatient status and surgical positioning (e.g., patients undergoing knee arthroscopy or placed in the lithotomy position). However, TNS can be readily distinguished from CES because the former is not associated with sensory or motor deficits or disturbance of bladder and bowel function.

Implications

CES is a rare but disastrous complication that may result from neurotoxic injury to the nerve roots below the conus medullaris. Because of its seriousness and lack of effective treatment, attention must be focused on the adoption of clinical strategies that minimize risk (see Prevention).

MANAGEMENT

Although some advocate the use of high-dose steroids, these agents have no proven benefit for nerve root injuries resulting from local anesthetic. As mentioned earlier, there are many potential causes of CES, including a compressive lesion (e.g., hematoma, abscess). Unlike neurotoxic damage, injury from compression is readily reversible, and the extent of recovery is related to the degree of functional loss and the time from the onset of deficits to surgical decompression. The clinical circumstances (coagulation status, difficulty placing the block, etc.) may provide guidance as to the likelihood of this alternative. Also, local anesthetic neurotoxicity presents as a block that does not recede, whereas a period of normal postoperative function followed by progressive loss in the absence of ongoing administration of local anesthetic is strongly suggestive of a compressive lesion. Because time is of the essence, any suspicion should be investigated by emergent magnetic resonance imaging.

PREVENTION

Analysis of the clinical reports of CES occurring with spinal and epidural anesthesia and data generated in experimental studies of neurotoxicity has led to the identification of factors that appear to potentiate risk. This information forms the basis of practice modifications.

Continuous Spinal Anesthesia

Injuries occurred with CSA because high doses of anesthetic were administered intrathecally to compensate for a restricted sensory block. Guidelines have been proposed that emphasize reliance on a test dose, adjustment of technique, and abandonment of the technique if adequate block is not achieved within the normal clinical dose range for single-injection spinal anesthesia (Box 154.1).

Repeat Injection After Failed Spinal Anesthesia

Similar to CSA, guidelines for the management of failed spinal anesthesia have been proposed. These include an assessment of the likelihood of technical error (e.g., failure to inject the drug intrathecally) and appropriate reduction of the dosage for the repeat injection. However, a more efficient (and perhaps safer) strategy is to simply limit the combined anesthetic dosage to the maximum amount a clinician would consider reasonable to administer as a single intrathecal injection.

Epidural Anesthesia

The potential for toxicity with inadvertent intrathecal injection of an epidural dose of anesthetic underscores the importance of a test dose and the fractional administration of anesthetic. Additionally, should high doses of anesthetic be administered through a misplaced intrathecal catheter, repetitive withdrawal of small volumes of cerebrospinal fluid and replacement with saline should be considered, regardless of the anesthetic agent.

Lidocaine Spinal Anesthesia

Most of the recent injuries associated with spinal and epidural anesthesia have been associated with the use of lidocaine. Experimental investigations have reinforced concerns about this anesthetic, suggesting that its inherent toxicity exceeds that of bupivacaine. In animal studies, intrathecal lidocaine caused apoptosis of spinal cord dorsal root ganglion neurons. Modified guidelines for the use of this agent are summarized in Box 154.2 and detailed in the following paragraphs

BOX 154.1 Continuous Spinal Anesthesia: Guidelines for Administration

Insert the catheter just far enough to confirm and maintain placement.
Use the lowest effective anesthetic concentration.
Administer a test dose, and assess the extent of block.
If maldistribution is suspected, use maneuvers to increase the spread of local anesthetic (e.g., change the patient's position, alter the lumbosacral curvature, switch to a solution with a different baricity).
If well-distributed sensory anesthesia is not achieved before the dose limit is reached, abandon the technique.

Adapted from Rigler ML, Drasner K, Krejcie TC, et al: Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* 72(3):275-281, 1991.

BOX 154.2 Lidocaine Spinal Anesthesia: General Guidelines

Dosage should be limited to 60 mg.
Concentration should not exceed 2%.
Use bupivacaine or mepivacaine to prolong block.

Data from Drasner K: Lidocaine spinal anesthesia: a vanishing therapeutic index? *Anesthesiology* 87(3):469-472, 1997.

(although lidocaine is the focus, most of these considerations apply to any intrathecal anesthetic agent).

Dose

Most studies indicate that the potency ratio of lidocaine to bupivacaine is approximately 1:4. Yet the maximum recommended doses of 100 mg and 20 mg, respectively, or the administration of whole ampules of these agents (100 mg and 15 mg), result in ratios of 5:1 or 6.7:1. The issue of relative toxicity aside, 100 mg exceeds the dose of lidocaine required for reliable spinal anesthesia. This, combined with case reports of probable neurotoxicity at the upper end of the dose range, leaves little justification for the continued use of a 100-mg ceiling. The data are inadequate to make a firm recommendation regarding the maximum safe dose, but many use 3 mL of 2% (60 mg) for reliable spinal anesthesia.

Concentration

Abundant data suggest that anesthetic neurotoxicity is, to some extent, concentration dependent. It is therefore hard to justify the continued use of concentrations that far exceed that required for adequate blockade. With respect to lidocaine, the injected concentration should not exceed 2% lidocaine because it will produce sensory anesthesia that is clinically equivalent to a 5% solution.

Glucose

A feature common to most recent cases of clinical injury is the use of an anesthetic solution with a high concentration of glucose and a tonicity far exceeding the normal physiologic range. Despite this association, 7.5% glucose does not affect the compound action potential in vitro or potentiate anesthetic-induced conduction failure. Moreover, dose-dependent loss of sensory function produced by intrathecal lidocaine in vivo is unaffected by the presence of 7.5% glucose, and the administration of 10% glucose does not induce impairment or morphologic damage. These findings suggest that glucose can be safely used to increase baricity.

Vasoconstrictors

Vasoconstrictors might contribute to toxicity by promoting ischemia, decreasing anesthetic uptake, or directly affecting neural elements. Epinephrine potentiates sensory block induced by intrathecal lidocaine. Recently in vivo animal experiments did not show histopathologic changes with the addition of epinephrine to either 5% or 7.5% lidocaine, which is in contrast to previous reports. Until the issue is definitive, if the goal is to provide a longer duration of surgical anesthesia, this can be readily achieved with bupivacaine or mepivacaine.

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155 Long QT Syndromes and Torsades de Pointes

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Case Synopsis

A 65-year-old woman undergoes laparoscopic hysterectomy under general anesthesia. She has paroxysmal atrial fibrillation, for which she takes sotalol, and has recently commenced diuretic therapy for pedal edema. After completion of uneventful surgery, ondansetron is administered, shortly followed by sudden-onset polymorphic ventricular tachycardia (VT). Because the patient is hemodynamically unstable, asynchronous DC cardioversion is performed and a magnesium infusion commenced. After successful cardioversion, her 12-lead electrocardiogram (ECG) demonstrated a QTc of 490 ms, and on arterial blood gas, her serum potassium was 3.0 mmol/L.

PROBLEM ANALYSIS

Definition and Causes

Long QT syndrome (LQTS) is a cardiac conduction disorder characterized by prolongation of the QT interval and an association with a specific polymorphic VT termed *torsades de pointes* (TdP). The unifying mechanism of this heterogenous disease is prolongation of repolarization with early after depolarizations (EADs), which, on reaching a threshold, trigger events such as ventricular arrhythmias. These can be self-terminating or progress to ventricular fibrillation (VF) and sudden cardiac death (SCD).

LQTS may be congenital (c-LQTS) or acquired (a-LQTS). A proportion of a-LQTS cases are patients with latent genetic mutations that reduce the "repolarization reserve," without meeting the diagnostic criteria for c-LQTS. The autosomal recessive Jervell Lange-Nielsen syndrome, associated with sensorineural hearing loss, was the first c-LQTS to be described followed by the autosomal dominant Romano-Ward syndrome. A multitude of mutations have since been identified, producing 13 subtypes of c-LQTS. LQT 1, LQT2, and LQT3 account for more than 92% of genetically confirmed cases.

The putative mechanism of drug-induced LQTS is inhibition of the potassium channel encoded by the KCNH2/HERG gene. Flow through this ion channel produces the rapidly acting outward-rectifying potassium current (IKr), responsible for phase 3 of the cardiac action potential. Dysfunction results in prolongation of repolarization, manifesting as prolonged QTc. Genetic mutations of KCNH2 cause LQT2 and may share causative mechanisms. It is worth noting that many drugs block IKr and do not produce TdP.

LQT1 is caused by a genetic mutation in KVLQT1, which encodes a protein component of the slow delayed rectifier potassium current (IKs). These patients comprise 30% to 35% of c-LQTS and are sensitive to sympathetic stimulation, on which they will display prolongation of QTc. This can be used for diagnostic purposes. Beta-blockade and sympathectomy in this group is particularly beneficial.

Prolonged repolarization can also be caused by inappropriate inward sodium current, as is the case in LQT3, where genetic mutations of SCN5A cause impaired inactivation of sodium channels.

The triggers for TdP in LQT1 are catecholamine mediated, whereas in LQT3 and a-LQTS slow heart rates, bradyarrhythmias, and pauses that follow premature extrasystoles can trigger TdP ("pause dependent"). Indeed, TdP and SCD occur mostly during sleep in LQT3. In such circumstances, increasing the heart rate will reduce the QTc (reverse use-dependence) and can be exploited for therapeutic effect (see Management).

Recognition

Prolonged QT interval on the surface ECG (Fig. 155.1) signifies prolongation of repolarization of the cardiac myocyte. Although it is the hallmark of LQTS, it may be absent at rest. Heterogeneity of repolarization across the ventricles is thought to provide the necessary milieu for EADs and reentrant circuits, causing and sustaining TdP. ECG features

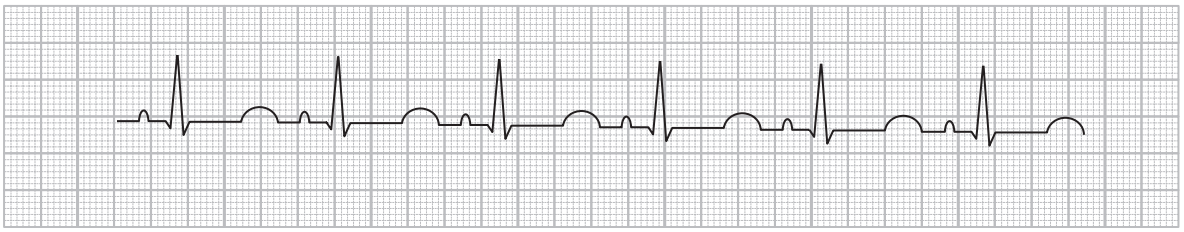

Fig. 155.1 ECG rhythm strip demonstrating prolonged QTc. QT is measured from the start of the Q wave to the end of the T wave.

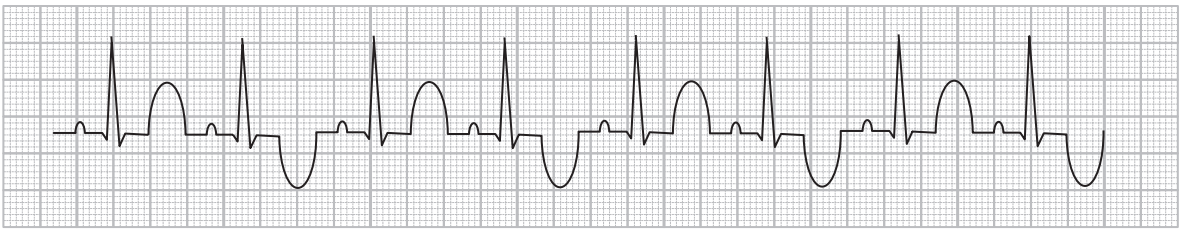

Fig. 155.2 T-wave alternans is the beat-to-beat variability of the polarity (seen here) or morphology of the T wave.

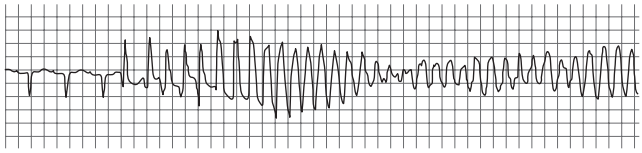

Fig. 155.3 Torsades de pointes preceded by sinus beats with prolonged QTc. Notice the "twisting of the points," the hallmark of TdP. (From Compton SJ: Ventricular tachycardia workup. 2015. Available at http://emedicine.medscape.com/article/159075-workup#c8. Accessed September 6, 2016.)

of this heterogeneity include increased QT dispersion (QT_{max}-QT_{min}), abnormal T-wave morphology, and T-wave alternans (Fig. 155.2).

The normal QT interval range, corrected for heart rate by Bazett's formula (QTc = QT interval/ $\sqrt{RR}$ interval), is less than 430 ms for men and 450 ms for women (sex hormone effect), with prolonged accepted as 450 ms and 470 ms, respectively. QTc varies with autonomic state, drugs, and diurnal variation.

The ECG features of TdP are as follows (Fig. 155.3):

- QRS complexes that vary in amplitude and appear to twist around the isoelectric baseline
- Rate between 200 and 250 beats per minute
- Associated with bradycardia and heart block (especially a-LQTS)

These may be brief and well tolerated, or sustained with hemodynamic collapse and degrade to VF.

Risk Assessment

c-LQTS

A history of syncope, presyncope, palpitations, and cardiac arrest may be elicited, or disclosure of a family history of sudden cardiac death. Indeed, most patients (60%) are diagnosed with ECG screening after an event in a family member. Symptomatic arrhythmias herald a high risk for cardiac events. Affected patients may be treated with β-blockers, whereas high-risk patients may have implantable cardioverter defibrillators (ICDs) in situ and/or undergone left cardiac sympathetic denervation.

The single most predictive factor of cardiac events is a QTc greater than 500 ms. Overt T-wave alternans (see Fig. 155.2) is another sign of electrical instability that warrants intervention.

Jervell Lange-Nielsen syndrome has a malignant course. LQT1 and LQT2 with QTc greater than 500 ms and males with LQT3 have the highest associated risks. There is an elevated risk during the postpartum period.

a-LQTS

Drugs

Many drugs have been implicated in prolonging QTc, although antiarrhythmics are largely responsible (Table 155.1). There is an

TABLE 155.1 Drugs Categorized as Known Risk of Torsades de Pointes

Antiarrhythmics	Amiodarone
	Disopyramide
	Dofetilide
	Dronedarone
	Flecainide
	Ibutilide
	Procainamide
	Quinidine
	Sotalol
Antibiotics	Azithromycin
	Ciprofloxacin
	Clarithromycin
	Erythromycin
	Gatifloxacin[a]
	Levofloxacin
	Moxifloxacin
	Sparfloxacin[a]
Antifungals	Fluconazole
	Pentamidine
Antimalarials	Chloroquine
	Halofantrine
Antiemetics	Chlorpromazine
	Domperidone
	Droperidol
	Ondansetron
Antipsychotics	Haloperidol
	Levomepromazine
	Mesoridazine[a]
	Pimozide
	Sulpiride
	Thioridazine
Antidepressants, selective serotonin reuptake inhibitors	Citalopram
	Escitalopram
Antihistamines	Astemizole[a]
	Terfenadine[a]
Opioid agonists	Levomethadyl[a]
	Methadone
Phosphodiesterase 3 inhibitors	Anagrelide
	Cilostazol
Anticancers	Arsenic trioxide
	Oxaliplatin
	Vandetanib
Miscellaneous	Bepridil[a]
	Cisapride[a]
	Donepezil
	Papaverine HCl
	Probucol[a]

Other drugs have "possible" and "conditional" risks—see www.crediblemeds.org: Arizona Center for Education and Research on Therapeutics.
[a]Removed from the U.S. market.

BOX 155.1 Factors Increasing the Risk of Drug-Induced Torsades de Pointes

Female gender
Advanced age
Diet disorders
Bradycardia
Recent conversion from atrial fibrillation
Congestive heart failure
Digoxin therapy
Baseline QT prolongation
Ventricular arrhythmia
Left ventricular hypertrophy

approximate but imperfect relationship between QTc prolongation and risk of TdP. Anomalies include amiodarone, which prolongs QTc but rarely causes TdP, and terfenadine, which is strongly linked to TdP with only modest effects on the QTc.

Risk factors relating to QTc-prolonging drugs include the concomitant use of two or more drugs, high drug concentrations, rapid intravenous administration, and combination with its metabolic inhibitor.

Patient Factors

A number of patient factors increase the susceptibility to drug-induced LQTS. There is a female preponderance, making up 70% of TdP case reports, ostensibly due to their longer baseline QTc and hence reduced repolarization reserve. Other cardiac disorders also render patients more vulnerable (Box 155.1).

Electrolytes

Electrolyte imbalances increase the QTc and predispose to TdP. Importantly:

- Hypomagnesemia
- Hypokalemia
- Hypocalcemia

Diuretic therapy, diarrhea and vomiting, metabolic disturbances, and imbalanced diets (anorexia nervosa, starvation, liquid protein diets) may be causative or contributive.

Implications

Prognostic information for c-LQTS is derived from the prospective International LQTS registry. It demonstrates that c-LQTS subtypes have distinct natural histories.

LQT1 and LQT2 groups experience cardiac events (syncope, cardiac arrest, or sudden death) at a younger age and are prone to multiple episodes. By age 15, 53% and 29% had suffered a cardiac event, respectively, in contrast to 6% in LQT3. Multiple events occurred in 37% and 36% of LQT1 and LQT2 groups, respectively, compared with just 5% in LQT3.

Despite these differences, mortality rate was 3% to 4% in all groups with a cumulative mortality rate of 6% to 8% at 40 years. This is partly explained by the higher mortality rate associated with cardiac events in LQT3 (20% vs. 4%).

The registry combines probands and family members together into a single group, and thus mortality is likely to be significantly higher in affected individuals. Indeed, a separate analysis of 479 probands and 1041 affected family members demonstrated that cardiac events occurred in 76% and 22%, respectively.

Although a-LQTS is more common, the implications are less clear. Estimates of TdP vary from 1% to 10% with antiarrhythmic drugs, and there is a much lower incidence with noncardiovascular drugs.

The incidence of perioperative TdP in children with c-LQTS in two retrospective cohort studies was reported at 2.6% (3 of 114 cases) and 3.2% (5 of 158 cases). A systematic review of case reports across all ages revealed 46 cases of perioperative TdP, with a 4% (2 of 46) case fatality rate.

MANAGEMENT

c-LQTS

The general management of c-LQTS includes appropriate lifestyle changes and avoidance of triggers. With improved understanding, genotype-specific treatment is becoming available. Antiadrenergic strategies are particularly effective in LQT1 and LQT2 (catecholamine-sensitive), sodium channel blockade in LQT3, and chronotropic strategies in LQT3 and a-LQTS (pause-dependent TdP susceptibility).

- Beta-blockade is recommended in all patients (although less effective in LQT3). It reduces cardiac events, especially in the postpartum period (risk reduction from 1 in 50 to 1 in 2500).
- ICD therapy is indicated in survivors of cardiac arrests and those with continued symptoms despite beta-blockade.
- Cardiac pacing is used in conjunction with beta-blockade and is thought to be particularly relevant in LQT3 where QTc shortens with increasing heart rate.
- Left cardiac sympathetic denervation in high-risk patients intolerant or refractory to beta-blockade and/or ICD is contraindicated.
- Sodium channel blockade with mexilitine, flecainide, or ranolazine in LQT3.
- Left stellate ganglion block can be considered for symptomatic patients requiring urgent/emergent surgery where ICD/cardiac pacing is absent.

a-LQTS

The overriding principle comprises withdrawal of the causative drug(s) and correction of electrolytes.

- Remove offending agent(s), and substitute as appropriate.
- Correct electrolytes, particularly potassium, magnesium, and calcium; likely with diarrhea and vomiting or diuretic use.
- Dietary imbalances should be addressed.

Torsades De Pointes

Management of TdP in a-LQTS and c-LQTS is broadly similar. Asynchronous DC cardioversion is indicated in the hemodynamically compromised patient. TdP is usually transient, however, and medical interventions can be instituted.

- Magnesium 2 g intravenously
  - Treatment of choice
  - Over 15 minutes, or 1 to 2 minutes in cardiac arrest
  - Consider infusion after bolus at 3 to 20 mg/min
- Transvenous pacing to achieve a heart rate of 100 beats per minute
  - *a-LQTS only:* isoproterenol: start at 2 μg/min and titrate (contraindicated in c-LQTS)
- Class 1B antiarrhythmic drugs have been used, although their efficacy is limited
  - Lidocaine, phenytoin, or mexilitine
- Potassium correction to 4.5 to 5.0 mmol/L
  - Evidence equivocal but easily achievable

TABLE 155.2 Anesthetic Drugs and Authors' Recommendations[a]

	Safe	Use With Caution[b]	Avoid/Unsafe[c]
Induction agent	Thiopentone Midazolam	Propofol	Ketamine
Muscle relaxants	Vecuronium Rocuronium Atracurium Mivacurium	Pancuronium	Suxamethonium
Volatiles	Isoflurane	Sevoflurane	Enflurane Halothane Nitrous oxide
Local anesthetics	Lignocaine Bupivacaine		Cocaine Avoid epinephrine additives
Opiates	Morphine Fentanyl	Sufentanil	Methadone
Antiemetics	Dexamethasone Metoclopramide	Cyclizine	5-HT3 antagonists (e.g., ondansetron) Droperidol Levomepromazine
Sympathomimetics	Metaraminol	Ephedrine Phenylephrine	Isoproterenol Epinephrine Dobutamine
Anticholinergics		Atropine Glycopyrrolate	
Others	Clonidine Dexmedetomidine	Neostigmine/glycopyrrolate	

[a]Due to the conflicting literature, this represents a guide rather than a consensus. Avoidance of tachycardia and bradycardia is key to safe use.
[b]Case reports and/or warnings exist but have been used safely. Avoid where possible.
[c]Extensive case reports or causative pharmacodynamic effects. Safe use may be described. Avoidance is recommended.

Polymorphic Ventricular Tachycardia

The principal differential of TdP is polymorphic VT (PMVT). Although largely indistinguishable during the ventricular arrhythmia, a normal QTc will be evident between episodes. PMVT is most commonly due to myocardial ischemia, which may also be apparent. Treatment in this context includes β-blockers, lidocaine, and amiodarone (contraindicated in TdP). Urgent coronary angiography is subsequently indicated.

As with TdP, magnesium administration and potassium correction should be undertaken and asynchronous DC cardioversion if hemodynamically compromised.

PREVENTION

Evidence for the perioperative management of LQTS is sparse and based on case reports and case series. The true incidence of intraoperative TdP in c-LQTS is not known, although retrospective studies place it at 2.6% to 3.2% in children. Emergence appears to be a critical period, with all 3 cases in one study (of 114 general anesthetics) occurring during this time. There is conflicting information regarding drugs and volatiles, with dichotomous outcomes reported with the same agents. The anesthetic technique and agents may be less important than providing adequate and balanced anesthesia during periods of maximal stress. An approach follows.

Preoperative:

- Calm environment and sedative/anxiolytic premedication (e.g., midazolam or fentanyl).
- Continue beta-blockade and antiarrhythmic treatment. Consider perioperative beta-blockade if not already instituted (c-LQTS).
- Check and correct electrolytes (Mg^{2+}, K^{+}, Ca^{2+}). Consider magnesium before treatment.
- Review ECG for prolonged QTc.
- Address acquired causes (e.g., drug induced, nutritional imbalance) and postpone surgery if appropriate, especially with a history of syncope and presyncope.
- ICD: switch off and have external defibrillator available.
- Pacemaker: usual preoperative checks. If none, have means for temporary transvenous pacing immediately available.

Intraoperative:

- Monitor QTc and consider invasive monitoring for major surgery (fluid and electrolyte shifts).
- General and regional anesthetic techniques are suitable; the latter has the advantage of optimal analgesia and avoidance of stress response. Total intravenous anesthesia techniques are described.
- Maintain normothermia—hypothermia delays recovery of inactivated sodium channels and increases QTc.
- Avoid sympathetic response.
  - Obtund laryngoscopy response, and consider topical local anesthetic.
  - Normocarbia, normoglycemia, normoxemia.
  - Excellent analgesia.
  - Avoid light anesthesia.
- Vagal stimulation causes bradycardia, which predisposes to pause-dependent TdP and prolongs the QTc. Hence:
  - Avoid bradycardia.
  - Avoid high intrathoracic ventilatory pressures.
  - Exercise vigilance during known surgical stimulation (e.g., laparoscopy).
- Avoid drugs known to cause LQTS (see Table 155.1) and implicated anesthetic agents (Table 155.2) where there is suitable experience with alternatives.

Postoperative:

- The postoperative period should remain stress free with adequate analgesia, monitoring of electrolytes and QTc, and continuation of beta-blockade.

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Metabolic Acidosis and Alkalosis

156

Patrick J. Neligan

Case Synopsis

A 56-year-old taxi driver presented to the emergency department (ED) with a 2-day history of abdominal pain and intractable vomiting. He was diagnosed with acute small bowel obstruction. His blood gas (room air) and chemistry panel on arrival were pH 7.38, $Paco_2$ 28 mm Hg, Pao_2 100 mm Hg, Na 145 mEq/L, K 3.8 mEq/L, Cl 90 mEq/L, HCO_{3-} 21 mEq/L, base deficit (BD) –3 mmol/L, lactate 12 mEq/L, albumin 4.2 g/dL, creatinine 1.5 mg/dL, ketones +++.

Before going to the operating room, directly from the ED, the patient was treated with 3 L of isotonic saline solution (normal saline [NS], NaCl 0.9%), and his stomach was decompressed with a nasogastric tube: 1000 mL of gastric fluid was drained. During the operation, 3 L of fluid was drained from the bowel, and the patient has received a further 3 L of NS and 3 L of lactated Ringer's (LR) solution.

The patient went to the intensive care unit postoperatively, and a full set of laboratory tests were sent (Fio_2 0.4): pH 7.38, $Paco_2$ 40 mm Hg, Po_2 100 mm Hg, HCO_{3-} 14 mEq/L, BD –10 mmol/L, Na 145 mEq/L, K 4.9 mEq/L, Cl 117 mEq/L, lactate 1.2 mEq/L, albumin 18 g/dL, creatinine 2.5 mg/dL, urea 25 mg/dL, glucose 145 mg/dL, ketones –ve, urinary output minimal.

PROBLEM ANALYSIS

Arterial blood gas analysis is a useful tool for the anesthesiologist; it gives us dynamic data about the function and reserve of critical systems and their response to therapy. For example, information about the partial pressure of oxygen (Pao_2) allows us to calculate the alveolar gas equation and titrate-inspired oxygen tension (Fio_2) and positive end-expiratory pressure. The partial pressure of carbon dioxide ($Paco_2$) can be used to adjust alveolar ventilation and look for a relationship between arterial and end-tidal CO_2, reflecting the dead space ratio. For patients with chronic obstructive pulmonary disease, advance knowledge of the blood gas illustrates the presence or absence of chronic hypoxemia and hypercarbia. The latter is achieved by looking at the $Paco_2$-[HCO_{3-}] relationship (Box 156.1).

In clinical medicine, acid-base balance has been used as a reliable and reproducible biomarker of acute illness for over 100 years.

BOX 156.1 Changes in the [HCO_{3-}] and $Paco_2$ Associated With Various Acid-Base Disturbances: The Six Rules

$Paco_2$ values are in mm Hg, [HCO_{3-}] in mEq/L or mmol/L.

1. Acute respiratory acidosis:
   Expected [HCO_{3-}] = 24 + ($Paco_2$ – 40)/10
2. Chronic respiratory acidosis:
   Expected [HCO_{3-}] = 24 + 4 × ($Paco_2$ – 40)/10
3. Acute respiratory alkalosis:
   Expected [HCO_{3-}] = 24 – 2 × (40 – $Paco_2$)/10
4. Chronic respiratory alkalosis:
   Expected [HCO_{3-}] = 24 – 5 × (40 – $Paco_2$)/10
5. Metabolic acidosis:
   Expected $Paco_2$ = 1.5 [HCO_{3-}] + 8
6. Metabolic alkalosis:
   Expected $Paco_2$ = 0.9 [HCO_{3-}] + 9

The presence of acute metabolic acidosis is indicative of the presence, severity, and duration of fluid and electrolyte abnormalities, systemic stress, and organ dysfunction. In a patient such as this who requires emergency surgery, analysis of acid-base status may alert the anesthesiologist to the presence of organ failure, the requirement for resuscitation, and the presence or absence of physiologic reserve. The anesthesiologist must have a sufficient understanding of acid-base physiology, a method of interpreting the data, and a decision tree process for optimizing the patient before surgery.

Acid-base chemistry refers principally to the arterial or venous concentration of hydrogen ions, simply expressed as pH. Alterations in pH are indicative of underlying abnormal physiology and disease, acute or chronic. If arterial pH is lower than 7.35, a state of acidosis exists. If pH is greater than 7.45, it represents a state of alkalosis. Changes in arterial pH result from alterations in the partial pressure of carbon dioxide, due to respiratory abnormalities, or changes in the relative concentrations of fully or partially dissociated ionic compounds in extracellular fluid. Of these, ions that do not freely associate into salts within the body are the most important and are known as "strong ions." Strong ions impart electrochemical charge throughout the body, and their relative concentration significantly affects acid-base balance. Strong ions are divided into cations—sodium (Na^+), potassium (K^+), magnesium (Mg^{2+}), and calcium (Ca^{2+})—and anions—principally chloride (Cl^-). These are always present in extracellular fluid but may be supplemented by a variety of often unmeasured anions, derived from metabolism, that may imbalance the relative ratio of strong cations to strong cations—known as the *strong ion difference* (SID). These metabolically derived anions include lactate, ketones, and a variety of metabolic byproducts that are excreted by the kidneys, conventionally referred to as "renal acids." Because, functionally, the appearance of new anions in extracellular fluid is associated with a corresponding hydrogen ion (electrical neutrality must be maintained), this results in narrowing of the SID (normally 44 mEq/L) and is associated with metabolic acidosis (Box 156.2). Three partially dissociated "weak"

acids may also affect acid-base chemistry—the serum phosphate level (PO_4^{2-}), the serum albumin, and the extracellular bicarbonate (HCO_{3-}). The latter principally reflects total body CO_2 stores and provides most of the extracellular buffering of metabolic acids. Carbon dioxide is, functionally, carbonic acid: a rise in $Paco_2$ results in acidosis—CO_2 delivers hydrogen ions into extracellular fluid (respiratory acidosis), and a fall in $Paco_2$ results in alkalosis.

From this paradigm it is possible to construct an understanding of acid-base chemistry based on only three observations: all acid-base abnormalities can occur due to a change in the (1) $Paco_2$; (2) SID; and (3) total concentration of weak acids, principally albumin and phosphate.

The presence or absence of acidosis or alkalosis is detected by looking at three interconnected pieces of data on the arterial blood gas: the pH, the $Paco_2$, and the HCO_{3-}. In general the pH should be in the range of 7.35 to 7.45. If the pH is less than 7.35 a state of acidosis exists; if it is greater than 7.45 the patient is alkalotic. However, the pH may be within the normal range if the acidosis or alkalosis is being physiologically corrected (compensation) or multiple processes are causing acidosis and alkalosis simultaneously. Hence the clinician must look at the carbon dioxide–related variables. A $Paco_2$ in excess of 40 mm Hg is abnormal, and if the $Paco_2$ is high and the HCO_{3-} is also raised the patient has respiratory acidosis. If the $Paco_2$ is below 40 mm Hg and the HCO_{3-} is also low, the patient is hyperventilating. If the pH is greater than 7.5, this is primary respiratory alkalosis, often due to pain or anxiety (and some poisonings such as salicylates). If the pH is less than 7.35, this represents compensation for acute metabolic acidosis. If the pH is greater than 7.5 and the $Paco_2$ and/or the HCO_{3-} is elevated, the patient has acute metabolic alkalosis (Box 156.3).

A final variable that is found on the blood gas is known as the base deficit (a negative number) or base excess (a positive number)—BD/BE. BD/BE uses a calculation to standardize the pH, respiratory component, and temperature to construct a numeric quantum for the degree of metabolic acidosis or alkalosis. For example, if the BD is –5 mmol/L, this means that there is a surplus of 5 mEq/L of anion in extracellular fluid that would require 5 mmol/L of cation (such as Na^+) to restore pH to 7.4. If the BE is +5 mmol/L, this means that there is a surplus of 5 mEq/L of cation in extracellular fluid that would require 5 mmol/L of anion (such as Cl^-) to restore pH to 7.4. Of course, in the presence of multiple acidifying and alkalizing processes going on simultaneously, the BD/BE does not specify the cause, but the major overall acid-base abnormality.

The anion gap (AG) was introduced in the 1970s as a method of differentiating metabolic acidosis caused by hyperchloremia from that caused by unmeasured anions. It is based on the concept of electrical neutrality and has no role in the investigation of metabolic alkalosis. The basic AG is calculated by the following formula:

$$\text{AG (simple)} = ([Na^+] - ([CL^-] + [HCO_{3-}])$$
$$= 12 \text{ to } 14 \text{ mEq/L}$$

BOX 156.2 Causes of Metabolic Acidosis

Reduced Strong Ion Difference (SID)

Dilutional Acidosis (↓Na^+:Cl^-)

1. Hypotonic fluid administration
2. Increased osmolar gap
   a. Ethanol
   b. Ethylene glycol poisoning
3. Increased sodium loss
   a. Diarrhea
4. Water overload (acute)
   a. Congestive heart failure
   b. Cirrhosis
   c. Acute kidney injury

Hyperchloremia (↑Cl^-:Na^+)

1. Increased administration
   a. 0.9% NaCl
2. Reduced excretion
   a. Renal tubular acidosis
   b. Ureteric implantation

Unmeasured Anions

1. Lactic acidosis
   a. Type A—anaerobic glycolysis
   b. Type B—aerobic glycolysis
2. Ketoacidosis
   a. Diabetic ketoacidosis
   b. Starvation/alcoholic ketoacidosis
3. "Renal acidosis"
   a. Hyperchloremia
   b. Hyperphosphatemia
   c. "Renal acids"
   d. Hyponatremia

Increased Weak Acids

Hyperalbuminemia

1. Albumin administration
2. Cholera

Hyperphosphatemia

1. Reduced clearance—acute kidney injury
2. Increased production:
   a. Refeeding syndrome
   b. Tumor lysis syndrome
   c. Rhabdomyolysis
   d. Bowel ischemia
   e. Neuroleptic malignant syndrome
3. Increased intake
   a. Intravenous
   b. Phosphate enemas

BOX 156.3 Causes of Metabolic Alkalosis

Increased Strong Ion Difference (SID)

Contraction Alkalosis (↑Na^+:Cl^-)

1. Hypertonic fluid administration
2. Water loss due to sweating, bowel obstruction, etc.
3. Loop diuretics

Hypernatremic Alkalosis

Administration of Na^+ with week acid buffer:

1. Sodium bicarbonate
2. Sodium citrate
3. Sodium acetate

Hypochloremia (↓Cl^-:Na^+)

1. Vomiting
2. Pyloric obstruction

Increased Weak Acids

Hypoalbuminemia

1. Crystalloid fluid resuscitation
2. Malnutrition
3. Sepsis

Hypophosphatemia

1. Malnutrition
2. Diuresis
3. Excessive removal (dialysis)

As potassium is universally measured in clinical practice, it should be added to the AG calculation:

$$\text{AG (conventional)} = \left(\left[\text{Na}^+\right] + \left[\text{K}^+\right] - \left(\left[\text{CL}^-\right] + \left[\text{HCO}_{3-}\right]\right)\right) = \text{14 to18 mEq/L}$$

The "gap" refers to the charge carried by albumin and phosphate and is usually approximately 8 to 18 mEq/L. As the $[HCO_{3-}]$ falls irrespective of the cause of acidosis, an increase in the $[Cl^-]$ is associated with a similar fall in $[HCO_{3-}]$: the gap remains the same (a "non-gap" acidosis). If unmeasured anions are present in the system, the AG appears to widen (a "widened anion gap" acidosis). As the majority of hospitals now directly measure lactate, it is appropriate to add the lactate measurement to the AG:

$$\text{AG (modern)} = \left(\left[\text{Na}^+\right] + \left[\text{K}^+\right] - \left(\left[\text{CL}^-\right] + \left[\text{HCO}_{3-}\right] + \left[\text{lactate}^-\right]\right) = \text{14 to 18 mEq/L}$$

Although remarkably popular, the AG is a flawed and frequently misleading calculation when applied to critically ill or fluid-resuscitated patients. Universally these patients have low serum albumin, and this masks the presence of unmeasured anions. Hence the AG should be corrected for both albumin and lactate:

$$\text{AG (corrected)} = \left[\left(\text{Na}^+ + \text{K}^+\right) - \left(\text{Cl}^- + \text{HCO}_{3-} + \text{lactate}^-\right)\right] - \left(2.5 \times \left[40 - \text{albumin in g/L}\right]\right)$$

As mentioned, the BD/BE is a useful screening tool for the presence of a major acid-base abnormality, but it lacks the ability to specify cause and identify multiple causes. Fortunately a number of "back of envelope" calculations are available that can separate out the causes of acidosis or alkalosis and detect the presence of unmeasured anions. The calculation is known as the base deficit gap (BDG), and the calculations for the BDG can be found in Box 156.4.

A more complex but more accurate method of calculating major acid-base abnormalities is to use the strong ion gap (SIG), effectively a "deluxe" version of the AG. The strong ion difference *apparent* (SIDa) reflects the difference in charge between all of the strong cations minus the strong anions: $[(Na^+ + Mg^{2+} + Ca^{2+} = K^+) - (Cl^- + A^-)]$. SIDa is always positive and has a magnitude of 40 to 44 mEq/L. This charge is balanced by an equivalent amount of anions—reflected by the charge carried on albumin, phosphate, and bicarbonate—the strong ion difference *effective* (SIDe). There is a small difference between SIDa and SIDe, the strong ion gap (SIG), that quantifies the amount of unmeasured anion present.

$$\text{SIDa} = \left(\left[\text{Na}^+\right] + \left[\text{K}^+\right] + \left[\text{Mg}^{2+}\right] + \left[\text{Ca}^{2+}\right]\right) - \left[\text{Cl}^-\right]$$

$$\text{SIDe} = \left[\text{HCO}_{3-}\right] + \left[\text{charge on albumin}\right] + \left[\text{charge on Pi}\right] \text{(in mmol/L)}$$

Weak acids' degree of ionization is pH dependent, so one must calculate for this:

$$\left[\text{alb}^-\right] = \left[\text{alb g/L}\right] \times \left(0.123 \times \text{pH} - 0.631\right)$$

$$\left[\text{Pi}\right] \text{(in mg/dL)} = \left[\text{Pi}\right]/10 \times \text{pH} - 0.47$$

$$\text{SIG} = \text{SIDa} - \text{SIDe}$$

BOX 156.4 Calculation of Base Deficit–Excess of Sodium Chloride–Free Water and Albumin

$BDE_{NaCl} = ([Na^+] - [Cl^-]) - 38$
$BDE_{Alb} = 0.25\ (42 - \text{albumin g/L})$
$BDE_{NaCl}^- BDE_{Alb} = BDE_{calc}$
$BDE - BDE_{calc}$ = BDE gap = the effect of unmeasured anions or cations

The Clinical Scenario

This patient has both a surgical problem (bowel obstruction) and medical problem (dehydration and significant electrolyte imbalance). Superficially, the pH is 7.38 (normal range). However, using the various approaches described previously will uncover a number of acid-base abnormalities. The simplest and highest-yield technique is to use the BDG approach described in Box 156.4. Preoperatively the patient had a base deficit of −10 and a compensated metabolic acidosis (as evidenced by the $Paco_2$ of 28 mm Hg and "normal" range pH). There was hypernatremia, hypochloremia, and elevated lactate. The BD/BE for sodium, chloride, and free water (BD/ENaCl) was +17, which means that the patient had a severe metabolic alkalosis from hypochloremia and a free water loss (contraction alkalosis)—the SID for NaCl was 55 mEq/L (Table 156.1). The albumin level is normal—there is no hypoalbuminemic alkalosis. The calculated base deficit is −3, but the base excess is +17: a base excess gap of 20. The lactate is 12, which means that there are 8 mEq/L of unmeasured anions in extracellular fluid—likely a combination of ketones and renal acids. So this patient, preoperatively, has a lactic acidosis, starvation ketoacidosis, possibly renal acidosis, contraction alkalosis, and hypochloremic alkalosis. The primary problem, fluid deficit and hypochloremia, was treated with large volumes of NaCl 0.9% intraoperatively.

This led to a different but similarly complex postoperative picture. Using the same methodology, one notes that the ketoacidosis and lactic acidosis have largely resolved (Table 156.2). The patient, however, has developed a significant hyperchloremic acidosis secondary to the nature of intravenous fluids administered. However, using the BD/BE gap approach reveals that there is a sinister secondary acidosis present, buried by the alkalizing effect of albumin dilution. There are 15.2 mEq/L of unmeasured anions present; in the absence of ketones, this is likely due to renal acidosis. In the setting of postoperative oliguria and severe "renal" acidosis, the patient may require renal replacement therapy.

TABLE 156.1 Evaluation of the Patient's Acid-Base Status Using the Base Deficit–Excess Gap—Preoperatively

Acidifying Process	Magnitude	BDC	Alkalinizing Process	Magnitude	BEC
Lactate	12 mEq/L	−12	Hypernatremia	145 mEq/L	+5
Ketones	++++	?	Hypochloremia	90 mEq/L	+12
Kidney injury	Creatinine 1.5 mg/dL	?	Hypoalbuminemia	4.2 g/L	0
Total		−12 + unknown, unmeasured anions	Total		+17

BDC, Base deficit corrected; *BEC,* base excess corrected.
BDC − BEC = BDE measured = (−12 + 17) = +5.
BD/BE calculated − BDE measured = BD/BE gap = −3 + 5 = −8 mmol/L = BDE gap consequent of unmeasured anions (ketones and renal acids).

TABLE 156.2 Evaluation of the Patient's Acid-Base Status Using the Base Deficit–Excess Gap—Postoperatively

Acidifying Process	Magnitude	BDC	Alkalinizing Process	Magnitude	BEC
Lactate	1.2	–1.2	Hypernatremia	145 mEq/L	+5
Hyperchloremia	117	–15	Hypoalbuminemia	1.8	+6
Kidney injury	Creatinine 2.5 mg/dL	?			
Total		–16.2 + unknown unmeasured anions	Total		+11

BDC, Base deficit corrected; *BEC*, base excess corrected.
BDC – BEC = BDE measured = (–16.2 + 11) = –5.2.
BDE calculated – BDE measured = BDE gap = –10 + (–5.2) = –15.2 mmol/L = BDE gap – consequent of unmeasured anions (renal acids).

MANAGEMENT

Lactic Acidosis

To plan out the management of patients with complex acid-base abnormalities, it is important to understand the underlying disease process.

Lactic acid is a physiologic product of glycolytic metabolism. It is continuously generated by lactate dehydrogenase from pyruvate. In anaerobic conditions, such as strenuous exercise, [LA^-] may increase dramatically. LA^- is also produced in aerobic conditions. β-Adrenergic receptor activation, from either stress (increased circulating catecholamines) or catecholamine infusions, increases [LA^-]. LA^- is metabolized in the liver to carbon dioxide and water or regenerated via the Cori cycle to glucose. This is usually termed *lactate clearance*. Lactic acidosis occurs when the production of LA^- is greater than the liver's capacity to clear it; thus [LA^-] may reflect excessive production or inadequate clearance. An [LA^-] of 2 mmol/L is clinically significant, and a level of 5 mmol/L or more is considered severe. In this patient, lactic acidosis has likely arisen from two different mechanisms. The first is volume depletion, excess oxygen extraction in the extremities, and reduced hepatic clearance of lactate due to hepatosplanchnic hypoperfusion. The second is increased "aerobic glycolysis" secondary to adrenoceptor activation—serum lactate levels mirror circulating epinephrine. The initial management of lactic acidosis is fluid resuscitation to normal circulating volume (it is difficult to assess preoperative crystalloid deficit), in this case several liters of fluid. In the operating room, modern dynamic monitors of circulating volume (e.g., pulse pressure or stroke volume variability devices, pulse contour analysis) may help restore euvolemia. Lactate is a poor endpoint of resuscitation—clearance, being hepatic, is relatively slow—and hyperlactatemia may take several days to disappear. However, in general a decline in the serum lactate concentration by 10% per hour is to be expected. A rising lactate is an ominous sign.

Ketoacidosis

Ketones are produced in the mitochondria of liver cells; they are end products of fat metabolism. Fatty acids are beta-oxidized to acetyl coenzyme A (acetyl-CoA). Acetyl-CoA normally enters the citric acid (Krebs) cycle and is metabolized to carbon dioxide and water. However, this process requires insulin, which is stimulated by glucose. In the absence of insulin, ketones—acetoacetate, β-hydroxybutyrate, and acetone—are produced. Ketosis is seen in starvation, consequent of limited food availability (malnutrition), bowel disease, or alcoholism. When the amount of ketones produced exceeds the hepatic clearance rate, ketoacidosis ensues, usually when serum ketone levels exceed 2 mmol/L. Although most clinicians are familiar with diabetic ketoacidosis, due to absolute insulin deficiency, ketoacidosis may occur in the critically ill surgical patient (such as in this case) due to lack of carbohydrates in the diet, hepatic hypoperfusion reducing ketone clearance, and underlying hepatic steatosis (such as is seen in obesity and alcoholism). The treatment for this patient's ketoacidosis is fluid resuscitation, including glucose, which suppresses ketone production; and insulin therapy, which drives ketone metabolism.

Renal Acidosis

Acute kidney injury is characterized by the inability of the nephron to excrete metabolic byproducts, primarily protein metabolites and excess electrolytes. Typically the patient develops uremia, hyperkalemia, hyperchloremia, hyperphosphatemia, and water overload, resulting in hyponatremia. Hence the metabolic acidosis associated with kidney injury is multifactorial, associated with both measured and unmeasured anions and hemodilution. Acidosis generally becomes manifest once the glomerular filtration rate falls below 25 mL/min/1.73 m^2. Although serum creatinine is widely used to identify acute kidney injury, in the setting of large-volume fluid resuscitation, serum creatinine may be diluted and misleadingly low. Hence the presence of metabolic acidosis in the setting of oliguria should alert the clinician to the potential for uremia, fluid overload, and abdominal compartment syndrome. In this scenario, particularly postoperatively, a conservative approach involving fluid restriction and diuretic therapy may be applied. However, if the patient develops clinically significant hyperkalemia, cardiovascular instability, clinically significant fluid overload (e.g., frank pulmonary edema or deteriorating gas exchange), or anuria, renal replacement therapy is indicated. Sodium bicarbonate therapy can be used to provide cardiovascular stability as a bridge to hemodiafiltration.

Hypochloremic Alkalosis/Hyperchloremic Acidosis

The relative ratio of sodium to chloride in the extracellular fluid is approximately 1.4:1. An increase in this ratio, which usually follows free water deficit, increases SID and results in metabolic alkalosis (in this scenario "contraction" alkalosis). In our case synopsis, where the serum sodium is within normal limits but serum chloride is depleted, it is likely that the patient has hypochloremic alkalosis secondary to loss of gastric juice, consequent of vomiting. The treatment is to administer chloride-rich fluid until serum chloride concentration is within normal limits. Isotonic ("normal" 0.9%) saline solution contains 154 mmol/L of sodium and 154 mmol/L of chloride—the SID is 0. As a result each liter of saline effectively delivers 50 mmol/L of HCl to the extracellular fluid. This will rapidly reverse hypochloremic alkalosis. However, when excessive quantities of NaCl 0.9% are administered, hypernatremia and progressive hyperchloremic acidosis results, as occurred in this scenario. Hyperchloremia is not benign, and there is an association between hyperchloremic acidosis and renal injury. In perioperative medicine and critical care, patients

who develop hyperchloremic acidosis have worse all-cause outcomes, including elevated mortality rate.

PREVENTION

Could this patient have been managed better? Small bowel obstruction results in significant fluid and electrolyte deficits and, in this case, hypochloremic alkalosis. Nasogastric drainage is essential to reduce the risk of aspiration pneumonitis. Initial fluid resuscitation with isotonic saline solution was appropriate, to rapidly correct hypochloremia. However, with bowel obstruction there is a significant deficit in most electrolytes and free water. Lactated Ringer's solution (LR), though slightly hypotonic (replacing free water), repletes sodium, potassium, and calcium and repletes extracellular buffer (lactate is converted to bicarbonate). The Na:Cl SID of LR is 20, so this fluid can be used to correct hypochloremic alkalosis, but the patient is unlikely to develop significant hyperchloremic acidosis. The continued administration of NaCl 0.9% certainly resulted in hyperchloremic acidosis and may have contributed to the development of acute kidney injury.

A strong argument could be made to delay the surgery until the patient's metabolic state is resolved. Fluid resuscitation and analgesia improves overall hemodynamics, reduces hyperadrenergic activity, and limits the production and increases the metabolism of lactate. In addition to rehydration and repletion of electrolytes, administration of intravenous glucose and insulin would have resolved the ketoacidosis rapidly preoperatively.

Intraoperatively a goal-directed approach to fluid resuscitation using a dynamic monitor of fluid status such as esophageal Doppler, stroke volume variation, pulse pressure variation, pulse contour analysis in response to fluid bolus, straight-leg raising, or end-expiratory occlusion would have resulted in a finely titrated approach to overall fluid therapy and prevented the potential development of postoperative abdominal compartment syndrome and acute kidney injury.

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157 Misidentification of a Patient

Kenneth Kuchta

Case Synopsis

A 12-year-old boy was brought to the operating room for a liver transplant late one Sunday evening. Frequent blood draws were done throughout the case, and the tests were run on a point-of-care machine in the operating room. The machine allowed for both manual and barcode input of the patient's medical record number. However, the manual input was disabled several years ago in all of the operating rooms when several providers found that the touch screen keypads were difficult to use and resulted in several instances of laboratory tests attributed to the wrong patient. The anesthesiologist used the barcode on a wristband removed from the patient because his arms were going to be tucked and thus inaccessible. Though used for several laboratory tests, this barcode proved to be difficult to scan, and the circulator was asked for the facesheet, which also contained the barcode. After several sets of tests, it was noted that the facesheet was incorrect, and further investigation revealed that it had been left at the circulating nurse's workplace from a prior liver transplant 2 days before. The anesthesia team traced that patient to the pediatric intensive care unit (PICU) and notified the team of the error. The team in the PICU had noted laboratory tests appearing in the medical record and was beginning an investigation of a drop in hemoglobin along with several other critical values, when an astute nurse noted that she had not sent any laboratory tests in the last several hours. After several lengthy calls to technology support for the hospital, the errant test results were finally assigned to the correct patient.

PROBLEM ANALYSIS

Definition

Throughout a patient's interaction with the health care system, his or her identity must be verified to match any intended intervention and any test result to that patient. Although the procedure is the main reason for the patient being in the operating or procedure room, his or her interaction with the health care system in that location is far more complex.

Thus patient misidentification in the perioperative setting can result in the following:

- A patient receiving a nonintended medical or surgical intervention
- A patient receiving mismatched or the wrong blood products
- A patient receiving the wrong drug or not receiving an intended drug
- A patient being identified with the wrong laboratory or test results
- A planned surgery being performed on the wrong limb, or a procedure being performed without a patient's informed consent

As demonstrated in the case synopsis, many of these errors can affect a second patient, and not infrequently one that the practitioner is not taking care of at the time. Any interaction with the health care system, even one far removed from the operating room, can affect the care of our patients (such as a history and physical from an outside medical group belonging to another patient being scanned for input into our patient's electronic record).

Recognition

Patients undergoing procedures under anesthesia are often recognized as the most vulnerable and dependent on those immediately caring for them. Sedation and general anesthesia renders them unable to notice and object to misidentification errors. Thus the goal of recognizing misidentification before it has an impact (finding the near misses before they become events with significant impact) often falls on health care workers. Still, patient and families play an important role, and engaging patients in their health care extends to ensuring the identity of the patient and matching this to the procedure being done, the laboratory tests being performed, and all other aspects of their interaction with the health care system. Much of this will occur in the preprocedure area with questions such as patient identity, medical history, allergies, and planned procedure being asked multiple times by all disciplines of the teams involved. Open-ended questions ("What operation are you having?" vs. "You are having an EVAR, correct?") are preferred to actively engage the patient. Finally, when all these barriers fail, patients, family members, or medical personnel may recognize a misidentification that has not been caught before having a consequence.

Risk Assessment

Patient misidentification is a heterogeneous group of events; therefore reported incidence varies tremendously by definition. The catastrophic wrong-site surgery is said to be rare with an incidence someplace between 1 in 25,000 and less than 1 in 100,000. The chance for a patient misidentification in general is much greater. One pediatric hospital found an identification band error rate of 20.4%, with errors defined fairly broadly: missing bands, inappropriately placed bands, illegible bands, and inaccurate data. However, the meaning and clinical significance of inappropriate and illegible were not further elucidated. Though incident reporting is far from comprehensive, the emphasis on patient safety and reporting of events

at the U.S. Department of Veterans Affairs resulted in an over 100 root-cause analysis involving patient misidentification from January 2000 to March 2003. In the United Kingdom between February 2006 and January 2007 there were 24,382 reports of patients receiving the wrong care, with an estimate that more than 2900 (>10%) of these were related to wristbands and their use. Between November 2003 and July 2005 the same agency had 236 reports related to missing wristbands or wristbands with incorrect information, likely indicating an increased reporting and/or a variation in defining the problem. And although wrong-site surgery is likely to be correctly recognized as a problem, the near misses related to patient identification are often compensated for and corrected by the medical personnel and thought of as just another annoyance that is part of modern medical care.

Implications

Many cases of patient misidentification, even when discovered, may cause no more than minor annoyance or embarrassment (e.g., a health care provider going to the wrong bed in a crowded preoperative area only to have the error discovered when the patient notes that he or she is being addressed by the wrong name). Even this event can lead to a lingering distrust in the safety of medical care on the part of patients (though they may be too polite to express this sentiment). At the other end of the spectrum, if an adverse outcome occurs, the consequences can be significant. The potential impact on the patient and family is obvious. The increased scrutiny can only be expected to have further consequences. One need only look at the popular press to see the implications in terms of large malpractice settlements, loss of licenses or accreditation, and tarnished reputations for both the individuals and their institutions. No matter how complex health care has become, clearly the public expects all procedures, medicines, and blood products to be delivered correctly.

MANAGEMENT

Although the emphasis is on minimizing misidentification to prevent adverse outcomes from occurring, a plan for management should also be in place. Errors, especially if they have serious consequences, can be devastating to the patient, the patient's family, and the health care worker. Appropriate support and guidance may be needed, especially for the more serious events.

In general, if an error in patient identification occurs, the following should be done:

- Be forthright regarding the incident (though do not speculate if the cause is uncertain).
- Promptly notify all parties and the appropriate risk-management and/or quality-improvement committees.
- Clearly document what has occurred in the patient's chart (again avoiding speculation of cause).
- Continue to follow the patient, and document these visits.
- Undertake an immediate investigation to prevent recurrences.

We are morally and ethically obligated to be forthright with patients when identification errors occur, especially when they may be associated with significant adverse outcomes. This approach is codified in health care policy (since 2001 the Joint Commission on Accreditation of Health Care Organizations [JCAHO] has required that patients be informed of unanticipated outcomes), and such disclosures are often surprisingly better received by patients than we might expect. In fact, candidness may actually reduce the likelihood of litigation. A show of empathy and continued interest in the patient's well-being is certainly better than avoiding the situation altogether. Documentation of these postevent visits is not only is good medicine but also confirms the practitioner's ongoing concern if the case goes to litigation. Undoubtedly, practitioners who make identification errors remember them for some time.

All parties involved in the case should be notified of the error immediately. This includes hospital risk-management and quality-assurance committees and any insurance companies that might be involved. Clearly document what has occurred in the patient's chart. An immediate investigation should ensue to determine how the mistake occurred and what preventive measures must be instituted immediately to avoid recurrences. Increasingly, with the emphasis on "just culture," such investigations focus less on the person who made the mistake and more on discovering the circumstances that led to the commission of the error.

PREVENTION

Given the complexity of modern health care, the chance of patient misidentification is ever present. Traditionally, when such errors occurred the usual solution was to counsel the health care provider closest to the event (the sharp end of the error) to be more careful in the future and to educate others to exercise more vigilance. This approach ignored the blunt end of the process that often contained latent errors (essentially flaws in the system) that make it likely for the active error (the one at the sharp end) to occur. More recently, health care institutions have conducted a more structured review, usually a root cause analysis, of the entire process that led to the event. The intent of these reviews is to uncover the latent errors, flaws in the system, that make the event likely to occur in the future, usually by another practitioner. The institution then usually devises policies and changes procedures to reduce the chance of a recurrence.

In tandem with the changing emphasis on system issues when reviewing events, JCAHO has continued its emphasis on patient misidentification. Its national patient safety goals for 2016 include the use of at least two patient identifiers (with neither being the room number or location) for procedures, for treatments, during medication or blood/blood product administration, or collecting specimens (including blood samples). Containers for blood and specimens are not to be prelabeled. Two-person verification (or one person plus automated identification, e.g., barcode) is required for blood administration. The Joint Commission's "Universal Protocol for Preventing Wrong Site, Wrong Procedure, and Wrong Person Surgery" continues to appear in these new safety goals. The protocol calls for three broad elements. The first is a preprocedure verification process intended to confirm that the correct patient will have the correct procedure on the correct site and that the necessary information and equipment are present. This may happen at more than one time/place before the operation. A standardized approach, with active involvement of the patient when possible, is stressed. The second element is site marking. The institution is tasked with identifying when site marking is needed (defined as when performing the procedure at an alternate location would adversely affect quality or safety). Of course the site needs to be marked before the procedure and with participation of the patient if possible. The marking is ideally done by the licensed practitioner who is ultimately accountable and present for the procedure, though exceptions are outlined to allow delegation. Unambiguous and institutionally consistent markings are called for. Written policies for exceptions (patient refusal, impossible or impractical sites) need to be in place. The final element is the time-out, which is a standardized active communication among all members of the operative team and occurs immediately before the procedure. JCAHO minimal elements are confirming the correct patient, site, and procedure, and this must be documented as completed. If a second procedure by another

surgeon is to occur at the same setting, a second time-out is done before the second procedure.

In the 2016 JCAHO patient safety goals, much of the specifics including the exact behavioral elements were left to the health care institutions. Yet the success of these goals may rely on the specifics of implementation. One large institution, the U.S. Veterans Administration, gives one example of extension of these recommendations to specifics. Its directive gives extensive definitions of the invasive procedures, beyond surgery, that are included in its correct surgery policy. Elements of the consent are much more extensive, as are the time-out elements, and the patient site and procedure is specifically a two-part process: the first at the time of site marking, and the second immediately outside the procedure room with the person doing the identification staying with the patient into the procedure room.

Fortunately, there is an increased emphasis on preventing misidentification of patients despite the seeming rarity of such events that result in significant harm to patients. Techniques to prevent or trap these errors have propagated across the health care system. Unfortunately, the effectiveness of these techniques has been difficult to prove. A 2015 Cochrane Review update on interventions for reducing wrong-sided procedures could find only two high-quality publications on the subject. The first was a previously noted article from the dental literature. To this was added a recent study showing a decreased incidence in neurosurgery at one university hospital that was confounded by a rate drop that was approaching zero shortly before the intervention. A recent broader article looking at the effectiveness of surgical checklists (although instituted for reasons beyond misidentification of patients) also showed no impact on patient outcomes.

Despite this disappointing outcomes research, clinicians look toward these measures to begin addressing patient misidentification. A simulator study from 2009, though done in an emergency department setting, is perhaps indicative of this dilemma. When faced with three patients, one with an incorrect identification (ID) band, only 61% found the error. Technology has been thought to offer assistance with the problem, though proposed solutions have yet to be widely implemented. One promising proof of concept paper used radiofrequency ID (RFID) tags to track the location of test patients in operating rooms (ORs). This information was tied to the electronic OR schedule to allow an alert to be generated via pager when the wrong patient was brought to an OR. A proposed update to the system would add RFID tags to the ID of OR personnel so that the staff member closest to the patient would receive the pager alert. Unfortunately, technologic solutions, though proposed, have been slow in being broadly implemented. Ultimately, we are left with heightened awareness, continued vigilance, increased reporting of events and near misses, comprehensive quality evaluation, and ultimately, outcomes research to solve the problem of patient misidentification.

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Perioperative Hypertension 158

Jerrold H. Levy

Case Synopsis

A 58-year-old man immediately postoperatively after open abdominal aortic aneurysm repair is noted to be hypertensive, with a blood pressure of 160/110 mm Hg. His heart rate is 72 beats per minute in sinus rhythm, pulmonary artery pressure is 45/25 mm Hg, pulmonary artery occlusion pressure is 6 mm Hg, and central venous pressure is 5 mm Hg. The patient also has ST-segment depression in the anterior precordial electrocardiogram leads. Preoperative evaluation revealed no prior history of hypertension, but a history of peripheral vascular disease.

PROBLEM ANALYSIS

Definition

The definition of perioperative hypertension differs from that of chronic hypertension. Perioperatively, patients may have acute changes in blood pressure (BP) because of multiple factors, including rapid intravenous volume shifts and changes in sympathetic tone secondary to surgical stimulation, stress responses, or pain. Patients with otherwise normal BP may develop hypertension perioperatively because of these factors. Also, this patient with a history of peripheral vascular disease has diffuse atherosclerotic changes that are also associated with endothelial and vascular dysfunction. Because oral antihypertensive therapy is not possible at this time, patients require parenteral treatment. Hypertension is a major problem after both cardiac and noncardiac surgery. The incidence of postoperative hypertension ranges from 6% to 20% in various noncardiac surgical studies, occurring more commonly in patients with preoperative hypertension, irrespective of anesthetic regimen.

Recognition

Because BP monitoring is an essential part of perioperative management, either invasive or noninvasive methods may be acceptable for diagnosis and institution of therapy. In cardiac surgical patients, BP is usually kept at arbitrary lower levels to avoid graft or suture line disruption, as well as bleeding. Based on data collected from an international survey, hypertension after cardiac surgery is defined as a sustained BP greater than 140/90 mm Hg. When pressures exceed this, most anesthesiologists institute therapy. Recently new BP guidelines in medical patients were formulated after the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Risk Assessment

Reported risk factors for hypertension in the postanesthesia care unit include increasing age, smoking, and renal disease. Patients with a preoperative history of angina and those with inadequate ventilation during the postoperative period are also at increased risk for hypertension. Hypertension and tachycardia are associated with increased long-term morbidity and mortality. Preexisting hypertension is also a risk factor.

Hypertension after surgery for coronary artery bypass grafting has been reported in 30% to 80% of patients. Augmentation of the stress response because of cardiopulmonary bypass has been suggested as the pathophysiologic basis of increased vascular resistance. Other factors to consider are rapid weaning from mechanical ventilation after cardiac surgery and coronary graft spasm. Ventricular dysfunction is common even in patients with normal preoperative function.

Implications

When to treat perioperative hypertension and how rapidly to decrease the BP are not well-resolved issues. Management goals to maintain hemodynamic stability depend on many factors, especially preoperative BP—that is, the patient's "normal" pressure. There are few data to guide management, and in selected patients (e.g., neurosurgical and cardiac surgical patients), BP is frequently maintained at even lower values immediately postoperatively to avoid complications such as hemorrhage, rupture of suture lines, cerebrovascular accidents, myocardial ischemia, and arrhythmias.

MANAGEMENT

Therapeutic approaches to perioperative hypertension include the following:

- Intravenous vasodilators, dihydropyridine (DHP), calcium channel blockers such as clevidipine, nicardipine, dopamine receptor agonists (fenoldopam), hydralazine, or, potentially, angiotensin-converting enzyme (ACE) inhibitors (enalaprilat)
- Intravenous β-adrenergic blockers
- Deepening anesthesia for intraoperative management

Vasodilators

Nitroprusside and nitroglycerin release nitric oxide to produce arterial vasodilation and venodilation, which contribute significantly to the labile hemodynamic state, especially in patients who are relatively

hypovolemic as in the case synopsis. In a hypertensive patient, intravenous volume administration is often used to allow nitroprusside to be infused when the patient is hypovolemic.* Although nitroprusside is often used to control postoperative hypertension in other surgical interventions, it may contribute to myocardial ischemia by producing nonspecific coronary vasodilation and coronary steal. Hydralazine, a more arterioselective vasodilator, is also used in obstetric patients and in perioperative settings, often concomitantly with a β-blocker.

Calcium Channel Blockers

There are three types of calcium channel blockers: verapamil, diltiazem, and the DHPs (e.g., nicardipine). Vasodilation can be produced by any of these drugs, which reduce calcium entry into vascular smooth muscle. DHP calcium channel blockers act by binding with high affinity to the L-type calcium channels, which modulates their voltage-dependent calcium conductivity. DHPs are mainly dilators of the peripheral resistance arteries. In doses that effectively reduce BP, the DHPs have little or no direct negative effect on cardiac contractility or conduction. Their lack of negative chronotropic effect allows an initial reflex increase in heart rate, which decreases during prolonged antihypertensive treatment. Calcium channel blockers do not affect venous smooth muscle; therefore unlike nitrodilators they are not venodilators and have little influence on filling pressure and preload. As a result, cardiac output is well maintained or increased when calcium channel blockers are given to reduce arterial pressure. Nicardipine also is a potent coronary and cerebral vasodilator, with important applications in neurosurgical and cardiac surgical patients.

Other Agents

Although ACE inhibitors are widely used to treat heart failure, the only intravenous form available is enalaprilat, an indirect-acting agent that is used on occasion to treat perioperative hypertension. ACE inhibitors are complex drugs that interfere with angiotensin II synthesis and may increase nitric oxide release from blood vessels by increasing bradykinin levels. Specific dopamine (DA) receptor agonists are a new class of agents that are under clinical investigation. Fenoldopam, a selective agonist to peripheral DA1-receptors, produces vasodilation, increases renal perfusion, and enhances natriuresis but may have variable effects on BP and heart rate.

β-Adrenergic Blockers

β-Adrenergic blockers reduce heart rate and myocardial contractility, decreasing cardiac output and thus reducing both diastolic and systolic BP. Therefore β-blockers should be considered in treating perioperative hypertension in patients with tachycardia. Because heart rate is a major determinant of myocardial blood supply, tachycardia must be treated aggressively in patients with ischemic heart disease, and β-blockers should be used as first-line therapeutic agents. Several β-blockers can be administered intravenously and are used as antihypertensive agents in the perioperative period: propranolol, metoprolol, atenolol, esmolol, and labetalol. Advantages of labetalol are its combined α- and β-blocking effect, whereas esmolol has a short elimination half-life (<10 minutes) and β1-selectivity.

Deepening Anesthesia

Increasing anesthetic depth is always a potential means of treating increased BP during surgery, but it may not always be possible or effective. Regional anesthetic techniques may also be effective at preventing perioperative hypertension. Not to be overlooked is the effect of positive-pressure ventilation or continuous positive airway pressure to impede venous return, effectively reducing preload and systemic BP.

PREVENTION

Perioperative hypertension commonly occurs as part of the normal response to induction, surgery, emergence, and pain. Continuing treatment for chronic hypertension is important in the perioperative management of hemodynamic stability. Increasing use of regional anesthetic techniques to better control perioperative pain may also have important effects in preventing perioperative hypertension. Although increasing anesthetic depth can be effective in maintaining hemodynamic control, this technique may not always be feasible; thus use of the specific antihypertensive agents reviewed here may be required.

Further Reading

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*Nitroprusside has prominent vasodilatory effects on the venous capacitance bed (i.e., is a potent venodilator) in addition to its arteriodilator effect. Venodilation reduces venous return and cardiac preload. Because patients with chronic hypertension are often preload restricted—an adaptive response to chronic increased systemic vascular resistance and ventricular wall stress (i.e., afterload)—they may become relatively hypovolemic when given antihypertensive drugs with prominent venodilator effects. Nitroprusside also became exceedingly expensive starting in 2015, with the cost skyrocketing to almost $1000 a vial (an important factor that clinicians may not recognize), and it requires an arterial catheter for frequent blood pressure monitoring.

Perioperative Hypoxia

159

Taras Grosh • Diana Ayubcha

Case Synopsis

A 42-year-old, 70-inch-tall, 95-kg man with chronic obstructive pulmonary disease and hypertension is undergoing a laparoscopic appendectomy. A satisfactory rapid-sequence induction with propofol and succinylcholine is performed, appropriate antibiotics are administered, and the abdomen is insufflated. Fifteen minutes into the procedure, the low oxygen pressure alarm sounds, the Fio_2 displays 16%, and oxygen saturation by pulse oximetry (Spo_2) reads 99% but steadily declines. Peak and plateau pressures, tidal volumes, and minute ventilation are minimally changed.

PROBLEM ANALYSIS

Definition

Hypoxia, or hypoxation, is abnormally low oxygen content in a tissue or organ that is unable to meet the needs of the body. The oxygen cascade depicts the declining partial pressure of oxygen from the atmosphere to the mitochondria (Fig. 159.1). A disruption anywhere along the oxygen cascade results in insufficient oxygenation of end organs. Hypoxia can be subdivided into hypoxemia (hypoxic hypoxia), anemic hypoxia, circulatory hypoxia, and histiocytic hypoxia.

Hypoxemia/Hypoxic Hypoxia

Hypoxemia is the failure of oxygen (O_2) to bind to hemoglobin or dissolve in plasma resulting in decreased blood O_2 content. Fig. 159.2 lists the causes of hypoxemia. The alveolar gas equation predicts the partial pressure of oxygen in the alveoli and is useful for calculating the A-a gradient to identify causes of hypoxemia:

$$Pa_{O_2} = FiO_2 \times (PB - PiH_2O) - Pa_{CO_2}/RQ$$

Pa_{O_2} and Pa_{CO_2} are alveolar partial pressures of O_2 and CO_2, respectively; Fio_2 is the fraction of inspired O_2; PB is atmospheric (barometric) pressure; PiH_2O is saturated H_2O vapor pressure; and RQ is the respiratory quotient (0.8).

A normal gradient exists as oxygen diffuses down from the alveoli into the blood.

$$A - a\ gradient = PA_{O_2} - Pa_{O_2}$$

PA_{O_2} is the partial pressure of O_2 in the alveoli; Pa_{O_2} is the partial pressure of O_2 in the blood.

The A-a gradient increases with age approximately 1 mm Hg for every decade of life.

$$Normal\ estimated\ A - a\ gradient = age/4 + 4$$

Hypoxemia can be due to a normal A-a gradient (<15 mm Hg) or high A-a gradient (>15 mm Hg) (Table 159.1).

Normal A-a gradient (<15 mm Hg) hypoxemia is caused by the following:

1. Low a fraction of inspired oxygen (Fio_2) such as inspiring a hypoxic mixture (Fio_2 <21%) due to excessive nitrous oxide or nitrogen, incorrect flowmeter settings, a faulty tank or hose connection, central gas distribution error, or inspiring at a barometric pressure below 760 mm Hg.
2. Hypoventilation whether central (central nervous system toxicity from drug overdose) or peripheral (obesity, kyphosis, myasthenia gravis) results in an accumulation of arterial and alveolar CO_2. In the setting of constant O_2, consumption hypoxia results.

High A-a gradient (>15 mm Hg) hypoxemia is caused by the following:

1. Ventilation (V)/perfusion (Q) mismatch is the most common cause (Fig. 159.3). Blood flows through well perfused, poorly perfused, or entirely bypasses the alveoli. The resulting arterial oxygen content is the summed average of all of these compartments. Extremes of V/Q mismatch are known as *deadspace* and *shunt.*
   - Deadspace (V > Q), a product of ventilation without perfusion, is more frequently in the apex of the lungs and seen with COPD or a pulmonary embolism. In the apex, PA > Pa > Pv. Distended alveoli cause capillary collapse, wasted ventilation, and minimal to no gas exchange with blood. This is corrected with supplemental O_2, but further widens the A-a gradient (Fig. 159.4). These areas have high Po_2 and low Pco_2.
   - Shunt Q > V, perfusion without ventilation, occurs most frequently at the lung bases. Here Pa > Pv > PA and most commonly a result of postoperative atelectasis, pneumonia, or pulmonary edema. The venous and pulmonary capillary oxygen content is nearly equivalent (low Po_2 and O_2 content). At the bases, the mixed venous blood traverses the pulmonary capillary bed without being oxygenated, further exacerbating the V/Q mismatch. These areas have low Po_2 and high Pco_2 content. Supplemental Fio_2 will not improve oxygenation.
2. Diffusion problems occur if the alveolar to capillary Po_2 gradient is lost by way of a saturated or poorly functioning Hb molecule, reduction of the surface area available for gas exchange, or thickening of the diffusion barrier. These are commonly encountered during interstitial lung disease, emphysema, fibrosis, or acute respiratory distress

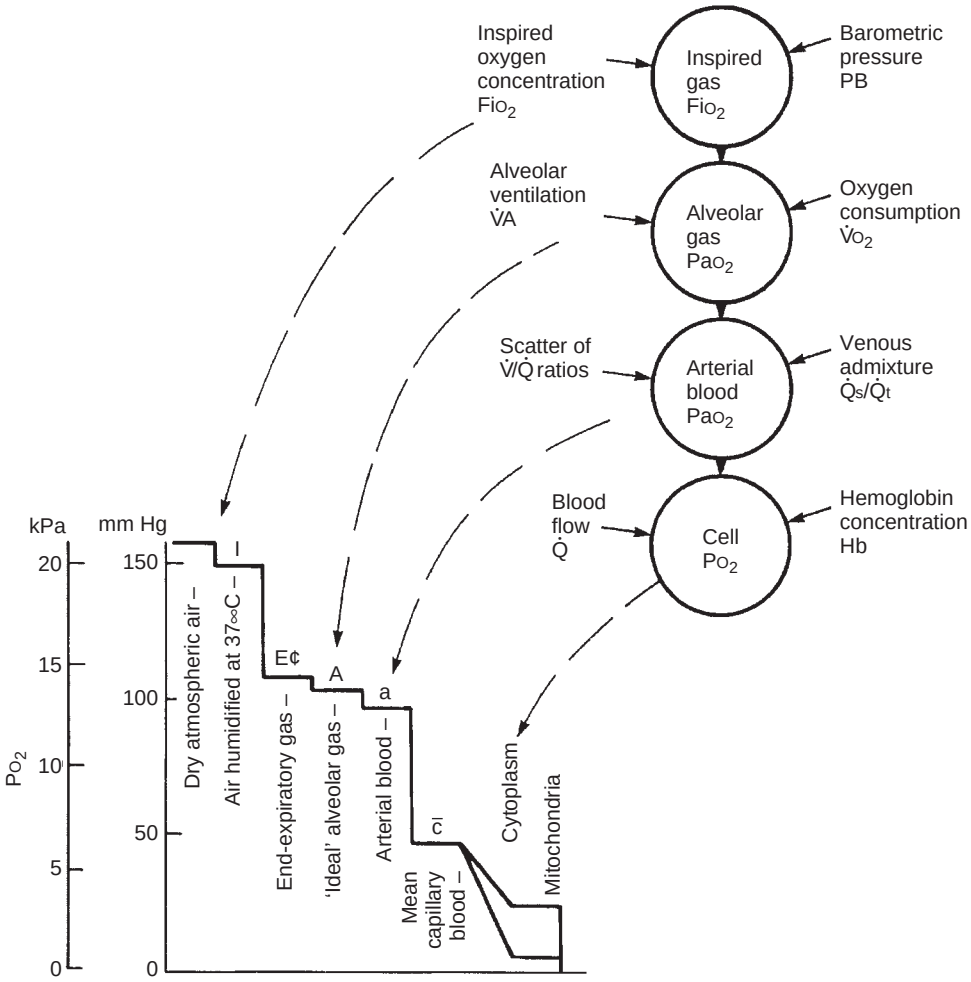

Fig. 159.1 Oxygen partial-pressure cascade from dry atmospheric air (160 mm Hg) to the mitochondria (3 to 20 mm Hg). From Lumb AB: *Nunn's applied respiratory physiology,* 5th ed. London, Butterworth-Heinemann, 2000, p 250.

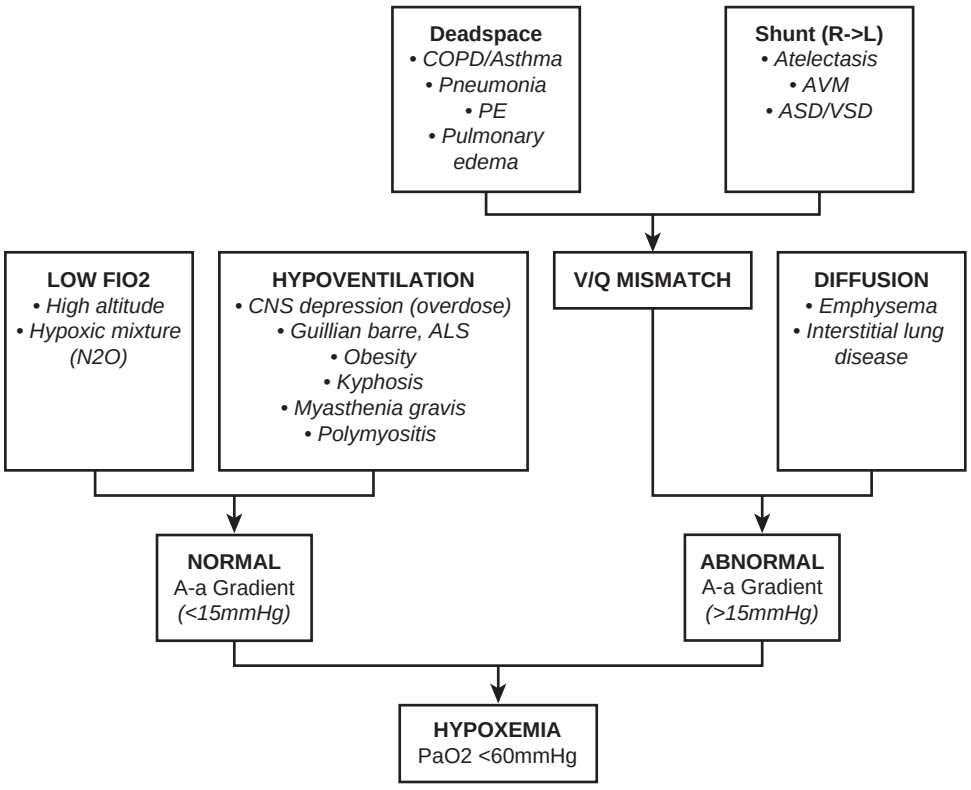

Fig. 159.2 Causes of hypoxemia.

TABLE 159.1 Causes of Hypoxemia and Their Effects on Alveolar-Arterial Oxygen Partial Pressure Difference, Response to 100% Oxygen, and Arterial Partial Pressure of Carbon Dioxide

Cause	$P(A\text{-}a)O_2$	100% O_2	$Paco_2$
Low Fio_2	Normal	Increased Pao_2	Normal
Hypoventilation	Normal	Increased Pao_2	Increased
V/Q mismatch	Increased	Increased Pao_2	Normal
Shunt (V_s/Q_t)	Increased	No change	Normal
Diffusion limitation	Increased	Increased Pao_2	Normal

Fio_2, fraction of inspired oxygen; *Pao_2*, arterial partial pressure of oxygen; *$P(A\text{-}a)o_2$*, alveolar-arterial oxygen partial pressure difference; *$Paco_2$*, arterial partial pressure of carbon dioxide; *V/Q*, alveolar ventilation-perfusion.

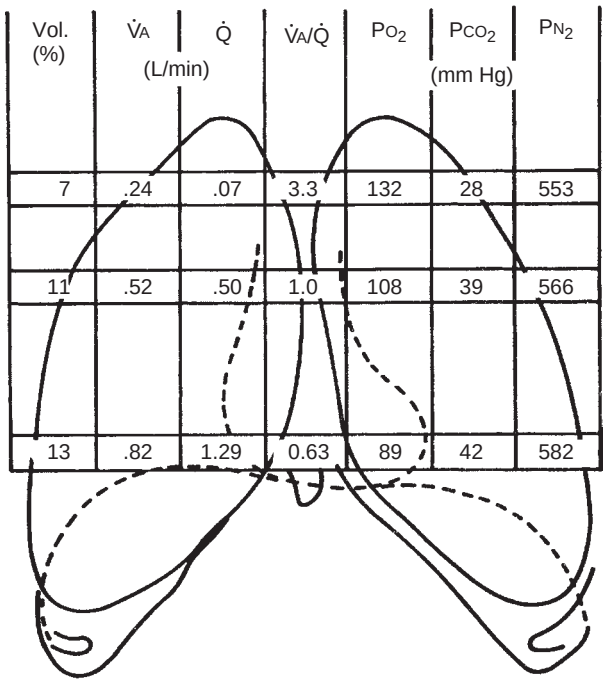

Fig. 159.3 Regional lung alveolar ventilation-perfusion (V/Q) ratios and gas composition for three zones of the upright lung. From West JB: *Pulmonary pathophysiology: the essentials.* Baltimore, Williams & Wilkins, 1980.

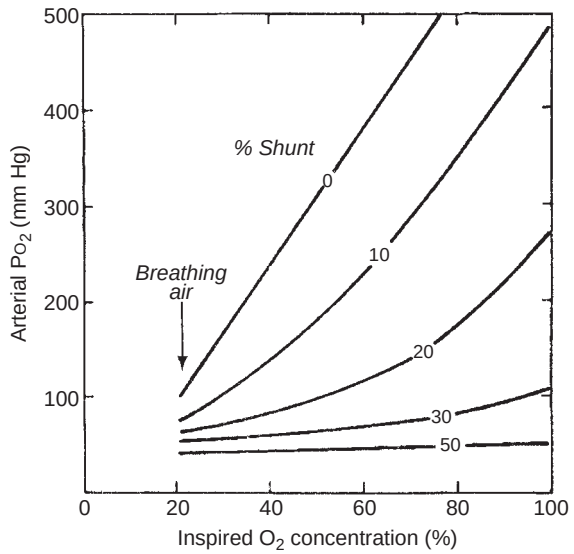

Fig. 159.4 The isoshunt diagram shows the effect of changing the inspired oxygen concentration (Fio_2) on arterial oxygenation (Pao_2) in the presence of varying amounts of pure shunt. Isoshunt lines hold for hemoglobin of 10 to 14 g/dL and arterial partial pressure of carbon dioxide ($Paco_2$) of 25 to 40 mm Hg. Modified from Nunn JF: *Applied respiratory physiology,* 4th ed. London, Butterworth-Heinemann, 1993, p 184.

syndrome. Alveolar-capillary gas exchange is limited by the diffusing capacity of a particular gas across the alveolar-capillary membrane (D). Diffusing capacity for O_2 (Do_2) varies from 21 mL/min per mm Hg $P(A\text{-}a)o_2$ at rest to 65 mL/min per mm Hg $P(A\text{-}a)o_2$ during exercise. The Pao_2/Fio_2 ratio is a common measure of oxygenation used for ventilated patients. A normal ratio is 300 to 500 mm Hg. A ratio less than 300 mm Hg indicates abnormal gas exchange; less than 200 mm Hg indicates severe hypoxemia. In a vented patient, the a-A oxygen ratio is a useful ratio for weaning. A normal a/A ratio (Pao_2/PAo_2) is greater than 0.75, and a ratio greater than 0.25 is predictive of successful weaning from the vent. In patients with central access, a mixed venous saturation (SVo_2) is useful to rule out anemia or low cardiac output as causes of an increased A-a gradient.

Anemic Hypoxia

Anemic hypoxia is caused by a low hemoglobin or abnormal hemoglobin function, significantly impairing oxygen-carrying capacity. The following considerations are relevant to the discussion of anemic hypoxia:

- Hemoglobin structure-function relationship
- Oxygen-hemoglobin (O_2-Hb) dissociation curve
- Oxygen content
- Other hemoglobin species
- Minimum hemoglobin concentration

Hemoglobin (Hb) structure. Hb is composed of four protein subunits to form a tetrameric molecule. There are several different subunits (denoted α through ε), but only two are contained in a single Hb molecule. Normal adult Hb has two α and two β subunits. Heme, the iron-containing moiety, fits into each Hb subunit, allowing it to bind one molecule of O_2 (oxygenation). Interactions between Hb subunits (subunit cooperativity) are responsible for the increased O_2 affinity that occurs as each successive O_2 molecule is bound to Hb This property accounts for the sigmoid shape of the O_2-Hb dissociation curve (Fig. 159.5).

Oxygen-hemoglobin dissociation curve. The O_2-Hb dissociation curve is sigmoidal and describes the affinity of hemoglobin for O_2. Each sequential O_2 molecule bound to the iron moiety in hemoglobin promotes subsequent oxygen molecules binding with greater affinity. The partial pressure at which 50% of the hemoglobin molecule is saturated with O_2 is P50; 26.6 mm Hg is normal adult P50. A shift to the right means that Hb unloads its O_2 to tissues more easily, and a shift to the left means that Hb unloads its O_2 with more difficulty. Four factors regulate the affinity of Hb for O_2: hydrogen ion (Bohr effect), 2,3-diphosphoglycerate, CO_2 (Haldane effect), and temperature. An increase in any of these factors decreases the affinity of Hb for O_2 and

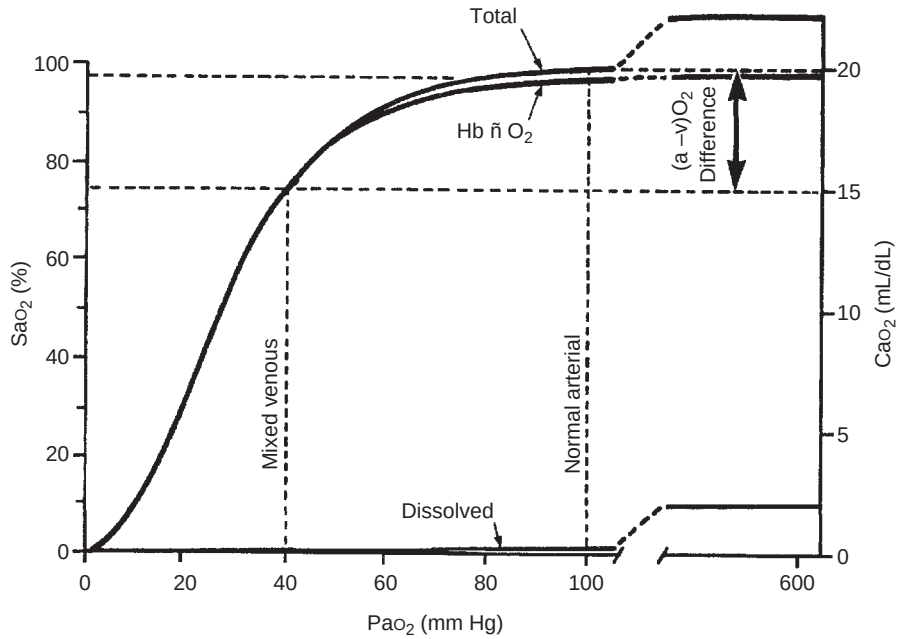

Fig. 159.5 Oxyhemoglobin dissociation curve relates arterial oxygen saturation (Sao_2; left ordinate) and content (Cao_2 [mL/dL]; right ordinate) to tension (Pao_2; abscissa). This assumes hemoglobin = 15 g/dL, Cao_2 = 20 mL/dL, and arteriovenous Cao_2 difference = 5 mL/dL. From Luce JM, Pierson DJ, Tyler ML: *Intensive respiratory care,* 2nd ed. Philadelphia, WB Saunders, 1993, p 27.

shifts the O_2-Hb dissociation curve to the right (i.e., increases P50), with more O_2 unloaded to tissues for a given Po_2. A decrease shifts the O_2-Hb dissociation curve to the left, with less O_2 unloaded to tissues at any given Po_2.

Oxygen content. Normal hemoglobin concentration is approximately 150 g/L or 15 g/dL by standard nomenclature. One gram of hemoglobin binds 1.39 mL O_2; however, this is typically lower in patients (about 1.34 mL/g), owing to the small amounts of methemoglobin and carboxyhemoglobin that are normally present. In addition, there is physically dissolved O_2 in plasma (0.003 mL/dL per mm Hg of Po_2) representing approximately 2% of total O_2 concentration in the blood. Cao_2 represents the arterial oxygen content when blood is fully saturated with oxygen, which is approximately 20 mL/dL.

$$Cao_2 = (Sao_2 \times Hb \times 1.34) + 0.003\,(Pao_2)$$

As hemoglobin concentrations change, so does the oxygen content, but the oxygen of each gram of hemoglobin does not change.

Other hemoglobin species. Myoglobin serves both as an O_2 buffer and to store O_2 in muscle. All known vertebrate myoglobins and β-hemoglobin subunits are similar in structure, but myoglobin binds O_2 more avidly at low Po_2 because it is a monomer (i.e., it does not undergo a significant conformational change with oxygenation). Thus myoglobin remains fully saturated at O_2 tensions between 15 and 30 mm Hg and unloads its O_2 to the muscle mitochondria only at very low O_2 tensions. Note that fetal hemoglobin also functions at a lower Po_2 than adult hemoglobin, with a P50 of 19 mm Hg.

Minimum hemoglobin concentration. The American Society of Anesthesiologists (ASA) in 2015 and the American Association of Blood Banks in 2016 addressed optimal hemoglobin concentrations in its Practice Guidelines for Blood Component Therapy. A two-tiered approach is indicated: transfuse at a Hb of 7 g/dL or less for hemodynamically stable adults, and 8 g/dL for patients with preexisting cardiovascular disease or those undergoing cardiac or orthopedic surgery. Transfusions should be initiated with 1 unit of packed red blood cells in patients without overt bleeding, recheck Hb levels after each transfusion, to a goal of 7 to 9 g/dL and 8 to 10 g/dL, respectively. In addition, the emphasis is on greater use of pharmacologic therapies to minimize blood transfusions, such as erythropoietin for the anemic patient, transfusion algorithms, especially those based on thromboelastographic testing, blood ordering schedules, and restrictive transfusion strategies.

Circulatory Hypoxia

Circulatory hypoxia or stagnant hypoxia results from insufficient flow through organ capillary beds resulting in insufficient supply at the tissue level; this may be general or local. General circulatory hypoxia is a byproduct of all conditions that reduce heart rate or stroke volume resulting in reduced cardiac output or severe systemic circulatory arrest as in shock. Local stagnant hypoxia occurs in conditions where flow is arrested in the periphery: Raynaud disease, Beurger disease, or application of a tourniquet. Oxygen consumption (VO_2) is approximately 250 mL/min in a 75 kg male, and basal O_2 delivery (DO_2) is about 200 mL O_2 per liter of cardiac output per minute (or 1000 mL O_2 for a cardiac output of 5 L/min); this is more than adequate to meet metabolic demands during normal aerobic metabolism. The oxygen extraction ratio (O_2ER) is the ratio of VO_2/DO_2 with normal being 25% at rest and 75% at maximal exertion.

$$O_2ER = VO_2/DO_2 = (Sao_2 - Svo_2)/Sao_2$$

Fig. 159.6 depicts the critical DO_2 (cDO_2) or maximum O_2ER, after which cells shift to anaerobic metabolism with tissue hypoxia depicted by elevated lactate production. But what is critical delivery for survival? One study in conscious, resting volunteers reported a rate of 7.5 mL/kg per minute (525 mL/min for a 70-kg adult). A case report of a Jehovah's Witness patient found critical DO_2 to be 184 mL/min per square meter.

Histiocytic Hypoxia

Histiocytic hypoxia is the inability to utilize delivered oxygen at the cellular level despite normal DO_2 resulting in impaired ATP production. Cyanide (CN^-) toxicity is a classic example and may occur

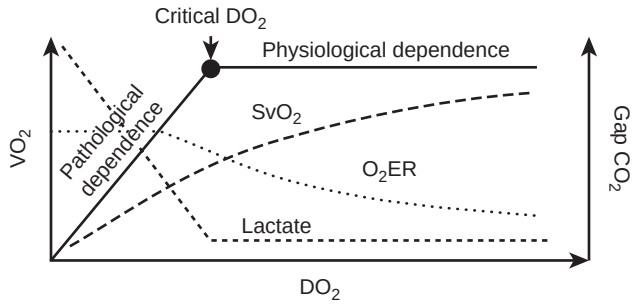

Fig. 159.6 Relationship between metabolic demand (VO_2) and oxygen delivery (DO_2). As VO_2 increases, or DO_2 decreases, the oxygen extraction ratio increases to maintain aerobic metabolism. Consumption is independent of delivery up to the critical DO_2 (cDO_2), at which point maximum O_2ER is reached (70%). Beyond cDO_2 any further increase in VO_2, or decline in DO_2, must lead to tissue hypoxia and anaerobic metabolism (elevated lactate). *DO_2,* Oxygen delivery; *VO_2,* oxygen consumption; *O_2ER,* relation with oxygen extraction ratio; *SvO_2,* mixed venous oxygen saturation; *Gap CO_2,* gradient of partial carbon dioxide pressure in the gastric mucosa. From Assuncao MS, Corrêa TD, Bravim Bde A, Silva E: How to choose the therapeutic goals to improve tissue perfusion in septic shock. *Einstein (São Paulo)* 13[3]:441-447, 2015.

with the administration of large amounts of sodium nitroprusside. CN^- binds to mitochondrial cytochrome oxidase, disrupting aerobic metabolism, resulting in anaerobic metabolism. Early signs of CN^- toxicity are tachycardia, increased mixed venous O_2 saturation (normal SVo_2 70%) as O_2ER decreases, bright-red venous blood, and lactic acidosis; all are due to the inability of tissue to utilize O_2. Similar hypoxia occurs with pesticides rotenone and antimycin A, which also interrupt the electron transport chain.

Carbon monoxide (CO) binds to cytochrome c and interferes with oxidative metabolism at the mitochondrial level. Once bound CO transforms the Hb molecule to carboxyhemoglobin shifting the curve to the left, as the remaining oxygen bound to the carboxyhemoglobin molecule binds with great affinity because of the conformational change afforded by CO, resulting in tissue hypoxia despite normal Pao_2 and normal two-channel pulse oximetry. The high affinity of CO for hemoglobin (200 times that of O_2) requires a high concentration of O_2 (100% at 1 to 3 atmospheres) to effectively treat CO poisoning. The subsequent regeneration of functional cytochrome c by the displacement of CO with O_2 may be the mechanism by which neuronal death is prevented. Methemoglobin is another abnormal form of Hb resulting from the iron moiety within Hb being in the ferric (Fe^{3+} oxidized) state rather than the ferrous (2+ reduced) state; as a result a left shift of the curve is expected. Methemoglobin can be hereditary or seen with G6PD deficiency, exposure to prilocaine, benzocaine, and nitrates and nitrites. In addition, it is induced in the treatment of cyanide toxicity.

Recognition

Cyanosis

Hypoxemia was the leading cause of anesthesia-related mortality before the widespread use of pulse oximetry. Afterward, there was a 20-fold reduction in anesthesia-related mortality. Clinical recognition of hypoxemia (Pao_2 <60 mm Hg) is difficult in the anesthetized patient, as anesthetic agents attenuate the physiologic status (tachycardia, hypertension, tachypnea) and mental status (restlessness, somnolence) changes caused by hypoxia. In the anesthetized patient, the presence of cyanotic mucosal membranes or dark blood in the operative field often provided the earliest warning. Nevertheless, cyanosis manifests only when 15% or 2 to 3 g of hemoglobin is desaturated and the presence of anemia makes detection even more difficult. The gold standard for the diagnosis of hypoxemia is direct Pao_2 measurement with a Clark electrode; however, this is invasive and is rarely a continuous parameter.

TABLE 159.2 Methods to Assess the Adequacy of Organ and Tissue Oxygen Delivery

Organ/Tissue	Method
Brain	Cerebral perfusion pressure (CPP = MAP – ICP), transcranial Doppler monitoring, electroencephalography, jugular venous O_2 saturation, near-infrared spectroscopy, SSEPs/MEPs
Heart	Electrocardiography, transesophageal echocardiography, coronary sinus O_2 saturation, pulmonary artery catheter
Lungs	Pao_2/Fio_2 ratio, lung injury score, pulmonary arterial pressures, airway pressures (lung compliance and resistance), bronchoalveolar lavage
Liver, kidneys, gut	Lactate production, hepatic enzymes, urine output and specific gravity, blood urea nitrogen and creatinine, gastric tonometry

CPP, Cerebral perfusion pressure; *Fio_2,* fraction of inspired oxygen; *ICP,* intracranial pressure; *MAP,* mean arterial pressure; *MEP,* motor evoked potential; *Pao_2,* arterial partial pressure of oxygen; *SSEP,* somatosensory evoked potential.

Pulse Oximetry

Pulse oximeters emit light at 660 nm (red) and 940 nm (infrared) with a photodetector on the other side. Using the Beer-Lambert law, the changes in the light absorbed by pulsatile versus nonpulsatile blood is analyzed and act as an estimate for the saturation. Pulse oximetry provides an early warning of hypoxemia (for Spo_2 from 70% to 100%), with ear and forehead probes responding quicker than finger probes to changes in oxygen saturation, provided that reduced or oxyhemoglobin is the only hemoglobin present. Carboxyhemoglobin and methemoglobin have similar absorption spectra to oxyhemoglobin and may provide misinformation; in fact, carboxyhemoglobin and oxyhemoglobin are indistinguishable. Pulse oximetry readings are falsely high in the presence of carboxyhemoglobin. As methemoglobin concentrations increase, pulse oximetry readings tend to approach 85%. Fluorescent lighting can also cause a falsely elevated Spo_2. Blue nail polish, tape adhesive, methylene blue, indigo carmine, and isosulfan blue may cause falsely low Spo_2 measurements. A cooximeter measures the amounts of dyshemoglobins in a blood sample: deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin. Such testing is indicated if Spo_2 readings are dubious (e.g., intravenous dyes have been injected or infiltrated for surgical mapping) or CO poisoning is suspected. One major manufacturer has developed a pulse cooximeter using eight light wavelengths and capable of measuring deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin.

Specific Organs

Methods used to assess the adequacy of O_2 delivery to organs and tissues are summarized in Table 159.2.

Risk Assessment

Inhalation and intravenous anesthetics, with the exception of ketamine, reduce the slope of the CO_2-ventilation response curve in direct proportion to dose. Inhalational anesthetics, propofol, and even dexmedetomidine have also been shown to depress the ventilatory response to hypoxia, even at low doses. Functional residual capacity decreases on the induction of anesthesia and does not return to normal until hours after anesthesia has been terminated, contributing

TABLE 159.3 Measures to Reduce the Risk of Perioperative Hypoxia Based on Cause

Cause	Measure
Hypoxemia	Verify O_2 supply (check anesthesia machine), confirm fail-safe function; use in-line O_2 analyzer; preoxygenate; increase Fio_2
Hypoventilation	Confirm breath sounds and end-tidal CO_2; increase Fio_2; assess lung compliance; use bronchodilators; maintain bronchopulmonary toilet
V/Q mismatch	Increase Fio_2; restrict volatile agents (inhibit hypoxic pulmonary vasoconstriction)
Shunt	Use larger tidal volumes (10–15 mL/kg), intermittent sighs, frequent suctioning; add PEEP in high-risk patients (low FRC, obesity, hypoalbuminemia)
Diffusion limitation[a]	Increase Fio_2
Anemia	Evaluate hematocrit frequently; give transfusions; increase Fio_2
Circulatory failure	Increase cardiac output (volume, inotropes, circulatory assist device); relieve surgical compression or traction; increase Fio_2
O_2 utilization	Limit SNP to ≤1 mg/kg over 1–3 h and 0.5 mg/kg/h over 24 h, use another vasodilator,[b] or combine another vasodilator or SNP with a β-blocker to reduce the need for SNP; increase Fio_2 (especially with CO poisoning)

CO, Carbon monoxide; *CO_2*, carbon dioxide; Fio_2, fraction of inspired oxygen; *FRC*, functional residual capacity; *PEEP*, positive end-expiratory pressure; *SNP*, sodium nitroprusside; *V/Q*, alveolar ventilation-perfusion.
[a]Uncommon cause in healthy patients; may contribute to hypoxia after lung resection in patients with a reduced alveolar capillary bed (emphysema) and high cardiac output (sepsis).
[b]Clevidipine/nicardipine intravenously may be preferred to SNP owing to the possibility of cyanide toxicity with large doses of the latter.

to atelectasis. At 1.0 minimum alveolar concentration (MAC) or greater, volatile, but not intravenous anesthetic agents, oppose hypoxic pulmonary vasoconstriction and increase the risk of hypoxia due to mismatch. During recovery, elimination of nitrous oxide lowers PAo_2 for several minutes secondary to diffusion hypoxia. Anesthetics also reduce the tone in muscles involved in maintaining pharyngeal patency, increasing the risk of partial or complete airway obstruction. For these reasons, any patient having an anesthetic is at risk for hypoxia.

Patients at increased risk for hypoxia include those with significant cardiopulmonary disease, severely reduced functional residual capacity (pregnancy and morbid obesity), major trauma, thromboembolism, sepsis, head injury, pulmonary aspiration, and drug overdose. Risk also increases when diagnostic or therapeutic procedures are performed with the patient under intravenous sedation and inattentive, untrained, or preoccupied personnel are responsible for patient monitoring (e.g., interventional radiology or cardiology, magnetic resonance imaging). The risk for postoperative hypoxia is increased with long-acting anesthetic agents or neuromuscular blockers and with hypothermia producing uncontrolled shivering or impaired drug metabolism and elimination.

Implications

Severe hypoxia leads to ischemia or death. The central nervous system is most vulnerable to hypoxia (tolerating ≤5 minutes of normothermic ischemia). With hypoxia, anaerobic metabolism replaces aerobic metabolism, with a consequent fall in intracellular high-energy compounds and acidosis. Insufficient high-energy compounds leads to the failure of intracellular pumps and the release of calcium from intracellular stores, damaging the intracellular elements. Acidosis and consequent anaerobic metabolism of glucose (causing lactic acidosis) produce further cell damage. As noted, the brain is most vulnerable, followed by the heart, the liver, and the kidneys.

MANAGEMENT

- Identify and correct the primary cause.
- Supply supplemental oxygen; increase Fio_2.
- Increase O_2 delivery (transfusion, inotropes, or both).
- Treat mismatch (positive end-expiratory pressure, sighs, inhaled nitric oxide, patient posturing).
- Protect vital organs (hypothermia, drugs, spinal drainage, steroids).
- Administer amyl nitrate, sodium nitrite, or thiosulfate for CN– toxicity.

PREVENTION

Measures to reduce the risk of perioperative hypoxia from the causes discussed herein are listed in Table 159.3.

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Perioperative Myocardial Ischemia and Infarction

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Jennifer M. Banayan • BobbieJean Sweitzer • Mark A. Chaney

Case Synopsis

A 62-year-old man is scheduled for cystectomy. He has a history of coronary artery disease (CAD) and underwent coronary artery bypass grafting 8 years ago. He has diabetes mellitus, hypertension, and hyperlipidemia. He takes aspirin, atenolol, pravastatin, and losartan. He is able to walk up a flight of stairs without symptoms. His intraoperative course is uneventful except for tachycardia during extubation. In recovery, he is tachycardic to 110 beats per minute but denies chest pain. Troponin levels are ordered and are elevated.

PROBLEM ANALYSIS

Definition

Myocardial ischemia results from an imbalance between myocardial oxygen supply and demand. Myocardial oxygen demand depends on preload, afterload, contractility, and heart rate. Myocardial oxygen supply depends on the capacity of the coronary arterial bed. Atherosclerosis of the coronary arteries limits coronary artery blood flow and consequently myocardial oxygen supply. A mismatch of supply and demand can lead to ischemia (Box 160.1). Ischemia that persists for an extensive period of time can lead to myocardial infarction (MI).

Perioperative myocardial infarction (PMI) can be divided into two subgroups: type 1 and type 2. Type 1 is a primary coronary event such as a coronary thrombosis. Type 2 is ischemia from a mismatch of supply and demand. More than 95% of all PMIs are caused by the type 2 subgroup. Higher perioperative oxygen demands and limited blood flow in patients with atherosclerotic lesions and coronary artery disease are factors. Common reasons for a mismatch in myocardial oxygen demand and supply in the perioperative period include hypotension, tachycardia, hypoxemia, hemorrhage, and fever. Clinically, a type 2 MI often resembles a non–ST-segment elevation MI with smaller increases in cardiac biomarkers than a type 1 MI. Acute coronary thrombosis leading to MI is less frequent but is associated with a significantly increased risk of cardiac death. Causes for thrombosis include surgical stresses such as inflammation, tachycardia, perioperative hypercoagulability, increased afterload, plaque ruptures, and withdrawal of antiplatelet therapies.

BOX 160.1 Factors That Contribute to Myocardial Ischemia

Increased Myocardial Oxygen Demand
Increased heart rate
Increased contractility
Increased left ventricular end-diastolic volume
Increased wall tension (afterload)

Decreased Myocardial Oxygen Supply
Decreased coronary blood flow
- Vasoconstriction
- Thrombosis
- Decreased diastolic time
- Decreased aortic diastolic pressure
- Increased ventricular end-diastolic pressure

Decreased blood oxygen content
- Decreased hematocrit
- Decreased oxygen saturation

Recognition

There is little consensus on the optimal method for diagnosing ischemia or a PMI. Perioperative myocardial ischemia can be difficult to recognize when patients are anesthetized and receiving opioids that can mask their chest pain. Electrocardiogram (ECG) changes can be subtle, if present at all. Typically two of three criteria are needed to diagnose PMI: clinical symptoms such as chest pain, ECG changes, and rise of a cardiac biomarker.

ECG is the most commonly relied-on modality to detect myocardial ischemia and acute MI. The ECG changes in myocardial ischemia (Table 160.1) and in patients with a history of MI (Table 160.2) may not be as useful as once thought because they are transient, subtle, or even absent. Other screening tools such as transesophageal echocardiography (TEE) and cardiac biomarkers increase the specificity of diagnosing a PMI.

TABLE 160.1 ECG Changes Indicative of Myocardial Ischemia

ECG Changes	ECG Description
ST-segment elevation	New ST-segment elevation at the J point in two or more contiguous leads with the cutoff points ≥0.2 mV in men or ≥0.15 in women of leads V2, V3, and ≥0.1 mV in other leads
ST-segment depression	New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads
T-wave abnormalities	T-wave inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio greater than 1
Left bundle branch block	New left bundle branch block

ECG, Electrocardiogram.

Detection of regional wall motion abnormalities with TEE is considered a more sensitive tool than ECG for detecting myocardial ischemia. Decreased systolic wall thickening or abnormal diastolic filling patterns may be detected by Doppler interrogation across the left ventricular inflow region at the tips of the mitral valve. However, transient systolic wall motion abnormalities without accompanying hemodynamic or ECG changes are not always associated with ischemia. Consequently, TEE may be most effective in patients who develop ST-segment changes intraoperatively to help confirm the diagnosis. Patients with new, persistent wall motion abnormalities perioperatively are more likely to experience a postoperative adverse cardiac outcome than are those with normal wall motion.

Elevation of cardiac biomarkers such as troponin-I, troponin-T, or CK-MB isoforms are of value for diagnosing an MI. Serum CK exceeds the normal range within 4 to 8 hours after acute MI and declines to normal by 2 to 3 days. Three isoenzymes of CK (BB, MM, MB) have been identified. Brain and kidney contain predominantly BB, skeletal muscle MM (with 1% to 3% MB), and myocardium both MM and MB (isoforms MB1 and MB2). One study found 59% and 92% sensitivity for the diagnosis of acute MI at 2 to 4 and 4 to 6 hours, respectively, for CKMB2 greater than 1 U/L or CKMB2/CKMB1 ratio greater than 1.5.

Cardiac troponins are highly sensitive and specific chemical markers for myocardial necrosis and predict increased risk of mortality and reinfarction in patients with acute coronary syndrome. The troponin (Tn) complex consists of three subunits (TnC, TnI, TnT) that regulate calcium-mediated contraction in striated muscle. TnC binds to calcium, TnI binds to actin, and TnT binds to tropomyosin. Both TnI and TnT are present in skeletal and cardiac muscle, but they are encoded by different genes and have different amino acid sequences. This permits the production of specific antibodies for cardiac Tn (cTn) and the development of quantitative assays for cTnI and cTnT. In patients with acute MI, cTnT and cTnI levels first begin to rise above their normal reference limits by 3 hours after the onset of chest pain or other symptoms associated with ischemia. Elevations of cTnI may persist for 7 to 10 days, and cTnT for 10 to 14 days, after acute MI. The kinetics of release are similar in those with Q-wave or non–Q-wave acute MI. The assay for cTnI is currently the most sensitive and specific marker of myocardial injury. The cTnT assay is probably capable of detecting episodes of myocardial necrosis below the detection limit of current CKMB assays. Hence the terms *minor myocardial damage* and *microinfarction* have been coined to describe myocardial changes in patients with chest pain and elevated TnT but normal CKMB levels. Regardless, it is well established that such patients are at increased risk for an adverse clinical outcome (e.g., recurrent MI, need for revascularization, or death). Elevation of TnT during the first 3 days after surgery is directly associated with an increase in 30-day mortality.

Without cardiomarker elevation, it is difficult, if not impossible, to identify perioperative myocardial injury. In the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study from 2014, 19% of patients who had elevated troponins and died from PMI did not have cardiac symptoms, and more than 70% of them did have ischemia-related ECG changes. Consequently, it has been suggested that high-risk patients be screened after high-risk surgery with cardiac biomarkers to detect ischemia and ensure early intervention, although the routine assessment of troponin levels is controversial.

TABLE 160.2 ECG Changes in Established Myocardial Infarction

ECG Changes	ECG Description
Q waves	Any Q wave in leads V1 through V3, Q wave or 5–30 ms (0.03 s) in leads I, II, aVL, aVF, V4, V5, or V6. (The Q-wave changes must be present in any two contiguous leads and be 0.5–1 mm in depth.)

ECG, Electrocardiogram.

Risk Assessment

The revised cardiac risk index (RCRI), also known as the Lee index, is a validated and accepted tool to assess perioperative risk of major cardiac complications (Box 160.2). Patients who have at least two risk factors on the RCRI are at increased risk of a major adverse cardiac event (MACE) and should have routine cardiac biomarker monitoring when undergoing major surgery to help identify perioperative myocardial injury. Two other tools to predict a MACE have been developed: the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest (MICA) (http://www.surgicalriskcalculator.com/miorcardiacarrest) and the American College of Surgeons NSQIP Surgical Risk Calculator (http://www.riskcalculator.facs.org/). Using these calculators a risk of MACE greater than 1% is considered elevated and warrants further efforts at risk reduction. Functional capacity is an integral component of the preoperative evaluation of the cardiac patient for noncardiac surgery. For patients undergoing major noncardiac surgery, the inability to climb two flights of stairs has a positive predictive value of 82% for death within 30 days of surgery. In addition, the inability to climb two flights of stairs is an independent predictor of more perioperative complications. Conversely, being able to climb two flights of stairs is an easy and informative screening test to predict patients at low risk.

Although routine screening with noninvasive stress testing is not recommended for patients undergoing low-risk noncardiac surgery, patients in whom no inducible ischemia is elicited are unlikely to have perioperative cardiac complications. Routine preoperative coronary angiography with the goal of reducing perioperative cardiac events is not recommended.

The presence of atherosclerotic disease of the coronary arteries is an important risk factor for PMI, but the location of greatest stenosis is not necessarily the location of an infarction. More often than not, the area of ischemia or infarction is in myocardium supplied by coronary arteries with less-than-critical stenoses.

Implications

Every year 200 million noncardiac surgeries are performed, and 8 million of them are complicated by ischemia within 30 days. In the placebo group of the POISE trial, 5.7% of patients suffered an MI within 30 days after noncardiac surgery. PMI is one of the most reliable predictors of morbidity and mortality associated with noncardiac surgery, with a mortality rate of almost 25%. Patients who experience ischemia perioperatively often have CAD. The American College of Cardiology (ACC) and the American Heart Association (AHA) recommend delaying noncardiac surgery at least 60 days after a recent MI to decrease the risk of PMI.

BOX 160.2 Revised Cardiac Risk Index

Planned suprainguinal vascular, intraperitoneal, or intrathoracic surgery
History of ischemic heart disease
Heart failure
Cerebrovascular disease
Diabetes mellitus requiring treatment with insulin
Preoperative serum creatinine greater than 2.0 mg/dL

Because the development of PMI is often preceded by a period of myocardial ischemia, early detection of perioperative myocardial ischemia should prompt therapeutic measures to relieve the ischemia, thereby reducing the incidence or extent of any subsequent MI.

MANAGEMENT

Management of perioperative myocardial ischemia can be divided into preoperative, intraoperative, and postoperative interventions.

Preoperatively, the anesthesiologist identifies high-risk patients with the RCRI or the NSQIP Surgical Risk Calculators. In addition, determining whether the procedure is emergent, urgent, or elective allows postponement of surgery to optimize medical management with perioperative β-blockers, iron therapy to avoid anemia, aspirin, and statins.

Intraoperatively, a clinician must prevent even modest increases in heart rate and limit intraoperative arterial hypotension. A greater than 20% decrease in mean arterial pressure has been associated with a statistically significant increase in the risk of postoperative complications, including PMI, stroke, and death. All causes of tachycardia, hypotension, anemia, hypoxemia, and pain should be treated aggressively because they are common causes of type 2 MI and may precipitate type 1 MI. Interventions that decrease myocardial oxygen demand or increase oxygen supply limit PMI (Box 160.3).

During anesthesia, stable intraoperative hemodynamic parameters should be maintained. No clear consensus exists as to what type of anesthesia (general vs. regional or neuraxial, inhalation vs. intravenous) decreases the incidence of perioperative ischemia or PMI in patients at risk. Numerous studies show that neuraxial anesthesia is associated with fewer incidents of deep vein thrombosis, pneumonia, fatal pulmonary embolism, or postoperative hypoxia. One study of patients undergoing joint replacement showed a lower mortality rate when general anesthetics were avoided. More recent studies have found more persistent hypotension in patients under general anesthesia than with neuraxial blocks. Hypotension needs to be aggressively treated to prevent PMI.

Aggressive control of postoperative pain with regional anesthesia or multimodal analgesia to attenuate associated stress may decrease cardiac morbidity and mortality rates in both cardiac and noncardiac surgical patients. Coagulation abnormalities, medications that affect coagulation, and patient preference should always be considered.

Patients at highest risk need to be monitored for 24 to 48 hours postoperatively. Because most PMIs are silent without symptoms or with atypical symptoms and subtle ECG changes, ordering routine troponins has been recommended for patients with at least one RCRI who will undergo a high-risk surgery.

BOX 160.3 Management of Myocardial Ischemia

Reduce Myocardial Oxygen Demand
- Decrease heart rate
- Decrease contractility
- Decrease left ventricular end-diastolic volume
- Reduce afterload

Increase Myocardial Oxygen Supply
- Increase coronary blood flow
  - Decrease vasoconstriction
  - Decrease thrombosis
  - Increase diastolic time
  - Increase aortic diastolic pressure
  - Reduce ventricular end-diastolic pressure
- Increase blood oxygen content
  - Optimize hematocrit
  - Increase oxygen saturation

PREVENTION

There continues to be debate regarding prevention strategies. The Coronary Artery Revascularization Prophylaxis (CARP) trial compared medical therapy with revascularization in almost 6000 patients with ischemic heart disease before major vascular surgery. Findings revealed no difference in mortality or PMI rates, suggesting that prophylactic revascularization does not improve outcomes. Medical management with aspirin, β-blockers, and statins is a superior alternative to intervention. Numerous studies have concluded that aspirin and statins reduce 30-day mortality rate.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly administered medications for chronic hypertension and heart failure. They improve symptoms and enhance survival in patients with low ejection fractions and decrease the risk of mortality in patients who have experienced an MI. Intraoperatively, ACEIs and ARBs can cause hypotension, especially for patients under the effects of general anesthesia. Consequently, some practitioners recommend discontinuing ACEIs and ARBs 24 hours before surgery to mitigate hypotension. Yet there is evidence that continuing these medications perioperatively is beneficial. Hypotension associated with ACEIs and ARBs and anesthesia has not been shown to worsen outcomes such as MI, stroke, or kidney failure, likely because of prompt treatment. In fact, if an ACEI or ARB is discontinued before surgery and not restarted in the immediate postoperative period, 30-day mortality rates increase.

Aspirin has been administered for decades to prevent MI or stroke in patients with CAD or cerebrovascular disease, and its efficacy is universally accepted. Despite evidence for its benefit, aspirin treatment is often discontinued perioperatively to prevent bleeding. The risk of bleeding should be balanced with the known benefit of continuing aspirin to prevent CAD, cerebrovascular disease, or peripheral artery disease. When aspirin is discontinued preoperatively, the acute withdrawal may increase one's risk of a major thromboembolic event. When the potential risk of bleeding is lower than the risk of a perioperative cardiac event, patients should continue taking aspirin. On the other hand, patients taking aspirin for primary prevention are instructed to discontinue aspirin 5 to 7 days before surgery.

β-blockers decrease myocardial oxygen demand by reducing heart rate and contractility. They increase oxygen supply by increasing diastolic time and reducing ventricular wall stress. They are the gold standard in prevention of MI. The Perioperative Ischemic Evaluation (POISE) trial, a large, randomized control study with over 8000 patients, showed a reduction in nonfatal perioperative MI but an increase in stroke in patients who took β-blockers on the day of major surgery. This increase in stroke and death rates was likely due to persistent, untreated hypotension. Wallace and colleagues showed a reduction in 30-day and 1-year mortality rates in patients treated with β-blockers when these drugs were started in the preoperative period. They created a Perioperative Cardiac Risk Reduction Therapy protocol to reduce cardiac risk perioperatively by starting β-blockers in patients who had CAD, peripheral vascular disease, or two risk factors for CAD (age >60, cigarette smoking, diabetes, hypertension, cholesterol >240 mg/dL). In summary, long-term β-blockade should not be discontinued, and hypotension should be treated perioperatively. When indicated, β-blockers should be started well before surgery and titrated before surgery to prevent hypotension.

Calcium channel blockers and α_2-agonists taken for hypertension are continued perioperatively. There is no evidence to support their use to reduce perioperative ischemia.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) stabilize coronary plaques and reduce the risk of perioperative plaque rupture, MI, and death. Statins also may lower the risk of acute renal failure. Abrupt discontinuation of statins can lead to plaque destabilization and increase the risk of PMI. Perioperative initiation of a statin is reasonable in patients undergoing vascular surgery or other procedures that increases patient risk.

Anemia also can lead to myocardial ischemia from a decrease in oxygen delivery to the myocardium and an increase in demand from greater cardiac output. Transfusions are associated with a variety of complications, and there is debate on the hemoglobin level at which a transfusion is indicated. A restricted transfusion strategy transfuses when the hemoglobin is less than 6 g/dL in asymptomatic patients without CAD. Patients with ischemic heart disease may benefit from a more liberal transfusion strategy: keeping hemoglobin greater than 9 g/dL. Preoperative iron therapy should be considered for patients who are anemic. Delaying surgery for evaluation and treatment of anemia can improve outcomes.

Patients who have had previous percutaneous coronary intervention are at risk of a subsequent cardiac event. A full discussion on stents can be found in Chapter 22.

In the past 2 decades, recommendations have changed for preventing perioperative ischemia and myocardial infarction. The focus is more on medical management and less on intervention. Medications such as aspirin, statins, and β-blockers; treating tachycardia and hypotension; and managing anemia preoperatively decrease the possibility of a poor outcome.

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Perioperative Tachyarrhythmias

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Alexander Michael Stewart • James Bromilow

Case Synopsis

A 68-year-old man develops sudden-onset fast atrial fibrillation during an emergency laparotomy under general anesthesia for an ischemic small bowel. The patient is hypotensive, with an irregular narrow complex tachycardia and a ventricular rate of 140 beats per minute. Cardiovascular stability is restored with an intravenous fluid bolus, vasopressors, electrolyte replacement, and an amiodarone infusion. Postoperatively the patient is transferred to the intensive care unit where he develops sudden-onset ventricular tachycardia necessitating immediate electrical cardioversion. The patient has further amiodarone loading and further electrolyte optimization.

PROBLEM ANALYSIS

Definition

An abnormal heart rhythm with a rate above 100 beats per minute is classified as a tachyarrhythmia. The onset of arrhythmia in the perioperative setting should trigger investigation to identify a reversible precipitant indicated by the nature of the arrhythmia, the acuity, and the patient's history.

Atrial fibrillation (AF) and atrial flutter (AFl) are the most common perioperative arrhythmias. Peak incidence occurs 1 to 3 days after surgery and is likely related to the sympathetic stimulation associated with inflammation and tissue trauma. Incidence is positively correlated with patient age, preoperative heart rate, and male sex.

Recognition

During preoperative assessment a systems inquiry should direct the clinician to a history of arrhythmia. Abrupt-onset palpitations are indicative, and associated symptoms may offer a guide to severity such as shortness of breath, chest pain, light-headedness, and syncope. Patients listed for elective surgery with these symptoms should be postponed pending appropriate consultation with a cardiologist.

Intraoperative arrhythmias are typically diagnosed via electrocardiogram (ECG), and the diagnostic features of tachyarrhythmias are summarized in Table 161.1. They can be broadly classified into supraventricular (narrow complex) and ventricular (broad complex) arrhythmias according to their site of origin within the myocardium. A broad complex regular tachycardia should be treated as ventricular in origin, unless a diagnosis of supraventricular tachycardia (SVT) with aberrant conduction or of antidromic atrioventricular (AV) reentrant tachycardia (AVRT) is certain (see Table 161.1.) Attempts to treat a ventricular tachycardia (VT) with AV nodal blocking agents such as adenosine will prove ineffective and potentially deleterious. Similarly, it is imperative to recognize preexcitation and Wolff-Parkinson-White syndrome on a resting ECG. These patients have an accessory pathway with a shorter refractory period than the AV node that is life threatening with atrial tachyarrhythmias. AV nodal blocking drugs (adenosine, diltiazem, verapamil, β-blockers, and digoxin) are contraindicated because blocking the AV node will promote conduction down the accessory pathway and potentiate ventricular fibrillation.

Risk Assessment

Risk factors for tachyarrhythmias are listed in Table 161.2. Perioperative investigations to aid the identification of risk factors for arrhythmia are listed in Table 161.3.

Implications

Cardiac arrhythmias should ideally be controlled and optimized preoperatively, as surgery and anesthesia can cause marked deterioration. Sudden loss of effective atrial contraction with an SVT will compromise cardiac output due to the loss of ventricular filling associated with atrial contraction. Diastolic ventricular filling is compromised further as the ventricular rate increases, which is especially deleterious in diastolic dysfunction and valvular heart disease.

Single ventricular ectopics or nonsustained VT usually does not require antiarrhythmic therapy but may signal reversible triggers that should be treated. However, sustained VT is a potentially life-threatening arrhythmia, which requires urgent diagnosis and management.

MANAGEMENT

On acute onset of a tachyarrhythmia, consider the etiology and correct any precipitating factors immediately. In extreme hemodynamic instability, electrical cardioversion may be required, but understand that this may be unsuccessful if the underlying cause has not been addressed. Oxygenation, ventilation, correction of hypovolemia, electrolyte replacement, or analgesia may improve hemodynamics without the need for antiarrhythmic drugs. See Fig. 161.1 for a treatment algorithm for sudden-onset intraoperative tachyarrhythmia.

PREVENTION

Patients with a preoperative history of AF or AFl who are clinically stable generally do not require modification of medical management

TABLE 161.1 Classification and Diagnostic Features of Tachyarrhythmias[a]

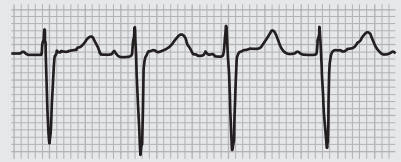
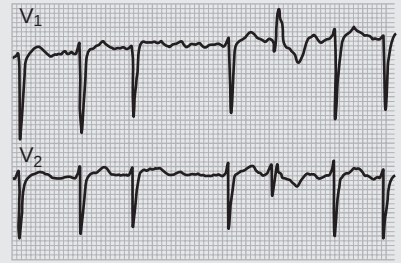
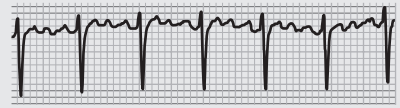
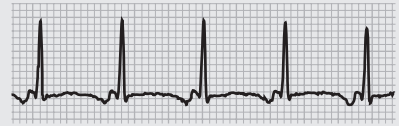
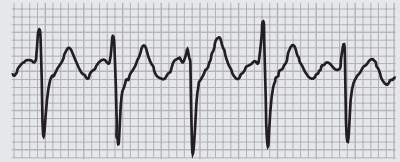
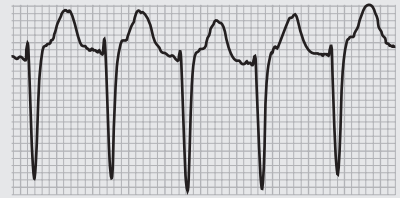
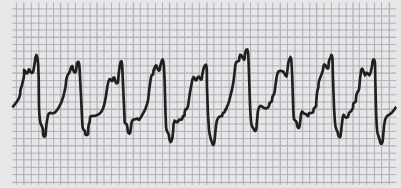
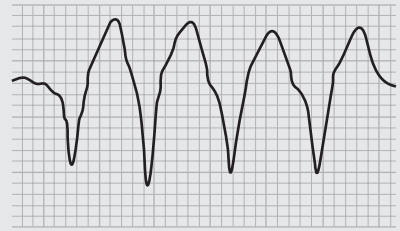
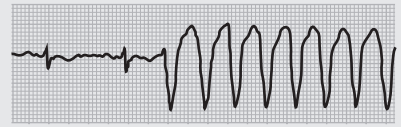
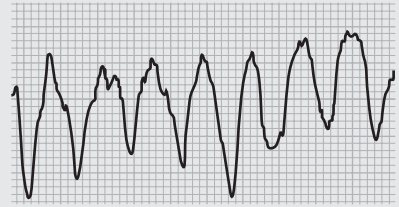
Arrhythmia	Causes	ECG Characteristics	Ventricular Rate (beats per minute)	Onset	Treatment Considerations	ECG
Sinus tachycardia	Stress response, sympathomimetics, anticholinergics, hyperthyroidism, malignant hyperthermia, idiopathic	Regular R-R intervals, normal P-R interval, similar to resting ECG	220 minus the patient's age (maximum)	Gradual	Treat the cause	
Atrial fibrillation	Cardiovascular disease, cardiac surgery, COPD, inflammation, hyperthyroidism, electrolyte derangement	Irregular R-R intervals, uncoordinated atrial activity with absent P waves	100–220	Sudden (new onset) or gradual (chronic)	Treat the cause, unlikely to cardiovert early in perioperative period therefore initiate rate control therapy	
Atrial flutter	See atrial fibrillation	Regular R-R intervals (irregular if variable AV conduction), regular flutter waves typical rate 300 beats per minute with 2:1 AV conduction	150	Sudden	More amenable to cardioversion than AF, adenosine will aid diagnosis but not cardiovert	
Focal atrial tachycardia	Cardiopulmonary disease, digitalis toxicity	Regular R-R intervals, monomorphic atrial activity with P-wave morphology distinct from sinus rhythm appearance	150–250	Abrupt onset over 3–4 beats	Treat the cause, initiate rate control therapy	
Multifocal atrial tachycardia	Pulmonary disease, theophylline toxicity	Irregular R-R intervals, polymorphic atrial activity	100–150	Gradual	Treat the cause, initiate rate control therapy, highly refractory to cardioversion	
AV nodal reentrant tachycardia	Often young patients, reentrant circuit within AV node but no accessory pathway	Regular R-R intervals, simultaneous atrial and ventricular activation obscuring the P wave within the QRS complex	150–250	Sudden	Vagal maneuvers if awake or adenosine	
AV nodal tachycardia	Congenital accessory pathway	Regular R-R intervals, narrow complex if anterograde conduction via AV node, broad complex if anterograde conduction via accessory pathway	150–250	Sudden	Vagal maneuvers if awake or adenosine for narrow complex; amiodarone or procainamide for broad complex	 (Anterograde via accessory pathway)

TABLE 161.1 Classification and Diagnostic Features of Tachyarrhythmias[a]—cont'd

Arrhythmia	Causes	ECG Characteristics	Ventricular Rate (beats per minute)	Onset	Treatment Considerations	ECG
AF with preexcitation	Above causes of AF, and a coexisting congenital accessory pathway	Irregular R-R intervals, broad complex with anterograde conduction via accessory pathway, evidence of Wolff-Parkinson-White Syndrome on resting ECG	150–250	Sudden	Treat the cause, consider early electrical cardioversion, and consider amiodarone or procainamide	
Monomorphic ventricular tachycardia	Cardiovascular disease, myocardial ischemia, direct myocardial manipulation, reperfusion, severe electrolyte derangement	Regular R-R intervals, broad complex QRS, normal QT interval on resting ECG	110–250	Sudden	Treat the cause, electrical cardioversion if unstable, consider amiodarone or lidocaine	
Polymorphic ventricular tachycardia	Myocardial ischemia, causes of QT prolongation if torsade de pointes	Normal or prolonged QT interval, QRS complexes varying in amplitude, axis, and duration	110–250	Sudden	See Chapter 155 for further details on long QT syndromes and ventricular arrhythmias	

[a]These are classic ECG features and treatment options for tachyarrhythmias occurring in the perioperative period. Note that variants will exist; for example, a patient may have a preexisting bundle branch block, so in this case a sinus tachycardia may be broad complex in nature. Always examine the preoperative ECG.

AF, Atrial fibrillation; *AV,* atrioventricular; *COPD,* chronic obstructive pulmonary disease; *ECG,* electrocardiogram.

TABLE 161.2 Risk Factors for Perioperative Tachyarrhythmias[a]

Acute Anesthetic Factors	Acute Surgical Factors
Hypervolemia and acute atrial stretch	Shock
Anesthesia-induced cardiac depression	Pain
Auto-PEEP	Trauma
Inotropes	Anemia
Local anesthetic toxicity	Local and systemic inflammation
Pulmonary artery catheter/misplaced central line	Mediastinal or cardiac manipulation
Acute Medical Factors	**Chronic Medical Factors**
Hypoxia	Aging (fibrosis and inflammation)
Hypovolemia	Atrial distention (heart failure, valvular disease)
Electrolyte derangement	Ischemic heart disease
Myocardial ischemia	Congestive cardiac failure
Metabolic/respiratory acidosis	Chronic hypoxia (e.g., COPD, OSA)
Sepsis	Cardiomyopathy
Pulmonary embolism	Persistent tachycardia-induced atrial remodeling
Hypoglycemia/hyperglycemia	Accessory pathways
Hypothermia/hyperthermia	Congenital heart disease
Myocarditis/pericarditis	Scarring after cardiac surgery
Pneumothorax	Pulmonary hypertension
Excessive alcohol or caffeine intake	Hyperthyroidism/hypothyroidism
Recreational drugs	Malignancy

[a]These factors can trigger a tachyarrhythmia in the perioperative setting and exacerbate cardiovascular instability. Where possible, identify and treat.
COPD, Chronic obstructive pulmonary disease; *OSA,* obstructive sleep apnea; *PEEP,* positive end-expiratory pressure.

TABLE 161.3 Perioperative Investigations Relevant for Tachyarrhythmias[a]

Investigation	Finding
Electrocardiogram	Rhythm, ischemia, accessory pathways
Echocardiogram	Volume status, valvular heart disease, atrial dimensions, ventricular size and function, cardiomyopathy, previous cardiac surgery, congenital heart disease, pericardial effusion, pulmonary hypertension
Chest radiograph	Pneumonia, pneumothorax, pulmonary edema, line position
Full blood count	Anemia
Arterial blood gas	Hypoxia, acidemia
Serum electrolytes	Electrolyte derangement (especially hypokalemia and hypomagnesemia)
Thyroid function tests	Hyperthyroidism
Drug screening	Recreational sympathomimetic use

[a]Consider these investigations preoperatively where indicated. New-onset intraoperative arrhythmia warrants thorough investigation to limit morbidity and guide therapy perioperatively.

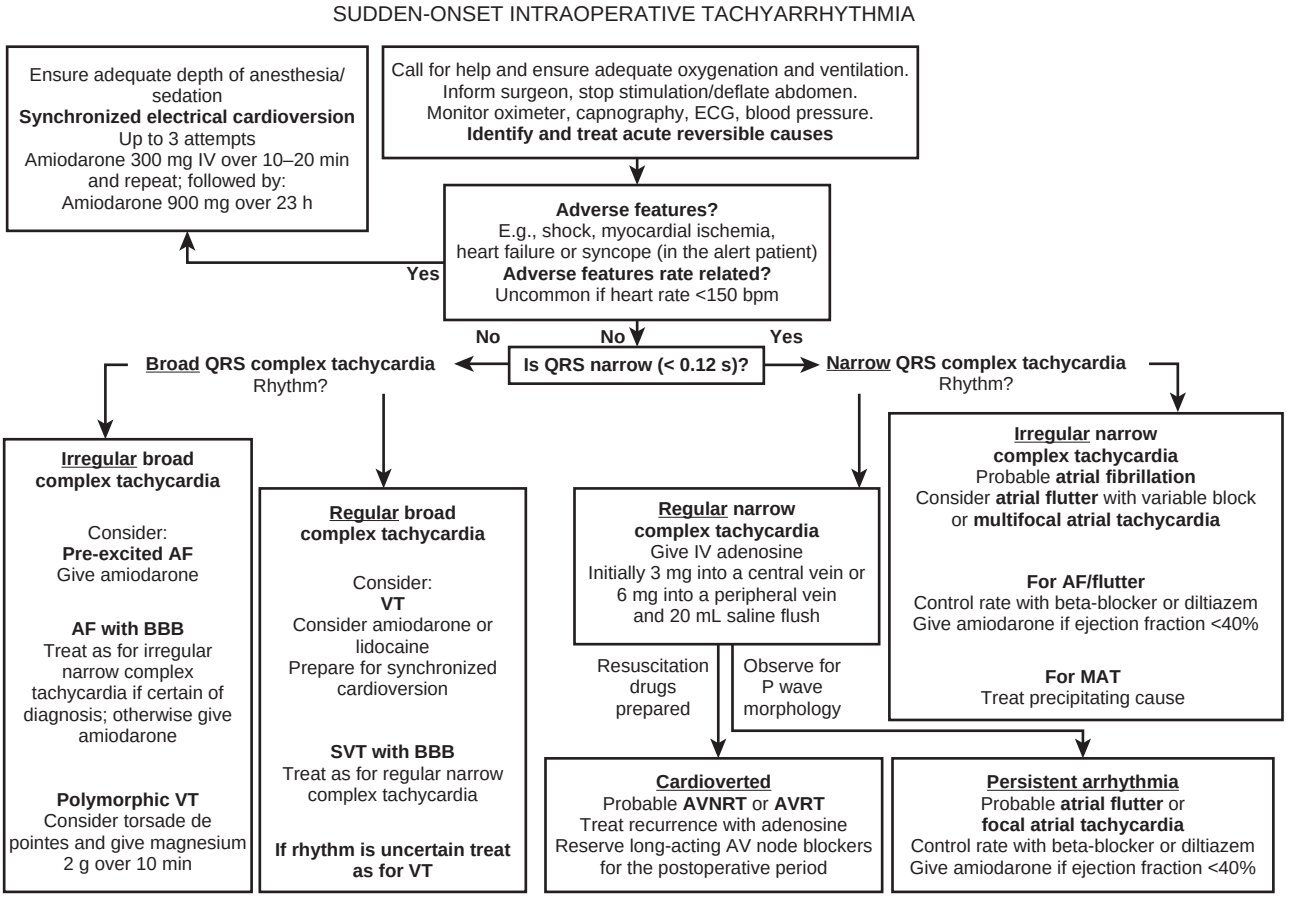


Fig. 161.1 Tachycardia management algorithm. Pharmacologic rhythm control is often ineffective in the perioperative period, and the adverse effects of antiarrhythmic drugs such as flecainide or procainamide may be exaggerated in the critically unwell, or under general anesthesia. Concentrate on reversing triggers and controlling heart rate.

or special evaluation in the perioperative period, other than adjustment of anticoagulation. Those at high risk of thromboembolism may require bridging therapy with low-molecular-weight heparin.

Those with a preoperative history of VT and a cardiac-implantable electronic device need assessment and advice from a cardiologist.

Patients prescribed rate control therapy should continue this medication through the perioperative period, as it reduces the incidence of arrhythmia. Dose adjustment may be required based on clinical circumstances (e.g., postoperative hypotension). Patients receiving diuretic therapy or with a history of chronic kidney disease should have serum electrolytes checked and optimized before surgery.

Further Reading

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162 Peripartum Neurologic Complications

Nathaniel Hsu

Case Synopsis

A 32-year-old woman, gravida 1, para 0, had uneventful epidural analgesia for labor using 0.125% bupivacaine and fentanyl 2 μg/mL. A 10-mL intravenous bolus was administered, followed by infusion of the same mixture at 10 mL per hour. Subsequently she required midforceps delivery with manual fetal version for occiput posterior vertex presentation. Before version and extraction of the infant, 20 mL of 2% lidocaine with 1:200,000 epinephrine was administered. The next day, the patient complained of sensory loss in, and inability to move, both lower extremities, and she had fecal incontinence. Two days later, she regained partial motor function and sensation in both lower extremities but still had fecal incontinence and subsequently developed urinary retention with overflow incontinence. A neurology consultation was obtained. Possible cauda equina syndrome was diagnosed on the fourth postpartum day. At 6 months, the patient still required a wheelchair but had some improvement in bowel and bladder function.

PROBLEM ANALYSIS

Definition

Although many surveys have attempted to identify the incidence of neurologic complications, the true incidence can vary widely depending on the skill of the practitioner, as well as the anesthetic practices of that era. More recent data from 2006 showed the reported incidence of transient neurologic complications in obstetric patients was 1 in 6700, whereas persistent neurologic injury was quoted to be 1 in 240,000. Persistent complications usually are not due to the anesthetic itself but are more often associated with obstetric trauma during birth. In a closed claim analysis of 1005 regional anesthetics by Lee and colleagues, neuraxial block was performed in all 368 obstetric and 453 of 637 nonobstetric claims. Injuries in 51% of obstetric and 41% of nonobstetric claims were related to neuraxial block. The obstetric group had a significantly greater proportion of neuraxial claims involving transient and low-severity injuries (71%) than did the nonobstetric group (38%), yet the proportion of obstetric claims involving severe adverse outcomes (including death or permanent brain injury) was significantly lower. Among the causes of these adverse outcomes were cardiovascular collapse, respiratory arrest, and neuraxial hematoma in patients with coagulopathies. In 2009 a UK national audit showed that the highest risk appeared to be with combined spinal-epidural (CSE) and lowest with epidurals in the obstetric population.

Wong and coworkers studied 60,057 women who gave birth to live infants and later interviewed 6048 of the women. Fifty-six (0.92%) had new lower extremity peripheral nerve injuries. By logistic regression analysis, multiparity and prolonged second-stage labor were significantly associated with nerve injuries. Patients with nerve injuries spent more time in a semi-Fowler lithotomy position "pushing" than did those without such injury. The median duration of symptoms was 2 months, and injuries involved one of the lower limb peripheral nerves or the lumbosacral plexus. Thus these findings suggest that neurologic injuries related to childbirth may be related more to childbirth itself rather than the anesthetic.

Recognition

When evaluating a patient with suspected neurologic complications, the answers to several questions are pertinent:

- What was the duration of labor?
- How long did the patient "push"?
- Was the patient placed in an exaggerated lithotomy position while pushing?
- Did the obstetrician use forceps to facilitate delivery?
- What was the weight of the neonate?
- What was the position of the presenting part (e.g., occiput posterior)?
- Did the patient have a history of back problems or preexisting neurologic impairment (e.g., multiple sclerosis, human immunodeficiency virus [HIV])?
- What type and amount of local anesthetic were used?
- Did the patient recover sensory or motor function before the onset of new symptoms?

If a peripartum neurologic complication develops, epidural analgesia or anesthesia is often implicated. Invariably, the anesthesiologist will be consulted. There are many potential causes of postpartum neurologic injury, and epidurals are only one of them. Such neurologic injuries often result from direct trauma to the major nerve roots or trunks that supply the lower extremities and are caused by the fetal head or forceps. Direct ischemic injury to the lower spinal cord is also possible. This may occur if the fetal head compresses the ascending spinal branch of the internal iliac artery. One should also consider the possibility of a spinal hematoma (see Chapter 179). A neurologist must be consulted urgently when extensive neurologic deficits are first noted. Also, magnetic resonance imaging (MRI) or computed tomography scans of the spinal cord should be obtained without delay.

Risk Assessment

When calculating the risk for peripartum neurologic injuries, consideration of the anatomy involved is important. Neurologic injuries resulting from childbirth may involve branches of the lumbosacral

plexus (i.e., iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous, anterior tibial, femoral, obturator, and sciatic nerves). Also involved may be the pudendal nerve, derived from the sacral (S3 and S4) nerve roots, and the coccygeal plexus, derived from the S4, S5, and coccygeal nerve roots. Occasionally, extensive injuries may result in the cauda equina syndrome. Involvement of the major plexuses (lumbar and sacral) may cause such extensive injuries, which can take weeks or months to resolve.

Branches of the lumbar plexus or sacral plexus (Fig. 162.1) include the sciatic nerve (which contains the common peroneal and tibial nerves), and these may be compressed by the fetal head as it crosses the posterior pelvic brim during birth. Such injuries are unilateral in 75% of cases and bilateral in the rest. Compression injuries are more common in nulliparous parturients with a platypellic pelvis, large fetus, cephalopelvic disproportion, vertex presentation, or forceps delivery. These injuries may involve multiple nerve root levels or present as injuries to the femoral or obturator nerves, with sensory impairment in the L4–L5 dermatomes. Table 162.1 describes some common peripheral nerve injuries in parturients, and Fig. 162.2 illustrates the dermatomes subserved by branches of the lumbosacral plexus.

With regard to the mechanisms for specific nerve injuries (see Table 162.1), multiple sclerosis relapses often contribute to lateral femoral cutaneous nerve injuries. Numbness of the anterior aspect of the thigh associated with lateral femoral cutaneous nerve injury is termed *meralgia paresthetica.* This nerve can also be injured by hyperextended lithotomy positioning, pressure from the fetal head, or improper surgical traction during cesarean delivery. When the femoral nerve is injured, hip flexion and knee extension become difficult. Injury is caused by active flexion of the hips during the second stage of labor, leading to compression of the nerve by the inguinal ligament. Therefore extreme flexion of the hip during "pushing" should be avoided. The legs should be rested between labor contractions and pushing. Also, use of a "squatting bar" to keep the hips hyperflexed during the second stage of labor may cause injury to the femoral nerve. Femoral nerve injury may also be caused by lumbosacral plexus compression by the fetal head.

The adductor magnus muscle receives dual innervation from the obturator and sciatic nerves. If the obturator nerve is involved, thigh abduction weakens, with sensory loss along the medial aspect of the thigh. The sciatic nerve is the largest peripheral nerve in the body. An important branch is the common peroneal nerve, which supplies both motor and sensory innervation to the leg. This nerve winds around the neck of the fibula, where it is the only manually palpable nerve in the lower extremity (Fig. 162.3), making it vulnerable to injury, especially by stirrups. Such injury leads to paralysis of the ankle and foot, resulting in footdrop and inversion, with sensory impairment of the anterior aspect of the foot.

Occasionally, inflammation or spasm of the piriformis muscle (caused by prolonged sitting or extensive weight bearing during pregnancy) may cause sciatic nerve irritation. When the thigh is extended and rotated medially, gluteal pain radiating to the knee occurs.

Blood supply to the spinal cord is often precarious and subject to important variations (Fig. 162.4). Damage to the spinal cord, can occur if the blood supply is interrupted. One anterior and two posterior spinal arteries supply the cord. At certain sites along the spinal cord, there are a number of reinforcing inputs from other arteries, one of which is the artery of Adamkiewicz (or the arteria radicularis magna); this usually arises from the aorta at T9 but can arise anywhere between T9 and T12. Arteries that supply the lower spinal cord usually originate from the left side from one or two of the thoracolumbar segmental arteries (T9 to L2). Thus injury to these arteries may be implicated in injuries to the lower portion of the spinal cord. In about 15% of cases, the artery of Adamkiewicz originates at the T5 level. If so, the major part of the blood supply to the lower spinal cord is provided by a lumbar branch from the internal iliac artery, which lies in front of the sacral ala and enters the spinal cord via L5–S1 intervertebral foramina. This branch can be compressed by the fetal head, leading to ischemia of the conus medullaris. Additionally, compression in the artery of Adamkiewicz due to a stiff epidural catheter in the same intervertebral foramen may impair blood supply to the spinal cord, leading to symptoms of anterior spinal artery syndrome. Acute spinal cord ischemia is often undetectable with conventional MRI. Echoplanar diffusion-weighted MRI is used to diagnose acute spinal cord ischemia, as well as epidural hematoma or abscess.

Implications

Neural tissue may be injured by local anesthetic neurotoxicity (chemical injury), direct trauma, ischemic compression by epidural hematomas, and neuraxial infections such as an epidural abscess and meningitis.

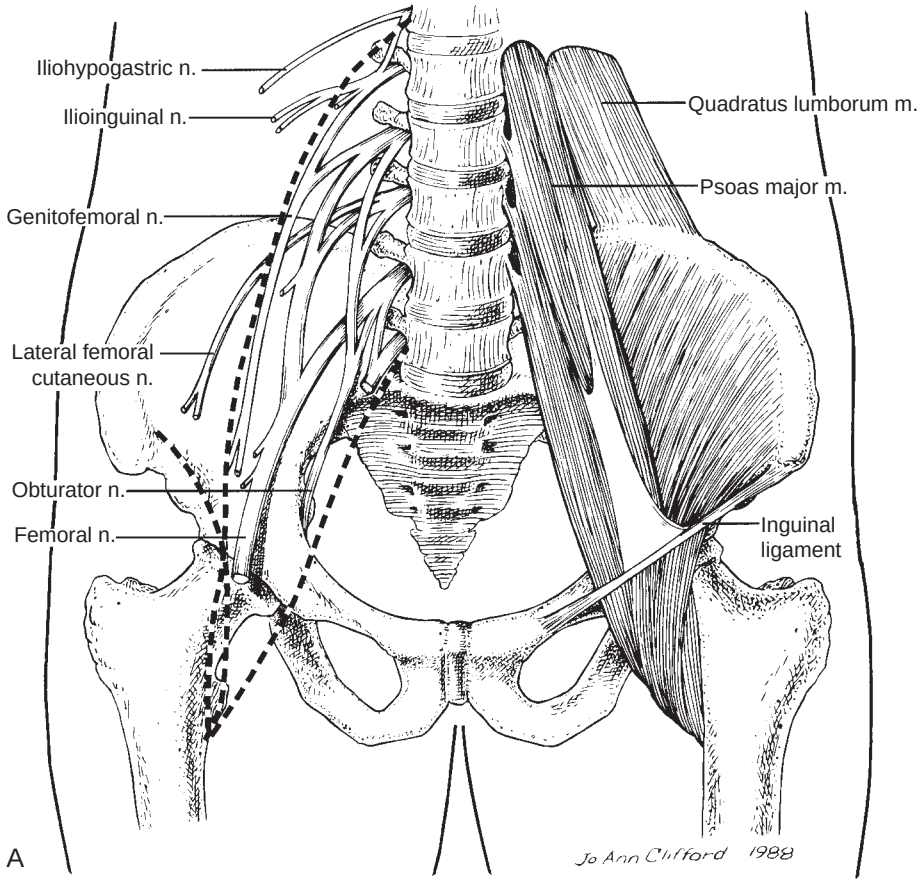
Chemical Injury

Chemical injury usually results from accidental injection of an irritant into the epidural or subarachnoid space. Preservatives and antioxidants such as sodium bisulfite have been implicated in the development of adhesive arachnoiditis or the cauda equina syndrome. Either disorder can also occur as a result of direct local anesthetic neurotoxicity, and both can obliterate the subarachnoid space. Such toxicity is believed to have resulted from poor distribution of local anesthetic within the cerebrospinal fluid, with subsequent deposition of toxic drug concentrations at the nerve roots. As such, the intrathecal injection of lidocaine, especially hyperbaric 5%, has been involved in numerous reports of cauda equina syndrome. An upper limit of 60 mg of intrathecal lidocaine has been recommended. The cauda equina syndrome has also been reported after the use of microcatheters for continuous spinal anesthesia. Although the U.S. Food and Drug Administration has advised against the routine use of spinal microcatheters, there is renewed interest in evaluating their utility for obstetric anesthesia. Finally, the cauda equina syndrome may also occur as a result of acute intervertebral disk herniation, which requires immediate surgical intervention.

Another similar form of neurologic injury due to a noxious intrathecal injection is transient neurologic syndrome (TNS), which presents with pain in the back, buttocks, and possibly radiation down the lower extremities. The risk factors for this complications mirror those for cauda equina syndrome; however, TNS is much more common in surgical than in obstetric patients.

Direct Neural Trauma

Direct nerve trauma during regional anesthesia uncommonly causes neurologic deficits. Pain or paresthesias on injection using needles or catheters should be a cause for concern. Repositioning is of paramount importance. Soft-tip catheters for continuous epidural anesthesia are associated with fewer paresthesias than the more rigid nylon catheters. Also, spinal anesthesia is more often associated with neurologic injury than is epidural anesthesia. If paresthesias occur during central neuraxial block, the anesthesiologist should document the severity and location of the paresthesias. Prolonged symptoms with a distribution of more than one spinal segment could be a sign of direct spinal cord injury. It may take anywhere from 48 hours to 3 months for complete recovery from neuropathy due to direct nerve trauma incurred during central neuraxial block.



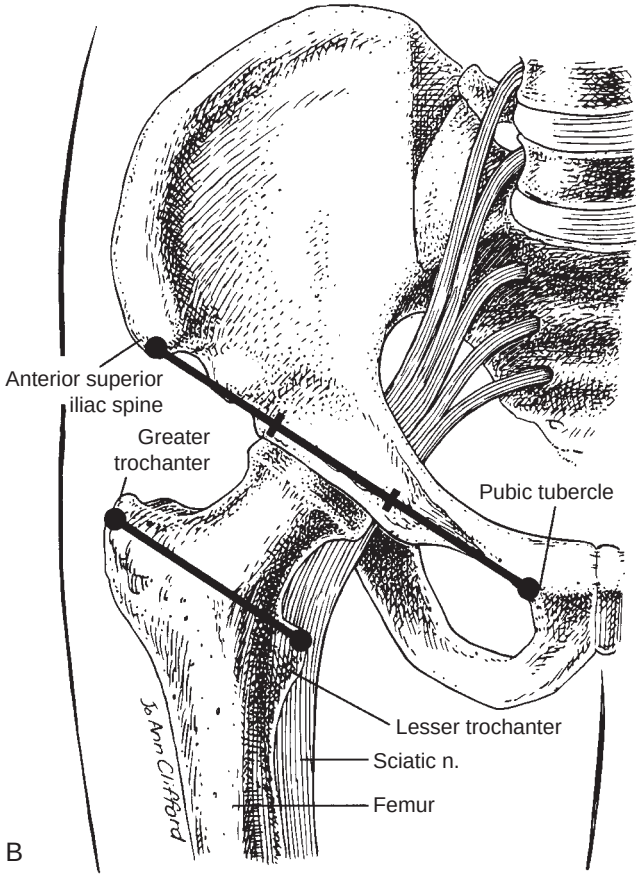


Fig. 162.1 A, The lumbar plexus is derived from the L1–L5 nerve roots and lies in the psoas compartment between the psoas major and quadratus lumborum muscles. **B,** The sacral plexus is formed by contributions from L4, L5, and S1–S3. Not shown are the origins of the pudendal nerve and coccygeal plexus, which are formed by branches of the third and fourth sacral roots and the fourth and fifth sacral and coccygeal nerves, respectively.

TABLE 162.1 Peripheral Nerve Injuries in Obstetric Patients

Nerve	Nerve Roots	Possible Mechanism	Clinical Picture
Lumbosacral trunk	L4–L5, S1	Forceps injury	Footdrop; quadriceps and adductors affected
Femoral nerve	L2–L4	Fetal head; retractors during cesarean section	Quadriceps weakness; weak hip flexion; absent patellar reflex; sensory impairment in thigh and calf
Lateral femoral cutaneous nerve	L2–L3	Stirrups; prolonged and exaggerated lithotomy position while pushing	Hypalgesia in anterolateral aspect of thigh
Common peroneal nerve (sciatic)[a]	L4–S2	Stirrups or bedside rails	Footdrop; hypesthesia in lateral calf and anterior aspect of foot
Tibial nerve (sciatic)	L4–S2	Stirrups or bedside rails	Footdrop (muscular branches innervate gastrocnemius and soleus muscles); medial (sural) branches lead to sensory loss in lower leg
Obturator nerve	L2–L4	Fetal head	Weakness on thigh adduction; reduced sensation in medial aspect of thigh

[a]Owing to its superficial nature, one of the more frequently injured nerves.

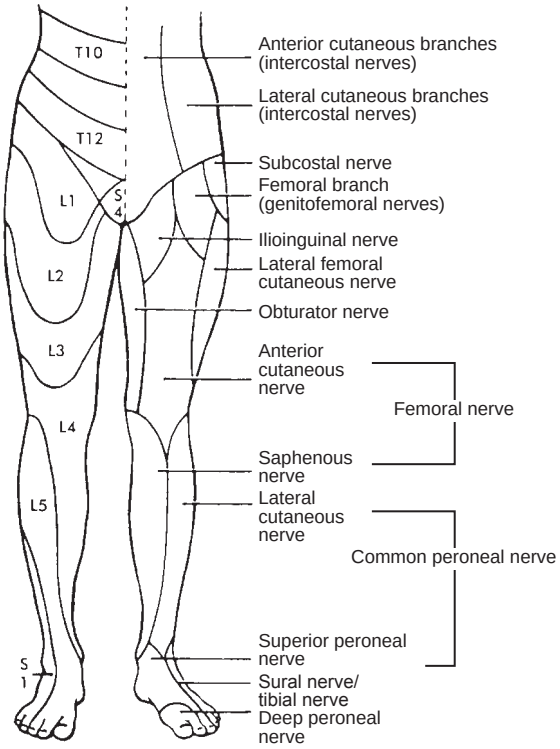


Fig. 162.2 Segmental and peripheral nerve distributions can help distinguish central from peripheral nerve injury. (From Redick LF: Maternal perinatal nerve palsies. *Postgrad Obstet Gynecol* 12:1-6, 1992.)

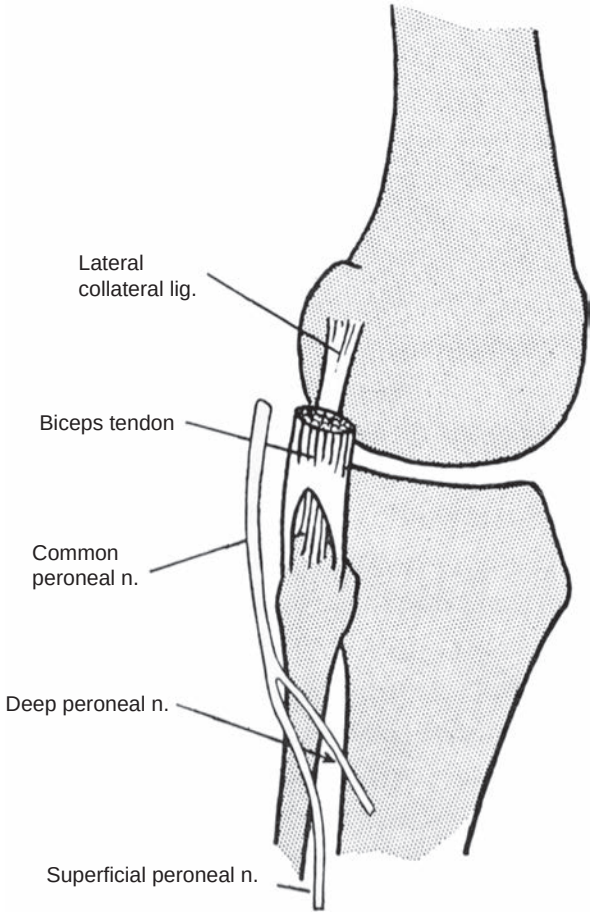


Fig. 162.3 The anatomic location of the common peroneal nerve makes it vulnerable to injury by direct pressure (e.g., stirrups). This is the most frequently damaged nerve in parturients.

Direct trauma to nervous tissue may occur at the level of the spinal cord, nerve roots, or peripheral nerves. Epidural needles or catheters are more likely to traumatize the nerve roots. Spinal needles may injure a nerve root or the cord itself within the subarachnoid space or nerve roots outside the subarachnoid space. Two thirds of neurologic sequelae are preceded by paresthesias (direct nerve trauma) or pain during injection (intraneuronal injection). Intraneural injection of local anesthetic is more likely to result in prolonged neurologic deficits. In one series of more than 103,000 regional anesthetics, of the 34 patients with neurologic sequelae, 29 had transient deficits, with full neurologic recovery occurring in 48 hours to 3 months. Of interest is that spinal anesthesia was significantly more likely than epidural anesthesia to be associated with neurologic injury (5.9 vs. 2 per 10,000) or radiculopathy (4.7 vs. 1.7 per 10,000). Injuries to the conus medullaris during spinal anesthesia may be related to the inaccurate identification of lumbar interspaces or an abnormally long spinal cord. Tuffier's line as a landmark can be inconsistent and, at times, impalpable in the morbidly obese. Therefore the use of neuraxial ultrasound may be a tool to improve the accuracy of identifying interspaces.

With mild nerve injury, conduction block occurs only through the damaged nerve segment (i.e., neurapraxia). If the condition is corrected, recovery occurs. However, the patient must be told that recovery may take several weeks, depending on the severity of the initial symptoms. Severe injuries cause axonal degeneration (axonotmesis). Regeneration may never be complete, with full or partial loss of

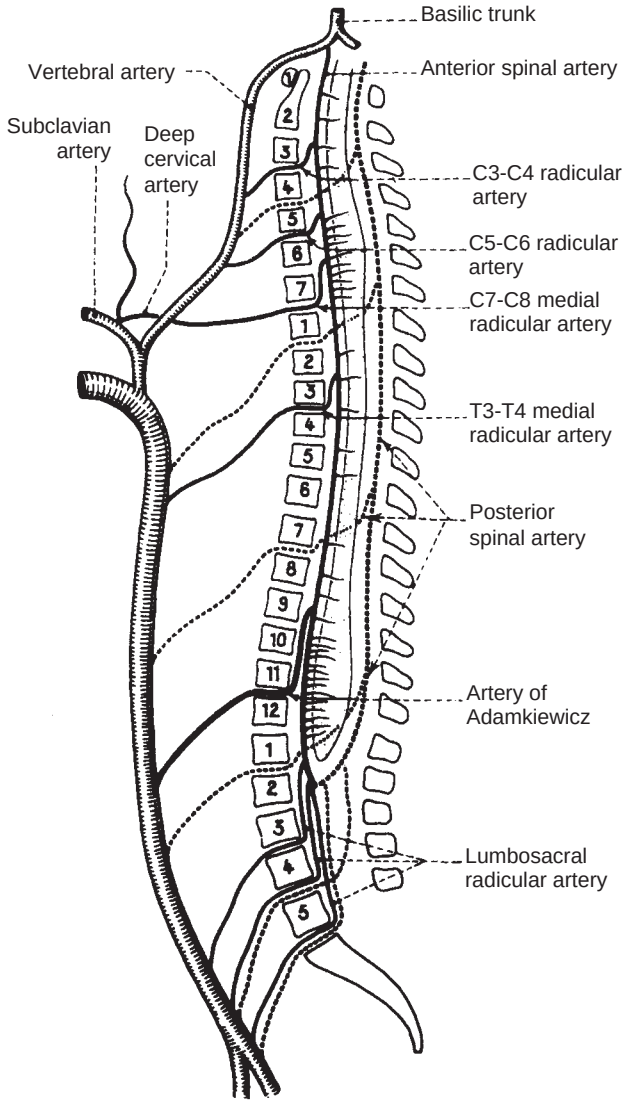


Fig. 162.4 Lateral view of the blood supply of the spinal cord, depicting the anterior and posterior radiculomedullary branches. The primary blood supply to the thoracolumbar spinal cord is the artery of Adamkiewicz. As shown, it arises from the aorta at T9 but can arise anywhere between T9 and T12. With high ARM takeoffs, a lumbar artery usually supplies the major portion of the conus medullaris. (From Djindjian R: Arteriography of the spinal cord. *Am J Roentgenol Radium Ther Nucl Med* 107:461-478, 1969.)

function in the affected area. Neurotmesis signifies disruption of epineurium as well. Surgical repair is necessary, but recovery may never be complete.

Infection

Infectious complications include both epidural abscess and meningitis. In a retrospective study, Green and Paech identified the rate of deep tissue infections related to epidural catheter to be 1 in 2371, whereas the incidence of meningitis after CSE and spinal anesthesia in obstetric patients was noted as 1 in 39,000. Symptoms of an epidural abscess typically start between 4 and 10 days after epidural catheter removal and may ultimately lead to cauda equina syndrome if left untreated. Mild symptoms can be treated conservatively with antibiotics, but surgical intervention may be necessary for complete drainage of abscess. In meningitis, symptoms may begin 12 hours to days postpartum, and antibiotic treatment should begin before microbiology culture results. Appropriate treatment usually leads to a full recovery.

Spinal Hematoma

As space-occupying lesions, spinal hematomas (epidural, subdural, subarachnoid) may compress nearby neural and vascular structures, leading to ischemia. Although the incidence of spinal hematoma is incredibly rare in the obstetric population, if the neurologic examination is concerning for a spinal hematoma, further imaging should be sought immediately. Delay in surgical decompression greater than 6 to 12 hours after symptom onset could result in permanent disability. (See Chapter 179 for more details.)

MANAGEMENT

When patients present with postpartum neurologic problems, one must be alert to other causes, including diabetes mellitus, acquired immunodeficiency syndrome (AIDS), and multiple sclerosis. Although diabetic neuropathy is a well-known entity, AIDS-related neuropathy is not, even though it is the most common neurologic complication of type 1 HIV infection and advanced AIDS. It manifests as a distal symmetric polyneuropathy and occurs mainly with advanced immunosuppression. The number of parturients with advanced HIV disease is increasing, and neurotoxicity may also occur with several antiretroviral agents. Progressive polyradiculopathy occurs with advanced immunosuppression, usually caused by cytomegalovirus infection.

In the initial evaluation, the anesthesiologist should document all sensory and motor deficits and consult a neurologist who is familiar with obstetric nerve injuries. Additional imaging includes computed tomography or MRI scans, which must be performed without delay. If urgent laminectomy is required to avoid permanent neurologic injury, surgical consultation should be obtained immediately as well.

Further neuromuscular electrophysiologic studies include electromyography (EMG) and nerve conduction studies. EMG is extremely useful for diagnosing the extent of injury to peripheral nerves; however, timing is critical. The presence of abnormal spontaneous activity in quiescent muscle (fibrillation potentials) or increased activity during insertion of the recording needle into muscle (insertion activity) usually indicates preexisting neurologic disease. Insertion activity becomes noticeable on EMG within a few days of injury, whereas fibrillation potentials take 2 to 4 weeks to develop. If fibrillation potentials are recorded soon after the alleged injury, they are more likely due to a previously undiagnosed neurologic condition rather than a new injury. Another EMG sign of nerve injury is the failure to recruit additional motor units when muscle is stimulated. In completely denervated muscle, no recruitment occurs. However, when the nerve is damaged, partial recruitment occurs due to slowed conduction. EMG may also help distinguish whether a plexopathy or radiculopathy exists.

Depending on the type and severity of injury, it may take up to 8 weeks for neurologic injuries to resolve completely. Repeat electrophysiologic studies are often necessary to assess progression or regression of injuries. Also, consultation with a physiotherapist is necessary to determine the best rehabilitation program to prevent muscle atrophy. A splint may be required for patients with significant footdrop to prevent permanent deformities.

The patient described in the case synopsis had extensive neurologic injury, indicative of damage to the lumbosacral plexus or the spinal cord. Bowel or bladder dysfunction usually indicates spinal cord injury. Although electrophysiologic studies suggested a lesion at the spinal root level or higher, MRI scans of the spinal cord 2 days

BOX 162.1 Differential Diagnosis for Prolonged Neural Block

Drug Effects
Prolonged action of local anesthetic
- Slow regression of block
- More common after multiple dosing
- Needle or catheter tip close to nerve root during local anesthetic injection

Direct neurotoxicity
- Rare effect of commonly used drugs (e.g., 5% hyperbaric lidocaine)
- Incorrect drug administered (e.g., potassium chloride)

Trauma
Peripheral nerve
- Compression from positioning
- Known peripheral nerve pattern

Central neuraxis
- Direct trauma to neural tissue caused by needle or catheter

External compression of nerve root or spinal cord
- Herniated intervertebral disk
- Epidural hematoma (early)
- Epidural abscess (late)
- Spinal stenosis

Vascular
Hemorrhage—spinal cord arteriovenous malformation
Decreased blood supply—no evidence of recovery; permanent injury
Anterior spinal artery syndrome
- Compression of arterial blood supply by fetal head
- Severe hypotension

Post–cardiac arrest
- Emboli (e.g., air, thrombotic, amniotic fluid)

Neurologic Disease (Preexisting or New Onset)
Multiple sclerosis
HIV, immunosuppressive therapy
Cytomegalovirus
Landry-Guillain-Barré syndrome

Miscellaneous Causes
Space-occupying lesions
- Epidural hematoma
- Epidural abscess

after delivery appeared normal. However, enhanced MRI performed 1 week later was consistent with spinal cord ischemia. Likely, this was due to compression of the lumbar spinal artery at the level of the sacrum. Other potential causes of prolonged neurologic deficits in parturients are listed in Box 162.1.

PREVENTION

For parturients with systemic disease, the anesthesiologist should thoroughly document any preexisting neurologic deficits to prevent potential medicolegal problems. Multiple sclerosis is particularly prone to relapse in the postpartum period. Coagulation status should be checked on insertion and removal of epidural catheters in patients who have risk factors for coagulopathy. In terms of prevention of infectious complications, the 2010 practice advisory by the ASA Task Force on Infectious Complications Associated with Neuraxial Techniques provides evidence-based recommendations for prevention and management. Also, anesthesia care providers in the labor-delivery suite must ensure that the patient has fully recovered from the effects of the local anesthetic before she is sent to the postpartum floor. If the patient develops a neurologic deficit after complete sensory and motor recovery from the anesthetic, the problem is unlikely related to neuraxial block or the agents used for the block.

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163 Persistent Paresthesia

Miguel A. Yaport • Ignacio Badiola

Case Synopsis

A 63-year-old woman with a history of breast cancer who has undergone chemotherapy will be undergoing a left carpometacarpal arthroplasty. An infraclavicular brachial plexus block is done using 30 mL of 0.5% ropivacaine. On her postoperative visit, she complains of numbness in the lateral hand. Electromyography and nerve conduction tests are performed 12 weeks after surgery and show a sensorimotor neuropathy of her left upper extremity. Over time her symptoms improve, and after 5 months her symptoms have completely resolved.

PROBLEM ANALYSIS

Definition

Regional anesthesia has been associated with a potential risk of nerve injury. Although generally considered safe, severe or devastating complications can occur and have been reported. Using the American Society of Anesthesiologists' closed claims database, Cheney and colleagues evaluated malpractice claims filed against anesthesia care to establish the role of perioperative nerve injury in malpractice claims against anesthesia providers; 670 of 4183 cases reviewed were for nerve injury related to anesthesia. Common injuries included the ulnar nerve, brachial plexus, lumbosacral roots, and spinal cord.

Data exist that strongly suggest perioperative neurologic deficits are more likely to be secondary to causes other than regional anesthesia. Horlocker and colleagues described 61 nerve injuries after 1614 upper extremity surgical procedures performed using an axillary brachial plexus block; 7 of 61 injuries were attributed to the anesthetic, and 54 of 61 were attributable to surgical factors. Brull and colleagues reviewed 32 studies over a 10-year period that investigated neurologic complications of regional anesthesia and estimated a risk of nerve injury associated with peripheral nerve blockade at approximately 3%. Nerve injuries associated with neuraxial anesthesia, though more severe in terms of complications, are associated with even lower risk, with an estimated incidence of less than 4 per 10,000 neuraxial anesthetics performed.

Recognition

Persistent paresthesia refers to a constellation of symptoms and signs involving either incomplete resolution of regional anesthesia after nerve blockade, or the development of new neuropathic symptoms such as weakness and/or paresthesia after surgery. The median duration of these symptoms is often cited as 2 to 4 months. Other more serious complications include permanent nerve injury and, rarely, complete loss of limb or severe spinal cord injury. Neurologic complications in the perioperative period can be due to nerve injury from surgical trauma, patient positioning, ischemia from prolonged tourniquet times, and compression from casts/dressings. Although occurring around the time of the regional anesthetic block, these causes are obviously not regional anesthesia related. Causes directly due to regional anesthesia can be due to nerve injury from the needle or perineural catheter, local anesthetic/adjunct agent neurotoxicity, and/or neural ischemia.

Risk Assessment

Risk factors for persistent paresthesia include factors attributable to the surgery itself, patient comorbidities, medications, and anesthesia-related factors.

Several surgical factors are associated with risk of injury, including exposure, positioning, and surgical approach. Shoulder arthroscopy is associated with a 0.1% to 10% risk of injury from surgical traction intended to improve exposure. Knee arthroscopic procedures involving the use of candy-cane stirrups are associated with common peroneal nerve injury. Total hip arthroplasty performed via an anterior approach is associated with significantly more risk of lateral femoral cutaneous nerve injury than a posterior approach.

Several patient factors are associated with increased risk of perioperative complications after regional anesthesia. Spinal canal pathology such as spinal stenosis, neural tube defects, and mass lesions can be associated with a higher risk of nerve injury after neuraxial anesthesia. Preexisting neurologic disorders such as Guillain-Barré syndrome and myasthenia gravis can be associated with nerve injury after both neuraxial and peripheral nerve blocks. Patients with a preexisting neurologic condition may be predisposed to a nerve injury by the known neurotoxic effects of local anesthetics or direct needle trauma. Known as a "double crush" injury, it is presumed that the preexisting neurologic condition provides the conditions such that a second "hit" leads to worse outcomes. Patient medications may also be associated with peripheral nerve injury. Anticoagulation therapy carries an injury risk of 1:4000 to 1:150,000. Similarly, chemotherapeutic agents associated with neuropathy (cisplatin, vincristine, paclitaxel) can put the patient at increased risk of nerve injury. Neurovascular disease, hypertension, and diabetes are also associated with an increased risk. The presence of diabetes seems to increase risk of nerve injury at least tenfold compared with the general population. Patients with microangiopathic processes, such as diabetes, demonstrate a reduction in neural blood flow, as well as a reduction in local anesthetic uptake, thus reducing anesthetic clearance from the focal injection site. Consequently the

presence of a peripheral neuropathy may reduce the amount of local anesthetic required to produce neural block and toxicity. Therefore these patients are more sensitive to the clinical effects of local anesthetic solutions.

Although the majority of data suggest that perioperative nerve injuries are uncommonly due to the nerve block itself, there are choices made by the anesthesiologist when performing a block that may be associated with an increased risk of nerve injury. Local anesthetic agent, presence of a vasoconstrictor, and volume injected may be associated with increased risk either from direct toxicity or ischemia to the nerve. However, there is no convincing evidence to support a particular practice. Local anesthetics may be directly toxic to nerves, with evidence noting that agents such as lidocaine and tetracaine may be more neurotoxic than bupivacaine. Additives such as epinephrine and bicarbonate may also potentiate local anesthetic toxic effects.

Even small volumes of local anesthetics can increase intraneural pressure that exceeds perfusion pressure leading to neural ischemia. Finally, blood flow to neural structures responds to adrenergic stimuli and can thus pose a theoretical risk of local nerve ischemia when using solutions containing epinephrine, especially in patients with microvascular disease or neural tissue that is already compromised.

Choice of technique may also affect risk. Moayeri and colleagues proposed that because proximal portions of nerves contain proportionately more neural tissue than distal portions (which contain a greater proportion of connective tissue), it can be posited that proximal nerve blocks may be riskier than distal approaches when considering peripheral nerve blockade. For neuraxial blockade, risk of hematoma is higher with epidural than with subarachnoid techniques.

The elicitation of a paresthesia while performing a block may represent direct needle-induced trauma and increased risk of persistent paresthesia. Selander and colleagues reported a nonstatistically significant 2.8% incidence of postoperative nerve injury in patients in whom paresthesia was sought during axillary brachial plexus block, compared with a 0.8% incidence in those undergoing a perivascular technique.

A comparison of paresthesia technique versus nerve stimulator for interscalene block done by Liguori and colleagues found no difference in the development of neurologic symptoms. Similarly, there is no evidence showing reduced risk of nerve injury when using ultrasound guidance versus peripheral nerve stimulation. Orebaugh and colleagues evaluated adverse outcomes associated with the two different techniques and were able to show that ultrasound technique reduced rates of local anesthetic systemic toxicity, but found no difference in rates of nerve injuries. Although a theoretical benefit of ultrasound guidance exists, it is possible that as anesthesiologists attempt to place the block needle as close to the nerve as possible, the risk of unintended subepineural injection increases. This tendency of practice may invoke unnecessary risk as studies suggest that injecting local anesthetic adjacent to the brachial plexus, rather than within the fascial sheath, results in equivalent neural blockade.

Finally, placing an indwelling catheter may be associated with complications that may lead to injury. Injury is often either from direct nerve catheter trauma, infection, accidental vascular puncture, and hematoma formation, or retained catheter fragment requiring open surgical excision. Fortunately, sequelae are rare. Although rates of colonization have been quoted as high as 57%, infection rates are less than 3.2%. Incidence of vascular puncture during catheter placement has been cited at 6%.

Implications

Neurologic deficits noted in the first 24 hours may have a different etiology than those noted later. Causes of immediate symptoms include intraneural edema or hematoma, or actual nerve lesion. Those that present later may be due to other causes such as scar formation around the nerve.

There is also growing evidence of inflammatory perioperative nerve injuries that are distinguished by their delayed onset, but still usually present within 30 days and may include an asymptomatic period. Patients will present with a period of intense pain, often out of proportion to what would be expected from the surgery. The pain may resolve spontaneously and subsequently be followed by weakness.

Additional concern applies to the postdischarge period. The absence of ambulatory patient follow-up or delay in recognition until after hospital discharge has been reported to occur in up to 90% of patients undergoing lower extremity arthroplasty. Recognition delays are often associated with nonoperative causes of nerve injury such as immobilization, dressing compression, infection, or inflammation.

MANAGEMENT

Although uncommon, neural injury after regional anesthesia can be devastating and life changing for the patient. Management begins before the nerve block is even performed. It is imperative that a thorough history and physical examination be performed with a focus on neurologic status. Patients with preexisting neurologic conditions should be told that they may be at increased risk of complications. Patients should be informed of the possible progression of their underlying disease and neurologic dysfunction. In these patients, a complete preoperative evaluation is even more important to document preblock function. However, stable underlying conditions are not absolute contraindications to using regional anesthesia. Like everything in medicine, risks need to be weighed against benefit.

PREVENTION

Preventing nerve damage and persistent paresthesia involves correct patient selection, avoiding direct needle injury and intraneural injections, using appropriate concentrations of local anesthetic, and hasty postoperative evaluations of new or worsening neuropathies.

It is imperative that patients with neurologic dysfunction after surgery be evaluated quickly and a multidisciplinary approach to management be implemented.

Evidence is emerging that shows patient outcomes being independently influenced by individual hospital systems. These institutions subscribe to practices that are vigilant and evidence based, leading to rapid diagnosis and early treatment. This leads to the implication that reduced injury rates and better patient outcomes are attainable when hospitals develop systems that evaluate and stratify risk factors, and implement diagnostic and therapeutic pathways.

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Postobstruction Pulmonary Edema

164

Katarzyna Luba

Case Synopsis

A 37-year-old, 77-kg, previously healthy man develops laryngospasm immediately after tracheal extubation, after an otherwise uneventful general anesthetic for repair of orbital floor fracture. Laryngospasm is managed with intravenous administration of succinylcholine after an unsuccessful attempt at bag-mask positive pressure ventilation. Fifteen minutes later he breathes spontaneously, with adequate tidal volume, but he coughs, his O_2 saturation is 92% while breathing O_2 via a nonrebreathing facemask, and his heart rate is 110 beats per minute. Lung auscultation reveals diffuse coarse rales. A chest radiograph demonstrates acute bilateral pulmonary edema and a normal cardiac silhouette.

PROBLEM ANALYSIS

Definition

Postobstruction pulmonary edema (POPE), also known as negative pressure pulmonary edema, is a noncardiogenic pulmonary edema that develops immediately after acute upper airway obstruction (type 1 POPE) or after relief of chronic partial airway obstruction (type 2 POPE).

Type 1 POPE is generated by forceful inspiratory efforts against a closed glottis (Mueller's maneuver) or an otherwise obstructed upper airway. Young, healthy patients can generate negative inspiratory pressure (NIP) with a maximum level of −140 cm H_2O. Repeated extreme increases in NIP increase venous return, pulmonary blood flow, and capillary pressure, and decrease pulmonary interstitial pressure. The hyperadrenergic state associated with airway obstruction causes peripheral vasoconstriction, further increasing venous return and pulmonary blood flow. Right ventricular distention and increased systemic vascular resistance act in synergy to impede left ventricular ejection and increase left ventricular diastolic pressure, left atrial pressure, and pulmonary venous pressure, further increasing pulmonary capillary hydrostatic pressure. The increased transcapillary hydrostatic pressure gradient favors transudation of fluid from the pulmonary capillaries into the interstitium. The clearing capacity of the pulmonary lymphatic system eventually becomes overwhelmed, which results in interstitial and intraalveolar pulmonary edema.

Sudden relief of chronic airway obstruction may be complicated by type 2 POPE. Chronic partial airway obstruction is accompanied by intrinsic positive end-expiratory pressure (PEEP) and chronic increase in intrathoracic pressure. Relief of obstruction causes an acute decrease in intrathoracic pressure and an increase in venous return and pulmonary blood flow. The resulting hydrostatic imbalance between pulmonary capillaries and interstitium favors the formation of acute pulmonary edema by a mechanism similar to the one presumed in type 1 POPE.

Recognition

POPE is a likely diagnosis when relief of a chronic or acute airway obstruction is promptly followed by respiratory distress with clinical features of acute pulmonary edema. Clinical presentation may include agitation, tachycardia, tachypnea, cough, diffuse rales and ronchi, and hypoxia. Pink, frothy secretions typical of pulmonary edema may not be observed until after intubation of the trachea. A chest radiograph demonstrates bilateral, perihilar, patchy infiltrates (Fig. 164.1). The onset of POPE is usually immediate, but a presentation delayed by up to 24 hours also has been reported, so extended observation is always warranted after an episode of airway obstruction.

Examples of surgical procedures that may be complicated by type 2 POPE include adenoidectomy/tonsillectomy, resection of a large thyroid goiter, or upper airway tumor resection. Type 1 POPE may be seen in multiple clinical scenarios, such as choking on a foreign body in the airway, strangulation, hanging, epiglottitis, croup, endotracheal tube obstruction, postoperative vocal cord paralysis, difficult intubation, or premature extubation in a setting of residual neuromuscular blockade. However, the most common cause of perioperative POPE in adults is laryngospasm. Laryngospasm may occur during induction of anesthesia, immediately after extubation, or during anesthesia with unprotected airway.

Differential diagnosis of a cause of acute perioperative respiratory distress should include aspiration, anaphylaxis, volume overload, pulmonary embolism, and cardiogenic or neurogenic pulmonary edema. A review of the patient's past medical history and the sequence of events leading to the onset of respiratory distress may help establish the correct diagnosis. Witnessed airway obstruction by laryngospasm or from another cause, accompanied by vigorous inspiratory efforts, makes POPE the most likely diagnosis. Echocardiography, invasive hemodynamic monitoring, or both may be needed to rule out other causes, especially cardiogenic pulmonary edema, fluid overload, or pulmonary embolism. Patients with POPE should demonstrate normal hemodynamic parameters after relief of upper airway obstruction. However, POPE may be accompanied by other concomitant causes of respiratory distress or failure (e.g., aspiration or residual paralysis).

Risk Assessment

POPE may develop after any episode of acute airway obstruction or relief of significant chronic airway compromise. However, this complication is more likely to occur in young, healthy adults or in children.

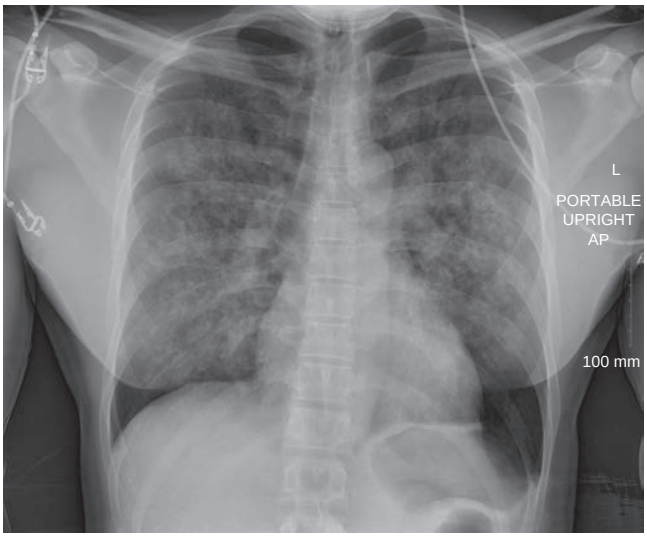

Fig. 164.1 Chest radiograph in postobstruction pulmonary edema.

Such patients are more prone to laryngospasm and strong enough to generate extreme negative intrapleural pressure against an obstructed upper airway. The incidence of POPE in adult and pediatric patients who require emergency intubation due to upper airway obstruction is estimated at 11% to 12%. In adult patients, laryngospasm during emergence from anesthesia is the most common cause of POPE, accounting for 50% of reported cases. In children younger than 10 years old, more than 50% of cases of POPE are associated with croup and epiglottitis.

Implications

POPE is a fairly common complication, frequently occurring in healthy children or young adults. In such patients, a promptly recognized and appropriately managed POPE is usually time limited and may resolve within 24 hours without further consequences. In its acute phase, however, it carries a significant risk of morbidity, and in a severe form it may be life threatening. Prompt diagnosis and aggressive management is therefore of the essence. Respiratory distress or failure usually becomes clinically evident within minutes of a precipitating episode of acute airway obstruction. However, cases of a delay in clinical presentation of up to 24 hours have been reported. An extended observation of any patient after an episode of acute airway obstruction is warranted, including transfer to a hospital if airway obstruction occurs in an outpatient setting.

MANAGEMENT

Management of POPE is supportive and is similar for POPE type 1 and type 2. Maintaining a patent airway, supplemental oxygen, and positive airway pressure are the mainstays of care. The method of airway maintenance and the mode of delivery of positive airway pressure depend on the severity of pulmonary edema, the resulting hypoxia and respiratory distress, mental status, and the presence of residual anesthesia. The majority of patients (nearly 85%) require endotracheal intubation or reintubation, and in half of the cases, mechanical ventilation is necessary. The remaining patients can be managed with noninvasive positive pressure ventilation. In general, the use of PEEP in mechanically ventilated patients or continuous positive airway pressure leads to rapid resolution of pulmonary edema. Diuretics are frequently used, but their use is controversial; there is no proof of their utility in POPE, and they may cause hypovolemia and end-organ hypoperfusion. Patients with mild POPE may require only supplemental O_2. Uncomplicated and immediately treated POPE ultimately resolves within 12 to 48 hours, but the most severe cases, those requiring intensive care unit admission, may take several days to full recovery.

PREVENTION

Most cases of POPE are caused by an unexpected, acute upper airway obstruction. There are, however, certain clinical situations where the risk of this complication is higher. Keeping these scenarios in mind and anticipating the possibility of airway obstruction and POPE allows preparedness and implementation of precautions.

Any airway manipulation maneuvers, such as bag-mask ventilation, placement of oropharyngeal or nasopharyngeal airways, oropharyngeal suctioning, supraglottic airway (SGA) placement, and laryngoscopy and intubation, may result in laryngospasm if performed during light planes of anesthesia. They all should be performed under adequate anesthesia depth. The same precaution applies to patients whose airway is managed with an SGA or left unprotected. In those patients, airway or surgical manipulation under light anesthesia may lead to laryngospasm. Extubation of the trachea or SGA removal should be done either under deep anesthesia or when the patient is fully awake. A bite block placed before emergence from anesthesia may prevent endotracheal tube obstruction by biting. Children, adolescents, and young, healthy adults are at a higher risk of developing laryngospasm and POPE. Residual neuromuscular blockade may compromise airway patency after extubation, yet leave the patient strong enough to forcefully breathe against the obstructed airway. In patients with a known or suspected difficult airway, awake fiberoptic intubation should be considered to avoid a failed intubation attempt and catastrophic airway obstruction during induction of anesthesia. Awake fiberoptic intubation itself may trigger laryngospasm and POPE. Liberal use of topical anesthesia and judicious intravenous sedation may prevent this complication while minimizing patient discomfort and facilitating the procedure.

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Postoperative Acute Kidney Injury

165

David Roberts • Andrew Shaw

Case Synopsis

A 75-year-old man with long-standing hypertension and type 2 diabetes mellitus underwent open repair of an infrarenal aortic aneurysm. His baseline creatinine was 1.6 mg/dL, and this rose to 2.0 mg/dL on the second postoperative day. On the fifth postoperative day, he developed progressive hypoxemia, fever, and hypotension. A contrast-enhanced scan of the pulmonary vessels was not suggestive of pulmonary embolism. He was started on a β-lactam and an aminoglycoside for probable pneumonia. Over the next 12 hours, he became hypotensive and anuric. Renal replacement therapy was started, and antibiotic therapy was shifted to a quinolone. The patient's renal function recovered after several weeks, and he was eventually discharged.

PROBLEM ANALYSIS

Definition

Postoperative acute kidney injury (AKI) is a term that describes a spectrum of diminished renal function that develops after surgery. The most current consensus guidelines provided by the Kidney Disease Improving Global Outcomes (KDIGO) Work Group provide a definition based on serum creatinine (S_{Cr}) and urine output. This definition consolidates two previously validated groups of consensus criteria known as RIFLE and AKIN into one system for clinical practice and research.

AKI is defined by any one of the following criteria and is then staged according to Table 165.1:

- Increase in S_{Cr} greater than or equal to 0.3 mg/dL (26.5 μmol/L) within 48 hours; *or*
- Increase in S_{Cr} greater than or equal to 1.5 times baseline, which is known or presumed to have occurred within 7 days; *or*
- Urine volume less than 0.5 mL/kg/h for 6 hours

The cause of AKI has traditionally been classified as prerenal (decreased perfusion), renal (parenchymal injury), or postrenal (urinary obstruction). Although these distinctions remain somewhat useful for conceptual understanding, they do not represent the complexity of the pathophysiology involved, and thus the field is moving away from them. In many cases, postoperative AKI is a consequence of sustained prerenal injury that culminates in an extreme form of AKI: ischemic acute tubular necrosis (ATN).

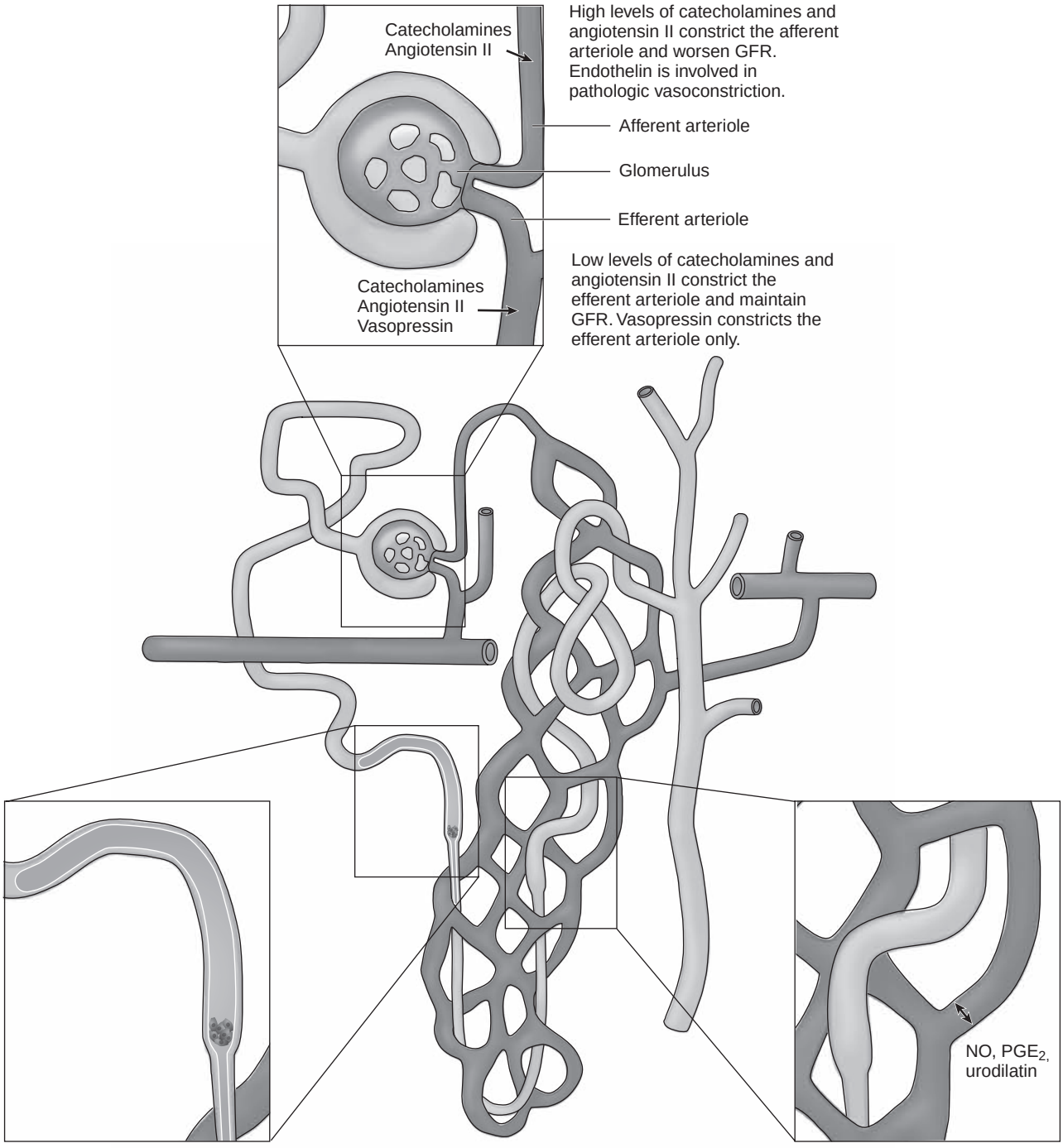
In animal models, transient low perfusion creates a prerenal state characterized by oliguria and low urinary sodium, with salt and water retention. This is the normal renal response to hypovolemia and is mediated by the renin-angiotensin-aldosterone system (RAAS), other neurohumoral factors, and intrinsic tubuloglomerular feedback. With increased perfusion, urine flow returns to normal. This is therefore a hemodynamic event with preserved tubular function; it is reversed by restoration of normal hemodynamic function. More prolonged perfusion deficits result in oliguria (with high urine sodium) that does not reverse when perfusion increases. In this scenario an intrinsic insult occurs, characterized by backleak of ultrafiltrate across the disrupted tubular basement membrane and facilitated by tubular obstruction with cellular debris. The latter is a *persistent* hemodynamic event with loss of tubular function; it is not reversed by restoration of normal hemodynamics.

The pathogenesis of AKI reflects the kidney's unique sensitivity to insult. Fig. 165.1 demonstrates several at-risk areas of the nephron. The medulla and inner cortex have marginal oxygenation and are therefore at risk for ischemic ATN from reductions in intrarenal oxygen delivery. This could result from intravascular volume depletion, hypotension, diminished cardiac output, and/or anemia. In nephrotoxic ATN, damage to the tubules is the result of inflammatory signaling, free radical damage, disturbances in cellular metabolism, and disruption of intrinsic renal vasodilators such as prostaglandins and nitric oxide. Tubular cell necrosis and apoptosis lead to loss of function, disruption of renal cellular architecture, and nephron obstruction by cellular debris. Once this has occurred, restoration of renal blood flow can no longer reestablish glomerular filtration rate (GFR).

TABLE 165.1 Staging of Acute Kidney Injury According to KDIGO Criteria

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline *OR* ≥0.3 mg/dL increase within 48 hours	<0.5 mL/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 hours
3	3.0 times baseline *OR* Increase in S_{Cr} to ≥4.0 mg/dL *OR* Initiation of RRT *OR* In patients <18 years, decrease in estimated glomerular filtration rate to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 hours *OR* Anuria for ≥12 hours

From Kidney Disease: Improving Global Outcomes (KDIGO), Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2(1):1-138, 2012.



Distal proximal convoluted tubule: High risk for ischemic injury. Alpha receptor predominance makes blood flow sensitive to catecholamines in the setting of hypovolemia. Necrotic tubular cells slough and obstruct the pars recta and sustain low GFR despite restoration of RBF.

Medullary thick ascending loop of Henle: Receives <10% of RBF and is at constant risk of ischemia. Blood flow is maintained by endogenous vasodilators (prostaglandins, nitric oxide). Impaired vasodilation induces ischemic-nephrotoxic injury (e.g., NSAIDs, intravenous contrast).

Fig. 165.1 The proximal tubule and medullary thick ascending loop of Henle are potential sites of ischemic and nephrotoxic tubular injury. Both segments have high oxygen consumption and are at risk owing to supply-demand imbalance. *GFR,* Glomerular filtration rate; *NO,* nitric oxide; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PGE_2,* prostaglandin E_2; *RBF,* renal blood flow.

Recognition

Although intraoperative urine output is frequently monitored, perioperative oliguria is an unreliable index of fluid balance. Factors such as vasoconstriction and sodium retention that occur secondary to activation of the sympathoadrenal, RAAS, and antidiuretic hormone systems during stress impair the physician's ability to use urine output as a surrogate for volume status. Furthermore, intraoperative oliguria has not been shown to correlate reliably with postoperative AKI. When AKI does develop, loss of renal solute clearance begins to result in the buildup of serum concentrations of electrolytes, urea, water, and other osmotic elements (azotemia). Blood urea nitrogen and S_{Cr} are the most commonly measured laboratory indices of renal function. Urea depends on tubular excretion but may be a misleading surrogate for tubular function because its blood level is affected by nonrenal pathology, such as gastrointestinal hemorrhage and protein catabolism (abnormally increased) or malnutrition and end-stage liver disease (abnormally decreased). S_{Cr} reflects the balance between creatinine production and excretion. These come into equilibrium when renal function is in a steady state. Therefore S_{Cr} is a reasonable surrogate for GFR. However, the relationship between S_{Cr} and GFR is neither direct nor linear; it is exponentially inverse. That is, a doubling of S_{Cr} implies a halving of GFR. Thus an increase in S_{Cr} from 0.6 to 1.2 mg/dL implies a 50% decrease in GFR. Moreover, S_{Cr} does not increase above normal limits until GFR has decreased below 50 mL/min. In cachectic patients with low creatinine production, S_{Cr} may be within normal limits with a GFR as low as 30 mL/min.

Creatinine clearance provides a real-time estimate of GFR because its calculation ($U \times V/S_{Cr}$, where U is urine creatinine and V is urine flow rate) incorporates the creatinine excretion rate ($U \times V$), which is directly proportional to GFR. If a patient has a urinary catheter and the urine flow rate is carefully measured, reliable estimates of GFR can be obtained with urine collection times of 2 hours or less. A shortcut that is often used in perioperative studies of renal function is to forgo the necessity of urine collection by calculating creatinine clearance from one of several nomograms, such as the Cockroft-Gault formula:

$$\text{Creatinine clearance} = \frac{[(140 - \text{Age [years]}) \times \text{Weight [kg]} \times 1.73\text{m}^2 \times 0.85\,^*]}{72 \times S_{Cr}\,[\text{mg/dL}] \times \text{Body surface area}\,[\text{m}^2]}$$

(**Note:* The 0.85 conversion factor is used for females only.)

In the presence of oliguria, evaluation of tubular function may help distinguish a prerenal syndrome from established AKI. The prerenal state is characterized by avid tubular sodium and water retention, leading to small quantities of concentrated urine with low urinary sodium (<10 mEq/L) and a fractional excretion of sodium (FE_{Na}) less than 1%. Prerenal states leading to elevated sodium excretion with intact tubular function (e.g., metabolic alkalosis, diuretic use) may spuriously elevate the FE_{Na} to greater than 3%. In this setting, a high FE_{Na} is unreliable, but persistence of FE_{Na} less than 1% is highly suggestive of a prerenal state. Fractional excretion of urea nitrogen has been proposed as a more sensitive and specific method to differentiate prerenal azotemia from ATN, especially when diuretics are used.

In established AKI, tubular function is lost. The kidney is unable to concentrate urine and retain sodium, leading to small quantities of dilute urine with high urinary sodium (>80 mEq/L) and high FE_{Na} (>3%).

Additional objective data may be derived from electrolyte disturbances and hemodynamic monitoring. Ultrasonography of the renal vasculature, kidneys, and urinary drainage system can help rule out obstructive uropathy and confirm the diagnosis of ATN (normal renal blood flow) or ischemic injury (regional or global deficits).

Many biomarkers currently used in research but not in clinical practice may ultimately demonstrate value in diagnosis. Cystatin C has a correlation with GFR that is evident at ranges where serum creatinine cannot detect changes (GFR between 60 and 90) and may best represent a more sensitive marker of presently subclinical acute renal injury. N-acetyl-beta-D-glucosaminidase (NAG) originates from the lysosomes of proximal tubule cells and is a sensitive marker for tubular cell injury. Kidney injury molecule–1 (KIM-1), a membrane glycoprotein involved in the immune response to injured tubular epithelial cells, appears in the urine within 12 hours of an initial ischemic insult. KIM-1 may represent an early warning marker of renal injury compared with serum creatinine, which requires 48 hours to appreciably rise after renal insult. Increased levels of neutrophil gelatinase associated lipocalin (NGAL), a well-studied biomarker, in the urine and plasma is an independent predictor of acute kidney injury. Tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7), in combination, provide the highest sensitivity and specificity for AKI risk demonstrated thus far, and a test for these two novel biomarkers is now commercially available. These are just a few of the many biomarkers that may someday enter into clinical practice and provide early warning of AKI, perhaps with nephron-segment–specific localization.

Risk Assessment

Identification of patients at risk permits more accurate prediction of postoperative AKI. The risk for postoperative AKI depends on patient-specific and procedure-related risk factors. For noncardiac surgery, the overall risk of postoperative AKI is approximately 1%. The presence of three or more risk factors (Box 165.1) is associated with an increased risk of perioperative AKI. Among patients undergoing cardiac surgery, the perioperative risk may approach 30%. Patients undergoing cardiac surgery are exposed to additional renal insult and have an expanded set of risk factors (Box 165.2). The potential for acute renal injury increases exponentially as risk factors accumulate. For example, exposure to a single nephrotoxin (e.g., ketorolac) seldom causes a problem, but if combined with other nephrotoxins (e.g., gentamicin) and decreased perfusion (hypovolemia) in the setting of a high-risk surgery, the likelihood for AKI becomes extremely high.

Of all preoperative risk factors, the most predictive is preexisting renal dysfunction. Other important risk factors include advancing age and markers for vascular disease and end-organ damage, such as diabetes, abnormal cholesterol metabolism, and hypertension.

BOX 165.1 Noncardiac Surgery Acute Kidney Injury Risk Index

Risk Factor
Age ≥56 years
Male sex
Active congestive heart failure
Ascites
Hypertension
Emergency surgery
Intraperitoneal surgery
Renal insufficiency—mild or moderate[a]
Diabetes mellitus—oral or insulin therapy
Risk Index based on number of risk factors present: class I (0–2 risk factors), class II (3 risk factors), class III (4 risk factors), class IV (5 risk factors), class V (6 or more risk factors).

[a]Preoperative serum creatinine value >1.2 mg/dL.

From Kheterpal S, Tremper KK, Heung M, et al: Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 110(3):505-515, 2009.

Severe obstructive jaundice and the hepatorenal syndrome are associated with abnormal portal absorption of endotoxin, which induces renal vasoconstriction and a refractory prerenal state characterized by low urine sodium. Sepsis induces a similar milieu, along with the insults of hypotension, systemic inflammation, and sympathetic renal vasoconstriction.

Intraoperative risk factors are related to the type of surgery (potential for complications such as bleeding, hypotension, or low cardiac output states) and specific interventions that may cause renal injury (e.g., aortic cross-clamping, cardiopulmonary bypass). Suprarenal aortic cross-clamping leads to a complete cessation of GFR, and recovery may take 24 to 48 hours. Infrarenal cross-clamping also induces a decrease in GFR through reflex vasoconstriction. In either event, the duration of cross-clamping correlates with the risk for AKI.

Cardiopulmonary bypass also increases the risk of AKI, but this is remarkably well tolerated by patients with normal preexisting renal function who have an uncomplicated course. Despite early optimism, off-pump coronary artery bypass graft does not consistently decrease the incidence of perioperative renal injury. The most important risk factors in cardiac surgery remain preoperative renal insufficiency, the complexity of the procedure, and postoperative cardiac dysfunction.

For all types of surgery, the most important modifiable perioperative risk factor is circulatory instability. Sepsis alone may induce renal injury through local vasoconstriction and nephrotoxicity without substantial hemodynamic perturbation. The risk is markedly exacerbated by the concomitant administration (or presence) of nephrotoxins. These include pigment nephropathy due to rhabdomyolysis, intravascular hemolysis, severe obstructive jaundice, contrast nephropathy, and drugs. In the case synopsis the patient had preoperative renal dysfunction (i.e., high S_{Cr}), underwent a high-risk procedure (aortic aneurysm repair, even though the clamp was infrarenal), and was later exposed to several other renal insults (sepsis, contrast exposure, and an aminoglycoside antibiotic).

Implications

Data suggest that an increase in serum creatinine level meeting criteria for AKI is independently associated with increased mortality risk and progression to chronic kidney disease. The risk of death increases significantly with worsening stages of AKI. This has been little altered despite the development of improved renal replacement therapy (RRT) techniques, including continuous venovenous hemodiafiltration (CVVH). Although RRT consistently controls electrolyte and acid-base abnormalities, circulatory overload, and acute uremia, it does not modulate the intrinsic renal injury, nor does it eliminate the risk of sepsis, multiorgan system dysfunction, or impaired wound healing, which also contribute substantially to postoperative morbidity and mortality. Furthermore, evidence suggests that a significant portion of patients who meet AKI criteria do not return to normal renal function and are at higher risk of progression to chronic kidney disease.

BOX 165.2 Risk Factors for the Development of Acute Kidney Injury After Cardiac Surgery

Risk Factor
Chronic kidney disease
Complex surgery (coronary artery bypass graft plus valve)
Cardiopulmonary bypass duration
Aortic cross-clamp time
Blood transfusions (dose dependent)
Venous congestion
Emboli
Vasopressor and inotrope exposure
Postoperative cardiogenic shock
Advanced age

MANAGEMENT

No specific management strategy has been proven to facilitate recovery from acute renal injury. Thus removing or treating the cause of AKI and maintaining homeostasis while avoiding future renal insults for the duration of recovery represents the crux of management. Once the patient is deemed at risk or diagnosed with acute renal injury and staged according to KDIGO criteria, the clinician proceeds with a coherent approach predicated on vigilance and supportive care (Table 165.2). Timely initiation of renal replacement therapy should be anticipated in the setting of worsening renal function with acidosis, electrolyte imbalance, fluid overload, and uremia (the so-called AEIOU indications). There are no clear thresholds for initiation of RRT, although some evidence suggests that early initiation is beneficial.

PREVENTION

The first step in prevention is to identify patients at risk for AKI as described earlier and then minimizing perioperative insults to renal function. The avoidance of perioperative hypotension and nephrotoxic drugs is perhaps the most readily modifiable risk factor, although an accurate monitor of intravascular volume status continues to elude modern-day practitioners. Patients at risk for hemodynamic shifts may warrant invasive arterial monitoring for the evaluation of beat-to-beat blood pressure. Data suggest that brief periods of hypotension are linked to perioperative acute renal dysfunction.

The avoidance of nephrotoxins such as aminoglycosides, amphotericin, and radiocontrast dye is a high-yield intervention.

The administration of chloride-rich crystalloid solutions has been demonstrated in both animal and human models to decrease renal perfusion pressure, although clinical trials have yet to demonstrate a difference in outcomes between chloride-rich solutions such as normal saline versus balanced solutions (Plasma-Lyte or lactated Ringer's). Chloride-rich solutions also induce hyperchloremic metabolic acidosis at volumes frequently administered in the perioperative period.

TABLE 165.2 Management of Acute Renal Injury

At Risk	Stage 1	Stage 2	Stage 3
Discontinue nephrotoxic drugs	Noninvasive diagnostic workup	Closely monitor for bleeding and infection	Avoid subclavian catheters if possible
Consider functional hemodynamic monitoring	Consider invasive diagnostic workup	Consider renal replacement therapy	Vascular access plan for hemodialysis or CVVH
Monitor S_{Cr} and urine output at regular intervals	Diuretics as indicated for volume overload	Consider intensive care unit admission	
Avoid hyperglycemia	Monitor electrolytes and pH at regular intervals		
Consider alternatives to radiocontrast procedures	Dose medications according to glomerular filtration rate		
	Maintain nutritional support		

Data from Kidney Disease: Improving Global Outcomes (KDIGO), Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2(1):1-138, 2012.

Given the potential for the aggravation of electrolyte and acid-base disturbances, and the risk of worsening renal blood flow, it is currently reasonable to suggest that balanced crystalloid solutions should be the default fluid for patients at risk of renal injury.

No specific pharmacologic therapy has been demonstrated to improve outcomes in acute renal failure. Loop diuretics have a theoretical benefit in acute renal injury secondary to decreased metabolic activity in the oxygen-poor milieu of the outer renal medulla via blockade of chloride channels, although they have failed to demonstrate improved outcomes in clinical trials. Osmotic diuresis with mannitol has similarly failed to demonstrate significant differences in either urine output or mortality rate. Diuretics may be used for the management of volume overload in oliguric renal injury, but the conversion of oliguric AKI to nonoliguric AKI with diuretics has failed to demonstrate benefit and may in fact worsen acute renal injury by excessive reduction of circulating volume.

Low-dose dopamine has failed to demonstrate benefit in appropriately powered randomized controlled studies. The potential adverse effects of dopamine related to tachyarrhythmias and myocardial ischemia suggest that its utilization in the prevention or management of acute kidney injury should be abandoned. Furthermore, some evidence suggests that renal vasomotor dysregulation in acute kidney injury is worsened by dopamine infusions resulting in reduced perfusion. Fenoldopam, a selective DA-1 receptor agonist, has also failed to consistently reduce the number of patients requiring renal replacement therapy, nor has it reduced mortality rate after cardiac surgery. The vasodilator properties of fenoldopam may place patients at risk for hypotension and thus it is not recommended for the management of acute renal injury.

Natriuretic peptides are in clinical use for the management of congestive heart failure and could theoretically be beneficial for acute renal injury. Small studies have demonstrated potential benefit. Despite promising attributes, there is not yet sufficient high-quality evidence to justify routine use in clinical practice.

No clear evidence from randomized controlled trials supports other pharmacologic interventions such as N-acetylcysteine, sodium bicarbonate, prostaglandin analogs, and human growth factors in the management of postoperative acute renal injury.

SUMMARY

Postoperative acute renal injury is a serious perioperative complication associated with significant morbidity and mortality and progression to chronic kidney disease. The absence of evidence-based pharmacologic management of acute renal injury underscores the importance of preoperative risk stratification and modulation of modifiable risk factors, postoperative surveillance, and supportive care. In the future, novel biomarkers may enhance our diagnosis of AKI and provide early warning systems to practitioners.

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166 Postoperative Delirium

Philip R. Levin

Case Synopsis

An 90-year-old man with a history of stable angina, renal insufficiency, chronic obstructive pulmonary disease, hypertension, depression, and hearing impairment undergoes general anesthesia for pinning of a femur fracture. The surgery and anesthetic are uneventful. In the postanesthesia care unit (PACU), the patient becomes disoriented and combative.

PROBLEM ANALYSIS

Definition

Postoperative delirium is an acute disorder of attention and cognition detected typically in the PACU but can be noted up to 3 days after surgery. Patients are usually noted to have altered consciousness and orientation.

Recognition

Postoperative delirium can have multiple causes and should be promptly evaluated by an anesthesiologist in the PACU. Assessment of the patient's breathing and circulatory status is extremely important to rule out life-threatening problems such as hypoxia, hypercarbia, and airway obstruction. A thorough medical history, a complete listing of medications administered during the perioperative period, and review of the anesthesia and surgical course (including the type of surgery) should be obtained. Then a detailed physical examination and any indicated laboratory testing are performed.

Severe pain (surgical, urinary, or gastric distention) can cause altered mental status and should be treated promptly. Certain metabolic, endocrine, and infectious disorders can also cause altered mental status and must be ruled out. Intracerebral pathology should be ruled out in patients with focal neurologic findings and gait disturbances. In addition, effects of residual anesthetic agents may mimic postoperative delirium. It may be difficult to distinguish residual sedation resulting from the effects of sedatives, antiemetics, or anesthetics that lead to disinhibition from causes that require treatment with sedatives.

Patients with postoperative delirium are at risk of physically harming themselves or PACU personnel. Patients may tear open their bandages or wounds or pull out their intravenous lines. Patients with postoperative delirium are also at risk for falls and fractures.

Risk Assessment

Studies have identified the following leading preoperative risk factors for developing postoperative delirium: age greater than 65 years, known dementia or chronic cognitive decline, hearing or vision impairment, history of alcohol abuse, having several medical comorbidities, and the presence of infection.

Intraoperative risk factors include the type of surgery. The highest rate of postoperative delirium is seen in cardiac/thoracic surgery, hip fractures, and other major surgeries. Having an emergency surgery versus elective surgery also appears to be a risk factor. Certain anesthetic drugs, including anticholinergics, benzodiazepines, and antihistamines, have been linked to an increase in postoperative delirium. Interestingly, several studies have found no difference in the effects of general, epidural, or spinal anesthesia on the development of postoperative delirium.

Implications

Postoperative delirium can result in complications such as prolonged hospital stay, increased medical care costs, delayed functional recovery, and psychological burden on the patient and the patient's family.

MANAGEMENT

Identifying and Correcting the Underlying Cause

Initially, it is important to identify and correct underlying causes. A thorough medical history is important, including any additional information that family members or caregivers may provide (e.g., baseline behavior and mental status). A careful physical examination, including a detailed neurologic and psychiatric examination, should be performed. The patient's vital signs and overall medical condition must be monitored carefully until underlying causes (e.g., change in respiratory status, infection, fluid or electrolyte imbalance) have been identified and corrected or stabilized. It is also important to review any pertinent laboratory and radiographic studies. Adequate pain control is important.

Pharmacologic Measures

Identification and correction of the underlying condition may be sufficient to reverse delirium. Specific pharmacologic intervention may be necessary to reduce the intensity and duration of delirium. Many studies have demonstrated the safety and efficacy of antipsychotics. In this category, haloperidol is the drug of choice because of its favorable cardiovascular and respiratory side-effect profile compared with other antipsychotics. Also, it has negligible

anticholinergic effects. Haloperidol can be administered orally, intramuscularly, or intravenously in doses ranging from 0.25 to 2 mg. This dose is repeated or doubled every 30 to 60 minutes until the patient is sedated and calm. Chlorpromazine is also effective, but it can lead to severe hypotension. Neuroleptic antipsychotic medications may lengthen the QT interval, thus increasing the risk of torsades de pointes. Patients who receive this treatment should have a baseline electrocardiogram. If the patient's QT interval becomes prolonged to greater than 25% of baseline or longer than 450 ms, dose reduction or discontinuation of therapy may be needed. Further studies are warranted.

Benzodiazepines are not effective therapy for postoperative delirium, except for that caused by withdrawal from alcohol or sedative-hypnotics. Lorazepam is the benzodiazepine most commonly used; it is administered orally, intramuscularly, or intravenously in doses ranging from 0.5 to 2 mg. The dose of lorazepam is repeated or doubled every 30 to 60 minutes, depending on the patient's level of sedation.

The use of physostigmine is controversial, but it may still be available in some locations. This drug was often used in the past to treat postoperative delirium, especially that due to central cholinergic crisis. Compared with quaternary anticholinergics (e.g., atropine, glycopyrrolate), physostigmine (a tertiary amine) crosses the blood-brain barrier more readily.

Environmental Interventions

Supportive measures are useful for treating the symptoms of delirium. These include reorienting the patient to time, place, and person and minimizing excessive noise. Having a family member near the bedside may help calm the patient. Because delirium can be aggravated by sensory impairment, restoring the patient's vision (eyeglasses or contact lenses) or hearing (replacing a hearing aid) may be helpful. The use of physical restraints should be minimized; they may aggravate the patient's confusion because they create the impression of being tied down.

Psychiatric and Neurologic Care

Obtaining a psychiatric consultation may be necessary if other treatment measures fail and more aggressive management is necessary. If postoperative delirium appears to have a neurologic cause, the appropriate neurologic or neurosurgical consultation should be obtained.

PREVENTION

Little is known about the prevention of postoperative delirium. There is some evidence that aggressive management of established risk factors may help. Some intraoperative measures that may be effective include maintaining good oxygenation and normal blood pressure, using correct drug dosages, and maintaining normal electrolyte levels. Limiting the number of drugs used may help because it is known that the use of five or more medications (polypharmacy) has been associated with an increased risk of delirium. Drugs associated with an increased risk of delirium should be used cautiously. If an anticholinergic is necessary, a quaternary amine such as glycopyrrolate should be used. In general, drugs with short elimination half-lives are preferable to long-acting drugs. A few recent studies have shown that the use of an intraoperative processed electroencephalographic monitor has helped clinicians give a lighter depth of anesthesia. This is pertinent because deep sedation compared with light sedation has been found to increase the risk of postoperative delirium. Adequate postoperative analgesia is also important for the prevention of postoperative delirium.

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167 Postoperative Hemodynamic Instability

Elizabeth Mahanna Gabrielli • Andrea Gabrielli

Case Synopsis

A 90-kg, 75-year-old man (body mass index 35) with a history of smoking, well-controlled hypertension, and chemotherapy in the distant past for lung cancer is transported to the postanesthesia care unit (PACU) and intubated after a complex, 6-hour hand surgery. Preoperative medications include metoprolol and hydrochlorothiazide. Intraoperative urine output is 300 mL. An arterial line is in place. In the PACU he receives a 2-mg dose of morphine and a 1-g dose of acetaminophen intravenously. Noninvasive blood pressure (BP) then reads 70/40 mm Hg. Heart rate is 80 beats per minute and regular. Oxygen saturation is 92% on Fio_2 of 0.6 and positive end-expiratory pressure (PEEP) of 5 cm H_2O. End-tidal CO_2 is 50 mm Hg.

PROBLEM ANALYSIS

Definition

As surgical volumes continue to grow to an estimated more than 312 million operations worldwide, so do postoperative complications. In a subset of nearly 2 million procedures from Medicare beneficiaries, including cases such as the one we present, major complications were observed in 24% to 50% of the cases, with "failure to rescue"—as defined by the National Quality Forum Initiative as a lack of recognition of an adverse event leading to worsening outcome—ranging from 4% to 41%.

Recognition

Avoidance of failure to rescue a patient from crisis requires the patient's caregivers to recognize that the patient is in crisis and institute effective action. Heart rate and rhythm and BP, as generic indicators of afterload, preload, and left and right ventricular function, all need rapid evaluation in the context of the clinical picture and recent surgery.

Heart Rate

Tachycardia is the most usual compensatory response to shock after an increased sympathetic outflow. Increased rate compensates for the biventricular decrease of stroke volume when preload or contractility is low. However, residual anesthetics interfering with vagal tone, residual regional anesthesia, and preoperative beta-blockade can often interfere with the compensatory response.

Sinus bradycardia is rarely responsible for hemodynamic instability if heart rate is more than 40 beats per minute. Sudden hypervagotonic reflexes can lead to severe bradycardia and hypotension requiring a positive chronotropic pharmacologic approach or pacing. A preexisting history of congestive heart failure or lack of response to a positive chronotropic agent necessitates a rapid escalation to a positive inotropic agent. Tachycardia associated with postoperative systemic hypertension is usually attributable to incisional pain or more rarely to acute hypercapnia, where it is associated with pulmonary hypertension.

Heart Rhythm

The paroxysmal presentation of an unstable heart rhythm is usually an indicator of a severe underlying process, cardiac comorbidities, and/or severe complications. Unstable, hypotensive, nonsinus tachycardia failing to respond to a fluid challenge is an indication to proceed to cardioversion, as any pharmacologic intervention could deteriorate the rhythm to a more malignant one. Cardioversion can sometimes convert a patient into a symptomatic bradycardia necessitating emergency pacing. The recognition of a pulseless, malignant rhythm should be rapid, by excluding lead disconnection or malfunctioning and followed by immediate implementation of the appropriate advanced cardiac life support protocol.

Afterload

Systemic blood pressure, although measured centrally, is autoregulated differently in each organ and different shock states. The intensivist community has settled at aiming to a BP mean of 65 to 70 mm Hg. The source of the evidence is a specific kind of shock, distributive or septic, in which hypotension is usually associated with a normal ventricular function and high flow. Recent evidence suggests a more individualized approach to BP goal in distributive shock. This may mean targeting a slightly higher pressure either for individuals with cerebral autoregulation right shifted due to preexisting long-term hypertension or for the kidney, which is autoregulated at a slightly higher pressure. The postoperative therapeutic approach to hypotension should be logical and systematic. Vasoplegia, third spacing, and acute blood losses are often the initial causes of hypotension or are concurrent with other causes of hypotension. In these patients, adequate venous return is often the back pressure of organ perfusion. Finally, in some forms of nondistributive shock (e.g., cardiogenic shock), increasing systemic vascular resistance by the use of a vasopressor may not lead to increased organ perfusion and can be counterproductive. Therefore treatment of "low BP" in the postoperative patient must always follow a functional evaluation of preload.

Postoperative hypertension occurs in 25% of hypertensive patients who undergo surgery and is another independent predictive factor of postoperative adverse events. Spurious causes of hypertension

such as arterial line calibration drift and BP cuff herniation should be ruled out. Increased BP in the postoperative phase is often a result of increased endogenous catecholamines from surgical stress or incisional pain. Acute elevations in BP beyond a systolic of 180 mm Hg and diastolic of 110 mm Hg can cause myocardial ischemia via increases in left ventricular end-diastolic pressure and myocardial oxygen consumption. A hypertensive crisis can exacerbate other comorbidities such as systolic heart failure, intracranial hypertension, and aortic dissection or precipitate postoperative bleeding. An ideal postoperative antihypertensive, when necessary, should be rapid, easily titratable intravenously, and short term.

Preload

During the initial phase of circulatory shock, awareness of decreased volume status is generally based on low urine output, increased heart rate, and decreased BP. Recent major surgery is often associated with an ongoing loss of intravascular volume by third spacing, insensible fluid losses, or bleeding. A positive BP response and increased urine output to a fluid challenge are interpreted as a boost of cardiac preload resulting in an increase of the stroke volume based on the Frank-Starling relationship. Unfortunately, this response is also dependent on the ventricular contractility, which is not always easy to estimate without a cardiac output monitor or by visualizing the heart with echocardiography. Simple maneuvers, such as a 15-second end-expiratory occlusion, a smaller "testing" fluid challenge, and passive leg raising–inducing gravitational transfer of preload, have been recommended before challenging the patient with massive boluses (the infamous "one-liter bolus") to limit unnecessary fluid overload. With impaired ventricular contractility, a large fluid challenge will cause pulmonary edema (left ventricle) or hepatic congestion (right ventricle).

A great deal of attention has been recently focused on the cyclic respiratory pulse pressure variability (PPV) in patients intubated on positive pressure ventilation. Although large fluctuations of plethysmograph waveforms may suggest hypovolemia, PPV is detectable only when an arterial line is in place. A PPV between 10% and 15%, in certain prescribed conditions, can reliably predict a positive response to volume challenge and an improvement of hemodynamic parameters. However, limitations to the applicability of PPV remain numerous: a low heart rate/respiratory rate ratio, dysrhythmias, low tidal volume ventilation (<8 mL/kg ideal body weight), spontaneous breathing, increased intraabdominal pressure, and an open chest can all provide misleading information. Despite these limitations, "dynamic" predictors of preload responsiveness provides physiologic feedback during intervention aiming to increase oxygen delivery. With the exception of severe distributive shock, hypotension in a postoperative patient unresponsive to increasing preload prompts the anesthesiologist to investigate the ventricular function as the primary reason for a low flow state. If a "pump failure" is suspected, timely escalation to invasive monitoring can dramatically improve outcome by enabling the anesthesiologist to guide resuscitation more effectively. A detailed review of monitoring in cardiogenic shock is covered elsewhere in this book and is beyond the scope of this chapter. Plasma lactate level, veno-arterial Pco_2 gap, and directed point-of-care ultrasound have been increasingly used as surrogates for tissue hypoperfusion.

Left Ventricular Failure

Pump failure of the left ventricle (left ventricular failure [LVF]) results from a loss of contractility, a major arrhythmia, and more rarely from an obstruction due to a tension pneumothorax or cardiac tamponade. In the majority of cases, postoperative LVF is due to myocardial ischemia and will be detected by electrocardiogram and myocardial biomarkers. A plethora of expert recommendations are available to guide the anesthesiologist to support the ventricular function and plan both revascularizations of the coronary arteries.

Right Ventricular Failure

The primary role of the right ventricle is to maintain low right atrial (RA) pressures through widely variable flow into the right ventricle (RV). Normally, the pulmonary vasculature can rapidly react via vasoconstriction and dilation to accommodate changing blood flow and volumes leading to minimal increases in pulmonary artery pressure. RV afterload is determined by alveolar pressure, increases in vasomotor tone, and distribution of pulmonary blood. Contrary to LVF, right ventricular failure (RVF) occurs more often when there is sudden acute impedance to outflow from the RV. This can occur either with increased pulmonary artery pressure or decreased pulmonary arterial system compliance. Common causes are acute LVF, pulmonary embolus (thrombus, air, fat, amniotic fluid), severe hypoxic pulmonary vasoconstriction, and increased intrathoracic pressure (increased intrathoracic volume, excessive PEEP or auto-PEEP, tension pneumothorax). In acute cor pulmonale, the RV dilates and RV end-diastolic volume increases causing a reciprocal decrease in left ventricular end-diastolic volume by ventricular interdependence. Systemic hypotension ensues, causing right coronary artery perfusion pressure to decrease, leading to further RVF. In addition, during acute RVF and dilation, the RA pressure increases, and if not matched by systemic filling pressures, decreased venous return will ensue. This vicious cycle, if left to continue, will lead to biventricular failure and cardiac standstill.

Recognizing RVF as a cause of systemic hypotension requires having a high degree of clinical suspicion. Invasive monitoring might not be able to discriminate the cause of the hypotension unless a direct measurement of cardiac output and pulmonary artery pressure is available. Bedside transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) revealing RV dilation, paradoxic septal shift, tricuspid regurgitation, increased RA pressure, and occasionally detecting the thrombus itself can be rapidly diagnostic. Treatment of RVF focuses on relieving the cause of increased impedance to outflow and inotropic support.

Risk Assessment

Postoperative hemodynamic instability is associated with worse outcome. Hypotension, decrease of 40% in mean arterial pressure (MAP), or MAP less than 50 mm Hg carries a higher cardiovascular and renal morbidity than hypertension. Preexistent BP autoregulation and duration of hypotension are other factors affecting perioperative morbidity and mortality.

Implications

When tissue oxygen consumption cannot be matched by adequate oxygen delivery postoperative hemodynamic instability evolves to a shock state, initially as insufficient perfusion of the most sensitive organs. If not promptly reversed, the shock state will become irreversible, and the patient will go into cardiac arrest.

MANAGEMENT

The case synopsis illustrates cardiogenic shock from RVF due to a pulmonary embolus. Risk factors include surgery and malignancy. Diagnosis was confirmed by TTE after being suspected by a decrease of Pao_2/Fio_2, persistent increase of lactic acid, and lack of response to preload

challenge. A central venous pressure (CVP) line placed in the PACU showed an initial value of 20 cm H_2O. Venoarterial CO_2 gap was increased. The CVP line was replaced with a pulmonary artery catheter, which showed a cardiac index of 1.2 and a pulmonary artery mean pressure of 40 mm Hg. TTE confirmed the diagnosis of RVF. The patient was supported with low-dose epinephrine, milrinone, vasopressin, and inhaled epoprostenol with some improvement in BP. Lack of tachycardia was attributed to preexistent beta-blockade. After discussion with the surgical team the patient was transported to interventional radiology where angiography confirmed the diagnosis. Selective pulmonary thrombolysis was performed with resolution of the hemodynamic crisis.

PREVENTION

A systematic approach to postoperative hemodynamic instability must include a rapid differential diagnosis of the determinants of the shock state. A measurement of patients' physiologic reserve by applying selective interventions and by assessing functional hemodynamic monitoring predicts reversal of the shock state. The recent introduction of point-of-care TTE and TEE, though not yet widespread, offers clarity in the differential diagnosis by allowing a direct visualization of all mediastinal structures, native or pathologic, as well as preload, left ventricular function, and right ventricular function.

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Postoperative Hepatic Dysfunction

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Kerri M. Wahl

Case Synopsis

A 60-year-old man with a history of hepatitis C and hepatocellular carcinoma is scheduled for elective partial liver resection. Preoperative hemoglobin is 10 g/dL. Albumin, creatinine, liver enzymes, and prothrombin time (PT) are within normal limits. The surgery is uneventful except for an intraoperative blood loss of 2 L, requiring transfusion with 5 units of packed red blood cells (RBCs). The patient is transferred to the surgical intensive care unit for postoperative care due to oliguria and a potassium level of 6.1 mEq/L. Recovery is uneventful, except that on postoperative day 5, the patient is noted to be jaundiced.

PROBLEM ANALYSIS

Definition

Clinically significant acute liver dysfunction is common after anesthesia and surgery. Major risk factors include the presence of preexisting liver disease (cirrhosis, fibrosis, or steatohepatitis), massive blood transfusion, a small remnant liver volume from massive liver resection, and perioperative liver insult (hypoxia, sepsis, drug toxicity, poor nutrition). Technical difficulties with biliary drainage or bile leak may also be contributory. Most postoperative jaundice is multifactorial in origin, is difficult to diagnose, and often requires supportive care. After elective abdominal surgery the incidence of abnormal liver function tests is 25% to 75%; however, the incidence of postoperative hepatic dysfunction is less than 1%.

Postoperative jaundice is usually evident within the first week after surgery and is not associated with acute liver failure. The normal serum bilirubin level is 0.3 to 1.1 mg/dL. Jaundice is clinically detectable when the serum bilirubin exceeds 3 to 5 mg/dL and the patient develops yellow discoloration of the sclera and skin. Increased conjugated bilirubin reflects a problem with bilirubin secretion due to hepatocellular dysfunction, intrahepatic cholestasis, or biliary tract obstruction. If the increase in total bilirubin is primarily unconjugated, the most likely cause is either hemolysis of erythrocytes producing a large bilirubin load or defects in liver uptake, transport, or conjugation of bilirubin.

Studies have shown a clear relationship between postoperative functional liver volume and the likelihood of developing clinically evident liver failure. In a patient with a healthy liver, up to 75% of the liver volume can be resected with little disturbance of liver function. The reported incidence of postresectional liver failure (PLF) varies between 0.7% and 9.1%. In the past decade the mortality rate after partial liver resection has ranged from 0% to 5%, with PLF being the main cause of death. Unfortunately, there is no consensus of a definition for PLF. In general, PLF is characterized as failure of one or more of the hepatic synthetic and excretory functions that results in hyperbilirubinemia, hypoalbuminemia, prolonged PT and serum lactate, and/or different grades of hepatic encephalopathy. On postoperative day 5, a prothrombin index less than 50% (international normalized ratio [INR] >1.7) and serum bilirubin greater than 2.9 mg/dL have been shown to be predictive of a 59% risk of mortality (sensitivity 69.6% and specificity 98.5%) in patients without underlying liver disease who have undergone major hepatic resection. In addition, a peak bilirubin of 7.0 mg/dL has been suggested as a predictor of PLF-related death.

Recognition

Owing to the large functional reserve of the liver, routine laboratory values may be normal despite significant underlying disease. Abnormal results of several common laboratory tests may loosely reflect hepatic dysfunction (Box 168.1). In acute hepatic injury, PT and, to a lesser extent, total bilirubin are the best indicators of severity of disease.

PT has been used traditionally in assessment of severity of liver disease in the Child Pugh score or as INR in the MELD score (discussed later in this chapter). PT measures activity of the extrinsic coagulation pathway and requires fibrinogen, prothrombin, and factors V, VII, and X, which are synthesized in the liver. If PT is prolonged more

BOX 168.1 Investigational Studies for Evaluation of Liver Function

Parenchymal Damage With Failure of Synthetic Function

- Coagulation studies: PT or INR elevated, decrease in platelet count and fibrinogen
- Liver function tests: elevated transaminases (aspartate aminotransferase, alanine aminotransferase), alkaline phosphatase, bilirubin, and ammonia
- Plasma lactate elevated
- Hypophosphatemia
- Screen for markers of viral hepatitis and autoimmune disorders
- Blood cultures in patients with suspected infection
- Abdominal ultrasonography or computed tomography
- Liver biopsy

Cholestasis or Biliary Tract Disease

- Bilirubin (total, conjugated and unconjugated): urine and serum levels
- Alkaline phosphatase
- Abdominal ultrasonography or computed tomography
- Endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography

INR, International normalized ratio; *PT*, prothrombin time.

than 3 seconds over control, this may reflect severe hepatic dysfunction, because only 20% to 30% of normal factor activity is required for coagulation. In reality, coagulation is a complex process involving the interaction of procoagulation and anticoagulation factors and the fibrinolytic system. As there is a reduction in both anticoagulant and procoagulant factors, global tests of coagulation may be normal in patients with acute and chronic liver disease. With obstructive biliary disease, the failure of bile salt secretion may result in poor absorption of vitamin K, which is a cofactor necessary for the posttranscriptional gamma-carboxylation and activation of factors II, VII, IX, and X. An INR greater than 1.5 not corrected by vitamin K within 24 hours suggests severe liver disease. A variety of more specific coagulation tests may be useful in detecting liver dysfunction (activated partial thromboplastin time, clotting time, bleeding time, thrombin time, whole blood clot lysis, plasma fibrinogen, serum fibrinogen degradation product, plasma D-dimer, euglobulin lysis time, factor assays for F XIII, protein C, protein S, and antithrombin III), as well as global hemostasis (thromboelastography, Rotem, INR liver).

Derangements in conventional markers of coagulation such as PT/INR, partial thromboplastin time, and platelet count are common and correlate with the extent of liver resection. An increase in PT/INR becomes evident within 12 hours of surgery. A corresponding decrease in platelet count and fibrinogen also occurs. Decreased synthetic function of the remnant liver and hemodilution and consumption of clotting factors are most likely responsible for this postoperative coagulopathy, which peaks 2 to 5 days after surgery.

Although tests that measure the level of serum liver enzymes are commonly referred to as liver function tests, they usually reflect hepatocyte integrity or cholestasis rather than liver function. After major liver resection, the pattern of liver function test abnormalities in the majority of patients is very predictable (Fig. 168.1). The liver transaminase enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are immediately elevated due to ischemic liver injury and fall progressively, as bilirubin increases often peaking around day 4 to 6. Of the liver transaminase enzymes, ALT is the gold standard biomarker for hepatocellular injury, as it is localized solely in the cellular cytoplasm. Full assessment of enzyme abnormalities involves careful evaluation of (1) the predominant pattern of enzyme alteration (hepatocellular vs. cholestatic); (2) the magnitude of change in serum concentration (mild, <5 times the upper limit; moderate, 5 to 10 times the upper limit; severe, >10 times the upper limit); (3) the rate of change (increase or decrease over time); and (4) the nature of the course of alteration (mild fluctuation or progressive increase).

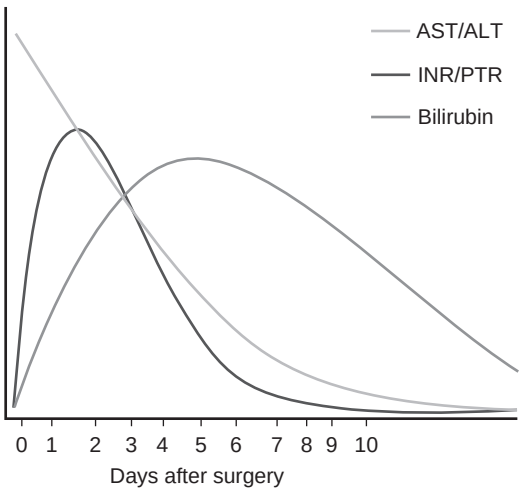

Fig. 168.1 Pattern of liver function test abnormalities following partial liver resection. (From Wigmore S: Why do people develop jaundice after liver resection? Prof Steve Wigmore [blog] 2012. Available at https://profstevewigmore.wordpress.com/2012/12/19/why-do-people-develop-jaundice-after-liver-resection/. Accessed September 26, 2016.)

The serum ammonia concentration represents the balance between ammoniagenesis (primarily in the gut and kidney) and hepatic urea synthesis. Because the normal liver's reserve capacity for urea synthesis is great, elevated serum ammonia concentrations usually indicate significant loss of hepatic function. Hyperlactemia and hypophosphatemia are common derangements in patients undergoing liver resection. Gluconeogenesis in the liver normally consumes 40% to 60% of lactate. During resection or stress, it produces rather than metabolizes it. As such, the arterial plasma lactate concentration is an independent predictor of morbidity and mortality, being higher in nonsurvivors. Hypophosphatemia is encountered in nearly all patients after major liver resection. The pathogenesis is poorly understood and is generally believed to be due to increased phosphate by regenerating hepatocytes or excessive urinary losses.

Jaundice is the most common and easily recognized sign suggesting hepatic dysfunction. Bilirubin is the primary end product of hemoglobin metabolism. The uptake and transport of unconjugated bilirubin into hepatocytes is followed by hepatic conjugation with glucuronide and subsequent excretion into bile canaliculi. A total bilirubin concentration greater than 1.5 mg/dL is considered abnormal. Diagnosing hyperbilirubinemia includes clinical history, physical examination, biochemical testing, and hepatobiliary imaging. Alkaline phosphatase (ALP) and bilirubin levels are routinely assessed, and the level of gamma-glutamyl transferase is often measured as an additional aid toward diagnosis in certain situations because of its high sensitivity but low specificity.

Postoperative jaundice can be categorized into three groups: (1) prehepatic (bilirubin production exceeds excretion); (2) intrahepatic (acute or subacute hepatocellular injury with or without preexisting liver disease); (3) posthepatic (cholestasis from obstruction of bile flow).

Prehepatic Causes

Classification of Prehepatic Causes of Postoperative Jaundice

1. Resorption of extravasated blood
2. Hemolysis
   a. Intravascular hemolysis after drugs, infection, or fasting
   b. Hemolytic anemia: congenital (enzyme deficiencies or hemoglobinopathies) or acquired (transfusion-related, ABO or Rh-incompatibility, mechanical RBC breakdown)
3. Idiopathic hyperbilirubinemia
   a. Decreased uptake by hepatocytes: Gilbert, Crigler-Najjar
   b. Impaired excretion of conjugated bile: Dubin-Johnson syndrome

Isolated elevated levels of unconjugated (indirect) bilirubin in a postsurgical patient most likely result from a prehepatic mechanism. Prehepatic causes are a result of overproduction of bilirubin and are usually from hemolysis (breakdown of RBCs) or resorption of extravasated blood in patients with internal bleeding. Usually, bilirubin concentrations peak within the first few postoperative days and resolve over days to weeks. No specific therapy is indicated, other than that directed toward reducing any ongoing red cell breakdown.

Pronounced postoperative jaundice commonly occurs in surgical trauma patients. Many of these patients have multiple injuries to muscle and soft tissue requiring major surgical intervention and volume resuscitation, often with massive transfusion of red cells and other blood products. During transfusion of RBCs, up to 10% of RBCs per unit of blood are hemolyzed within the first 24 hours to generate a bilirubin load of 250 mg/100 mL of blood. When levels

exceed 3 times normal daily bilirubin production (250 to 400 mg in adults), the liver's capacity to excrete and/or conjugate bilirubin may be transiently overwhelmed, and jaundice may develop.

Diagnosis of hemolytic anemia requires reticulocytosis, unconjugated hyperbilirubinemia, elevated lactate dehydrogenase, and an absent or low haptoglobin concentration. Patients may present with pallor, fatigue, fever, confusion, and weakness, with dark urine and yellowing of the skin and sclera. The clinical manifestations caused by hemolysis are likely to be accentuated if the patient has underlying chronic liver disease, sustained acute ischemic injury to the liver, or impaired renal function.

Surgery can exacerbate hemolysis in patients with a preexisting hemolytic disease or a genetic predisposition to hemolysis (sickle cell disease, hereditary spherocytosis, or glucose-6-phosphate dehydrogenase deficiency) due to stress, infection, and fasting. Patients at greatest risk of mechanical RBC breakdown are those having cardiac surgery with cardiopulmonary bypass, long operative times or hemodynamic support from a left ventricular assist device, intraaortic balloon pump, or extracorporeal membrane oxygenation. Sepsis due to streptococci, *Escherichia coli, Bacteroides* species, and *Clostridium* species can also cause hemolysis. The mechanism is poorly understood, but it is likely due to bacterial hemolysins and reduced liver uptake of bilirubin associated with hypotension. The most common cause of drug-induced hemolytic anemia is from cephalosporins. Others include levodopa, levofloxacin, methyldopa, nitrofurantoin, nonsteroidal antiinflammatory drugs, penicillin, pyridium, and quinidine.

Intrahepatic Causes

Intrahepatic jaundice is due to injury to hepatocytes or biliary epithelial cells mediated by a process of inflammation, ischemia-reperfusion, necrosis, or hepatic resection leaving insufficient functional reserve. The clinical course depends on the presence of preexisting liver disease, its severity, the surgical procedure, and type of anesthesia. The major causes of perioperative liver injury include ischemia, drug toxicity (including inhaled anesthetics and antibiotics), sepsis, newly acquired viral hepatitis, and total parenteral nutrition (TPN).

Classification of Intrahepatic Causes of Postoperative Jaundice

1. Acute
   a. Ischemic injury (hypoxia, reduced hepatic blood flow, anemia)
   b. Drug toxicity
   c. Sepsis
   d. Newly acquired viral hepatitis
   e. TPN
   f. Small remnant liver volume
2. Chronic
   a. Hepatitis/fibrosis/cirrhosis
   b. Primary biliary cirrhosis/primary sclerosing cholangitis
3. Benign postoperative cholestasis

Ischemic liver injury is due to acute hypoperfusion and hypoxia in the perioperative period. The liver has a complex vascular supply and high metabolic activity, which makes it susceptible to diffuse ischemic injury with hemodynamic insult. Total hepatic blood flow is 1.5 L/min, which represents 25% to 30% of the normal adult cardiac output. The hepatic artery supplies 25% of total hepatic blood flow and the portal vein supplies 75%. However, they contribute equally to hepatic oxygenation. In essence, the portal venous system is a passive vascular bed. Flow is dependent on perfusion pressure, cardiac output, and splanchnic vascular resistance. Reductions in portal inflow are usually associated with reciprocal hepatic artery vasodilation, thereby maintaining total hepatic blood flow and oxygen supply.

Ischemic Injury

Reduced cardiac output and blood pressure during general anesthesia and surgery decrease hepatic blood flow and jeopardize liver oxygenation. Contributing factors include anesthetic drugs and adjuncts, hypovolemia, hypoxemia, anemia, acidosis, and mode of ventilation (hypercarbia/continuous positive airway pressure). Surgical manipulation of the right upper quadrant of the abdomen can reduce hepatic blood flow by as much as 60% owing to sympathetic stimulation or direct compression of the vena cava and splanchnic vessels. Compensatory hepatic artery vasodilation and reduced portal inflow are opposed in a dose-dependent manner by volatile anesthetics. Thus portal perfusion becomes pressure dependent.

Cirrhotic patients are at increased risk for ischemic liver injury (shock liver) due to preexisting impaired perfusion, as well as multiorgan system failure from the release of cellular inflammatory mediators. Ischemic hepatitis causes centrilobular hepatic necrosis, not inflammatory necrosis. Usually the hemodynamic insult is evident clinically before liver injury is recognized. The onset of jaundice occurs 1 to 5 days after surgery and peaks after 9 to 18 days. Liver function tests reveal elevated bilirubin, a massive rise in lactate dehydrogenase levels, and transaminase concentrations often 25 to 250 times the upper limits of normal. Clinical studies indicate that low perfusion pressure alone is insufficient to cause this clinical picture in patients without preexisting liver or cardiac disease where elevated central venous pressure and portal venous congestion may contribute to a further reduction in hepatic blood flow.

Drug Toxicity

Drug-induced liver injury may be difficult to diagnose, as the relationship between drug exposure and hepatic toxicity is not always clear. Propofol, midazolam, and fentanyl have not been shown to significantly alter liver function. Very large doses of thiopentone (>750 mg) may cause hepatic dysfunction. The degree of hepatic metabolism of inhaled anesthetic agents correlates with the likelihood of a toxic reaction. Isoflurane, desflurane, and sevoflurane undergo less hepatic metabolism than halothane or enflurane and have the lowest risk of hepatitis. Evidence exists for "cross-sensitization" between these agents.

Halothane hepatitis is well known and is still a common surgical diagnosis for postoperative jaundice in adult patients, despite the fact that halothane has become obsolete in most institutions. Among the volatile agents, halothane causes the greatest reduction in hepatic blood flow, which parallels the decrease in cardiac output, and may promote a mild, self-limited form of hepatitis in 1 in 10,000 exposures. Clinical features include high fever on postexposure days 3 to 14, with the onset of jaundice 1 to 2 days later. There is leukocytosis with eosinophilia in 20% of cases. Fulminant hepatic necrosis is rare (1 in 35,000 exposures) but is associated with a 40% mortality rate. Adverse outcomes are associated with patient age older than 60 years, obesity, repeated exposures over a short interval, serum bilirubin greater than 10 mg/dL, and PT greater than 20 seconds. The most likely mechanism of injury is direct hepatotoxicity, reduction of hepatic blood flow, and immunologic reactions.

Common hepatotoxic drugs include oral contraceptives, steroids, chlorpromazine, phenytoin, alcohol, amiodarone, statins, hydralazine, acetaminophen, aspirin, isoniazid, methyldopa, and antibiotics. Tetracycline has been associated with fatty infiltration; penicillin and cephalosporins with hepatitis; sulphonamides cause hypersensitivity and focal hepatocellular necrosis.

TPN in critically ill patients has been associated with liver necrosis and cholestasis, causing jaundice. Excessive caloric intake appears to be a risk factor for liver dysfunction.

Severe bacterial infections or intraabdominal sepsis is commonly associated with cholestasis. Contributory factors include hypotension, hemolysis, drug therapy, and the effect of endotoxin-mediated cytokine release that causes impairment of bilirubin and bile salt transport. By analogy, small-bowel ileus in trauma patients may interrupt the normal endogenous circulation of bile acids between the gut and liver. If so, this would render hepatocytes more sensitive to the cholestatic effect of bilirubin overload. In early sepsis, splanchnic blood flow is increased as a consequence of increased hepatic oxygen extraction to support phagocytosis of bacterial endotoxins. In septic shock, systemic vasoparesis causes hypotension despite splanchnic vasoconstriction. Dysregulation of the hepatic arterial buffer response contributes to lactic acidosis.

Viral Hepatitis

Acute viral hepatitis is an uncommon cause of postoperative jaundice, but can occur in patients with preoperative exposure to type A, B, or C viruses. Less commonly, it is due to type D or Epstein-Barr virus or cytomegalovirus. Testing for antigens and antibodies is required for a definitive diagnosis, because many classes of drugs cause hepatitis that is clinically and histologically identical to viral hepatitis. General symptoms include dark urine, fatigue, anorexia, vomiting, dehydration, low-grade fever, myalgias, and right upper quadrant pain. Elevation of liver enzymes in the early phase of hepatitis precedes the appearance of jaundice. The mortality rate for intraabdominal surgery in patients with severe acute inflammatory hepatitis ranges from 15% (viral) to 55% (alcohol related). Therefore all elective surgery should be delayed until the infection has resolved, as indicated by normal liver function test results. Recovery may take up to 4 months. The incidence of posttransfusion hepatitis from any cause is negligible and probably warrants a case report. Since 2004, 85% of posttransfusion infections were caused by hepatitis C virus, with an incidence of less than 1 in 1 million units of blood or blood products transfused.

Chronic Hepatitis

There are two types of chronic hepatitis: chronic persistent hepatitis and chronic active hepatitis. The latter is more serious and more commonly progresses to cirrhosis and liver failure. Patients with cirrhosis, regardless of cause, have a reduced life expectancy. Although the probability of hepatic decompensation may be relatively low, after the onset of the first major complication (i.e., ascites, variceal bleeding, jaundice, encephalopathy), the mortality risk is high. Anesthesia and surgery are implicated in hepatic decompensation. Significant factors (by multivariate analysis) associated with perioperative hepatic complications and mortality in the cirrhotic patient include male gender, high Child-Pugh score (or MELD score), cirrhosis other than primary biliary cirrhosis (especially cryptogenic cirrhosis), renal insufficiency, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure, preoperative sepsis, gastrointestinal bleeding or ascites, emergency surgery with a high surgical severity score, and documented intraoperative hypotension.

Benign Postoperative Cholestasis

Benign postoperative intrahepatic cholestasis is a diagnosis of exclusion. It is usually a self-limiting process that subsides in 3 to 4 weeks that is seen in patients after lengthy operative procedures and a stormy intraoperative course that lends itself to multiple possible causes of postoperative jaundice. Severe jaundice with conjugated bilirubin levels as high as 40 mg/dL with elevated serum alkaline phosphatase and normal to mildly elevated aminotransferases is typical. Biopsy typically shows centrilobular congestion and cholestasis.

Posthepatic Causes

Extrahepatic obstruction rarely causes postoperative jaundice but should be excluded, as the jaundice is correctable. Causes include bile duct injury, tumor, stone, or stricture; acute cholecystitis, cholangitis, or pancreatitis.

Risk Assessment

Most surgical procedures, whether performed under general, spinal, or epidural anesthesia, are followed by minor elevations in serum liver biochemical test levels. Minor postoperative elevations of serum aminotransferase, alkaline phosphatase, or bilirubin levels in patients without underlying liver disease are not clinically significant. However, in patients with underlying liver disease, and especially those with compromised hepatic synthetic function, surgery can precipitate hepatic decompensation.

Operative risk correlates with the severity of the underlying liver disease, comorbid medical conditions, and the nature of the surgical procedure. In patients with cirrhosis, the Child-Pugh classification (Child-Turcotte-Pugh [CTP] score) and the Model for End-stage Liver Disease (MELD) score provide reasonable estimations of perioperative mortality. The CTP scoring system is based on the patient's serum bilirubin and albumin levels, PT, and severity of encephalopathy and ascites. Historically, mortality rates for patients undergoing surgery have been 10% for those with Child class A, 30% for those with Child class B, and 76% to 82% for those with Child class C cirrhosis. In addition to predicting perioperative mortality, the Child class correlates with the frequency of postoperative complications, which include liver failure, worsening encephalopathy, bleeding, infection, renal failure, hypoxia, and intractable ascites. A general consensus is that elective surgery is well tolerated in patients with Child class A cirrhosis, permissible with preoperative preparation in patients with Child class B cirrhosis without portal hypertension (except those undergoing extensive hepatic resection or cardiac surgery), and contraindicated in patients with Child class C cirrhosis.

The MELD score was created to predict mortality after transjugular intrahepatic portosystemic shunt, then implemented to risk stratify patients awaiting liver transplantation, and more recently used to predict perioperative mortality. The MELD score is a linear regression model based on a patient's serum bilirubin, creatinine, and INR. The largest retrospective study of the MELD score as a predictor of perioperative mortality evaluated 772 patients with compensated cirrhosis who underwent open abdominal, orthopedic, and cardiovascular surgery. Patients' median preoperative MELD score was 8, and few had a MELD score greater than 15 (equivalent to Child class C). Patients with a MELD score of 7 or less had a mortality rate of 5.7%; patients with a MELD score of 8 to 11 had a mortality rate of 10.3%; and patients with a MELD score of 12 to 15 had a mortality rate of 25.4%. The increase in relative risk of death was almost linear for MELD scores greater than 8. Based on this study, Mayo developed a mortality risk prediction model (http://www.mayoclinic.org/meld/mayomodel9.html) to calculate 7-day, 30-day, 90-day, 1-year, and 5-year surgical mortality risk based on a patient's age, American Society of Anesthesiologists class, and MELD score. Use of the MELD score and Child class are not mutually exclusive and may complement one another, but the MELD score is probably the most precise single predictor of perioperative mortality.

Hepatic Resection

Mortality rates as high as 25% are reported after partial liver resection in patients with cirrhosis. Risk stratification based on the Child class

and MELD score have allowed more appropriate selection of patients, leading to lower mortality and morbidity rates. In an analysis of 82 cirrhotic patients who underwent hepatic resection, the perioperative mortality rate was 29% in patients with a MELD score greater than or equal to 9 but 0% in those with a MELD score less than or equal to 8. In addition to predicting mortality, the MELD score can predict morbidity after liver resection. In one study, the frequency of post–liver resection liver failure was 0%, 3.6%, and 37.5% in patients with MELD scores of less than 9, 9 to 10, and greater than 10, respectively. The extent of hepatectomy is also a predictor of mortality, as is a low serum sodium concentration. Postresectional liver failure has been defined as an INR greater than 1.7 and serum bilirubin greater than 2.9 mg/dL, the so-called "50-50" criteria. When these criteria are met, the postoperative mortality rate is 60%, compared with 1.2% in patients not meeting these criteria.

Surgical risk factors for postoperative hepatic dysfunction and isolated hyperbilirubinemia include emergency surgery and surgery with a high severity score, including the following:

- Open-heart surgery (cardiopulmonary bypass effects, congestive heart failure, vasopressors)
- Open versus laparoscopic cholecystectomy
- Trauma surgery, especially involving the liver or biliary tract
- Major abdominal surgery (particularly biliary tract surgery, liver resection)
- Large blood or blood product transfusion requirements

Cholelithiasis occurs twice as often in patients with cirrhosis than in those without. Despite advances in laparoscopic versus open surgical techniques, in patients with cirrhosis and portal hypertension, perioperative rates of mortality (7% to 20%) and morbidity (bleeding, renal failure, and sepsis) remain high. Surgery-related release of inflammatory mediators and hepatic ischemia can be minimized using a laparoscopic technique for cholecystectomy. Yet hepatic perfusion may still be reduced by the head-up tilt positioning and dependent venous pooling and increased intraabdominal pressure with CO_2 insufflation. Further, manipulation of the liver, hypercarbic acidosis, and the neurohumoral stress response with upper abdominal surgery increase the risk for multiorgan system failure.

Differentiation between acute inflammatory liver failure and acute exacerbation of chronic liver disease affects the prognosis. Contraindications to elective surgery in patients with liver disease include acute viral, drug-induced, and alcoholic hepatitis; acute liver failure; acute renal failure; cardiomyopathy; hypoxemia; and severe coagulopathy.

Patients with asymptomatic chronic hepatitis likely present little increased anesthetic risk. However, those with symptomatic cirrhosis or chronic hepatitis are at significantly increased risk for postoperative complications, with the degree of risk related to the extent of their disease.

Patients with severe obstructive jaundice have reduced peripheral resistance and splanchnic pooling. In addition, renal salt wasting, reduced left ventricular function, and risk of arrhythmia from sinoatrial node dysfunction put them at risk for hypotension with minimal blood loss. Risk factors for perioperative mortality in these patients include hematocrit less than 30%, bilirubin greater than 11 mg/dL, malignant biliary obstruction, cholangitis, renal insufficiency, and low serum albumin concentration. Postoperative complications in patients with severe obstructive jaundice include infection, renal failure, disseminated intravascular coagulation and further deterioration in liver function.

Implications

Most postoperative jaundice is usually self-limited and resolves with general supportive therapy. The importance of diagnosing the most likely cause is to determine whether the jaundice is correctable by endoscopic or surgical intervention. Patients with acute inflammatory hepatitis, evidence of hepatocellular necrosis, or compensated cirrhosis with portal hypertension and MELD score greater than 15 (Childs C) are poor surgical candidates. Patients with chronic liver disease and preserved function may not be at increased surgical risk. Those with cholestatic disease have lower morbidity and mortality rates compared with patients with compensated cirrhosis.

A focused preoperative assessment is necessary to identify high-risk patients. The surgical procedure and anesthetic technique should be chosen with the understanding that an acute insult on chronic hepatocellular injury may lead to liver failure. Clinical indicators of suboptimal liver function may include persistent hypothermia, coagulopathy, acidosis or hyperglycemia (later, hypoglycemia), oliguria and renal insufficiency, hemodynamic instability, worsening (A-a) oxygen gradient, and delayed postoperative awakening.

MANAGEMENT

For adults with postoperative jaundice, evaluation is based on a careful review of the patient's history, medications, perioperative course, and laboratory and imaging results. The most important questions are these:

1. Does the pattern of elevated bilirubin and altered liver function studies or imaging tests reflect hepatocellular injury, cholestasis, or biliary tract obstruction? What was the history of the onset of jaundice?
2. Does the patient have known liver disease or risk factors for liver disease?
3. What is the likelihood of acute hepatitis from drugs, alcohol, or sepsis?
4. Is there any evidence of hemolysis?
5. What was the surgical procedure? Is there evidence of significant soft tissue bleeding?
6. What type of anesthesia did the patient receive? Was a volatile gas used? Identify periods of hypotension, hypoxemia, and transfusion requirements. Review the list of medications administered perioperatively, including pressors.

If the urinalysis is negative for bilirubin and there is increased serum unconjugated bilirubin, this suggests a prehepatic cause due to a large bilirubin load. However, if the urine is positive for bilirubin and there is increased total and conjugated bilirubin, this suggests an intrahepatic or posthepatic cause. If both alkaline phosphatase and liver transaminases are elevated, hepatobiliary imaging is indicated. If this is negative, hepatitis serology, alpha-fetoprotein, antimitochondrial antibody, and endoscopic retrograde cholangiopancreatography are indicated. Evidence of bile duct dilation is investigated with cholangiography. Focal lesions are further studied with abdominal ultrasound, computed tomography, magnetic resonance cholangiopancreatography, magnetic resonance imaging, endoscopic ultrasound, and possibly a liver biopsy. Stratify the patient according to the Child Classification or MELD scoring system.

A strategic management plan includes the following recommendations:

1. General supportive measures.
2. Ensure a homeostatic environment (normalize electrolytes, acid-base status, and hematocrit).
3. Cardiovascular stability (euvolemia, mean arterial pressure >60 to 75 mm Hg).

4. Treat bacterial infections and complications related to liver disease (encephalopathy, ascites, hyponatremia, variceal bleeding, coagulopathy).
5. Avoid hepatotoxic and nephrotoxic drugs. Discontinue blood transfusions if there is evidence of hemolysis.
6. Optimize renal perfusion: identify intrinsic renal parenchymal disease; provide intravascular volume expansion; institute drug therapy with splanchnic vasoconstrictors or renal vasodilators; treat hemoglobinuria with urine alkalinization and diuresis.

Management and prognosis depend on the identification of high-risk patients and causes for which specific intervention is possible. After treatment and supportive care, jaundice will resolve in weeks to months. For the majority of fulminant liver failure patients, survival ultimately depends on medical stabilization and urgent liver transplantation.

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Postoperative Peripheral Neuropathy

169

David A. Nakata • Adam J. Lemmon

Case Synopsis

A 28-year-old man with insulin-dependent diabetes mellitus for 15 years was diagnosed with testicular cancer. His chemotherapy regimen consisted of bleomycin and cisplatin. He underwent post-chemotherapy retroperitoneal lymph node dissection under general anesthesia. The surgery, which took 2 hours, was unremarkable, as was his stay in the postanesthesia care unit. On postoperative day 3, the patient noted a decreased level of sensation in the fourth and fifth digits of his left hand. He had no prior history of peripheral neuropathy. He was subsequently diagnosed with a left ulnar neuropathy.

PROBLEM ANALYSIS

Definition

Neuropathies are classified into three histologic groups, with increasing levels of severity: neurapraxia, axonotmesis, and neurotmesis. Clinically, any or all of these injury patterns can be present in the affected nerve. With neurapraxia, there is no disruption of actual anatomic neural elements. However, there may be temporary conduction block during ischemia or some degree of demyelination, with greater effects on the function of large fibers (i.e., motor, joint position sense, soft touch). Changes accompanying neurapraxia usually resolve within a few weeks, with complete recovery expected. With axonotmesis, axons are disrupted, but the nerve sheaths remain intact. Wallerian degeneration follows, but axon regeneration results in recovery of function over weeks to months. Even so, some degree of sensory or motor deficit may persist. Neurotmesis is the most serious injury, with disruption of the entire nerve, including transection of the axons and myelin sheaths. This typically prevents regeneration and recovery, resulting in poor functional recovery. Often the nerve is replaced with fibrous scar tissue.

The majority of postoperative neuropathies are due to nerve ischemia. Most commonly, this is caused by either stretch or compression. Direct mechanical compression can obviously lead to reduced blood flow, and stretch produces a reduction in the cross-sectional area of the neural structures, leading to compression of the vasculature (Fig. 169.1).

Recognition

Postoperative neuropathies are commonly ascribed to events that occur intraoperatively. In numerous cases, however, despite close follow-up, symptoms are not reported until days after the operative procedure. It stands to reason that if intraoperative events were responsible for the development of these neuropathies, symptoms would be reported more proximate to the patient's emergence from anesthesia. Given the reporting delay, consideration must be given to the possibility that many of these neuropathies stem from events occurring in the postoperative period. This is in sharp contrast to the historical belief, still held by many, that the development of neuropathy represents an intraoperative deviation from the standard of care.

Risk Assessment

Many factors are known to be associated with the development of postoperative neuropathies (Box 169.1). In the patient described in the case synopsis, male gender, preoperative chemotherapy, and diabetes mellitus are known risk factors associated with the development of neuropathies.

In males, the ulnar nerve appears to be at greater risk of injury owing to anatomic differences between the sexes. The tubercle of the coronoid process is approximately 1.5 times larger in men than in women, perhaps predisposing to increased bony compression of the nerve. In addition, women generally have a larger fat pad within the medial aspect of the elbow, which may help protect the ulnar nerve (Fig. 169.2). Also, it has been suggested that the cubital tunnel retinaculum in men is more robust and may place greater compressive force on the ulnar nerve when stretched (Fig. 169.3).

Peripheral nerves are much more tolerant to ischemia than are nerves within the central nervous system. Peripheral nerves are commonly subjected to ischemia during the placement of vascular tourniquets for hemostasis. When inflated, the applied force is often greater

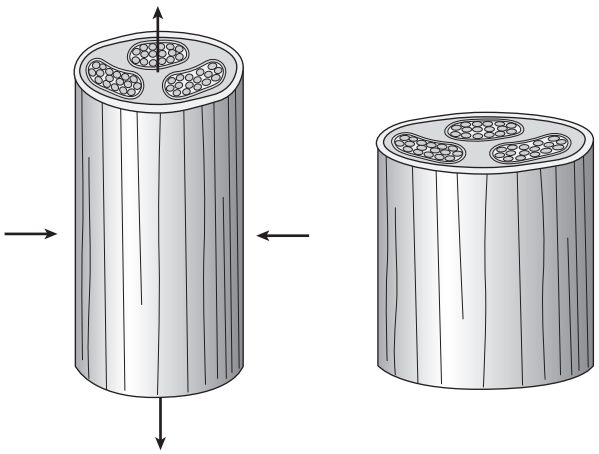

Fig. 169.1 Nerve stretch is associated with a decrease in cross-sectional area and an increase in intraneural pressures. (From Butler DS: *Mobilization of the nervous system.* New York, Churchill Livingstone, 1991.)

BOX 169.1 Factors That May Increase the Risk of Perioperative Neuropathy

Alcoholism	Direct nerve trauma
Amyloidosis	Gender (male)
Arthritis	Hepatic failure
Atherosclerotic disease	Hypothyroidism
Autoimmune disorders	Infectious diseases
Bell's palsy	Malnutrition
Cancer	Nerve entrapment syndromes
Chemotherapy	Renal failure
Connective tissue diseases	Trauma to adjacent structures
Diabetes mellitus	Vitamin deficiencies

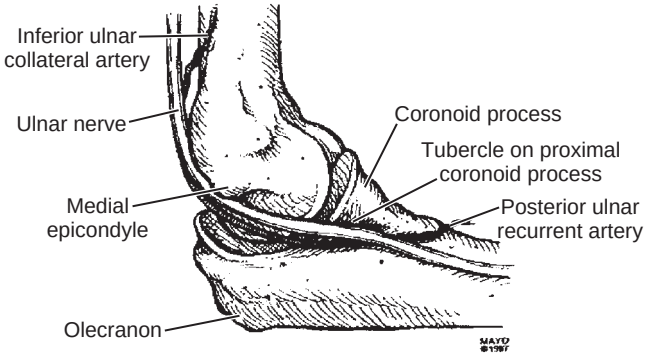

Fig. 169.2 The ulnar nerve and ulnar collateral artery at the elbow are relatively superficial and easy to compress. The coronoid process in males is larger than in females, and the adipose layer is less prominent. These factors increase the risk of compression to the ulnar nerve in males. (From Warner M: Perioperative neuropathies, blindness, and positioning problems. American Society of Anesthesiologists 53rd Annual Refresher Course Lectures, 2002, Orlando, FL.)

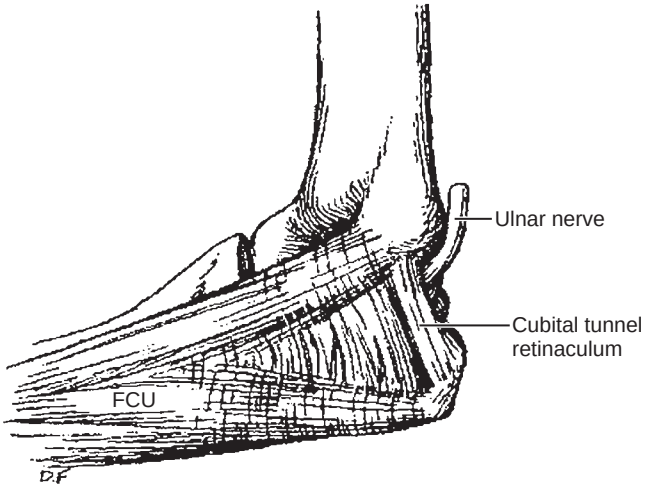

Fig. 169.3 The cubital tunnel retinaculum is a tough, fibrous band that is in close proximity to the ulnar nerve. Compression of the ulnar nerve can occur between this retinaculum and the medial epicondyle. *FCU,* Flexor carpi ulnaris (ulnar head). (From Warner M: Perioperative neuropathies, blindness, and positioning problems. American Society of Anesthesiologists 53rd Annual Refresher Course Lectures, 2002, Orlando, FL.)

than 100 mm Hg above the systolic pressure. This degree of pressure has been shown to produce slowing of nerve conduction directly under the area of compression, followed by more distal slowing as tourniquet times increase.

In clinical practice, an "ischemic" tourniquet time of less than 2 hours is generally accepted. Animal studies have shown that ischemia is tolerated for up to 4 hours without causing permanent nerve damage. Compressive forces produced by tourniquets are generally greater than those produced by placing the arms or legs on a padded operating room table. Thus individuals who undergo operative procedures lasting less than 2 hours should be almost immune to the development of postoperative neuropathies from tourniquet application or accepted positioning maneuvers.

The patient described in the case synopsis had multiple risk factors for the development of neuropathies, including a long history of diabetes mellitus and recent chemotherapy. Preexisting conditions likely play an important role in the development of neuropathies in many individuals. This patient had no preexisting symptoms of peripheral nerve involvement, but neuropathies associated with metabolic conditions (e.g., diabetes mellitus, chemotherapy) generally have an insidious onset. This gradual onset provides an opportunity for subclinical neuropathies to become well established before the onset of symptoms, and it also leads to increased susceptibility for the development of a symptomatic neuropathy. A well-described potential cause for such increased risk is the double crush syndrome.

Double crush syndrome is a peripheral nervous system disorder in which dual lesions in the same nerve act synergistically to enhance each one's severity. Nemoto and coworkers showed that placing a low-compression clamp on a dog's peripheral nerve could produce an incomplete conduction block. This caused only mild axonal degeneration, with no obvious clinical sequelae. If a second, equally low-compression clamp was placed more distally on the same peripheral nerve, complete conduction blockade with marked axonal degeneration was shown. This double crush injury model provides insight into how comorbidities may increase the risk of perioperative neuropathies. The model may also explain why some individuals develop neuropathies whereas others do not, despite the use of similar positioning precautions.

Double crush syndrome likely plays an important role in the development of neuropathies in patients with preexisting nerve entrapment syndromes. For example, cubital tunnel syndrome is a common nerve entrapment syndrome, second in frequency only to carpal tunnel syndrome. The cubital tunnel is an enclosed space surrounded by tough fibrous materials and bone. Because of these anatomic boundaries, the cubital tunnel has a limited ability to expand during fluid accumulation. Postoperatively, patients retain third-space (i.e., interstitial) fluid, some of which accumulates in the cubital tunnel. This accumulation may increase pressure within the cubital tunnel, leading to double crush ulnar nerve compression. Pregnancy-induced carpal tunnel syndrome is a well-known example in which fluid retention can lead to a clinically significant peripheral neuropathy.

Implications

The American Society of Anesthesiologists' closed claims analyses recognize postoperative ulnar neuropathies as among the most common, if not the most common, postoperative peripheral neuropathy. In 1999, 28% of all claims for such nerve injuries involved the ulnar nerve. More recent analyses of claims in which anesthesia care was implicated suggest that some injuries did not occur until after anesthesia care had ended.

In a prospective study, Warner and colleagues found that the median time for reporting symptoms of ulnar neuropathy was 4 days after surgery (range, 2 to 7 days). Another prospective study by Warner's group showed that ulnar neuropathies also occurred in medical patients who did not undergo surgery. Considering these reports, it is implausible to assume that all perioperative neuropathies occur during

the intraoperative and perianesthetic care periods. Thus other mechanisms for such neuropathies need to be sought.

Postsurgical patients routinely receive opiates for pain control. These drugs blunt not only pain sensation but also the sensation of any paresthesias the patient might experience. Pain medications also produce sedation, so that patients are less mobile. Such immobility might extend the time patients spend in positions that could result in nerve stretch or compression injury.

Finally, during postoperative rounds, it is common to find patients resting with their arms folded across the chest or abdomen. Elbow flexion is known to raise the pressure within the cubital tunnel and also to stretch the ulnar nerve, either of which can increase the likelihood of nerve ischemia (Fig. 169.4). Often this crossed-arm position places the cubital tunnel directly in contact with the bed, further compressing the ulnar nerve. Finally, the ulnar nerve may be injured when patients sit in armchairs with their arms flexed, which can place the cubital tunnel in direct contact with the armrests.

MANAGEMENT

No specific guidelines exist regarding when a neurologist should be consulted for the complaint of peripheral neuropathy. Consideration of the duration and severity of the findings is required. If the supposed peripheral neuropathy resolves within a short period, neurapraxia is the most likely diagnosis, and a full recovery can be expected. However, if the findings persist with no improvement, a neurology consultation should be considered to assist in both diagnosis and management. In some instances, nerve conduction studies may be warranted.

PREVENTION

In 2000 the American Society of Anesthesiologists published a practice advisory for the prevention of perioperative peripheral neuropathies. This advisory made several recommendations that may decrease the incidence of ulnar neuropathy:

- Arm abduction should be limited to 90 degrees in supine patients; patients who are positioned prone may comfortably tolerate arm abduction greater than 90 degrees.
- Arms should be positioned to decrease pressure on the postcondylar groove of the humerus (ulnar groove). When arms are tucked at the sides, a neutral forearm position is recommended. When arms are abducted on armboards, either supination or a neutral forearm position is acceptable.
- Padded armboards may decrease the risk of upper extremity neuropathies.
- Padding at the elbow and at the fibular head may decrease the risk of upper and lower extremity neuropathies, respectively.

Given the multitude of factors that may contribute to perioperative ulnar neuropathy, it cannot be assumed that all perioperative nerve injuries are due to a violation of the standard of care. This idea is reinforced, in most cases, by the relatively long interval between the operative procedure and the initial report of symptoms.

ACKNOWLEDGMENT

The authors wish to thank Dr. Robert K. Stoelting for his contribution to the previous edition of this chapter.

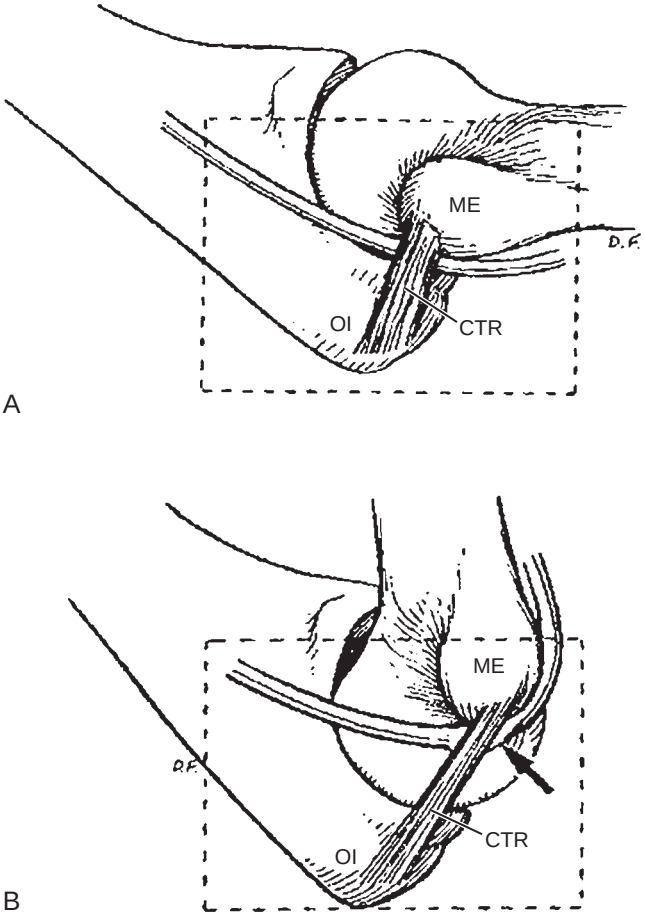

Fig. 169.4 A, Anatomy during elbow extension. **B,** During elbow flexion, the cubital tunnel retinaculum (CTR) is stretched between the medial epicondyle (ME) and the olecranon process (OI), leading to compression of the ulnar nerve *(arrow).* Also, the ulnar nerve is physically stretched during elbow flexion, causing reduction in its cross-sectional area and blood flow. (From Warner M: Perioperative neuropathies, blindness, and positioning problems. American Society of Anesthesiologists 53rd Annual Refresher Course Lectures, 2002, Orlando, FL.)

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170 Postoperative Pulmonary Hypertension

Regina E. Linganna • Jiri Horak

Case Synopsis

A 50-year-old woman with chronic thromboembolic pulmonary hypertension is to undergo open partial colectomy with primary reanastomosis for colonic adenocarcinoma. She is on warfarin therapy, which she was instructed to stop 7 days before surgery. She is on no other medications for pulmonary hypertension. She is able to walk less than one block before she needs to stop because of dyspnea. Her preoperative echocardiogram showed moderate-to-severe pulmonary hypertension. Her last right-sided heart catheterization was 6 years ago. Mean pulmonary arterial pressure at that time was 40 mm Hg. A pulmonary artery catheter was placed after induction due to the patient's past medical history. The case was uneventful, and the patient was recovered in the postanesthesia care unit (PACU). Twenty minutes into her PACU course, her heart rate increases from 85 to 120, and her blood pressure is now 70/35. Her Spo_2 on 100% O_2 at 10 L/min is 92%. Her temperature is 36.5°C. Her pulmonary artery catheter showed her pulmonary artery pressure to be 75/45 mm Hg, an increase from her baseline of 45/28 mm Hg. She was reintubated in the PACU. A transesophogeal echocardiogram (TEE) was performed, revealing a severely dilated right ventricle, the intraventricular septum bulging into the left ventricle, and a hypovolemic left ventricle.

PROBLEM ANALYSIS

Definition

The pulmonary vascular system is a high-flow, high-compliance, low-pressure system. As such, pulmonary artery pressure (PAP) is normally substantially lower than systemic arterial blood pressure. Pulmonary hypertension is a disease that may be suspected clinically, diagnosed initially with echocardiography, and confirmed with a right-sided cardiac catheterization (RHC). Symptoms are usually nonspecific. Most commonly, patients will have dyspnea, but they may also have chest pain, palpitations, or syncope. Once pulmonary hypertension is suspected, it will need to be confirmed by RHC. Mean PAP greater than 25 mm Hg, or peak pressure greater than 40 mm Hg, is interpreted as pulmonary hypertension. Degrees of pulmonary hypertension are inconsistently defined and may be classified as mild (systolic PAP 40 to 49 mm Hg), moderate (systolic PAP 50 to 59 mm Hg), or severe (systolic PAP 60 mm Hg or above).

Pulmonary hypertension is classified into five groups (Table 170.1). Group 1 is pulmonary arterial hypertension and involves disease primarily of the pulmonary artery itself. Groups 2 to 5 are pulmonary hypertension secondary to other causes.

Recognition and Risk Assessment

In the preoperative period, it is important to identify patients who may have undiagnosed pulmonary hypertension. Any patient who has one of the diseases associated with Groups 2 to 5 of pulmonary hypertension should be suspected of having elevated pulmonary artery pressure. For instance, a patient with known sarcoidosis who is having progressive dyspnea on exertion should be suspected of having pulmonary hypertension. Similarly, a patient with mitral stenosis with worsening symptoms should also be suspected of having new-onset pulmonary hypertension in addition to progressive valvular disease. Additionally, smokers are always at risk for having pulmonary hypertension. In addition to frequently carrying the diagnosis of chronic obstructive pulmonary disease, they have increased levels of endothelin-1, a known pulmonary vasoconstrictor. Endothelin-1 acts as a vasoconstrictor on the pulmonary vasculature, thereby increasing pulmonary vascular resistance (PVR).

If a patient is known or suspected to have pulmonary hypertension, it is important to have objective data before proceeding with an elective procedure. As mentioned, the most accurate, gold standard, diagnostic test for pulmonary hypertension is RHC. This gives a direct measure of the PAP. However, a preoperative echocardiogram is often the only preoperative objective data available. It can provide valuable information about both the PVR and the function of the right ventricle. A patient with long-standing pulmonary hypertension will have a dilated and hypertrophic right ventricle that may be mildly hypokinetic. Additionally, they will have a dilated right atrium resultant secondary to the increased pressure in the right ventricle. As the pressure of the pulmonary vascular system increases, the right ventricle needs to adapt to overcome this pressure and provide forward blood flow to the lungs. As such, the patient's echocardiogram will also have an increased right ventricular systolic pressure. The pulmonary artery systolic pressure may also be estimated on echocardiogram if tricuspid regurgitation is present.

A routine chest radiograph may show right-sided cardiac silhouette enlargement. This, in conjunction with the other risk factors mentioned earlier, should cause the clinician to be suspicious for pulmonary hypertension. An electrocardiogram with right-axis deviation should raise a similar suspicion. Arterial blood gas should also be obtained to determine baseline oxygenation and ventilation status of the patient.

The severity of a patient's preexisting pulmonary hypertension can be evaluated based on the objective data described earlier, the patient's

TABLE 170.1 Classification of Pulmonary Hypertension

		Examples
Group 1	Pulmonary arterial hypertension (PAH)	Inherited PAH Connective tissue diseases Toxins
Group 2	Secondary to left-sided heart disease	Mitral valve disease Systemic hypertension
Group 3	Secondary to lung disease	COPD ILD OSA
Group 4	Secondary to chronic thromboembolic disease	Factor V Leiden Protein C deficiency Protein S deficiency Antiphospholipid syndrome
Group 5	Miscellaneous	Polycythemia vera Sarcoidosis Histiocytosis X

COPD, Chronic obstructive pulmonary disease; *ILD,* interstitial lung disease; *OSA,* obstructive sleep apnea.

symptoms, and the patient's medication regimen and oxygen requirement. The management of a patient on a prostacyclin who walks 20 minutes a day is much different from that of the patient on continuous epoprostenolol infusion and 6 L/min of oxygen.

Acute, or acute on chronic, right ventricular systolic decompensation will present with decreased contractility of the right ventricle, worsening dilation, and increased severity of tricuspid regurgitation. Increased pressure in the right ventricle will cause the intraventricular septum to shift into the left ventricle, which will further compromise the right ventricular failure. This will in turn cause left ventricular dysfunction. Stroke volume will resultantly be decreased, and cardiac output will become dependent on the heart rate.

Implications

The most feared complication of pulmonary hypertension is cardiovascular collapse secondary to right ventricular failure from the inability of the right ventricle to adapt to the increased afterload of the pulmonary circulation. As the right ventricle fails, it displaces the ventricular septum to the left. The left ventricular function is subsequently impaired due to inadequate diastolic filling and its decreased ability to contract during systole. Right ventricular coronary perfusion is also reduced due to wall stretching and intracavitary hypertension. This leads to right ventricular ischemia, further worsening the right ventricular failure. As this right-sided heart failure continues to worsen, the cardiac output will continue to diminish. Stroke volume will decrease, and the cardiac output will become heart rate dependent.

When systemic hypotension develops from reduced cardiac output, right ventricular coronary perfusion pressure is further reduced. Progressive right ventricular ischemia ultimately results in cardiovascular collapse.

MANAGEMENT

In addition to the preoperative evaluation previously discussed, medical management should be optimized before proceeding with elective surgery. An adequate pain management strategy should also be discussed preoperatively. It is important to reduce the amount of sympathetic stimuli that the patient responds to during surgery, as that will increase the severity of the pulmonary hypertension. This can be attained through a combination of systemic and regional or neuraxial techniques. For the patient in our case, an epidural would decrease her sympathetic responses both intraoperatively and postoperatively.

TABLE 170.2 Medications That Decrease Pulmonary Vasculature Resistance

Class of Medication	Examples
Prostacyclins	Epoprostenol (continuous IV infusion)
Endothelin receptor antagonist	Bosentan Ambrisentan
Phosphodiesterase inhibitor	Sildenafil Tadalafil
Guanylate cyclase stimulant	Rocociguat Cinaciguat
Recombinant BNP	Nesiritide

IV, Intravenous; *BNP,* brain natriuretic peptide.

Intraoperative management of these patients can be very challenging, as their hemodynamics must be maintained within a very narrow range. Ventilator management must be carefully titrated throughout the case. As in all patients, it is important to avoid hypoxemia. It is especially important in these patients because they are very sensitive to hypoxic vasoconstriction. Hypoxic vasoconstriction will increase the PAP, which will increase right ventricular afterload, which these patients may be unable to tolerate. It is also important to avoid hypercarbia, as the resultant acidosis will increase pulmonary vascular resistance. Excessive positive end-expiratory pressure will also increase PVR due to the increase in alveolar pressure. Additionally, it is necessary to avoid atelectasis, which will increase the likelihood of hypoxic vasoconstriction. There are many ways that the right ventricle can be adversely affected by ventilator management, so it is important to titrate ventilator settings throughout the case to optimize the work of the right ventricle.

Nonpharmacologic management includes avoiding sepsis and other causes of acidosis that will lead to increased PVR. Maintaining normothermia is also important as hyperthermia will lead to an increase in PVR and hypothermia will lead to a decrease in myocardial contractility. It is additionally important to avoid any increases in sympathetic discharge secondary to laryngoscopy or surgical stimulus.

Pharmacologic management can be divided into two broad categories: medications that decrease PVR and those that provide inotropic support to the right ventricle. Medications that reduce PVR are generally ones that are taken as an outpatient. They include prostacyclins, endothelin receptor antagonists, phosphodiesterase inhibitors, guanylate cyclase stimulants, and recombinant brain natriuretic peptide (Table 170.2). Additionally, inhaled nitric oxide (iNO) and inhaled epoprostenol can also lower PVR. Nitric oxide is a direct pulmonary vasodilator that is rapidly degraded by the pulmonary vasculature, with virtually no systemic hemodynamic effects. iNO is very costly to administer and has multiple adverse effects, including production of methemoglobin and bronchospasm caused by the metabolite N_2O. Milrinone is also a pulmonary vasodilator. Unlike iNO, milrinone is not specific to the pulmonary vasculature and has the unwanted side effect of systemic hypotension. For this reason, it is often administered in conjunction with vasopressin. As the lungs are without vasopressin receptors, vasopressin is able to counteract the vasodilatory effects of milrinone in the systemic circulation without increasing PVR.

Medications that provide inotropic support to the right ventricle include epinephrine and dobutamine. Epinephrine works directly on the right ventricle to increase inotropy. Dobutamine is also able to directly support the right side of the heart, with the adverse effect

of systemic hypotension. Unlike epinephrine, dobutamine primarily stimulates β-receptors, making it an inodilator. As such, a systemic vasopressor such as vasopressin or phenylephrine would need to be given in conjunction with dobutamine to avoid systemic hypotension. For this reason, dobutamine is less attractive as an initial agent to treat pulmonary hypertension.

Fluid management is also very important in this group of patients. Although the patients are preload dependent in the setting of an acute increase in PVR, further fluid loading of the right ventricle may also lead to a detrimental septal shift. TEE is an invaluable resource to guide fluid management. A right ventricle that is dilated, hypertrophied, and hyperkinetic is one that is likely to respond with an increase in output in response to a fluid challenge. This is because this is a ventricle that has adapted to pump against an increased PVR. This ventricle has become dependent on preload for its output. In contrast, a ventricle that is dilated and hypokinetic will not respond well to a fluid challenge, as this is the patient with acute right ventricular failure from either new onset or acutely worsening pulmonary hypertension. A fluid challenge in this situation will only worsen the right ventricular failure, as the right ventricle will not be able to handle this increase in preload. As is apparent from these two examples, depending on the time course of the disease, fluid management for two patients with pulmonary hypertension can be vastly different.

Postoperative management in these patients should include restarting their home medications as soon as possible. If the patient has Group 4 pulmonary hypertension, it is important that the patient's anticoagulant be restarted as soon as possible from a surgical standpoint. The perioperative period is one where a patient is at increased risked for a thromboembolic event, so anticoagulation, including bridging, should be of the utmost importance. A perioperative thromboembolic event is likely what caused the acute right ventricular failure in the patient in the case scenario. Incentive spirometry should also be initiated in the postoperative period to decrease the incidence of atelectasis that can lead to hypoxic vasoconstriction and a resultant increase in PVR.

PREVENTION

Pulmonary hypertension is a disease without many modifiable risk factors. However, one such risk factor is smoking. Smoking cessation, in addition to its many other benefits, will reduce the levels of endothelin-1, which will reduce the stimulation for vasoconstriction. For patients with Group 4 pulmonary hypertension, bridging anticoagulation before surgery will reduce the time period for which the patient is not therapeutically anticoagulated and is therefore at risk of additional thromboembolic events. It is also possible for a patient to have an inferior vena cava filter placed before surgery to prevent additional pulmonary emboli from occurring during the period of subtherapeutic anticoagulation.

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Postoperative Respiratory Failure

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Michael J. Stentz • Maurizio Cereda

Case Synopsis

A 75-year-old man is taken to the operating room for urgent cholecystectomy. He becomes hypotensive intraoperatively despite adequate fluid resuscitation. At the end of the case, his arterial partial pressure of oxygen (Pao_2) is 80 mm Hg with a fraction of inspired oxygen (Fio_2) of 100%. He is taken to the intensive care unit, where a chest radiograph shows diffuse bilateral pulmonary infiltrates. He remains intubated for 5 days postoperatively, and is eventually discharged to a subacute rehabilitation facility after a prolonged hospital stay.

PROBLEM ANALYSIS

Definition

Postoperative respiratory failure has been defined as the need for prolonged mechanical ventilation for 48 hours or longer postoperatively or the need for unplanned reintubation after surgery. The most common causes of postoperative respiratory failure are acute respiratory distress syndrome (ARDS), atelectasis, pulmonary edema, and pneumonia. Appropriate recognition and treatment of the underlying cause is essential to the reversal of postoperative respiratory failure. Careful intraoperative management can play an important role in minimizing the risk of postoperative respiratory failure.

Recognition

The clinical presentation of postoperative respiratory failure depends largely on the underlying cause. In addition to the pulmonary causes of respiratory failure discussed later, postoperative reintubation may also be indicated for upper airway obstruction or narcotic-induced respiratory depression. Nocturnal oxygen levels reach their nadir on postoperative day 3, suggesting that patients are at especially high risk for reintubation during this period.

Atelectasis is present in nearly all patients intraoperatively, but persists into the postoperative period in one-fifth of patients. It usually presents with hypoxemia and basilar consolidation on chest radiograph. Although postoperative fever has traditionally been attributed to atelectasis, multiple studies have failed to find any association between the two.

The diagnosis of postoperative pneumonia can be challenging. Pneumonia should be suspected in any postoperative patient with increased oxygen requirement. The combination of an infiltrate on chest radiography, fever, and leukocytosis is highly suggestive of a pneumonia, although these signs are nonspecific. Further signs of a developing pneumonia include purulent sputum or an increased requirement for airway suctioning, worsening cough or dyspnea, and pleuritic chest pain. Physical examination findings may again suggest the diagnosis, but are likewise nonspecific. Laboratory testing, including Gram stain and culture of respiratory secretions and immunostaining for conditions such as *Legionella,* may confirm the diagnosis and help guide antibiotic therapy.

Postoperative pulmonary edema can be classified into two broad categories, hydrostatic and permeability, depending on its presentation and predisposing risk factors. Hydrostatic pulmonary edema results from increased pressure across the pulmonary capillary walls, forcing fluid out of the capillaries and into the alveoli and interstitium. Hydrostatic pulmonary edema is often seen in ventricular failure or valvular disease, where it is termed *cardiogenic edema.* Even in the absence of heart disease, however, acute fluid overload can lead to hydrostatic pulmonary edema in the otherwise healthy postoperative patient. The excess fluid in the interstitium and alveolar air spaces impairs gas exchange and reduces the total volume of alveoli available for ventilation, which manifests as dyspnea and hypoxemia. Chest radiographs will classically reveal cephalization of the pulmonary vasculature, "bat wing" pulmonary opacities, peribronchial cuffing, and pleural effusions.

ARDS is a clinical condition in which inflammation leads to increased pulmonary capillary permeability. The resulting diffuse alveolar and interstitial edema decreases lung compliance and severely impairs oxygenation. The pathogenesis of ARDS is complex and multifactorial, and can be triggered by either intrapulmonary or extrapulmonary processes. ARDS presents with dyspnea, increased work of breathing, impaired oxygenation, and bilateral patchy infiltrates on chest radiograph (Fig. 171.1). The clinical diagnostic criteria for ARDS were updated in a consensus statement in 2012 and are listed in Box 171.1. Half of all hospital-acquired ARDS cases occur in surgical patients. The vast majority (nearly 80%) are associated with severe sepsis; other causes, including trauma, blood transfusion, aspiration, and pancreatitis, account for a small minority of cases.

Risk Assessment

Postoperative changes in respiratory patterns contribute to an increased risk of respiratory failure. Pain leads to shallow breathing without periodic deep "sigh" breaths, which promotes basilar atelectasis. Diaphragmatic dysfunction is also seen, particularly with upper abdominal incisions. The combination of impaired mucociliary function and prolonged bed rest leads to poor clearance of pulmonary secretions. There is also an association between long-acting

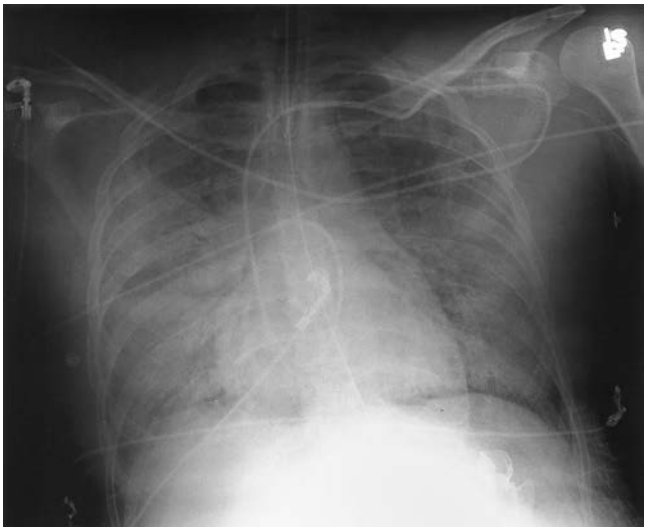

Fig. 171.1 Chest radiograph showing diffuse bilateral infiltrates, consistent with acute respiratory distress syndrome.

BOX 171.1 Diagnostic Criteria for Acute Respiratory Distress Syndrome

Acute onset within 7 days of causative insult
Bilateral opacities on chest imaging not due to effusion, collapse, or nodules
Respiratory failure not fully explained by cardiac failure or fluid overload
Pao_2:Fio_2 ≤300 with PEEP ≥5 cm H_2O
- Mild (Pao_2:Fio_2 >200–300)
- Moderate (Pao_2:Fio_2 >100–200)
- Severe (Pao_2:Fio_2 ≤100)

Data from ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al: Acute respiratory distress syndrome: the Berlin definition. *JAMA* 307(23):2526-2533, 2012.
Fio_2, Fraction of inspired oxygen; *Pao_2,* arterial partial pressure of oxygen; *PEEP,* positive end-expiratory pressure.

neuromuscular blockade and postoperative respiratory failure, suggesting that residual weakness contributes to inadequate airway protection and secretion clearance. Taken together, these changes put a significant number of postoperative patients at risk for pulmonary complications, and greatly increase the risk to those patients who already have compromised reserve.

Recent interest in defining and studying postoperative respiratory failure has led to the development of multiple scoring systems to identify patients at risk for pulmonary complications. Not surprisingly, patients with more comorbidities are at an increased risk for postoperative respiratory failure. Patients undergoing major vascular, thoracic, or upper abdominal surgeries are also at increased risk of postoperative respiratory failure, given their increased risk for postoperative pain, shallow breathing, and postoperative diaphragmatic dysfunction. Many of these scoring systems include similar risk factors, which are shown in Table 171.1.

Implications

Postoperative respiratory failure complicates 3% to 5% of surgeries and is associated with a nearly 30% mortality rate. Postoperative pulmonary complications result in higher total hospital costs and longer hospital lengths of stay than any other postoperative complication. Early identification of patients at risk for respiratory failure allows for more timely implementation of treatment and mobilization of resources, as these patients will require mechanical ventilation and intensive care postoperatively.

TABLE 171.1 Risk Factors Predisposing to Postoperative Respiratory Failure[a]

Patient Risk Factors	Surgical Risk Factors	Anesthetic Risk Factors
Age (>60 years)	Upper abdominal, thoracic, vascular, neck, or neurologic surgery	Higher tidal volumes
Low preoperative Spo_2	Surgery length >2 hours	Higher driving pressures
Respiratory infection in previous 30 days	Emergency surgery	Higher Fio_2
Preoperative anemia		Transfusion
Albumin <30 g/L		Higher crystalloid volume
BUN >30 mg/dL		
COPD		
ASA physical status ≥3		

[a]Based on several proposed scoring systems for predicting postoperative respiratory failure, postoperative ARDS, and/or early postoperative reintubation.
ASA, American Society of Anesthesiologists; *BUN,* blood urea nitrogen; *COPD,* chronic obstructive pulmonary disease; *Fio_2,* fraction of inspired oxygen; *Spo_2,* peripheral oxygen saturation.

MANAGEMENT

Atelectasis

The application of positive end-expiratory pressure (PEEP) has been shown to resolve atelectasis, as have successive recruitment maneuvers. Unfortunately, atelectasis will frequently redevelop after the positive pressure is discontinued. Early postoperative continuous positive airway pressure has been shown to improve postoperative atelectasis and reduce the need for reintubation. Many treatment modalities for atelectasis have been proposed, including deep breathing exercises, intermittent positive-pressure breathing, and incentive spirometry. Current literature suggests that all three modalities are equivalent in reducing postoperative pulmonary complications.

Pneumonia

If pneumonia is suspected as the cause of postoperative respiratory failure, early initiation of appropriate antibiotic coverage is crucial to improve patient survival. Delay in antibiotic initiation or selection of inadequate antibiotics has been shown to increase mortality several-fold. Patients who have been in the hospital or extended care facilities before surgery are at an increased risk for health care–associated pneumonia (HCAP), as well as multidrug-resistant organisms. Initial choice of empiric antibiotics in these patients should be broad and targeted toward organisms known to cause HCAP, such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Pseudomonas aeruginosa, Acinetobacter* spp., *Enterobacter* spp., and *Klebsiella pneumoniae.* Local patterns of resistance should also be considered when selecting appropriate antibiotic therapy. Once culture and sensitivity data are available, antimicrobial therapy should be narrowed accordingly.

Pulmonary Edema

The management of postoperative pulmonary edema is largely dependent on the underlying cause. Positive pressure ventilation increases intrathoracic pressure, reducing cardiac preload and afterload and thereby improving cardiac output. In cases of fluid overload, diuretics or ultrafiltration may be beneficial. Cardiogenic edema may require support with inotropes and will often require more invasive monitoring, such as central venous pressure or pulmonary artery pressure

measurements. Once the underlying cause of the edema has been addressed, oxygenation should improve as the lymphatic system removes the excess edema fluid.

Acute Respiratory Distress Syndrome

Management of ARDS is largely supportive, with an emphasis on avoiding further lung injury while maintaining adequate oxygenation. Although noninvasive ventilation is being used more frequently for patients with mild ARDS, most patients will require intubation and mechanical ventilation to support oxygenation and reduce work of breathing. A high fraction of inspired oxygen (Fio_2) has been shown to increase alveolar inflammation and worsen lung injury. Whenever possible, Fio_2 should be decreased to the lowest level necessary to maintain oxygenation. Recognizing that alveolar congestion leads to smaller lung volumes available for ventilation and a concomitant increase in dead space ventilation ratio, these patients must be ventilated with much smaller tidal volumes than their healthy counterparts. Low tidal volume ventilation with 6 to 8 mL/kg of predicted body weight (PBW; calculated for men as PBW [kg] = 2.3 [height (in) – 60] + 50 and for women as PBW [kg] = 2.3 [height (in) – 60] + 45.5) has become standard of care based on the findings of the ARDS Network trials, which showed a significant mortality benefit with low tidal volumes compared with higher tidal volume ventilation. PEEP is often used to improve oxygenation, but using high levels of PEEP (≥12 cm H_2O) does not seem to improve outcomes and may actually contribute to hemodynamic instability. Nevertheless, many practitioners continue to employ a moderately high PEEP strategy in managing patients with ARDS.

In patients with severe ARDS, judicious ventilator management may not be enough to ensure adequate oxygen delivery. Because the edema and consolidation of ARDS tends to favor the more dependent areas of the lungs, placing the patient in a prone position for long periods (≥16 hours per day) has been associated with improved oxygenation and decreased mortality risk. Neuromuscular relaxation within the first 48 hours has also been shown to reduce oxygen demand and improve mortality risk. The role of glucocorticoids in treatment of ARDS is still a topic of active debate. Several studies failed to show any improvement in patient outcome, although recent meta-analyses have suggested that methylprednisolone may confer a mortality benefit if used early in the course of ARDS. Without prospective confirmatory data, it is difficult to make a strong recommendation for steroids, but they may have a role in the treatment of ARDS.

Other advanced therapies have been suggested for postoperative respiratory failure, although there are limited data to support them. Inhaled prostacyclins (epoprostenol, iloprost) and inhaled nitric oxide (iNO) are potent pulmonary vasodilators that have been shown to improve oxygenation marginally, but extensive study has failed to show a mortality benefit for either therapy. Furthermore, these therapies are very costly, limiting their availability. In recent years, there has also been a substantial increase in the use of extracorporeal membrane oxygenation (ECMO) to support patients with respiratory failure. Although outcomes in patients on ECMO support have improved in recent years, it is still an invasive therapy with its own associated risks, and it is generally reserved for those patients in whom all other options have been exhausted.

PREVENTION

Intraoperative management can have a significant impact on postoperative pulmonary outcomes. Even in otherwise healthy patients, intraoperative lung-protective ventilation with low tidal volumes and moderate PEEP has been associated with decreased rates of postoperative respiratory failure and shorter hospital stays. The use of shorter-acting neuromuscular blocking agents has been associated with fewer postoperative pulmonary complications compared with long-acting agents. The relationship between incomplete reversal of neuromuscular blockade, postoperative respiratory failure, and mortality is well established in the literature, yet a significant proportion of anesthesiologists report that they do not follow evidence-based guidelines for monitoring train-of-four ratios at the time of neuromuscular blockade reversal.

Respiratory depression from narcotic medications is most pronounced in the first 24 hours after surgery. Patients with sleep-disordered breathing are particularly sensitive to opioid-induced respiratory depression and should be monitored closely for signs of impending respiratory failure. Neuraxial techniques may reduce the risk for postoperative pulmonary complications, although the data on this subject are conflicting.

Although no one approach can eliminate postoperative respiratory failure, meticulous attention to anesthetic technique can reduce the risk, particularly in patients with predisposing comorbidities or surgical procedures. Given the high morbidity, mortality, and cost associated with postoperative respiratory failure, even modest risk reductions can have very significant implications for individual patients and the health care system at large.

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Postoperative Urinary Retention

172

Eric Pan • D. Janet Pavlin

Case Synopsis

A 73-year-old man undergoes total hip arthroplasty performed under spinal anesthesia using 1.5 mL of 0.75% bupivacaine (11.25 mg) with 100 μg of morphine. The patient receives approximately 1500 mL of intravenous fluids during the 2-hour procedure. After 3 hours in the recovery room, he complains of moderate bladder fullness and strains to void 150 mL of urine. A postvoid ultrasound evaluation reveals a residual volume of 700 mL, and an indwelling catheter is placed. The urinary catheter is discontinued after 24 hours, and the patient resumes adequate, spontaneous voiding. He is discharged to home and has no further complications.

PROBLEM ANALYSIS

Definition

Postoperative urinary retention (POUR) is defined as the inability to adequately void in the presence of a full bladder. The normal adult bladder capacity is approximately 400 to 600 mL. Risk factors for POUR include the nature and location of surgery, type of anesthesia used, medications, and the patients' underlying physiology and medical conditions. Left untreated, it can cause incontinence, and when prolonged for several hours, it can cause bladder wall ischemia.

Knowledge of normal bladder function is a prerequisite to understanding how and why urinary retention occurs. Normal voiding is a reflex response to a full bladder—known as the micturition reflex (Box 172.1). It requires bladder distention followed by transmission of sensory input from the bladder to the midsacral region of the spinal cord, involuntary simultaneous contraction of the bladder, and reflex inhibition of the internal urethral sphincter. Micturition follows voluntary relaxation of the external urethral sphincter. Visceral sensory afferents from the bladder travel primarily in the pelvic splanchnic nerves and synapse in the midsacral spinal cord (S2–S4), with projections to the micturition center of the brain. The efferent limb consists of the following:

- Preganglionic parasympathetic fibers originating at S2–S4 travel in pelvic splanchnic nerves to peripheral cholinergic receptors within the bladder wall and stimulate bladder contraction during the active phase of voiding.
- Sympathetic efferent fibers originating from T10 to L2 travel via superior and inferior hypogastric plexuses to the internal urethral sphincter. Their output maintains sphincter tone during continence and is reflexively inhibited during voiding.
- Somatic efferent fibers course in the pudendal nerves to striated muscle of the external urethral sphincter, which must be voluntarily relaxed during voiding.

The micturition reflex is subject to modulation by higher brain centers, including the pontine micturition center (dorsolateral pons), areas of the diencephalon, and the cerebral cortex. Receptors in the spinal portion of the pathway are susceptible to modulation by opioids, acetylcholine, dopamine, serotonin, norepinephrine, γ-aminobutyric acid, excitatory and inhibitory amino acids, and other neuropeptides.

BOX 172.1 Neural Control of Voiding

Bladder distention
Visceral afferent fibers via pelvic splanchnic nerves
Synapse at the micturition center in the midsacral cord (S2–S4)
Parasympathetic efferent cholinergic fibers (arise at S2–S4, travel with the pelvic splanchnic nerves, synapse at cholinergic sites in the bladder wall, and then stimulate contraction)
Sympathetic efferent fibers (arise at T10–L2, travel via hypogastric plexuses to the internal urethral sphincter, and are involuntarily inhibited during voiding)
Somatic efferent fibers (travel via the pudendal nerve to striated muscle of the external urethral sphincter and are voluntarily relaxed during voiding)
The entire reflex arc is subject to control by the pontine micturition center and higher centers in the brain via the spinobulbar tracts

Recognition

The three primary methods of diagnosing POUR are history/physical examination, bladder catheterization, and ultrasound examination. Although the *specific* criteria used to define POUR vary from study to study (Box 172.2), the diagnosis is generally made in the presence of an inability to void completely with a full bladder and/or a significant postvoid residual bladder volume documented by catheterization or ultrasound.

History and physical examination, specifically the presence of lower abdominal pain and discomfort, with or without the presence

BOX 172.2 Commonly Used Criteria for Defining POUR

Patient discomfort, sensation of "full bladder"
Palpable bladder distention
Inability to void with full bladder
Inability to void 6–10 hours after Foley catheter removal
Inability to void 6–10 hours after the end of surgery
Need for bladder catheterization within the first 24–48 hours after surgery
Ultrasound assessment
  Inability to void with bladder volume ≥600 mL
  Residual volume ≥300–500 mL
Postvoid catheterization volume ≥200 mL

of a palpable bladder is commonly used to identify the presence of POUR, although neither is highly sensitive for detecting retention. Furthermore, preexisting patient comorbidities, as well as anesthetic and surgical factors, may mask the conventional signs and symptoms of POUR. In fact, one study reported that over 60% of patients admitted to the postanesthesia care unit after general anesthesia did not endorse symptoms despite bladder volumes in excess of 600 mL.

Intermittent and indwelling bladder catheterization can be both a diagnostic and therapeutic tool, although the procedures are not without risk. Possible complications include urethral trauma, infection, and patient discomfort and should be considered before proceeding to catheterization.

Bladder volume is readily assessed by ultrasound, and the current body of evidence generally supports its use. In the unconscious patient, a portable ultrasound scan may be the only practical, reliable, and noninvasive means of diagnosing urinary retention. One caveat, however, is that variability appears to be minimized when the same individual is performing the assessment, which indicates that consistent and reliable measurements require a standardized approach.

Although the duration of surgery and the amount of intraoperative fluids given are correlated with bladder volume at the end of surgery, the relationships are variable enough to limit their value in predicting bladder volume in individual patients. In one study, the correlation between surgery duration and urinary bladder volume after surgery was 0.32 ($P = .0002$). The correlation between intraoperative intravenous fluid volumes and urinary bladder volume was 0.26 ($P = .0021$). Interestingly, Pavlin and colleagues reported that when bladder volume measured by ultrasound was compared with characterization of the bladder as being empty, moderately full, or overdistended, patient estimates of volume were incorrect in 56% of cases, and nurses erred in 46% of cases.

Risk Assessment

Risk factors for POUR are listed in Box 172.3. Urinary retention is often related to the use of neuraxial blockade, and the incidence may be greater than 60% when long-acting local anesthetics are used. The effects on bladder function after spinal anesthesia with 10 mg of bupivacaine can last approximately 10 hours. Epidural morphine effects can last up to 16 hours. However, with low-dose, short-acting local anesthetics without vasoconstrictors or opiates (i.e., plain lidocaine or 2-chloroprocaine), the incidence is relatively low. Mulroy and colleagues reported POUR in 3 of 201 patients after using short-acting spinal or epidural anesthesia. Brouwer and colleagues recently published results comparing neuraxial to general anesthesia and demonstrated a twofold increase in risk of catheterization after spinal anesthesia with a short-acting local anesthetic, and a tenfold increase when using longer-acting agents.

Surgery within the lumbosacral nerve distribution can also contribute to urinary retention. Hernia repair and rectal surgery are commonly associated with urinary retention (14% to 35% for hernia repair; 1% to 52% for rectal surgery). Furthermore, urinary retention can be caused by surgical pain and increased sympathetic activity in the distribution of the lumbosacral nerves. Mechanical trauma to the urethra or preexisting outlet obstruction accounts for most cases of urinary retention after urologic surgery. Lumbosacral spinal cord pathology, as in patients with spinal cord injury, can experience interference of micturition or impairment of central coordination of voiding.

Mandatory recumbency is associated with an inability to void in some patients, and an incidence of 18% has been reported in patients confined to bed after foot surgery. Other factors including systemic opioids, anticholinergics, and excessive intravenous fluids can contribute to difficulty with micturition and POUR. A history of urinary retention also increases the likelihood of POUR. Mechanisms include any of the aforementioned causes possibly coupled with inherent differences in sensitivity to influences that tend to impair voiding.

BOX 172.3 Risk Factors for Urinary Retention

- Neuraxial local anesthetics
- Neuraxial or systemic opioid therapy
- Anticholinergics
- Preexisting obstructive symptoms (i.e., benign prostatic hypertrophy)
- Surgery of the lower urinary tract or surrounding area
- Surgery in a lumbosacral nerve distribution area (groin, perirectal, penile)
- Previous history of retention
- Spinal cord disease or dysfunction
- Recumbency
- Excessive fluid administration
- Age ≥50 years
- Male
- Prolonged surgical time
- Previous pelvic surgery

Implications

Overdistention of the bladder can cause pain, and incontinence may ensue. It can also cause a reflex-induced increase in sympathetic activity leading to systemic hypertension; this is more likely in patients with spinal cord transection (autonomic hyperreflexia). Studies in animal models have also shown that bladder overdistention can lead to bladder wall ischemia. If sustained for longer than 3 to 10 hours, urothelial cell damage, hemorrhage, and edema can occur. Ultimately, parasympathetic nerve ending loss, reduced parasympathetic activity, and eventual failure of the detrusor muscle to contract normally can result.

Symptoms of impaired parasympathetic activity include an inability to empty the bladder fully, leading to frequent, small voidings (frequency, nocturia), weak stream, hesitancy, dribbling, and bladder instability. Prolonged urinary stasis can lead to urosepsis. Most often, cellular regeneration will occur over several weeks, with eventual recovery of normal bladder function. However, intercellular junction rupture and interstitial collagen deposition can occur resulting in permanent impairment of impulse transmission throughout the bladder wall.

Complications of POUR aside, catheterization itself is associated with complications including infection and iatrogenic urethral injury. One institution reported an incidence of urethral injury of 3.2 per 1000 patients, some of whom experienced significant morbidity including recurrent stricture requiring multiple dilations. Protracted indwelling bladder catheter drainage has also been associated with an incidence of infection that is directly correlated with the duration of catheterization. Zaouter and colleagues reported a urinary tract infection rate of 14% in patients in whom an indwelling urinary catheter was used for the entire duration that thoracic epidural analgesia was used. This rate decreased to 2% when the urinary catheter was discontinued on the day of surgery.

MANAGEMENT

POUR typically results from overfilling of the bladder when the micturition reflex is impaired by anesthesia or surgery. Because this is usually temporary, some episodes of retention can be prevented simply by ensuring that the patient has an empty bladder before surgery and by avoiding excessive perioperative fluid administration. This

TABLE 172.1 Predicted Time to Achieve Critical Bladder Volume

	TIME (h) TO ACHIEVE >600 mL FOR >4 h	
Starting Residual Bladder Volume (mL)	Urine Formation at 50 mL/h	Urine Formation at 100 mL/h
0	16	10
100	14	9
200	12	8
400	8	6
600	4	4

is particularly relevant when either the surgery or the anesthetic is known to predispose to urinary retention or when there is a history of urinary retention.

Given that the normal rate of urine formation in adults is about 75 mL per hour, the time until a bladder is full (approximately 600 mL) is roughly 8 hours. Based on animal investigations, the critical duration for bladder overdistention to avoid potential neurologic injury is 4 hours. Thus clinicians can assume that it is undesirable to have an overdistended bladder for longer than 4 hours.

Table 172.1 shows the estimated time required to attain a bladder volume that exceeds 600 mL for 4 hours, assuming a rate of urine formation of either 50 or 100 mL per hour. Assuming an empty bladder at the outset, the critical time would be 10 hours at a rate of 100 mL per hour and 16 hours at a rate of 50 mL per hour. However, if the initial volume was 400 mL, the critical times would be 6 and 8 hours, respectively. Thus to avoid complications related to postoperative retention, the following steps are prudent:

- Ensure all patients void before surgery.
- Ensure postoperative patients void or are catheterized within approximately 8 to 10 hours of their last voiding.
- Use an indwelling catheter for procedures expected to last longer than 5 to 6 hours, assuming that the patient will be unable to void until 1 to 2 hours after surgery.

Though pharmacologic treatment of POUR is generally not within the purview of most anesthesiologists, it is worth mentioning that several medications have been used including cholinergic agents, α-blockers, sedatives, and prostaglandins. In a recent review by the Cochrane Collaboration, no significant improvement was seen with the use of cholinergic agents, α-blockers, or sedative medications when employed as monotherapies. However, a significant association exists between successful treatment and the use of intravesically administered prostaglandin, as well as cholinergic agents, when used in conjunction with sedative agents.

PREVENTION

If a patient has not voided within 6 to 8 hours of his or her last voiding, the bladder volume should be assessed before the patient leaves the recovery room. Bladder volume can be determined noninvasively by ultrasound, and it should be drained if the volume is more than approximately 600 mL. Alternatively, if a scanner is not available, bladder volume can be assessed by palpation and the bladder emptied by in-out catheter drainage. This is especially important in patients with known POUR risk factors.

It is worth noting that the volume at which catheterization should be used is not well defined. In an effort to quantify a patient's individual bladder volume at which he or she should undergo catheterization, Brouwer and colleagues had patients measure their maximum bladder capacity in the weeks leading up to surgery. Using this as the trigger, rather than an arbitrary volume threshold (500 mL), a significant decrease in the incidence of catheterization was found, with the most pronounced effect in patients younger than 60 years old.

For outpatient surgery, a decision must be made whether patients should be required to void before discharge. At least two studies suggest that patients without underlying risk factors for urinary retention should be allowed to go home without voiding before discharge. In such patients, the incidence of urinary retention is reported as less than 1%. In patients with risk factors for urinary retention, it is prudent to require them to void before discharge, as well as check the postvoid residual to demonstrate that the bladder is indeed empty. This can prevent a potentially overdistended bladder if the patient fails to seek medical attention in a timely manner. Thus patients having rectal, groin, or urologic surgery and/or those with spinal cord disease or a history of urinary retention should be required to void or be catheterized before discharge.

After spinal or epidural anesthesia, patients should be required to void or be catheterized, with some possible exceptions. Patients who have had neuraxial blocks with short-acting local anesthetics (i.e., lidocaine or 2-chloroprocaine) can be safely discharged without voiding if a bladder scan reveals a bladder volume of less than 400 mL at the time of discharge. Owing to the short duration of action of these two agents, it is almost certain that any residual effects of local anesthetic will resolve before a "critical volume" is exceeded for longer than 4 hours. However, patients who have received longer-acting agents (e.g., bupivacaine) or neuraxial opioids should not be discharged without voiding or having catheter drainage of the bladder.

As mentioned, high-risk patients who do void should have a postvoid residual volume checked to ensure that the bladder is indeed empty. In many cases, voiding by straining results in expulsion of a small quantity of urine, and residual volume may still exceed 400 to 600 mL as the micturition reflex may not have fully recovered. If an ultrasound scan is unavailable, one can reasonably suspect a high postvoid residual volume (>400 mL) if the patient has voided less than 300 mL. Patients should be requested to stay until they have voided again and fully emptied their bladder. Alternatively, the bladder can be drained by in-out catheterization to ensure an empty bladder before discharge. Finally, all outpatients, both high and low risk, should be instructed to return to a medical facility if they are unable to void within 8 to 10 hours of discharge from the hospital. Similar protocols should also be adopted for patients who are admitted to a hospital ward after being discharged from the recovery room.

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Perioperative Visual Loss 173

Kerri M. Wahl

Case Synopsis

A 49-year-old man weighing 125 kg is scheduled for decompression laminectomy and instrumented fusion of the lumbar spine at multiple levels for lumbar stenosis. General anesthesia proceeds uneventfully with prone positioning, and the patient's face and eyes are protected from direct pressure with a horseshoe headrest. Somatosensory evoked potentials are monitored intraoperatively. The surgery lasts 8 hours with an estimated blood loss of 2.5 L, replaced with intravenous (IV) blood transfusion, crystalloid, and antifibrinolytic therapy. The lowest hematocrit reading is 25%. On postoperative day 2, the patient complains of blurred vision in both eyes.

PROBLEM ANALYSIS

Definition

Perioperative visual loss (POVL) associated with spine surgery has been reported as 1 in 500 operations (0.2%). POVL refers to permanent impairment or total loss of sight associated with a surgical procedure during which general anesthesia is administered. The perioperative period includes the time period from the immediate preoperative assessment through discharge from the acute health care facility.

The American Society of Anesthesiologists (ASA) Closed Claims Project (www.asaclosedclaims.org) established the Postoperative Visual Loss Registry in 1999 in an attempt to identify risk factors in patients who develop visual deficits within 7 days after nonophthalmic surgery. The most common cause of ocular injury is corneal abrasion, which may or may not be associated with visual loss. The common causes of permanent POVL are ischemic optic neuropathy (ION), central retinal artery occlusion, and cerebral visual loss. A variety of causes or contributing factors have been suggested, including the following:

- Preoperative conditions such as vascular risk factors (atherosclerosis, diabetes mellitus, hypertension, coronary artery disease); anemia, morbid obesity, male sex, age over 50 years; unusual anatomy of the eye, the optic nerve, and its blood supply
- Elevated venous pressure in the head and neck for prolonged durations (prone surgery or head-down position)
- Specific types of surgical frames that may increase the venous pressure in the head
- Prolonged procedures (exceeding 6.5 hours) in the prone or head-down position with substantial blood loss (average of 44.7% of estimated blood volume) and administration of large amounts of crystalloid
- Hypotension
- Anemia

Since the Food and Drug Administration approved the use of spinal interbody cages in 1996, spinal instrumentation has resulted in longer operative times and increased surgical blood loss. Additional perioperative risk factors include use of tranexamic acid, fluid management (crystalloid versus colloid), facial swelling, external globe compression, emboli, adverse drug effects, use of vasoconstrictors such as epinephrine, and infrequently deliberate hypotension. None of these factors has been causally linked to visual loss in randomized controlled trials or animal studies.

Less common causes of POVL include acute angle-closure glaucoma, retrobulbar hematoma, pituitary apoplexy, posterior reversible encephalopathy syndrome, and glycine-induced visual loss.

Recognition

Corneal abrasion that manifests with painful eye is the most common perioperative ocular complication. The reported incidence ranges from 0.1 to 1 event per 1000 general anesthetics. The mechanisms of perioperative injury are based on direct trauma of the corneal epithelium (corneal abrasion), corneal drying, or blockage of the outflow of aqueous fluid with acute rise in intraocular pressure (angle-closure glaucoma). Patients with incomplete lid closure or those with protruding eyes may be at increased risk. The type of anesthesia provider has been reported to be significant, with higher rates of injury found among student registered nurse anesthetists compared with certified registered nurse anesthetists and residents.

ION is the most frequently cited cause of permanent POVL in adults after nonocular surgery. It is more common after cardiac, spine, and orthopedic procedures compared with abdominal surgery. It has also been reported after bilateral radical neck procedures and in cases performed in the steep Trendelenburg position, such as laparoscopic gynecologic and urologic procedures. Major tertiary care centers that perform extensive spinal reconstruction procedures report rates of ION ranging from 0.28 to 1.2 per 1000 spine surgeries.

ION may be arteritic (e.g., giant cell arteritis due to systemic vasculitis) or nonarteritic (e.g., postoperative ION). Postoperative ION has two types: anterior ischemic optic neuropathy (AION), from ischemia to the anterior portion of the optic nerve supplied from the short posterior ciliary arteries and peripupillary choroid; and posterior ischemic optic neuropathy (PION), which results from an infarction of the retrobulbar optic nerve that receives its blood supply from the pial capillary plexus.

Postoperative AION is most common after cardiac surgery but also occurs after major vascular procedures, prone spinal fusion surgery, and head and neck procedures. Affected patients present with a wide range of visual acuities and visual field defects. The optic disc is initially swollen, which gradually evolves into optic atrophy over the ensuing month. This is a multifactorial disease that affects middle-aged patients who have a morphologically small or crowded optic nerve head, the so-called "disc-at-risk" configuration. Other risk factors for ischemic damage to the optic nerve include diabetes, high cholesterol,

smoking, physiologic nocturnal arterial hypotension, an inability to properly autoregulate optic nerve head blood flow, and interindividual variations in the vascular supply of the optic nerve head.

Postoperative PION is more common than AION after spinal surgery. Patients present with visual acuity ranging from normal to no light perception or with optic nerve–related visual field defects. Early funduscopic examination in PION is normal, but after about 5 to 6 weeks the optic discs became pale from atrophy. The pupillary light reflex becomes delayed or absent. Bilateral involvement occurs in more than 50% of patients, with some recovery in 40% to 45% of cases. Diagnostic studies include ophthalmic examination (visual acuity, intraocular pressure, color testing, visual fields, pupillary reflexes, funduscopy with pupillary dilation), fluorescein fundus angiography, and optic nerve enhancement on magnetic resonance imaging (MRI). Computed tomography (CT) is not useful for the diagnosis of ION. Visual evoked potentials are useful before optic disc pallor is detectable but cannot be used as an intraoperative monitor of optic nerve function owing to the effects of general anesthesia (intravenous or volatile).

Central retinal artery occlusion (CRAO) causes sudden, acute, persistent, and painless loss of vision in the range of counting fingers to light perception in 90% of patients. CRAO is found in 1 per 10,000 outpatient visits. Of these patients, 1% to 2% present with bilateral involvement. The classic funduscopic findings of a "cherry-red spot" with surrounding pale retina may take hours to develop. The most likely cause of CRAO is embolism of cholesterol, but it also can be calcific, bacterial, or talc from IV drug abuse. Profound hypotension and prolonged globe compression may also lead to CRAO.

Cerebral or cortical visual loss is usually caused by embolic infarction of the occipital cortex (usually unilateral) or profound hypotension and/or hypovolemia resulting in ischemia in the parietooccipital watershed zones (bilateral). Postoperative cerebral visual loss is more common in patients less than 18 years of age (4.3 per 10,000 cases) compared with 0.38 per 10,000 discharges after cardiac, spinal fusion, nonfusion orthopedic, and abdominal surgery. With bilateral infarction, the patient may be completely blind or have only small areas of preserved central vision. With unilateral infarction, the patient presents with a contralateral homonymous hemianopia. Pupillary light reflexes and funduscopic examination are normal. CT or MRI of the brain will show infarction in the distribution of the posterior cerebral artery or parietooccipital watershed regions.

Risk Assessment

For "patients in whom prolonged procedures, substantial blood loss, or both are anticipated, there is a small, unpredictable risk of perioperative visual loss" (ASA Task Force, 2012).

The etiology of ION remains unknown, and the majority of the literature on perioperative ION after spine surgery is based on case reports and retrospective studies. In 2006, the ASA Committee on Professional Liability published an in-depth analysis of 93 cases (72% of all registry cases) associated with spine surgery in the prone position from the ASA POVL Registry. Ischemic optic neuropathy was the cause of visual loss in 83 (89%) of these cases (56: PION, 19: AION, 8: unspecified) and CRAO in the remaining 10 POVL cases. The mean age of patients with ION was 50 ± 14 years, and most patients were relatively healthy males. Blood loss of 1000 mL or greater or anesthesia duration of 6 hours or longer was present in 96% of these cases. Mayfield pins supported the head in 16 of 83 cases, which demonstrated that ION occurs in the absence of pressure on the globe. The findings are consistent with the lack of retinal ischemia on ophthalmologic examination in ION. Moreover, the occurrence of ION in both eyes in the majority of cases (55 patients) is more consistent with a systemic etiology, rather than globe compression that usually affects only one eye. Complete visual loss in the affected eye(s) occurred in 47 cases. The ASA Task Force (2012) believes that there is no pathophysiologic mechanism by which facial edema can cause perioperative ION. In addition, there is no evidence that ocular compression causes isolated perioperative anterior ION or posterior ION. Direct pressure on the eye should be avoided to prevent CRAO.

Autoregulation of blood flow in the cerebral circulation has been well demonstrated in humans. It is not clear whether the optic nerve also has the ability to autoregulate in both anterior and posterior regions. Twenty-seven percent of cases used deliberate hypotension to decrease blood pressure with the goal of reducing blood loss. The occurrence of ION in many cases without apparent hypotension makes the role of blood pressure management unclear. It has been hypothesized that prone positioning may increase venous pressure within the optic nerve and intraocular pressure. High venous pressure and interstitial tissue edema may then compromise blood flow in the optic nerve due to a "compartment syndrome." Proponents of this hypothesis have recommended a head-up body position and colloid-based fluid resuscitation in prone surgery to decrease the potential for interstitial edema around the optic nerve.

Implications

An updated practice advisory was released by the ASA Task Force on Perioperative Visual Loss in 2012 with the following recommendations:

Preoperative patient evaluation and preparation:

1. Identifiable preoperative risk factors include anemia, prolonged procedures, and/or substantial blood loss.
2. There are no identifiable patient characteristics that predispose patients to POVL.
3. There is no evidence that an ophthalmic or neuroophthalmic evaluation is useful in identifying at-risk patients.

Intraoperative management:

1. Blood pressure management: systemic blood pressure should be monitored continually in high-risk patients; the use of deliberate hypotensive techniques during spine surgery has not been shown to be associated with POVL and should be determined on a case-by-case basis.
2. Management of intraoperative fluids: central venous pressure monitoring should be considered in high-risk patients; colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss.
3. Management of anemia: hemoglobin or hematocrit values should be monitored; the transfusion threshold for preventing POVL is unknown.
4. Use of vasopressors: the prolonged use of high-dose α-adrenergic agonists should be made on a case-by-case basis.
5. Patient positioning: avoid direct pressure on the eyes; high-risk patients should be positioned so that the head is in a neutral forward position, level with or higher than the heart.
6. Staging of surgical procedures: consideration should be given in high-risk patients.

Postoperative management:

The consensus of the Task Force was that a high-risk patient's vision should be assessed when the patient becomes alert. If there is concern regarding suspected ION and potential visual loss, an urgent ophthalmologic consultation should be obtained to determine its cause. Additional management may include adjusting hemoglobin or hematocrit values upward, increasing blood pressure, and administering oxygen. To rule out intracranial causes of visual loss, consider magnetic resonance imaging. The Task Force believes that there is no role for antiplatelet

agents, steroids, or intraocular pressure–lowering agents in the treatment of perioperative ION.

Deliberate hypotensive techniques:

Blood pressure management of high-risk patients depends on multiple patient characteristics, such as preoperative chronic hypertension, cardiac dysfunction, and renal and vascular disease. In addition, there are many intraoperative factors such as fluid management, rate of blood loss, hypotension, and administration of vasopressors that affect blood pressure management. Case reports indicate POVL occurring after procedures in which intraoperative hypotension was maintained for patients without hypertension or for patients with well-controlled chronic hypertension. The use of deliberate hypotension techniques in this patient population is controversial. It has been suggested that deliberate hypotension may be used in patients without preoperative chronic hypertension if the blood pressure is maintained on average within 24% (0% to 40%) of estimated baseline mean arterial pressure or with a minimum systolic blood pressure of 84 mm Hg.

MANAGEMENT

Perioperative visual loss is a devastating complication that is most frequently reported after major spinal fusion surgery in the prone position, cardiopulmonary bypass, and lower extremity joint replacement surgery. Ischemic optic neuropathy is the commonest cause. Early consultation with an ophthalmologist is strongly advised. At this point, preventive strategies appear to be the best option to reduce this complication, as effective treatment has not been identified. Independent risk factors associated with ION after spinal fusion surgery include male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and lower percent colloid administration (ASA Task Force, 2012).

Further Reading

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174 Postpartum Headache Other Than Post–Dural Puncture Headache

David Wlody

Case Synopsis

A 24-year-old primigravida underwent cesarean section for breech presentation under uncomplicated spinal anesthesia performed with a 27-gauge Whitacre needle. On the second postpartum day, she complained of a severe, diffuse headache. On the third postpartum day, she suffered a grand mal seizure. The obstetrician believes the headache is a spinal headache, and the anesthesiologist is consulted.

PROBLEM ANALYSIS

Definition

Postpartum headache has been defined as any headache occurring during the first 6 weeks after delivery. Such headaches can be caused by a preexisting condition, may be a manifestation of an intrapartum event, or can be due to an unrelated disorder arising coincidentally in the postpartum period. There is a natural inclination, particularly on the part of patients and obstetricians, to blame any postpartum headache on a neuraxial anesthetic, but not all postpartum headaches are post–dural puncture headaches, even when a large-gauge dural puncture is known to have occurred. This chapter discusses the most common causes of headache in the postpartum period, as well as some less common conditions whose misdiagnosis can lead to a potentially catastrophic outcome.

Recognition

Although the incidence of a particular type of headache may be different in women who have recently delivered, any headache that is seen in the general population can occur in the postpartum period. In 2013 the International Headache Society published a beta version of the third edition of its diagnostic and classification criteria. A complete discussion of these criteria is beyond the scope of this review, but the division of headaches into primary and secondary provides a useful framework for discussion (Box 174.1).

Primary Headache (i.e., No Other Causative Disorder)

Migraine

Migraine is divided into two main subtypes: migraine with aura and migraine without aura. In the former, reversible neurologic symptoms develop gradually over 5 minutes or longer and last for less than 60 minutes. These symptoms are typically visual; they include flashes of light, a blind spot with shimmering edges ("scintillating scotomas"), or formations of zigzag lines. Numbness of the face or weakness of an arm or leg may also occur. Speech disturbances including aphasia are occasionally described. Otherwise, the characteristics of the two subtypes are similar:

- Unilateral location
- Pulsating quality
- Aggravation by routine physical activity
- Associated with nausea and/or photophobia and phonophobia

Migraine headaches usually begin in adolescence and occur in up to 6% of men and 17% of women. Although there is not a consistent mendelian pattern of inheritance, there is clearly a familial propensity to migraine; migraine is up to 3 times more common in relatives of migraineurs than in those without any family history of migraine.

The increased incidence of migraine in women suggests a hormonal influence. Up to 50% of women describe an association between migraine and menstruation, which appears to be related to changes in estrogen levels. Most women experience a decreased frequency of migraine during pregnancy, especially in the second and third trimesters. This effect is most pronounced in women with migraine without aura. It is common for migraines to recur early in

BOX 174.1 Classification of Postpartum Headache

Primary Headache
Migraine (with or without aura)
Tension-type headache

Secondary Headache
Headache attributed to cranial vascular disorders
- Intracranial hemorrhage
- Cerebral venous and sinus thrombosis

Headache attributed to nonvascular intracranial disorders
- Tumor
- Idiopathic intracranial hypertension
- Pneumocephalus

Headache attributed to a substance or its withdrawal
Headache attributed to disorder of homeostasis
- Preeclampsia
- Metabolic disorders

Headache from infectious causes
- Meningitis
- Sinusitis

Data from Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 33(9):629-808, 2013.

the postpartum period. New-onset migraine during pregnancy or postpartum is unusual and bears close investigation to ensure that another less benign process is not the cause.

Tension-Type Headache

This is the most common type of headache, with a reported lifetime prevalence as high as 69% in men and 88% in women. The least studied of the primary headache disorders, once thought to be primarily psychogenic, it is now being recognized as having an organic basis, possibly through peripheral activation of myofascial nociceptors and, in patients who develop chronic tension headache, central sensitization. Tension-type headache is subdivided into infrequent, frequent, and chronic subtypes, which are defined by the number of episodes suffered per month. They otherwise share the following characteristics:

- Bilateral location
- Pressing, nonpulsating quality
- Not aggravated by routine physical activity
- Mild to moderate intensity
- Absence of nausea, photophobia, and phonophobia

Like migraine, tension headaches are more common in women. Unlike migraine, they seldom begin in adolescence, but are more likely to occur in middle age. They are also associated with chronic anxiety or depression. The relationship between tension headache and pregnancy has not been extensively investigated, and although some studies have suggested a decreased frequency during pregnancy, this decrease is not seen to the same extent as in migraine.

Secondary Headache (i.e., New Headache Occurring in Close Temporal Relation to a Disorder Known to Cause Headache)

Headache Attributed to Cranial Vascular Disorders

Intracranial hemorrhage. This includes subarachnoid hemorrhage, intracerebral (parenchymal) hemorrhage, or subdural hematoma. Characteristics of headache secondary to intracranial hemorrhage include the following:

- Sudden onset
- Intense severity
- May be associated with focal signs or alterations in the level of consciousness

The incidence of spontaneous subarachnoid hemorrhage does not appear to be greater in pregnant women than in other populations. About 75% are due to a ruptured berry aneurysm, and the remainder are due to bleeding arteriovenous malformations. Hypertension and proteinuria are not uncommon, and subarachnoid hemorrhage can therefore be confused with preeclampsia. Intracerebral hemorrhage is usually seen in the setting of severe preeclampsia or eclampsia. Subdural hematoma has been reported in the setting of post–dural puncture headache; decreased intracranial pressure presumably leads to rupture of bridging veins.

Cerebral venous and sinus thrombosis. Cerebral venous thrombosis is estimated to occur in 1 per 2500 to 10,000 deliveries. Pregnant women, in fact, represent an extremely large proportion of patients presenting with cerebral venous thrombosis. The hypercoagulable state produced by pregnancy is a contributing factor; patients should also be evaluated for the presence of a hereditary thrombophilia (protein S or C deficiency, factor V Leiden). Nearly 80% of cases occur during the first two postpartum weeks, but it has been reported as late as 3 months postpartum. Features of headache secondary to intracranial thrombosis vary depending on whether a large sinus or an isolated cortical vein is thrombosed. With the former, headache, seizures, intracranial hypertension (due to impaired absorption of cerebrospinal fluid), and alterations in the level of consciousness are common. When a cortical vein is thrombosed, focal motor and sensory deficits and seizures are more likely to be seen. Interestingly, there are several reported cases of intracranial thrombosis that were initially treated as dural puncture headaches; the presence of signs and symptoms suggesting intracranial hypertension should lead to a more aggressive workup before epidural blood patch is performed. Magnetic resonance imaging and magnetic resonance angiography are considered the gold standard for diagnosing intracranial thrombosis. Although controversial, there is some evidence that a normal D-dimer level excludes cerebral venous thrombosis.

Venous thrombotic occlusion leads to increased capillary pressure, often causing hemorrhagic infarcts. With recanalization of the vessel, capillary pressure decreases, and further hemorrhage is prevented. Although heparin has no thrombolytic properties, it prevents further propagation of thrombus; therefore its use is indicated, even in patients with preexisting hemorrhage. Anticonvulsants are typically reserved for patients with evidence of hemorrhage or focal neurologic deficits.

Headache Attributed to Nonvascular Intracranial Disorders

Intracranial neoplasm. Features of headache associated with intracranial neoplasm include the following:

- Diffuse, nonpulsating
- Often associated with nausea or vomiting
- Worsened by physical activity, Valsalva maneuver, coughing, or sneezing

The incidence of brain tumor is not increased in pregnancy, but it is not unusual for symptomatology to first become manifest during pregnancy, secondary to increased extracellular fluid. There is also a well-established hormonal influence on certain tumors, particularly meningiomas and pituitary adenomas. Symptomatology will be influenced by location, size, and the presence of elevated intracranial pressure.

Idiopathic intracranial hypertension (IIH). Previously known as benign intracranial hypertension or pseudotumor cerebri, this disorder is most commonly seen in obese young women, suggesting a hormonal component. It is characterized by the following:

- Diffuse, nonpulsating pain
- Daily occurrence
- Aggravated by coughing

Patients are alert and may have a normal neurologic examination. The most common neurologic findings are papilledema, VI nerve palsy, and visual field defects, which are progressive if the patient is untreated. IIH is a diagnosis of exclusion, and other intracranial, metabolic, toxic, or hormonal diseases must be ruled out. It is not unusual for IIH to present for the first time during pregnancy, and symptoms typically worsen in patients with previously recognized disease. Improvement can be expected after delivery.

Pneumocephalus. The use of air to identify the epidural space is sometimes complicated by its accidental subarachnoid injection. The headache usually occurs immediately after injection, can be quite intense, and is worsened by the upright position. Plain skull films can easily identify intracranial air. Absorption can be accelerated by administering 100% oxygen.

Headache Attributed to a Substance or Its Withdrawal

Headache is common during magnesium sulfate therapy, particularly during the loading dose. In patients consuming more than 200 mg/day of caffeine, sudden cessation can lead to a headache that is relieved within 1 hour by administration of caffeine. Cessation of chronic opioid therapy can lead to headache within 24 hours. It has been suggested that abrupt termination of corticosteroids, tricyclic antidepressants, and nonsteroidal antiinflammatory drugs can lead to headache.

Headache Attributed to Disorder of Homeostasis

Preeclampsia/eclampsia. Headache is, of course, a hallmark of severe preeclampsia, and may be a precursor to the development of eclampsia. Typical features include the following:

- Bilateral, pulsating quality
- Aggravated by physical activity
- Accompanied by hypertension and proteinuria
- Visual disturbances (blurred vision, scotomas)

Headache associated with preeclampsia generally occurs before delivery but may present in the postpartum period. Such patients are at risk of developing eclampsia and should be carefully monitored.

Metabolic disorders. Fasting can precipitate headache, even in the absence of hypoglycemia. Approximately 30% of patients with chronic hypothyroidism have a generalized, nonpulsatile headache that responds to thyroid replacement therapy.

Headache From Infectious Causes

Meningitis. Features of headache secondary to meningitis include the following:

- Diffuse, progressively increasing pain
- Altered level of consciousness
- Fever
- Nuchal rigidity
- Nausea, vomiting, photophobia

Meningitis is an exceedingly rare complication of regional anesthesia, but the failure to diagnose and treat it in a timely fashion can have catastrophic consequences. Post–dural puncture headache shares many characteristics with headache due to meningitis. Diagnostic lumbar puncture should be seriously considered in patients with a presumed post–dural puncture headache accompanied by fever, leukocytosis, and meningismus; initiation of broad-spectrum antibiotic therapy should be considered pending definitive identification of a causative organism, if any.

Sinusitis. Headache due to sinusitis is often accompanied by purulent nasal discharge and fever. Tenderness over the affected sinus is common. Chronic sinusitis is not considered a likely cause of headache in the absence of an acute exacerbation.

Risk Assessment

Headache can occur at any time in the peripartum period, and it is extraordinarily common after childbirth. Patients with a history of headache or depression are at particularly high risk. Patients with preeclampsia or known intracranial pathology must be carefully evaluated, particularly if the headache is of greater than usual severity, and especially if there are any accompanying neurologic deficits.

Implications

Postpartum headache is not necessarily related to regional anesthesia, even in those patients known to have sustained a large-bore accidental dural puncture. Other causes for headache must be considered before epidural blood patch, especially when atypical features are present, such as fever, leukocytosis, or focal neurologic deficit. Vigilance must be particularly intense when the headache fails to respond to blood patch.

MANAGEMENT

Management of postpartum headache depends on etiology and is summarized in Table 174.1.

TABLE 174.1 Management of Postpartum Headache

Etiology	Treatment
Migraine headache	β-Blockers, tricyclic antidepressants, serotonin receptor agonists; avoid known triggering agents; avoid ergot alkaloids in nursing mothers
Tension headache	Analgesics, tricyclic antidepressants
Intracranial hemorrhage	Decompressive surgery
Cerebral venous and sinus thrombosis	Anticonvulsants, anticoagulants
Intracranial neoplasm	Mannitol, glucocorticoids, surgery
Idiopathic intracranial hypertension	Glucocorticoids, carbonic anhydrase inhibitors, lumbar puncture
Pneumocephalus	Analgesics, denitrogenation
Headache attributed to a substance or its withdrawal	Avoidance or adjustment of dosage of causative agents
Preeclampsia	Antihypertensives, magnesium sulfate
Headache associated with metabolic disorders	Correction of metabolic derangement
Infectious	Antibiotics

PREVENTION

- Migraine headache sufferers should avoid known triggering agents such as red wine, cheese, and cured meats.
- Chronic analgesic therapy should be maintained to avoid rebound headache.
- Aggressively control blood pressure in patients with preeclampsia.
- Maintain strict sterile technique during neuraxial anesthesia to minimize the risk of infectious complication.

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Psoas Compartment Block: Potential Complications

175

Daryl S. Henshaw • Robert S. Weller

Case Synopsis

A 68-year-old man with a history of atrial fibrillation was scheduled for left total hip arthroplasty. He was chronically anticoagulated with 10 mg of rivaroxaban (Xarelto) daily to decrease his risk of stroke and thromboembolism, and this medication was stopped 72 hours before his arrival for surgery. Preoperative laboratory studies demonstrated a hemoglobin of 13 g/dL, a platelet count of 175 × 10^3/μL, creatinine of 0.9 mg/dL, and a glomerular filtration rate greater than 60 mL/min/1.73 m^2. A posterior approach lumbar plexus block (psoas compartment block) was performed for postoperative pain control, and a subarachnoid block was performed for surgical anesthesia; both blocks were uncomplicated. His vital signs remained stable, estimated blood loss was 300 mL, and the surgery and recovery room stay were uneventful. Eighteen hours later, on the morning of postoperative day 1, rivaroxaban 10 mg daily was restarted. Throughout the day, his blood pressure gradually declined from his usual 140/90 to 95/55 mm Hg, and he became confused and oliguric. He received several 500-mL normal saline fluid challenges. The blood pressure improved, but urine output remained low. The next morning, his hemoglobin was 7.3 g/dL, and 2 units of packed red blood cells were given. Repeat hemoglobin was 7.7 g/dL. He was moved to the intensive care unit, rivaroxaban was discontinued, and a computed tomography (CT) scan of the abdomen showed a large left retroperitoneal hematoma.

PROBLEM ANALYSIS

Definition

Retroperitoneal hemorrhage (RPH) is bleeding into the potential space posterior to the parietal peritoneum, which may occur following psoas compartment block (PCB) as a result of an arterial injury combined with abnormalities of coagulation. The large potential retroperitoneal space, containing loose areolar tissue and extending from diaphragm to pelvis, can accommodate a significant amount of blood before a tamponade effect occurs.

The major causes of RPH are traumatic and iatrogenic. Additionally, spontaneous RPH is possible and is most common in patients who are on anticoagulation therapy or hemodialysis, and in those who have underlying bleeding abnormalities. In fact, spontaneous iliopsoas hemorrhage with femoral nerve palsy is the most common nerve palsy caused by spontaneous bleeding in hemophiliacs. The incidence of spontaneous RPH is increased sixfold in patients on oral anticoagulant therapy. All of the reported cases of RPH after a PCB have been associated with abnormal coagulation and/or the use of anticoagulant medications.

Recognition

Retroperitoneal bleeding is deep, concealed, and rarely becomes obvious until significant blood loss has occurred. Signs and symptoms of RPH depend on the rate and extent of bleeding and whether the hematoma compresses adjacent structures.

The most common signs of retroperitoneal hemorrhage are hypotension and tachycardia due to intravascular volume depletion, as well as anemia (Box 175.1). Initially, hypotension and tachycardia may respond transiently to fluid administration. Ultimately, the patient may develop hemorrhagic shock with oliguria and mental status changes. Although oliguria can also result from ureteral obstruction, retroperitoneal hematoma usually does not extend across the midline and would not be expected to compress both ureters. Therefore oliguria is more commonly due to hypovolemia.

Additional symptoms of retroperitoneal hematoma may include abdominal, flank, groin, or leg pain; a palpable abdominal mass; and lumbar plexus irritation or dysfunction. Spontaneous RPH of renal origin, known as Wünderlich syndrome, has been classically associated with Lenk's triad of flank pain, a palpable abdominal mass, and hypovolemic shock. Over time, patients may also develop either periumbilical (Cullen's sign) or flank ecchymoses (Grey Turner's sign; Fig. 175.1), but these are often late sequelae.

In one case series and literature review involving spontaneous RPH in patients on anticoagulation, 83% of patients had abdominal pain, 44% had severe hypotension or shock, 40% had a palpable abdominal

BOX 175.1 Signs and Symptoms of Retroperitoneal Hemorrhage

- Hypotension
- Anemia
- Shock
- Abdominal, flank, groin, or leg pain
- Palpable mass
- Femoral neuropathy
- Flank ecchymosis (Grey Turner's sign)
- Periumbilical ecchymosis (Cullen's sign)

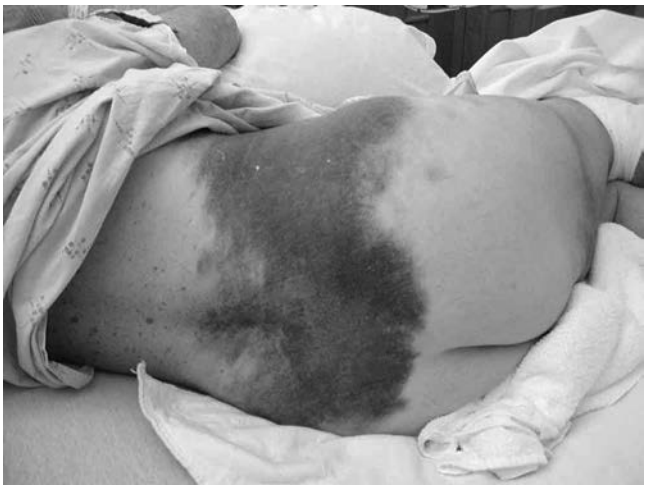

Fig. 175.1 Patient in the left lateral decubitus position showing widespread flank ecchymoses (Grey Turner's sign) due to retroperitoneal hematoma after psoas compartment block.

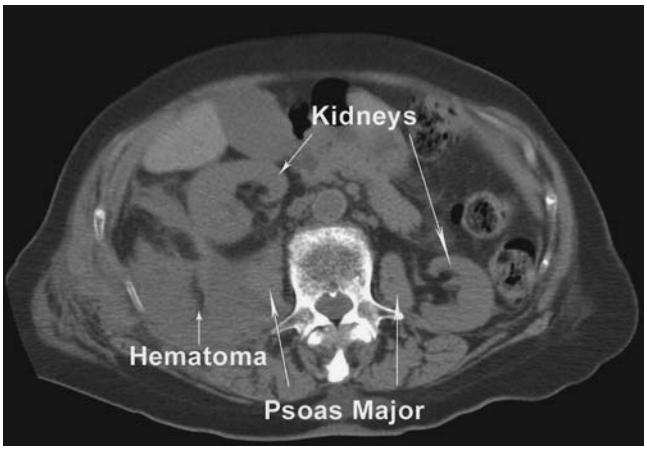

Fig. 175.2 Abdominal computed tomography scan showing a large retroperitoneal hematoma after psoas compartment block.

mass, and 29% had neuropathy. In another series looking at RPH after cardiac catheterization, 64% of patients had hypotension (systolic blood pressure <90 mm Hg), and 73% showed progressive anemia. Additionally, 45% of patients in this group complained of pain in the lower extremity, and 55% had femoral nerve palsy.

Because the signs and symptoms of RPH are mainly nonspecific and may appear gradually, an astute clinician must have a high level of clinical suspicion to make an early diagnosis of RPH after PCB. The more common etiologies and differential diagnosis for hypotension and anemia hours after hip surgery with PCB include inadequate surgical blood loss replacement or continued surgical bleeding. Perioperative hypotension and tachycardia may also be a result of sepsis, but anemia is usually absent and fever present. After patient resuscitation and elimination of more common causes of perioperative hypotension/hypovolemia, an abdominal CT should be performed, as it is highly sensitive for demonstrating RPH formation (Fig. 175.2).

Risk Assessment

The translumbar, posterior psoas approach to lumbar plexus block or PCB was first described in 1974. Since that time several modifications to the approach and landmarks have been suggested. The most popular contemporary approach for PCB requires the use of a nerve stimulator to identify the femoral nerve component of the lumbar plexus by motor stimulation of the quadriceps muscle. More recently, several approaches using ultrasound guidance have been described, but using ultrasound guidance may not always be possible in obese patients given the depth of the lumbar plexus and the current resolution limitations of ultrasound.

BOX 175.2 Complications After Psoas Block

- Retroperitoneal hematoma
- Renal injury and subcapsular hematoma
- Intrathecal, epidural, intradiscal, or intraabdominal catheter placement
- Femoral neuropathy
- Epidural spread
- Total spinal anesthesia with cardiac arrest
- Systemic toxicity with cardiac arrest
- Death

When considering a PCB as a component of surgical anesthesia or postoperative analgesia, one must take into account its success rate, benefits, and risks compared with those of alternative techniques. The analgesic benefit of PCB after hip replacement surgery has been well established. PCB has been shown to decrease pain scores and opioid consumption compared with systemic opioid therapy and to decrease perioperative blood loss. With respect to risk, however, in a survey of major complications associated with regional anesthesia, Auroy and colleagues cautioned that PCB may be associated with a higher rate of life-threatening complications, such as total spinal, systemic toxicity, and cardiac arrest (8:1000), than other peripheral nerve block procedures. This survey, however, included only 394 PCBs, which was a small percentage of the total number of peripheral nerve blocks performed. Another important complication or side effect of PCB is epidural spread of local anesthetic. The incidence of this complication may be as common as 27% in adults and 92% in children. Although the selected approach to PCB was previously thought to influence the incidence of epidural spread, not all studies have supported this explanation. More recently, high injection pressure has been shown to increase the likelihood of neuraxial spread. Epidural and even intrathecal catheter placement has also occurred during attempted continuous PCB. This is not unexpected, given the anatomic proximity of the intervertebral foramen to the intended site of needle or catheter placement. The complications of PCB are listed in Box 175.2.

Although PCB is usually safe and successful, RPH is a potential risk with significant morbidity and mortality. The retroperitoneal space contains a rich network of arteries and veins. Segmental lumbar arteries arise from the aorta, run along the vertebral bodies, and then course behind the psoas major and lumbar plexus between the lumbar transverse processes. The iliolumbar arteries ascend from their origin at the hypogastric arteries and anastomose with the fourth lumbar artery at the medial border of the psoas major. Segmental lumbar veins connect to each other by the ascending lumbar vein (Fig. 175.3), which feeds into the inferior vena cava. Given this abundant vascular supply in the vicinity of the lumbar plexus, it is not surprising that needles or catheters may occasionally enter or injure these vessels during PCB, producing hemorrhage or systemic local anesthetic toxicity.

Several cases of RPH have been reported after lumbar sympathetic block and PCB, with both single-injection and continuous catheter techniques, and anticoagulant therapy at the time of or after the block was involved in each of those cases. The risk of this complication increases as the degree of anticoagulation increases.

The true incidence of clinically significant retroperitoneal bleeding after single-injection or continuous PCB with the typical dose of drugs used for perioperative thromboprophylaxis or anticoagulation therapy is not known. However, the reported incidence after cardiac catheterization through the femoral vessels is 0.49% and is higher

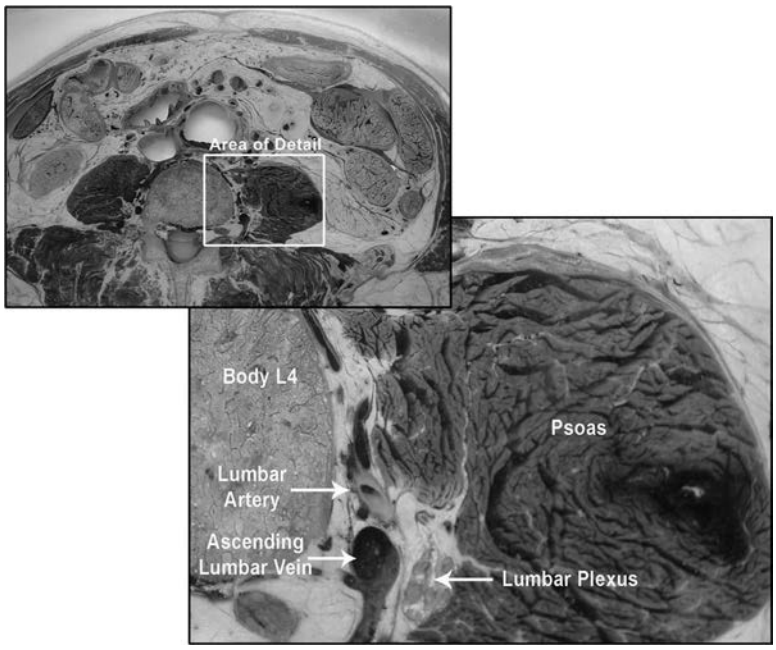

Fig. 175.3 Anatomic cross section through the L4 vertebral body. The enlarged image shows the lumbar artery and much larger ascending lumbar vein close to the lumbar plexus.

in patients with chronic renal insufficiency, a more proximal arterial puncture site, or those treated with glycoprotein IIb/IIIa inhibitors.

The potential for concealed, significant hemorrhage must be taken into account when calculating the risk-benefit ratio of PCB for each patient. Alternative techniques, the use of anticoagulant or antiplatelet drugs, and the degree of anticoagulation must be included in this analysis. The American Society of Regional Anesthesia and Pain Medicine (ASRAPM) has developed consensus guidelines for the performance of central neuraxial blocks in the setting of anticoagulant therapy and recommend that these guidelines be equally applied to deep plexus blocks such as the PCB. However, some clinicians have suggested that it is not necessary to apply the ASRAPM guidelines when performing PCB or at the time of removal of an indwelling PCB catheter. A study that included 200 patients with a continuous PCB that received rivaroxaban after surgery, and in whom catheter removal occurred after 1 to 2 doses of rivaroxaban, reported no apparent bleeding complications. In this study the exact timing of block placement and removal was not reported or standardized, and the management of bleeding noted at the time of block placement was not described. In addition, even with zero events in 200 patients, the statistical risk for bleeding could be greater than 1%. In fact, the rate of major bleeding in this study was 1.9%, although none were attributed to the performance of the blocks.

Implications

Retroperitoneal bleeding after PCB, if diagnosed early and treated with transfusion and supportive care, typically results in complete recovery and usually does not require surgical intervention. However, the treatment of this complication usually still requires costly imaging and treatment, substantial transfusion, an extended hospital stay, and the reversal of anticoagulation, with its attendant risks. Even worse, retroperitoneal hemorrhage after PCB can cause persistent femoral neuropathy and even death.

Although the specific mortality rate for RPH after PCB is unknown, the mortality rate associated with RPH after cardiac catheterization is reportedly 4% to 12%. Additionally, the mortality rate associated with spontaneous RPH in anticoagulated patients in one series was as high as 20%. Therefore the potential for death as a result of RPH after PCB should be considered when weighing the benefits of a PCB.

BOX 175.3 Management of Retroperitoneal Hemorrhage After Psoas Block

- Restore intravascular volume
- Measure blood counts and coagulation activity
- Transfuse blood and coagulation factors as indicated
- Reverse anticoagulation pharmacologically
- Transfer to high-acuity unit until cardiovascular stability achieved
- Perform abdominal computed tomography scan to confirm diagnosis when stable
- Consider interventional radiology consultation for continued hemorrhage
- Consider surgical exploration for continued hemorrhage, femoral palsy, or abdominal compartment syndrome

MANAGEMENT

Early diagnosis is important so that treatment can be initiated quickly. Box 175.3 details the management of RPH after PCB. Intravascular volume repletion is the first priority, and laboratory studies including hemoglobin concentration, platelet count, and coagulation parameters should be performed to guide transfusion and other therapies. Discontinuation or reversal of anticoagulation may be necessary, as well as transfer of the patient to a high-observation unit until cardiovascular stability has been achieved. Once the patient has stabilized, a CT scan can confirm the diagnosis and demonstrate the extent of bleeding. If active bleeding continues, technetium-99 scanning can help identify its source and guide embolization of the bleeding vessel. Endovascular stent or graft placement is an additional treatment option for ongoing bleeding.

Many authorities believe that patients with continued or progressive nerve dysfunction from compression of branches of the lumbar plexus should undergo urgent decompressive surgery. Others believe that surgical intervention is a last resort and recommend that evolving femoral neuropathies be managed more expectantly, especially

in patients with congenital coagulopathies. One concern with open approaches is that they may relieve the tamponade effect of the hematoma and lead to rebleeding. Open surgical treatment is often reserved for patients who do not respond to conservative management or endovascular approaches to stop ongoing bleeding, and for those patients who develop abdominal compartment syndrome.

PREVENTION

The vascularity of the tissues through which the needle passes for PCB makes it impossible to completely avoid arterial or venous trauma. Even with the assistance of ultrasound guidance, vascular injury cannot be entirely avoided, and there is no evidence yet for PCB that ultrasound guidance reduces vascular punctures at this site. Because the larger needles and catheters used for continuous epidural anesthesia carry a higher risk for epidural hematoma than does single-injection spinal anesthesia, it seems logical that this would also be true for peripheral nerve blocks such as PCB.

When an insulated needle and nerve stimulator are used to locate the lumbar plexus for PCB, vascular puncture can go unrecognized, and RPH has been reported despite negative aspirations for blood during the performance of a PCB. Even with hollow-core needles, vascular injury might not be obvious. Regardless of the type of needle used, RPH after PCB has been reported. Thus the following precautions are prudent:

- Follow the ASRAPM evidence-based guidelines related to the performance of regional anesthesia in patients receiving antithrombotics or thrombolytic therapy.
- Avoid PCB if thrombolytic therapy is likely to be required.
- Maintain a high index of suspicion for concealed bleeding in patients who have undergone PCB and are anticoagulated postoperatively.
- If known vascular puncture occurs during PCB, communicate this to the surgical team and consider delaying potent thromboprophylactic therapy postoperatively. Careful patient follow-up and monitoring of serial hematocrits are advised.
- Remove PCB catheters in accordance with ASRAPM guidelines, and maintain a high index of suspicion for bleeding after catheter removal in patients at increased risk for bleeding, such as those on multiple anticoagulant medications.
- Communicate the potential for concealed bleeding with members of the primary surgical service so that they too have the appropriate index of suspicion for bleeding complications after PCB, especially when unanticipated anemia or hypovolemia occurs in the postoperative period.

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Pulmonary Aspiration

176

Andrew Davidson • Michael Robinson

Case Synopsis

A hypertensive 76-year-old woman presents for total hip arthroplasty after sustaining a fractured neck of femur during a mechanical fall. After uneventful intravenous induction, anesthesia is maintained by spontaneous ventilation of a volatile anesthetic via a supraglottic airway device. Soon after positioning on the operating table, the patient becomes tachypneic. A few minutes after surgery commences, the patient develops hypoxemia, respiration becomes noisy, and yellow liquid is identified in the breathing circuit and in the patient's mouth.

PROBLEM ANALYSIS

Definition

Pulmonary aspiration is defined by the inhalation of oropharyngeal or gastroesophageal contents below the vocal cords into the bronchial tree. Pulmonary aspiration occurs during anesthesia due to the attenuation of normal protective laryngeal reflexes, such as coughing, expiration, and laryngospasm. It most commonly occurs when an anesthetized patient with an unprotected airway regurgitates, meaning that patients at greatest risk of regurgitation are at greatest risk of pulmonary aspiration.

Recognition

Aspiration may cause symptoms ranging from mild respiratory disturbance such as tachypnea or transient laryngospasm to profound hypoxemia and cardiovascular collapse or death from multiorgan failure.

The quantity, physical nature, and acidity of the aspirated material determine the likely clinical course. Teeth, solid food fragments, or blood, which may subsequently clot, have the potential to cause rapidly fatal asphyxia. Large volumes of strongly acidic gastric juices may precipitate a severe chemical pneumonitis, which presents as progressive dyspnea, hypoxemia, bronchial wheeze, and pulmonary infiltrates on chest x-ray.

Aspiration may be readily apparent in the event of sudden respiratory deterioration after the active vomiting of a large amount of gastric material, but in more subtle cases, recognition requires a high index of suspicion in the event of respiratory complications in the anesthetized patient with an unprotected airway.

Risk Assessment

The likelihood of pulmonary aspiration is strongly determined by patient risk factors. Depending on those risk factors, aspiration complicates between 1 in 900 and 1 in 10,000 general anesthetics. Although pulmonary aspiration is 3 or 4 times more likely to occur in emergency anesthesia, more cases of aspiration are seen in the elective setting due to the far greater numbers of patients presenting for elective rather than emergency surgery.

Recent evidence has shown that approximately 50% of airway-related deaths in anesthesia are a consequence of aspiration. Aspiration in the event of inappropriate risk assessment or airway management remains a significant cause of litigation.

The need to take the appropriate action after an accurate and comprehensive assessment of risk is vital to reducing the likelihood and severity of pulmonary aspiration. Evidence consistently shows that in cases of pulmonary aspiration the conduct of anesthesia was not altered to take into account a patient's increased risk of regurgitation despite the performance of an appropriate risk assessment.

The risk factors according to patient, surgery, and anesthesia risks are shown in Table 176.1. If an increased risk of aspiration is identified, anesthetic technique should be modified accordingly.

Patient risk factors are related to the potential presence of a full stomach, such as emergency surgery, delayed gastric emptying, and an incompetent lower esophageal sphincter leading to reflux and potentially regurgitation. Surgical risk factors include laparoscopy, reverse Trendelenburg positioning, and gastrointestinal pathology including

TABLE 176.1 Risk Factors for Aspiration

Patient Factors	Surgery	Anesthesia
Full stomach • Emergency surgery • Inadequate fasting time • Gastrointestinal obstruction	Positioning • Reverse Trendelenburg • Lithotomy	Preoperative assessment • Emergency surgery • Failure to risk assess • Failure to modify anesthetic technique
Delayed gastric emptying • Diabetic gastroparesis • Autonomic neuropathy • Chronic kidney disease • Recent trauma • Raised intracranial pressure • Opioids • Pregnancy and active labor	Surgical disease • Gastrointestinal obstruction • Previous upper gastrointestinal surgery • Morbid obesity	Airway • Difficult airway • Supraglottic airway devices (more likely with first-generation supraglottic airway devices)
Incompetent lower esophageal sphincter • Hiatal hernia • Recurrent regurgitation • Dyspepsia • Gastroesophageal reflux	Procedure • Laparoscopy • Cholecystectomy • Upper gastrointestinal surgery	During anesthesia • Excessively light anesthesia • Duration of surgery longer than 2 hours • Positive pressure ventilation

bowel obstruction. Anesthetic risk factors include the use of inappropriate airway techniques in high-risk patients, sedation in patients with a full stomach, and an overly light depth of anesthesia. Aspiration most commonly occurs with the failure to protect the airway with a cuffed endotracheal tube or use of rapid-sequence induction when they are indicated.

Although defined patient risk factors are well known and remain unchanged, the increasing incidence and severity of obesity, as well as the use of laparoscopic surgery and prolonged Trendelenburg positioning, has increased the overall incidence. The relatively recent relaxation of previously strict and prolonged fasting of solid food or liquids has not itself increased the risk of pulmonary aspiration; and the recommendations for preoperative fasting continue to be 6 hours for food, including surgery drinks and nonhuman milk; 4 hours for human breast milk; and 2 hours for clear fluids.

PREVENTION

When an elevated risk of aspiration is identified, anesthetic technique should be modified to reduce the risk. Strategies to reduce the risk of aspiration are shown in Table 176.2 and include avoiding general anesthesia by using neuraxial, regional, or local anesthetic techniques. Preoperative preparation includes the consideration of adequate preoperative fasting or the use of premedication to reduce gastric volume and the acidity of gastric contents.

If general anesthesia is required, airway strategies to reduce aspiration risk should be employed and matched to the degree of risk. For example, if a patient has a mildly elevated risk of aspiration, the use of a second-generation supraglottic airway device may be considered; but in cases where the patient has a higher risk of aspiration, endotracheal intubation with a cuffed tube should be used. When a very high risk exists, such as in emergency situations, rapid-sequence induction with immediate endotracheal intubation is strongly recommended.

Cricoid pressure (Sellick's maneuver) is often recommended as a method of preventing the passive regurgitation of stomach contents above the upper esophageal sphincter during rapid-sequence induction, although it should be noted that it may hamper visualization of the larynx during direct laryngoscopy and may be emetogenic in some patients. If active vomiting was to occur during cricoid pressure, it should be released immediately, otherwise esophageal rupture with mediastinitis may ensue.

Aspiration risk does not only apply at induction of anesthesia, but persists throughout maintenance, during extubation, and potentially even after emergence of anesthesia. The oral cavity and oropharynx should be suctioned before extubation to remove secretions, preventing their subsequent aspiraspiration; this this should be especially meticulous if blood might be present, for example, after tonsillectomy or dental extractions. If the risk assessment mandated the use of rapid-sequence induction, emergence from anesthesia should be managed so that extubation only occurs after the full return of consciousness and airway reflexes with the patient in either a lateral or near-sitting position. Box 176.1 gives the latest clinical advice on how to prevent aspiration.

TREATMENT

Once aspiration is recognized, treatment is directed toward supportive treatment and organ support. The airway should be secured by intubation with an endotracheal tube after the administration of a rapidly acting muscle relaxant such as suxamethonium. The trachea should ideally be suctioned before instituting positive pressure ventilation in an attempt to remove aspirated material from the upper airway.

TABLE 176.2 Summary of Available Strategies for Reducing Aspiration Risk

Reducing gastric volume	• Adequate preoperative fasting • Gastric tube aspiration if present • Prokinetic premedication (e.g., metoclopramide)
Avoidance of general anesthetic	• Regional anesthesia
Reducing pH of gastric contents	• Antacids (e.g., sodium citrate) • H_2 histamine antagonists (e.g., ranitidine) • Proton pump inhibitors (e.g., omeprazole)
Airway protection	• Endotracheal intubation • Second-generation supraglottic airway devices
Prevent regurgitation	• Cricoid pressure • Rapid-sequence induction
Extubation	• Awake after return of airway reflexes • Position (lateral, head down, or near sitting)

BOX 176.1 Latest Clinical Advice on How to Prevent and Manage Aspiration

1. Ensure thorough and accurate preoperative assessment of aspiration risk. If in doubt, assume a higher risk.
2. Choose airway strategies consistent with identified risk.
3. Have equipment, skills, and experienced assistance to detect and manage regurgitation and aspiration available at all times.
4. Intubate (or strongly consider intubating) in the following situations:
   - All emergencies
   - Delayed gastric emptying (diabetic gastroparesis, pregnancy, opioids, chronic kidney disease)
   - Raised intraabdominal pressure (obesity, ascites, abdominal masses)
5. Use rapid-sequence induction for those at high risk, including emergencies.
6. Consider using second-generation supraglottic airway devices in patients with mildly elevated risk of regurgitation.
7. Ensure meticulous oral suctioning before extubation when blood might be present.
8. Remember that if patients are deemed to be at risk before anesthesia, strategies should be used to minimize risk at emergence/extubation (e.g., awake extubation, lateral, head-up or near-sitting position).

Oxygenation should be maintained by ensuring an adequate fraction of inspired oxygen (Fio_2) and ventilation optimized by using positive end-expiratory pressure and adjusting respiratory frequency and inspiratory time.

Hypotension may indicate circulatory shock and should be treated by aggressive intravenous fluid boluses and/or administration of vasopressor medication.

Consideration may be given to waking and extubation only if the patient has no signs of requiring ongoing organ support and the clinician believes it is safe to do so. However, an extended period of observation after emergence should be considered for the patient in the postanesthesia care unit or on the critical care wards. If the patient requires ongoing organ support, mechanical ventilation and sedation may be required for prolonged periods, and transfer to an appropriate critical care facility will be required. If the patient displays signs of shock, a urinary catheter and invasive arterial and central venous lines should be inserted.

Oxygenation and ventilatory adequacy should be monitored by continuous pulse oximetry, capnography, and serial arterial blood gas measurement. Chest x-ray will identify consolidation in most cases, and typically affects the right side more in patients who aspirated while supine because of the more vertical orientation of the right main bronchus. Early therapeutic bronchoscopy may help prevent distal atelectasis and lung collapse, especially if particulate material has been aspirated. Rigid bronchoscopy may be used to remove solid material in the trachea and upper bronchial airways such as teeth.

Antibiotics should only be used after pneumonia develops, as the injudicious administration of antibiotics may cause the selection of antibiotic-resistant or virulent bacteria such as *Pseudomonas aeruginosa*. Despite potential theoretic benefits of reducing inflammation with the use of corticosteroids, there is no evidence that they improve the prognosis or reduce mortality risk, and they may in fact be harmful because their immunosuppressive effect increases the risk of secondary infections.

Further Reading

American Society of Anesthesiologists Committee: Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anaesthesiologists Committee on Standards and Practice Parameters, *Anaesthesiology* 114(3):495–511, 2011.

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177 Pulmonary Aspiration in the Parturient

Laura J. Alexander • William R. Camann

Case Synopsis

A 32-year-old woman, gravida 2, para 1, with a full-term pregnancy, undergoes general anesthesia for emergency cesarean delivery owing to prolonged fetal bradycardia. The patient receives a rapid-sequence induction using propofol and succinylcholine. The trachea is intubated using a 3.0 MacIntosh blade, cricoid pressure, and a styletted 6.5 endotracheal tube. After cesarean delivery, the patient is extubated and transferred to the postanesthesia care unit. She is breathing spontaneously with supplemental oxygen. Vital signs include blood pressure of 110/78 mm Hg, heart rate of 96 beats per minute, and arterial oxygen saturation of 88% on 6 L of oxygen by facemask. On physical examination, the patient is noted to have bilateral wheezing, and the chest radiograph reveals a right lower lobe infiltrate.

PROBLEM ANALYSIS

Definition

Pain relief during childbirth has long been of interest to anesthesiologists. As the quest for optimal analgesia and anesthesia for childbirth continues, so does that for the prevention and management of one of the most important peripartum complications: pulmonary aspiration of gastric contents. Hall first noted an increased incidence of this complication in obstetric patients in 1940. The term used to describe such pulmonary aspiration, *chemical pneumonitis,* soon gained popularity. In 1946 Mendelson more completely defined this condition.

Parturients belong to a special category of patients at increased risk for difficult or failed intubation and aspiration. The incidence of failed intubation in obstetric patients is estimated to be greater than that in the general surgical population, although the exact increase is a dynamic question without a definitive answer. Aspiration pneumonitis most often occurs with difficult or failed intubation. However, there are pregnancy-specific factors that contribute to the increased risk of aspiration, including the following:

- Increased levels of progesterone
- Reduced sphincter tone at the gastroesophageal junction
- Elevation of the gravid uterus against the stomach
- Mechanical obstruction of the duodenum by the stomach

The gravid uterus further compromises esophageal sphincter tone due to distortion of the gastroesophageal angle. Also, "pushing" during the second stage of labor, manual pressure on the lower abdomen, and the lithotomy position act in concert to increase intraabdominal pressure and decrease gastric emptying (Table 177.1).

The production of motilin, a hormone that speeds gastric emptying, is depressed throughout pregnancy and returns to near normal by 1 week postpartum. Nevertheless, gastric emptying appears to be normal throughout most of pregnancy. The cause of delayed gastric emptying during advanced labor, despite satisfactory epidural analgesia, is unknown. However, recent work suggests that gastric volume and acidity at term gestation are no different from those parameters in the nonpregnant state, during early pregnancy, or in the postpartum period.

Iatrogenic factors that may increase the risk of gastric aspiration include parenteral or epidural opioids and the use of anticholinergic drugs (e.g., glycopyrrolate). Opioids slow gastric motility, and anticholinergics reduce esophageal sphincter tone.

Recognition

Signs and symptoms of chemical pulmonary aspiration are quite variable and are largely a function of volume and pH (Box 177.1); however, such aspiration may also be "silent." Further, the anesthesiologist may be unable to see aspirate in the posterior oral pharynx. Coughing and bronchospasm may also be infrequent symptoms. Often, radiographic changes provide the first evidence of aspiration; such changes are found in dependent parts of the lung, often in the right lower lobe.

TABLE 177.1 Aspiration Risk Factors Related to the Parturient

Cause	Effect
Gastric volume and acidity	No change at term or during early pregnancy
Increased levels of progesterone	Reduced gastroesophageal sphincter tone
Reduced levels of motilin	Delayed gastric emptying in advanced labor
Gravid uterus	Mechanical compromise of esophageal sphincter
Parenteral or epidural opioids	Decreased gastric motility and sedation
Anticholinergic drugs	Decreased esophageal sphincter tone

BOX 177.1 Signs and Symptoms of Chemical Pulmonary Aspiration

None
Gastric contents in oropharynx
Cough
Bronchospasm
Oxygen desaturation
Circulatory shock
Infiltrates on chest radiograph

The outcome for patients with chemical pulmonary aspiration can be categorized as follows: Roughly 10% to 15% of patients have rapid clinical deterioration, with hypoxia and early circulatory shock. Of the remaining patients, approximately two-thirds improve rapidly within 1 to 4 days; they may require ventilatory support. The other one-third develop bacterial lung infections necessitating antibiotic therapy. Most lung injuries eventually resolve.

Risk Assessment

The actual incidence of maternal chemical aspiration is unknown. It is likely that minor degrees of aspiration often go unnoticed, and only maternal deaths or other serious morbidity from aspiration are reported. In a retrospective review of 185,000 anesthetic inductions, Olsson and colleagues found that the incidence of aspiration was 1 in 2131 (0.047%) for nonobstetric inductions and 1 in 661 (0.15%) for inductions before cesarean delivery (i.e., a threefold increase in aspiration risk during pregnancy). Warner and colleagues found the incidence to be 1 in 3216 (0.031%) for general anesthesia and 1 in 895 (0.11%) for emergency operations. Although Warner's group evaluated all types of emergency cases, cesarean delivery is often emergent. More recently, Ezri and colleagues retrospectively studied patients having general anesthesia around the time of delivery (e.g., manual extraction of placenta) or immediately after delivery (e.g., repair of lacerations) from 1979 to 1993. They found a 0.05% incidence of aspiration (1 in 1870 cases). All patients were breathing spontaneously, were not intubated, and had general anesthesia induced and maintained with intravenous agents. The lower incidence of aspiration in this group compared with the general surgical population might be related to reduced intraabdominal pressure. Also, many cases of chemical pulmonary aspiration occur with difficult or failed intubations that require mask ventilation. The most recent data available are from the SCORE project. This multiinstitutional survey in the United States, published in 2014, studied over 250,000 anesthetics for birth and approximately 5000 general anesthetics. The authors reported a 0% incidence of aspiration.

Not all general anesthetics in obstetrics require an endotracheal tube, and the laryngeal mask airway (LMA) may be a useful adjunct in the setting of difficult or failed intubation. Han and coworkers reported the use of LMA for elective cesarean delivery in 1060 patients. Although there were no reported cases of aspiration, this success may be attributed to careful patient selection. Among the patients excluded were those with symptoms of gastric reflux, an American Society of Anesthesiologists (ASA) classification higher than II, a known difficult airway, or a prepregnancy body mass index greater than 30, as well as those who had fasted for less than 6 hours. Also, antacid prophylaxis was used preoperatively, and cricoid pressure was applied. However, in practice, almost all parturients requiring general anesthesia are those with obstetric emergencies, especially the unexpected need for cesarean delivery. We believe that such nonfasting patients require a rapid-sequence induction and tracheal intubation. However, in the circumstance of a failed airway, even in the emergent obstetric patient, the LMA may allow for life-saving oxygenation, and should be considered.

Finally, anesthesia-related maternal mortality rate has decreased in recent years due to the increased use of regional anesthesia. Even so, Hawkins and coworkers reported that 23% of all anesthesia-related deaths in obstetric patients were a direct result of aspiration. Although data on maternal morbidity with perioperative aspiration are generally not reported, several studies now indicate that there is still significant morbidity associated with this condition in obstetric patients. Although all parturients are at increased risk for chemical pulmonary aspiration, the timing and nature of peripartum surgery, as well as the circumstances under which general anesthesia is performed, must be considered when interpreting studies of the incidence of peripartum pulmonary chemical aspiration.

Implications

The volume, content, and character of any gastric aspirate determines the severity of pneumonitis after pulmonary aspiration. Many believe that gastric pH is more critical for determining the severity of lung injury after pulmonary aspiration than is the actual volume (provided it is less than 25 mL). Others, notably James and associates, believe that regardless of volume, lower pH correlates with higher mortality.

Particulate matter increases the risk of lung injury after aspiration, because large particles can lodge in major bronchi, causing asphyxiation within minutes. However, nonacid aspirates may produce only mild, transient hypoxia, with no evidence of parenchymal injury; such hypoxia may be due to bronchospasm and microatelectasis. As the acidity of the aspirate increases, the potential for parenchymal injury and pulmonary hemorrhage increases. Amplification of this response may lead to the acute respiratory distress syndrome, which is characterized by persistent lung inflammation with radiologic evidence of bilateral pulmonary infiltrates. These infiltrates are due to increased vascular permeability and reduced arterial oxygen tension (irrespective of the fraction of inspired oxygen or the use of positive end-expiratory pressure), with no increase in left atrial pressure. Survival has improved with better supportive care and ventilatory strategies, but mortality rates from gastric aspiration and associated acute respiratory distress syndrome are still very high, with current estimates ranging from 35% to 40%.

MANAGEMENT

Immediately after aspiration, airway management is critical (Box 177.2). Any aspirate identified in the posterior oral pharynx should be quickly evacuated, and the airway should be secured. Although several authors recommend a head-down tilt or left lateral decubitus position to minimize the spread of aspirate, this position has not been proven to reduce such spread. Tracheal suctioning without saline lavage is advised for removal of the aspirate. Saline lavage may disseminate the aspirate to more distal airways and worsen the situation. The pH of the aspirate may be measured to help identify the nature of the gastric contents.

The most important factors for reducing morbidity are quick identification of aspiration, expeditious airway intubation, and ventilation with supplemental oxygen and positive end-expiratory pressure. Bronchospasm may be relieved by the administration of an intravenous β-agonist. Although acid-injured lungs are more susceptible to bacterial infection, there is no evidence that prophylactic antibiotic administration alters the incidence of infection, nor does it affect the outcome. Prophylactic antibiotics may even facilitate the development of infection with resistant organisms. Similarly, the administration of systemic glucocorticoids is controversial. Several animal models suggest a reduction in pulmonary damage if steroids are given immediately after the insult. Other data suggest that any benefit may be outweighed by steroid-caused reduction of macrophage activity and subsequent increased susceptibility to gram-negative pneumonia. Although it is not uncommon to administer methylprednisolone (30 mg/kg) or dexamethasone (1 mg/kg), current thinking does not advocate this practice. The use of fluids must be restricted. Damaged pulmonary endothelium exudes protein-rich edematous fluid, and patients may be further compromised by pulmonary edema from the overly aggressive use of intravenous fluids.

BOX 177.2 Indicated Therapy After Suspected Pulmonary Aspiration

Secure airway; provide supplemental oxygen and positive end-expiratory pressure
Place patient in head-down position and turn head to one side
Alternatively, place patient in left lateral decubitus position
Provide tracheal suctioning (intubate to protect airway, if not already done)
Once airway is protected, consider gastric decompression with orogastric or nasogastric tube
Initiate β-agonist therapy for bronchospasm
Consider systemic steroids (dexamethasone 1 mg/kg or methylprednisolone 30 mg/kg)
Institute conservative fluid management

PREVENTION

Perhaps the single most important treatment measure is prevention. Preventive measures include the following:

- Implementation of ASA fasting guidelines in patients in labor
- Regional anesthesia
- Cricoid pressure
- Administration of nonparticulate antacid
- Metoclopramide administration
- H_2-receptor antagonist administration

Prevention approaches can be categorized as pharmacologic and nonpharmacologic. The nonpharmacologic approach includes implementing ASA fasting guidelines in patients in labor and minimizing their exposure to general anesthesia with the appropriate use of regional techniques. However, emergencies may arise that require general anesthesia under conditions that are less than optimal for intubation. In these situations, prevention is often a combination of pharmacologic and classic full-stomach precautions.

Recent national trends encourage the oral intake of fluids during labor, and the ASA Task Force on Obstetric Anesthesia supports this practice. Of note, other national societal guidelines, such as that from the European Society of Anesthesiology, support the use of clear liquid intake throughout labor as well. Owing to the adverse metabolic consequences of prolonged starvation during labor, modest amounts of clear fluids, including isotonic "sports drinks," are now recommended for patients with uncomplicated labor. In support of this practice, data suggest that the gastric emptying of clear fluids in a laboring patient is no different from baseline fasting levels in nonlaboring patients. In fact, the emptying half-time of a larger amount of fluid may even be shorter for laboring patients with less fluid. However, in patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes, difficult airway) or an increased risk of operative delivery, more restricted oral intake may be required; this should be decided on a case-by-case basis. Of note, evidence suggests that chewing gum can not only improve patient satisfaction, but could also promote gastric emptying. Although still controversial, many clinicians will not cancel or postpone elective surgery based on recent gum chewing, and we agree with this practice. Solid food should be avoided in all patients in active labor and those who have received opioid-containing analgesics.

Cricoid pressure is a simple technique that may help prevent passive regurgitation during induction of general anesthesia. Pressure must be maintained until the trachea is intubated, the endotracheal cuff is inflated, and intubation is confirmed. It should be noted that cricoid pressure may not completely occlude the esophagus, may reduce the tone of the lower esophageal sphincter, and may not prevent aspiration.

In some obstetric patients, intubation is difficult to perform. If a difficult airway is anticipated, an awake intubation may be appropriate. Just as these patients are at risk for aspiration during induction, similar precautions must be observed during extubation. Extubation should occur only when the patient is conscious and able to follow commands appropriately. It is important to differentiate between the excitement phase of recovery and actual emergence. Airway assessment, management of failed intubation, and alternative techniques of airway management should be reviewed before the induction of general anesthesia.

Pharmacologic approaches to reducing the risk of aspiration often begin with the administration of a nonparticulate antacid. Antacids are one of the most effective and practical means of altering gastric pH. However, the maximal effects of nonparticulate antacids are limited to approximately 30 minutes' duration. Similarly, the administration of 10 mg of intravenous metoclopramide is beneficial. Although metoclopramide does not directly affect gastric pH, it possesses antiemetic properties, increases lower esophageal sphincter tone, and decreases gastric emptying time. A reduction in gastric volume can be observed after about 20 minutes of intravenous administration. H_2-receptor antagonists, such as cimetidine, ranitidine, and famotidine, are effective in reducing hydrochloric acid production by the gastric parietal cells. With histamine blockers, timing is important; effects can be seen 30 minutes after intravenous administration, but 60 to 90 minutes are required for maximal effect. This delay in onset limits their efficacy during an emergency. In addition to histamine and gastrin, acetylcholine is an endogenous secretagogue. Administration of anticholinergic medications can inhibit gastric fluid production, with variable results. Of the anticholinergics, glycopyrrolate has the most profound effect on gastric secretion and pH. However, this benefit is outweighed by concurrent reduction of lower esophageal sphincter tone and delayed gastric emptying. Consequently, these medications are not recommended for aspiration prophylaxis.

Further Reading

American Society of Anesthesiologists Committee: Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters, *Anesthesiology* 114(3):495–511, 2011.

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178 Spinal Anesthesia: Post–Dural Puncture Headache

Christina M. Spofford

Case Synopsis

A 25-year-old woman undergoes spinal anesthesia with a 25-gauge Quincke needle for outpatient hysteroscopy. The following day, she complains of a severe headache. Her headache is worse when she is in the upright position and resolves when she is supine.

PROBLEM ANALYSIS

Definition

Post–dural puncture headache (PDPH) is a well-known complication of spinal anesthesia. It commonly occurs 24 to 48 hours after dural puncture (in 92% of affected patients), but the presentation can be delayed for as long as 5 days. Loss of cerebrospinal fluid (CSF) from the puncture site is the key initiating factor (Fig. 178.1), with reduction in CSF fluid and pressure. This allows sagging of the brain and supporting structures when the patient assumes the upright position. Sagging of the brain places direct traction on pain-sensitive structures and can also cause painful reflex vasodilation of cerebral blood vessels. This theory is also supported by PDPH's pathognomonic feature of occurrence or exacerbation in the upright position and resolution in the supine position. Typically, 70% of PDPHs resolve spontaneously by 1 week after dural puncture, and 95% resolve by 6 weeks.

Recognition

PDPH should be considered a diagnosis of exclusion. Medical conditions that have been misdiagnosed as PDPH include hypothalamic tumors, eclampsia, spinal meningitis, and superior sagittal sinus thrombosis.

Clinical features of PDPH include the following:

- History of dural puncture
- Positional nature of headache (exacerbated when upright within 15 minutes and resolved when supine after 15 minutes)
- Headache that is typically frontal or occipital in nature
- Headache plus one of the following symptoms: neck stiffness, tinnitus, hypacusia, photophobia
- Spontaneous resolution within 1 week after dural puncture (95% of cases; if headache persists, consider other diagnoses)
- Resolves within 48 hours of blood patch

Risk Assessment

With current anesthetic practice, the incidence of PDPH typically ranges from 1% to 7% after spinal anesthesia. Both patient characteristics and anesthetic technique have been implicated as risk factors for the subsequent development of PDPH.

Patient factors that increase the risk include the following:

- Younger age, probably owing to changes in the elastic properties of the dura with aging
- Female gender
- Previous history of PDPH

Anesthetic factors that reduce the risk of PDPH are the following:

- Smaller-diameter spinal needles, probably owing to smaller dural punctures (Figs. 178.2 and 178.3)

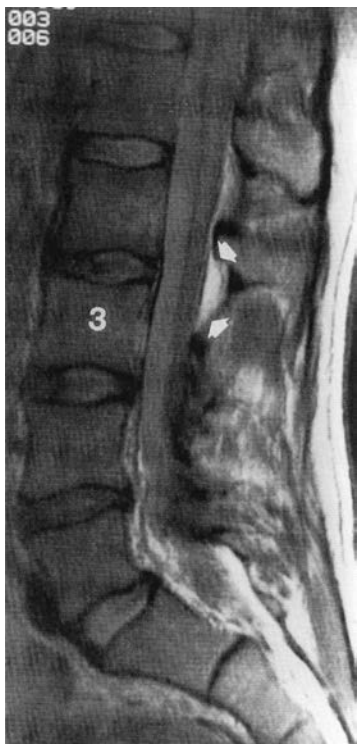

Fig. 178.1 Lumbar spine magnetic resonance image in a patient with post–dural puncture headache before the administration of an epidural blood patch. The static collection of fluid at L2–L3 *(arrows)* corresponds to leakage of cerebrospinal fluid from the dural puncture site. From Vakharia SB, Thomas PS, Rosenbaum AE, et al: Magnetic resonance imaging of cerebrospinal fluid leak and tamponade effect of blood patch in postdural puncture headache. *Anesth Analg* 84[3]:585-590, 1997.

- Use of pencil-point rather than cutting-tip spinal needles—the former result in less CSF leakage in vitro (see Figs. 178.2 and 178.3)
- Orientation of the bevel of cutting-tip needles parallel to the long axis of the arachnoid mater, which may produce a smaller rent in the tissue because of the longitudinal splitting of fibers, as opposed to direct transection (cutting)

Implications

PDPH can result in significant discomfort and limitation of activity. For patients in the postpartum period, this can create difficulty with nursing and caring for a newborn. Most affected patients can be treated with oral analgesics and adjuncts until spontaneous resolution occurs. Of these patients, approximately 18% will have slight restriction of physical activity, 31% will be partially bedridden with restricted physical activity, and 51% will be entirely bedridden.

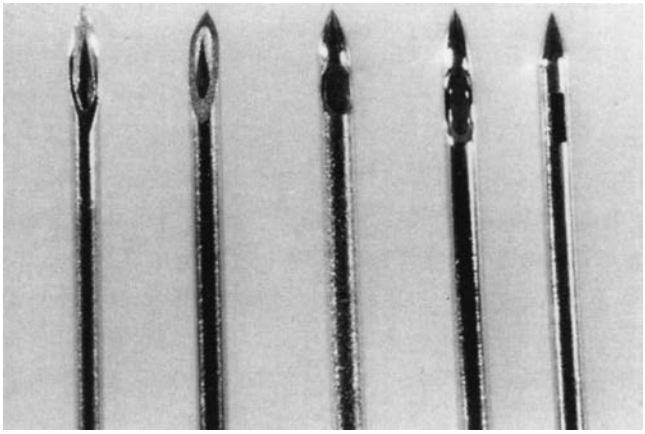

Fig. 178.2 From the left: Atraucan, Quincke, Gertie Marx, Sprotte, and Whitacre needles. Note the cutting points on the Atraucan and Quincke needles. Also, note the differences in the configuration of the lateral eyes of the pencil-point needles. The eye of the Gertie Marx needle is the smallest and situated closest to the needle tip. The left horizontal markings are in 2-mm increments. From Vallejo MC, Mandell GL, Sabo DP, et al: Postdural puncture headache: a randomized comparison of five spinal needles in obstetric patients. *Anesth Analg* 91[4]:916-920, 2000.

MANAGEMENT

Both systemic and invasive therapies have been advocated for the treatment of PDPH. It is reasonable to try systemic treatments before instituting more invasive therapies (Fig. 178.4).

Systemic Therapy

Caffeine

The intravenous administration of caffeine (500 mg) has been observed to decrease cerebral blood flow by 22% in patients suffering from PDPH. Success rates with intravenous caffeine therapy range from 40% to 80%, with mild side effects (dizziness, flushing). Oral caffeine can also be an effective therapy, with an approximately 50% success rate after 300 mg of oral caffeine.

Adrenocorticotropic Hormone and Sumatriptan

Anecdotal evidence suggests a success rate of 70% to 95% with adrenocorticotropic hormone (ACTH), but the sole randomized controlled trial to date showed no benefit. There have been case reports of seizures in obstetric patients treated with ACTH analogs. Likewise, although beneficial for other types of headache, use of sumatriptan in PDPH is not reliably helpful. A large Cochrane Review of seven randomized controlled trials failed to show conclusive evidence to support use of ACTH or sumatriptan. However, gabapentin, theophylline, and hydrocortisone decreased pain scores compared with a placebo.

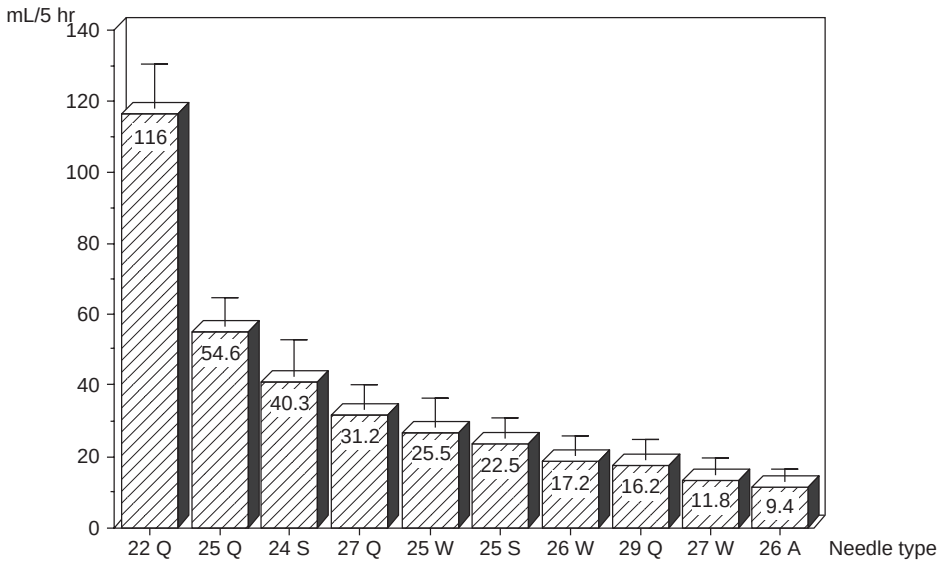

Fig. 178.3 Relationship between needle size and bevel type and leakage of cerebrospinal fluid after dural puncture in a laboratory model. From Holst D, Möllmann M, Ebel C, et al: In vitro investigation of cerebrospinal fluid leakage after dural puncture with various spinal needles. *Anesth Analg* 87[6]:1331-1335, 1998.

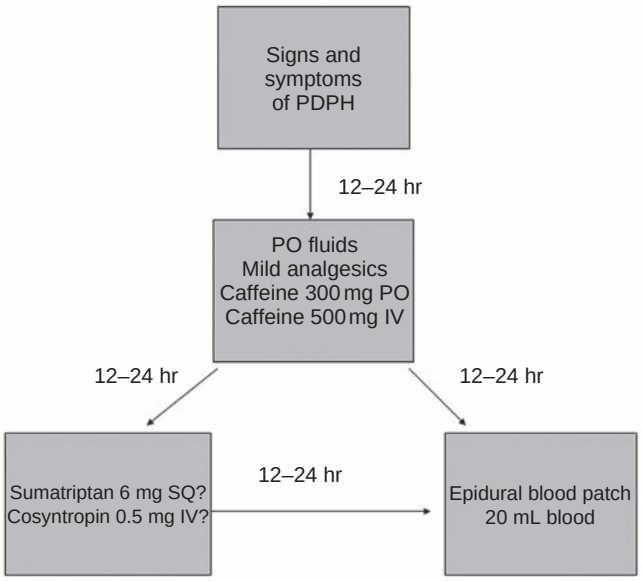

Fig. 178.4 Suggested treatment algorithm for post–dural puncture headache.

Posture and Fluids

Prolonged bed rest along with aggressive fluid hydration has been used to treat PDPH once it has started. In a Cochrane review of 23 trials, there was not a beneficial effect associated with bed rest compared with immediate mobilization on the incidence of PDPH. Likewise, fluid supplementation did not find any benefit for the prevention of PDPH.

Invasive Therapy

Epidural Blood Patch

Epidural injection of autologous blood was first proposed as a treatment for PDPH in 1960, after anecdotal observations of a reduced incidence of PDPH after "bloody" dural punctures. Epidural blood patch (EBP) is currently the gold standard for PDPH treatment when conservative measures have failed. Success rates for EBP are greater than 90%. Its mechanisms of action are thought to involve increased intracranial CSF pressure due to mass effect and sealing of the dural puncture site with fibrin clot (Fig. 178.5). Injection of blood into the epidural space results in an immediate mass effect persisting for at least 3 hours. Mature clot formation and sealing of the dural rent occur by 7 hours after injection. Initial reports of EBP used small volumes of blood (2 to 3 mL), but recent recommendations are for larger volumes (15 to 20 mL). These larger volumes provide greater spread of clot (five to nine spinal segments), greater mass effect, and a higher incidence of successful treatment. Although safe and effective, the use of EBP is not free of risk. Contraindications to EBP include systemic infection, localized infection of the back, and active neurologic disease. One must also consider the difficulty with the first procedure that resulted in the PDPH before initiating this treatment. Reported complications of EBP include transient backache (35% to 100% incidence), mild temperature elevation (5%), sudden bradycardia, and radicular pain. Prolonged sequelae from EBP may also occur. Less successful epidural analgesia after prior EBP has been reported.

Epidural Injection of Other Solutions

Both saline and dextran have been injected into the epidural space for the treatment of PDPH. Highly variable success rates have been reported, ranging from no effect to 90% success. The variable and often temporary nature of relief from saline or dextran, coupled with the inherent risk of an epidural injection, makes their use questionable. One case report documented the successful use of 3 mL of fibrin glue to treat a PDPH resistant to three EBPs.

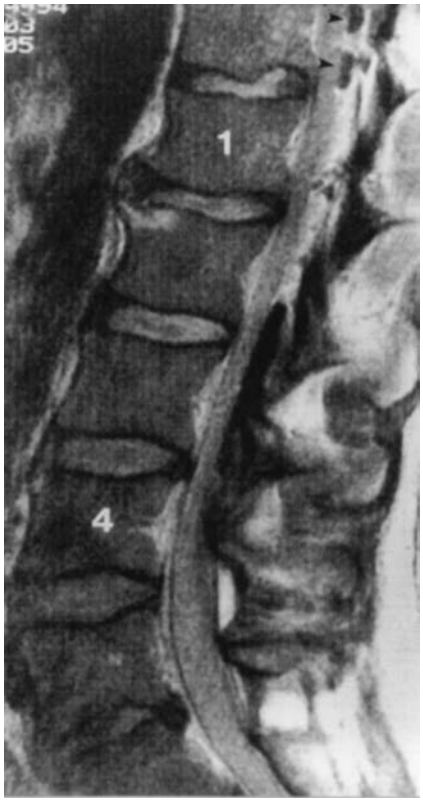

Fig. 178.5 Magnetic resonance image of 20-mL epidural blood patch demonstrating sealing of the dural leak and spread from L4 to T12 *(arrowheads).* From Vakharia SB, Thomas PS, Rosenbaum AE, et al: Magnetic resonance imaging of cerebrospinal fluid leak and tamponade effect of blood patch in postdural puncture headache. *Anesth Analg* 84[3]:585-590, 1997.

PREVENTION

The cornerstone of preventing PDPH is the selection of small, non–cutting-tipped needles for dural puncture. The prophylactic administration of systemic and invasive therapies has not been well studied. Because not all patients undergoing dural puncture will develop PDPH, most recommend EBP only after the development of symptoms. Another argument against the prophylactic use of EBP is its questionable efficacy when administered early (<24 hours after dural puncture). Several studies of the early administration of relatively small volumes of blood (7 to 10 mL) via an epidural catheter after dural puncture with a large-gauge Tuohy needle reported virtually no effects on the subsequent development of PDPH. However, these studies have been criticized for using small volumes of blood. A recent study administering a larger volume of blood (15 mL) via an epidural catheter after dural puncture with a large-gauge Tuohy needle reported a marked reduction in the incidence of PDPH in obstetric patients (5% in treated vs. 88% in untreated patients). Another recent controlled trial demonstrated the efficacy of the immediate injection of 10 mL of saline after inadvertent dural puncture (32% of treated patients developed PDPH vs. 62% of those untreated). Thus if patient and anesthetic risk factors are considered great enough to warrant prophylactic therapy, a large-volume EBP or immediate saline injection may be a reasonable and effective therapy.

ACKNOWLEDGMENT

The author wishes to thank Dr. Matthew P. Feuer and Dr. Spencer S. Liu for their contributions to the previous edition of this chapter.

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179 Spinal Hematoma

Mahmoud I. Wagih

Case Synopsis

A 69-year-old man underwent open abdominal aortic aneurysm repair under general anesthesia. An epidural catheter was inserted before induction for postoperative pain control. The anesthesiologist successfully placed the epidural catheter after the third attempt. Aspiration after insertion of the catheter yielded a blood-tinged column that cleared when the catheter was pulled out by 2 cm.
Despite using a relatively diluted mixture of local anesthetics (bupivacaine 0.125% and fentanyl 1 μg/mL), the patient experienced complete unilateral motor block in the first 2 hours after surgery that persisted despite the discontinuation of the epidural infusion. A magnetic resonance image revealed an epidural hematoma at T10. Immediate surgical decompression resulted in complete neurologic recovery.

PROBLEM ANALYSIS

Definition

In 1850 Tellegen was the first to describe the clinical symptoms of spinal cord hematoma (SCH). Anatomically, hematomas can occur in the epidural, subdural, or intramedullary areas of the spinal cord. Due to rarity of neurologic complications associated with central neuraxial blockades (CNBs), it is difficult to reach an accurate estimate of SCHs associated with them. Different authors based their findings on varying numbers/cohorts of patients, but the National Audit Project 3 (NAP3), which was conducted by the Royal College of Anesthetists and other organizations, identified 8 cases of SCH in 700,000 CNBs. The incidence of SCH was higher with epidural and combined spinal epidural anesthesia (17, 18 of 100,000) than with spinal or caudal anesthesia (2 of 100,000). Permanent neurologic deficit occurred in 5 cases of the 707,425 cases included in the audit. SCHs were rare when CNBs were used for labor, pediatric analgesia, or chronic pain management. The incidence increased substantially in patients over 70. Whether this increase is due to the associated comorbidities or the technique remains unknown.

Approximately 50% of SCHs are associated with catheter removal, and as many as 13% of cases are seen in patients without any preoperative risk factors. SCHs have widely varied etiologies (Box 179.1) and occasionally occur spontaneously.

Recognition

Classically, SCHs are known to present as localized back pain of varying intensity and nerve compression symptoms (motor, sensory, and autonomic). Significant percentage occurs after CNBs catheter removal. Back pain was less dominant a clinical feature when compared with motor weakness. Unilateral symptoms should be a red flag for spinal hematoma. Incomplete resolution of sensory or motor block after discontinuation of CNB infusion or after a single bolus should always be followed up and investigated.

Risk Assessment

Factors contributing to the occurrence of SCH can be divided into patient-related, technique-related, and drug-related factors.

Patient-Related Factors

- Older age group (>70 years of age)
- Females more often than males
- Nonobstetric (1 of 505,000), nonpediatric indication
- Coagulation abnormalities
- Spinal cord anomalies

Technique-Related Factors

- Combined spinal and epidural anesthesia greater than epidural greater than spinal greater than caudal
- Catheter techniques
- Technical difficulty
- Multiple attempts
- Bloody tap

Drug-Related Factors

The incidence of SCH increases dramatically in patients who receive perioperative anticoagulation/antiplatelets. Agents used for anticoagulation include the following:

- Standard (unfractionated) heparin
- Low-molecular-weight heparin (LMWH)
- Oral anticoagulants, including new-generation agents such as dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis)
- Antiplatelet medications (different generations)

BOX 179.1 Causes of Spinal Cord Hematoma

Vascular malformations
Coagulopathies (congenital or acquired)
Myelitis/vasculitis
Syringomyelia
Mechanical trauma
Lumbar/epidural puncture
Neoplastic
Postsurgical
Idiopathic

Standard (Unfractionated) Heparin

The use of standard heparin for complete anticoagulation and cardiopulmonary bypass (e.g., during vascular and cardiac surgery) is well established. Sanchez and Nygard report a large prospective series of 558 patients without complications. Despite that, there is not enough data to establish the exact incidence of complications. The general advice remains to insert the epidural 24 hours before surgery.

In NAP3 SCHs occurred in 15 patients within hours of catheter removal. Nine of these cases were on therapeutic heparin. This mirrors what was described by Vandermeulen and colleagues in their reviews of SCHs documented in their patient cohort from 1906 to 1994.

Intraoperative anticoagulation (e.g., for vascular procedures) seems to be associated with increased risk of SCHs when insertion was technically difficult or when full anticoagulation was initiated within 1 hour of insertion. There has been a trend to cancel surgery when epidural insertion was traumatic even though this approach is not evidence based. It seems sensible to communicate with the surgical team openly and conduct individual risk assessment. If anticoagulation is to continue postoperatively, 4 hours should be allowed between heparin cessation and epidural catheter removal. The same 4 hours (preferably with normal partial thromboplastin time [PTT]) should be observed if epidural anesthesia is to be inserted after a heparin dose. Subcutaneous heparin has been associated with a negligible number of cases of SCH, and the exact time interval is difficult to determine, but a 4-hour gap might avoid the peak plasma level.

Low-Molecular-Weight Heparins

LMWHs have a different pharmacologic profile from unfractionated (standard) heparin. In addition to their longer duration of action, they are only partially reversible by protamine, dependent on kidney functions for clearance, and difficult to monitor closely (even when anti-Xa levels are measured). The twice-daily regimen approved by the Food and Drug Administration has been associated with a high incidence of SCHs when it was first introduced.

The following advice was issued by the American Society of Regional Anesthesia and Pain Medicine (ASRA):

- Allow 12 hours after prophylactic dose and 24 hours after therapeutic dose before CNBs.
- If used in combination with antiplatelets, consider alternative pain control methods to CNBs.
- Do not leave a catheter in patents on twice-daily regimen of LMWHs.
- Delay postoperative LMWHs for 24 hours if catheter insertion was bloody or traumatic.
- Allow 2 hours after epidural catheter removal before starting postoperative LMWH twice-daily regimen (usually 24 hours postoperatively).

Oral Anticoagulants

Warfarin acts on vitamin K–dependent factors (II, VII, IX, X) to a varying degree. The international normalized ratio (INR) accurately reflects the effect of warfarin on factor VII but it is limited in terms of assessing its effect on factors II and X. The following advice has been issued by the ASRA:

- Stopping warfarin for 4 to 5 days and normal INR are mandatory before CNBs in patients who are on long-term therapy.
- INR less than 1.5 is recommended before CNB catheter removal.
- If INR is 1.5 to 3, cautious approach to removal and strict neurologic monitoring are strongly advised.
- The concomitant use of medications that affect the coagulation pathway (aspirin, LMWHs, aspirin) is not advisable for patients on warfarin.

The new oral anticoagulants dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) have not been used long enough to accumulate significant clinical data regarding their use when CNBs are planned. The advice by Benzon and colleagues is based on their pharmacokinetic profile because INR does not reflect their activity level. Allowing 2 to 3 half-lives between discontinuation of the drug and neuraxial injections is advisable in patients who are at high risk for venous thromboembolism or stroke. This should be increased to 4 to 6 half-lives in most patients at low risk of thrombosis. Creatinine clearance should be used in patients with chronic renal impairment to tailor the dose. Anticoagulants can be resumed within 24 to 48 hours after a CNB or removal of an epidural catheter.

Antiplatelet Medications

- Clopidogrel: ideally held for 7 days before neuraxial block, but 5 days probably safe; if concerns arise, obtain and document normal platelet study.
- Newer agents: prasugrel ideally stopped 7 to 10 days before spinal or epidural anesthesia; ticagrelor should be held 5 days.

PREVENTION

Considering the potential for a catastrophic outcome, every effort should be invested in prevention.

If a regional technique is considered, preoperative assessment should include details of coagulation anomalies, medications, and their timing (history of bleeding tendency/easy bruising, bleeding after previous surgery, anticoagulants/antithrombotics). Investigations such as INR or PTT (occasionally thromboelastography) might be required on the same day of surgery before CNBs. Timing the CNB should follow the aforementioned guidelines (Table 179.1). A protocol should in place for monitoring those patients not only in the early postoperative period but as long as a catheter is in place and after its removal. Such protocol should identify the team/individual responsible for that aspect of patient care and the timing for any interventions. System errors were identified in 70% of SCHs with permanent nerve damage. An ongoing audit and training system should be in place.

ACTIVE MANAGEMENT

Unilateral Motor Block or Persistent Sensory Loss

A number of "red flags" should alert the anesthesiologist to potential complications (Box 179.2). Early detection is vital. Laminectomy—even when performed promptly—does not always lead to complete neurologic recovery in SCHs (more effective in spinal canal abscess), but responders almost always occurred in the early intervention group. Lower limb weakness is expected for a limited period of time after spinal anesthesia and for as long as an infusion is ongoing if a lumbar epidural is used. In thoracic epidural, the segmental nature of the block precludes lower limb motor block and any motor deficit should be thoroughly and actively investigated. The use of a dilute mixture of local anesthetics with or without an opioid would allow early detection of neurologic complications, and a dense motor block would be the exception. Any dense motor block should be reported to the anesthesiologist in charge. The local anesthetic infusion should be stopped, and return of motor functions should be seen within 4 hours. Any persistent weakness should be labeled significant and investigated further. The use of the Bromage leg weakness score has proven practical and easy to use and teach in this context. If such standards of monitoring cannot be upheld, the use of CNBs is deemed unsafe. If an epidural catheter is removed after an unexplained or persistent weakness, neurologic monitoring should continue for 24 hours after catheter removal (see Table 179.1).

TABLE 179.1 Use of Central Nerve Blocks With Anticoagulants and Antiplatelets

Drug	Use With Central Nerve Blocks
Standard heparin—prophylactic dose	Central neuraxial blockade (CNB) to be attempted after at least 4 hours from the last heparin dose. Heparin to be administered 4 (ideally 6) hours after CNB or catheter removal.
Standard heparin—full anticoagulation	In cardiac/complex vascular surgery, CNB catheters are to be inserted 24 hours before full anticoagulation.
Standard heparin—intraoperative anticoagulation	Allow 1 hour after CNB before any single heparin dose. If bloody block, assess individually the risk benefit of anticoagulation.
Low-molecular-weight heparins (LMWHs)	Allow 12 hours after prophylactic LMWH before attempting CNB. Allow 24 hours after therapeutic LMWH before attempting CNB. Administer LMWH in a once-daily dose if possible. If used in combination with antiplatelets, consider alternative pain control methods to CNB. Do not leave a catheter in patients on twice-daily regimen of LMWH. Delay postoperative LMWH for 24 hours if catheter insertion was bloody or traumatic. Allow 2 hours after epidural catheter removal before starting LMWH.
Warfarin	Stopping warfarin for 4–5 days and normal INR are mandatory before CNBs. INR less than 1.5 is recommended before CNB catheter removal.
Dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis)	Allow three half-lives between discontinuation of the drug and CNBs (3 days for rivaroxaban and apixaban and 5 days for dabigatran). Anticoagulants can be resumed within 24–48 hours after a CNB or removal of an epidural catheter.
Antiplatelets	Clopidogrel: stop for 7 days. Prasugrel: stop for 7–10 days. Ticagrelor: stop for 5 days.

INR, International normalized ratio.

BOX 179.2 Red Flags After Central Nerve Blocks

- Significant motor block with a thoracic epidural
- Unexpectedly dense motor block, including unilateral block
- Markedly increasing motor block during epidural infusion
- Motor block that does not regress when an epidural is stopped
- Recurrent unexpected motor block after restarting an epidural infusion that was stopped because of motor block

Further Reading

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Supraclavicular and Infraclavicular Block: Pneumothorax

180

David A. Olsen • Sandra L. Kopp

Case Synopsis

A 42-year-old man complains of shortness of breath and mild right-sided chest pain in the outpatient recovery area, shortly after a right wrist fusion. A preoperative ultrasound-guided brachial plexus block was placed using the supraclavicular approach. On examination, the patient's respiratory rate is 20 breaths per minute, and his room-air saturation is 94%. His blood pressure and heart rate are normal. A chest radiograph is positive for a small, right-sided pneumothorax.

PROBLEM ANALYSIS

Definition

Pneumothorax is an accumulation of air or gas in the space between the lung and the chest wall (pleural space). With the supraclavicular approach, the brachial plexus is blocked at the level of the proximal divisions, where it is compactly arranged (Fig. 180.1). There are several advantages to the supraclavicular brachial plexus technique, including neutral position of the arm, quick onset of blockade, shallow needle approach with good ultrasound visualization, and a very homogeneous block. Limitations of this approach include potential phrenic nerve block and the risk of pneumothorax. General risks of nerve blocks, including nerve damage, infection, hematoma, and local anesthetic toxicity, are discussed elsewhere. Special consideration must be given to patients who could not tolerate the respiratory compromise that may accompany a pneumothorax or phrenic nerve block, such as those with severe respiratory disease.

The infraclavicular approach to brachial plexus block allows local anesthetic injection above the level where the musculocutaneous and axillary nerves branch off the plexus. This approach is more proximal than the axillary technique and more distal than the supraclavicular approach, thus leading to blockade of all the nerves derived from the plexus, but with a lower incidence of pneumothorax or phrenic nerve involvement (Fig. 180.2). As with the supraclavicular approach, the arm can remain in a neutral position. This approach is especially useful in patients requiring a continuous catheter technique, because maintaining an aseptic dressing at this site is much more practical than in the axilla.

Recognition

Recognition of a pneumothorax is based largely on the clinical presentation. A pneumothorax may occur immediately during block placement, or it may present hours later. The diagnosis of pneumothorax should be suspected if air is aspirated through the needle during performance of the block, if the patient coughs during needle advancement, or if the patient becomes acutely dyspneic after block placement. Unilateral phrenic nerve paralysis and concomitant elevation of the hemidiaphragm must be ruled out, as this is very common after proximal

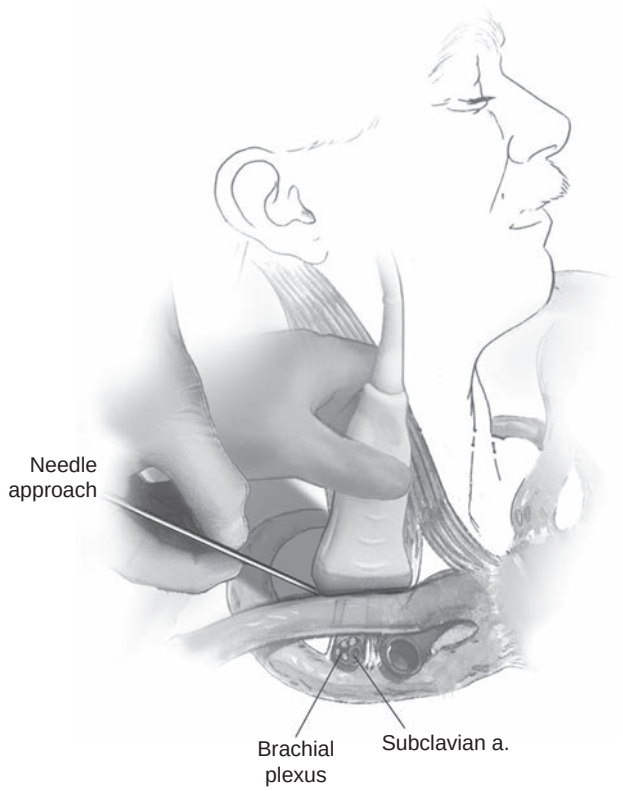

Fig. 180.1 Supraclavicular block. The needle is advanced in-plane toward the posterior aspect of the compactly arranged brachial plexus at the level of the first rib. (From Brown DL, Sites BD, Spence BC: Supraclavicular block. In Brown DL, editor: *Atlas of regional anesthesia*, 4th ed. Philadelphia, Saunders, 2010, p 57.)

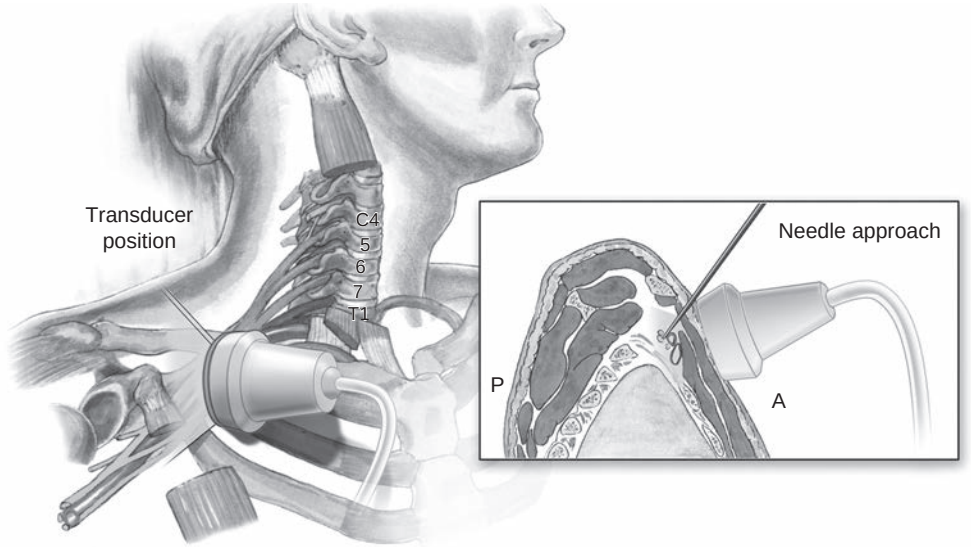

Fig. 180.2 Infraclavicular block. The brachial plexus is identified at the level of the cords. (From Infraclavicular block. In Brown DL, editor: *Atlas of regional anesthesia*, 4th ed. Philadelphia, Saunders, 2010, p 65.)

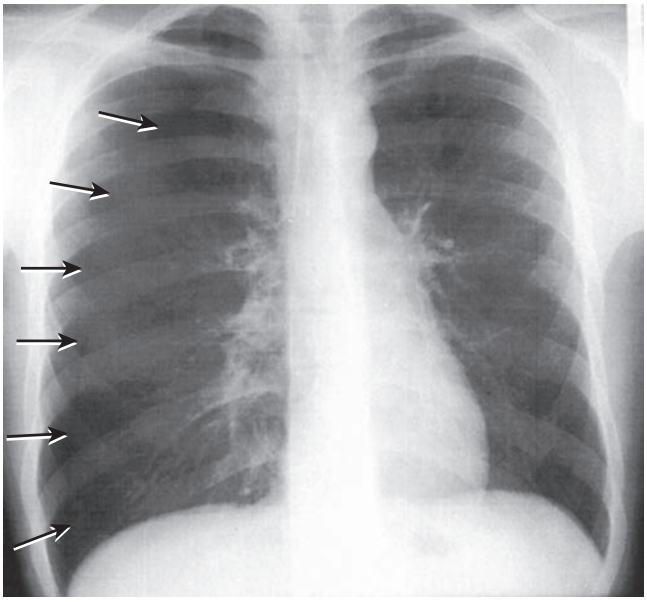

Fig. 180.3 Right-sided 40% pneumothorax. *Arrows* mark the visceral pleural line.

brachial plexus blocks (e.g., interscalene blocks). Although the incidence of hemidiaphragmatic paresis is significantly lower in patients having supraclavicular block compared with interscalene block, it is still estimated to occur in up to 50% of all patients. Infraclavicular block is rarely associated with changes in pulmonary function. If a patient's clinical condition suddenly deteriorates during mechanical ventilation, pneumothorax must be considered. Patients with a pneumothorax who are being ventilated with volume-controlled ventilators present with increased peak and plateau pressures, whereas those ventilated with pressure-controlled ventilators have reduced tidal volumes.

The chest may have a hyperresonant or tympanitic sound during percussion. Breath sounds may also be absent on the affected side. These signs are most notable when there is at least a 25% reduction in lung volume.

Although a computed tomography scan is the most sensitive study, a chest radiograph is usually diagnostic. Radiographs obtained at the end of expiration allow easier visualization because the pneumothorax takes up a greater proportion of the hemithorax during this part of the respiratory cycle. The main radiographic feature of a pneumothorax is a white visceral pleural line, separated from the parietal pleura by an avascular collection of gas. In most cases, no pulmonary vessels are visible beyond the visceral pleural edge (Fig. 180.3).

A modality that is gaining increased acceptance in the diagnosis of a pneumothorax is lung sonography. Among physicians with appropriate training, lung ultrasound has sensitivity that may exceed chest radiography. As ultrasonography equipment is now conveniently available in most regional block locations, lung sonography can allow for rapid detection of a pneumothorax when clinically suspected. Ultrasound features of a pneumothorax include the absence of both lung sliding and comet tail artifacts when imaging the anterior chest wall of a supine patient.

Risk Assessment

There has been a renaissance in popularity of supraclavicular brachial plexus blocks with the introduction of ultrasound imaging. Without ultrasound imaging the risk of pneumothorax during supraclavicular blocks ranged from 0.5% to 6.1%, whereas with ultrasound the incidence is in the range of 0.04% to 0.06%. Routine chest radiography after a supraclavicular block is not justified because of the low incidence of pneumothorax and the fact that the onset of symptoms may take up to 24 hours.

Implications

Normally, the pressure in the pleural space is negative with respect to the alveolar pressure during the entire respiratory cycle. If the needle punctures the chest wall during block placement, it creates a communication between the atmosphere and the pleural space. Air begins to enter the pleural space until the pressure gradient is eliminated or the communication is repaired. The main physiologic changes associated with a pneumothorax are decreased arterial partial pressure of oxygen (Po_2) and decreased vital capacity. The consequences are much more pronounced in patients with poor lung function, because a decrease in vital capacity can lead to respiratory insufficiency, which manifests as hypoventilation and ultimately respiratory acidosis.

Although a tension pneumothorax is unlikely in a spontaneously breathing patient, those who have positive-pressure mechanical

ventilation are at significantly increased risk. A tension pneumothorax occurs when the positive pressure of inspiration forces more air into the pleural space than exits during expiration. A sudden decline in the patient's cardiopulmonary status should raise suspicions of the presence of a tension pneumothorax. The deterioration in cardiopulmonary status is likely due to the combination of decreased cardiac output secondary to decreased venous return and extreme hypoxia due to ventilation-perfusion mismatching.

MANAGEMENT

If the patient has minimal symptoms and the pneumothorax is less than 15% of the lung volume, simple observation is advised. It is also necessary to provide the patient with supplemental oxygen, which will increase the rate of absorption of the pneumothorax. Because nitrogen is the primary gas in the pleural space, the gradient for nitrogen absorption into the blood is the main factor in determining the rate of reabsorption of a pneumothorax. Reabsorption can be accelerated by breathing 100% oxygen, which lowers the partial pressure of nitrogen in the blood, thereby increasing the gradient for nitrogen absorption from the pleural space.

If the patient has more than minimal symptoms or if the pneumothorax occupies more than 15% of the hemithorax, aspiration with a plastic catheter is the treatment of choice. If aspiration does not prevent expansion of the pneumothorax, tube thoracostomy should be performed.

Treatment of patients who are undergoing positive-pressure mechanical ventilation should include tube thoracostomy to prevent the development of a tension pneumothorax. Most often, the chest tube is inserted via an incision at the fourth or fifth intercostal space in the anterior axillary or midaxillary line and directed apically.

A tension pneumothorax is a medical emergency. When it is suspected, the patient should immediately receive 100% oxygen to alleviate hypoxia. A large-bore angiocatheter should be inserted into the pleural space through the second intercostal space, along the midclavicular line. If the diagnosis is confirmed by the aspiration of air through the catheter, the patient should undergo immediate tube thoracostomy.

PREVENTION

Many modifications have been made to supraclavicular and infraclavicular blocks to decrease the complication rate. In 1949 Bonica and colleagues first recommended a careful, gentle technique; thorough familiarity with anatomic relationships; use of the first rib as a protective shield over the lung; and use of a short, fine needle to help prevent complications, including pneumothorax. Now in the era of ultrasound-guided nerve blocks, real-time visualization of the needle tip and pleura should further reduce the incidence of pneumothorax. As in all ultrasound procedures, maintaining needle-tip view with good needle-to-beam alignment, optimizing the angle of incidence of the beam to the needle, and advancing only under direct guidance should reduce this complication. Intermittent hydrodissection and echogenic needles may enhance needle-tip visibility. Although the techniques have changed since being described by Bonica, the use of the first rib as a protective shield and a careful, gentle technique remain as excellent advice in the ultrasound era.

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181 Syringe Swaps

Carsten Nadjat-Haiem • Michael J. Sopher

Case Synopsis

A healthy 32-year-old woman is scheduled for elective myomectomy. General endotracheal anesthesia is induced, and the surgeon requests a dose of prophylactic cefazolin. The anesthesiologist administers the contents of a 10-mL syringe but realizes immediately that he has given phenylephrine instead. He administers incremental doses of nitroglycerin to reduce the anticipated hypertension from the syringe swap. The patient suffers no apparent ill consequences.

PROBLEM ANALYSIS

Definition

Syringe swaps constitute a significant subset of medication administration errors. Medication administration errors occur at a rate of 18 per 100,000 anesthetics, and syringe swaps account for about 6.4% of these. Syringe swap occurs when a syringe is mislabeled, or correctly labeled but mistaken for a different medication. Other common causes of medication administration errors are overdose or selection error of drugs, inadvertent high spinal anesthesia, and local anesthetic toxicity. These administration errors are not discussed in this chapter.

Recognition

A syringe swap is usually recognized when unexpected results are obtained after the administration of a drug or when an event occurs without a readily apparent explanation. The swap may also be recognized before any effect is observed. The most common error is administering another dose of muscle relaxant when reversal is desired.

Risk Assessment

Any patient is at risk for a syringe swap. Although studies show that fatalities from syringe swaps are rare, they still can cause significant morbidity. Interestingly, most syringe swaps have been shown to occur in "simple" anesthetics of American Society of Anesthesiologists (ASA) 1 and 2 patients. This is only partially explained by the fact that a majority of all anesthetics occur in ASA 1 and 2 patients. Less healthy patients are, however, more likely to be adversely affected by syringe swaps. Although syringe swaps constitute only a small subset of all medication errors, they are not a rare event: 85% to 94% of all respondents in surveys reported to have had at least one syringe swap in their career, and a significant number reported to have actually harmed patients.

Common causes of syringe swap include the following:

- Lack of vigilance when drawing up medications
- Lack of vigilance during administration of drugs (i.e., not actually reading the label)
- Failure to label syringes; mislabeling
- Failure to label syringes using color-coded labels
- Similar appearance of drug vials and syringes
- Poor drug tray organization
- Fatigue (sleep deprivation, boredom, alterations in circadian rhythm, work overload)
- Stressful environments, pressure to proceed, unfamiliar environments
- Change of shift
- Communication problems
- Inexperience; inadequate knowledge
- Distractions (computers, cellphones, loud music)

MANAGEMENT

Management of syringe swaps includes the following measures:

- Recognition of the mistake
- Treatment of consequences
- Investigation of the incident
- Institution of measures to prevent recurrence

If an incorrect drug has been administered, management initially consists of recognizing the mistake and treating any acute consequences. If the error is discovered quickly, as in the case synopsis, the practitioner should treat the consequences expectantly. If the mistake is not immediately apparent and an adverse event occurs, an immediate investigation in the operating room should occur. The room should be sealed off and subsequent cases postponed or moved to a different room to prevent a recurrence. The investigation should be systematic and include drugs used during the case. Inspection of vials used for the day should be performed. Analysis of the contents of syringes may also be necessary. Preventive measures should be instituted immediately by the anesthesia department to ensure that the mistake is not repeated.

If a complication results from the mistake, the patient and all parties immediately involved in the patient's care should be notified. All events should also be clearly documented in the chart. The risk management/quality assurance committee should also be notified, as well as other parties that may be involved, such as the pharmacy. If the syringe swap is the result of similar labeling of medications, the drug companies involved should be notified of the problem. The anesthesia department or responsible pharmacy should also take steps to differentiate drug vials further.

From a medicolegal standpoint, syringe swap is a violation of the standard of care and a clear-cut case of negligence. Advice from risk management should be sought at an early stage.

PREVENTION

Methods of prevention include three main categories:

- Vigilance
- Checking and rechecking
- Specific measures

The best method to prevent syringe swaps is vigilance on the part of the anesthesiologist in drawing up and administering medications. One should adhere to a strict routine in drawing up medications and recheck all drugs before administration. The following specific suggestions will help to prevent medication errors:

1. Check all drug vials closely before drawing them up into a syringe. This should include checking the name, expiration date, and concentration of the drug as labeled on the vial. A recent report identified the nearly identical appearance of 0.2% and 0.75% ropivacaine. One should also inspect the solution for any abnormal appearance or odor.
2. All syringes should be labeled *before* drawing up medications. A system is to have organized, preprinted, color-coded labels on the cart (Fig. 181.1). Blank labels are helpful for seldom-used medications. Syringes should be labeled circumferentially so the drug can be identified regardless of syringe orientation.
3. Use of different sizes of syringes is helpful. For example, induction agents are placed in larger 20-mL syringes, muscle relaxants in 10-mL syringes, and narcotics and other sedatives in smaller 3- or 5-mL syringes. Most syringe swaps occur between syringes of equal size.
4. Avoid drugs packaged in premixed syringes that have similar appearances. For example, lidocaine and epinephrine both come packaged in prelabeled glass syringes that have a very similar appearance. These labels can be particularly hard to read in poorly lit environments. If drugs are used in this type of packaging, place an additional label on the plastic part of the syringe that can be easily recognized, or restrict use to just one prepackaged medication (e.g., epinephrine).
5. Avoid drug containers that have a similar appearance. If drugs with similar packaging are placed on the cart, bright warning labels should be placed on the vials. Also, high-strength medications should be identified as such by additional labels, or not routinely placed on the drug tray. Medications should be clustered by group on the medication tray.
6. Never administer any drug from an unlabeled syringe.
7. Consistency in the way the anesthesia cart is stocked is of utmost importance. Drugs should always be placed in the same location on the cart, and be clustered by group (e.g., reversal agents, antihypertensive, muscle relaxants) (Fig. 181.2).
8. Resident education should include teaching techniques to ensure that meticulous attention is paid to the handling of drugs. Residents should be encouraged to develop strict routines when labeling and organizing syringes on top of the anesthesia cart. Separation of syringes into induction agents, muscle relaxants, opioids, and other medications on top of the cart might be helpful.
9. Recent evidence suggests that systems improvement measures can significantly reduce the incidence of syringe swaps. One such system employs barcode scanning of medications, and then auditory and visual confirmation of the drug chosen by a computer/dispensing device (Fig. 181.3). This has been shown to reduce the incidence of syringe swaps by 35% or more and has a high satisfaction rating among users.

Fig. 181.1 Color-coded syringe labels. An organized, well-stocked tray of color-coded syringe labels facilitates quick labeling of drug syringes. The standard D4774 of user-applied drug labels in anesthesia was introduced in 1983 and continues to be used today. These labels reduced the incidence of syringe swap, but certainly have not eliminated the problem.

Fig. 181.2 Drug tray organization. Consistent clustering of drugs into pressors *(top left),* reversal agents *(bottom left),* induction agents *(middle),* antihypertensives *(top right),* and paralytics *(bottom right)* reduces the risk of syringe swaps. Especially crucial is the spatial separation of reversal agents and paralytics. Additional labels on similar-appearing vials can further reduce risk (excluded in this specific tray). Note also the commercially available predrawn syringes in this tray, which are both horizontally and vertically labeled to reduce the risk of label "invisibility" when viewed at certain angles.

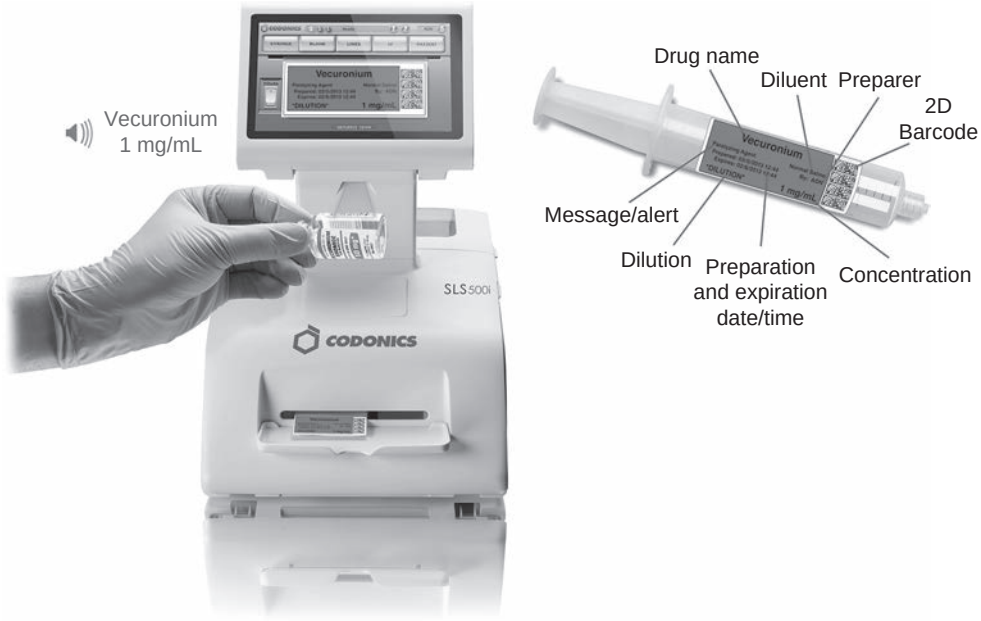

Fig. 181.3 Modern color-coded labeling system. New on the horizon are commercially available systems that scan drugs, print appropriate labels, and help confirm both visually (on the device monitor) and by auditory identification (by the device calling out the name of the drug) the drug being drawn up. Early studies show that these devices significantly reduce the incidence of syringe swap. (Image courtesy Codonics, Middleburg Heights, Ohio.)

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The Hostile-Combative Patient

182

Krzysztof Laudanski

Case Synopsis

A 14-year-old boy with an established diagnosis of autistic spectrum disorder is scheduled for a semielective release of hand contracture that he suffered as a sequela to a burn injury at age 5. He has had three prior surgeries and is known to have difficult emergence. Currently he is in the holding area obsessively playing a computer game on his tablet and ignoring requests to go to the operating room. His parents are distressed and apprehensive about the situation and frequently question the staff's ability to address the situation in an adequate manner.

PROBLEM ANALYSIS

Definition

The general assumption is that patients are coming for a procedure with the intention of having it performed. But that assumption is not universally true. A hostile patient is an individual who is uncooperative with the recommendations of the health care provider. Uncooperative behavior may be encountered during the initial interview, while inducing the case, or in the postanesthesia care unit (PACU).

Some patients actively resist treatment because of a limited ability to comprehend the procedure and its ramifications (e.g., intellectual disability), lack of psychological skills to cope with surgical stress (e.g., autistic spectrum disorder), or maladaptive coping strategies. There is also a cohort of intoxicated patients who display aggressive behavior due to an intake of psycho-stimulating substances. Some individuals may appear to be uncooperative due to the discomfort related to their primary illness or comorbidities (pain). Finally, an anesthesiologist may face a hostile and violent patient with clear and determined intent to sabotage treatment, inflict self-harm, or harm medical staff (violent prisoners). These clinical scenarios are further complicated by the presence of third parties (parents, police officers, friends, nursing staff) accompanying an individual and occasionally compounding an already complex situation. In summary, there is a plethora of reasons why patients may resist treatment or appear to do so. The anesthesiologist must be flexible enough to address several scenarios that will be unique in nature (Table 182.1).

Recognition

Careful examination of prior records can often reveal a preexisting difficult situation. Conversation with medical staff caring for the patient on a regular basis or with parents can be equally helpful. Also, the initial interview allows for assessment of the patient's potential for difficulty during a case. Patients coming from prison or an assisted-living institution should be assessed carefully for their ability to provide consent and general willingness to undergo a procedure.

During the initial interview, it is paramount that the patient's rights and preferences be respected because a wrong initial impression may result from misinterpretation of a patient's behavior. This may be especially true in individuals suffering from posttraumatic stress disorder or individuals who have experienced severe hospital-related trauma. Their high level of anxiety or reaction to seemingly similar situations as a result of psychological injury may be misinterpreted by medical staff.

Risk Assessment

The risks related to the interaction with difficult patients can be divided as related to the patient himself or herself, people accompanying the patient, and the medical staff. Also, a difficult behavior can be present at any point, sometimes surprising staff in the PACU, but most of the time it happens during transport of the patient. Often parents can elaborate on potential triggers initiating difficult behavior, its severity, and the best strategy to deal with them. Police can often provide some details on anticipated problems. In emergency situations, such assessments are much more difficult to anticipate.

TABLE 182.1 Potential Causes of Hostile or Combative Patient

Pharmacologic	Organic	Behavioral	Developmental	Social
Withdrawal syndromes	Delirium	ADD	Intellectual disability	Incarceration
Substance abuse	Dementia	Autism	Young age	
Delirium	Encephalopathy	PTSD		
Postanesthesia emergence	Uncontrolled pain	Anxiety		
	Urinary retention (postoperative)	Psychotic disorder		

ADD, Attention-deficit disorder; *PTSD*, posttraumatic stress disorder.

TABLE 182.2 Critical Parts of Anesthesia Planning for Difficult Patients

Organization	Environmental	Pharmacologic	Psychological
Interview with parents/caregivers Reassurances Securing extra staff Rehearse situation	Preoperative visit Avoiding interruptions and surprises Dim environment	Use nonintravenous methods to premedicate Inhalation anesthesia	Extensive interview

Implications

Performing anesthesia on a hostile patient may be challenging and have several serious implications. Obtaining consent may be difficult. In the case of a minor or a patient with an appointed guardian, securing permission for anesthesia may be relatively easy if documentation is unequivocal. This is frequently not the case. Hospital administration or a social worker can help in establishing a responsible party and obtaining contact information. An emergent court order may be sought, and all states have clearly delineated procedures on how to obtain one. In cases of delirious, encephalopathic (e.g., liver failure, posttraumatic brain injury), or demented patients, finding a responsible party may be challenging. A hostile patient with the capacity to make an informed decision scheduled for a nonemergent procedure but refusing to consent to the procedure will necessitate cancellation of the procedure.

In the case of an emergency procedure, the patient's general requests should be taken into account. For example, a patient who refuses a blood transfusion should have the case done with efforts to spare the patient's own blood and prevent anemia, but surgery or anesthesia should not be denied. In the case of a minor, legal emergency consent may be sought. Sometimes the patient may insist on one type of anesthesia. The patient's wish should be granted if the patient understands the implications of the decision and no unreasonable harm will come to the patient. However, if the anesthesiologist cannot grant the patient's request, the case should be delayed until the situation is resolved.

Choosing an anesthetic plan is of paramount importance because it will determine patient safety and satisfaction, as well as the safety of medical personnel. Regional anesthesia may be out of the question because it requires active patient cooperation; however, for some patients with anxiety related to general anesthesia, this may be a favorable way to perform anesthesia. Placing intravenous access can be problematic. Using EMLA, empathic support, and intramuscular anxiolytics can be considered. Another option is inhalation induction with subsequent placement of an intravenous access or using an inhalation anesthetic to lower anxiety.

Hostile patients may not cooperate with an airway examination. Thus a difficult airway should be anticipated. Uncooperative patients with a history of difficult airway is a real challenge, and prior medical records are pivotal for defining the strategy with which to establish a secure airway. Optimal conditions for denitrogenation may not be achieved, especially in a combative patient with increased closing capacity (e.g., obesity, obstructive sleep apnea). Placing appropriate monitoring may be impossible or postponed until the patient is rendered unconscious by the anesthesiologist.

An uncooperative patient is also at risk of injury if he or she falls. Self-harm may not be apparent, and sudden patient activity may surprise the staff. Often such behavior is exhibited by severely cognitive-impaired individuals on both ends of the age spectrum. Often such behaviors surprise staff during transport or when preparations for moving the patient are taking place. Conversation with the caregiver is pivotal in anticipation of such behavior. Proper planning may include using continuous monitoring of patient behavior, padding the bed, using personal protection equipment, having a dedicated staff member watch the patient, and, last, resorting to physical or pharmacologic restraints.

An intoxicated patient exhibiting aggressive behavior should be removed from the schedule. Frequently acute intoxication results in hemodynamic instability and a high incidence of emergence delirium. These risks outweigh the potential benefit if the scheduled case is nonemergent. In emergent cases, anticipation of emergence delirium should be considered, and the patient may be premedicated with adjunct medications (e.g., antipsychotic, clonidine).

Patients with intentional aggressive behavior should be accompanied by security or a police officer. Often the presence of these officers is required by prison regulations in the operating room or PACU. Hence adequate planning to accommodate their needs and requirements must be undertaken.

MANAGEMENT

It is advisable to discuss the management strategy to deal with any potential scenario with nurses, operating room staff, and people accompanying the patient. Anticipatory planning reduces confusion, especially if the situation is getting out of control. It is always good practice to secure extra resources to help if the situation quickly escalates.

The key to successful handling of the difficult, uncooperative patient is patience, planning, and vigilance. Surprises and hastiness increase lack of understanding. Thus avoidance of rapid interruption should be a rule. Persuasion, reasoning, and openness are pivotal for success. These are determined by the nature of the interaction between the anesthesiologist and difficult patients.

In the presented case, the parents are the primary source of information and support. They may accompany the child to the operating room until induction, allowing for stress reduction and avoidance of medications with prior paradoxic reaction. However, one has to bear in mind that overanxious parents can be a source of distraction, and the wise anesthesiologist will address the needs of both the child and parents. Often, parents of children with preexisting conditions are stressed out and well versed in medical terminology. This may add to an already difficult situation if this aspect is not handled well. Using premedication should be reserved as one of the last resorts because children with cognitive or coping impairment more often respond with an increased agitation to anxiolytics. In some situations, stress to the child can be reduced by organizing a preoperative visit. This allows for habituation of the child with a coping problem to the environment of an operating room. However, this solution may not be possible due to busy schedules.

Toys can be used as a distraction while a variety of agents can be applied even if the patient has no intravenous access. If the patient is agreeable to receiving premedication, the oral route is usually preferred. Otherwise, an intravenous or (more commonly) intramuscular approach is used. Some advocate the use of physical

restraints, but this is a measure of last resort considering that it may aggravate the situation. Restraints should be reserved for situations in which the patient is clearly going to harm himself or herself or the staff. After induction, the anesthesia maintenance period provides a break for the staff. Emergence from anesthesia may be difficult, and sometimes dexmedetomidine or propofol is recommended, but the response may be variable. A history of good reaction to any agent is the best prognostic. Consequently, the value of interview with parents and review of medical records cannot be overestimated. Deep extubation, assuming that the patient has a favorable airway condition, may be one way to avoid agitation, but emergence delirium may occur regardless. Parents' presence and reassurance are often the best measures. Sometimes resorting to an antipsychotic agent may be indicated. Having a difficult patient experiencing emergence delirium should not abolish the investigation of other reasons for patient behaviors (excessive pain, metabolic derangement, full bladder, ischemia, etc.).

PREVENTION

Preparation is key for successful anesthesia in cases of hostile and combative patients. Involving the parent, child, and all medical staff is paramount for success. Providing a calm environment with a favorite distraction is helpful. There is a lack of conclusive studies on the best way to manage difficult patients at the beginning of anesthesia. The experience of the anesthesiologist is the key for successful resolution.

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183 Thromboembolic Complications

Gerard R. Manecke

Case Synopsis

A 53-year-old man underwent posterior spinal fusion with instrumentation, involving segments L1–L4. His past medical history included protein S deficiency, for which he received warfarin therapy. He discontinued his warfarin therapy 2 weeks before surgery without telling his health care providers. His uneventful surgery lasted 8 hours. One hour postoperatively he became tachypneic, his blood pressure dropped from 130/80 to 88/50 mm Hg, and his oxyhemoglobin saturation dropped from 99% to 88%. Acute pulmonary embolus was diagnosed.

PROBLEM ANALYSIS

Thromboembolic events, being some of the most feared complications of the perioperative period, represent the most common cause of in-hospital mortality. They are often life threatening (pulmonary embolus), limb threatening (peripheral arterial embolus), or of great danger to the central nervous system (cerebrovascular embolus). Anesthesiologists, as leaders in the perioperative surgical home, are expanding their role in the perioperative period. They are increasingly relied on to prevent and treat complications such as thromboembolism.

Definition

Thromboembolism is a spectrum of vascular occlusive disorders involving intravascular blood coagulation. Thrombosis refers to the formation of clot, and embolism the dissemination of clot or other substances to parts of the vascular tree. In addition to clot, substances such as intravascular gas and bone marrow can result in embolus (Table 183.1). The venous or arterial sides of the circulation may be involved, including the cerebral vasculature, chambers of the heart, coronary arteries, and pulmonary arteries (Table 183.2). The focus of this chapter is on two manifestations of venous thromboembolism (VTE): deep venous thrombosis (DVT) and pulmonary embolus (PE).

RISK ASSESSMENT AND MANAGEMENT

The risk of DVT has been estimated to be as high as 30% in general surgical patients, although the data supporting this include older data that do not reflect newer, more effective means of prophylaxis. The risk of PE in general surgical patients may be as high as 1%. Surgical patients often present with hypercoagulable states resulting from such conditions as cancer, chemotherapy, pregnancy, and inherited disorders such as protein C deficiency. Prior histories of DVT or PE are strong risk factors, and smoking and obesity are risk factors as well. Importantly, major surgery and trauma themselves result in hypercoagulability, placing those patients at very high risk for perioperative thromboembolic complications.

The risk of VTE should be considered in all patients undergoing surgery, with prolonged, major surgery presenting greater risk. Patients with additional risk factors (Table 183.3) require particular attention. Various methods have been used to stratify the risk in hospital patients, with the Caprini scoring system being popular (Fig. 183.1). Based on this scoring system, prophylactic measures such as early ambulation, unfractionated low-dose heparin, sequential compression stockings, and elastic stockings are used. Because patients undergoing surgery are at risk, perioperative protocols that include pneumatic sequential compression stockings, pharmacologic prophylaxis, and early mobilization are common. A "three-bucket" model for prevention of perioperative VTE can be used, with low-risk patients requiring minimal prophylaxis, medium-risk patients receiving either pneumatic compression devices or low-dose heparin (fractionated or unfractionated), and high-risk patients receiving *both* pneumatic compression *and* low-dose heparin (Table 183.4). The risk of increased bleeding from low-dose thromboprophylaxis is low, so the "three-bucket" model is applicable to most surgeries.

TABLE 183.1 Sources of Embolus

Embolism Source	Clinical Scenarios
Venous thrombus	Deep venous thrombosis, immobility, hypercoagulable state
Air	Surgery in the sitting position; back surgery with surgical site elevated above the level of the heart; accidental air in venous infusion; open chamber cardiac surgery; accidental entrainment in coronary artery during coronary surgery
Carbon dioxide (CO_2)	Gas embolus during laparoscopic surgery; open chamber cardiac surgery in which CO_2 is used
Oxygen	Orthopedic use of hydrogen peroxide as irrigant in long bone surgery
Catheters, catheter fragments, guidewires, guidewire fragments	Complications of vascular access attempts
Septic embolus	Prolonged infection (catheter site, endocarditis, abscess)
Tumor embolus	Renal cell carcinoma, cardiac chamber tumor
Fat embolus	Long bone fracture, surgery

TABLE 183.2 Selected Thromboembolic Phenomena and Their Clinical Manifestations

Site	Predisposing Factors	Clinical Consequences and Sequelae
Deep venous thrombosis	Venous stasis	Pulmonary embolus, inferior vena cava thrombosis, superior vena cava syndrome
Pulmonary embolus	Deep venous thrombosis, hypercoagulable state	Shock, death, residual pulmonary hypertension
Peripheral arterial thrombosis or embolus	Atrial or ventricular septal defect, thoracic aortic or peripheral arterial surgery	Organ, limb ischemia or infarction
Cerebral artery thrombosis or embolus	Arterial atherosclerosis, atrial or ventricular septal defect, surgery involving the carotid artery or aortic arch	Stroke
Coronary artery thrombosis	Coronary stent, withdrawn from antiplatelet agents, severe coronary artery disease	Sudden myocardial infarction
Coronary artery embolus	Arterial atherosclerosis, atrial or ventricular septal defect, surgery involving the aortic arch	Myocardial ischemia or infarction
Cardiac chamber thrombosis	Atrial fibrillation, heart failure	Arterial embolus

TABLE 183.3 Risk Factors for Perioperative Thromboembolism

Hereditary hypercoagulability	Protein C deficiency
	Protein S deficiency
	Factor V Leiden
	Antiphospholipid syndrome
	Dysfibrinogenemia
	Antithrombin deficiency
Acquired hypercoagulability	Major surgery, trauma
	Cancer
	Chemotherapy
	Oral contraceptives
	Hormone replacement therapy
	Polycythemia vera
	Acute illness
Other risks	Venous stasis disease, history of deep venous thrombosis or pulmonary embolism
	Smoking
	Atrial fibrillation
	Advanced age
	Immobility, orthopedic cast, obesity
	Central vein catheter
	Atrial septal defect: paradoxic embolism

Venous Thromboembolism

Deep Venous Thrombosis

DVT is relatively common, usually presenting with calf pain and lower extremity swelling. Risk factors include hypercoagulable states, venous stasis, and endothelial injury ("Virchow's triad"). Prolonged immobility, resulting from such entities as spinal cord injury, travel, or surgery, has been identified as an important risk factor, likely because it results in venous stasis. In addition, the humoral stress response to surgery results in hypercoagulability.

The diagnosis of DVT is made by maintaining a high index of suspicion in the perioperative period, detecting its common signs and symptoms, and confirmation with ultrasound or radiographic tests. Common signs of DVT include swelling in a lower extremity, often along the path of a leg vein, pain, redness, and warmth. The diagnosis is confirmed by ultrasound studies of the lower extremities, venography, or magnetic resonance imaging (MRI). Venous thrombi can form in the proximal veins of the extremities, as well as in the pelvis, with the larger, more proximal thrombi presenting the greatest risk of vascular compromise and embolus. Patients undergoing major surgery often have their anticoagulants "held" because of the risk of surgical bleeding, but the other edge of this "two-edged sword" is that the patients are thus placed at increased risk of thrombus formation and embolus.

When DVT develops in the perioperative period, it must be diagnosed quickly and treated aggressively with anticoagulation and mobilization, because it can lead to PE and arterial (paradoxic) embolus in patients with connections between the right and left sides of the circulation (e.g., atrial septal defect, patent foramen ovale). Bleeding is a risk in the surgical patient receiving higher-dose anticoagulation, making the management of perioperative VTE very challenging. Aggressive approaches such as heparin infusion or thrombolytic therapy, although often appropriate for nonsurgical patients, may place surgical patients at great risk for hemorrhage. Thus the timing and dose of the anticoagulant should be discussed with the surgeon, along with the potential risks of delaying treatment. Consultation with a hematologist may be helpful as well. An inferior vena cava filter, to decrease the risk of PE, may be indicated, particularly in those in whom anticoagulation is contraindicated. Patients with perioperative DVT require continued postoperative care for many months after the event, and planning for this should occur before discharge from the hospital.

Patients such as those with trauma or liver disease who are bleeding are often treated with blood products such as fresh frozen plasma, platelet concentrates, cryoprecipitate, and concentrates of factor VII or IX. It is not uncommon for these patients, in the course of such treatments, to become hypercoagulable. This hypercoagulable state, together with low cardiac output, can predispose the patient to thrombosis of the inferior vena cava (IVC). This is life threatening, causing a dramatic decrease in cardiac output because of decreased venous return to the heart. IVC thrombosis in these circumstances is best prevented by careful monitoring of the coagulation system during treatment of coagulopathies, and administration of factor VII or IX concentrates in divided doses. The diagnosis may be made with abdominal ultrasound, computed tomography, or MRI.

Venous thrombosis may also form in the upper extremities or superior vena cava, resulting in superior vena cava syndrome. This is characterized by swelling of the face, neck, and upper extremities, and may lead to airway and vascular compromise.

Pulmonary Embolus

PE is a potentially life-threatening condition in which venous thrombosis has embolized to the pulmonary circulation. In the case of large emboli, significant portions or sometimes all of the pulmonary circulation may be occluded, resulting in right-sided heart failure and interrupted pulmonary gas exchange. Hypotension with shock or cardiac arrest may occur, along with hypercarbia, hypoxemia, and acidosis. In the case of smaller emboli, pulmonary infarction with hemoptysis may be present.

Awake patients, such as the one described in this chapter's case synopsis, may complain of dyspnea and occasionally pleuritic chest

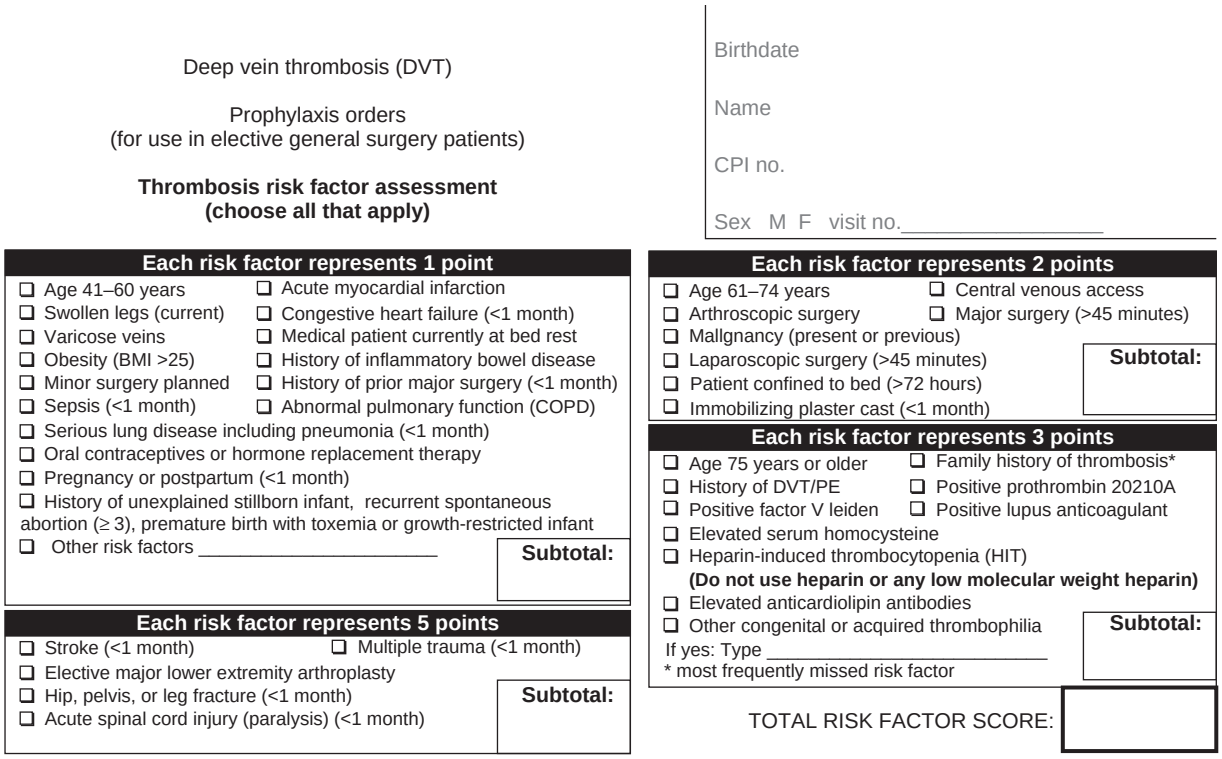

Fig. 183.1 **The Caprini scoring system allows risk stratification for the development of venous thromboembolism.**

TABLE 183.4 A "Three-Bucket" Approach to Thromboprophylaxis in Surgical Patients

Low risk: Minor surgery, early ambulation	Minimal prophylaxis: antithromboembolism stockings
Medium risk: Most general, thoracic gynecologic laparoscopic or open surgery	Pneumatic compression stockings *or* low-dose heparin (UFH 5000 U SQ q 8–12 h, or enoxaparin 40 U SC qd or 30 U SC q 12 h)
High risk: Hip or knee arthroplasty, trauma, spinal cord injury, abdominal and pelvic surgery for cancer	Pneumatic compression stockings *and* low-dose heparin (UFH 5000 U SC q 8–12 h, or enoxaparin 40 U SC qd or 30 U SC q 12 h)

SC, Subcutaneous injection; *U,* units; *UFH,* unfractionated heparin.

TABLE 183.5 Common Causes of Shock

↓ Left Ventricular Preload	↓ Afterload	↓ Contractility
Hypovolemia • Hemorrhage	Vasodilation • Anesthetic • Antihypertensive	Myocardial infarction Myocardial ischemia
Right ventricular failure • PE • Bronchospasm • Fat embolism • Pneumothorax • Protamine	Anaphylaxis • Latex • Antibiotic • Muscle relaxant	Cardiac trauma, contusion
Cardiac tamponade	Anaphylactoid reaction • Vancomycin • Protamine	Hypoxia Cardiomyopathy

PE, Pulmonary embolus.

pain. Wheezing, neck vein distention, hypotension, and cyanosis may be noted as well.

In anesthetized patients, the sudden onset of hypotension along with a large decrease in end-tidal carbon dioxide ($ETCO_2$) may be the first sign of massive PE. Arterial blood gas may reveal hypercarbia and a large gradient between arterial Pco_2 and $ETCO_2$, indicating the significant dead-space ventilation that is characteristic of PE. Minimally invasive cardiac output monitoring, such as esophageal Doppler or arterial-based systems, will show a decrease in cardiac output, helping to distinguish PE from high cardiac output shock states resulting from vasodilation (e.g., anaphylaxis). Central venous pressure will be high, distinguishing PE from hypovolemia. The differential diagnosis of shock states is rather broad (Table 183.5), so a high index of suspicion facilitates the diagnosis of PE. The same risk factors that predispose patients to DVT are risk factors for PE, and patients with previous or current DVT are at particularly high risk.

The quickest bedside test to help in the differential diagnosis of sudden-onset shock is echocardiography. Either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) can be used. TEE may be preferred because of superior visualization of the pulmonary arteries. In massive PE, either TTE or TEE will show signs of right-sided heart failure, including right atrial dilation, right ventricular dilation, and interventricular septal shift to the left (Fig. 183.2). Emboli may be noted in the right-sided chambers or in the proximal pulmonary arteries, although their presence is not absolutely necessary for the diagnosis because they may migrate distally by the time the echocardiography is performed. PE can often be confirmed by thoracic MRI, and the source may be found using abdominal MRI or other imaging modalities of the extremities. Laboratory studies may include D-dimers, a sensitive but nonspecific marker of PE.

Management of PE may require full cardiopulmonary resuscitation. Subsequently decisions must be made about anticoagulation and possible thrombolysis. These decisions are best made in concert with the surgeon and other consultants because the risk of bleeding

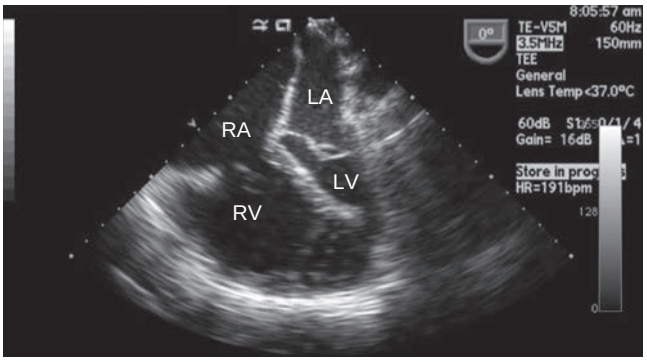

Fig. 183.2 Transesophageal echocardiograph in a patient with acute pulmonary embolus. The midesophageal four-chamber view shows severe dilation of the right ventricle (RV) and right atrium (RA), indicating RV failure. There is bowing of the ventricular and atrial septae toward the left ventricle (LV) and left atrium (LA). Severe compression of the LA and LV causes decreased filling and poor function of those chambers.

from these treatments, particularly in perioperative surgical patients, is high. In some centers surgical pulmonary embolectomy is performed, although this is not common.

A common, underappreciated long-term sequela of PE is chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary thromboendarterectomy is the most effective treatment of this condition and is now increasingly performed around the world. Patients with CTEPH presenting for other surgery should be receiving long-term anticoagulation; and anticoagulation must be continued with the shortest window of withdrawal possible. These patients often have residual pulmonary hypertension, so complete preoperative assessment with full knowledge of functional status and condition of the pulmonary circulation must be obtained whenever possible. In patients receiving pulmonary vasodilators, it is advisable to continue this treatment throughout the perioperative period, because its withdrawal (particularly prostaglandins) may result in catastrophic rebound pulmonary hypertension.

Paradoxic Embolus

Patients with or at risk for VTE who have connections between the right and left sides of the circulation, such as atrial septal defect, ventricular septal defect, or patent ductus arteriosus, are at risk for travel of embolic material from the right to the left side of the circulation. This can result in stroke or infarction of various organs such as the spinal cord, mesentery, and kidney. Patients with such defects in whom major noncardiac surgery is planned should undergo cardiology assessment with consideration of closing the defect, either with interventional cardiology or surgery. This is especially important in patients who already have a history of paradoxic emboli.

Arterial Thrombosis

Patients with severe peripheral vascular disease, poor cardiac output, and hypercoagulability are at risk for arterial thrombus, or left ventricular thrombus leading to embolus. These patients should be managed accordingly, with thromboprophylaxis and early mobilization as tolerated.

Coronary Artery Thrombosis

Patients with coronary stents, particularly drug-eluting stents, are at risk for coronary stent thrombosis in the perioperative period. This is a potentially fatal complication, resulting from rapidly progressing myocardial infarction. Patients with drug-eluting stents are often receiving antiplatelet therapy. Such therapy should be continued perioperatively with the shortest window of interruption possible. Close collaboration among the anesthesiologist, surgeon, and cardiologist is critical, and complete information about the anatomy, date of placement, and type of stents should be available. Ideally, each institution should develop a protocol for managing patients with coronary stents, with a multidisciplinary team consisting of anesthesiologists, cardiologists, and surgeons overseeing the process and agreeing on the approach.

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184 Unanticipated Hospital Admission and Readmission

Zhuang T. Fang

Case Synopsis

A 45-year-old woman, body mass index (BMI) 24, American Society of Anesthesiologists (ASA) physical status 2, underwent left eye orbitotomy for the correction of thyrotoxic exophthalmos under general anesthesia in a freestanding ambulatory surgical center. The patient tolerated the procedure well without anesthetic complications. However, the surgery was unexpectedly difficult and lasted more than 2 hours. The estimated blood loss (EBL) was about 50 mL. Postoperatively, the patient complained of severe pain in her left eye, which did not improve and worsened after multiple doses of intravenous fentanyl and hydromorphone. The surgical team was called and came to the postanesthesia care unit (PACU) to examine the patient. They found that the patient's left orbit was swelling, and the intraocular pressure was elevated, likely due to an intraorbital hemorrhage. The patient was taken back to the operating room late in the afternoon for exploration of the orbit. A blood clot was evacuated from the orbit, but continued oozing persisted. The EBL was 300 mL for this procedure. The patient was transferred by ambulance to the hospital for angiography to determine the source of bleeding and further treatment. No active bleeding was identified, and the patient lost her vision in the operated eye. She was an inpatient for several days for observation and treatment. Her vision eventually recovered.

PROBLEM ANALYSIS

Definition

Unanticipated hospital admission is defined as any admission of a patient after scheduled outpatient surgery that was not planned preoperatively. Overall, the incidence of unanticipated hospital admission has been reported to range from 0.6% to 9.4% depending on the setting of the surgical centers (hospital-affiliated vs. freestanding), the types of surgeries performed, and the patient population. Unanticipated hospital readmission includes patients who are readmitted to the hospital within 30 days after being discharged and ranges from 0.15% to 1.3%.

Unanticipated Hospital Admission

Outpatient surgery has been steadily increasing over the last three decades, accounting for 65% of all surgeries, or over 53.3 million procedures annually in the United States. The advantages of outpatient surgery include greater convenience for both surgeon and patient, and considerable cost savings. These advantages disappear when an unplanned hospital admission is required due to surgical or anesthesia complications. From a management standpoint, unanticipated hospital admission after outpatient surgery is an important measure not only for patient morbidity, but also for quality and safety of ambulatory surgical centers.

Unanticipated Hospital Readmission

The majority of patients usually recover well after outpatient surgery. However, about 1% to 3% of patients will visit emergency departments within 30 days after being discharged to home. Among these patients, 46% to 85% were admitted to the hospital. The main reasons for readmission are bleeding, pain, urinary retention, fever, and infection.

Recognition

In the last decade, the complexity of surgical procedures has increased, and a wider range of patients who used to be considered not suitable for outpatient surgery are now considered acceptable. This increase has occurred mainly because of the advances in noninvasive surgical techniques, new anesthetics with decreased side effects, and the increased use of regional anesthesia in conjunction with monitored anesthesia care (MAC). Studies have shown that increased age, higher ASA physical status, increased duration of surgery, and complex medical problems are associated with higher likelihood of intraoperative and postoperative complications leading to unanticipated hospital admission. Identification of surgical, anesthetic, and socioeconomic risk factors for unanticipated hospital admission during preoperative evaluation is essential for the prevention of these events. Vigilant monitoring and early recognition of surgical and anesthetic complications that are refractory to adequate intervention and treatment in the PACU are also important for timely hospital transfer to a higher level of care to prevent patient harm. In addition, careful evaluation of patients and identifying risk factors at the time of discharge to home are also important measures for the prevention of hospital readmission.

Risk Assessment

Approximately 40% of unanticipated hospital admission after ambulatory surgery is because of surgical complications; 20% are due to anesthesia complications. These include postoperative nausea and

TABLE 184.1 Odds Ratios for Short-Term Hospitalization Based on the Outpatient Surgery Admission Index (OSAI)

OSAI	Odds Ratio (OR) of Unanticipated Hospital Admission
0 and 1	
2	9.5
3	20.6
4, 5, and 6	31.96

Adapted from Fleisher LA, Pasternak LR, Lyles A: A novel index of elevated risk of inpatient hospital admission immediately following outpatient surgery. *Arch Surg* 142(3):263-268, 2007.

vomiting (PONV), somnolence and aspiration, medical complications related to diabetes mellitus, ischemic heart disease, sleep apnea, and socioeconomic reasons.

Excessive surgical bleeding, oozing, and severe pain, as presented in the case synopsis, account for the majority of unanticipated hospital admissions due to surgical complications. For this young, nonsmoking female patient, nausea and vomiting secondary to poorly controlled pain further increased her likelihood of hospital admission. Temporary or permanent vision loss is a severe complication of orbital surgery, possibly caused by direct nerve injury, compression of the ophthalmic nerve by a hematoma leading to ischemia, or increased intraocular pressure.

In general, the following risk factors have been identified in association with unanticipated hospital admission:

1. Length of surgery of more than 120 minutes
2. Unexpected extensive surgery
3. ASA class III or higher
4. Advanced age (>80 years)
5. General anesthesia
6. Obesity with BMI greater than 30

Elderly patients with complex medical problems potentially face a higher incidence of medical and anesthesia complications intraoperatively and postoperatively. The Outpatient Surgery Admission Index (OSAI) has been studied to assess the elevated risk of inpatient admission after outpatient surgery due to patient comorbidities (Table 184.1). Patients with an OSAI score of 3 are 21 times more likely to be admitted to the hospital after outpatient surgery compared with those with a score of 0 or 1. The odds of an unanticipated hospital admission will increase to 32 times in patients with a score of 4, 5, or 6. However, patients with a high OSAI score are not necessarily to be excluded from outpatient surgery because the overall incidence of unanticipated hospital admission is still low.

The odds ratio compares each level to 0 and 1. One point is given for each of the following risk factors: operating time longer than 120 minutes, each of the medical comorbidities (cardiac, peripheral vascular disease, cerebrovascular disease, malignancy, and seropositive human immunodeficiency virus status), regional anesthesia, and 65 years or older. Two points are given for general anesthesia.

Obesity and obstructive sleep apnea (OSA) are not independent risk factors for unanticipated hospital admission after ambulatory surgery. However, if OSA patients who are on continuous positive airway pressure (CPAP) at home are having surgery of the airway or face making the use of CPAP impossible postoperatively, they will not be candidates for outpatient surgery. Obese patients are more likely to have at least one hospital-based acute care encounter within 30 days of discharge (7.3% vs. 3.6%) or serious adverse event (3.2% vs. 0.9%) compared with nonobese patients in a study of outpatient plastic surgery. Obese patients also had adjusted hospital charges, on average, $3700 to $7400 greater than those of nonobese patients for their procedures. In addition, obese patients have greater rates of surgical and anesthesia complications because of their medical comorbidities, including hypertension, diabetes, mental health diagnosis, chronic respiratory disease, and sleep apnea. The increased respiratory complications under general anesthesia or MAC during surgery or PACU recovery may require a prolonged PACU stay and possible hospital admission if their hypoventilation and hypoxia persist. One study found that the rate of unplanned admission was 7.0% versus 5.6%, respectively, in obese patients with or without OSA.

Implications

The need for transfer/admission is an unanticipated outcome of ambulatory surgery and could be the result of insufficient accuracy in patient or procedure selection. Hospital transfers/admissions can result in unplanned cost and time burdens that must be borne by patients and payers. It also reflects the quality of the outpatient surgery service. In addition, both the patients and their family are affected by the unscheduled hospital admission, especially for the pediatric patients and their parents, whose work schedules unfortunately have to be changed.

MANAGEMENT

When surgical or anesthesia complications are anticipated, patients should be treated aggressively to prevent patient injury. When unplanned hospital admission is indicated, the admission process should be activated in a timely and orderly fashion to ensure patient safety during transfer. Adequate communication among anesthesiologists, surgeons, PACU nurses, patients, and family members is essential for a smooth process. In surgical centers with capacity for overnight observation without a high level of surgical or medical treatment, such as PONV or pain, this is often the least expensive alternative. Pediatric patients with respiratory complications are usually not appropriate for a 23-hour stay in the freestanding surgical center due to inadequate support of nursing personnel and equipment, and therefore must be admitted to the hospital. Detailed documentation of complications, treatment, and necessity for hospital admission is essential for both insurance and medicolegal justification.

Surgeons are usually the primary team taking care of patients who are admitted to the hospital after ambulatory surgery. Like the patient in the synopsis, the majority of patients were readmitted for additional surgery. The risk of unanticipated hospital admission is highest for general surgery, followed by obstetrics/gynecology, urology, and ears/nose/throat. During the hospitalization, patients need to be treated aggressively for either surgical or anesthetic complications, especially pain, which is a common reason for hospital readmission.

PREVENTION

Careful preoperative evaluation of patients and procedures is the key for the prevention of unanticipated hospital admission after outpatient surgery. Patient selection should focus on identification of risk factors and determination of the surgery venue (e.g., outpatient surgical center vs. hospital operating rooms), as well as adequate planning for treatments and hospital transfer when potential surgical and anesthesia complications occur.

Key Factors for Preoperative Consideration

1. Assess risk factors for unanticipated hospital admission.
2. Pay special attention to the invasiveness and length of surgery.

3. Evaluate elderly patients thoroughly for comorbidities.
4. Refer high-risk cases to a hospital inpatient surgery venue.

Key Factors for Intraoperative Management

1. Use regional anesthesia or MAC whenever possible.
2. Avoid drugs causing oversedation and altered mental status.
3. PONV prophylaxis in patients with history or at high risk for PONV:
   a. Use total intravenous anesthesia technique, or combine propofol with volatile agents except nitrous oxide.
   b. Administer multimodal antiemetic therapy (hydration, dexamethasone, serotonin inhibitors, metoclopramide, H2 receptor inhibitors).
   c. Provide adequate hydration.
   d. Consider the use of analgesic adjuncts (e.g., intravenous acetaminophen, ibuprofen, ketorolac).
4. For patients at high risk of postoperative pain, use a multimodal approach:
   a. Regional blocks or wound infiltration with local anesthetics.
   b. NSAIDs and opioids.
5. In pediatric patients with mild upper airway infection, avoid intubation

Key Factors for Postoperative Management

1. Early intervention for hypoventilation and hypoxia.
2. Treat hypotension aggressively.
3. Treat pain early and effectively.
4. Treat PONV early and adequately.
5. Maintain adequate hydration, but be careful in patients with congestive heart failure or on hemodialysis.

The prevention of unanticipated hospital admissions needs a systematic approach, including assessment of the risk factors during preoperative screening, early recognition of high-risk patients who are not candidates for outpatient surgery, and deferring their surgery to an inpatient venue. Early intervention of patients' underlying diseases intraoperatively and postoperatively, early identification of surgical complications in the PACU, and aggressive treatment of pain and PONV are also required. For obese patients, especially those with OSA, or with high OSAI scores undergoing extensive surgery, ambulatory surgery may not be an appropriate choice of venue. With this approach, it is possible to avert or decrease unanticipated hospital admissions, as well as the morbidity and mortality associated with ambulatory surgery.

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Uncontrolled Acute Postoperative Pain

185

Ronnie H. Zeidan • Peter K. Yi

Case Synopsis

A 35-year-old woman is scheduled for a partial colectomy due to complications from her ulcerative colitis. She has a history of migraine headaches, endometriosis, fibromyalgia, and nonspecific low back pain. She is currently on a high-dose oral opioid regimen. She is nervous, having catastrophizing thoughts about not surviving, and having chronic and difficult-to-treat pain after her surgery.

PROBLEM ANALYSIS

Definition

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective; each individual learns the application of the word through experiences related to injury in early life."

Postoperative pain can be divided into one of two broad categories: acute postoperative pain and chronic postoperative pain. *Acute pain* is defined as "pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease" and is typically expected to last up to 7 days. In contrast, *chronic pain* "commonly persists beyond the time of healing of an injury and frequently there may not be any clear identifiable cause" (IASP, 2014) and persists for more than 3 months.

Recognition

Assessment of the patient's postoperative pain is the first step in appropriately managing acute postoperative pain. Pain is a subjective experience that is a result of multiple variables that encompass physiologic and psychological components, which does not allow for objective measurement. However, a 10-point pain assessment scale, where 1 is no pain and 10 is the worst possible pain imaginable, has been nationally accepted. The rating given to the patient's pain depends on both the patient and the observer. An important part of the evaluation is documented follow-up assessments to note the efficacy of the therapy and the patient's satisfaction with it in order to intervene early before pain becomes uncontrolled.

Risk Assessment

The risk for uncontrolled acute postoperative pain is applicable to almost anyone exposed to unpleasant sensory and emotional experiences associated with a surgical procedure. According to the Centers for Disease Control and Prevention, 51.4 million surgical inpatient procedures were performed in 2010 in the United States, which makes this issue extremely relevant. Studies have shown that at 24 hours postsurgery, 60% of patients had a pain score of 5 or more on movement (0 = no pain; 10 = unbearable or very severe); at 7 days postoperatively, 39% had a pain score of 5 or more on movement; and 8% reported a pain score of 8 to 10. Box 185.1 lists risk factors for those most susceptible to uncontrolled postoperative pain.

Implications

Perioperative pain results from inflammation caused by tissue trauma (i.e., surgical incision, dissection, burns) or direct nerve injury (i.e., nerve transection, stretching, or compression). Tissue trauma releases local inflammatory mediators that can produce augmented sensitivity to stimuli in the area surrounding an injury (hyperalgesia) or misperception of pain to nonnoxious stimuli (allodynia). Other mechanisms contributing to hyperalgesia and allodynia include sensitization of the peripheral pain receptors (primary hyperalgesia) and increased excitability of central nervous system neurons (secondary hyperalgesia). These physiologic responses can potentially contribute to uncontrolled pain responses in the postoperative period, as well as increased morbidity and mortality after surgery (Table 185.1).

A surge in sympathetic efferent nerve activity increases heart rate, contractility, and blood pressure. As sympathetic activation increases myocardial oxygen demand, the risk of cardiac ischemia increases. Special considerations and appropriate interventions should be implemented to

BOX 185.1 Risk Factors for Postsurgical Pain

- Preoperative factors
  - Pain, moderate to severe, lasting >1 month
  - Repeat surgery
  - Psychological vulnerability
  - Preoperative anxiety
  - Female gender
  - Younger age (adults)
  - Workers' compensation
  - Genetic predisposition
  - Inefficient diffuse noxious inhibitory control
- Intraoperative factors
  - Surgical approach with risk of nerve damage
  - Avoidance of nitrous oxide anesthesia
- Postoperative factors
  - Pain (acute, moderate to severe)
  - Radiation therapy to surgical site
  - Neurotoxic chemotherapy
  - Depression/psychological vulnerability
  - Neuroticism
  - Anxiety

TABLE 185.1 Negative Effects of Uncontrolled Postoperative Pain

Short-Term Effects	Long-Term Effects
• Cardiovascular effects • Impaired bowel movement • Effects on respiratory function • Delayed mobilization • Increased risk of deep venous thrombosis	• Acute pain can lead to chronic pain • Behavior changes • Depression, anxiety, opioid addiction

BOX 185.2 American Society of Anesthesiologists Task Force on Acute Pain Management Guideline Recommendations (2012)

Anesthesiologists who manage perioperative pain should, after thoughtfully considering the risks and benefits for the individual patient, use therapeutic options such as the following:
- Epidural or intrathecal opioids
- Systemic opioid patient-controlled analgesia
- Regional techniques

Unless contraindicated, patients should receive an around-the-clock regimen of nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, or acetaminophen.

Dosing regimens should be administered to optimize efficacy while minimizing the risk for adverse events.

The choice of medication, dose, route, and duration of therapy should be individualized.

ensure adequate control of acute postoperative pain of those patients with preexisting cardiac disease. Enhanced sympathetic activity can also reduce gastrointestinal motility and contribute to ileus. Severe pain after upper abdominal and thoracic surgery limits the ability to cough and reduces functional residual capacity, resulting in atelectasis, ventilation-perfusion abnormalities, hypoxemia, and an increased incidence of pulmonary complications. The injury response also contributes to a suppression of cellular and humoral immune function and a hypercoagulable state after surgery, both of which can contribute to postoperative complications. Evidence suggests that surgery suppresses the immune system in a manner that is proportionate to the invasiveness of the surgery.

MANAGEMENT

Pain is complex and multifactorial, therefore appropriate management requires a balanced and multimodal approach. *Multimodal therapy* is defined as the synchronous administration of more than two pharmacologic agents or therapeutic approaches, each with a distinct mechanism. The American Association of Anesthesiologists Task Force on Acute Pain Management in the Perioperative Setting practice guidelines recommend that "whenever possible, anesthesiologists should use multimodal pain management therapy" (Box 185.2).

Systemic Opioids

Opioids are the most widely used treatment for postoperative pain. Opioids act as agonists on central and peripheral opioid receptors. Administration methods vary and the drug can be delivered via oral, rectal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, or neuraxial routes. Due to the unpredictable drug concentration levels of various delivery systems, intravenous infusion administration results in a more constant blood level, allowing for more accurate prediction of drug effect; however, there is a higher risk of side effects. All opioids share common side effects including somnolence, depression of brainstem control of respiratory drive, urinary retention, and nausea and vomiting due to direct stimulation of the chemoreceptor trigger zone. Histamine release often follows opioid administration and may produce flushing, tachycardia, hypotension, pruritus, and bronchospasm. The use of patient-controlled analgesia (PCA) may offer more patient satisfaction for pain control while reducing the risk of harm.

Nonopioid Adjunctive Medication

Systemic nonopioid adjunctive medications are used as part of a multimodal approach to analgesia. This class includes a variety of types of drugs, including nonsteroidal antiinflammatory drugs, *N*-methyl-D-aspartate antagonists (ketamine), and acetaminophen. These drugs are an important part of acute pain management because they target different pain pathways; have synergy with various classes of pain therapy medications, including opioids; and allow for dose reduction of individual agents, reducing the risk for adverse effects.

Regional Techniques

Neuraxial and other regional techniques may be effective treatments for postoperative pain and may provide superior pain control compared with systemic opioids. Epidural and spinal analgesia have been shown to improve surgical outcomes by decreasing intraoperative blood loss, postoperative catabolism, and the incidence of thromboembolic events while improving vascular graft blood flow and postoperative pulmonary function. Epidural and spinal opioids provide better analgesia than systemic opioids, but side effects and inherent risks are still present, and therefore monitoring protocols are necessary. The neuraxial narcotics may cause insidious delayed respiratory depression, and pruritus may occur in a significant number of patients (Table 185.2).

PREVENTION

Management of postoperative pain should begin before surgical stimulus when applicable. The concept of "preemptive" analgesia as defined by the selected analgesic strategies administered before surgical incision can modify processing of noxious stimuli in the peripheral and central nervous system, thereby reducing central sensitization, hyperalgesia, and allodynia. Studies have shown that preoperative treatment is more effective than the identical treatment administered after incision or during surgery.

TABLE 185.2 Summary of Management Techniques

Technique	Example	Advantages	Disadvantages
Peripheral regional analgesia	Peripheral nerve blocks with local anesthetic (e.g., bupivacaine, ropivacaine)	Improved pain relief and lower analgesic consumption compared with saline	Temporary motor blockade
	Surgical site infiltration	Generally, improved pain relief and lower analgesic consumption compared with saline	None noted
Neuraxial	Intrathecal or epidural opioid	Improved pain relief	Increased frequency of pruritus and delayed respiratory depression
	Epidural opioid + local anesthetic	Improved pain scores	Increased motor weakness
Systemic opioids	Staff administered IV opioid	Similar pain control to PCA	Gaps in pain relief, opioid adverse drug reactions
	PCA	Better pain control and greater patient satisfaction compared with PO	Higher opioid consumption and more pruritus compared with PO
Nonopioid systemic analgesia	Acetaminophen	Similar benefit to IV PCA opioid, fewer adverse drug reactions	None noted
	NSAIDs	Improved pain scores, reduced analgesic use	Negative effects associated with NSAIDs on gastrointestinal, neurologic, renal, hemostasis, and allergic effects
	Anticonvulsants (gabapentin and pregabalin)	When combined with opioids, improved pain scores and reduced analgesic use	Sedation and dizziness
	α_2-Receptor agonist	When combined with opioids, reduces the undesirable physiologic and psychological effects of opioid withdrawal	Episodes of bradycardia, hypotension, and sinus arrest have been associated with rapid IV administration
	NMDA antagonist (ketamine)	When combined with opioids, reduces hyperalgesia and opioid tolerance, thereby decreasing postoperative opioid requirements and, possibly, chronic postsurgical pain	Potential to cause hallucinations and a dissociative mental state

IV, Intravenous; *NMDA, N*-methyl-D-aspartate; *NSAID,* nonsteroidal antiinflammatory drug; *PCA,* patient-controlled analgesia; *PO,* by mouth.

Further Reading

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186 Venous Air Embolism

Maurice S. Albin • Gwendolyn L. Boyd

Case Synopses

Gravitational Pressure Gradient of 10.0 cm H_2O

During a repeat L4–L5 lumbar laminectomy in the prone position, a 43-year-old woman arrested 45 minutes after onset of surgery with an unrecordable blood pressure (BP) and end-tidal CO_2 ($ETCO_2$) of 15 mm Hg. Rapid resuscitation efforts were successful, with $ETCO_2$ rising to 36 mm Hg, BP to 82/60 mm Hg, heart rate of 90 beats per minute, and elevated ST segments returning to normal. With the incision rapidly closed, the patient was turned to the supine position, and the BP dropped to 40/30 mm Hg, and the placement of precordial Doppler indicated that air was passing the sensor. Resuscitation measures were instituted, but failed. Moderate-sized air bubbles were found in the right atrium at postmortem. There were no comments about a patent foramen ovale.

Gravitational Pressure Gradient of 22.0 cm H_2O

A 6-year-old girl weighing 20.0 kg with a right cerebellar mass and a ventricular cannula in place for cerebrospinal fluid drainage was anesthetized. A precordial Doppler and a 20-gauge radial artery catheter and a Bunegin-Albin central line air aspiration catheter were in place. She was positioned in the 90-degree upright position, and 30 minutes into the surgical procedure, there was an acoustic change in the Doppler tones indicating the possibility of venous air embolism (VAE), with 1.0 mL of air aspirated. Over the next 1½ hours, four episodes of Doppler activation occurred, and 4.0 mL of air was aspirated from the central line. The patient was hemodynamically stable until the last VAE episode, when the $Paco_2$ went from 36 to 31 mm Hg and BP to 60/30 mm Hg. Therapeutic measures were successful, and a total of 11.0 mL of air was evacuated from the central line. However, in the short time remaining to complete the case, the Doppler sounded intermittently, and on closure an open scalp vein was noted and ligated, ending the positive Doppler response. The patient was responsive on entering the recovery area, breathing spontaneously and showing no neurologic deficit.

VAE During Endoscopic Retrograde Cholangiopancreatography

A 78-year-old man, under general endotracheal anesthesia, suddenly arrested and was unable to be resuscitated. A postmortem examination found air in the pulmonary artery (PA), right side of the heart, superior vena cava and inferior vena cava, hepatic veins, and right hemisphere of the brain. Neither the inflation pressure nor the type of gas used for inflation was noted.

VAE During Vitreoretinal Surgery

A 63-year-old man underwent endoresection of a choroidal melanoma with vitrectomy under general anesthesia using 50% oxygen in air. During the air/fluid exchange, the patient's $ETCO_2$ dropped precipitously, and the patient developed cardiac arrest from which he could not be resuscitated. Postmortem x-ray revealed massive air in the heart, which further was noted to be buoyant at autopsy, and when the pericardium was opened under water, air bubbles emerged. No air was found in the infusion line.

PROBLEM ANALYSIS

Definition

Air can enter the venous circulation when there is a negative pressure gradient between the right atrium and the upper area of incision or the air's point of entrance. The pressure may be due to gravitational forces, and Albin and coworkers have reported that a 5.0 cm H_2O gravitational gradient was sufficient to entrain air in a neurosurgical case. Negative pressure gradients can also be due to increased ambient pressure as noted with various endoscopic procedures (gastrointestinal, ophthalmologic, etc.) where gases are employed as the pressurizing medium or where a narrow beam of fluid or gas may have a destructive (jet) effect on tissue aside from the response to an elevated pressure environment. The entry of a bolus of 100 mL of air into the venous circulation can be fatal, and it has been calculated that this volume of air can pass through a 14-gauge needle with a gradient of 5.0 cm H_2O in a matter of seconds. Factors modifying air entrainment include body position, depth of ventilation, volume of air entering the vessel, rate of gaseous entry, and composition and concentration of gases in the inhaled anesthetic mixture. Animal studies and human cases have shown that the transpulmonary passage of air can occur without a patent foramen ovale. Reduced central venous pressure due to a contracted blood volume (hemorrhagic hypovolemia), or decreased intrathoracic pressure due to the use of a table or frame to reduce abdominal compression, can help increase the gravitational pressure gradient and enhance the entrainment of air.

The fate of entrained air is illustrated in Fig. 186.1. In the first case synopsis, the gravitational gradient was probably less than 10.0 cm H_2O, but was enhanced by blood loss and use of an orthopedic frame

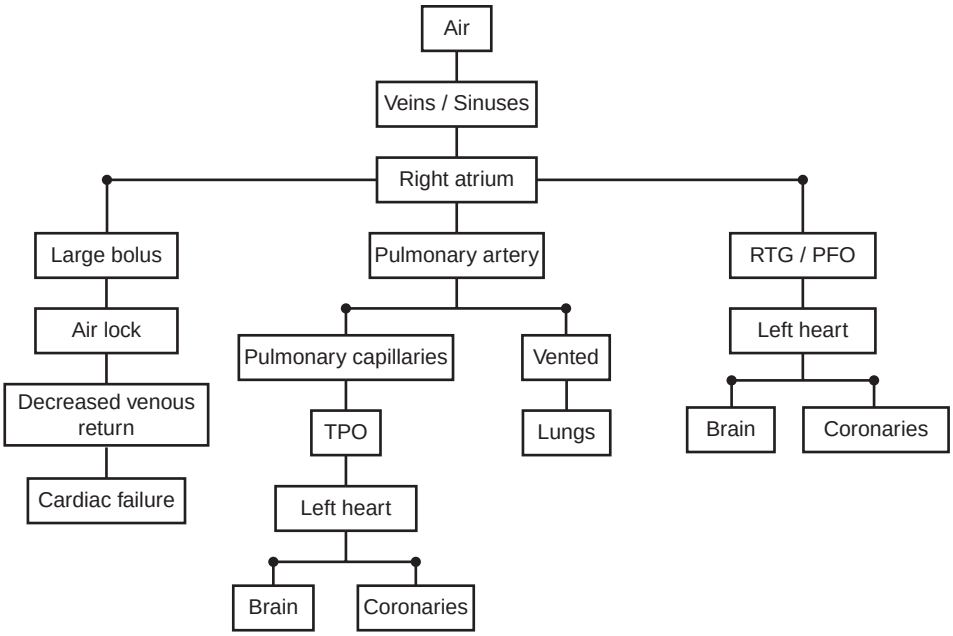

Fig. 186.1 Fate of entrained air after venous air embolism. *PFO,* Patent foramen ovale; *TPO,* transpulmonary overflow; *RTG,* reverse transatrial gradient.

that reduced abdominal pressure, thus allowing the development of negative intrathoracic pressure with expiration. Because 50% nitrous oxide (N_2O) was used, this increased the air bubble size by a factor of about 2. Autopsy revealed air in the right side of the heart.

In the second case synopsis, a 6-year old child sustained four separate episodes of VAE while undergoing posterior fossa exploration with a considerable gravitational gradient. Although the anesthetic management in this case appears to be optimal, it appears that impeccable hemostasis was not carried out along with borders of the scalp incision. Hagen and coworkers studied the incidence of probe patent foramen ovale (PFO) in 965 normal hearts and noted an incidence of 27.3%, with the mean PFO diameter being 5.0 mm, making the pediatric population at high risk for paradoxic air embolism. It must be emphasized that because of solubility factors, air bubble size can be increased with the use of nitrous oxide, and at a 50% N_2O–O_2 concentration, the entering air bubble volume is doubled, which may have occurred in the first case. In the second case synopsis, because of the large gravitational gradient, we are concerned that if VAE occurs in the presence of a probe PFO, air might pass into the coronary arteries in the left side of the heart and/or the cerebral vessels.

These cases demonstrate that VAE can occur in any position, as long as a pressure gradient allows the ingress of air between the procedural area and the heart. Evidence has accumulated that VAE is far from rare in patients undergoing procedures in the prone position, especially spinal procedures; there have been at least 22 cases reported, with a total of 13 deaths, 10 of which were in the pediatric age group (Albin and colleagues, 2006). In addition to neurosurgery, VAE has been reported with virtually all surgeries and endoscopy as well. It also occurs with catheterization for cardiac or central vascular access, arteriovenous shunts, intravenous infusions, and transfusion therapy.

Recognition

Physical signs and symptoms include gasping respiration in spontaneously breathing patients, increased central venous and pulmonary artery pressures, cardiac arrhythmias, electrocardiographic (ECG) changes, hypotension, abnormal heart sounds, changes in heart rate, decreased peripheral resistance, reduced cardiac output, cyanosis, a mill-wheel murmur, and cardiac arrest. Increased pulmonary artery pressure is the most prominent physical sign of VAE during controlled ventilation, irrespective of the volume or rate of air entrainment. The more rapidly air enters the pulmonary circulation, the more rapidly and severely the pulmonary artery pressure will rise. If it rises dramatically over the systemic pressure, a right-to-left shunt can occur through a septal defect (i.e., PFO) and cause paradoxic embolism of air into the left side of the heart. The ECG changes with air embolism are quite variable and include tachyarrhythmias, varying degrees of atrioventricular block, right ventricular strain, and ST-segment changes. Very large volumes of entrained air may cause such severely increased right ventricular afterload that the right ventricle becomes ischemic and fails acutely. Right-sided heart failure is the primary cause of acute hypotension, reduced cardiac output, and cardiac arrest after massive air embolism. A mill-wheel murmur indicates that a significant volume of air has entered the right-sided heart chambers. If so, cardiac arrest may be imminent. Air causes this churning sound and is one of the last signs observed before cardiac arrest.

Besides physical signs and symptoms, the other methods for detecting intraoperative air embolism, in order of sensitivity, are transesophageal echocardiography (TEE), precordial Doppler ultrasonography, $ETCO_2$, pulmonary artery catheter, pulse oximetry, and direct observation of the surgical site. TEE can detect both venous and paradoxic air embolism consisting of as little as 0.02 mL/kg of air. However, it is costly and may be inaccessible in some surgical locations; it has no audible alarms and may be difficult for solo practitioners to use when they are occupied with urgent patient care duties. A well-positioned precordial Doppler probe detects 0.05 mL/kg of intravascular air, is noninvasive, and alerts both the anesthesiologist and the surgeon simultaneously. As mentioned, although pulmonary artery catheters can show early and prominent signs of air embolism, they are highly invasive and less sensitive than precordial Doppler.

A sudden reduction in $ETCO_2$ concentration is the most convenient and widely used noninvasive method for detecting air embolism. The magnitude and duration of the decrease in $ETCO_2$ correlate positively with the volume of air entrained, and detection is possible during any general anesthetic. In contrast, pulse oximetry is relatively insensitive, because decreases in arterial oxygen saturation often occur late with a decrease in arterial oxygen tension. Further, the surgical field is often overlooked, especially in high-risk surgery where it may

be easy to note whether there is a lack of venous oozing, indicating subatmospheric venous pressure. In high-risk procedures, combined precordial Doppler ultrasonography and $ETCO_2$ monitoring should be used as Doppler tone activation and reduced $ETCO_2$ signal air entrainment. VAE is confirmed if gas bubbles can be aspirated from a central line.

Risk Assessment

The incidence of VAE is uncertain, largely because the criteria for VAE vary. Nevertheless, we have a general idea about the incidence of VAE and the associated morbidity and mortality rates for neurosurgical procedures performed with the patient in the sitting position. The overall incidence is about 25%, ranging from 2% to 60%. In 10 studies of more than 5000 patients, the mortality rate did not exceed 1% in any individual report. Morbidity data, even in neurosurgical sitting cases, are more difficult to ascertain. Albin and coworkers reported 100 cases of VAE in 400 patients operated on in the sitting position. These patients were considered to have VAE only if both Doppler activation *and* visual aspiration of air from a central line occurred. Under these conditions, 25 of the 100 patients with recognized VAE developed symptoms ranging from severe hypotension to cardiac arrest. Paradoxic air embolism (air entering the left side of the heart via a patent foramen ovale or transpulmonary passage) caused significant mortality in the small number of cases reported. Somewhat surprisingly, most VAE-related mortality appears to occur in nonneurosurgical cases, possibility because anesthesiologists fail to appreciate that it can occur in these cases, and the patient is not monitored adequately for VAE. Adding to this lack of appreciation is the medicolegal "fear factor," which likely leads to underreporting of VAE in the medical literature. There is a significant risk of VAE in cesarean section, spinal surgery, total hip arthroplasty, gastrointestinal endoscopic procedures, and vitreoretinal surgery when air/fluid exchange is used.

Because of coalescence and filming of bubbles at the blood-bubble interface, the passage of air into the right atrium can impede or even halt venous return to the right side of the heart. The consequences are hypotension, arrhythmias, and even circulatory arrest, because cardiac output can be severely compromised, and the occurrence of an "airlock" in the right ventricle has been postulated as the cause for hemodynamic collapse with massive VAE. However, more recent studies indicate that right ventricular dysfunction is more likely the result of an acute increase in afterload. Continuous entrainment and passage of large volumes of air may lead to the inability of the lungs to adequately vent air from the pulmonary circulation. This results in the liberation of vasoactive substances from the blood-air interface, leading to pulmonary perfusion deficits.

Ventilation-perfusion inhomogeneity is due to the redistribution of pulmonary perfusion. Areas of dead space and high ventilation-perfusion ratios reduce $ETCO_2$ and increase arterial CO_2 tension. Hypoxia results from altered intrapulmonary shunt, mixed venous oxygen saturation, and redistribution of pulmonary blood flow to regions that are relatively overperfused and underventilated (low ventilation-perfusion ratio). These ventilation-perfusion defects can be variable, because the distribution of air in the pulmonary vessels is a function of both buoyancy and regional pulmonary perfusion. Although ventilation-perfusion inhomogeneities may resolve in as little as 30 minutes after VAE, they can also become progressively worse as a result of the inflammatory response to air in the vascular space. Continuous entrainment of large volumes of air can lead to progressive pulmonary compromise, pulmonary capillary leak, and acute respiratory distress syndrome. Such volumes of air may also reach or exceed the threshold for transpulmonary passage of air, so that it can enter the left side of the heart and coronary sinuses and move into the brain. This can lead to coronary occlusion and cardiac arrest, as well as cerebral air embolization, with stroke and associated dysfunction.

MANAGEMENT AND PREVENTION

Given the severity of VAE sequelae, prevention and early detection are far preferable to management after the fact. The key to preventing VAE is a greater appreciation of risk factors. Patients who will undergo procedures in which gravitational gradient or compressive forces will be present, blood loss may be significant, or the surgical site is in a highly vascular environment are predisposed to air entrainment and VAE. Good examples from the literature include radical retropubic prostatectomy and repeat lumbar or thoracic laminectomies in the prone position. Optimal monitoring for VAE should include ECG, blood pressure, pulse oximeter, $ETCO_2$, precordial Doppler, arterial line, and a multiorifice catheter with its tip 1 to 2 cm past the junction of the right atrium and superior vena cava. Although the last is important for treatment, the ability to aspirate air from the catheter leaves no doubt about the diagnosis. Further, the transducer of the right atrial catheter can be placed at the level of the surgical site to determine whether a negative pressure gradient exists. In patients thought to be at risk for VAE and in whom invasive monitoring is contemplated, the use of an indwelling catheter for arterial blood gas and pressure monitoring is also advised.

Preventive measures for VAE are few and may be contraindicated in certain patients. Hydration can be used to decrease the pressure gradient between the right side of the heart and the surgical site, provided the patient can tolerate increased right ventricular preload. Many patients with intracranial pathology are not suitable candidates. Although the use of positive end-expiratory pressure to increase intrathoracic pressure has been proposed, it may increase high ventricular preload and is also controversial because it may increase the transatrial gradient and open a PFO, thus allowing air to egress into the left side of the heart and the brain. For intracranial surgery, bilateral manual jugular venous compression temporarily elevates cerebral venous pressure, thereby preventing ongoing cerebral air embolism, and it may also help localize the source. This maneuver is safe and effective, but only if applied gently and transiently in patients without preexisting carotid artery disease.

With Doppler activation, a decrease in $ETCO_2$, or both, the central line must be aspirated immediately (using a 50-mL syringe attached to a stopcock). A delay of even a few seconds might allow the entrance of large volumes of air. At the same time, inspired N_2O or air should be replaced with 100% oxygen, and the surgeon should be notified to flood the field with water and look for any open veins. Any resulting hypotension or cardiac arrhythmias should be treated symptomatically with positive inotropes and vasopressors to improve contractility and support the circulation. Epinephrine is the drug of choice for resuscitation from massive VAE. If recovery to pre-VAE physiologic levels does not occur in a very short time, or if air continues to be aspirated, the patient should be returned to a position in which there is no gradient present.

If VAE is suspected and the patient remains comatose after surgery or has a neurologic deficit that is thought to be unrelated to the surgical procedure, neurology or neurosurgery consultation is in order, and magnetic resonance imaging should be performed to diagnose the presence of intraaxial air. If air is visualized, a course of hyperbaric oxygen therapy should be considered.

VAE in Gastrointestinal Endoscopic Procedures

During gastrointestinal endoscopic procedures, the major problems concerning VAE revolve around contacts with very vascular tissue; a limited visual field; a pressurized gaseous environment usually using air as the medium; procedures often carried out in very poor-risk patients; and using an instrument that itself may be destructive for tissues with their vascular components. The combination of these factors

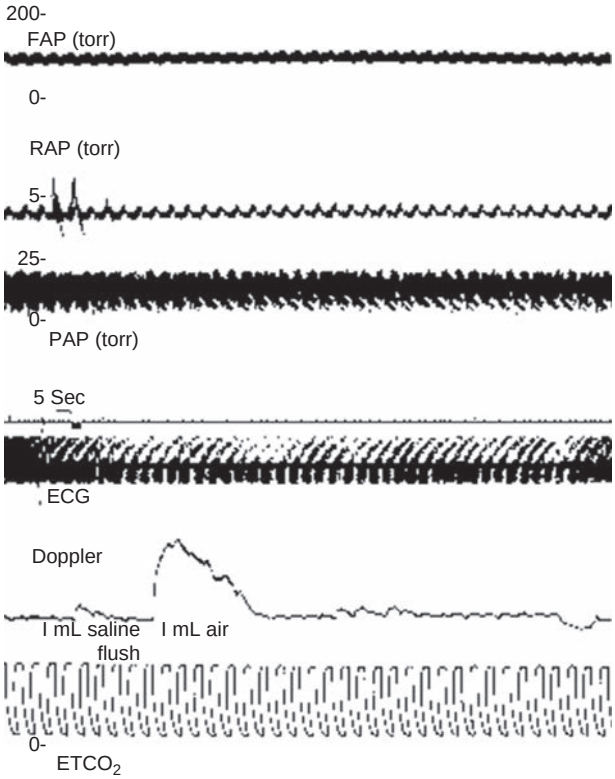

Fig. 186.2 Monitoring for venous air embolism. *ECG,* Electrocardiogram; *$ETCO_2$,* end-tidal CO_2; *FAP,* femoral artery pressure; *PAP,* pulmonary artery pressure; *RAP,* right atrial pressure.

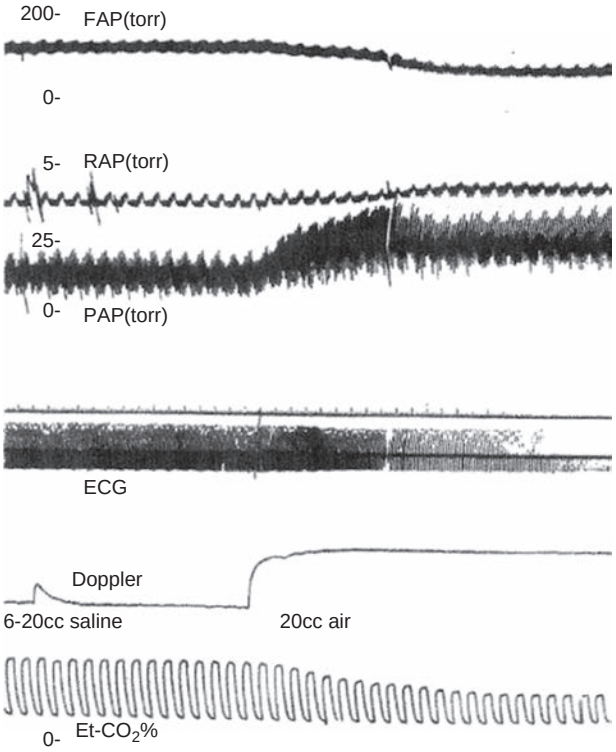

Fig. 186.3 In addition to changes in PAP, Doppler wave, and $ETCO_2$ after an injection of 20 mL (1.0 mL/kg) of air, note an increase in RAP and decrease in blood pressure and premature ventricular contractions occur. (From Chang JL, Albin MS, Bunegin L, et al: Analysis and comparison of venous air embolism detection methods. *Neurosurgery* 7[2]:135-141, 1980.)

demonstrates that the entrainment of air can be extraordinarily rapid, and because the ingress of 100 mL of air can be fatal, this leads one to think that the problem may be attenuated by preventive measures such as the following:

1. *Gases.* It appears that a literature review indicates that in a large number of reports, air is used as the main pressurizing medium. This is surprising because the use of CO_2 instead of air can often obviate VAE because of the absorptive properties of CO_2 and is harmless in patients without severe pulmonary disease. Using echocardiography TEE, Derouin and coauthors studied the use of CO_2 in 16 patients during laparoscopic cholecystectomy. Using a battery of cardiorespiratory tests, they identified gas embolism in 11 of 16 patients yet found *no* episodes of cardiorespiratory failure indicating rapid CO_2 absorption.
2. *Use of N_2O in the anesthetic mixture.* It has been established by a number of studies that in a 50:50 mixture of O_2:N_2O, because of solubility factors, the air bubble size will double in volume.
3. *Gaseous infusion pressure.* The pressure gradient is critical in moving air into the vascular system. High-pressure insufflation of air can raise the gradient to a point where air is essentially forced into open vessels. Unfortunately, gaseous infusion pressures were rarely mentioned in the 30 papers reviewed. It would seem worthwhile to ensure that pressure-limited infusion valves are used.
4. *Monitoring for VAE.* Early warning instrumentation and techniques include the following:
   a. The precordial Doppler (PCD) (Figs. 186.2 and 186.3) is simple to apply; gives real-time data; is relatively inexpensive; has excellent reliability; has a low false-negative rate of only 3%; and correlates well with the TEE, *K* value = 1.
   b. TEE has a higher degree of sensitivity than the PCD, although existing in the same range. Its drawbacks are that it needs specific skills to use, it is costly, and in the time necessary to apply it, a significant amount of air may be entrained.
   c. The PA catheter also has a high degree of sensitivity, but its small lumen and the narrow diameter of its atrial port limits its ability to extract significant amounts of air.
   d. $ETCO_2$ monitoring is an effective and practical method of detecting VAE with a lower sensitivity than the PCD (see Figs. 186.2 and 186.3).
   e. The Bunegin-Albin central line multiorifice air aspiration catheter gives absolute verification of the presence of air bubbles when aspirated, usually on change of heart tones by the PCD.

The combination of the PCD and $ETCO_2$ unit makes a formidable tool for VAE detection. The further addition of the Bunegin-Albin central line multiorifice air aspiration catheter placed at the onset of anesthesia allows for central venous pressure monitoring, as well as air aspiration, and these three monitoring modalities can be used for the high-risk patient and those undergoing a high-risk therapeutic procedure.

The severity of the complications of air embolism can be noted in the review article by Donepudi and coworkers (Table 186.1), in which they presented 26 cases of endoscopic retrograde cholangiopancreatography (ERCP) procedures, all of which were diagnosed as having episodes of air embolism. Of the 26, 19 were 60 years of age or older. One had an age that was not reported, and 18 were below age 60, with the youngest being 5 years of age. Twelve of the patients died, and 14 survived. Of interest is that the authors have classified air embolism episodes into venous, spinal, pulmonary, cardiac, and cerebral categories, with cerebral air embolism accounting for 12 of the 26 cases (46%). This categorization targets the end organ involved, but appears to ignore the physiopathology of this entity. Paradoxic air embolism occurs when air is entrained into the left side of the heart

TABLE 186.1 Report Cases on Air Embolism Complicated Endoscopic Retrograde Cholangiopancreatography

Case	Ref.	Age/Sex	Risk Factor(s)	Diagnosis	Outcome
1	Bisceglia et al[7]	78/male	Surgical gastroduodenal resection	Pulmonary air embolism	Dead
2	Rabe et al[12]	87/male	Metal stent placement	Cerebral air embolism	Survived
3	Rabe et al[12]	54/male	Billroth II operation, metal stent placement	Cardiac air embolism	Dead
4	Jow et al[38]	65/male	Biliary duct stones/inflammation	Cardiac air embolism	Dead
5	Maccarone et al[1]	45/male	Percutaneous transhepatic biliary drainage	Cerebral air embolism	Survived
6	Siddiqui et al[37]	43/female	Biliary sphincterotomy, liver biopsy	Venous air embolism	Dead
7	Nayagam et al[39]	57/male	—	Cerebral air embolism	Dead
8	Kennedy et al[8]	63/female	Biliary sphincterotomy	Venous air embolism	Dead
9	Stabile et al[6]	65/male	Biliary sphincterotomy, PTC	Cerebral air embolism	Dead
10	Mohammedi et al[4]	27/male	Biliary sphincterotomy, blunt hepatic trauma	Cardiac air embolism	Survived
11	Romberg[40]	53/male	Biliary duct stones	Cardiac air embolism	Survived
12	Rangappa et al[41]	50/female	Biliary duct stones	Cerebral air embolism	Dead
13	Bechi et al[33]	79/female	Biliary sphincterotomy	Cerebral air embolism	Survived
14	Goins et al[16]	72/female	Cholangiocarcinoma	Cerebral air embolism	Survived
15	Cha et al[42]	50/female	Biliary duct stones, liver abscesses, choledochoduodenostomy	Cardiac air embolism	Dead
16	Di Pisa et al[13]	8/male	Splenomesenteric portal shunt	Venous air embolism	Survived
17	Giuly et al[43]	60/female	Biliary sphincterotomy, choledochal varices	Venous air embolism	Survived
18	van Boxel et al[44]	82/male	—	Cerebral air embolism	Survived
19	Tan et al[45]	82/female	Metal stent placement	Cerebral air embolism	Dead
20	Nern et al[46]	58/female	Cholangiocarcinoma	Cerebral air embolism	Dead
21	Simmons[47]	Not available	Biliary sphincterotomy	Venous air embolism	Survived
22	Merine et al[48]	39/female	Biliary sphincterotomy	Venous air embolism	Survived
23	Barthet et al[49]	31/male	Biliary sphincterotomy	Venous air embolism	Survived
24	Efthymiou et al[11]	62/female	Cholangioscopy	Cerebral air embolism	Survived
25	Our case[50]	66/male	Metal stent placement	Cerebral air embolism	Dead
26	Our case[50]	51/female	Status post–Whipple's operation	Spinal air embolism	Survived

Reference citations are specific to the original published article.
PTC, Percutaneous transhepatic cholangiography.
From Donepudi S, Chavalitdhamrong D, Pu L, et al: Air embolism complicating gastrointestinal endoscopy: a systematic review. *World J Gastrointest Endosc* 5(8):359-365, 2013.

either through a PFO, or else due to very large volumes of air overwhelming the ability of the lungs to handle this large volume load. This phenomenon, the transpulmonary passage of air across the pulmonary bed, then has to cope with entrained air entering into the coronary vessels, brain, and spiral cord vasculature (see Fig. 186.1).

In summary, preventive measures to rapidly identify the presence of air embolism can be secured by the use of the PCD, using CO_2 for insufflation pressures that may force the compressive gases into the fragile and/or damaged organs' vascular systems. The combination of PCD and $ETCO_2$ units is the basis of an efficient early-warning system.

Although there are a number of historical reviews and many case reports of endoscopic gastrointestinal diagnostic and surgical procedures, this literature is retrospective in nature, and there is a paucity of prospective studies. The only exception seen in a review of the literature has been the prospective observational trial by Crutchley and coworkers. Their emphasis was on early detection of VAE using the PCD and also the $ETCO_2$ monitors. Another feature was risk stratification of the 528 enrolled patients that were subjected to ERCP procedures. VAE was detected in 3 of the 528 patients, and, most important, all 3 of those with VAE were in the high-risk group (n = 180), who may have been subjected to either or a combination of sphincterectomy, stent manipulation, biopsy, cholangioscopy, or necrosectomy. Because this report is part of a continuing study reaching 1000 patients, it will be interesting to see the final report. However, since CO_2 has replaced air to improve visualization by the endoscopist, there have been no incidents of VAE.

VAE During Vitreoretinal Procedures

The fourth case synopsis describes a patient undergoing endoresection with vitrectomy of a choroidal melanoma under general anesthesia

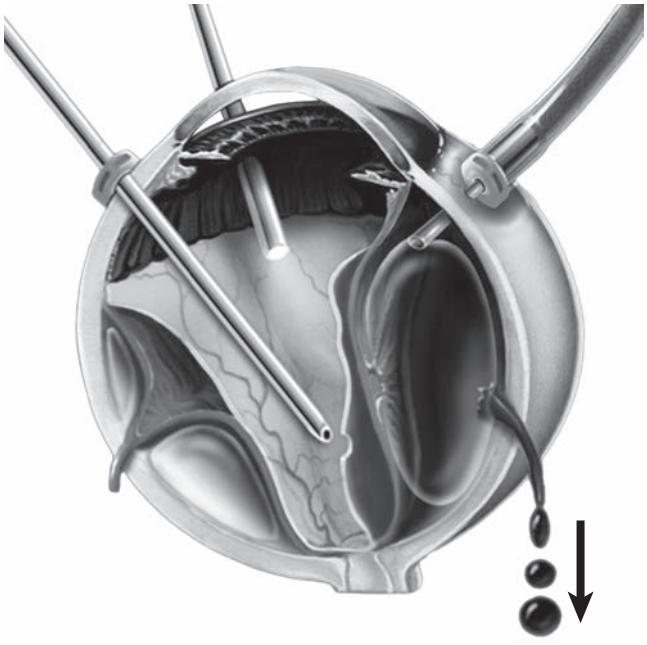

Fig. 186.4 The standard three intraocular cannulas used for vitrectomy. The center trocar has the camera and light, the left-sided trocar aspirates the vitreous, and the third on the right is the injection port that has come out of the vitreous cavity, allowing the injectate to enter the venous circulation via the vortex veins. (From Morris, RE, Sapp MR, Oltmanns MH, et al: Presumed air by vitrectomy embolisation [PAVE] a potentially fatal syndrome. *Br J Ophthalmol* 98[6]:765-768, 2014.)

who developed a fatal VAE during the air/fluid exchange (AFX) performed to stabilize the retina. Rice and colleagues confirmed this episode of VAE was the cause of death using postmortem x-ray and a forensic autopsy. To date, six cases of ocular VAE have been reported in the anesthesia literature. Query of the ASA Closed Claims Project database (Posner K, personal communication) revealed an additional case of VAE during vitrectomy for repair of a retinal detachment with scleral buckle placement.

After the publication of the first three cases (Ledowski, Ruest, and Dermigny), Lim and colleagues and Gamulescu and colleagues sent a warning to ophthalmologists of this potentially fatal intraoperative complication. However, ophthalmologists were skeptical that ocular AFX could lead to near-fatal or fatal VAE because the vortex venous system did not have the capacity to support the entrance of a large volume of air. However, Morris and colleagues demonstrated the ease with which potentially fatal VAE may occur using pressures up to 120 mm Hg infusion pressure that modern vitrectomy machines are capable of delivering. The authors measured 350 mL of air per minute that was delivered using a 25-gauge vitrectomy infusion cannula under 40 mm Hg pressure, well above the 100 mL known to be fatal (Fig. 186.4). They predicted that the current smaller, sutureless vitrectomy infusion cannulas may easily slip out of the vitreous cavity. This would allow the pressurized air to readily exit out the damaged choroid into the vortex veins, which then enter the central venous circulation, potentially increasing the incidence of VAE. Recently Shin and colleagues and Wu and colleagues reported two more cases of ocular VAE for whom prompt initiation of cardiopulmonary bypass was successful in one case, but death resulted in the other.

When retinal tamponade is indicated, vitreoretinal surgeons have multiple choices at the conclusion of vitrectomy surgery. Air, as described earlier, is used in about 15% of these vitrectomy procedures and holds the retina in place for about 5 days before being absorbed. About 50% of vitrectomy procedures use sulfur hexafluoride (SF_6) gas, which lasts 10 days to 2 weeks; during this time it is imperative not to undergo anesthesia with nitrous oxide because it will significantly increase the size of the gas bubble in the eye, leading to blindness. Air travel is also contraindicated during this time period. Approximately 1.5 mL of SF_6 is injected into the vitreous cavity. Another gas, perfluoropropane (C_3F_8), lasts up to 2 months and has the same caveat as SF_6 for avoidance of nitrous oxide, as well as for air travel. In the remaining one-fourth of vitrectomy procedures for which stabilization of the retina is indicated, silicone oil is used. Oil is reserved for more complicated vitrectomy procedures, including those for diabetic proliferative retinopathy, especially with tractional retinal detachments, giant tears, inferior detachments, and other difficult surgical procedures. The oil needs to be removed with a separate operation. Many vitrectomy procedures do not require retinal tamponade at the end of the case, such as those for vitreous hemorrhage removal or for floaters. Thus pressurized air infusion is used in less than 10% of vitreoretinal surgeries.

Vitrectomy surgical procedures that involve choroidal trauma before the AFX appear to be at higher risk of VAE than most routine vitrectomy procedures. All reported VAE patients had significant choroidal trauma either from an intraocular foreign body, choroidal tumor undergoing resection, or scleral buckle for retinal detachment repair. Furthermore, all reported cases of ophthalmic VAE have been done under general anesthesia, which masks early signs of VAE. Fortunately, fewer and fewer vitrectomy procedures are being performed under general anesthesia, currently 20% in our institution, as the surgical techniques have improved with increasingly smaller-gauge cannulas. Indeed, there is a trend toward topical anesthesia for the newer 27-gauge cannulas used for vitrectomy surgery being performed for floaters or other indications that do not require laser of the retina or gas infusion.

The critical steps to prevent VAE for the vitreoretinal surgeon as described by Morris and colleagues are (1) reconfirming that the air infusion cannula remains in the vitreous cavity, and (2) immediately stopping the infusion of air if choroidal elevation occurs during the AFX.

For the anesthesia provider, capnography, which is presently used for all anesthetics, whether MAC or general anesthesia, is an invaluable tool to assess the presence of VAE during AFX. Attention by the anesthesia provider should always be directed toward the capnograph during the AFX. Close communication with the ophthalmologist is imperative during this time.

Finally, we believe anesthesia providers should use a PCD when pressurized air infusion is chosen for ocular surgery cases that are higher risk for VAE (i.e., those with preexisting choroidal trauma being performed under general anesthesia). Thus the already low reported incidence of VAE during vitrectomy surgery may become a rare occurrence. With knowledge that VAE is a possibility during this critical portion of the surgical procedure, ophthalmologists may help prevent it, and anesthesia providers may markedly decrease its severity, by observation of the capnograph and listening to the PCD, especially when pressurized air is used in high-risk patients. In other words, to borrow from the Latin, "*Praemonitus, praemunitus*—forewarned is forearmed!"

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187 Delayed Emergence in Pediatric Patients

Alexandra Szabova • John B. Rose

Case Synopsis

A 2-year-old 14-kg girl with trisomy 21 remains unresponsive and intubated in the operating room 35 minutes after anesthetic agents were discontinued following adenotonsillectomy for obstructive sleep apnea. Intraoperatively she received propofol 2 mg/kg^{-1}, morphine 0.1 mg/kg^{-1}, and cisatracurium 0.2 mg/kg^{-1}. General anesthesia was maintained with sevoflurane 2.5% in a mixture of oxygen and air (Fio_2 0.6). Neuromuscular blockade was antagonized with glycopyrrolate 0.01 mg/kg^{-1} and neostigmine 0.05 mg/kg^{-1}.

PROBLEM ANALYSIS

Definition

Delayed emergence is defined as failure to recover consciousness after discontinuation of general anesthesia within a reasonable amount of time, in most cases less than 30 minutes. The time it takes to recover consciousness is variable and depends on several factors, such as the length of the procedure, the agents and techniques used, and the patient's preoperative physical and mental status.

Recognition

Evaluation of Patients

Drug effects, physiologic disturbances, disorders of metabolism, central nervous system (CNS) injury, and preexisting CNS conditions may all result in delayed emergence from general anesthesia (Box 187.1). Initial evaluation should be completed promptly and may include some or all of the following:

- Review of the patient's medical history and anesthetic record
- Physical examination including assessment of vital signs and temperature; airway patency, adequacy of ventilation, oxygenation, and circulation; and neurologic examination (pupillary size and reactivity, reflexes, response to verbal and tactile stimulation, presence of gag reflex)
- Assessment of neuromuscular function with nerve stimulator
- Blood glucose, electrolytes, blood urea nitrogen, creatinine, arterial blood gas analysis
- Computed tomography scan of head, consultation with neurologist

For the patient in the case synopsis, her airway was patent, and her ventilation and oxygenation were adequate. There was no sevoflurane in exhaled gases. Her vital signs, temperature, end-tidal CO_2, and oxyhemoglobin saturation were normal. Neuromuscular blockade was adequately reversed as assessed with nerve stimulator. It was noted that she had a prolonged preoperative fast (15 hours) and received dextrose-free intravenous fluids during the procedure. Hypoglycemia was considered and confirmed by blood glucose testing (glucose = 42 mg/dL). Corrective therapy was instituted, and the patient regained consciousness and fully recovered.

Drug Effects

A common cause of delayed emergence is prolonged action of anesthetic drugs. Although inadvertent overdose of one drug may be responsible, it is more often attributed to a combination of drugs. Individually, drugs may be given in appropriate doses, but when combined, without dose adjustment, relative overdose may occur owing to the potentiation of CNS depressant effects. This is especially true in cases where a general anesthetic is supplemented with regional anesthesia. Several studies have examined the effects of premedication on recovery in pediatric outpatient surgeries. Whereas some studies showed delayed emergence after premedication (oral midazolam), others demonstrated no or minimal effect (e.g., rectal diazepam, oral midazolam, and nasal midazolam).

BOX 187.1 Differential Diagnosis of Delayed Emergence

Drug Effects
Drug overdose (accidental or error in judgment)
Multiple CNS depressants or drug interactions
Medication error (in preparation or administration)
Impaired drug metabolism (reduced elimination or protein binding; increased sensitivity)
Residual neuromuscular blockade

Physiologic Imbalance or Disorders of Metabolism
Hypoxia; hypercarbia
Electrolyte imbalance (hyponatremia, hypocalcemia, hypomagnesemia)
Hypothermia or hyperthermia
Sepsis
Hypoglycemia

CNS Injury or Undiagnosed Preexisting Condition
Intracranial hemorrhage or hypertension
Cerebral ischemia, edema, or embolism (air or particulate)
Seizure disorder (especially postictal states)
Brain tumor
Stroke (e.g., in sickle cell disease, hypercoagulable states)

CNS, Central nervous system.

Adapted and modified from Denlinger JK: Prolonged emergence and failure to regain consciousness. In Gravenstein N, Kirby RR, editors: *Complications in anesthesiology.* Philadelphia, Lippincott-Raven, 1996, pp 441-450.

Reduced drug metabolism and elimination may contribute to delayed emergence, especially in premature and full-term newborns. Respiratory depression and hypoventilation secondary to opiates and sedatives can delay the elimination of inhalation agents and prolong emergence in spontaneously breathing infants or children. Extremes of weight such as in morbidly obese adolescents can contribute to delayed emergence after propofol anesthesia.

Home medication regimen may include several drug classes with potential for drug-drug interactions, paradoxic or idiosyncratic reactions with anesthetics, manifesting as delayed emergence (e.g., a child with schizophrenia who is treated with clozapine). There is an abundance of case reports of unusual scenarios in adult patients, but to a much lesser degree in pediatric patients, limiting our ability to generalize. Herbal and over-the-counter medications can affect emergence from anesthesia. Their use is underreported by parents and caregivers.

Intraoperative use of opioids and ondansetron can precipitate serotonin syndrome in patients treated with certain antidepressants and antipsychotic drugs that result in increased CNS levels of serotonin, and this may slow emergence from anesthesia. Similarly, central anticholinergic syndrome can result from drug interactions between home medications and anesthetics. In contrast to nonanesthetized patients, the clinical signs of tachycardia, mydriasis, and dry and warm skin can be diminished in anesthetized patients, causing delay in diagnosis and treatment. A summary of published case reports can be found in Tzabazis and colleagues. The incidence of serotonin and central cholinergic syndromes in pediatric patients undergoing anesthesia is unknown.

In infants and children, biologic variability in their response to the hypnotic effects of anesthetic drugs can be marked. If so, increased sensitivity to these effects may contribute to prolonged emergence in some children. However, this must be a diagnosis of exclusion in healthy children with no prior history of cognitive impairment or developmental delay.

Physiologic Imbalance or Disorders of Metabolism

The existence of various preoperative states (e.g., prolonged fasting, dehydration, malnutrition, renal or hepatic disease, diuretic or antacid therapy, severe anemia, sickle cell disease, diabetes, and seizure disorder) or the occurrence of adverse intraoperative events (e.g., hypoventilation, hypotension, hypoperfusion, large blood loss with massive blood and fluid resuscitation) raises the possibility that physiologic imbalance or metabolic disturbances are responsible for delayed emergence.

The routine use of pulse oximetry and capnography has greatly enhanced the ability of anesthesiologists to detect and treat life-threatening conditions associated with hypoxemia and hypercarbia. Metabolic acidosis should be considered in children who have experienced periods of hypotension or hypoperfusion or in those who have lost large amounts of blood, necessitating massive fluid replacement with crystalloid, colloid, and blood products. Hypoglycemia should be suspected in children who have fasted preoperatively for long periods, especially if they have received non–glucose-containing intravenous fluids intraoperatively, or if they are insulin-dependent diabetics and have received insulin perioperatively.

Metabolic disturbances are key features of some syndromes in children, and if present may contribute to delayed emergence.

Central Nervous System Injury or Disease

CNS injuries during anesthesia in children are rare but may contribute to delayed emergence. Congenital heart lesions with right-to-left shunts place patients at risk for cerebral air embolism after even small amounts of air have been introduced via intravenous infusions. In addition, cerebral embolism with air or particulate matter is a known complication of cardiopulmonary bypass. Intracerebral or intraventricular hemorrhage has been reported during awake laryngoscopy and endotracheal intubation in premature and term neonates and is also a complication of ventriculoperitoneal shunt revision and other neurosurgical procedures. Cerebral ischemia can occur with the delivery of hypoxic gas mixtures, prolonged hypotension with hypoperfusion, and carotid artery compression injury secondary to malpositioning. Bilateral supratentorial hematomas were described after cervical spinal surgery in adolescents.

Undiagnosed, preexisting CNS conditions can also contribute to delayed emergence. Late-onset central hypoventilation syndrome is a neurologic disorder that can present with postoperative respiratory complications and delayed emergence in children after anesthesia. Intracranial hypertension may exist in patients with malfunctioning ventriculoperitoneal shunts or in those with previously unrecognized brain tumors or foramen magnum stenosis; it can be exacerbated by hypercarbia, hypoxemia, or hyperextension of the neck. Seizures are difficult to detect in anesthetized and paralyzed patients. They can occur during general anesthesia, and the postictal state may present as delayed emergence. Finally, unrecognized muscle weakness or paralysis can make the patient appear to be unconscious. This must be distinguished from the conditions outlined earlier by careful assessment of neuromuscular function.

Conversion disorder, narcolepsy, and sleep paralysis have been described in adults as rare causes of delayed emergence. A case of sleep paralysis was successfully treated with physostigmine.

Risk Assessment

The incidence of delayed emergence is unknown. Based on investigations of anesthetic complications in infants and children, its incidence appears to be low. In one study of anesthetic complications in 29,220 infants and children, there were no reported cases of delayed emergence or coma. In a review of complications in 40,240 infants and children, one case of coma was described; this occurred in a 13-year-old boy after nitrous oxide–opioid–neuroleptic anesthesia. In another study, 2 of 10,000 pediatric ambulatory surgery patients were hospitalized after surgery owing to excessive sleepiness.

Underreporting of this complication may be a significant issue. The time required to emerge from general anesthesia is highly variable, so individual anesthesiologists must determine whether an emergence is delayed and report the complication. If most cases of delayed emergence are related to prolonged drug effects and the ultimate outcome is good, many practitioners are likely reluctant to report what appears to be an insignificant event.

Implications

When delayed emergence results from prolonged drug action, long-term patient outcomes are good when proper measures are taken to support the airway and ensure adequate oxygenation, ventilation, and hemodynamic parameters. However, when delayed emergence is a consequence of metabolic abnormalities or CNS injury, it is imperative to recognize that there is a problem, determine the underlying cause, and institute corrective measures expeditiously to avoid a catastrophic outcome.

Aside from its impact on patient outcome, delayed emergence can have a significant effect on perceived quality of care, parental satisfaction, operating room (OR) efficiency and health care cost. Even small delays in emergence, if frequent, can disrupt the OR schedule, consume OR and recovery room time and personnel, and prevent an anesthesiologist from starting other scheduled cases on time.

BOX 187.2 Antagonists to Reverse the Sedative Effects of Anesthetic Agents

Naloxone: 1–4 μg/kg IV titrated to effect; maximum dose, 10 μg/kg
Flumazenil: 2.5–5 μg/kg IV titrated to effect; maximum dose, 10 μg/kg
Physostigmine: 25–50 μg/kg IV; maximum dose, 2 mg

IV, Intravenously.

MANAGEMENT

Management of delayed emergence entails the following steps:

- Ensure adequate airway, oxygenation, and ventilation
- Review medical history and anesthetic management
- Drug antagonism trials
- Rule out metabolic and electrolyte abnormalities
- Rule out CNS injury

The management of delayed emergence begins with ensuring that the patient has an adequate airway and that he or she is well oxygenated and ventilated. Next, the patient's medical history and anesthetic management are reviewed to identify potential causes and determine what further actions are required. Frequently, opioid or benzodiazepine overdose cannot be ruled out, and a diagnostic and therapeutic trial of naloxone, flumazenil, or both is indicated (Box 187.2). The nonspecific antagonist physostigmine may be beneficial when delayed emergence is due to volatile anesthetics, scopolamine, ketamine, phenothiazines, or tricyclic antidepressants. It should be emphasized that any of these antagonists may produce only a transient recovery of consciousness. If prolonged anesthetic drug effects are not suspected, blood should be sampled to determine arterial blood gases, electrolytes, glucose, calcium, and magnesium concentrations. If no discernible cause is identified after the initial review and examination, neurology consultation, CNS imaging studies, or electroencephalography may be indicated.

PREVENTION

Delayed emergence is often preventable. Drug errors, inadequate patient surveillance or monitoring, and positioning injuries, especially when surgery involves the head and neck or when patients are in the prone or lateral decubitus position, are some of the more common preventable causes of this complication.

ACKNOWLEDGMENT

The authors wish to thank Dr. Hector Nicodemus for his contribution to the previous edition of this chapter.

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Difficult Pediatric Airway 188

Herodotos Ellinas

Case Synopsis

A 3-year-old child is scheduled for tonsillectomy and adenoidectomy. His past medical history is significant for Treacher Collins syndrome (Fig. 188.1), and thus a difficult airway is anticipated. After inhalation induction with spontaneous respirations, successful intubation is performed with the use of a fiberoptic bronchoscope via a supraglottic device placement.

PROBLEM ANALYSIS

Definition

A difficult airway is one in which there is moderate-to-severe difficulty in performing mask ventilation, direct laryngoscopy, or both. This situation may result from anatomic (congenital or acquired) or physiologic defects.

Recognition

Performing a thorough history and physical examination is the best means of recognizing and predicting a difficult pediatric airway. Understanding the significant differences between the pediatric and adult airways is mandatory for the successful management of a child with a difficult airway (Fig. 188.2). Anatomic differences exist in the size, shape, and position of the airway, as well as the airway epithelium and its supporting structures. Physiologic differences between the neonatal and adult respiratory systems are due to differences in anatomy and respiratory control mechanisms.

Upper Airway

The upper airway of the newborn is unique. The tongue is relatively large and fully occupies the cavity of the mouth and oropharynx. This may make manipulation of the laryngoscope and endotracheal tube more difficult during attempted intubation. Neonates are obligate nose breathers up to about 6 months of age. This is because the epiglottis, positioned high in the pharynx, almost meets the soft palate, making mouth breathing difficult.

Lymphoid Tissue

Unlike older infants and children, neonates have almost no upper airway lymphoid tissue. The tonsils and adenoids appear during the second year of life and reach their maximum size by 4 to 7 years of age, and after that they gradually recede. Enlarged tonsils and adenoids may increase bleeding during attempted nasal intubation.

Epiglottis

The epiglottis in infants is large and U shaped, and it protrudes over the larynx at a 45-degree angle. The use of a straight blade facilitates vocal cord visualization, as it requires direct lifting of the epiglottis.

Larynx

In the newborn, the body of the hyoid bone is situated at the level of C3–C4. As the infant grows, the glottis moves caudally and reaches C5–C6 at maturity. The high position of the epiglottis and larynx enables the infant to breathe and swallow simultaneously. Similarly, both the thyroid and the cricoid cartilages move caudad as the thyrohyoid and cricothyroid membranes develop.

Airflow

Airflow in the upper airway is turbulent even during quiet respiration. Laminar flow begins at the level of the fourth and fifth bronchial divisions, where the rapid increase in airway cross-sectional area reduces airflow velocity. The resistance to turbulent gas flow is inversely proportional to the fifth power of the radius of the airway. Thus 1 mm of edema within the trachea (reduction in radius from 2 to 1 mm) increases resistance to gas flow about 32-fold.

Respiratory Mechanics

The highly compliant chest wall in young infants reduces the work of breathing. Such increased compliance is attributed to the softer, noncalcified ribs, which articulate with the vertebral column and sternum at right angles. The diaphragm is the mainstay of ventilation in infants. The infant diaphragm has fewer type I (slow) muscle fibers than the adult diaphragm does, rendering it less efficient and easy to tire.

Risk Assessment

Although pediatric airway difficulties are usually anticipated, successful management of a child with a difficult airway requires a thorough history and physical examination. The history should focus on the following:

- Review of prior records, especially anesthetic records for evidence of a difficult airway
- Evidence of congenital or acquired airway defects
- Evidence of airway obstruction or obstructive sleep apnea

Features of the physical examination most pertinent to perioperative airway management are listed in Box 188.1. Occasionally, additional studies (e.g., awake laryngoscopy, radiologic imaging, flow-volume loops) may be necessary to adequately assess a potentially difficult airway.

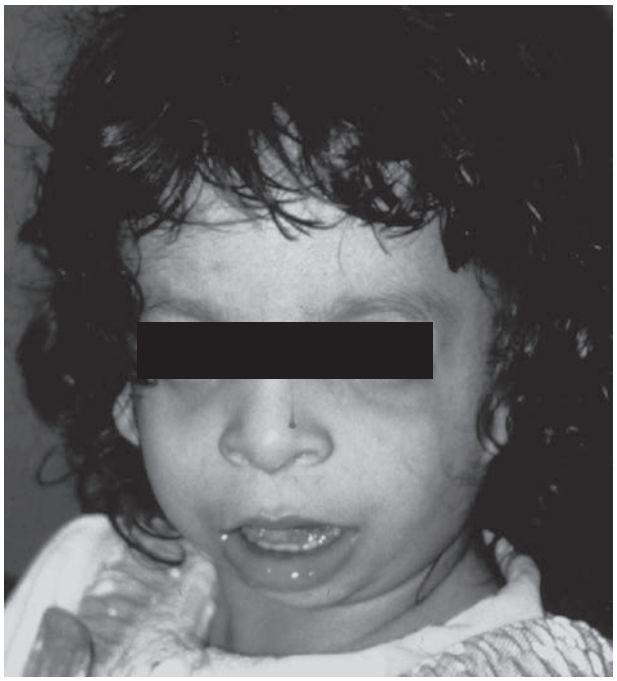

Fig. 188.1 Abnormalities pertinent to airway management in a patient with Treacher Collins syndrome (mandibulofacial dysostosis) include mandibular and malar hypoplasia, microstomia, and choanal atresia.

BOX 188.1 Examination of the Pediatric Airway

Size and shape of the head
Dysmorphic facial features and facial asymmetry
Mandibular size and position (e.g., retrognathia)
Size of the tongue
Shape of the palate (e.g., high arched palate)
Prominence of the upper incisors
Jaw, head, and neck range of motion

Implications

If the ability to ventilate by mask is absent or lost, and if it is determined that the patient cannot be intubated, the situation becomes a true emergency. Gas exchange must be restored immediately to avert the imminent threat of brain hypoxic injury and death.

MANAGEMENT

Premedication

Premedication should be individualized. Administration of sedatives (e.g., benzodiazepines, opioids) should proceed cautiously; these drugs can result in loss of muscle tone, worsening known airway obstruction or causing respiratory depression. In some older children in whom awake intubation is contemplated, careful sedation by a practitioner experienced in difficult airway management is reasonable. Anticholinergic agents should be considered both for their antisialagogue effect and to protect against vagal responses during airway manipulation.

Induction

Recent guidelines supported by the Association of Pediatric Anaesthetists of Great Britain and Ireland (APA) and the Difficult Airway Society (DAS) outline steps in managing difficult airways in children ages 1 to 8 years old. Three scenarios are presented here:

1. *Difficult mask ventilation*
   a. Call for help
   b. Provide 100% Fio_2
   c. Ensure good head positioning
      i. In children less than 2 years old—use of shoulder roll
      ii. In older children—use of chin lift and extended neck, or place in lateral position
   d. Consider two-hand bag-mask ventilation (BMV)
   e. Use oropharyngeal (OP) or nasopharyngeal (NP) airway; proper measurement is paramount to improve rather than obstruct the airway (OP: mouth to angle of the mandible; NP: naris to tragus of the ear)
   f. Check equipment for malfunction, and consider use of self-inflating bag
   g. Provide effective depth of anesthesia (ensure stage 3 with inhalation or intravenous anesthetics), laryngospasm being more common in children
   h. Decompress stomach with orogastric (OG) or nasogastric (NG) tube
   i. Use propofol (1 to 2 mg/kg IV) or suxamethonium (1 to 2 mg/kg IV or 2 to 4 mg/kg IM) for complete laryngospasm with persistent hypoxemia
   j. Use a supraglottic device or attempt to intubate
2. *Difficult intubation in an elective case—unanticipated*
   a. Call for help
   b. Provide 100% Fio_2
   c. Limit intubation attempts to less than or equal to 4 by all involved
      i. Use of Miller blade (straight) in children under 3 years old and Mac blade (curved) in older children
      ii. Consider smaller-size endotracheal tube (ETT)
      iii. Consider releasing cricoid pressure if applied
      iv. Use of videolaryngoscope or indirect laryngoscope if available
   d. Use supraglottic device, oxygenate, ventilate, and either maintain for surgical procedure or intubate with the aid of a fiberoptic bronchoscope
   e. Consider waking patient up and postponing the surgery
3. *Difficult ventilation and intubation in a muscle-relaxed child*
   a. Call for help
   b. Provide 100% Fio_2
   c. Consider above maneuvers including head positioning, OP/NP airway placement, two-hand BMV, OG/NG tube stomach decompression, supraglottic device, wake up patient (consider reversal of muscle relaxant if used)
   d. Proceed to percutaneous cricothyrotomy and jet ventilation or rigid bronchoscopy/surgical tracheostomy if ears/nose/throat (otolaryngologist) available

The vast majority of children with a difficult airway require general anesthesia. If possible, every effort should be made to keep them breathing spontaneously during induction.

Airway Adjuncts

Successful management of a difficult pediatric airway requires the necessary equipment and the know-how to use it. Standard equipment includes assorted sizes of facemasks, OP and NP airways, laryngoscope blades, ETTs, and stylets. Additional equipment must be readily available (e.g., in a designated "difficult airway cart").

Supraglottic Devices

Since the introduction of the laryngeal mask airway in the late 1980s, supraglottic devices (a term used to incorporate devices placed above the larynx to allow for ventilation) have evolved to include ones with gastric

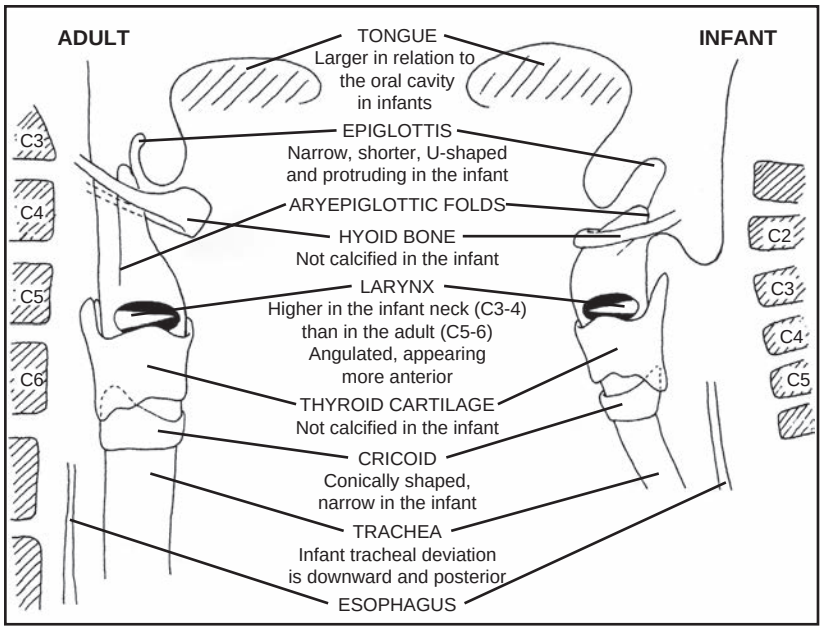

Fig. 188.2 Comparison of the anatomy in adult and infant airways. (From Ho M: The pediatric airway. In Bell C, Hughes C, Oh T, editors: *The pediatric handbook.* St Louis, Mosby–Year Book, 1991, p 130. Adapted from Coté CJ, Todres ID: The pediatric airway. In Ryan JF, Todres DI, Coté CJ, editors: *A practice of anesthesia for infants and children.* Orlando, FL, Grune & Stratton, 1986.)

access for stomach decompression (second generation). They may be used as the sole airway of choice when endotracheal intubation or mask ventilation is undesirable or difficult. Although older devices have ample data to support safety, newer devices have been shown to be successful in improving specific difficult situations; once proper placement and good ventilation ($ETCO_2$ tracing) is achieved, these devices can be used to facilitate fiberoptic intubation of the trachea (Fig. 188.3) with a cuffed ETT.

Bullard Laryngoscope

The Bullard laryngoscope, which is available in both pediatric and adult sizes, permits indirect visualization of the larynx with minimal mouth opening or movement of the neck. It does not require alignment of the oral, pharyngeal, and laryngeal axes. The pediatric blade is narrower and has more acute terminal angulation than does the adult version. The trachea is intubated by advancing a previously loaded endotracheal tube over an intubating stylet fastened to the laryngoscope blade. It has been used less frequently with the advent of the videolaryngoscope and the need for a considerable learning curve to master its use.

Videolaryngoscope (e.g., Glidescope)

These devices have provided anesthetists the ability to use "direct laryngoscopy" and at the same time allow others present during the procedure adequate view of the airway. They are intended for oral intubation and have similar limitations as direct laryngoscopy (e.g., blood, secretions, small mouth opening).

Flexible Fiberoptic Bronchoscope

The flexible fiberoptic bronchoscope for children varies in external diameter from 2.2 to 4.9 mm. Those with 2.2- or 4.9-mm external diameters will pass through 2.5- and 5.5-mm endotracheal tubes, respectively. The 2.2-mm ultrathin fiberoptic bronchoscope has a flexible tip but lacks a suction port, but it is invaluable for managing a younger child with a difficult airway.

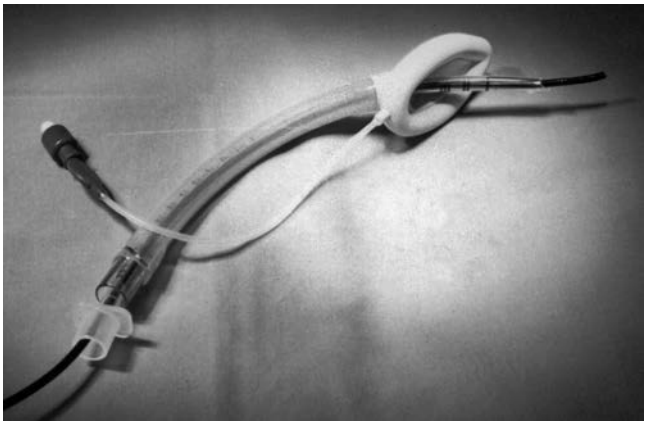

Fig. 188.3 The laryngeal mask airway can be used to facilitate either blind or fiberoptic endotracheal intubation.

PREVENTION

Studies have shown that children have a higher risk of anesthesia-related morbidity than adults do. Untoward respiratory events are the major reason for this morbidity. A thorough understanding of pediatric airway anatomy and physiology will help reduce this risk. Preoperative identification of a child with a difficult airway must be coupled with sufficient personnel and equipment to secure the airway without life-threatening sequelae. The existence of a difficult airway can be communicated to future care providers via detailed notes in the chart, a letter given to the child's parents, and a Medic-Alert bracelet.

ACKNOWLEDGMENT

The author wishes to thank Dr. Hernando De Soto for his contribution to the previous edition of this chapter.

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Emergence Agitation and Emergence Delirium

189

Tyson Olds • B. Craig Weldon

Case Synopsis

An otherwise healthy 4-year-old boy undergoes general anesthesia for circumcision. The surgery proceeds without incident. When the child arrives in the postanesthesia care unit (PACU), he is noted to be restless, irritable, crying, and not responsive to routine calming measures. His agitated behavior escalates to incoherent screaming, thrashing of his extremities, and intermittent combativeness.

PROBLEM ANALYSIS

Definition

Emergence agitation (EA) in young children is characterized by crying, restlessness, and irritability during the emergence from anesthesia, whereas emergence delirium (ED) is a dissociated state of consciousness in which the child is hyperkinetic and incoherent, with inconsolable crying, screaming, kicking, or thrashing. It is likely that EA and ED are two manifestations of the same cognitive state.

Recognition

Emergence agitation is a common event after even minor surgery in toddlers, preschoolers, and young school-age children. An episode of emergence agitation may last 20 to 30 minutes and may not respond to routine comforting measures. Between 5% and 10% of children manifest severe symptoms that resemble delirium. Adolescents and young adults seem to have a higher incidence of delirium versus simple agitation in the PACU.

Risk Assessment

Developmental Factors

Young children lack mature coping mechanisms. Therefore they are less able to tolerate being separated from their parents in a strange place, the psychological stress associated with medical illness or surgery, and the altered mental state associated with emergence from anesthesia. Parental anxiety or lack of understanding about what to expect in the perioperative period may also have a negative effect on their child's behavior.

Preoperative Anxiety and Baseline Temperament

Children with high levels of preoperative anxiety are less able to cooperate during mask induction, have a higher incidence of EA in the PACU, and have more severe episodes of EA. Likewise, children who are highly distressed during mask induction of anesthesia tend to demonstrate more agitation during emergence. Children's baseline temperament affects their postoperative behavior, and parents can frequently predict whether their child is going to have trouble dealing with events on the day of surgery. Neither parental presence during induction of anesthesia nor preanesthetic sedation with oral midazolam appears to lessen the risk for EA.

Preexisting Mental Disturbances

Children and adolescents with autism, intellectual disability, bipolar disorder, or disruptive behavior (e.g., those with oppositional defiant disorder or other conduct disorders) may have more behavioral problems in the postoperative period. These patients should receive their regular psychotropic medications on schedule on the day of surgery. They may also benefit from the administration of a preanesthetic sedative.

Inadequate Postoperative Analgesia

Unrecognized postoperative pain is a common cause of EA in all age groups. It is difficult to assess preverbal and developmentally delayed infants and children with subjective pain scoring systems. Also, most young children are notoriously poor self-reporters of pain intensity. Those who emerge from anesthesia in pain often show agitated or even delirious behavior but do not indicate their pain to caregivers. Other causes for discomfort, such as gastric or urinary bladder distention, surgical drains, or overly tight bindings and dressings, must be ruled out.

Underlying Medical Conditions

The following are potentially life-threatening medical conditions that may present in the PACU as emergence agitation or delirium:

- Hypoxemia or hypercapnia
- Reduced cerebral blood flow with shock states or severe hypotension
- Hypoglycemia, hyperthyroidism, or hyperparathyroidism
- Hyponatremia
- Seizures or elevated intracranial pressure

These diagnoses are considered within the proper clinical context if a cause for emergence agitation or delirium cannot be rapidly identified or if the period of agitation is prolonged or accompanied by a decreasing level of consciousness.

Anticholinergics

Scopolamine and, to a lesser extent, atropine have been associated with postoperative mental disturbances. These agents cross the blood-brain barrier to cause a central anticholinergic crisis (or syndrome) due to the blockade of acetylcholine-mediated neuroinhibitory pathways. Full-blown central anticholinergic syndrome is characterized by warm, flushed, dry skin; visual disturbances; fever; and delirium. Some

ophthalmic preparations used to produce mydriasis, as well as numerous antihistamines and nonproprietary drugs, have central anticholinergic effects that may contribute to disturbed behavior in patients emerging from anesthesia. Many of these drugs are tertiary versus quaternary amines and thus cross the blood-brain barrier more easily.

Anesthetic Agents

Low blood-soluble volatile anesthetics (cyclopropane, desflurane, sevoflurane) have been associated with EA in children. The mechanism for this phenomenon is unknown but may be related to the rapid emergence from anesthesia with these less-soluble agents. However, the incidence of EA in children receiving propofol is significantly lower than those receiving sevoflurane despite the similar rapid emergence achieved from both agents. It is possible that the rapid loss of analgesic effects (greater with desflurane than sevoflurane) might contribute to inadequate postoperative analgesia and provoke or aggravate agitated behaviors.

Ketamine has long been associated with dysphoria and disturbing psychological reactions in adolescents and adults. However, in younger children, the evidence suggests that ketamine administered intraoperatively during sevoflurane anesthesia decreases the incidence of EA.

Implications

The most immediate concern for a child suffering from EA is the increased risk of self-harm. Children with severe EA/ED can accidentally injure themselves or their caregivers as a result of combativeness or hyperkinesis. Displacement of intravenous (IV) or monitoring lines and surgical drains/dressings further complicates the postoperative care of these patients. In the tumult that often surrounds these children in the PACU, the nurses and anesthesiologist may be required to turn their attention from other patients, possibly leading to reduced monitoring and care for nonagitated PACU patients. The care of a delirious patient is very labor intensive and prolongs PACU stays and increases costs. Most parents of severely agitated children find the experience frightening and emotionally draining.

MANAGEMENT

The initial approach to a child with mild to moderate EA includes the following: (1) reduce environmental stimuli other than those required for routine comfort, (2) involve the child's parents in his or her care as soon as possible, and (3) seriously consider the possibility of inadequate analgesia and administer an IV opioid.

Children with severe agitation who are thrashing about must be protected from bodily harm and have their IV and other vascular access lines adequately secured. This must be accomplished quickly and may require physically restraining the child. These children should be administered repeated doses of a rapid-onset IV opioid such as fentanyl if there is any doubt about the adequacy of their analgesia. This may be followed by dexmedetomidine (0.2 to 0.5 $\mu g/kg^{-1}$) if the agitation persists. Physostigmine 0.025 mg/kg^{-1} is the treatment of choice to counter the central anticholinergic effects of atropine, scopolamine, and other drugs with similar effects.

If postoperative pain has been sufficiently treated or ruled out and dexmedetomidine fails to reduce the severity of agitation, repeated doses of 0.1 to 0.5 mg/kg^{-1} of propofol should be administered until the child is unconscious. This state can be maintained with a low-dose propofol infusion until the child can be allowed to slowly reemerge.

A severely agitated/delirious older child or adolescent who has lost IV access can be quickly sedated with 1 to 2 mg of haloperidol administered intramuscularly, and younger children can be treated with 0.2 to 0.3 mg/kg^{-1} of ketamine intranasally. A new IV line can then be started without further agitating the patient.

Refer to Fig. 189.1 for a treatment algorithm for severe EA.

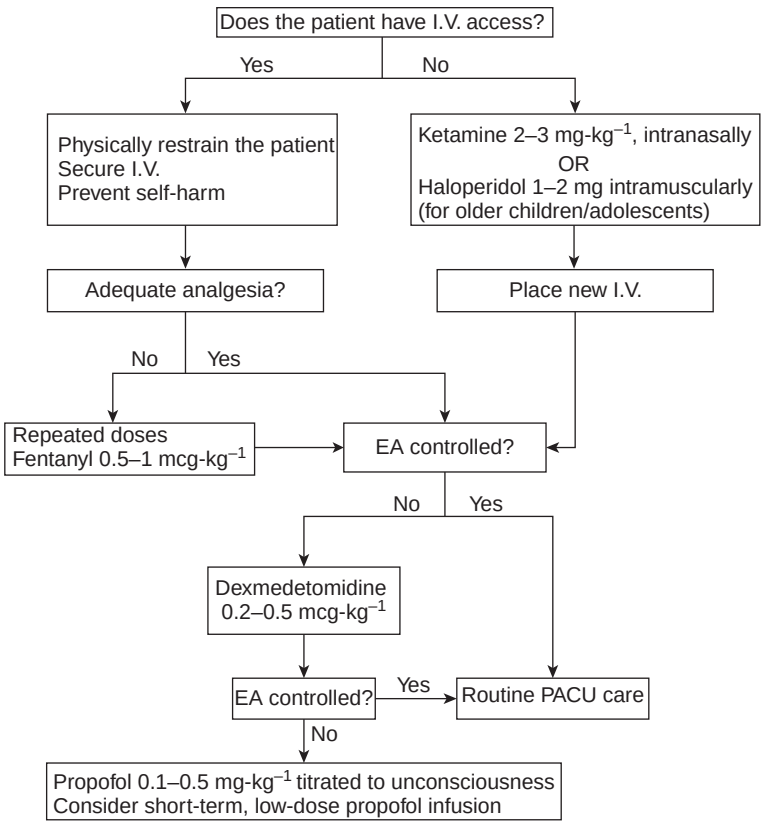

Fig. 189.1 Treatment of severe emergence agitation/delirium.

PREVENTION

- Consider the developmental level of the patient.
- Allay parental anxiety with preoperative education before the day of surgery.
- Assess the child's level of preoperative anxiety on the day of surgery.
- Administer preanesthetic sedation to high-risk pediatric age groups (1 to 6 years) and children with high levels of preoperative anxiety.
- Implement a multimodal analgesia plan, and maintain a high degree of suspicion for the inadequacy of postoperative analgesia.
- Consider administering intraoperative dexmedetomidine, ketamine, IV opioids, propofol (as a continuous infusion or preemergence bolus), or clonidine before emergence in patients who are at risk for EA.
- Rapidly reunite the child with his or her parents in the PACU.

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190 Hypoglycemia and Hyperglycemia

Ari Y. Weintraub

Case Synopsis

An otherwise healthy 4-year-old boy is scheduled for inguinal hernia repair. He has dinner at 5 PM the evening before surgery, as well as milk and cookies before going to bed at 9 PM. He is offered apple juice at 5:30 AM (2 hours before his scheduled surgery), which he refuses. Owing to a surgical emergency, the boy's surgery is delayed 4 hours. Before induction of anesthesia, his vital signs are stable, but he is drowsy and somewhat fussy. His serum glucose concentration in the operating room after induction of anesthesia is 64 mg/dL.

PROBLEM ANALYSIS

Definition

Clinical hypoglycemia can be defined as a plasma glucose concentration that is low enough to manifest as signs or symptoms of impaired brain function. Although hypoglycemia is often defined as a blood glucose concentration less than 55 mg/dL (3 mmol/L) in infants and older children and 35 mg/dL (2 mmol/L) in premature and term neonates, these values have been derived statistically and cannot necessarily be applied to individual patients without regard to clinical findings. (*Note:* To convert mmol/L to mg/dL, simply multiply by 18.)

Hyperglycemia is usually defined as a blood glucose concentration greater than 200 mg/dL (11 mmol/L).

Recognition

Hypoglycemia

Most hypoglycemic children are asymptomatic; some are lethargic, irritable, or jittery. In infants and older children, symptoms may occur at a blood glucose concentration below 75 mg/dL, and unconsciousness at less than 35 mg/dL. In neonates, chronic low blood glucose concentrations can be associated with adverse changes in somatosensory evoked potentials and neurodevelopmental outcomes. Clinical signs of hypoglycemia (tachycardia, hypertension) may be masked by preoperative sedation or general anesthesia or attenuated by β-blockers.

Hyperglycemia

The stress response to surgery, and perhaps to anesthesia, may result in a temporary intraoperative increase in blood glucose concentration. Intraoperative narcotics and regional analgesia ameliorate the stress response to surgery by reducing catecholamine release, which in turn attenuates the increase in blood glucose concentration. Hyperglycemia is not recognized clinically during anesthesia, except perhaps by the osmotic diuresis it may induce. A blood glucose determination is necessary to confirm any suspicion.

Risk Assessment

The incidence of preoperative hypoglycemia in healthy infants and children who have fasted between 4 and 19 hours is quite low. Also, there appears to be no correlation between blood glucose concentration and the duration of fasting (hours) in this population. The risk of hypoglycemia has been significantly reduced by allowing healthy children to ingest glucose-containing clear liquids up until 2 hours before the induction of anesthesia.

The following patients, however, are at risk for preoperative hypoglycemia when fasting:

- Premature infants and small-for-gestational-age neonates
- Newborns and infants born to diabetic mothers, and children with diabetes or insulinomas
- Patients with reduced oral intake (e.g., feeding aversions, vomiting) or excessive fluid losses (e.g., diarrhea, bowel preparation for colonoscopy)
- Malnourished patients
- Patients with severe hepatic failure
- Patients with abnormalities of lipolysis or amino acid metabolism
- Patients with myopathies, mitochondrial diseases, or glycogen storage diseases
- Those receiving certain drugs (e.g., propranolol, alcohol)
- Patients receiving hyperalimentation solutions or simple dextrose infusions (10% or 12.5%), especially when these infusions are discontinued acutely

Factors resulting in intraoperative hyperglycemia include the following:

- Exogenous glucose administration at high rates (e.g., ≥20 mL/kg per hour) or massive transfusion
- Exogenous corticosteroid administration (either chronic or acute/intraoperative)
- Alteration of hormone levels affecting glucose control (e.g., stress)
- Decreased peripheral glucose utilization
- Continuation of 10% or 12.5% dextrose solution at the preoperative rate

Implications

Hypoglycemia

Unrecognized hypoglycemia can lead to neurologic injury. The absolute value at which hypoglycemia impairs neurologic function is unknown but is seemingly related to its duration measured in hours or days. Brain glucose metabolism increases markedly during development. Unlike the adult brain during ischemia, the neonatal brain is able to use alternative substrates such as lactate and glycogen for energy.

Throughout the 1980s, routine intraoperative administration of dextrose to infants and children was the recommended practice. However, mounting concerns about the risks of hyperglycemia have led to most clinicians avoiding the routine use of solutions containing glucose, except perhaps in neonates, infants who are small for gestational age, and children with special problems. It is worthwhile to note that due to the common administration of large doses of glucocorticoids, exogenous catecholamines, and glucose-containing blood products to infants and children undergoing open heart surgery, the elimination of dextrose from intravenous solutions for these patients does not seem to be associated with hypoglycemia.

Hyperglycemia

Hyperglycemia can induce diuresis, dehydration, and electrolyte disturbances and may increase the incidence of cerebral hemorrhage in very small newborns. In adults, hyperglycemia existing before an ischemic or hypoxemic event may increase neurologic injury. It is postulated that in the presence of either insult, oxidative metabolism of glucose fails and glycolysis increases, producing excess lactate. With sufficient intracellular lactate accumulation, intracellular pH decreases, which may lead to compromised cellular function or cell death.

In neonates, however, moderate to profound hyperglycemia seems to protect the brain from ischemic damage through several mechanisms, including increased glycogen stores and cerebral high-energy reserves, slower accumulation of lactate due to slower glucose uptake and metabolism compared with adults, and enhanced lactate clearance. Thus during pediatric cardiac surgery, the role of hyperglycemia (if any) in neurologic injury is unclear. In fact, in one study of neonates undergoing arterial switch operations, no relationship between poor long-term neurologic and developmental outcomes and hyperglycemia could be demonstrated.

Hyperglycemia is also associated with adverse outcomes in adults with sepsis. Glucose control in septic infants is poorly defined. However, most clinicians reduce 10% or 12.5% dextrose infusion rates by one-third or one-half during surgery on septic infants.

MANAGEMENT

The goals of intraoperative fluid management are to provide an appropriate amount of parenteral fluids (water plus electrolytes) to maintain adequate intravascular volume, cardiac output, and urine output and, in some instances, to provide sufficient glucose to prevent hypoglycemia or minimize the risk of perioperative hyperglycemia. To avoid both hypoglycemia and hyperglycemia during surgical procedures, some have suggested administering 2.5% dextrose in lactated Ringer's (LR) solution at maintenance rates, along with a glucose-free fluid (e.g., LR or normal saline) for replacement of blood and third-space losses. Because 2.5% dextrose–LR solution is not commercially available, either the practitioner or a pharmacist must prepare it. Blood obtained from central venous or arterial catheters or from finger or heel sticks is used to monitor glucose concentrations. Glucose testing is usually available at the point of care. If not, concentrations are measured in the blood gas laboratory. Serial blood glucose determinations can be made, with the amount of intravenous glucose adjusted accordingly.

PREVENTION

Prevention of hypoglycemia and hyperglycemia requires a case-specific risk-benefit analysis. Some caveats deserve special mention:

- Be aware of patients at increased risk for hypoglycemia or hyperglycemia.
- Be judicious when administering glucose-containing solutions to patients at risk for hypoglycemia.
- Withhold glucose-containing solutions when appropriate.
- Frequently monitor blood glucose concentrations.

ACKNOWLEDGMENT

The author wishes to thank Dr. D. Ryan Cook for his contribution to the previous edition of this chapter.

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191 Hypothermia in the Pediatric Patient

Barbara M. Dilos

Case Synopsis

A 3-month-old girl, born at 32 weeks of gestation, presents to the magnetic resonance imaging (MRI) scanner for sedation for MRI of the brain. Her weight is 4.2 kg, and she is on nothing-by-mouth status for 6 hours. She is currently on no medications. She receives a general anesthetic, and the MRI is completed in 1 hour. After the MRI she is taken to the postanesthesia care unit, where her temperature is found to be 35°C, and she is very slow to wake up to feed.

PROBLEM ANALYSIS

Definition

Core body temperature is a vital sign, and the normal core body temperature is 37°C ± 0.2°C. Humans maintain a constant core body temperature within a limited range when exposed to different ambient temperatures. This tightly controlled thermoregulation can be very easily disrupted by anesthesia and surgery, especially in the pediatric population and most commonly in the neonatal patient. Recent studies have shown that older children between the ages of 12 and 18 are also at greater risk of developing postoperative hypothermia. This may be due to the type of procedures done in this age group, or perhaps there is less attention to maintaining normothermia due to the fact that they are older. Mild hypothermia, a change of 1°C to 2°C, is commonly seen in the pediatric patient receiving general anesthesia. It is crucial that the core-to-peripheral gradient is maintained during anesthesia so that core heat is not distributed and lost in the peripheral tissues. Neonatal patients are specifically susceptible to hypothermia due to their immature thermoregulatory system, their lack of subcutaneous fat that can act as an insulator, and their inability to shiver.

Implications

Hypothermia during and after anesthesia causes several derangements in the pediatric population. In older children, postoperative shivering can increase oxygen consumption by 400% to 600%. Hypothermia has an effect on acid-base balance and on the metabolism of anesthetic drugs. It prolongs the duration of action of muscle relaxants and reduces the minimum alveolar concentration of inhaled anesthetics. It increases oxygen consumption, disrupts coagulation factors, and affects wound healing. Mild core hypothermia has been shown to impair immune function, thus directly impairing neutrophil function. Hypothermia also triggers vasoconstriction, which in turn produces tissue hypoxia, which interferes with wound healing and promotes wound infection. Mild hypothermia has been associated with an increased risk of blood loss and increased incidence of blood transfusion. In moderate-to-severe cases, hypothermia can cause cardiac arrhythmias.

Recognition

Mechanisms of Heat Loss

The first step of heat dissipation is the transfer of heat from the core to the periphery. The second step is the transfer of heat from the periphery (the skin) to the environment. After anesthetic induction the core temperature typically drops 1.0°C to 1.5°C within the first hour. In infants this occurs more rapidly within the first 10 minutes. In infants and children, there is an elevated risk of hypothermia, which is largely due to their large body surface area, especially over large structures such as the trunk and the head. To prevent hypothermia in pediatric patients after anesthesia, one must understand the mechanisms by which temperature regulation is affected in the pediatric patient while anesthetized and, more important, even before the induction of anesthesia. Four factors affect heat loss in the pediatric patient: radiation, convection, conduction, and evaporation.

Radiation

Radiation is the transfer of infrared energy between two objects of different temperatures. Energy is transferred from the warmer to the cooler object. Radiation heat loss is proportionately greater in the pediatric population due to their larger skin surface area in relation to their body weight. Radiation accounts for 39% of heat loss in the pediatric patient.

Convection

Convection is the transfer of energy due to air molecule movement around the patient. If there is cold air moving around the pediatric patient, more heat will be lost to the environment. Convection is comparable to the "wind chill" effect in outdoor temperatures. It contributes to 30% of the heat loss in a patient lying uncovered on an operating room table.

Conduction

Conduction is the direct transfer of heat from one object to another when they are in contact. For example, a patient who is lying on a cold operating room table will lose heat to the operating room table even before induction. Cold irrigation fluids in a wound or body cavity will result in heat loss through conduction. Intravenous administration of cold blood and products will also have a deleterious effect of heat loss by conduction.

Evaporation

Evaporation is heat loss to the environment via loss from the skin, bodily cavities, and surgical incisions. The latent heat of vaporization is expended to convert a liquid to a gas. Open wounds, especially large ones, are a great source of heat loss due to evaporation. For example, in a case of gastroschisis, evaporative heat loss would be a major concern even before induction of anesthesia.

MANAGEMENT

Monitoring of Temperature During Anesthesia

Thermoregulation is the process whereby the body maintains normal core temperature despite environmental factors. During general and regional anesthesia, there is disruption of the body's thermoregulatory mechanisms. In addition, the stress of surgery compounds this disruption. Therefore continuous temperature monitoring is extremely important, especially in the pediatric population, so that there is prompt detection of temperature change and active resolution to maintain normothermia. The American Society of Anesthesiologists requires that temperature monitoring is part of the minimum basic monitoring standards.

Body temperature varies. The core temperature is usually 2°C to 4°C warmer than the extremities. The skin is even cooler. According to Sessler, core temperature is the best indicator of the body's thermal state.

Core temperature monitoring can be measured at several different sites during anesthesia:

- Esophageal temperature is measured at the level of the carina posterior to the heart via an esophageal probe. Children do not have a lot of thermal insulation between the esophagus and trachea, so the temperature of the inspired gases can have an effect on esophageal readings.
- Nasopharyngeal temperature is measured at the level of the soft palate via a nasal probe. It is a good way to measure core temperature because this is very close to the brain.
- Tympanic membrane and pulmonary artery temperatures are also considered core temperatures. The tympanic membrane is very close to the carotid artery and the hypothalamus. However, these sites are not very easily monitored. Tympanic temperature probes run the risk of tympanic membrane injury, and if used, the external ear canal must be covered to prevent inaccurate readings due to air movement in the ear canal. Cerumen may also pose an obstruction and cause inaccurate temperature readings.
- Sites that are considered close to core temperature are rectal, bladder, axilla, and mouth temperatures. Bladder temperature is only accurate when there is adequate urine output.
- Mouth temperature is dependent on patient cooperation and can be affected by ingestion of food or drink of different temperatures.
- Skin temperature is the least reliable measure of body temperature.

Thermoregulatory Mechanisms

It is known that the hypothalamus is the main thermoregulatory system in mammals. There are signals from all different types of tissues that are sent to the hypothalamus. There are three different ways whereby the processing of this information occurs: afferent thermal sensing, central regulation, and efferent response. Autonomic control is centered in the anterior hypothalamus, and behavioral control such as protective clothing and positioning is centered in the posterior hypothalamus. Central control of thermoregulation takes place mostly in the hypothalamus. Most ascending thermal information travels along the anterior spinothalamic tract. Efferent responses include sweating, nonshivering thermogenesis, shivering, and vasodilation or vasoconstriction. Autonomic control consists of precapillary vasodilation, vasoconstriction in arteriovenous shunts primarily in the extremities, and shivering. Nonshivering thermogenesis is the primary response in infants. Brown adipose tissue is converted into heat by norepinephrine, which uncouples a protein that induces aerobic respiration, which in turn generates heat. This brown adipose tissue is present around blood vessels of the adrenals, anterior mediastinum, and neck. It has a light brown color because it has a great amount of mitochondria. Because infants and small children have very little shivering ability, they depend on nonshivering thermogenesis to generate heat. Nonshivering thermogenesis can double the amount of heat produced in infants.

Shivering is muscle activity that raises the metabolic rate, thereby raising temperature. It begins in older children and adults when vasoconstriction fails to maintain normothermia.

Shivering is not as effective as previously thought in raising core temperature. The vasodilation needed to move the muscles may counteract the vasoconstriction needed to prevent heat loss from the periphery.

Anesthesia and Thermoregulatory Control

General anesthesia and neuraxial anesthesia greatly affect thermoregulation in the pediatric patient. General anesthesia completely eliminates the behavioral aspect of thermoregulation. There is also anesthetic-induced, dose-dependent impairment of vasoconstriction and shivering. Volatile anesthetics, intravenous anesthetics, and opioids all have an effect by not triggering thermoregulatory defenses so that core temperature can fluctuate by as much as 4°C as opposed to the 0.2°C fluctuation seen in the nonanesthetized patient. Inhaled anesthetics and intravenous anesthetics such as propofol have a negative effect on nonshivering thermogenesis. General anesthesia reduces metabolic heat production by approximately 30%. After the induction of general anesthesia, the first phase of redistribution begins. This is due to vasodilation caused by the inhaled anesthetics. Core temperature declines as heat is lost to the peripheral tissues. During the second phase, there is reduced heat produced due to the decrease in metabolic rate, and there is increased heat lost to the environment from the periphery. During the third phase, heat loss is exceeded by metabolic heat production, and the temperature stabilizes.

During neuraxial anesthesia, there is disruption of autonomic control, thereby affecting thermoregulation. In the pediatric patient receiving both general and neuraxial anesthesia, there is no additive effect on thermoregulation.

PREVENTION

Perioperative thermal management is extremely challenging in the pediatric patient but nonetheless must be very aggressively pursued. Prewarming the patient does not increase core temperature but increases peripheral temperatures, thereby decreasing the core-to-periphery tissue temperature gradient. The effects of radiation, convection, conduction, and evaporation as mechanisms of heat loss must be minimized and counteracted intraoperatively.

Raising the operating room temperature to 23°C or above is ideal when trying to prevent hypothermia in the anesthetized pediatric patient. This may not be comfortable for the surgical staff; however, once the patient is prepped and draped, other techniques can be employed.

Techniques for mitigating heat loss are through both passive and active warming. The operating room temperature is very important in preventing heat loss from radiation and convection. Passive warming is accomplished by covering exposed areas of the patient with insulators such as a cotton sheet or a plastic cover.

Active warming is achieved most commonly by forced air devices that in the pediatric patient are most commonly placed under the body due to the need of better exposure of the surgical field. In the past, underbody mattresses with circulating warmed water were used. However, they are not as effective. In addition, the combination of heat and decreased local perfusion in the tissues directly on the mattress predisposes the patient to pressure heat necrosis.

Warmed fluids to 37°C are very important when administering them rapidly. In the adult patient, that would be equivalent to 1 L per hour. Irrigation fluid must be warmed as well to reduce conductive heat loss. Air humidification via the breathing circuit is also important in decreasing heat loss through evaporation from the tracheobronchial tree.

With all the devices used to prevent hypothermia, great care must be taken to avoid thermal injury to patient tissues such as the skin or airway mucosa. There have been reports of severe burns using these devices. It is paramount that they be used as per the manufacturer's recommendation with no modifications. Prevention and prompt recognition of hypothermia in the pediatric population is crucial due to the many derangements that even mild hypothermia can promote. The key is to make every possible effort to preempt the lowering of body temperature rather than waiting to rewarm the patient once hypothermia is recognized.

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Hypoxemia in the Pediatric Patient

192

Lori A. Aronson • Jennifer E. Lam

Case Synopsis

An otherwise healthy 5-year-old girl with adenotonsillar hypertrophy secondary to recurrent infections underwent an uneventful tonsillectomy and adenoidectomy with general anesthesia, was extubated, and was sent to recovery. The recovery nurse notifies you that the patient is stridulous with retractions. Cyanosis, tachycardia, and percutaneous arterial oxygen saturation (Spo_2) less than 60% are noted.

PROBLEM ANALYSIS

Definition

Hypoxemia is defined as an abnormally low concentration of oxygen in the blood. This differs from *hypoxia,* which is a state of inadequate oxygen delivery to tissues resulting in the inability to sustain normal cellular aerobic metabolism. Normal age-related values of arterial oxygenation (Pao_2) are found in Table 192.1. Oxygen affinity of hemoglobin changes with age, after the transition from fetal to adult hemoglobin and eventual decrease in 2,3-diphosphoglycerate (2,3-DPG) levels (Table 192.2).

Implications

According to the Pediatric Perioperative Cardiac Arrest (POCA) Registry, 27% of cardiac arrests were due to respiratory causes, primarily laryngospasm, most often occurring during the postsurgical phase of care. Intraoperative hypoxemia in children is associated with younger age (Fig. 192.1). Thus it is imperative to recognize adverse respiratory events and treat hypoxemia expeditiously in children undergoing anesthesia.

Recognition

The pulse oximeter has become the standard of care for oxygen saturation monitoring, improving patient safety in anesthesia by allowing the provider the opportunity to respond sooner to desaturation than would be recognized by clinical signs alone. Pulse oximetry can measure the adequacy of oxygenation, but can only assess ventilation in the absence of supplemental oxygen. Even small amounts of supplemental oxygen will mask hypoventilation (rise in $Paco_2$) by allowing for a less significant drop in Pao_2, making capnography important as well (Fig. 192.2).

Clinical signs of hypoxemia, which vary with age, must also be recognized. Preterm infants and neonates tend to respond to hypoxemia with respiratory *depression* and *bradycardia,* whereas older infants and children respond with *tachypnea* and either *tachycardia* or *bradycardia.* Other more global clinical signs of hypoxemia include cyanosis, pallor, restlessness, or altered mental status, many of which are masked by anesthesia. Upper airway obstruction signs include stridor, grunting, retractions, nasal flaring, and ventilatory effort without air movement. Lower airway obstruction signs include wheezing, rhonchi, and decreased breath sounds. Both can lead to no air movement, making differentiation difficult.

Determining the cause of hypoxemia is critical to establishing a treatment strategy. A systematic approach to ascertaining the etiology must be taken. In addition to physical assessment, one might take a "wall to the alveoli" approach, assessing oxygen supply, integrity of the anesthesia machine and circuit, and the patient's airway before laboratory evaluation. The physiologic impact of other organ systems (i.e., pulmonary, cardiovascular, hematologic, central nervous systems) should also be considered.

Risk Assessment

The risk of hypoxemia in pediatric patients is related to many factors, including age, anatomic and physiologic characteristics, and underlying disease. The anesthesiologist must assess the degree these risks will contribute to hypoxemia in an individual patient. Box 192.1 lists the principal causes of hypoxemia. In fact, the incidence of hypoxemia

TABLE 192.1 Normal Arterial Oxygen Tension (Pao_2) in Infants and Children

Age	Pao_2 (mm Hg)
Preterm	60
Full term	70
1 month	95
1 year	93
12 years	98

TABLE 192.2 Age-Related Oxygen Affinity for Hemoglobin at an Oxygen Saturation of 50% (P50)

Age	Pao_2 (mm Hg)[a]
Neonate	20
Infant (>3 mo)	30
Adult (>18 yr)	27

[a]Oxygen affinity is highest in the neonate and lowest in the infant before reaching adult levels.

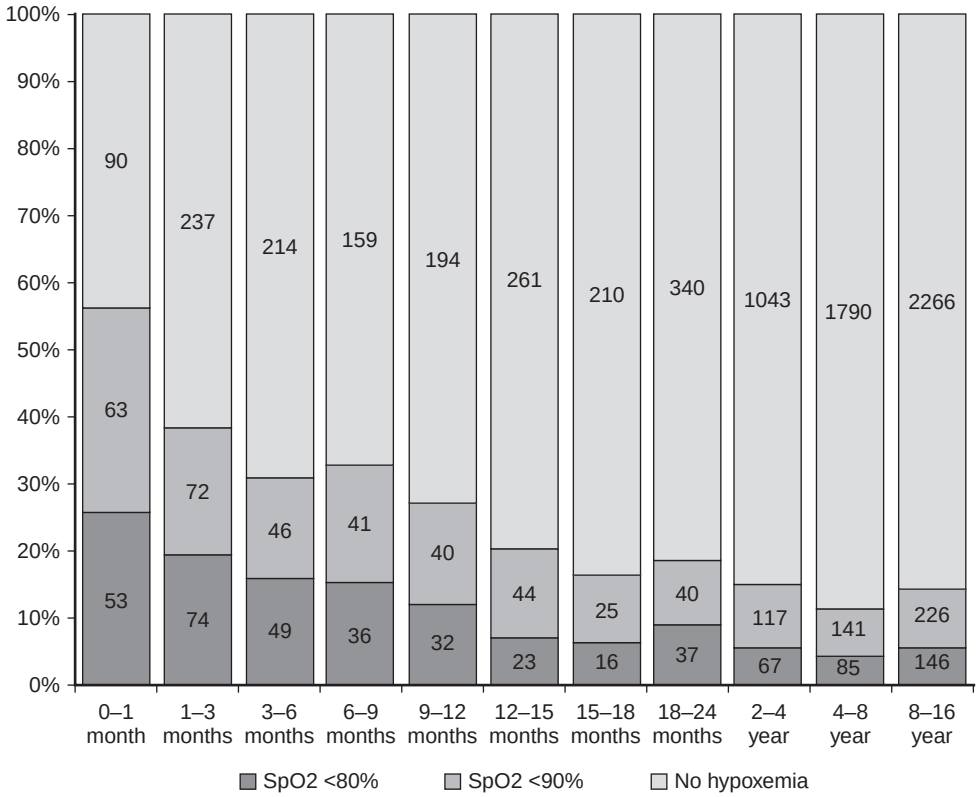

Fig. 192.1 Incidence of intraoperative hypoxemia in children in relation to age. Percentage of cases (with numbers of cases presented in bars) with at least 1 period of hypoxemia for at least 1 minute in relation to age group in the retrospective cohort (uncorrected data are presented, $n = 8277$). *Spo*$_2$, Oxygen saturation. (From de Graaff JC, Bijker JB, Kappen TH, et al: Incidence of intraoperative hypoxemia in children in relation to age. *Anesth Analg* 117[1]:169-175, 2013.)

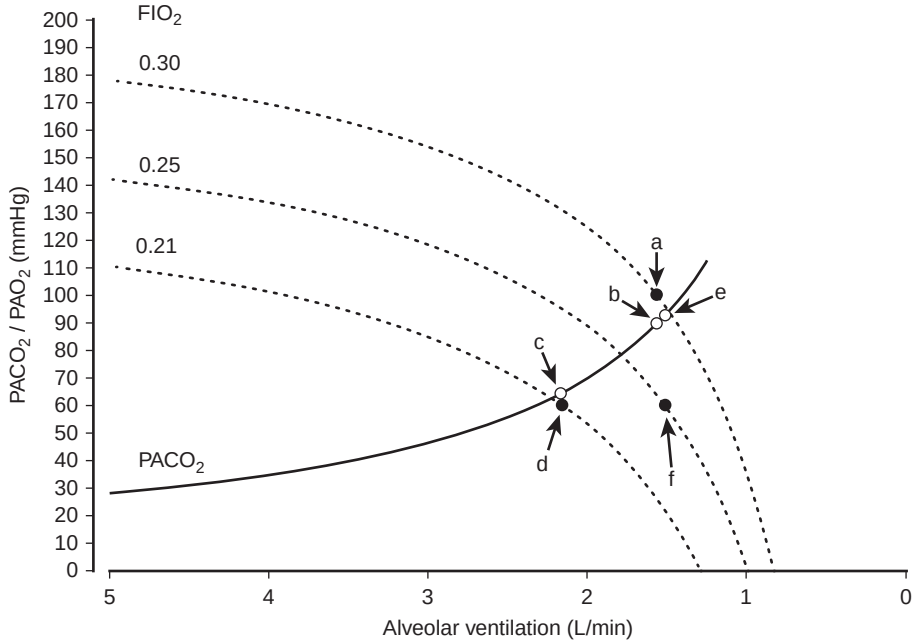

Fig. 192.2 Effect of supplemental O_2 on Pa_{O_2} in relation to Pa_{CO_2}. Mathematical modeling of Pa_{O_2} *(closed circles)* and Pa_{CO_2} *(solid line, open circles)* as a function of alveolar ventilation with varied Fi_{O_2}. This model assumes a respiratory gas exchange quotient of 0.8, no physiologic shunting of blood, and a steady state. With an Fi_{O_2} of 0.3, Pa_{O_2} is still 100 mm Hg (point a) when Pa_{CO_2} is 90 mm Hg (point b). With an Fi_{O_2} of 0.21, by the time Pa_{CO_2} has increased to 65 mm Hg (point c), Pa_{O_2} has decreased to 60 mm Hg (point d). With an Fi_{O_2} of 0.25, Pa_{CO_2} can rise to 100 mm Hg (point e) before Pa_{O_2} decreases to 60 mm Hg (point f). (From Fu ES, Downs JB, Schweiger JW, et al: Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. *Chest* 126[5]:1552-1558, 2004.)

BOX 192.1 Causes of Hypoxemia in Pediatric Patients

I. Central Nervous System and Respiratory Centers
a. Apnea
b. Head trauma
c. Brain tumor
d. Seizures
e. Impaired medullary perfusion/increased intracranial pressure
f. Anesthetic agents
   1. Opiate overdose
   2. Inhalation agents
   3. Barbiturates, sedatives
   4. Combination of the above

II. Airway
a. Epiglottitis, croup
b. Tracheomalacia, laryngomalacia
c. Retropharyngeal abscess
d. Vascular ring
e. Infantile stridor
f. Laryngospasm
g. Webs
h. Mediastinal mass
i. Foreign body, ETT obstruction
j. Thermal airway injury (burns)
k. Subglottic stenosis
l. Upper respiratory infection

III. Respiratory Muscles
a. Residual neuromuscular blockade
b. Debilitation/malnutrition
c. Myasthenia gravis
d. Muscular dystrophy
e. Phrenic nerve injury

IVa. Pulmonary: Physiologic Causes
a. V/Q mismatch
   1. Shunt (atelectasis)
   2. Dead-space ventilation
b. Diffusion abnormality (rare)

IVb. Pulmonary: Pathologic Causes
a. Respiratory distress syndrome
b. Bronchopulmonary dysplasia, chronic lung disease
c. Primary pulmonary hypertension
d. Aspiration pneumonitis
e. Diaphragmatic hernia
f. Tracheoesophageal fistula
g. Pulmonary edema
h. Near-drowning
i. Asthma, bronchospasm
j. Pneumonia
k. Pulmonary contusion
l. Pulmonary embolus (air, fat, thrombus)
m. Pulmonary fibrosis, cystic fibrosis
n. Bronchiectasis

V. Chest Wall and Pleura
a. Pneumothorax
b. Flail chest
c. Pleural effusion
d. Obesity
e. Kyphoscoliosis
f. Abdominal mass

VI. Cardiovascular
a. Congenital heart disease
b. Congestive heart failure
c. Arteriovenous malformation
d. Hypovolemia, hemorrhage

BOX 192.1 Causes of Hypoxemia in Pediatric Patients—Cont'd

VII. Hematologic
a. Anemia
b. Sickle cell disease or crisis
c. Thalassemia

VIII. Oxygen Delivery
a. Main-stem bronchial intubation
b. ETT kinking
c. Low Fio_2, hypoxic gas mixture
d. Ventilator disconnection
e. Anesthesia machine failure
f. Esophageal intubation

IX. Increased Oxygen Consumption
a. Shivering (hypothermia)
b. Hyperthermic states (sepsis)
c. Malignant hyperthermia
d. Hyperthyroidism

X. Miscellaneous
a. Positioning
b. Carbon monoxide
c. Cyanide poisoning (sodium nitroprusside overdose)
d. Hepatic failure

ETT, Endotracheal tube; *V/Q*, ventilation/perfusion.

increases with decreasing age, and is highest in the neonatal population (see Fig. 192.1).

Knowledge of the unique anatomic and physiologic characteristics of infants and children is critical to their anesthetic management and include the following:

Anatomy

- Infants have relatively large heads, short necks, and large tongues, which makes them prone to obstruction. As such, a shoulder roll may be beneficial. With age, large tonsils may further contribute to obstruction.
- The larynx seems more anterior in the infant because it is higher in the neck than in the adult (C3–C4 versus C4–C5), and the vocal cords are angled more cephalad, thus requiring a more acute angle at the tip of the endotracheal tube (ETT). Additionally, the floppy, omega-shaped epiglottis makes a straight blade more suitable for intubation.
- The narrowest part of the pediatric airway by *measurement* is the larynx; however, *functionally* the narrowest part of the pediatric airway is the rigid cricoid ring. Airway epithelium is easily traumatized, so care must be taken in selecting an appropriately sized ETT.
- An infant's trachea is significantly shorter than an adult's, and the angle of tracheal bifurcation (about 45 degrees) is nearly the same for both main-stem bronchi. Therefore one must be diligent to avoid bronchial intubation. In contrast, in older patients the bifurcating angle is less for the right main-stem bronchus (about 30 degrees) than for the left, explaining the higher risk for right main-stem bronchial intubation in older children and adults.
- The larynx, trachea, and bronchi are highly compliant and more subject to distention and compression, leading to dynamic airway collapse (laryngomalacia, tracheomalacia, bronchomalacia). The tendency toward extrathoracic tracheal collapse below the level of an obstruction is often accompanied by inspiratory stridor. Infants and young children with reactive airway disease can lead to significant intrathoracic airway collapse.
- The newborn chest wall is very compliant and tends to move inward on inspiration. The rib angle is more horizontal, further

limiting chest expansion on inspiration. Thus infants often rely on their abdominal muscles during inspiration.
- A distended abdomen (from aggressive positive pressure ventilation or crying) can markedly impede diaphragmatic movement.
- Pulmonary development is incomplete at birth. Alveoli are present in adult numbers by 3 years, but continue to grow in size until 7 to 8 years of age. Certain neonatal disease states lead to fewer ventilating airway components or inadequate surfactant, causing alveolar collapse, decreased compliance, and hypoxemia.

Physiology

- Respiratory control is not well developed, and infants and neonates respond to hypoxemia with transient tachypnea, followed by respiratory depression. Infants also have fewer type I muscle fibers in the diaphragm and intercostals, making them more prone to fatigue, hypoventilation, and hypoxemia. There is also immature coordination between respiratory efforts and oropharyngeal motor and sensory input, making infants obligatory nasal breathers.
- Periodic breathing (apnea lasting ≤10 seconds) is a normal benign process that occurs in both term and preterm infants and decreases dramatically in frequency by 12 months of age.
- Infant apnea (cessation of breathing lasting longer than 20 seconds or shorter with associated bradycardia, cyanosis, pallor, or hypotonia) can be central, obstructive, or mixed and is more common in prematurity. Younger postmenstrual age, earlier gestational age, and anemia are significant risk factors for postoperative apnea.
- Oxygen consumption and alveolar ventilation in infants is nearly twice that of an adult (7 vs. 4 mL/kg/min and 130 vs. 60 mL/kg/min, respectively), whereas functional residual capacity is almost half that of an adult (25 vs. 40 mL/kg). Infants also have a higher closing volume and faster respiratory rate. Thus infants have limited oxygen reserve in the face of increased O_2 consumption contributing to rapid onset of hypoxemia.
- With the onset of respiration at birth and the clamping of umbilical vessels, pulmonary vasculature resistance (PVR) decreases and systemic vasculature resistance (SVR) increases, leading to functional closure of the foramen ovale and shunt reversal through the ductus arteriosus. Until these pathways close anatomically, reversion to fetal circulation with subsequent hypoxemia may occur secondary to acidosis, hypoxia, hypercarbia, or hypotension.
- With congenital heart disease, anatomic shunting of blood through right-to-left communications can result in hypoxemia from an imbalance in PVR to SVR. A true right-to-left shunt does not respond to oxygen with an increase in SpO_2. Congestive heart failure may also contribute to hypoxemia.
- In newborns, hemoglobin levels, blood volume, and cardiac output are increased in compensation for the higher affinity of fetal hemoglobin for oxygen (less oxygen is released to the tissues at a given Fio_2). The transition to adult hemoglobin at 3 to 6 months of age results in a physiologic anemia. A compensatory increase in 2,3-DPG shifts the oxyhemoglobin dissociation curve rightward, allowing for greater O_2 delivery to the tissues. By 10 to 12 years, 2,3-DPG levels drop to adult levels with a slight leftward shift of the curve (see Table 192.2).

MANAGEMENT

Initial management of hypoxemia is directed at improving oxygenation by increasing the Fio_2 to 1.0 while ensuring airway patency and adequate ventilation. This is accomplished by bag-mask ventilation, oropharyngeal or nasopharyngeal airways, laryngeal mask airway, endotracheal intubation, cricothyrotomy, or tracheostomy. Due to the anatomic differences in infants and children, proper equipment selection and optimal positioning will facilitate airway management: a shoulder roll may be necessary to optimize the laryngeal view, an oral airway can relieve obstruction, and a straight blade is preferred when intubating the airway in neonates and infants.

Further management is directed at remedying the underlying cause of hypoxemia. Rapid diagnosis of the cause allows for timely reversal of hypoxemia and avoidance of further complications. If hypoxemia is prolonged, advanced life support may become necessary.

PREVENTION

Prevention of hypoxemia and its adverse outcomes begin with a thorough patient evaluation, understanding the implications of the planned procedure, and checking all equipment before anesthesia and surgery. Preoperative evaluation involves assessing the patient's chronic and acute medical issues, recognizing the urgency and risks of the procedure, and determining whether further medical treatment before surgery could reduce patient risk.

Some common anesthesia practices that may reduce hypoxemia include proper positioning with preoxygenation or denitrogenation before intubation and extubation, reversal of neuromuscular blocking agents, cautious use of opiates in neonates and infants, caffeine use in preterm infants prone to apnea, administering supplemental oxygen during maintenance and patient transport, avoiding shivering, and utilization of pulse oximetry, capnography, and Fio_2 monitors. Although critical incidents may still occur despite the anesthesiologist's vigilance, prompt recognition and treatment is instrumental to minimizing adverse outcomes of hypoxemia.

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Intraoperative Cardiac Arrest: Pediatric

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Case Synopsis

A 9-month-old boy, American Society of Anesthesiologists (ASA) class II, is undergoing craniosynostosis repair with general anesthesia consisting of 2.5% sevoflurane with oxygen and fentanyl. He has an endotracheal tube in place and is positioned prone on a gel roll. During craniectomy, tachycardia is appreciated on electrocardiogram (ECG) waveform, and the arterial line tracing demonstrates new hypotension. The pulse oximetry and end-tidal carbon dioxide waveforms have disappeared. There is no palpable pulse.

PROBLEM ANALYSIS

Definition

Intraoperative cardiac arrest is defined by the need to begin cardiopulmonary resuscitation (CPR) or by death. This is generally an unplanned event, although it may be anticipated when dealing with critically ill patients. CPR is indicated when palpable pulses and measurable blood pressure are absent or when cardiac output is inadequate to provide acceptable organ perfusion (e.g., bradycardia with a heart rate of <60 beats per minute in an infant) despite a palpable pulse.

Recognition

Early signs of patient deterioration under anesthesia can usually be detected by changes in the electronic monitoring signals. Unfortunately, electronic monitor alarms may activate falsely for any number of reasons. Nonetheless, when an alarm sounds, it is imperative to evaluate the patient before attributing the alarm to artifact. Loss of signal from the pulse oximeter, sudden loss or diminished amplitude of the capnograph waveform, or the inability to measure blood pressure can signify impending cardiac arrest.

Risk Assessment

All patients undergoing anesthesia are at risk for intraoperative cardiac arrest. In 1954 Beecher and Todd reported higher anesthetic morbidity and mortality rates for children compared with adults. In 1961 Rackow and colleagues reported that this increase was due to a higher incidence of cardiac arrest in anesthetized children younger than 1 year old. Subsequent studies from Sweden, France, and Canada published between 1988 and 1990 further supported this finding. The Pediatric Perioperative Cardiac Arrest (POCA) registry has been the major source of recent data on the subject. A review of 193 cases of anesthesia-related cardiac arrest suggested proportionally fewer cardiac arrests in patients with ASA class I and age less than 1 year compared with earlier data. This may be related to the declining use of halothane in pediatric anesthesia, with fewer associated cases of volatile agent–induced cardiovascular depression.

The final POCA update was a review of 397 perioperative cardiac arrests, 193 (49%) of which were judged to be related to the administration of anesthesia. Cardiovascular (41%) and respiratory (27%) causes were most common, together accounting for 68% of all cardiac arrests. The most common single cause identified was hypovolemia related to blood loss, the majority occurring during spinal fusion or craniotomy. During maintenance of anesthesia, 50% of arrests were attributed to cardiovascular etiology, and 50% of the arrests during the postsurgical phase were respiratory. Common respiratory etiologies included laryngospasm, bronchospasm, inadequate oxygenation/ventilation, and premature extubation. Only 4 cases (1%) of cardiac arrests were attributed to difficult intubation. Of the patients who suffered cardiac arrest, 28% died, 5% suffered permanent injury, and 61% had no sequelae. ASA category III to V and emergency surgery were associated with increased mortality. Age was not a risk factor for mortality. Analysis of cardiac arrest in children with heart disease showed higher mortality rates (33% vs. 23%). Single cardiac ventricle variant was the most common defect (19%) in patients with congenital cardiac disease who suffered anesthesia-related cardiac arrest.

MANAGEMENT

Prearrest

Early recognition and intervention in cardiac arrest is essential, as delayed therapy can lead to devastating morbidity or mortality. Delayed administration of epinephrine for in-hospital pediatric cardiac arrest has been associated with decreased survival and less favorable neurologic outcome.

Simulation of emergencies has been used by high-reliability organizations such as aviation and nuclear energy for years; only recently has this been adapted to medicine. In a 2003 statement, the International Council of Resuscitation suggested that training include more hands-on practice with lifelike manikins and training modules and frequent refresher sessions. Simulation of operating room cardiac arrests allows teams to practice the American Heart Association consensus recommendations emphasizing high-quality CPR (especially adequate depth and rate, as well as decreased interruptions of chest compressions) and early defibrillation. Implementing systems to improve training, ensure

timely access to equipment, and real-time feedback may improve outcomes in cardiac arrest. All staff members must know the location of code carts and defibrillators and how to use them.

Intraarrest

Unanticipated cardiac arrest (such as that described in the case scenario) is best handled with formalized protocols for managing life-threatening events. Anesthesiologists should adhere to the current pediatric advanced life support (PALS) protocols.

I. Communication and teamwork:
- Remain calm and focused.
- Maintain good communication with the intraoperative team (surgeons, nurses, technologists). Explain clearly what you are witnessing on the monitors and by the patient's vital signs. Ask if there has been any recent action that could explain the patient's sudden hemodynamic deterioration. Verbalize the situation for the team; for example, "This a cardiac arrest; the patient is in pulseless electrical activity (PEA)."
- Call *early* for help. A system should be in place to call for and receive help rapidly. It is important to know how this system operates for each location. Examples are a "CODE" button on the wall or an internal emergency telephone system.
- An organized response by all members of the anesthesia and surgery care team is needed to maximize the opportunity for a favorable outcome. Roles must be assigned: (1) team leader (who directs the resuscitation effort but does not assume any specific task); (2) airway manager (responsible for hand ventilation with 100% oxygen and endotracheal intubation, if necessary); (3) a person designated to perform chest compressions; (4) someone to confirm patent intravenous (IV) access and to administer medications (according to PALS guidelines); (5) a person delegated to obtain the code cart and defibrillator; and (6) a recorder to provide a written record of the events. Most anesthetic records are not designed to adequately document events and therapies during a cardiac arrest. Even in settings with an electronic anesthesia record, manual recording on a separate standardized form for intraoperative cardiac arrest is recommended, allowing the sequence and timing of events to be clearly noted and reviewed later (Fig. 193.1).
- The team leader plays an important role in controlling the entry of outside responders into a code in progress, ensuring that all the designated code roles are filled, prioritizing and directing team actions, maintaining situational awareness, and providing clear instructions to team members concerning the resuscitation protocol. This must occur at a time when panic, disorder, and lack of leadership can readily occur.
- Human factors such as training and leadership skills help teams perform higher-quality CPR with better technical performance, shorter preshock pauses, and earlier defibrillation.

II. PALS: Establish circulation, airway, and breathing.
- Assess the circulation. Brachial or femoral pulses are reliable sites in small children and infants, whereas the carotid is best in older children and adolescents.
- If the pulse is absent, immediately begin high-quality chest compressions. Limit interruptions in chest compressions. It has been shown that consistent and adequate heart massage before and during defibrillation greatly improves the likelihood that spontaneous circulation will return.
- Turn off anesthetic agents, and deliver 100% oxygen via manual ventilation.
- Assess airway patency by listening for breath sounds with a stethoscope while the patient is manually ventilated.
- Place an endotracheal tube if one is not already in place.
- Obtain the crash cart and defibrillator. High-quality chest compressions should be continued during defibrillator pad placement and while charging the defibrillator. Pauses longer than 10 seconds have been associated with decreased defibrillation success.
- End-tidal CO_2 monitoring, metronomes, and pressure-sensing feedback devices can be used to improve the timing and quality of chest compressions during CPR.
- Determine the cardiac rhythm from the ECG.
- Treat arrhythmias according to the current PALS protocols.
- If IV access is poor or unobtainable after 90 seconds, placement of an interosseous needle is mandated (Fig. 193.2). This allows for the administration of emergency drugs and rapid fluid delivery, including blood. Early epinephrine administration can be lifesaving.

III. PALS: Assess the underlying cause.

Once the airway, breathing, and circulation have been assessed and appropriate therapy implemented, attention must be directed to determining the cause of cardiac arrest. Always consider tension pneumothorax in intubated patients. If this is suspected, perform left- and right-sided needle thoracentesis. A chest radiograph can be helpful and should be requested early during the resuscitation. Point-of-care ultrasound is also an emerging technology that can assist with diagnosis of pneumothorax

Obtain blood for laboratory analysis as soon as possible, including arterial blood gases, electrolytes (sodium, potassium, chloride, bicarbonate, calcium), glucose, and hematocrit.

The duration of CPR is handled on a case-by-case basis. Failure to reestablish perfusion should raise the following questions:
- Have all anesthetic agents been discontinued?
- Is CPR being performed correctly?
- Are all team roles filled and being performed effectively?
- Does the patient have an underlying problem that could be contributory?
- Is the patient profoundly hypovolemic owing to fluid or blood loss?
- Has the patient had an anaphylactic reaction?
- Does the patient have a tension pneumothorax?
- Does the patient have cardiac tamponade?
- Is the patient hypothermic?
- Has there been a medication overdose or the wrong medication administered?

If perfusion is reestablished but lost again, consider the following iatrogenic causes:
- Trauma related to closed-chest cardiac massage, including pneumothorax from rib fracture or splenic or hepatic rupture
- Pneumothorax or hemothorax from attempted central venous access or overinflation from mechanical ventilation
- Pericardial tamponade (if intracardiac medications were administered or a vascular cannula was placed into the right atrium)

Postarrest

After resuscitation, it is extremely important to do the following:
- Discuss the incident with the family, using language that they can understand. Explain what is known, but do not speculate on the cause if this is unclear. Inform the family what will occur next.
- Allow the family to ask questions.
- Allow the family to grieve alone or with designated support personnel.
- Sequester equipment and waste materials (especially opened medication vials) if an investigation is indicated.

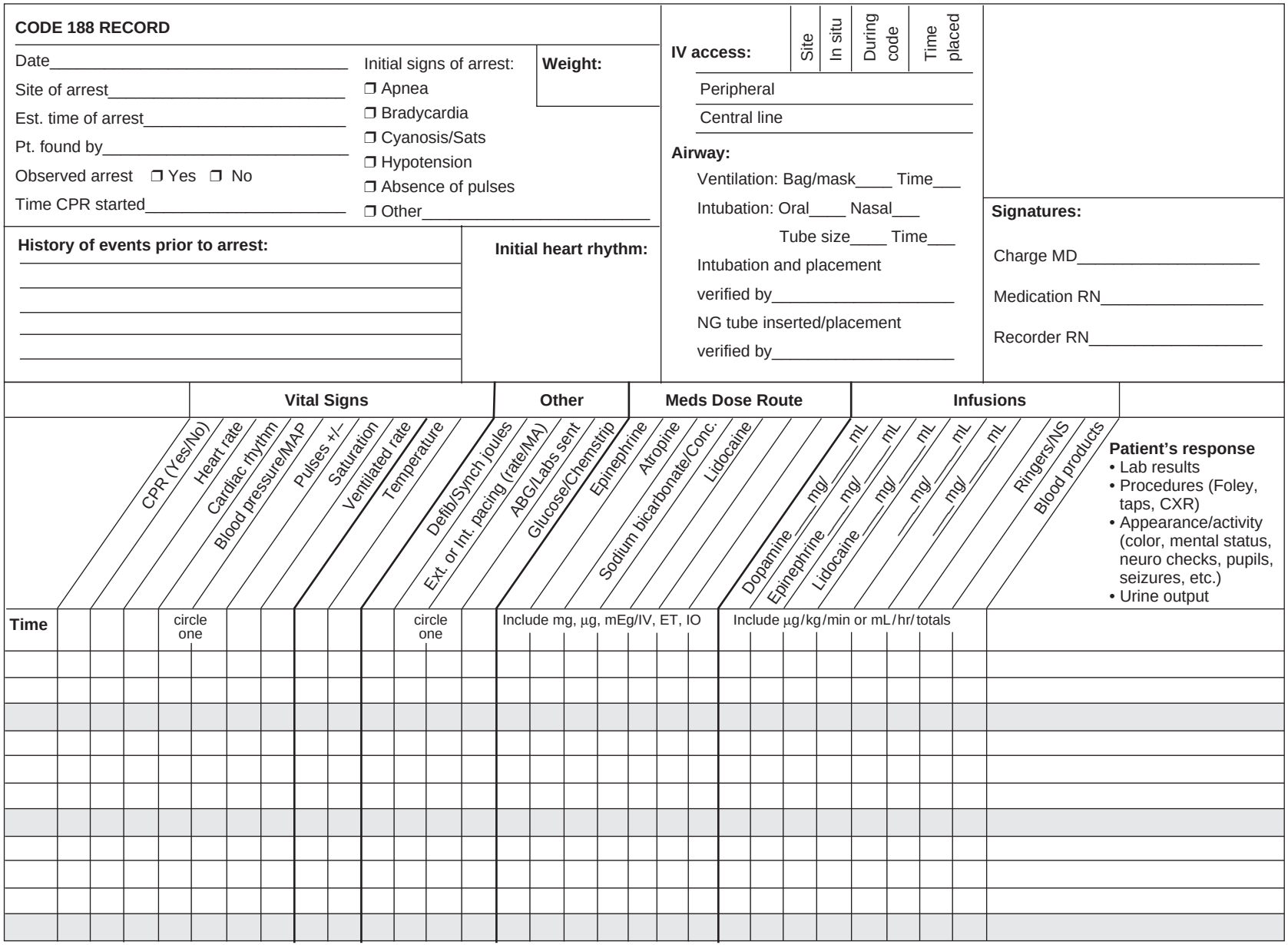

Fig. 193.1 This form is an example of a standardized institutional record for cardiac arrest (intraoperative or otherwise). It can be used for most medical emergencies in which frequent interventions and the administration of medications occur. Courtesy Seattle Children's Hospital, Seattle, Washington.

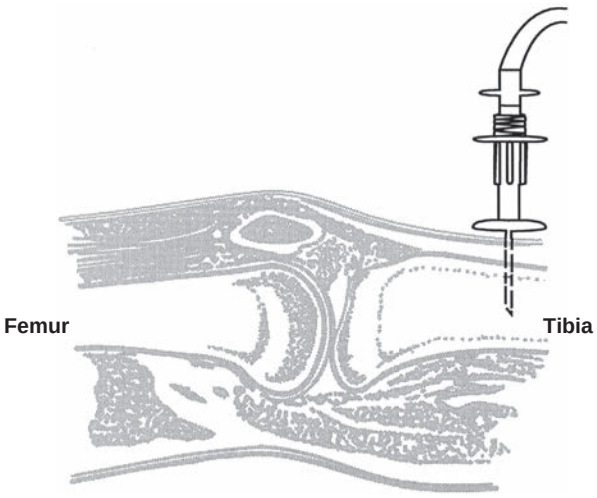

Fig. 193.2 Example of an intraosseous vascular access system with a battery-operated power driver. Intraosseous needles can be inserted into the tibia to administer fluids and medications. The insertion point is approximately 2.5 cm (1 inch) distal to the medial tibial tubercle on the flat portion of the tibial surface, with the needle oriented at right angles to the bony surface. Other possible sites include distal tibia and distal femur. Care should be taken to prevent insertion beyond the bone marrow. During insertion, the hand not used to advance the needle into the bone should grasp the leg distal to the insertion site to minimize the potential for operator injury. The site should be regularly assessed because of the risk of needle migration and compartment syndrome.

- Do not reuse equipment (including the anesthesia machine) unless the cause of the intraoperative cardiac arrest has been determined.
- Enter a narrative of events in the medical record.
- If the patient has died unexpectedly, in most instances the medical examiner should be notified.
- Debrief the code team. Make sure that team members have access to emotional support. Unanticipated intraoperative cardiac arrest with a poor outcome can be emotionally devastating to members of the code team, as well as to the patient's family and friends.
- Notify the risk management office at the institution.

PREVENTION

Many pediatric intraoperative cardiac arrests are the result of the patients' underlying conditions, and these may not be easily reversed. Others can result from any number of factors, including human error, errors in judgment or vigilance, equipment malfunction, and unexplained events. For many of the identified causes of cardiac arrest in anesthetized children, the incidence may be reduced by vigilance and preventive measures. Early detection of problems with timely corrective intervention to reverse further patient deterioration before intraoperative cardiac arrest occurs decreases the likelihood of devastating morbidity or death.

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Latex Allergy

194

Mahmoud I. Wagih

Case Synopsis

A 25-year-old woman with spina bifida was undergoing flexible cystoscopy through a suprapubic catheter. She underwent several genitourinary procedures in the past and has been self-catheterizing for 10 years. Twenty minutes after an uneventful anesthetic induction and endotracheal intubation, her oxygen saturation started to drop. Rash was observed all over her torso. Her blood pressure was maintained initially within the preinduction range.

PROBLEM ANALYSIS

Definition

Latex is harvested from the rubber tree *Hevea brasiliensis.* More than 200 polypeptides have been isolated from latex. Protein content varies with harvest location and manufacturing process. Freshly harvested latex from Malaysia, Indonesia, Thailand, and South America is treated with ammonia and other preservatives to prevent deterioration during transport. Halstead first used latex surgical gloves in 1890, and their use increased dramatically a century later when the risk of transmission of human immunodeficiency virus and other blood-borne pathogens to health care workers was recognized. Latex is the second most common cause of anaphylaxis under anesthesia. In 1984, Turjanmaa and colleagues described the first cases of latex-associated intraoperative anaphylaxis. By 1996 latex was reported to account for approximately 20% of anesthetic anaphylaxis, and by 2000 it had been reported to account for as much as 17% of these reactions in the general population and 27% to 76% in a pediatric population.

Skin and mucous membranes are the most common entry routes of latex antigens. In addition to these routes, latex proteins can be deposited in the respiratory tract when carried by cornstarch powder, used as a donning agent for gloves, and can remain airborne for up to 5 hours. Other means of exposure include urinary catheters, tourniquets, rubber plungers of syringes, rubber stoppers of vials, and intravenous (IV) catheters. Wound inoculation, ingestion, and IV injections are other means of exposure.

Latex allergy can present in two clinically and immunologically distinct entities (which are not mutually exclusive): type I hypersensitivity reaction (anaphylaxis) and type IV hypersensitivity reaction (contact dermatitis). Irritant dermatitis is a non–immune-mediated latex reaction.

The pathophysiology of latex allergy always involves prior exposure (within a medical or nonmedical context). On reexposure, latex allergens cross-link specific immunoglobulin E (IgE) antibodies located on allergic effector cells, mast cells, and basophils releasing preformed mediators, such as histamine, tryptase, and carboxypeptidase A (preformed early mediators). Downstream activation of phopholipase A2 (PLA2), followed by cyclooxygenases and lipoxygenases, produces late-phase mediators: prostaglandins, leukotrienes, and cytokines (interleukin-4 [IL-4], IL-13, and tumor necrosis factor–α) (Table 194.1).

Recognition

The multitude of drugs given when a modern anesthetic is administered increases the challenges around diagnosis, especially considering that recent evidence negates the historically perceived timeline for latex versus pharmacologic agents as causes for anaphylaxis (early vs. late manifestations).

The French GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques) network study examined anaphylaxis under anesthesia in 467 referred cases. Atopy was present in 121 cases (25.4%) and asthma in 41 cases (8.6%). The incidence increases progressively with age and peaks in the fourth decade for women and fifth decade for

TABLE 194.1 Mediators of Anaphylaxis

Mediator	Effect
Histamine	H1: Mucus secretion, edema, cardiac depression, coronary vasoconstriction, renin release H2: gastric acid secretion, nitric oxide induction, vasodilation, tachycardia H3: decreased norepinephrine level H4: chemotaxis, inflammation
Heparin	Anticoagulation, activates prekallikrein and contact systems, bradykinin
Tryptase	Activates prekallikrein and complement, bradykinin, anaphylatoxins
Chymase	Renin production, compensatory norepinephrine secretion, dysrhythmias
Carboxypeptidase A	Prostaglandin and leukotriene synthesis, inflammation
Platelet-activating factor	Bronchoconstriction, decreased coronary blood flow and contractility, nitric oxide induction, vasodilation, hypotension, platelet aggregation, recruitment of neutrophils and eosinophils, biphasic late response, anticoagulation
Leukotriene LTC4	Bronchoconstriction, airway remodeling, angioedema, nitric oxide induction, increased vascular permeability, hypotension
Prostaglandin D2	Bronchoconstriction, pulmonary and coronary vasoconstriction, peripheral vasodilation, vascular permeability, hypotension, flushing, urticaria
Kallikrein	Renin production, complement activation, fibrinolysis, clotting
Tumor necrosis factor	Neutrophil activation, chemokines, cytokines, effector cell recruitment

Data from Stone KD, Prussin C, Metcalfe DD: IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 125(2 Suppl 2):S73-S80, 2010.

men. Female patients represented 74% of cases of anaphylaxis. Angioedema was the clinical feature that never presented alone. In almost 10% of cases, cardiac arrest was the presenting feature. Bronchospasm is more common in those with a history of bronchial asthma or on β-blockers. The incidence of latex anaphylaxis has been falling steadily over the past 15 years, and it is associated with a milder clinical picture and more favorable outcome than other causes of anaphylaxis.

The manifestations of anaphylaxis under anesthesia include the following:

- Hypotension or cardiovascular collapse (75% of cases)
- Bronchospasm or wheezing (44% of cases)
- Rash or urticaria (70% of cases)
- Angioedema and stridor (11.7%)

Unfortunately, in the operating room (OR) the first sign may be cardiovascular collapse because general anesthesia and surgical drapes obscure earlier indicators. Bronchospasm can be a manifestation of worsening asthma, and electrocardiogram changes may reflect myocardial ischemia or decreased coronary blood flow secondary to hypotension. Most anesthetic agents cause hypotension, and when a central nerve block is used, it compounds the picture further. Cutaneous manifestations might be masked by the surgical drapes, and various combinations of symptoms might give rise to variety of clinical presentations. The time from latex exposure to symptoms is unpredictable and can range from 5 to 150 minutes.

Risk Assessment

The following groups of patients are more susceptible to latex allergy:

- Patients with atopy
- Children undergoing multiple surgical procedures, such as spina bifida, or children undergoing surgery at a very young age
- Patients with severe dermatitis of their hands
- Health care professionals
- Patients with allergy to fruits, most frequently banana, chestnut, and avocado
- Industrial workers using protective gear

Latex allergies affect up to 70% of spina bifida patients. Their repeated exposure during urinary cauterization, multiple surgical procedures, and manual removal of impacted feces is the confounding factor.

Implications

The wide array of presentations of latex anaphylaxis hinders its timely diagnosis. There is no in vivo test to predict anaphylactic reactions. The clinical features might be typical of anaphylactoid reactions or type IV hypersensitivity and may flourish hours after the initial presentation. The mortality rate from anaphylactic reactions under anesthesia is around 4% (all causes).

MANAGEMENT

The treatment of anaphylaxis is as follows.

- Primary
  - Removal of the antigen
  - IV epinephrine bolus (1 to 10 μg/kg)
  - Rapid IV crystalloid infusion (50 mL/kg)
- Secondary
  - Epinephrine infusion (0.05 to 0.1 μg/kg per minute)
  - Inhaled/IV β-adrenergic receptor agonist (e.g., salbutamol)
  - IV diphenhydramine 0.5 to 1 mg/kg slowly *plus* IV ranitidine 1 mg/kg slowly
  - Corticosteroids (e.g., IV hydrocortisone 5 to 10 mg/kg)

Careful consideration should be given to all potential sources of latex in the OR, including gloves and Foley catheters, IV administration sets, drug vial stoppers, syringe plungers, face masks, and adhesive tape. Special consideration should be given to aerosolized cornstarch that carries adsorbed latex antigens from powdered gloves in the OR and on the clothes of OR personnel.

Past exposure to latex does not exclude anaphylaxis on reexposure.

Investigation

Due to the multitude of allergens patients are exposed to preoperatively, a generic approach to investigating anaphylaxis should be followed. An allergist with interest in perioperative allergic reactions should conduct the investigations after a standardized referral protocol through an allergy lead clinician in the anesthetic department. The main tests used are as follows.

Mast cell tryptase (MCT) peaks at 1 hour and has a half-life of 2 hours after anaphylaxis onset. Baseline plasma levels have their physiologic variations, hence the importance of relative changes rather than the absolute level. Physiologic stresses contribute to rises in MCT such as hypoxia or myocardial ischemia. MCT levels do not reflect severity, and it can be normal after anaphylactic reactions. It can also be diluted by IV infusion of plasma expanders. The initial sample of MCT should be obtained as soon as feasible after resuscitation has started. The second sample should be obtained at 1 to 2 hours after the start of symptoms, and the third sample either at 24 hours or in convalescence (some protocols include a 6-hour postexposure sample). This provides baseline MCT levels.

Blood testing for allergen-specific IgE (formerly known as RAST) is an in vitro test for IgE antibody directed toward latex. It is quite specific for latex allergy, but its variable sensitivity (65% to 85%) and cost make it less useful as a screening test. Normal results do not exclude latex allergy. It is a reasonable preliminary test when full anaphylaxis was the presenting feature, as it is safer than the direct exposure tests mentioned next.

Skin-prick testing (SPT): There is no commercially available Food and Drug Administration–approved testing kit for latex. The International Union of Immunological Societies recognizes 14 latex allergens that bind to human immunoglobulin (Ig) E (Hev b 1 to Hev b 14). This explains the wide variation in sensitivity and specificity among the 7 SPT solutions approved in Europe. The test involves dropping latex antigen in solution onto skin and pricking the skin gently with a needle through the solution on the inner forearm with a control inoculation. The latex-allergic patient exhibits a wheal-and-flare reaction compared with the control. There is a very small but definite risk of anaphylaxis.

Intradermal testing is similar to SPT, but the antigen is injected intradermally. It is associated with a higher risk of systemic reaction. It must be conducted in a hospital setting and requires technical expertise. It is not routinely used for latex but for anesthetic agents as part of the workup of latex allergy.

Bronchial challenge testing is employed in some centers. It is sensitive and specific but associated with a significantly high risk of bronchospasm. Other challenge tests exist involving mucous membranes with various degrees of sensitivity and specificity.

PREVENTION

- Careful preoperative assessment is essential to identify potential latex allergy patients. In addition to identifying the risk factors listed previously (especially atopy as a broad term), history of itching or swelling of the hands or lips after latex contact (e.g., rubber gloves, toys, balloons, dental examination) should be sought.

- Preoperative immunologic testing is reserved for patients who answer positive to any of the previously discussed risk factors or deemed high risk.
- Latex-free protocols to minimize the incidence of sensitization have proven successful in spina bifida patients, as the incidence has been declining gradually over the past 2 decades.
- Every anesthetic department should have its own protocol for management of known latex allergy patients. Examples of aspects of these protocols include the following:
  - On the day of the procedure, latex allergy patients should be done first on the list (the OR takes few rounds of air circulation before vaporized latex particles are removed).
  - They should be recovered in the OR to minimize exposure.
  - A list of latex-free products should be available.
  - Minimize the number of staff, and avoid staff change as much as possible.
- Medic-Alert bracelets and autoinjectable epinephrine should be used by all latex allergy patients.
- Patient and caregiver education remains an integral approach to any preventive measures.
- Both parents and physicians can obtain useful information about latex content and possible substitutions of medical and nonmedical items from the Spina Bifida Association (1-800-621-3141) and online.
- There is no evidence for the use of prophylactic antihistamines and/or corticosteroids.

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195 Malignant Hyperthermia

Herodotos Ellinas

Case Synopsis

A healthy 12-year-old boy presents for reduction of a humerus fracture. Anesthesia is induced with sevoflurane. Fifteen minutes later, there is an abrupt increase in end-tidal carbon dioxide to greater than 70 mm Hg. He becomes tachycardic, with a heart rate of 150 beats per minute, and his temperature increases from 36.7°C to 39.4°C.

PROBLEM ANALYSIS

Definition

Malignant hyperthermia (MH) is a rare but potentially fatal subclinical myopathy. MH remains latent until susceptible individuals are exposed to triggering anesthetic agents, such as volatile inhalation anesthetics and succinylcholine. MH is characterized by an increase in myoplasmic calcium ions (Ca^{2+}) due to dysregulation in skeletal muscle. Presenting signs include increased metabolism, muscle rigidity, and fever.

Similar manifestations were noted in one breed of pigs on exposure to stress (porcine stress syndrome). This breed experienced increased metabolism, acidosis, fever, and death, just as with human MH, and in 1966 Hall reported that succinylcholine and halothane induced MH in these animals. They soon became the animal model for the disease. Although a single point mutation on chromosome 6 was responsible for porcine stress syndrome, accounting for a homogeneous disease, in human MH the disease shows significant genetic heterogeneity. More than 30 different genetic abnormalities lead to a similar final pathway. The human MH is considered an autosomal dominant (with predominantly male expression) disorder in half of the cases, the other half thought to be new mutations.

The pathophysiology of MH lies in disordered excitation-contraction coupling in skeletal muscle. In normal muscle, an action potential is propagated along the sarcolemma and down the T tubule, leading to Ca^{2+} release from the sarcoplasmic reticulum. Ca^{2+} then binds troponin, exposing active actin binding sites, which leads to muscle contraction. This process is terminated by the active transport of Ca^{2+} back into the sarcoplasmic reticulum.

The sarcoplasmic reticulum is the intracellular organelle responsible for Ca^{2+} regulation. As propagated action potentials cause voltage changes in the T tubule, a conformational change occurs in the α subunit of the dihydropyridine receptor. This activates the ryanodine receptor *(RYR1),* which in turn leads to the opening of *RYR1,* causing Ca^{2+} efflux and muscle contraction.

In MH, a defect in Ca^{2+} release is expressed on exposure to a triggering agent. This defect results in a prolonged opening of *RYR1* and enhanced Ca^{2+} efflux into the myoplasm, leading to prolonged interaction of actin and myosin (contracture) and increased muscle metabolism. Two known sites for this defect are the *RYR1* and the *CACNA1S* (a calcium channel, voltage-dependent, dihydropyridine receptor) genes.

Recognition

Understanding the underlying pathophysiology of MH leads to an appreciation of its clinical manifestations (Box 195.1). The increased muscle metabolism is initially aerobic, resulting in increased oxygen consumption, hypercarbia, respiratory acidosis, and heat production. As adenosine triphosphate (ATP) is depleted, metabolism becomes anaerobic, resulting in lactic acid production, metabolic acidosis, and further heat production. In the presence of hyperthermia, acidosis, and ATP depletion, the cell loses the ability to maintain the integrity of its membrane. Rhabdomyolysis leads to the release of potassium, myoglobin, and creatine kinase. Hypercarbia is the earliest and most sensitive sign of MH; generalized muscle rigidity is the most specific sign. Prompt diagnosis and effective treatment of MH are imperative and may avoid its associated complications (Box 195.2). The initial signs and symptoms of MH are nonspecific, thus a broader differential must be considered to prevent long-term morbidity and mortality (Box 195.3).

Risk Assessment

Although precise estimates are difficult owing to the rarity of human MH, the incidence is thought to be 1:30,000 in children and 1:1,000,000 in adults, with 1:2000 patients having a genetic abnormality causing MH susceptibility. Determining a patient's risk for MH includes careful questioning during the preoperative interview. A personal or family history of MH during a previous anesthetic should raise concerns. Further, a family history of unexpected intraoperative

BOX 195.1 Clinical Manifestations of Malignant Hyperthermia

Early
Tachycardia
Hypercarbia
Muscle rigidity
Tachypnea
Cardiac arrhythmias

Late
Rapid increase in temperature
Skin mottling
Myoglobinuria
Hyperkalemia
Elevated creatine kinase
Mixed respiratory and metabolic acidosis

death or cardiac arrest should increase the suspicion for MH. The MH clinical grading system may be used to assist with the likelihood of an MH event. Although there are numerous case reports of patients with different diseases experiencing episodes of MH, the only diseases that are consistently associated with MH are central core disease and King-Denborough syndrome.

The current diagnostic test for confirming MH is the caffeine-halothane contracture test (CHCT) and the European counterpart, the in vitro contracture test (IVCT). Although the CHCT was developed in the 1970s, it remains the gold standard, with 97% sensitivity and 78% specificity. The muscle biopsy must be performed on freshly harvested muscle at one of the designated U.S. CHCT centers. Although the biopsy is performed on an outpatient basis, the dwindling number of testing sites in the United States may be an obstacle for some patients who need to have this test.

For the CHCT, a fresh strip of thigh muscle is harvested and then longitudinally dissected into six strips. Small sutures are placed at both ends of the muscle, and the strips are placed into a tissue bath. One end is attached to a stationary hook and the other to a force transducer. Halothane is added to the fresh gas flow via an in-line vaporizer in three of the baths, and caffeine is incrementally added to the other three baths. A patient is diagnosed with MH syndrome if a contracture or increase in the muscle's baseline tension develops on exposure to these agents.

Although the CHCT remains the gold standard for diagnosing MH, genetic testing has been added to the armamentarium in recent years. To have successful genetic profiling, the patient's DNA is tested for a known mutation in the *RYR1* gene, and if present, family members are tested for that causal mutation. Multiple mutations have been described in this gene, along with mutations in the α subunit of the dihydropyridine receptor gene. As new information on the genetic makeup of MH is developed, genetic testing may provide the means for screening at-risk patients, avoiding the need for open muscle biopsy.

Implications

MH is a grave and potentially fatal disease. Untreated, the mortality rate is as high as 70% to 80%. With the administration of dantrolene, however, this rate decreases to 5% to 10%. Thus anesthesiologists have a critical role in diagnosing and appropriately treating MH patients to avoid its complications (see Box 195.2).

BOX 195.2 Complications of Malignant Hyperthermia

- Cardiac arrhythmias
- Massive myocardial infarction
- Congestive heart failure
- Acute respiratory distress syndrome
- Pulmonary edema
- Acute renal failure
- Hepatic dysfunction
- Severe muscle pain/generalized weakness
- Seizures
- Coma
- Death

BOX 195.3 Differential Diagnosis of Malignant Hyperthermia

- Anaphylaxis
- Sepsis
- Thyrotoxicosis
- Pheochromocytoma
- Stimulant drugs
- Inadequate anesthesia/analgesia
- Neuroleptic malignant syndrome
- Heatstroke

As with any inherited disease, the diagnosis of MH carries implications for both the patient and his or her family members. The Malignant Hyperthermia Association of the United States (MHAUS) can be an invaluable resource for patients and physicians. Established in 1981, its goal is to provide information about MH to patients and health care providers and to help individuals cope with the diagnosis and reduce its associated morbidity and mortality. Its MH hotline (1-800-MH-HYPER; 1-800-644-9737) provides access to physician consultants 24 hours a day, 7 days a week.

The North American Malignant Hyperthermia Registry, a division of the MHAUS, acquires and analyzes patient-specific clinical and laboratory data on MH. It provides a central repository for MH-susceptible patients, it investigates the epidemiology of MH, and it helps referral centers standardize diagnostic tests. Health care professionals can support this registry by completing an Adverse Metabolic Reaction to Anesthesia (AMRA) form whenever they suspect an MH-related event.

A recent topic of concern is the possibility of "awake triggering" of MH, occurring while a patient is not anesthetized or exposed to one of the known anesthetic triggers. Returning to the patient described in the case synopsis, the boy was diagnosed with MH intraoperatively, appropriately treated with dantrolene, and recovered uneventfully. Eight months later, however, he developed muscle weakness and stiffness after playing in a football game. His condition progressed to seizures and respiratory arrest. When paramedics arrived, the electrocardiogram showed sinus tachycardia, and intubation was unsuccessful secondary to jaw clenching. His temperature on arrival at the hospital was higher than 42.2°C, and he was successfully intubated. The patient developed ventricular fibrillation, and cardiopulmonary resuscitation was continued as he was treated for hyperkalemia and with dantrolene. Resuscitation was unsuccessful, and subsequent DNA studies identified an altered *RYR1* sequence, consistent with the diagnosis of MH.

It is known that hypermetabolic states can occur in individuals both with and without MH syndrome. Although rare, these episodes can be fatal. Health care professionals recommend that patients with MH syndrome limit their activity only if severe muscle cramps or symptoms suggestive of a hypermetabolic state develop. Although death due to awake triggering of MH may represent only a small percentage of patients presenting with heatstroke, MH should be considered in the differential diagnosis, and treatment with dantrolene may be indicated.

Interestingly, mutations in the cardiac ryanodine receptor gene *(RYR2)* have been associated with sudden unexplained death in patients with catecholaminergic polymorphic ventricular tachycardia and arrhythmogenic right ventricular dysplasia type 2. *RYR2* is the major Ca^{2+} release channel on the sarcoplasmic reticulum in cardiomyocytes, and mutations in *RYR2* result in disordered Ca^{2+} regulation during exercise or stress-induced activation of the sympathetic nervous system. Thus both *RYR1* and *RYR2* mutations cause disorders in Ca^{2+} metabolism in skeletal and cardiac muscle, respectively. Newer data suggest that cardiac events and death may also be associated with higher muscle bulk.

MANAGEMENT

Once the diagnosis of MH is made, the severity of the situation must be communicated to the surgical team, and additional help should be summoned to the operating room. Checklists such as ones from the American College of Surgeons and the Society for Pediatric Anesthesia

provide succinct management guidelines for operating room events in adults and children, respectively; one of these critical events is MH. Treatment includes the following:

- Discontinue triggering agents (any volatile inhalation anesthetic agent, succinylcholine).
- Hyperventilate with 100% oxygen.
- Administer dantrolene.
- Monitor arterial blood gases for pH, base excess, and serum potassium; check serial creatine kinase concentrations and coagulation panel.
  - Treat acidosis with sodium bicarbonate.
  - Treat hyperkalemia with Ca^{2+}, glucose, and insulin.
- Place Foley catheter and maintain diuresis with furosemide or mannitol.
- Institute core body cooling with ice packs, cold saline lavage of body cavities and the surgical site; consider cardiopulmonary bypass.
- Call the MH hotline (1-800-MH-HYPER).
- Complete an AMRA form.

Dantrolene is a direct skeletal muscle relaxant that binds to the *RYR1* receptor, thereby reducing its open-state probability and blocking Ca^{2+} release from the sarcoplasmic reticulum. It is administered as a 2.5 mg/kg intravenous bolus; this can be repeated every 5 minutes until the hypermetabolic state resolves, up to a maximum dose of 30 mg/kg. Older preparations of dantrolene took a long time to dilute, but a newer formula requires less than 1 minute to prepare, making administration a more swift process. The maintenance dose of dantrolene is 1 mg/kg intravenously every 6 hours for 24 hours to prevent recurrence of the hypermetabolic state. For this reason, patients are monitored in the intensive care unit for at least 24 hours after an MH episode.

If there is no change in the patient's condition after giving large amounts of dantrolene, other diagnoses must be entertained (see Box 195.3). One possible drug interaction involves dantrolene and nondepolarizing muscle relaxants; dantrolene has been shown to potentiate neuromuscular blockade with vecuronium. Also, cardiovascular collapse has occurred in anesthetized swine when dantrolene and verapamil were administered simultaneously. Thus calcium channel blockers are contraindicated.

PREVENTION

When susceptible or high-risk patients present for surgery, the anesthesia team must plan carefully for the administration of a safe anesthetic:

- The anesthesia machine must be prepared with a new disposable circuit and new carbon dioxide absorbent.
- The vaporizers should be disabled, and the machine should be flushed per machine recommendations.
- Activated charcoal filters placed on both the expiratory and inspiratory circuit limbs can effectively remove potent volatiles from anesthesia machines in less time, and they are good for 12 hours when used for MH precautions; they are good only for 1 hour if used during an acute MH event.

Although triggering agents should be avoided, there are many safe anesthetic medications that can be used in these patients (Box 195.4). Dantrolene prophylaxis is not recommended for these patients perioperatively. Postoperatively, patients should be monitored for a minimum of 4 hours with continuous electrocardiography, as well as core temperature monitoring. If this recovery period is uneventful, it is safe to discharge patients to an in-house ward or even home in the case of ambulatory surgery.

BOX 195.4 Safe Drugs for Patients With Malignant Hyperthermia Syndrome

Barbiturates (e.g., methohexital)
Benzodiazepines
Dexmedetomidine
Etomidate
Ketamine
Local anesthetics
Nitrous oxide
Nondepolarizing muscle relaxants
Opioids
Propofol

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Ophthalmic Problems and Complications

196

Scott D. Cook-Sather

Case Synopsis

A 5-year-old girl with no prior ophthalmic history has a thyroglossal duct cyst excision under general anesthesia. On awakening, she complains that "something hurts in my eye." Although there is no obvious foreign body in the eye, excessive tearing is noted. Her eyes had been taped closed after tracheal intubation. Corneal abrasion is suspected, and an ophthalmology consultation is obtained.

INTRODUCTION

For nonocular surgery, the incidence of anesthesia-related eye injury is estimated at 0.06%; this accounts for 3% of the American Society of Anesthesiologists (ASA) nondental closed claims cases. Risk factors for perioperative ocular injury include general anesthesia, long procedures, head and neck procedures, and lateral positioning. For ocular surgery, anesthesia-related eye injury is exceedingly rare. When it occurs, it may be related to perioperative coughing or severe postoperative vomiting, with a related sudden increase in intraocular pressure (IOP). Important ophthalmic complications and issues relevant to pediatric anesthesia include corneal abrasion, postoperative visual loss, retinopathy of prematurity, penetrating ocular trauma, oculocardiac reflex, and postoperative nausea and vomiting. The last occurs in 40% to 90% of children after strabismus surgery.

CORNEAL ABRASION

PROBLEM ANALYSIS

Definition

Corneal abrasion is the most common perioperative ophthalmic complication, with an incidence of 0.1% to 44%. A higher incidence was reported in the 1970s for anesthetized patients without eye protection or lubrication. Most corneal abrasions result from corneal drying associated with lagophthalmos during general anesthesia.

Recognition

Symptoms of corneal abrasion include photophobia, pain, and foreign body sensation. Excessive tearing and miosis are characteristic physical findings. Staining with fluorescein reveals the abraded zone in green under a cobalt blue light (Fig. 196.1).

Risk Assessment

Although the inciting event for corneal abrasion is not always clear, factors such as prone or lateral positioning and exophthalmos place patients at higher risk. General anesthesia increases the risk, in part owing to lost protective corneal reflexes, abolished Bell's phenomenon (in which the globe turns upward during sleep), and diminished tear production and stability.

Implications

The majority of children sustaining intraoperative corneal abrasion have a full recovery within 24 hours with appropriate treatment. Extensive injury or delayed treatment results in a 16% incidence of permanent injury. Permanent scarring is usually related to secondary corneal infection or abrasions that are chronic.

MANAGEMENT

Patients with corneal abrasion should be evaluated by an ophthalmologist to document the extent of injury and initiate treatment. Usual recommendations include lubrication, application of a topical antibiotic or cycloplegic agent (or both), and patch closure.

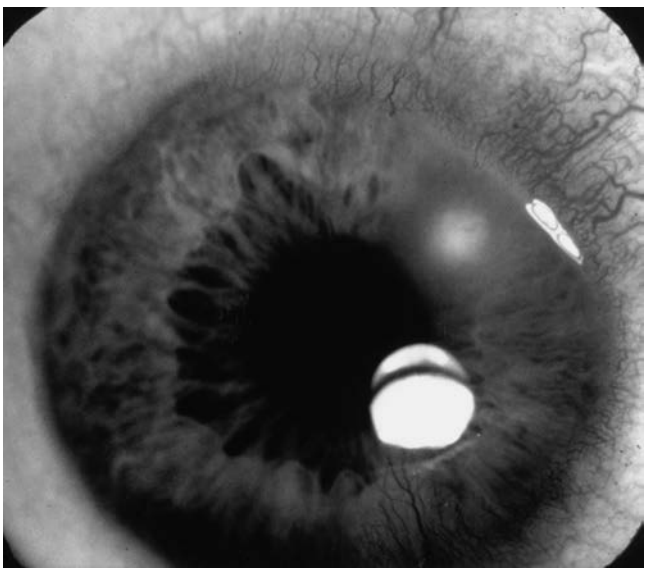

Fig. 196.1 The opacified zone overlying the iris at the 2 o'clock position is a corneal abrasion with surrounding edema. These lesions are most easily seen with fluorescein staining. (Courtesy Dr. Katrinka Heher.)

PREVENTION

To prevent corneal abrasion, ocular contact with masks, stethoscopes, name tags, intubation equipment, sheets, and padding material must be avoided. Eye protection should be established early, before laryngoscopy. Tape should be used to keep the eyelids closed, with ophthalmic lubricants used for longer procedures. Petroleum-based ophthalmic ointments are more likely to cause foreign body sensation and blurred vision postoperatively than are aqueous solutions. Placement of a disposable pulse oximeter probe on the child's ring finger as opposed to the index finger may lessen the chance of inadvertent eye contact and potential corneal injury in the postoperative period.

POSTOPERATIVE VISUAL LOSS

PROBLEM ANALYSIS

Definition

Postoperative visual loss (POVL) is the most catastrophic perioperative ophthalmic complication and may manifest as either partial visual field loss or total blindness. The incidence of POVL in the general, nonocular surgical population is 1 in 61,000 to 1 in 125,000, but after spinal surgery in the prone position, it is estimated to be 1 in 1100. There is also a higher relative incidence after open heart and head and neck surgeries. From the inception of the ASA Postoperative Visual Loss Registry in July 1999 until July 2004, there were three reported pediatric cases of POVL in patients ranging in age from 5 to 18 years.

Recognition

Visual changes may be appreciated in the immediate postoperative period, but delays in diagnosis may occur when such changes are incorrectly attributed to "normal recovery" after anesthesia and instilled ophthalmic lubricants. In one study of 28 POVL cases, visual changes were recognized in 50% of patients in the recovery room and in 80% by postoperative day 2. Some patients initially had normal vision but experienced symptoms 1 to 12 days later. Younger pediatric patients may have difficulty expressing symptoms. When there is local ecchymosis around the affected eye or periorbital numbness, compression injury should be suspected.

Risk Assessment

Ischemic optic neuropathy (ION) associated with spinal surgery in the prone position accounts for the majority of cases in the ASA POVL Registry. Three pediatric patients developed bilateral ION following prolonged (>8 hours) surgery in the prone position, two for scoliosis and one for reconstruction of the cranial vault. Intraoperative events included large blood loss and episodes of hypotension. One proposed mechanism of injury involves the complex interaction of transient anemia, arterial hypotension, increased central venous pressure, and increased IOP in the prone position, which results in decreased optic perfusion pressure and limited hemodynamic reserve in the optic pathways.

Adult patients with hypertension, smoking, diabetes, or peripheral vascular disease appear to be at increased risk for ION. Direct orbital compression (e.g., from patient malposition on a headrest) is not required for ION to occur. However, such compression can result in POVL via central retinal artery occlusion, in which case POVL can be attributed to ION. POVL may also be consequent to perioperative cortical ischemia.

Implications

Most postoperative visual deficits do not improve significantly over time. Those who experience complete absence of light perception are unlikely to regain vision.

MANAGEMENT

Early ophthalmology consultation must be obtained for unequivocal vision deficits (absence of light perception, unilateral visual loss), periorbital ecchymosis or obvious trauma, and milder visual symptoms that do not improve in the first few hours after anesthesia and surgery. Visual acuity tests, funduscopic examination, and head magnetic resonance imaging are often required to establish a diagnosis; however, few (if any) therapies are currently available. Thus ensuring adequate hemodynamics, hemoglobin concentration, and oxygenation in the postoperative period cannot be expected to reverse the initial injury but may prevent further damage.

PREVENTION

Although direct pressure is not a common cause of POVL, protecting the eyes from external compression is vital. Anesthesia providers must carefully position patients and then monitor their positioning, because patients may shift in relation to headrests and other equipment during surgery. Special headrests with mirrors allow instant assessment of the periorbital area in prone patients. Slight reverse Trendelenburg position may reduce orbital venous pressure and promote better perfusion for any given mean arterial pressure.

Although deliberate hypotension may help reduce operative blood loss, it may increase the risk for POVL. Deliberate hypotension has been used in tens of thousands of uneventful cases, but two of the three pediatric cases in the ASA POVL Registry involved deliberate hypotensive techniques. The current practice at my institution is to avoid deliberate hypotension for posterior spinal fusion surgery, because somatosenory and motor-evoked potentials are better preserved with normotension.

Precise transfusion parameters for reducing POVL risk are not well defined, but significant anemia should be avoided. Current recommendations also include minimizing the time the patient is in the prone position. Staged procedures should be considered if total operative time is expected to exceed 8 hours.

RETINOPATHY OF PREMATURITY

PROBLEM ANALYSIS

Definition

Retinopathy of prematurity (ROP) occurs in more than 50% of premature infants weighing less than 1500 g at birth. It is caused by abnormal proliferation of vascular tissue, with destruction of the retinal capillary bed. ROP ranges in severity from reversible regional neovascularization to complete retinal detachment with permanent blindness. Although multiple, interrelated factors predispose to ROP, the immature retina appears to be more susceptible if exposed to high oxygen (O_2) concentrations and accompanying free radicals.

Recognition

Ophthalmologic examination can document the development or exacerbation of ROP. The stages of ROP are as follows:

- Linear separation of posterior vascular retina from the anterior avascular portion
- Elevation of the demarcation line and ridge formation
- Extraretinal neovascular tissue proliferation
- Partial retinal detachment
- Complete retinal detachment—also known as retrolental fibroplasia

Risk Assessment

ROP is associated with low birth weight (<1500 g), young gestational age (≤32 weeks), hemorrhagic shock at birth, anemia and transfusion, and prolonged exposure to high O_2 tensions. The temporal portion of the retina does not mature until 40 to 44 weeks of postconceptual age. Neonates up to 44 weeks of postconceptual age who require surgery are therefore presumed to be at risk for the development of ROP or for worsening of existing pathology.

Implications

Although approximately 85% of acute ROP cases undergo spontaneous regression, outcomes depend on the stage, with fibrous tissue traction and retinal detachment having worse prognoses. Laser photocoagulation is the treatment of choice in 90% of cases. Cryotherapy, scleral buckle, or vitrectomy may be required.

MANAGEMENT AND PREVENTION

ROP is primarily a concern in neonatal intensive care units, where prolonged O_2 exposure may place infants at risk; however, efforts to reduce intraoperative O_2 concentrations also may be beneficial. Older studies indicated that an arterial O_2 tension (Pao_2) of 150 mm Hg for 1 to 2 hours could affect the immature retina. More recent data suggest that even lower Pao_2 values may contribute to ROP. Consistent damage occurs after only several days of hyperoxia. Prudent preventive management thus includes the lowest fraction of inspired O_2 (Fio_2) required to achieve a percutaneous arterial O_2 saturation of 90% to 95% ($Pao_2 \approx 70$ mm Hg). However, neonates with severe pulmonary pathology who require a high Fio_2 to maintain adequate tissue oxygenation should receive it.

PENETRATING OCULAR TRAUMA AND VITREOUS EXTRUSION

PROBLEM ANALYSIS

Definition

Penetrating ocular trauma, with the concomitant risk of extrusion of ocular contents, is a classic management challenge for pediatric anesthesiologists. Patients present emergently, are often uncooperative, and usually require rapid anesthetic induction to minimize the risk of pulmonary aspiration of gastric contents. However, sudden increases in IOP during anesthesia, especially during induction, may increase the risk of vitreous humor extrusion. Loss of ocular contents solely due to anesthetic management is exceedingly rare, relegated to a few anecdotal reports.

Recognition

The patient's history may include either handling or being struck by a sharp object, with subsequent eye pain, swelling, erythema, obvious ocular rent, or an in situ foreign body. Poor eye turgor and exposed vitreous are signs of vitreous extrusion.

Risk Assessment

Penetrating eye injury is more likely to result in vitreous extrusion in children with large defects and in those who continue to cry, cough, retch, or vomit.

Implications

Extrusion of ocular contents is catastrophic and requires immediate wound closure and possible posterior sclerotomy to release suprachoroidal blood. The prognosis is extremely poor—most victims lose all vision in the affected eye.

MANAGEMENT AND PREVENTION

Evaluation and management strategies for children with penetrating ocular trauma are summarized in Box 196.1. The most important concerns are preventing the aspiration of gastric contents and preventing a sudden increase in IOP, as occurs with coughing. Coughing can transiently increase IOP by 30 to 40 mm Hg and may cause vitreous extrusion, iris or lens prolapse, or choroidal hemorrhage. Smaller increases in IOP may also cause extrusion of vitreous humor, although the absolute minimum increase in IOP required to do so is unknown; it is clearly dependent on the degree of baseline injury.

Succinylcholine administered during a rapid-sequence intubation may increase IOP by 6 to 8 mm Hg for 5 to 10 minutes via

BOX 196.1 Anesthetic Evaluation and Management of Patients With Penetrating Eye Injuries

Nature of Injury, Urgency, and Expected Duration of Procedure
Small defects: less risk of extrusion
Simple injury: short-duration procedures
Complex injury: prolonged retinal reattachment
Copper: causes early vitreous clouding
Protruding foreign body: true ophthalmic emergency
Nonviable eye: can wait several hours

Risk of Pulmonary Aspiration
Recent full meal
Impaired gastrointestinal function
Severity of trauma
Opioid administration
Gastroesophageal reflux, hiatal hernia

Airway Evaluation
Difficult: consider a fiberoptic approach
Normal or not anticipated to be difficult: rapid-sequence induction

Anesthetic Management Options
Possible delayed start: 8 hours after solids; 2 hours after clear liquids
Rapid-sequence induction variants: lidocaine 1.5–2 mg/kg; remifentanil 1 μg/kg or fentanyl 1–2 μg/kg; thiopental 4–6 mg/kg or propofol 2–3 mg/kg; SCh 1.5–2 mg/kg (± defasciculating NDMR dose); high-dose NDMR (rocuronium 1.2 mg/kg) in place of SCh if surgery will be prolonged
Monitoring: train-of-four to determine earliest time for intubation and ongoing muscle relaxation

NDMR, Nondepolarizing muscle relaxant; *SCh*, succinylcholine.

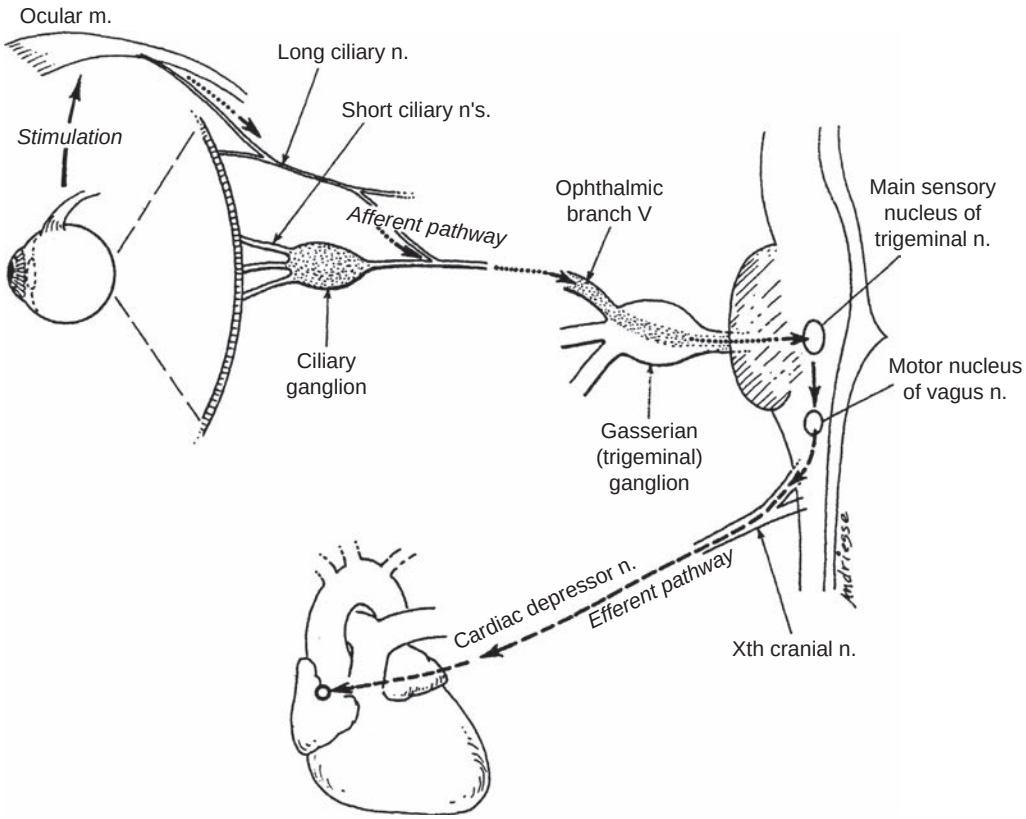

Fig. 196.2 Oculocardiac reflex (OCR). The ophthalmic division of the trigeminal nerve (afferent limb) is stimulated via the long and short ciliary nerves. Afferent impulses are transmitted to the gasserian ganglion and main trigeminal sensory nucleus. From there, they are relayed to the efferent (motor) nucleus of the vagus nerve. The efferent pathway includes the vagus nerve and the cardiac depressor nerve. (From Vassallo SA, Ferrari LR: Anesthesia for ophthalmology. In Coté CJ, Ryan JF, Todres ID, et al, editors: *A practice of anesthesia for infants and children,* 2nd ed. Philadelphia, WB Saunders, 1993, p 325.)

the depolarization of extraocular, facial, and smooth orbital muscles. There are no credible case reports of vitreous extrusion following succinylcholine administration; however, concern stemmed from a single anecdotal report. Defasciculating doses of nondepolarizing muscle relaxants (NDMRs) may attenuate the rise in IOP associated with succinylcholine. Priming doses of NDMRs may hasten the achievement of adequate intubation conditions after the induction of anesthesia, but there are reports of intervening weakness, difficulty breathing, agitation, and even aspiration. In general, pediatric patients poorly tolerate the potential difficulties associated with NDMR priming; also, in theory, these would increase the risk of further injury to the eye. Large doses (2 to 3 times the ED95) of NDMRs such as cisatracurium, mivacurium, rocuronium, or vecuronium may permit intubation within 60 to 90 seconds, but recovery from the block may be prolonged. Finally, throughout the operation, one should maintain adequate neuromuscular relaxation and administer sufficient opioid to minimize coughing on emergence.

OCULOCARDIAC REFLEX

PROBLEM ANALYSIS

Definition

Decreased heart rate associated with pressure on the globe or traction on the extraocular muscles is common in children. The reported incidence of the oculocardiac reflex (OCR) is 20% to 90% during strabismus surgery. The afferent OCR limb is via the long ciliary nerve and the short ciliary nerves. The latter first come together at the ciliary ganglion; these two inputs then converge to form the ophthalmic division of the trigeminal nerve (Fig. 196.2). The efferent limb of the OCR is vagal via the cardiac depressor nerve.

Recognition

The OCR results in a slowed or irregular heart rate. It can be detected by precordial heart sounds, pulse oximetry, or electrocardiographic monitoring. Sinus bradycardia is the most common rhythm disturbance. Sinus pause, transient asystole, wandering atrial pacemaker, atrioventricular junctional rhythm, atrioventricular heart block, and ventricular arrhythmias (extrasystoles, bigeminy, escape beats) may also occur. Although ventricular tachycardia and fibrillation have been reported, they are most likely to occur after prolonged asystole (presumably due to myocardial hypoxia) or treatment with anticholinergics or β-adrenergic agonists, especially in patients anesthetized with sensitizing inhalational anesthetics such as halothane.

Risk Assessment

Younger patients, because of a relative increase in vagal tone, are most predisposed to the OCR during strabismus surgery. Although sudden, forceful traction on *any* of the extraocular muscles is the most common provocative stimulus, there can be others (Box 196.2). Prophylactic atropine and other chronotropic agents do not abolish

BOX 196.2 Perioperative Stimuli for Oculocardiac Reflex

Traction on *any* extraocular muscle
Traction on conjunctiva or orbital structures
Ocular trauma or retrobulbar hematoma
Pressure on globe or tissue in orbital apex (after enucleation of the eye)
Performance of retrobulbar block

the OCR but may reduce its incidence and the severity of associated bradycardia. However, as just noted, prophylaxis with anticholinergics or β-adrenergic agonists has the potential to cause worse arrhythmias, especially with older inhalational anesthetics such as halothane. Hypercarbia and hypoxia augment the potential for arrhythmias with the OCR, as does inappropriate anesthetic depth.

Implications

The OCR is usually transient and relieved with release of traction. There is a significant association between intraoperative OCR and postoperative nausea and vomiting. Indeed, children with OCR episodes in the operating room are 2 to 3 times more likely to experience postoperative nausea and vomiting than are those without such episodes.

MANAGEMENT

Although the OCR is a common cause of arrhythmias during strabismus surgery, it is important to investigate and treat other primary causes, including hypoxia, hypercarbia, and inadequate anesthesia. All of these have the potential to worsen the OCR. However, if arrhythmias persist, the surgeon should relax tension on the eye muscle. Administering a chronotropic agent before the stimulus is removed and normal rhythm is restored is not advised; this only increases the risk for more serious arrhythmias. In general, the OCR fatigues with repetitive and more gentle traction, making treatment with chronotropic drugs unnecessary.

PREVENTION

Recommendations include the use of controlled, mild hyperventilation to prevent hypercarbia during strabismus surgery. Compared with halothane, sevoflurane can reduce OCR incidence and the magnitude of bradycardia in children during both spontaneous and controlled ventilation. Although intravenous atropine given 30 minutes before eye muscle traction may reduce OCR incidence or attenuate its magnitude, it does not guarantee protection against significant arrhythmias. Because atropine is not universally effective for OCR prophylaxis, and because of the generally low incidence of severe OCR leading to hemodynamic compromise, routine anticholinergic prophylaxis is no longer recommended. Retrobulbar block with 1 to 3 mL of 1% to 2% lidocaine may prevent the OCR in adults but is rarely used in pediatric practice.

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197 Pediatric Hyperthermia

Kate E. Balbi • Ronald S. Litman

Case Synopsis

A healthy 12-year-old boy is undergoing a tympanomastoidectomy under general anesthesia with sevoflurane in oxygen and air, and supplemented with fentanyl. He has also received dexamethasone, ondansetron, and cefazolin. Approximately 2 hours into the case, he is noted to have an esophageal temperature of 38.1°C. His heart rate is 120 beats per minute, and his blood pressure is 122/78 mm Hg. Except for a great aunt who died during surgery 25 years ago for unknown reasons, there is no other history of familial problems with anesthesia.

PROBLEM ANALYSIS

Definition

Although anesthetic and opioid impairment of thermoregulatory control often predisposes anesthetized patients to temperature instability, hyperthermia can cause serious complications, and anesthesiologists must be able to identify the underlying causes.

Strictly speaking, hyperthermia can be defined as any elevation in core temperature, but the usually accepted definition of hyperthermia is a core body temperature greater than 38°C. Temperature is regulated by a hypothalamic set point to which current core body temperature is continually compared. Hyperthermia occurs when the set point in the hypothalamus is raised, when thermoregulatory responses such as sweating or vasodilation are impaired, or as a result of excessive heat exposure. Regardless of the cause, hyperthermia is metabolically stressful and can affect end-organ function when severe (Box 197.1).

The American Society of Anesthesiologists' standards for basic anesthetic monitoring state that "every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected." The Malignant Hyperthermia Association of the United States (MHAUS) recommends core temperature monitoring for all patients who receive general anesthesia for more than 30 minutes, because lack of temperature monitoring in this setting has been associated with increased mortality related to development of acute MH.

Recognition

Core temperature can be measured in the pulmonary artery, distal esophagus, tympanic membrane, or nasopharynx and is the best indicator of thermal status. However, core temperature measurements may not be feasible for all surgical procedures; thus estimates of core temperature are obtained using oral, axillary, rectal, bladder, and skin-surface temperature probes that have variable accuracy (Table 197.1). In particular, skin-surface and rectal temperatures may not track core temperature in a timely manner and should be used with caution.

Risk Assessment

Iatrogenic Hyperthermia

Because anesthetized patients are usually predisposed to hypothermia, warming techniques are an often essential component of anesthetic management. Occasionally, however, these warming methods (e.g., increased ambient room temperature, forced hot-air warmers, airway humidifiers) may result in iatrogenic hyperthermia. Other iatrogenic causes of hyperthermia include prolonged tourniquet application, transfusion reaction, and monitor or probe malfunction.

Drug-Induced Hyperthermia

Malignant hyperthermia (MH) is an inherited disorder characterized by a life-threatening hypermetabolic reaction on exposure to inhaled volatile anesthetics or succinylcholine. Manifestations of MH include hypercarbia, tachycardia, muscle rigidity, acidosis, and hyperthermia. Additional causes of drug-induced hyperthermia include neuroleptic malignant syndrome, administration of anticholinergic medications, response to antibiotic administration, interaction of monoamine oxidase inhibitors with opioids (especially meperidine), and serotonin syndrome.

BOX 197.1 Adverse Effects of Severe Hyperthermia

Cardiovascular
- Increase in cardiac output
- Conduction defects (QT and ST changes, T-wave abnormalities)

Respiratory
- Pulmonary edema

Renal
- Decrease in GFR
- Renal hypoperfusion contributing to acute kidney injury

Hepatic
- Hepatocellular damage resulting in elevations of AST and ALT
- Coagulopathy

Hematologic
- Thrombocytopenia
- DIC

Neurologic
- Cognitive dysfunction
- Disruption in the blood-brain barrier

Gastrointestinal
- Ischemia
- Hemorrhage

ALT, Alanine transaminase; *AST*, aspartate transaminase; *DIC*, disseminated intravascular coagulation; *GFR*, glomerular filtration rate.
Data from Walter EJ, Hanna-Jumma S, Carraretto M, et al: The pathophysiological basis and consequences of fever. *Crit Care* 20(1):200, 2016.

TABLE 197.1 Temperature Monitoring Locations and Considerations

Core Temperature Sites

Location	Considerations
Pulmonary artery	Invasive and only used during cardiac or similarly complicated procedures; potential pulmonary and cardiac complications with insertion
Distal esophagus	Temperature probe incorporated into esophageal stethoscope must be positioned at point of maximal heart sounds or more distally for accurate temperature readings
Tympanic membrane	Difficult to place accurately; fear of perforation
Nasopharynx	Difficult to place accurately

Sites That Approximate Core Temperature

Location	Considerations
Axillary	Most accurate when probe is placed over the axillary artery and when the arm is kept maximally adducted
Bladder	Invasive; must have urine flow to be accurate
Skin	Does not reliably track core temperature; forehead skin temperature typically 2°C cooler than core
Rectal	Difficult to place accurately; depends on rectal contents; often lags behind core temperature

Hyperthermia Secondary to Medical Conditions

Underlying medical conditions may cause hyperthermia in the perioperative period; they include thyrotoxicosis, pheochromocytoma, acute brain injury or stroke, adrenal insufficiency, deep venous thrombosis, pulmonary embolus, Parkinson disease, aspiration pneumonia, status epilepticus, connective tissue diseases, sepsis, and hypothalamic pathology.

Postoperative Fever

Hyperthermia is common postoperatively, once the thermoregulatory effects of anesthesia have dissipated. Causes of postoperative fever include an inflammatory response to surgery and infection or bacteremia. Epidural anesthesia does not suppress fever and has been associated with mild hyperthermia.

The case synopsis describes a hyperthermic reaction during general anesthesia. The most likely cause is iatrogenic overwarming due to relatively high ambient room temperature and use of warming devices in a procedure with little blood or fluid loss, or exposed surfaces that would dissipate heat. However, other less common possibilities must be kept in mind, such as MH, especially when considering the vague history of the relative who died during surgery under unknown circumstances (Box 197.2).

MANAGEMENT

The primary goal for the management of hyperthermia is to treat the underlying cause. Active cooling should be considered when the patient's temperature exceeds 39°C. Cooling methods include removing drapes and warming devices; lowering the ambient room temperature; applying ice to the groin, axilla, or neck; cold intravenous solutions; ice water lavage in the surgical wound; and, for the most severe cases that are causing end-organ impairment, cardiopulmonary bypass (Box 197.3).

PREVENTION

Iatrogenic causes of hyperthermia can be prevented by monitoring intraoperative core temperature and appropriate use of warming or cooling devices. Some drug-induced hyperthermic reactions can be prevented by recognition of medications known to induce hyperthermia, such as avoidance of opioids in patients currently taking monoamine oxidase inhibitors.

BOX 197.2 Differential Diagnosis for Hyperthermia

Intraoperative

- Infection
- Iatrogenic active warming
- Prolonged tourniquet application
- Malignant hyperthermia
- Thyrotoxicosis
- Pheochromocytoma
- Acute brain injury or stroke
- Adrenal insufficiency
- Deep venous thrombosis
- Pulmonary embolus
- Parkinson disease
- Aspiration pneumonia
- Status epilepticus
- Connective tissue diseases
- Sepsis
- Hypothalamic pathology

Postoperative

- Infection or bacteremia (from surgical translocation)
- Epidural anesthesia
- Inflammatory response to surgery
- Drug-induced

BOX 197.3 Cooling Methods

- Removing drapes and warming devices
- Lowering the ambient room temperature
- Applying ice to the groin, axilla, or neck
- Cold intravenous solutions
- Ice water lavage in the surgical wound
- Cardiopulmonary bypass

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198 Pediatric Laryngospasm

Nancy B. Samol • Eric P. Wittkugel

Case Synopsis

After extubation at the conclusion of adenotonsillectomy, a 5-year-old boy coughs and then develops high-pitched inspiratory stridor that progresses to silent rocking chest movements. Chest wall retractions are noted, and the breath sounds diminish until none are heard. Mask ventilation is attempted without success, and the patient desaturates rapidly.

PROBLEM ANALYSIS

Definition

Among other functions, the larynx protects the upper airway and lungs from aspiration of foreign materials. The glottal closure reflex is most evident during swallowing. Laryngospasm is an exaggerated form of the glottic closure reflex in response to noxious stimuli. Partial or complete airway obstruction due to laryngospasm can persist even after removal of the stimulus. Laryngospasm is mediated by the vagus nerve. The afferent limb of this reflex is the internal branch of the superior laryngeal nerve, and the efferent limb is the recurrent laryngeal nerve.

Complete laryngospasm consists of two phases: (1) glottic spasm causes adduction of the true vocal cords, causing partial airway obstruction via a "shutter" mechanism that leaves a small lumen open at the posterior commissure, followed by (2) a "ball-valve" mechanism with constriction of the ventricular cords (false vocal cords) as the paraglottis (intralaryngeal portion of the epiglottis) moves posteriorly and the arytenoid cartilages both perform a ventral movement, effectively sealing the larynx.

Recognition

Heralding signs of laryngospasm include paradoxic chest movement, nasal flaring, intercostal retractions or tracheal tug, inspiratory stridor, diminished or absent breath sounds, and hypoxemia followed by bradycardia and cyanosis. Laryngospasm can be partial (often described as "glottic spasm") or complete. The case synopsis describes the progression from partial to complete laryngospasm. Differentiation of partial laryngospasm from other causes of upper airway obstruction may be difficult. Typically, partial laryngospasm presents with chest movement and a stridulous "crowing" noise from the apposed vocal cords while minimal ventilation remains possible via the open lumen at the posterior commissure. Bronchospasm is diagnosed via auscultation of wheezing. Obstruction due to the tongue or other soft tissues in the pharynx is associated with snoring or gasping, whereas obstruction due to secretions is usually accompanied by gurgling sounds.

Prompt recognition and immediate treatment of complete laryngospasm are essential, as gas exchange is impossible via a closed glottis. During the progression from partial to complete laryngospasm, signs of extrathoracic airway obstruction (chest wall retractions, nasal flaring, paradoxic breathing) intensify until breath sounds deteriorate along with oxygenation and hypercapnea develops.

Risk Assessment

The incidence of laryngospasm in the pediatric population ranges from 0.04% to 14%. A recent trend toward reduction in these numbers reflects both improvement in early recognition and refinement in anesthetic and surgical techniques. In the largest single-institution study to date of laryngospasm in pediatric patients, Burgoyne and Anghelescu reviewed 21,452 anesthetics administered between 1999 and 2002 and found a rate of 1 per 1000 cases (0.1%). Risk factors for laryngospasm can be classified into three categories: patient-related, surgery-related, and anesthesia-related factors.

Patient-Related Factors

The most important patient-related factor is young age. In fact, the incidence of laryngospasm after general anesthesia correlates inversely with age. Additionally, the increased airway irritability caused by upper respiratory infections (URIs) (particularly those with parental confirmation) are strong predictors of laryngospasm, increasing the risk by a factor of 10, as does active asthma. Von Ungern-Sternberg demonstrated an increased risk for laryngospasm due to excess secretions and airway hyperreactivity only when cold symptoms were present on the day of surgery or less than 2 weeks before. This association was confirmed by Flick, who showed a significant association between laryngospasm and the presence of a structural or congenital airway anomaly. Exposure to tobacco smoke causes a tenfold increase in the incidence of laryngospasm, so preoperative history should include questions about "passive smoking." Finally, a history of gastroesophageal reflux is an additional risk factor for laryngospasm.

Surgery-Related Factors

Airway procedures, including adenotonsillectomy (21% to 27% incidence) and bronchoscopy, have a high incidence of laryngospasm. Bleeding in the airway increases the risk of laryngospasm. Esophageal endoscopy predisposes to laryngospasm secondary to stimulation of distal afferent esophageal nerves.

Anesthesia-Related Factors

The most important anesthesia-related risk factor is insufficient depth of anesthesia during both induction and emergence. Airway irritation with volatile anesthetics, mucus, or blood and airway manipulation with a suction catheter or laryngoscope blade may also induce or worsen laryngospasm. An animal model of acid-induced

laryngospasm demonstrated that lighter levels of anesthesia increase the activity of laryngeal adductor neurons. Some anesthetic practices commonly used in children increase the likelihood of airway stimulation during light anesthesia. During inhalation induction, the duration of stage II (light) anesthesia is longer than intravenous induction, which increases the period of vulnerability to laryngospasm. Because propofol decreases airway responsiveness and depresses laryngeal reflexes, propofol induction is associated less with laryngospasm than induction with sevoflurane. Stimulation of the glottis by secretions or airway management devices (e.g., oral airway) during this vulnerable period may trigger laryngospasm. There is controversy in the literature regarding the choice of airway device and risk of laryngospasm. Recent data indicate that use of a laryngeal mask airway (LMA) is strongly associated with laryngospasm even when adjusted for presence of URI or airway anomaly. Laryngospasm is especially likely when intubation is attempted without muscle relaxants before reaching an adequate depth of anesthesia. After extubation under deep anesthesia, patients are at risk for laryngospasm while passing through stage II with an unprotected airway. Finally, laryngospasm is more likely to occur in children who are cared for by less experienced anesthesia providers.

Implications

Although laryngospasm is commonly treated without sequelae, severe or ineffectively treated laryngospasm may progress to complete airway obstruction with subsequent hypoxia, hypercarbia, and bradycardia and result in serious complications, including negative-pressure pulmonary edema and cardiac arrest. In the case of complete airway obstruction, markedly negative intrapleural pressures generated by the patient in an effort to overcome the obstruction of the closed glottis can lead to transudation of fluid into the alveoli. Negative-pressure pulmonary edema is managed supportively with supplemental oxygen and diuretics. Rarely, endotracheal intubation and positive-pressure ventilation with positive end-expiratory pressure are required for resolution of negative-pressure pulmonary edema.

Five of 1000 patients who develop laryngospasm experience cardiac arrest. Immediate recognition and effective intervention are essential if this progression is to be avoided.

PREVENTION

Prevention is the best treatment for laryngospasm and can generally be achieved by identifying and minimizing the risk factors when possible. Take the following measures:

- Postpone elective airway surgery 2 to 3 weeks in children with a URI and any combination of passive smoking, copious nasal congestion or sputum, history of reactive airway disease, or history of sleep-disordered breathing.
- Consider avoiding nitrous oxide for induction of high-risk patients to achieve higher oxygen reserve and prevent early desaturation in the event of laryngospasm.
- Use muscle relaxants when appropriate to facilitate tracheal intubation.
- Avoid noxious airway or surgical stimulation during light anesthesia.
- Consider endotracheal intubation rather than using an LMA or mask anesthetic when the risk of laryngospasm is high and cannot be effectively mitigated.
- Maintain inhaled anesthesia with sevoflurane or isoflurane rather than desflurane, which has been associated with a significant increase in perioperative respiratory adverse events.
- Suction oropharyngeal secretions thoroughly before tracheal extubation.
- Extubate the trachea when the patient is fully awake. Premature extubation is a leading cause of laryngospasm.

In addition, the following measures *may* help prevent laryngospasm:

- Intravenous lidocaine given shortly before extubation may prevent or attenuate laryngospasm via central interruption of the reflex pathway or a direct peripheral action on sensory and motor nerve terminals.
- Lidocaine applied topically to the posterior oropharynx and vocal cords may suppress laryngeal mucosal sensory nerve activity.
- Before extubation, have the patient breathe 100% oxygen for 3 minutes to provide a margin of safety should airway obstruction or laryngospasm occur.
- The "no touch" technique described by Tsui and colleagues consists of suctioning the oropharynx, turning the patient lateral with the head down to keep the vocal cords clear of secretions, discontinuing anesthesia, and avoiding stimulation until the patient becomes fully awake for extubation to avoid laryngospasm after adenotonsillectomy.
- During extubation, inducing an "artificial cough" by holding the breathing bag momentarily at end inspiration with a positive pressure of 15 to 20 cm H_2O to maintain a high lung volume as the endotracheal tube is removed may reduce laryngospasm. In animal models, such positive intrathoracic pressure inhibits the glottal closure reflex and decreases the adductor response of the laryngeal muscles. Also, extubation with the lungs inflated facilitates the expulsion of airway secretions as the endotracheal tube is withdrawn, thereby reducing the likelihood of laryngospasm and aspiration of secretions.

It is still controversial whether the trachea should be extubated and the LMA removed when the patient is in a deep plane of anesthesia or when awake to reduce laryngospasm. More than a dozen studies over the past 2 decades fail to provide a consensus on the best practice, but evidence seems to favor removal of the LMA in a deep plane of anesthesia and extubation with the patient awake. It is important to identify children at increased risk for developing laryngospasm. Although it may not be possible to modify all preoperative risk factors, prudent choice of anesthetic technique and agents can reduce the likelihood of laryngospasm.

MANAGEMENT

If prevention fails, the management of laryngospasm varies, depending on whether airway obstruction is partial or complete, the severity of the laryngospasm, and its cause. In all cases, prompt recognition and immediate aggressive management are essential to prevent or reverse hypoxemia, which is why success has proven to depend in large part on the experience of the anesthesia provider. If recognition and treatment are delayed, management can be complicated by depression of cardiac output, which reduces the effectiveness of drug therapy. Many authors recommend applying airway manipulation first, beginning with removal of the irritant stimulus, then administering pharmacologic agents if necessary. Algorithms for managing complete or partial airway obstruction due to laryngospasm are presented in Figs. 198.1 and 198.2, respectively. Initial management includes the following:

- Continuous monitoring with pulse oximetry, electrocardiogram, and precordial stethoscope
- Capnography to confirm the presence or absence of effective ventilation
- Continuous positive airway pressure (CPAP) with delivery of 100% oxygen via a well-sealed facemask

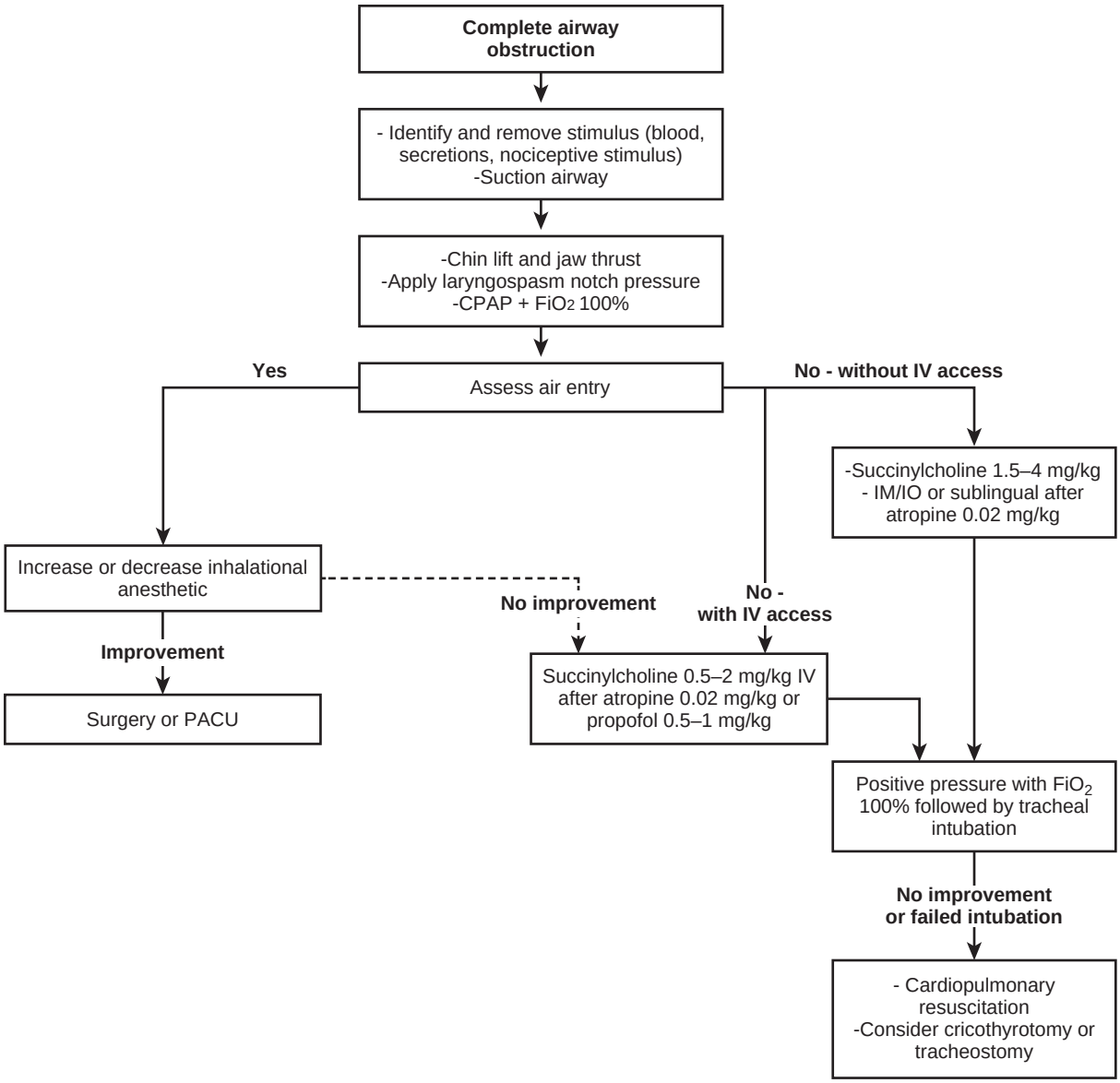

Fig. 198.1 Algorithm for management of complete airway obstruction. *CPAP,* Continuous positive airway pressure; *Fio_2,* fraction of inspired oxygen; *IM,* intramuscular; *IV,* intravenous; *IO,* intraosseous; *PACU,* postanesthesia care unit.

- Opening of the mouth along with anterior displacement of the mandible
- Removal of noxious airway stimuli (e.g., suctioning of blood and secretions, removal of airway devices)
- Firm, constant inward pressure at the "laryngospasm notch"
- Lightening or deepening the anesthetic with intravenous or volatile anesthetics
- "Fluttering the bag"
- Administration of muscle relaxants for complete obstruction unresponsive to other measures

In most instances, partial laryngospasm is effectively managed with bag-mask positive-pressure ventilation. On inspiration, there is often a brief moment of relative relaxation of the larynx. A firm squeeze on the anesthesia bag in phase with this brief moment of relative laryngeal relaxation provides "pressure support" for the patient's respiratory efforts. This technique can provide the minimal air exchange needed to maintain oxygenation and facilitate deepening or lightening of the anesthetic to relieve laryngospasm. However, care must be taken to avoid excessive CPAP. This can lead to gastric distention, which may further compromise ventilation or cause regurgitation and will necessitate insertion of an orogastric tube for decompression. Of note, with complete laryngospasm and ball-valve obstruction, the application of positive airway pressure can actually worsen airway obstruction by distending the piriform fossa on either side of the larynx and pressing the aryepiglottic folds more firmly against each other.

Anterior displacement of the mandible (i.e., the jaw thrust–chin lift maneuver) causes a painful stimulus and stretches the geniohyoid muscle to partially open the larynx. This may be especially beneficial with complete laryngospasm. It also ensures that airway obstruction from laryngeal closure is not exacerbated by soft tissue obstruction. Laryngospasm is often precipitated by regurgitation or retained upper airway secretions. Pharyngeal suctioning, even during the acute event, prevents further stimulation of the superior laryngeal nerve.

Larson and others have described a simple technique of pressure on the "laryngospasm notch" located behind the ear. This point is bounded anteriorly by the ascending ramus of the mandible adjacent to the condyle and posteriorly by the mastoid process and cephalad by the base of the skull. In Larson's technique, firm pressure is applied

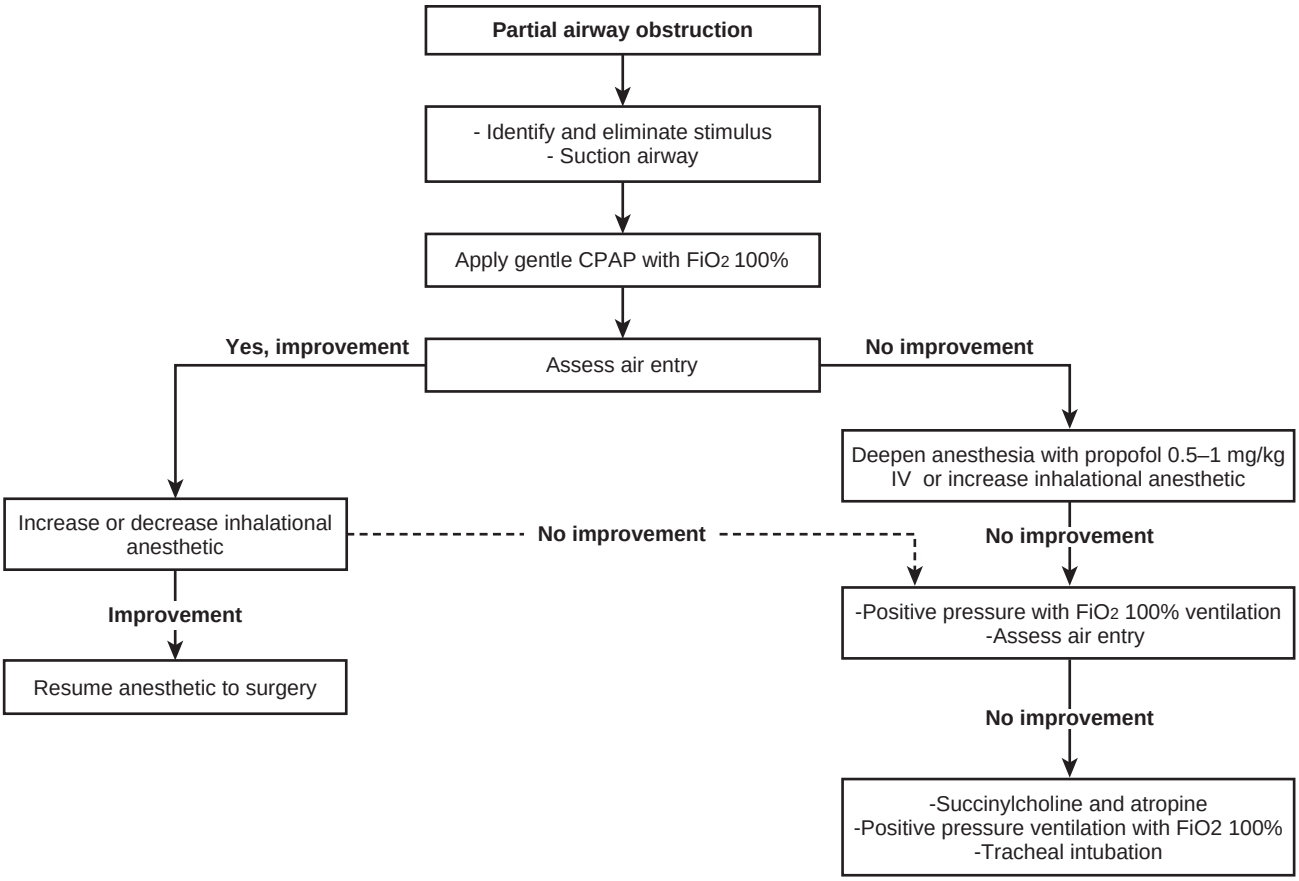

Fig. 198.2 Algorithm for management of partial airway obstruction. *CPAP,* Continuous positive airway pressure; *Fio_2,* fraction of inspired oxygen; *IV,* intravenous.

toward the base of the skull with both fingers, accompanied by anterior displacement of the mandible. This induces periosteal pain resulting in autonomic nervous system reflex and vocal cord relaxation. "Fluttering the bag" is a technique of manual high-frequency ventilation in which the anesthesia bag is very rapidly squeezed and released in a staccato rhythm similar to atrial flutter. Recently a new technique involving gentle chest compression with application of 100% oxygen has been proposed as an alternative to standard practice (100% oxygen with CPAP) for relief of laryngospasm.

Because laryngospasm often occurs in light planes of anesthesia, deepening the anesthetic or awakening the patient may relieve it, depending on whether the spasm occurs during induction, maintenance, or emergence. Propofol (0.5 to 0.8 mg/kg) may be useful for rapidly deepening the level of anesthesia and has proven to relieve laryngospasm in greater than 75% of cases. So long as cardiac output is adequate, propofol may be superior to succinylcholine (a depolarizing agent) with advantages that include lack of interaction with a previously administered nondepolarizing drug, eliminating the risk of prolonged paralysis, as well as safe use in patients with burns, muscular dystrophy, spinal cord transection, or hyperkalemia when succinylcholine is contraindicated.

If the preceding maneuvers do not improve airway obstruction, a muscle relaxant is indicated. Because of its rapid onset and short duration of action, succinylcholine is the most commonly used muscle relaxant to treat laryngospasm. Another advantage of succinylcholine is that it can be administered intramuscularly or sublingually if intravenous access is unavailable. However, owing to its vagotonic properties in children, succinylcholine should be given with atropine. Atropine is also indicated to treat bradycardia caused by persistent hypoxemia. Intravenous doses of succinylcholine range from 0.5 to 2 mg/kg. Higher doses (up to 4 mg/kg) are required for intramuscular administration. Smaller doses of succinylcholine can effectively treat laryngospasm, but larger doses are needed if emergency intubation is indicated.

If laryngospasm is sustained and the child is in extremis due to prolonged hypoxemia, intubation without muscle relaxants may be necessary. If apposition of the vocal cords interferes with intubation, topical application of lidocaine may relax the larynx and facilitate intubation. If air exchange has not been restored after these measures and intubation proves impossible, cricothyrotomy or emergent tracheostomy may be required.

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Perioperative Aspiration Pneumonitis

199

Marc Mecoli • Joseph Previte

Case Synopsis

A 5-year-old boy with eosinophilic gastroenteritis, chronic dysphagia and vomiting, and radiographic evidence of delayed gastric emptying presents for repeat esophagogastroduodenoscopy to evaluate disease progression. Previous endoscopy studies have revealed the presence of stomach contents despite adherence to appropriate fasting guidelines.

PROBLEM ANALYSIS

Definition

Pulmonary aspiration is defined as the presence of bilious secretions or particulate matter in the tracheobronchial tree. It most commonly occurs from passive regurgitation of gastric contents or active vomiting, but aspiration of blood or pharyngeal secretions can also cause significant pneumonitis. Of pediatric patients who aspirate during anesthesia, 40% actively vomit, and the remainder passively regurgitate. When anesthetized patients aspirate, 80% do so during induction, 14% during emergence, 4% during the procedure, and 2% postoperatively.

Recognition

After significant pulmonary aspiration, the physical examination may reveal fever, tachypnea, apnea, tachycardia, refractory laryngospasm, bronchospasm, wheezing, or cough. Rales and rhonchi can be heard, and cyanosis may be observed. A chest radiograph may reveal alveolar and, less commonly, reticular infiltrates. Radiographic findings may be localized but are more often extensive and frequently bilateral. The full extent of changes on the chest radiograph may not be demonstrated until 6 to 24 hours after pulmonary aspiration. Ninety percent of patients with significant pulmonary aspiration have symptoms within 1 hour, and almost all have symptoms within 2 hours. A pH determination of the aspirated material can be used to predict the severity of pulmonary damage.

Risk Assessment

Pulmonary aspiration occurs in 1 to 10 of 10,000 pediatric anesthetics. Pediatric patients may have a higher incidence of pulmonary aspiration associated with a greater risk of severe pulmonary damage compared with adults; however, the anesthesia literature is conflicting. Pediatric patients have some unique risks for pulmonary aspiration (Box 199.1) compared with adults (Box 199.2).

Although the critical pH and volume of gastric contents that place a child at risk for aspiration are unknown, based on an extrapolation of unpublished experimental data in rhesus monkeys, the thresholds for gastric pH (<2.5) and residual gastric volume (>0.4 mL/kg) have been applied to humans. Based on these limits, the risk of pulmonary aspiration would be increased in children compared with adults, because 76% of pediatric patients have gastric contents whose pH is less than 2.5 and whose volume is greater than 0.4 mL/kg, versus 32% to 55% of adults who meet these criteria.

Infants are at the highest risk for pulmonary aspiration. Gastroesophageal reflux disease (GERD) occurs in almost 50% of term neonates and is considered normal for the first 6 months of life. GERD can occur with intragastric pressures as low as 23 cm H_2O. If the fundoesophageal angle decreases during tracheal intubation, GERD can occur at even lower intragastric pressures. Owing to a smaller stomach, air swallowing during crying, and diaphragmatic breathing, the resting intragastric pressure in infants is higher than in older children or adults, which contributes to an increased risk of GERD.

The incidence of pulmonary aspiration with laryngeal mask airways may not be higher when used in healthy patients having elective surgery. However, the laryngeal mask airway does not form a tight seal around the larynx. Further, it causes reflex relaxation of the lower esophageal sphincter secondary to pharyngeal muscle distention, as during swallowing of a food bolus. The laryngeal mask airway may also increase the likelihood of pulmonary aspiration by contributing to gastric distention during positive-pressure ventilation and directing regurgitated gastric contents into the larynx. Consequently, children at high risk for aspiration should have their airways secured with endotracheal tubes.

Laryngeal competence, an important protective mechanism against pulmonary aspiration, is depressed by anesthetic induction agents, local anesthesia of the larynx and trachea, and greater than 50% concentrations of nitrous oxide. In adults, laryngeal competence is depressed for 2 to 8 hours after tracheal extubation, even in patients who appear alert. It is likely that a similar depression of laryngeal competence occurs in children. Depressed laryngeal competence is attributed to the mechanical effects of tracheal intubation and is distinct from residual anesthetic effects.

BOX 199.1 Risk Factors for Pulmonary Aspiration Unique to Children

- Transient pharyngeal weakness of the newborn
- Tracheoesophageal fistula (gastrointestinal reflux common after repair)
- Chronic pulmonary disease (asthma, croup, bronchopulmonary dysplasia, cystic fibrosis)
- Prematurity
- Cerebral palsy, developmental delay (swallowing dysfunction)
- Acute gastric distention in pediatric trauma patients

BOX 199.2 Risk Factors for Pulmonary Aspiration in Adults and Children

- ASA physical status III or IV
- Surgery outside regular working hours[a]
- Emergency surgery[a]
- Obesity, ascites, large abdominal mass
- Gastritis, history of ulcers
- Gastroparesis
- Autonomic neuropathy (familial, acquired)
- Muscular disorders
- Long-lasting general anesthetics
- Vocal cord paralysis
- Diabetes mellitus
- Electrolyte, metabolic imbalance
- Insufficient anesthetic depth
- Airway difficulty
- Preexisting gastroesophageal reflux disease
- Esophageal and upper abdominal surgery
- Elevated intracranial pressure
- Degenerative neuropathies
- Opioids, methylxanthines, β-agonists
- Reduced level of consciousness
- Laryngeal malfunction or spasm
- Collagen vascular disease
- Renal, pelvic, bladder, or uterine distention

[a]Increases risk by fivefold to sixfold.

ASA, American Society of Anesthesiologists.

Implications

The occurrence and severity of pneumonitis depend more on gastric pH than on volume. Low-volume aspirates with a pH less than 1.8 result in severe pneumonitis, whereas volumes as high as 2 mL/kg with a pH greater than 2.5 produce minimal pulmonary damage.

Pulmonary aspiration leads to loss of the protective mucosal barrier of the trachea and major bronchi by causing edema and desquamation of epithelium. Damaged tissue is vulnerable to subsequent viral or bacterial infection. Highly acidic liquid aspirates produce pulmonary injury within 12 to 18 seconds and extensive atelectasis by 3 minutes. By 1 hour after pulmonary aspiration, pulmonary injury has progressed to bronchial epithelial degeneration, pulmonary edema, and hemorrhage. The consequent increased pulmonary capillary leak is followed by a neutrophil response. As a result of alveolar cell damage, fluid and protein move into the alveoli and interstitium and reduce pulmonary surfactant activity. Increased airway resistance and decreased pulmonary compliance due to reduced pulmonary surfactant activity lead to severe hypoxia. Also, severe hypotension may occur due to a reduction in intravascular volume (from the transudation of fluid into the alveoli), along with impaired venous return caused by the high airway pressures required for adequate ventilation.

With particulate aspiration, hypoxemia occurs earlier and is more severe. Although fluid shifts are less extensive than with acidic liquid aspiration, there is a greater increase in arterial carbon dioxide tension and a greater decrease in arterial pH. Mortality rate with clinically significant pulmonary aspiration is 5% or less.

MANAGEMENT

Treatment includes immediate suctioning of the airway and administration of supplemental oxygen by nasal cannula or facemask. This is often sufficient, but tracheal intubation and mechanical ventilation may be required in severe cases.

Bronchopulmonary lavage is not recommended for acidic aspirates because damage to the lungs occurs within 12 to 18 seconds. In addition, more extensive pulmonary damage may occur due to the spread of acidic aspirates to lower regions of the lung.

An immediate danger of particulate aspiration is mechanical obstruction. Bronchoscopy to remove particulate material should be performed in this situation. Corticosteroids have not been shown to reduce morbidity or mortality rates after pulmonary aspiration and are not advised, because they can predispose the patient to gram-negative pneumonia.

Antibiotics should be administered according to the results of cultures of tracheal aspirates. Empirical use is reserved for patients who have aspirated grossly contaminated material (e.g., feces, pus). Leukocytosis, pulmonary infiltrates, thick sputum, and fever are all nonspecific responses to chemical pneumonitis and are not sufficient reasons to institute antibiotic therapy. Postural drainage and respiratory therapy with bronchodilators may be useful. Most patients have resolution of clinical symptoms within 2 weeks.

TABLE 199.1 Pharmacologic Agents Used for the Prophylaxis of Pulmonary Aspiration

Drug	Dose and Schedule	GV	pH	LEST
Antacids				
Alka-Seltzer	2 tbsp/30 mL water (1 h BS)	↑	↑	0
Sodium citrate	0.5–1 mL/kg (30 mL max; 1 h BS)	↑	↑	0
Anticholinergics				
Glycopyrrolate	7.5–10 μg/kg (1 h BS)	?	?	0
H_2-Blockers				
Cimetidine	7.5 mg/kg (PM/AM)	↓	↑	0
Famotidine	0.5 mg/kg (PM/AM)	↓	↑	0
Ranitidine	1.5–2 mg/kg (1–2 h BS)	0	↑	0
Prokinetic Agents				
Metoclopramide	0.1 mg/kg IV or PO (1 h BS)	↓	0	↑
Proton Pump Inhibitors				
Lansoprazole	1.5 mg/kg (PM/AM)	↓	↑	0
Omeprazole	0.3 mg/kg (PM/AM)	↓	↑	0
Pantoprazole	1.4 mg/kg QID	↓	↑	0

BS, before surgery; *GV*, gastric volume; *IV*, intravenously; *LEST*, lower esophageal sphincter tone; *PM/AM*, night before and morning of surgery; *PO*, by mouth, orally; *QID*, 4 times a day.

PREVENTION

Prevention and amelioration of pulmonary aspiration rely on the use of conventional antacids and drugs that promote gastric emptying and increase lower esophageal sphincter tone (prokinetic agents), reduce gastric volume (H_2-blockers), or increase the pH of the gastric contents (H_2-blockers, proton pump inhibitors). Doses, schedules, and principal actions of these agents are summarized in Table 199.1.

There are well-defined fasting guidelines for healthy children undergoing surgery or procedures requiring anesthesia (Table 199.2). Recently more liberal fasting guidelines including allowing clear liquids until surgery have been studied in healthy children having elective surgery without evidence of increased morbidity in this population (Andersson and colleagues, 2015). There are no published fasting guidelines for children considered to be at increased risk for pulmonary aspiration. Removal of gastric contents before induction is recommended for these patients. If gastric suctioning is not possible preoperatively, the gastric contents should be suctioned immediately after the airway has been secured after rapid-sequence induction to reduce the risk of pulmonary aspiration during emergence from anesthesia and extubation.

To prevent regurgitation, rapid-sequence induction is used to minimize the vulnerable period between loss of consciousness and securing

TABLE 199.2 Fasting Guidelines for Healthy Children Undergoing Elective Procedures

Age	Solids	Clear Liquids[a]	Formula
0–6 mo	6 hr	2 hr	6 hr
6 mo–2 yr	6 hr	2 hr	6 hr
>2 yr	6 hr (light meal)[b]	2 hr	NA
>2 yr	8 hr (fat-containing foods)	2 hr	NA

[a]Some consider breast milk to be a clear liquid.
[b]By American Society of Anesthesiologists guidelines, a light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period.
NA, Not applicable.

of the airway. Historically, cricoid pressure has been an integral part of rapid-sequence induction. Cricoid pressure, with or without the presence of a nasogastric tube, is an effective means of preventing passive regurgitation of gastric fluids in infants, children, and adults. Cricoid pressure with a force of 20 newtons (equivalent to a 2-kg mass acted on by the force of gravity) must be applied before the loss of consciousness. This amount of pressure is uncomfortable for awake patients. Loss of upper esophageal barrier pressure occurs before loss of consciousness in all age groups after the intravenous induction of anesthesia. The force of cricoid pressure should be increased to 40 newtons (which is painful for awake patients) with unconsciousness. Higher pressures may distort or occlude the trachea and upper airway and has the potential to make intubation challenging. Cricoid pressure during active vomiting has the potential to cause esophageal rupture.

Most episodes of aspiration during induction begin with coughing or gagging during airway manipulation as a result of inadequate anesthesia or the absence of muscle relaxation. Ensuring complete muscle relaxation before laryngoscopy reduces the likelihood of regurgitation. Controlled rapid-sequence induction with gentle facemask ventilation before intubation may result in less hypoxia without increased incidence of pulmonary aspiration (Neuhaus and colleagues, 2015). The use of cuffed endotracheal tubes in children during prolonged intubation (e.g., intensive care unit patients) has led to a reduction in the incidence of silent aspiration from passive regurgitation.

In patients at high risk for pulmonary aspiration, extubation should be performed only when the patient is fully awake and has full return of neuromuscular function. Children should demonstrate mouth opening, hip flexion, and return of the sucking, cough, and gag reflexes. Patients should be in the lateral, 10- to 15-degree head-down (Trendelenburg) position so that any secretions or regurgitant material can accumulate in the cheek and drain passively. Finally, the application of 15 to 20 cm H_2O positive end-expiratory pressure immediately before extubation induces a reflex cough, which pushes secretions or materials away from the larynx.

ACKNOWLEDGMENT

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200 Postintubation Croup

Barbara M. Dilos

Case Synopsis

A 4-year-old girl undergoes a general anesthetic for laparoscopic repair of an umbilical hernia. A few minutes after arriving in the postanesthesia care unit, she is noted to have inspiratory stridor.

PROBLEM ANALYSIS

Definition

One of the complications of general anesthesia with an endotracheal tube is postintubation croup. It presents by inspiratory stridor occurring in the postoperative period. It is a manifestation of subglottic edema that causes an increased resistance to breathing. Endotracheal tubes are thought to be the main culprit in causing postintubation injury to the tracheal mucosa.

There is a wide range of severity of postintubation croup that is dependent on the degree of tracheal edema present after extubation. The main reason why postintubation croup is mainly a pediatric complication rather than an adult one is the anatomic difference between the two airways.

Pediatric Airway Anatomy

The infant airway is different from the adult airway. It becomes similar to the adult airway by about age 8. The infant has a large tongue in relation to the mouth. The larynx is more cephalad in the infant than the adult larynx. It is at the level of about C2, and the adult larynx is at the level of about C5 anterior to the cervical spine. The epiglottis is more omega shaped rather than U shaped, and it lies at a more acute angle in the airway than the adult. It was thought in the past that the pediatric larynx is conical and circular; however, newer information shows that it is elliptical. The narrowest point of the pediatric airway remains at the cricoid ring below the larynx, whereas in the adult it is at the vocal cords. Due to the narrow caliber of the pediatric airway, a small degree of circumferential edema can have a large effect on laminar air flow resistance. Under laminar conditions the resistance is inversely proportional to the radius of the trachea raised to the fourth power. In an airway that is only 3 to 4 mm in diameter, a circumferential 1-mm edema will have a great effect on resistance than it would have in an airway that is 7 to 8 mm in diameter.

Risk Assessment

Supraglottic airways use in general anesthetics in the pediatric population has increased tremendously over the past years. Postintubation croup is not an issue when these devices are used; however, there are numerous cases where it is required to secure the airway with an endotracheal tube during anesthesia.

Intubation with a cuffed endotracheal tube in children younger than age 8 has been thought for many years to be a risk factor for developing postintubation croup. The impact of the cuff pressure on the tracheal mucosa especially at the narrow cricoid ring can lead to edema and postintubation croup. More recent studies have shown that the choice of the size of the endotracheal tube is important, not only whether it is cuffed or uncuffed. Cuffed tubes chosen should be half a size smaller than the uncuffed endotracheal tubes because the airway must accommodate the cuff.

Checking for a leak that is between 20 and 30 cm of H_2O pressure is very important after intubation when using both cuffed and uncuffed endotracheal tubes, as it is an indicator that the tube is not putting pressure on the mucosa. Not having a leak, however, is not a definite indicator that there will be postintubation stridor. Studies have also shown that high-volume, low-pressure cuffs are less inclined to cause mucosal edema. Moreover the placement of the cuffed tube in the airway is important. The cuff must be farther down the trachea to avoid the narrow cricoid ring. This poses somewhat of a challenge because the pediatric trachea is short, so improper sizing and placement of the tube may not avoid both the cricoid ring and blocking of the carina by the cuff.

Cases in which there is a higher risk of postintubation croup are those in which there is instrumentation of the airway and those in which the neck is not in neutral position. Furthermore, if patients have an upper respiratory infection and are intubated for their anesthetic, they are at higher risk for having postintubation croup. In patients with Down syndrome, the incidence of postintubation croup is higher due to the specific anatomic differences in their airway, such as subglottic stenosis. Longer operative times and repeated attempts at intubation are also associated with an increased risk of postintubation stridor.

Recognition

The diagnosis of postintubation croup is made by observation. There should be high suspicion of its occurrence if the patient has any of the risk factors described previously. Stridor is a high-pitched inspiratory noise produced when air passes through an extrathoracic obstruction. The obstruction is caused by the subglottic mucosal edema. Stridor may occur immediately after extubation or much later when the patient is in the postanesthesia recovery unit. It may appear as mild to severe obstruction that may or may not manifest along with oxygen desaturation. Accessory muscles of respiration may be involved if the edema is severe enough, and if not recognized and treated in a timely manner, it may progress to total obstruction and respiratory failure requiring reintubation.

Different scales have been developed that quantify the severity of viral and postintubation croup. One of these is the Westley system score, which rates clinical findings to five criteria: level of consciousness, cyanosis, stridor, air entry, and retractions. It has a total of 17 points and stratifies mild croup as 0 to 2 points, moderate as 3 to 5

points, severe as 6 to 11 points, and impending respiratory failure as 12 to 17 points. It is important to remember that many of the criteria depend on observation. Spirometry and esophageal manometry are ways that actual measurements can be obtained; however, in the clinical situation, these measurements will most definitely not be easy to obtain.

Once stridor is recognized, there should be immediate measures to treat so that the progression of tracheal edema is halted before possible complete obstruction of the trachea occurs.

MANAGEMENT

In cases of mild postintubation stridor, humidified oxygen has been shown to be beneficial. In moderate to severe cases, nebulized racemic epinephrine is the first line of treatment. Nebulized racemic epinephrine has been studied extensively in its use for the treatment of viral croup in the pediatric population. The racemic mixture of L and D epinephrine is thought to be preferred as a way to minimize the adrenergic cardiac side effects of L epinephrine. Studies have shown that there is no difference in treatment and in side effects whether racemic of L epinephrine is used as a nebulizer to treat croup. The effect on reduction of symptoms is seen within 30 minutes of treatment. The nebulized epinephrine results in local vasoconstriction of the tissues that are affected by airway edema. There are no formal studies regarding its use in postintubation stridor; however, it has been used successfully for many years in postanesthesia care units and in pediatric intensive care units. It may be delivered as a nebulizer or during noninvasive positive-pressure ventilation. The effect subsides after discontinuation of use, and although the edema may not return to baseline, a second treatment may be warranted. It is prudent to monitor patients who have been treated for postintubation stridor with nebulized epinephrine for at least 8 to 12 hours to ensure that the airway edema does not return.

Helium oxygen mixture or heliox has also been used in viral croup as a way to increase laminar flow, and it does have potential benefit in postintubation croup.

Intravenous steroids such as dexamethasone can also work, but it would take many hours for the drug to take effect. As for prophylactic steroids, no studies have shown that routine use of prophylaxis in the pediatric population prevents postintubation croup. If there is no response to treatment and there is worsening respiratory failure, the decision must be made whether to reintubate.

PREVENTION

Prevention measures are critical in postintubation stridor. Understanding the risk factors and ensuring that those risk factors are minimized can be very effective in prevention. Early recognition and prompt treatment to minimize tracheal edema and posttreatment observation are the cornerstones to averting complete respiratory failure and reintubation.

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201 Postobstruction Pulmonary Edema in Pediatric Patients

Lourdes Al Ghofaily

Case Synopsis

A 5-year-old obese child with developmental delay, asthma, and obstructive sleep apnea presents for a tonsillectomy. Inhalation induction is begun. The airway is partially obstructed intermittently until nasopharyngeal and oral airways are inserted. On completion of surgery, pink, frothy fluid is noted in the endotracheal tube. A chest radiograph (Fig. 201.1) is obtained, and the child is transferred to the intensive care unit for positive-pressure ventilation with positive end-expiratory pressure (PEEP). The following morning the chest radiograph is normal (Fig. 201.2), and the child is extubated without incident.

PROBLEM ANALYSIS

Definition

Postobstruction pulmonary edema (POPE), also known as negative pressure pulmonary edema (NPPE), is a noncardiogenic form of pulmonary edema driven by acute changes in hydrostatic forces at the level of the alveolus. Two subtypes have been described. Type 1 POPE occurs in response to forced inspiration against an obstructed upper airway, as occurs in laryngospasm, epiglottitis, croup, or aspiration of an obstructing foreign body. Type 2 POPE occurs in response to relief of a chronic obstruction, such as obstructive sleep apnea (OSA), or in patients presenting for tonsillectomy and adenoidectomy with relief of chronic upper airway obstruction. In type 2 POPE, the changes in transpulmonary pressure gradients occur primarily during expiration.

In both types of POPE, a change in the equilibrium between intraalveolar pressures and extraalveolar pressures lead to transudation of fluid into the alveolar space, causing pulmonary edema.

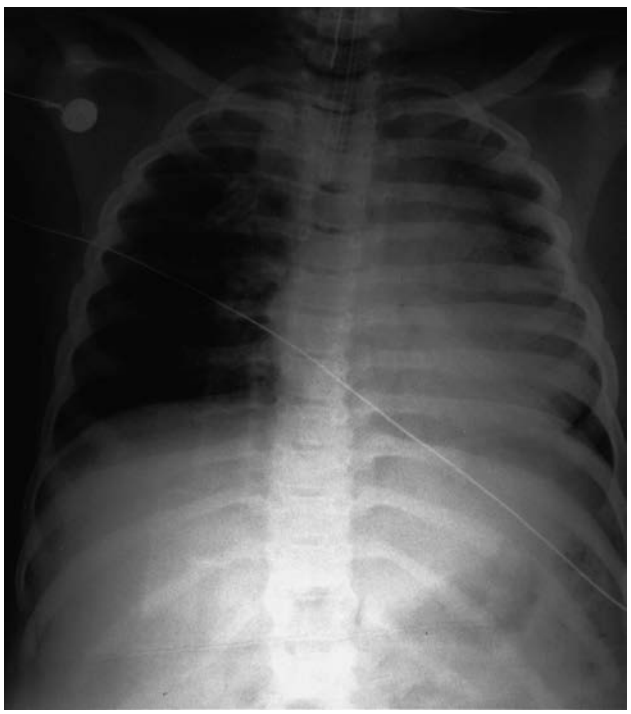

Fig. 201.1 Chest radiograph obtained at the completion of surgery. Note perihilar fluffy infiltrates in a butterfly pattern, consistent with pulmonary edema. Also present is left lower lobe atelectasis.

Recognition

Recognition of POPE involves an understanding of its pathophysiology. Under normal conditions, there is a balance between the hydrostatic and colloid osmotic pressures between the alveolus and surrounding tissue, as described by the Starling equation.

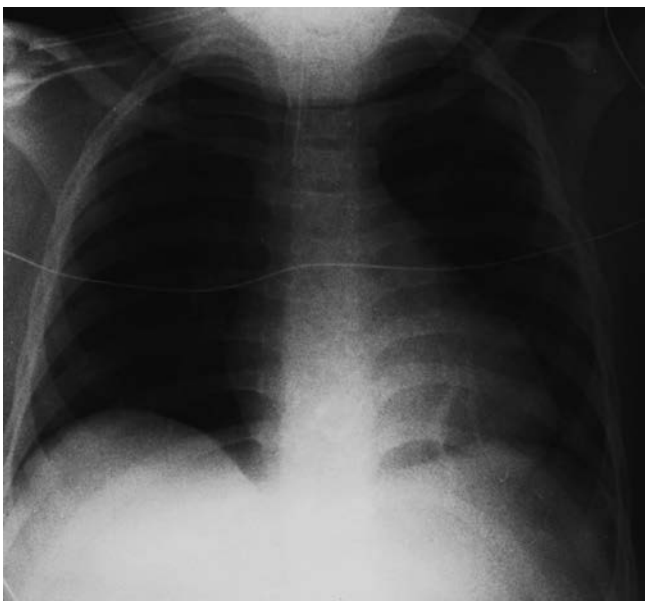

Fig. 201.2 Chest radiograph taken the following morning. Note resolution of the perihilar infiltrates.

$$\text{Fluid filtration rate} = K_f\left[(P_c - P_i) - \sigma(\pi_c - \pi_i)\right]$$

In this equation, K_f is capillary permeability, P_c is pulmonary capillary hydrostatic pressure, P_i is pulmonary interstitial hydrostatic pressure, σ is the reflection coefficient for proteins, π_c is pulmonary capillary osmotic pressure, and π_i is pulmonary interstitial osmotic pressure. This balance of pressures prevents any net movement of fluid across the alveolar-capillary membrane. The result is that only a small amount of fluid enters the pulmonary interstitium and, once there, is promptly removed by the pulmonary lymphatics.

In type 1 POPE, patients generate extremely negative intrathoracic pressures, increasing venous return to the right atrium. This increases pulmonary blood volume and capillary hydrostatic pressure. At the same time, a marked decrease in pulmonary interstitial hydrostatic pressure occurs, resulting in increased transfer of fluid into the interstitium. If lymph removal mechanisms are overwhelmed, signs and symptoms of pulmonary edema develop. The hypoxemia and increased sympathetic tone that frequently accompany airway obstruction also increase pulmonary vascular pressures and left ventricular afterload to facilitate edema formation (Figs. 201.3 and 201.4). Acutely, left ventricular dysfunction may contribute to the development of pulmonary edema. However, such dysfunction is typically extremely short lived, as evidenced by normal or near-normal central venous, pulmonary artery, and pulmonary capillary wedge pressures when measured after the obstructive event.

In type 2 POPE, chronic upper airway obstruction creates baseline PEEP within the alveolus. On relief of the PEEP, the intraalveolar pressure decreases, with Starling forces favoring a net flow into the alveolus from the interstitium.

An example of the relative pressures maintaining a normal fluid filtration rate (assuming constant values for K_f and σ) is the following:

$$P_c = 12 \text{ mm Hg},\ P_i = 4 \text{ mm Hg},\ \pi_c = 23 \text{ mm Hg},\ \pi_i = 9 \text{ mm Hg} \approx 2 \text{ mm Hg}$$

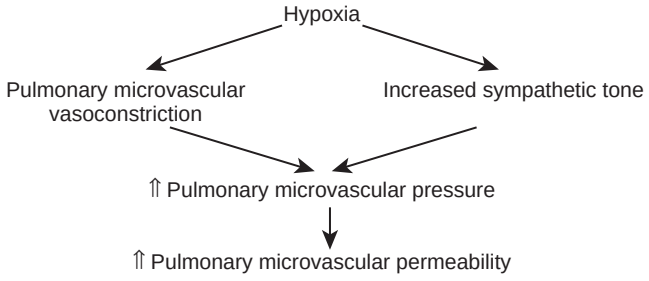

Fig. 201.3 Role of hypoxia in the generation of postobstruction pulmonary edema.

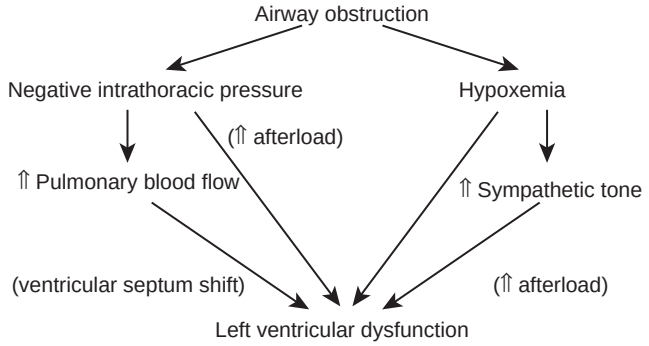

Fig. 201.4 Proposed mechanisms leading to left ventricular dysfunction during airway obstruction.

Relative pressures promoting an increased fluid filtration rate and the development of POPE are as follows:

$$P_c = 22 \text{ mm Hg},\ P_i = 50 \text{ mm Hg},\ \pi_c = 23 \text{ mm Hg},\ \pi_i = 9 \text{ mm Hg} \approx 58 \text{ mm Hg}$$

P_c elevation reflects increased pulmonary capillary blood volume and left ventricular afterload; P_i elevation reflects decreased intrapleural pressure.

POPE typically occurs in young, healthy individuals. The onset of edema is usually soon after relief of the obstruction, but it may be delayed for up to 24 hours. The patient exhibits an increased alveolar-to-arterial oxygen tension gradient, manifested by a requirement for supplemental oxygen; this, along with the pulmonary edema, typically resolves in less than 36 hours. Chest auscultation is consistent with pulmonary edema and may reveal rales and occasional rhonchi and wheezes. The chest radiograph and computed tomography scan show pulmonary edema, with peribronchial cuffing predominantly involving the perihilar and more central lung parenchyma. The peripheral lung regions remain remarkably free of alveolar edema, resulting in a "butterfly" pattern. The cardiac silhouette is normal. POPE usually results in rapid resolution of radiographic changes.

The following causes of pulmonary edema should also be considered and eliminated:

- Aspiration pneumonia
- Iatrogenic volume overload
- Pulmonary embolus
- Primary cardiac abnormality
- Myocardial dysfunction secondary to ischemia
- Anaphylaxis
- Asthma

At least initially, aspiration pneumonia is the most difficult alternative diagnosis to eliminate. Massive aspiration of gastric contents can produce the same radiographic picture as POPE, but it more commonly involves the right upper lobe or posterior segments. Further, the clinical course is more protracted owing to the chemical injury to the lung parenchyma. Radiographic changes from acute aspiration of gastric contents typically lag behind the patient's clinical course.

Risk Assessment

The overall incidence of POPE is unknown, despite clinical reports describing the phenomenon since the mid-1970s. General risk factors include the following:

- Laryngospasm
- Obesity and OSA
- Epiglottitis
- Croup
- Partial tracheal obstruction by a foreign body
- Upper airway pathology or surgical manipulation (e.g., tracheomalacia, vocal cord paralysis)
- Partial tracheal obstruction by an esophageal foreign body
- Obstructed endotracheal tube or laryngeal mask
- Difficult intubation

No specific anesthetic drugs have been shown to increase the incidence of POPE. However, anesthetic agents or techniques that increase the likelihood of laryngospasm or soft tissue upper airway obstruction have the potential to increase a patient's risk for type 1 POPE.

With increasing recognition of type 2 POPE in pediatric patients undergoing adenotonsillectomy for upper airway obstruction, retrospective studies estimate the incidence of type 2 POPE to be 1.2% to 1.4% in this subset of patients. In this group, risk factors for all pulmonary complications include the following:

- Age less than 2 years
- Apnea-hypopnea index greater than 24
- Spo_2 less than 90% on room air in the postanesthesia care unit (PACU)
- PACU stay longer than 100 minutes

Maintaining a high index of suspicion for pulmonary complications in this patient population regardless of whether they suffer a recognized episode of laryngospasm facilitates early recognition and treatment of both subtypes of POPE.

Implications

The clinical course of POPE is usually self-limited. Case reports among the pediatric population describe increased level of service, longer hospital stay, diuretic use, and respiratory support ranging from use of supplemental oxygen, continuous positive airway pressure or bilevel positive airway pressure, to intubation and intensive care unit admission.

MANAGEMENT

Treatment of POPE involves reestablishing and maintaining a patent airway, followed by supportive care. Supplemental oxygen is necessary, and most patients require tracheal intubation for a period of time; this may be as short as several hours in some instances. Many patients receive positive airway pressure, either as continuous positive airway pressure or as positive-pressure ventilation with PEEP. Rarely, hemoptysis and frank pulmonary hemorrhage have been reported after acute upper airway obstruction. Both require significant ventilatory and cardiovascular support. Aggressive, invasive hemodynamic monitoring, such as pulmonary artery catheterization, is not indicated except to rule out other causes of pulmonary edema. Use of diuretics is controversial because the edema is not due to excessive intravascular volume (as supported by normal pulmonary capillary wedge pressure measurements), and edema resolution is typically rapid. In addition to diuresis, furosemide increases venous capacitance, and it may have a role in the management of POPE. Corticosteroids and antibiotics have no role in the treatment of POPE unless they are indicated for other reasons. Resolution of clinical symptoms and radiographic findings is usually rapid and typically occurs within 2 to 3 days.

PREVENTION

Prevention of POPE involves (1) recognition of clinical scenarios in which upper airway obstruction is likely to occur, and (2) the development of an anesthesia management plan to avoid potential obstruction. The latter includes the following:

- Ensure an adequate depth of anesthesia during the use of a facemask or laryngeal mask airway.
- Consider the use of "bite blocks" to ensure patency of artificial airways during emergence from anesthesia.
- Perform tracheal extubation in fully awake patients to avoid laryngospasm or soft tissue airway obstruction.
- Use fiberoptic intubation in patients with known airway abnormalities.

Anesthesiologists are frequently faced with situations that cannot be avoided, such as anesthetizing a child with epiglottitis. In such cases, multiple strategies for avoiding the complications of airway obstruction, including surgical intervention, should be available if obstruction occurs.

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Postoperative Apnea in Infants

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Benjamin B. Bruins • C. Dean Kurth

Case Synopsis

A 2.5-kg, 4-month-old male infant presents for a large, irreducible inguinal hernia repair. His history is significant for premature birth at 26 weeks of gestation, intraventricular hemorrhage, and immature lung disease requiring mechanical ventilation for 3 weeks. He was discharged home at 3 months. Combined spinal epidural (caudal) anesthesia is performed as the sole anesthetic technique for this procedure. After subarachnoid block in sitting position using 1 mg/kg of isobaric bupivacaine injected at the L3–L4 level, the intravenous catheter is inserted in the lower extremity. An epidural catheter is inserted through sacral hiatus (caudal) using ultrasound guidance to confirm the catheter at the L1 level. The pacifier is dipped in sucrose solution, and the infant is allowed to suck on the pacifier during the procedure. At 75 minutes into the procedure, 0.25% bupivacaine 1.5 mg/kg was injected slowly via epidural catheter to maintain the block for the 2-hour surgical procedure. After 3 hours in the neonatal acute care unit, he is noted to have episodes of apnea. Caffeine 20 mg/kg is administered intravenously to prevent further apneic episodes.

PROBLEM ANALYSIS

Definition

Postoperative apnea is defined by periods of no ventilation during recovery after anesthesia and operation, usually in former premature infants or full-term neonates. This is distinguished from apnea of prematurity and apnea of infancy, which occur in premature and full-term infants, respectively, who have not had anesthesia or surgery.

Postoperative apnea is characterized by duration and type. Cessation of airflow for greater than 15 seconds is diagnostic for apnea. Alternatively, shorter periods of periodic breathing (>6 seconds) are considered to be apnea if associated with bradycardia or hypoxemia. In terms of type, apnea can be central, obstructive, or mixed (Fig. 202.1):

- Central apnea occurs without respiratory effort.
- Obstructive apnea occurs with respiratory effort, but without ventilation.
- Mixed apnea is characterized by absent ventilation with occasional respiratory effort.

Recognition

The incidence of postoperative apnea depends on detection methods. Studies using continuous recording devices (pneumograms) including flow and chest wall sensors reported rates of 31% to 49% compared with apnea rates of 5% to 10% from studies that relied on nurse observation or bedside cardiorespiratory monitor alarms.

Risk Assessment

The incidence of postoperative apnea is influenced by patient, surgical, and anesthetic factors. Of these, premature birth history is the most important. Prematurely born infants less than 60 weeks of postconceptual age are at risk for postoperative apnea, although full-term infants less than 4 weeks of postnatal age are also at risk. In formerly premature infants, factors that influence the incidence of postoperative apnea include the following.

Postconceptual Age

Postconceptual age (PCA), defined as the sum of postnatal age and gestational age, is the most important determinant of postoperative apnea. The incidence of postoperative apnea varies inversely with PCA (Fig. 202.2). The incidence is high in prematurely born infants younger than 40 weeks of PCA. After this, the incidence decreases sharply until the infant is 50 weeks of PCA. The incidence of postoperative apnea is low at that point and decreases gradually thereafter.

Gestational Age

The gestational age of the infant modifies the incidence of postoperative apnea. Fig. 202.2 displays the relationship of postoperative apnea incidence versus PCA for an infant born at 32 weeks of gestation, with an approximate 85% incidence of postoperative apnea. The incidence-versus-PCA curve shifts upward as the gestational age decreases. Conversely, the curve shifts downward as gestational age approaches term. Thus at any given PCA, the incidence of postoperative apnea is greater for infants born at 26 weeks of gestation than at 32 weeks of gestation.

Anemia

The presence of anemia (hematocrit <30%) also modifies the incidence of postoperative apnea in formerly premature infants. The incidence-versus-PCA curve shifts upward with anemia (see Fig. 202.2). It was previously believed that anemia was an independent risk factor, but more recent studies have not corroborated this, and

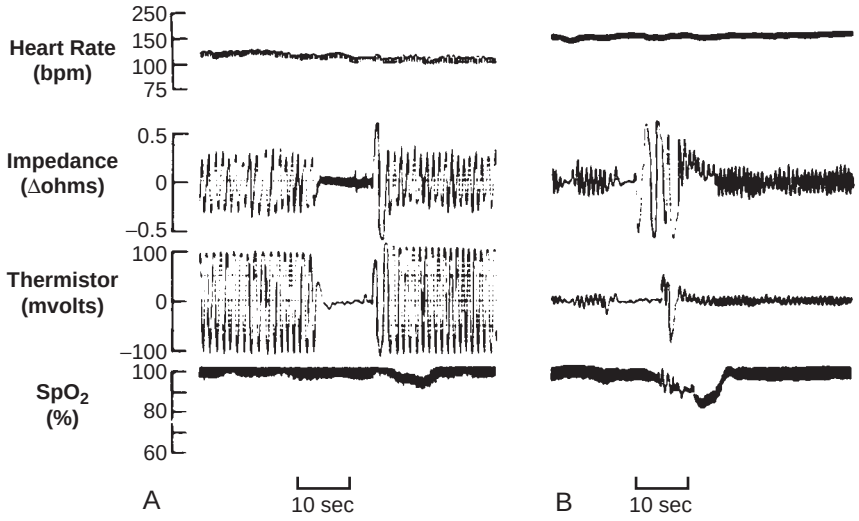

Fig. 202.1 Postoperative recording of heart rate, chest wall movement (impedance), nasal airflow (thermistor), and oxygen saturation ($Sp0_2$) from an infant after general inhalation anesthesia for inguinal hernia repair. A, Recordings obtained in the postanesthesia care unit depict brief central apnea. This is denoted by a lack of chest wall motion and airflow. Note mild arterial desaturation after the apnea. **B,** Another recording, also obtained in the postanesthesia care unit, illustrates mixed apnea. During the initial 6 seconds of apnea, there is no chest wall motion or airflow (brief central apnea), followed by 6 seconds of chest wall motion with no airflow (obstructive apnea). Note that arterial desaturation with the latter is more severe than with comparable central apnea in **A**.

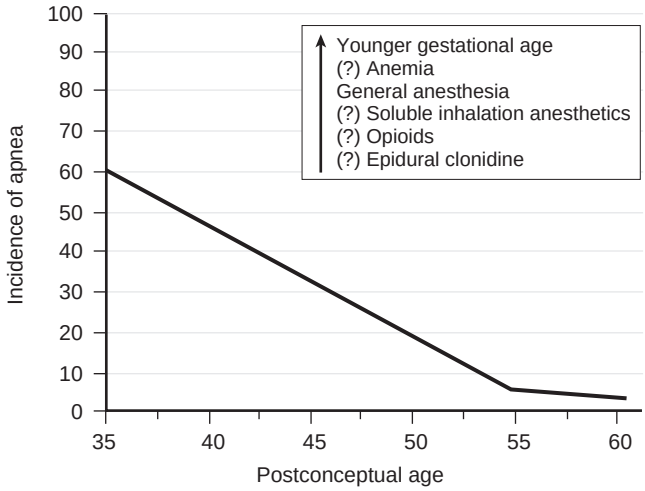

Fig. 202.2 The incidence of postoperative apnea varies inversely with the postconceptual age in formerly premature infants. The incidence curve shifts upward for babies (1) born at younger gestational ages, (2) with postoperative anemia or residual diseases related to prematurity (e.g., bronchopulmonary dysplasia), (3) after general anesthesia versus pure regional anesthesia, and (4) after general anesthesia with soluble versus insoluble inhalation agents. Administration of clonidine epidurally or opioids intravenously may also shift the curve upward.

it may just be a marker of a general medical condition in a previous preterm infant.

Prematurity-Associated Comorbidity

Today, survival of extremely low-birth-weight infants (gestational age 24 to 28 weeks) is quite common. Bronchopulmonary dysplasia, retinopathy of prematurity, hydrocephalus, seizures, and cerebral palsy occur frequently in extremely low-birth-weight survivors. For a given PCA, the risk of postoperative apnea is greater in formerly premature infants with residual diseases of prematurity.

Surgical Procedure

While apnea can occur even after anesthesia without surgery (e.g., after MRI), surgical factors appear to play a role in the pathogenesis. The risk of postoperative apnea is increased after major surgical procedures (e.g., laparotomy). The central nervous system alkalosis associated with the chronic vomiting of pyloric stenosis likely exacerbates the increased risk of apnea after pyloromyotomy. Premature infants undergoing cryotherapy for retinopathy of prematurity under topical anesthesia or inguinal hernia repair under spinal anesthesia may experience postoperative apnea.

Anesthetic Management

Postoperative apnea may occur after general anesthesia, regional anesthesia, or combined general and regional anesthesia. A randomized trial evaluating the incidence of apnea in cases of neonatal inguinal herniorrhaphy noted that apnea within 30 minutes of postanesthesia care unit (PACU) arrival was less frequent after spinal anesthetics than general anesthetics. However, spinal anesthesia has an appreciable failure rate (19%), requiring the use of sedation or conversion to general anesthesia to complete the hernia repair. The incidence of postoperative apnea after regional anesthesia plus sedation approached, but did not reach, the general anesthesia incidence. Supplementation with mask sevoflurane may have less apneic potential than IV sedatives. Additionally apnea episodes after spinal anesthetics were associated with less hypoxemia and were less likely to require intervention greater than tactile stimulation. The use of muscle relaxants or intubation as part of the general anesthetic regimen does not appear to alter the incidence of postoperative apnea.

Of note, a history of apnea of prematurity is *not* predictive of postoperative apnea. Formerly premature infants with no history of apnea can develop postoperative apnea. Conversely, formerly premature infants with a history of apnea can undergo anesthesia and surgery without developing postoperative apnea. Sleep studies with pneumocardiography to document the presence or absence of apnea are often performed on premature infants to help determine whether the baby needs at-home monitoring. However, a normal sleep study (no apnea) before surgery does not guarantee that the baby will not develop postoperative apnea.

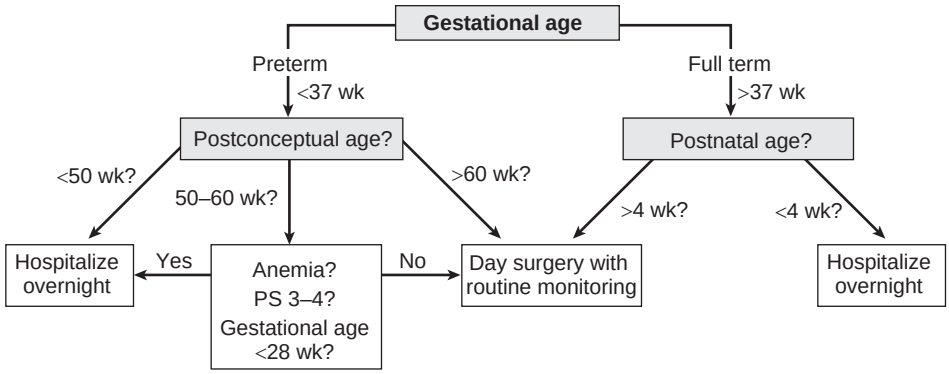

Fig. 202.3 Possible day surgery algorithm. If the infant is full term and younger than 4 weeks, hospital admission for overnight monitoring is planned. If a term infant is older than 4 weeks, day surgery may be performed. If an infant was born prematurely, is older than 50 weeks of postconceptual age, and there is no history of anemia or significant comorbidities, ambulatory surgery is planned. If the infant was born prematurely and is older than 60 weeks of postconceptual age, regardless of anemia or comorbidities, day surgery is planned. All infants born prematurely and younger than 50 weeks of postconceptual age are admitted to the hospital for overnight monitoring. *PS,* Physical status.

Implications

Postoperative apnea can be life threatening. Cardiopulmonary arrest and death have been reported after postoperative apnea. The relationship between postoperative apnea and sudden infant death syndrome is unknown. Postoperative apnea is characterized by its variable onset and offset in relation to emergence from anesthesia. Postoperative apnea begins in the PACU in about two-thirds of affected infants. In the remaining infants, it begins between 2 and 12 hours after surgery. Usually it is characterized by multiple events of variable duration that can continue for days after surgery. Apneic episodes are mostly self-limited. Occasionally, apneic infants require manual stimulation, such as flicking the soles of the feet, to restore ventilation. Sometimes they require bag and mask ventilation. Rarely, cardiopulmonary resuscitation must be instituted to revive the patient. A recent study including over 700 infants demonstrated an incidence of 6.1% in prematurely born and 0.3% in full-term infants. Regional anesthesia reduced the risk of early postoperative apnea (first 30 minutes in the PACU) compared with general anesthesia. There was no difference in apnea later in the PACU or in the ward between regional and general anesthesia. Life-threatening apnea can occur either in the PACU or in the ward several hours later from both techniques.

MANAGEMENT

The anesthetic management of young infants at risk for apnea includes preoperative, intraoperative, and postoperative considerations.

Preoperative Considerations

Nonemergency surgery should be postponed based on the PCA, because the risk of postoperative apnea decreases sharply between 40 and 50 weeks of PCA and then gradually decreases until 70 weeks of PCA. The risk for postoperative apnea is minimized by delaying nonemergency surgery until the infant is at least 50 weeks of PCA. Elective surgery in full-term infants should be postponed until the infant is at least 4 weeks old.

A thorough preoperative assessment should focus on neurologic and respiratory comorbidities because sequelae of prematurity are known to increase the risk of apnea. Additionally, it may be helpful to assess serum hematocrit before anesthesia.

Limitations for same-day surgery should be set. An algorithm is used to determine which infants must be monitored for postoperative apnea in the hospital overnight (Fig. 202.3).

Intraoperative Considerations

General inhalation anesthesia, spinal anesthesia, caudal epidural anesthesia, or combined general and regional anesthesia may be administered to infants at risk for postoperative apnea.

To decrease the incidence of postoperative apnea with general inhalation anesthesia, caffeine citrate (20 mg/kg intravenously) should be administered intraoperatively shortly after anesthesia induction. Caffeine reduces the incidence of apnea and severity of oxygen desaturation with apnea. Although postoperative apnea may occur even if caffeine has been administered (caffeine's effectiveness has been questioned), the risk-benefit ratio favors administration; caffeine has few side effects and has an excellent safety profile.

Regional anesthesia (subarachnoid or caudal epidural) may be suitable for lower extremity or inguinal surgery, especially for infants with chronic lung disease (e.g., bronchopulmonary dysplasia, tracheomalacia, subglottic stenosis). Subarachnoid block can be done in sitting position, using 0.6 to 1 mg/kg of isobaric or hyperbaric bupivacaine through a 22-gauge, 1.5-inch spinal needle. The duration of spinal blockade is 60 minutes and can be increased to 90 minutes with epinephrine admixed with the bupivacaine. Infants may not remain immobile in the upper extremities or trunk, or they may cry if they are hungry or anesthesia is incomplete. Supplemental intravenous sedation or sevoflurane 1% by facemask improves compliance, although intravenous sedation increases the risk of postoperative apnea whereas sevoflurane by mask does not increase the risk of apnea. Surgical procedures are often difficult in these infants and may take longer than expected, making spinal anesthesia less advantageous than caudal epidural or general anesthesia. Combined spinal caudal epidural anesthesia can be performed to increase the duration of regional anesthesia. The spinal anesthetic is performed first to provide anesthesia for inserting the epidural by the caudal route. Ultrasound is employed to identify the tip of catheter as it is threaded to L1. Bupivacaine 0.25% can be infused through the epidural catheter to maintain anesthesia if the surgical procedure extends beyond 60 minutes. Caudal epidural clonidine should be avoided in premature infants and in term infants less than 4 weeks of age because it may cause respiratory depression.

Postoperative Considerations

Cardiorespiratory monitoring is the most important postoperative treatment for infants at risk of postoperative apnea. Nurses must be familiar with how to respond to the cardiorespiratory alarm, including recognition of apnea in young infants, and how to treat apnea, from manual stimulation to cardiopulmonary resuscitation. The infant should be monitored in a location where a nurse will hear the cardiorespiratory alarm. Visual confirmation of breathing or apnea is important, because false-positive alarms are frequent. Cardiorespiratory monitors that employ impedance technology to detect respiratory rate and heart rate are sensitive and easily applied. These monitors have alarms for high and low heart and respiratory rates, as well as for apnea duration. For young infants, the apnea alarm is set to 15 seconds, and the low heart rate alarm is set to 80 beats per minute (relative bradycardia for young infants).

Postoperative pain control is often reliant upon local anesthetics and acetaminophen. Continuous caudal epidural catheters with chloroprocaine allow for excellent analgesia without systemic opioid exposure and with minimal risk of local anesthetic toxicity. Alternatively, opioid and local anesthetic continuous infusions are effective but carry some risk of systemic absorption of opioids, especially lipophilic agents.

Even though continuous caudal epidural analgesia with opioids is the mainstay of analgesic therapy, there is a lack of properly controlled, randomized clinical trials that have evaluated postoperative regional analgesia versus more conventional (intravenous) analgesia strategies.

PREVENTION

Despite medical advances during the past 20 years, the incidence and risk factors of postoperative apnea have not changed significantly. The following recommendations can reduce the risk of postoperative apnea:

- Delay elective surgery until 50 to 60 weeks of PCA.
- Use general endotracheal inhalational anesthesia and administer caffeine citrate (20 mg/kg intravenously) after anesthetic induction.
- Use regional anesthesia for groin and lower extremity surgery: spinal block or combined spinal epidural block. If the block is incomplete or fails, adding sevoflurane by mask is more preferable than intravenous ketamine, midazolam, or opioids.
- Decrease the dose of opioids, or avoid opioids altogether and use intravenous acetaminophen.

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The authors wish to thank Dr. Liana Hosu for her contribution to the previous edition of this chapter.

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Postoperative Nausea and Vomiting: Pediatric

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Case Synopsis

A 10-year-old girl with a history of motion sickness is scheduled for adenotonsillectomy. This will be her third surgery under general anesthesia. She had multiple episodes of postoperative nausea and vomiting (PONV) after the two previous procedures (dental rehabilitation and correction of strabismus), despite receiving antiemetic prophylaxis intraoperatively. After the strabismus surgery, she was hospitalized with dehydration caused by refractory postoperative emesis. Her mother gives a similar history of severe PONV after gynecologic surgery. Both the patient and her parents are extremely anxious and ask what can be done to avoid a similar experience.

PROBLEM ANALYSIS

Recognition

Although *postoperative nausea and vomiting* (PONV) has been called the big "little problem" in anesthesia, it decreases patient satisfaction with anesthetic care, delays hospital discharge, and may increase costs resulting from unplanned hospital admission. In adults, postoperative nausea occurs in 50%, vomiting in 30%, and postdischarge nausea and vomiting (PDNV) in 37%, with rates as high as 80% for various subsets. Many younger pediatric patients are unable to convey the subjective feeling but indicate that they have the subjective symptoms of nausea. The rate of postoperative vomiting (POV) is therefore used as an endpoint in pediatric studies. The incidence of POV is higher in children than in adults.

PONV is increasingly used as a quality care marker. A revised set of Consensus Guidelines for PONV management was published in 2014. These are listed in Table 203.1 and have been endorsed by many professional anesthesiology associations worldwide. The first recommendation was to assess the individual patient's risk for PONV based on defined risk factors, followed by the use of various strategies to reduce baseline risks. The guidelines stated that the administration of prophylactic antiemetics for adults and children should be based on the estimated risk for the individual patient, with no prophylaxis for those at lowest risk, one- to two-drug prophylaxis for moderate risk, and multimodal combination therapy (≥2 interventions) for subjects at the highest risk. The recommendation for rescue treatment for established PONV differed for those who had not received prophylaxis versus subjects with a failure of antiemetic prophylaxis. In the latter case, it was recommended that a drug from a class other than that used for prophylaxis be used for rescue therapy. Finally, the guidelines advocated steps to facilitate wider implementation of these recommendations.

Risk Assessment

Although many factors are associated with increased PONV, the Consensus Guidelines focused on those shown to be independent in large cohort studies and not the confounding factors. For example, increased PONV in adults undergoing abdominal surgery may reflect the effect of confounding issues, such as duration of surgery or increased opioid use. Different independent risk factors are used in pediatric and adult risk stratification scores. The most important independent risk factors in adults are female gender, previous history of PONV/motion sickness, postoperative opioid administration, and nonsmoking status, with each factor increasing the relative risk of PONV by approximately 20%. The independent risk factors in children were (1) duration of surgery longer than 30 minutes; (2) age greater than 3 years; (3) prior POV in the patient, parent, or sibling; and (4) strabismus surgery. If 0, 1, 2, 3, or 4 of these factors were present, the patient's risk for POV was approximately 9%, 10%, 30%, 55%, and 70%, respectively. This score by Eberhart and colleagues was validated in another pediatric patient population.

A new, simpler, 6-point pediatric vomiting in the postoperative period (VPOP) score was obtained from a study of 2392 children

TABLE 203.1 Consensus Guidelines for the Management of Postoperative Nausea and Vomiting

Guideline No.	Title
1	Identify patient's risk for PONV
2	Reduce baseline risk factors for PONV
3	Administer PONV prophylaxis using 1–2 interventions in adults at moderate risk for PONV
4	Administer prophylactic therapy with combination (≥2) interventions/multimodal therapy in patients at high risk for PONV
5	Administer prophylactic antiemetic therapy to children at increased risk for POV: as in adults, use of combination therapy is most effective
6	Provide antiemetic treatment to patients with PONV who did not receive prophylaxis or in whom prophylaxis failed
7	Ensure PONV prevention and treatment is implemented in the clinical setting
8	Use general multimodal prevention to facilitate implementation of PONV policies

PONV, Postoperative nausea and vomiting.
Data from Gan TJ, Diemunsch P, Habib AS, et al: Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 118(1):85-113, 2014.

TABLE 203.2 Clinical Risk Score for Vomiting in the Postoperative Period: The VPOP Score

	POINT SCORE		
	0	**1**	**2**
Age	Below 3 years	3–6 years *or* >13 years	Between 6 and 13 years
Predisposition to POV Previous POV, motion sickness, or family history of POV	No predisposition	Predisposition present	
Duration of anesthesia >45 minutes	No	Yes	
High-risk surgery (tonsillectomy, tympanoplasty, strabismus)	*Not* high PONV risk procedures	High PONV risk (tonsillectomy, tympanoplasty, strabismus)	
Multiple doses of opioids	No	Yes	

Low risk: Total score of 0–1. *Moderate risk:* Total score of 2–3. *High risk:* Total score of 4–6.
PONV, Postoperative nausea and vomiting; *POV,* postoperative vomiting.
Modified from Bourdaud N, Devys JM, Bientz J, et al: Development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients: the VPOP score. *Pediatr Anesth* 24(9):945-952, 2014.

BOX 203.1 Strategies to Reduce Baseline Risk for Postoperative Nausea and Vomiting

- Use regional anesthesia whenever feasible
- Use propofol for induction and maintenance of general anesthesia
- Adequate patient hydration
- Avoidance of nitrous oxide use
- Avoid use of volatile inhalation anesthetics
- Minimize use of intraoperative and postoperative opioids

Adapted from Gan TJ, Diemunsch P, Habib AS, et al: Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 118(1):85-113, 2014.

and was based on age, predisposition to POV, duration of anesthesia longer than 45 minutes, type of surgery, and use of multiple doses of opioids (Table 203.2). The age-related risk for pediatric POV in children is lowest for those less than 3 years, highest for 6 to 13 years, and intermediate for a group ages 3 to 6 years or greater than 13 years. A predisposition to POV was defined as prior history of POV, motion sickness, or family history of POV. The study also identified tonsillectomy and tympanoplasty in addition to strabismus surgery as independent risk factors. The authors considered patients with a risk score of 0 to 1 as being at low risk, 2 to 3 as moderate, and 4 to 6 as high risk for POV. This new score had a greater area under the receiver operating characteristics curve compared with the earlier score by Eberhart and colleagues, suggesting that the VPOP score could be used to guide management of POV in children.

Patient-Related Factors Not Associated With Increased POV

Preoperative anxiety has not been shown to be associated with increased POV in children. Although adult smokers have lower PONV rates, the effect of secondhand smoking on POV in children is unknown.

MANAGEMENT

Strategies to Reduce Baseline Risks of POV

The Consensus Guidelines recommended the following strategies to reduce baseline risk and incidence of POV (Box 203.1):

1. Avoidance of general anesthesia by the use of regional anesthesia
2. Use of propofol for induction and maintenance of anesthesia
3. Avoidance of volatile anesthetics
4. Avoidance of nitrous oxide
5. Minimization of perioperative opioids
6. Adequate hydration

Regional Versus General Anesthesia

Regional anesthesia is associated with less PONV than general anesthesia in both children and adults. In the pediatric patient population, regional anesthesia is usually performed after induction of general anesthesia to reduce patient stress associated with needle insertion. Studies have shown that placing blocks after induction is not associated with more nerve trauma than performing the block in a less-than-cooperative child who has been inadequately sedated. A major benefit of a combined general and regional anesthetic technique is the reduction in perioperative opioid and volatile anesthetic requirements and, consequently, reduced POV.

Propofol Infusions

A number of procedures cannot be supplemented by regional anesthesia, and a pure general anesthetic technique is required. In these cases the use of propofol for induction and maintenance of anesthesia lowers the incidence of POV in the first 6 hours postoperatively. However, single-induction doses of propofol have no effect on POV. Children receiving intraoperative propofol in subhypnotic doses (bolus of 1 mg/kg followed by an infusion at 20 μg/kg/min) combined with dexamethasone or tropisetron during tonsillectomy procedures had less emesis than those receiving dexamethasone or tropisetron alone.

Avoidance of Nitrous Oxide

The combination of propofol and air/oxygen (total intravenous [IV] anesthesia) has additive effects, reducing PONV risk by approximately 25% in adults. Nitrous oxide has little impact when the baseline risk for PONV is low, but avoidance of nitrous oxide is associated with decreased POV in high-risk adults and children.

Minimization of Opioids

Baseline risk for POV can also be reduced by administering supplemental nonopioid analgesics, which have morphine-sparing effects. These include nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, α_2-agonists such as clonidine and dexmedetomidine, acetaminophen, and ketamine. A systematic review of 12 trials with 928 children showed less emesis in a group receiving NSAIDs compared with placebo (odds ratio 0.49, 95% confidence interval 0.29–0.83).

Hydration

Adequate hydration is a simple and inexpensive strategy to reduce emesis. A liberal IV fluid regimen (30 mL/kg) is associated with less

TABLE 203.3 Antiemetic Doses for Postoperative Vomiting Prophylaxis in Children

Drug	Dose	Maximum
Dexamethasone	150 μg/kg	5 mg
Dimenhydrinate	0.5 mg/kg	25 mg
Droperidol[a]	10–15 μg/kg	1.25 mg
5-HT_3 Antagonists		
• Ondansetron	50–100 μg/kg	4 mg
• Tropisetron	0.1 mg/kg	2 mg
• Granisetron	40 μg/kg	0.6 mg
• Dolasetron	350 μg/kg	12.5 mg

[a]Food and Drug Administration black box warning calls for 12-lead electrocardiogram (ECG) to rule out prolonged QT syndrome before administering droperidol and continuous ECG monitoring for at least 2–3 hours after administering droperidol.
Adapted from Gan TJ, Diemunsch P, Habib AS, et al: Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 118(1):85-113, 2014.

emesis than the standard 10 mL/kg therapy in children undergoing short procedures with minimal blood loss.

Strategies That Have Not Been Shown to Work

Routine gastric decompression and limiting oral intake after surgery are ineffective in reducing pediatric POV. A strategy of intraoperative delivery of recorded therapeutic suggestions via headphones also did not work. Other strategies that were initially thought to be effective but were later shown to have minimal or no effects include supplemental oxygen and minimization of neostigmine.

Prophylactic Antiemetic Therapy in Children at Increased Risk for POV

Pediatric POV rates are approximately double that in adults, indicating a greater need for POV prophylaxis in this population. Effective POV prophylaxis can be achieved with 5-HT_3 antagonists, steroids, antihistamines, anticholinergic drugs, and dopamine antagonists (Table 203.3).

Ondansetron and Other 5-HT_3 Antagonists

Systematic reviews show that the most effective antiemetics for pediatric POV prophylaxis are 5-HT_3 antagonists and dexamethasone. Ondansetron was more effective than metoclopramide in 557 children undergoing adenotonsillectomy. Both the 5-HT_3 antagonists and perphenazine are effective compared with placebo in children, with superior efficacy shown by a 5-HT_3 antagonist (ondansetron or granisetron). A Bayesian meta-analysis of single and combination antiemetic drugs noted that single-drug prophylaxis with the 5-HT_3 receptor antagonists or dexamethasone would result in a minimum relative risk reduction (RRR) of 50% to 60% and the combination would have an RRR of at least 80%, in contrast to 40% with droperidol.

Generic ondansetron is the most widely used antiemetic because it has similar efficacy and side-effect profile, greater availability, and lower cost than other first-generation 5-HT_3 antagonists such as granisetron, dolasetron, and tropisetron. Confirmation of the findings of greater efficacy of the second-generation 5-HT_3 antagonists such as palonosetron and ramosetron is required in different pediatric patient populations to justify replacing ondansetron as the first choice for POV prophylaxis.

Data to base a recommendation on the timing of administration of these drugs in children are sparse. There were no differences in POV in children who receive tropisetron immediately after induction or at the end of surgery during short tonsillectomy procedures.

Dexamethasone

Corticosteroids are very effective in prevention of POV in children, with administration at induction recommended rather than toward the end of anesthesia. Steroids may act by depleting tryptophan, a serotonin precursor. Other suggested mechanisms include the reduced gut serotonin release and increased serotonin receptor sensitization to other antagonists. Most studies of POV prophylaxis with steroids have been performed with dexamethasone 0.5 mg/kg, but methylprednisolone 2.5 mg/kg has been shown to be noninferior. However, the dose-effect relationship of dexamethasone in POV prophylaxis is unclear, with one study failing to show differences in POV rates or secondary outcomes in children receiving 0.0625, 0.125, 0.25, 0.5, or 1 mg/kg during adenotonsillectomy procedures, and another study suggesting that the best response was achieved with 0.5 mg/kg compared with 0.05 and 0.15 mg/kg doses. An updated Cochrane review of steroids for tonsillectomy patients stated that "the question of appropriate dosing remains unanswered and final recommendations must await randomized dose-control trials."

The effect of steroids on posttonsillectomy bleeding rates is controversial, and a recent systematic review concluded that the overall risk of bleeding was not increased, but reoperation rates increased with dexamethasone. The American Academy of Otolaryngology–Head and Neck Surgery concluded that the preponderance of benefits justified the use of a single dose of dexamethasone in children undergoing tonsillectomy.

Older Drugs

A number of older drugs are also effective in POV management (Table 203.4). These include antihistamines (dimenhydrinate), dopamine antagonists such as butyrophenones (e.g., droperidol, haloperidol), phenothiazines (promethazine, prochlorperazine, and perphenazine), benzamides (metoclopramide), and anticholinergics (scopolamine). There are few dose-ranging data and limited evidence for the efficacy of these drugs. In addition, the 5-HT_3 antagonists are more effective and associated with a lower side-effect profile. Concerns about the effect of droperidol on cardiac rhythms have led to a black box warning that may not be entirely justified, as similar effects on cardiac rhythm are seen with other antiemetics, including the antiserotonin group of drugs. Side effects for metoclopramide and phenothiazines include extrapyramidal symptoms (see Table 203.4). With the greater availability and efficacy of lower-priced generic ondansetron and the lower side-effect profile, the use of the older drugs is now limited to second-line options as rescue therapy when other drugs have failed or when 5-HT_3 antagonists are contraindicated.

Nonpharmacologic Therapy

Two meta-analyses show that both acupuncture and acustimulation are effective in reducing POV in children, with no differences between the two methods.

Combination Therapy

Prophylaxis with drugs acting at different receptor sites may be more effective, even if this is an additive and not a synergistic effect. Although low-risk patients may not require prophylactic antiemetics, those with a moderate to high risk of POV and children with a potential for medical sequelae from emesis (e.g., wound dehiscence, wired jaws) should receive prophylactic combination therapy with two or three antiemetics from different classes. The prophylactic use of a combination of dexamethasone and ondansetron is strongly recommended in most pediatric patients at highest risk for POV unless there are contraindications.

TABLE 203.4 Older Drugs to Be Used as a Second-Line Option[a]

Drug	Dose (mg/kg)	Maximum Single Dose (mg)	Side Effects
Diphenhydramine	1.0	25	Sedation, dry mouth, blurred vision, urinary retention
Metoclopramide	0.25[b]	10	Extrapyramidal reactions more common in children; not recommended below age 1 year
Phenothiazines			Sedation, hypotension (especially in hypovolemic patients), extrapyramidal reactions
Perphenazine	0.07	2.0	
Prochlorperazine[c]	0.1–0.2	2.5	
Promethazine[d]	0.25–0.5	25	Promethazine is contraindicated in children below 2 years; it is also an IV irritant with a risk for severe tissue injury
Scopolamine (IM, IV, SC)[e]	0.006	0.3	Drowsiness, dry mouth, visual disturbances, dizziness

[a]Dose-ranging and efficacy studies are sparse for these older drugs. These drugs may be used for rescue therapy after failure of 5-HT3 antagonists and are usually not used for routine prophylaxis.
[b]Although higher doses may be more effective, there is a higher incidence of side effects.
[c]Prochlorperazine is not recommended for children under the age of 2 years or less than 10 kg body weight.
[d]Promethazine has two black box warnings by the Food and Drug Administration: (1) Not to be used below 2 years because of the potential risks of fatal respiratory depression, and (2) severe tissue injury and gangrene with perivascular extravasation or unintentional intraarterial injection. The preferred route of administration is deep intramuscular injection, and subcutaneous injection is contraindicated.
[e]Scopolamine patches should not be divided. The patch should not be used in children less than 12 years old.

Scopolamine

The incidence of complications with scopolamine patches may be higher in children than adults. It is difficult to control the dose received when a patch is divided, as the distribution of the drug in the patch may not be uniform. In addition, continued absorption is possible even after patch removal. These concerns have led many anesthesiologists to avoid using scopolamine patches in younger children.

Rescue Therapy for Those Who Have Received No Prophylaxis or When Prophylaxis Has Failed

Some low-risk patients who have received no prophylaxis and higher-risk patients who received prophylactic therapy may still experience POV. Rescue therapy should be initiated, preferably with a 5-HT_3 antagonist if no prophylaxis was used. However, in patients where antiemetic prophylaxis failed to prevent POV, rescue therapy should be with a drug from a different class of antiemetics. This may require the administration of older drugs such as metoclopramide, diphenhydramine, or a phenothiazine, recognizing that this may be associated with sedation and a longer postanesthesia care unit (PACU) stay. If rescue therapy is needed more than 6 hours after the previous dose, medication given for prophylaxis may be repeated (except dexamethasone or transdermal scopolamine). Although these recommendations are based on adult data, it is reasonable to extend this approach to children.

Despite the large volume of literature on this topic, considerable gaps in knowledge about POV management remain in the pediatric population. A research agenda should focus on providing evidence to support clinical practices. An important unanswered question is a recommendation for rescue therapy after failed prophylaxis with a combination of steroids and ondansetron. Studies are also required to determine the role of NK_1 antagonists for both prophylaxis and rescue therapy in children, as pediatric POV data on this class of drugs are unavailable.

Anesthetic Plan for Our Patient

Based on the information presented, we can construct an anesthetic plan for the preoperative, intraoperative, and postoperative phases. The pediatric VPOP score for this child would be 6, indicating she is at highest risk. Given the concerns, it is important to communicate with the family before the date of surgery to establish rapport by thorough discussion and planning. The conversation should emphasize the importance of adhering to a clear liquid regimen until 2 hours before the procedure to avoid dehydration. The patient and family should also be educated about the increased risks of POV following postoperative opioid analgesia management, as well as the need to titrate drugs to achieve a balance between pain and POV based on the individual patient's comfort with each condition.

Although preoperative anxiety is not an independent factor associated with POV in children, reducing it still provides for a better anesthetic experience. There are systematic reviews suggesting midazolam is beneficial in reducing both anxiety and PONV in adults. Although there are limited studies of midazolam and POV in children, the judicious use of this drug in the preoperative period may be beneficial. This may be given intravenously if vascular access is able to be established before induction or orally if IV access is assessed to be difficult or the patient is uncooperative. The added advantage of having the IV line placed while the child is awake is that it will permit induction with propofol and the avoidance of an inhalation induction with volatile anesthetic agents and nitrous oxide.

A propofol infusion should be used to maintain anesthesia throughout the procedure, and nitrous oxide should be avoided at all times. These steps will further decrease the risk of POV.

Tracheal intubation may be preceded by laryngotracheal application of lidocaine to reduce tracheal stimulation and allow lower opioid use. Steroids should be administered shortly after induction; and IV acetaminophen, NSAIDs known not to increase posttonsillar bleeding (e.g., diclofenac), and dexmedetomidine may be given to minimize opioid requirements. During the procedure, IV fluids should be provided liberally, and ondansetron should be given. The anesthesiologist should consider the use of acustimulation at the P6 acupoint.

Experienced PACU nurses have often stated that frequent and rapid changes in position (e.g., from supine to sitting upright to walking) in children who have received opioids increase the likelihood of PONV in the immediate postoperative period. Although there may not be data from randomized trials to confirm these impressions, there is little to be lost by gentle handling and the avoidance of rapid positional changes. In addition, the insistence that patients take fluids by mouth before being discharged from the day surgery center may increase the likelihood of PONV. It may be useful to continue IV fluid infusions until just before discharge. If these measures fail, rescue treatment will be required from a class other than steroids and antiserotonin drugs. Parents should also be informed that their child may have PDNV, often on the ride home. It may be useful to provide the family with a second dose of ondansetron (perhaps in the oral disintegrating tablet preparation) to be given 6 hours after the first dose.

Best practice in managing pediatric POV calls for a multimodal approach, but additional research is needed to resolve this issue.

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