

through the caudal needle while palpating the skin overlying the sacrum. If no midline bulge is detected, the needle is probably positioned correctly. In contrast, if a midline bulge is detected during saline injection, the needle is positioned incorrectly.

After ensuring correct needle position and before injection of the therapeutic dose of caudal anesthetic, aspiration should be performed and a test dose administered because, as in lumbar epidural anesthesia, a vein or the subarachnoid space can be entered unintentionally.

## Complications

The physiologic effects of neuraxial blocks may be misinterpreted as complications; however, clear distinction should be made between the physiologic effects of the neuraxial technique and complications, which imply some harm to the patient.<sup>320</sup> The material risks associated with neuraxial anesthesia must be intimately understood and respected because catastrophic injury is not unknown and serves to remind us that a person's nervous system is at the other end of the needle.<sup>321</sup>

### NEUROLOGIC

Serious neurologic complications associated with neuraxial anesthesia are rare. As such, prohibitively large numbers of patients are required for study to estimate the frequency of these events. The true incidence of most neurologic injury after neuraxial anesthesia is unknown with published accounts of neurologic complications invariably influenced by the differing identification and reporting processes. The ASRA comprehensively addresses this important topic in their updated Practice Advisory on Neurologic Complications.<sup>76</sup>

#### Paraplegia

The frequency of paraplegia related to neuraxial anesthesia is reported to be approximately 0.1/10,000,<sup>322,323</sup> and the mechanism of such a severe injury is likely multifactorial and difficult to identify for certain.<sup>324</sup> Although injury resulting from direct needle trauma to the spinal cord<sup>325-329</sup> may be self-evident, historical cases highlight the fundamental danger that accompanies the injection of a foreign substance into the CSF. The highly publicized cases of Woolley and Roe, two healthy, middle-aged men who became paraplegic after spinal anesthesia by the same anesthesiologist using the same drug on the same day for minor surgery at the same hospital in the United Kingdom in 1947, arguably set back the practice of spinal anesthesia for decades despite evidence that contamination by the descaling liquid used to cleanse the procedure tray had most likely been responsible.<sup>4</sup> Another example of catastrophic injury related to intrathecal injectate was the chloroprocaine neurotoxicity experience in the early 1980s, during which several patients developed adhesive arachnoiditis, cauda equina syndrome, or permanent paresis thought to be related to a combination of low pH and the antioxidant sodium bisulfite preservative used in early (and discontinued) preparations of the short-acting ester local anesthetic chloroprocaine.<sup>136-139,330</sup>

Profound hypotension or ischemia of the spinal cord can be important contributing factors in cases of paraplegia associated with neuraxial anesthesia. Anterior spinal artery syndrome, characterized by painless loss of motor and sensory function, is associated with anterior cord ischemia or infarction with sparing of proprioception, which is carried by the posterior column. The anterior cord is believed to be especially vulnerable to ischemic insult because of its single and tenuous source of arterial blood supply (the artery of Adamkiewicz). Ischemia caused by any one or a combination of profound hypotension, mechanical obstruction, vasculopathy, or hemorrhage can contribute to irreversible anterior cord damage.<sup>331-333</sup>

#### Cauda Equina Syndrome

The rate of cauda equina syndrome is approximately 0.1/10,000 and invariably results in permanent neurologic deficit.<sup>322</sup> The lumbosacral roots of the spinal cord may be particularly vulnerable to direct exposure to large doses of local anesthetic, whether it is administered as a single injection of relatively highly concentrated local anesthetic (e.g., 5% lidocaine)<sup>334</sup> or prolonged exposure to a local anesthetic through a continuous catheter.<sup>5,335,336</sup> The US Food and Drug Administration withdrew approval for spinal catheters smaller than 24-g in size in 1992 because of concerns about a perceived association between the small-bore catheters and the development of cauda equina syndrome.<sup>337</sup> Although small-bore catheters can reduce the risk of headache, they can predispose to pooling of local anesthetic around the lumbosacral nerve roots, possibly because of slow injectate flow through the fine-bore catheter, thereby exposing them to high concentrations of local anesthetic. However, small-bore spinal catheters are being used effectively in Europe, and they are beginning to reappear in the United States, although it has taken nearly 15 years for them to emerge from the regulatory cloud of the early 1990s.<sup>338</sup> Another risk factor for cauda equine syndrome may be spinal stenosis wherein local anesthetic distribution may be limited, thus exposing the cauda equine to higher concentrations of local anesthetic.

#### Epidural Hematoma

Bleeding within the vertebral canal can cause ischemic compression of the spinal cord and lead to permanent neurologic deficit if not recognized and evacuated expeditiously. Many risk factors have been associated with the development of an epidural hematoma, including difficult or traumatic needle or catheter insertion,<sup>339</sup> coagulopathy, elderly age, and female gender.<sup>340</sup> Radicular back pain, prolonged blockade longer than the expected duration of the neuraxial technique, and bladder or bowel dysfunction are features commonly associated with a space-occupying lesion within the vertebral canal and should prompt magnetic resonance imaging on an urgent basis. Before the recently published United Kingdom National Health Service (NHS) audit, the largest contemporary studies reported rates of epidural hematoma of less than 0.06/10,000 after spinal anesthesia, whereas the reported rates of epidural hematoma after epidural blockade in the audit were as much as 10-fold higher.<sup>294,341-345</sup> The United Kingdom NHS audit arguably provides the

most accurate rates of neurologic complications associated with neuraxial anesthesia in contemporary practice. This unique prospective nationwide audit found five cases of epidural hematoma among 707,455 neuraxial techniques (0.07/10,000), all of which occurred among 97,925 perioperative epidural techniques (0.5/10,000) performed over the course of 1 year.<sup>323</sup>

### Nerve Injury

In 1955, Vandam and Dripps<sup>346</sup> were the first to capture data prospectively on nerve injury from more than 10,000 patients who underwent spinal anesthesia. No severe neurologic injuries occurred in this population. In 1969, Dawkins<sup>347</sup> published the classic review of neurologic complications after 32,718 epidural anesthetics and reported the frequency of transient and permanent nerve injury to be 0.1% and 0.02%, respectively. Despite interim advances in practice and research methodology, some of the largest contemporary studies available<sup>341,344,348-350</sup> suggest that the rate of neurologic injury related to neuraxial anesthesia is mostly unchanged compared with that reported nearly a half century ago. Most notable from these contemporary data are that epidural (including CSE) anesthesia is likely associated with a more frequent rate of radiculopathy or peripheral neuropathy compared with spinal anesthesia,<sup>322</sup> and that neuraxial anesthesia performed in adults for the purposes of perioperative anesthesia or analgesia is apparently associated with a higher likelihood of neurologic complications compared with that performed in the obstetric, pediatric, and chronic pain settings.<sup>323,341,342,351,352</sup> The rate of permanent nerve injury after neuraxial blockade is even more difficult to determine because methods of investigation and diagnosis, determination of causation, and reporting of outcomes are highly variable within the literature.<sup>353</sup> The United Kingdom NHS audit found the overall rate of permanent nerve injury to be 7 in 707,455 or 0.1/10,000,<sup>323</sup> which is remarkably similar to studies published a half century earlier by Dawkins. Three cases of nerve injury occurred among 293,050 epidurals (0.1/10,000), 3 among 324,950 spinal anesthetics (0.1/10,000), and 1 among 41,875 CSEs (0.2/10,000), mostly in young, healthy patients. Procedure-related risk factors traditionally associated with nerve injury after neuraxial anesthesia in the perioperative setting include radicular pain or paresis occurring during the procedure.<sup>321,344,354,355</sup>

### Arachnoiditis

Arachnoiditis, an inflammatory reaction of the meninges, is rare after neuraxial anesthesia and its true incidence is unknown. The potential contributory effects of chlorhexidine disinfectant solution has led to the recommendation that chlorhexidine must dry fully before needle puncture,<sup>76</sup> and measures must also be taken to avoid splashing of any chlorhexidine solution onto the needles or syringes, and especially contamination of the injectate drugs.

### Post-Dural Puncture Headache

A relatively common complication of neuraxial anesthesia is post-dural puncture headache. As the name implies, post-dural puncture headache is believed to result from unintentional or intentional puncture of the dura membrane in the setting of neuraxial anesthesia or after

myelography and diagnostic lumbar puncture. There are two possible explanations for the cause of the headache, neither of which has ever been proven. First, the loss of CSF through the dura is proposed to cause traction on pain-sensitive intracranial structures as the brain loses support and sags. Alternatively, the loss of CSF initiates compensatory yet painful intracerebral vasodilation to offset the reduction in intracranial pressure.<sup>356</sup> The characteristic feature of a post-dural puncture headache is a frontal or occipital headache that worsens with the upright or seated posture and is relieved by lying supine. Associated symptoms can include nausea, vomiting, neck pain, dizziness, tinnitus, diplopia, hearing loss, cortical blindness, cranial nerve palsies, and even seizures. In more than 90% of cases, the onset of characteristic post-dural puncture headache symptoms will begin within 3 days of the procedure,<sup>357</sup> and 66% start within the first 48 hours.<sup>358</sup> Spontaneous resolution usually occurs within 7 days in the majority (72%) of cases, whereas 87% of cases resolve by 6 months.<sup>359</sup>

Post-dural puncture headache can occur in the setting of either spinal or epidural anesthesia, the former associated with certain modifiable risk factors during intentional dural puncture and the latter associated with unintentional puncture of the dura by advancing the Tuohy needle. Orienting a needle bevel parallel with the axis of the spine, such that the longitudinal fibers of the dura would more likely be separated than cut, results in a lower incidence of postspinal puncture headache.<sup>360</sup> This clinical observation is supported by laboratory investigations<sup>361</sup> showing that simulated spinal puncture with cone-shaped (pencil-point) spinal needle tips produces slower transdural loss of fluid than a similar puncture with cutting-tipped needles. Indeed meta-analysis has confirmed that noncutting needle tip designs have a lower frequency of post-dural puncture headache than do cutting spinal needle tip designs.<sup>362</sup> Other studies suggest that the collagen layers of the dura are oriented in a multidirectional fashion, not always in a cephalocaudad direction, and are variable in thickness, leading to the suggestion that damage to the longitudinal cells of the arachnoid membrane is more likely to be influenced by the type of bevel and may even be the predominant factor affecting post-dural puncture headache.<sup>9</sup> Reports vary as to whether the incidence of post-dural puncture headache is increased with the CSE technique compared with epidural alone.<sup>363,364</sup>

Aside from the type of needle tip (cutting vs. pencil-point) and the bevel direction, there are additional risk factors common to the performance of both spinal and epidural anesthesia that contribute to the likelihood of developing a post-dural puncture headache. These risk factors are listed in Box 45.2.<sup>365</sup>

Conservative management for post-dural puncture headache includes supine positioning, hydration, caffeine, and oral analgesics. Sumatriptan has also been used with varying effect but is not without side effects.<sup>366,367</sup> Epidural blood patch is the definitive therapy for post-dural puncture headache.<sup>368</sup> This therapy was introduced by Gormley<sup>369</sup>; its safety and efficacy have been well documented, and contemporary practice has validated that a single epidural blood patch continues to have up to a 90% initial improvement rate<sup>370</sup> and persistent resolution of symptoms in 61% to 75% of cases.<sup>371</sup>

Epidural blood patch is ideally performed 24 hours after dural puncture and after the development of classic

## BOX 45.2 Relationships Among Variables and Post–Spinal Puncture Headache

### Factors That Can Increase the Incidence of Headache After Spinal Puncture

- Age: Younger, more frequent
- Sex: Females > males
- Needle size: Larger > smaller
- Needle bevel: Less when the needle bevel is placed in the long axis of the neuraxis
- Pregnancy: More when pregnant
- Dural punctures: More with multiple punctures

### Factors That Do Not Increase the Incidence of Headache After Spinal Puncture

- Insertion and use of catheters for continuous spinal anesthesia
- Timing of ambulation

post–dural puncture headache symptoms. The efficacy of prophylactic epidural blood patching is not supported by evidence.<sup>372,373</sup> By injecting radionuclide-labeled red blood cells epidurally, Szeinfeld and co-workers<sup>374</sup> demonstrated that approximately 15 mL of blood will spread over a mean distance of nine spinal segments, and that the direction of spread was preferentially cephalad relative to the level of blood injection. As a result, these authors recommend inserting the blood patch needle at or caudad to the level of the previous culprit dural puncture. These findings have since been validated by magnetic resonance imaging of epidural blood patch spread.<sup>375</sup> One multinational, multicenter, randomized, blinded trial suggested that 20 mL of blood is a reasonable starting target volume.<sup>376</sup> A second epidural blood patch may be performed 24 to 48 hours after the first in the case of ineffective or incomplete relief of symptoms.

### Transient Neurologic Symptoms

Traditionally associated with lidocaine, TNS have been described after intrathecal administration of every local anesthetic used for spinal anesthesia. TNS, previously known as transient radicular irritation,<sup>377</sup> are usually characterized by bilateral or unilateral pain in the buttocks radiating to the legs or, less commonly, isolated buttock or leg pain. Symptoms occur within 24 hours of the resolution of an otherwise uneventful spinal anesthetic and are not associated with any neurologic deficits or laboratory abnormalities.<sup>378</sup> The pain can range from mild to severe and typically resolves spontaneously in 1 week or less.<sup>379</sup> The likelihood of TNS are highest after intrathecal lidocaine and mepivacaine, and are far less frequent with bupivacaine and other local anesthetics.<sup>147,159,380</sup> The phenomenon is not related to the concentration of lidocaine,<sup>147</sup> the addition of dextrose or epinephrine, or solution osmolarity. The type of needle can influence the likelihood of TNS, with the rate reduced by a double-orifice needle,<sup>381</sup> possibly because single-orifice needles increase the risk of injecting anesthetic caudally in the thecal sac. TNS are not commonly associated with epidural procedures but have occurred with epidural lidocaine and other local anesthetics.<sup>253,382</sup> Finally, TNS occur more commonly in patients who are placed in the lithotomy position for surgery. Nonsteroidal

antiinflammatory drugs are the first line of treatment, but pain can be severe and may even require opioids.

## CARDIOVASCULAR

### Hypotension

Hypotension may be considered a complication of neuraxial blockade if the patient faces harm. Recent guidance has placed more emphasis on avoiding hypotension during neuraxial anesthesia (defined as 20%–30% below baseline) in order to reduce the possibility of spinal cord ischemia or infarction.<sup>76</sup> In the setting of spinal anesthesia, hypotension (defined as systolic blood pressure <90 mm Hg) is more likely to occur with a variety of factors including peak block height greater than or equal to T5, age older than or equal to 40 years, baseline systolic blood pressure less than 120 mm Hg, combined spinal and general anesthesia, spinal puncture at or above the L2-L3 interspace, and the addition of phenylephrine to the local anesthetic.<sup>51</sup> Hypotension (defined as a reduction in mean arterial blood pressure >30%) is independently associated with chronic alcohol consumption, history of hypertension, BMI, and the urgency of surgery.<sup>383</sup> Nausea is a common symptom of hypotension in the setting of neuraxial anesthesia, as are vomiting, dizziness, and dyspnea. Although prevention of hypotension caused by vasodilatation using a prophylactic (“preloading”) infusion of colloid or crystalloid during the performance of the neuraxial block (“coloading”) has been reported,<sup>384</sup> this is no longer recommended as a routine practice.<sup>384</sup>

### Bradycardia

The development of severe bradycardia after spinal anesthesia has long been recognized as an important risk of spinal anesthesia.<sup>385,386</sup> Bradycardia stems from blockade of the thoracic sympathetic fibers (preganglionic cardiac accelerator fibers originating at T1-T5), as well as reflexive slowing of the heart rate as vasodilation reduces the venous return to the right atrium where stretch receptors respond by a compensatory slowing of the heart rate. Factors that may increase the likelihood of exaggerated bradycardia (40–50 beats/min) include baseline heart rate less than 60 beats/min, age younger than 37 years, male gender, non-emergency status,  $\beta$ -adrenergic blockade, and prolonged case duration. Severe bradycardia (<40 beats/min) is associated with a baseline heart rate less than 60 beats/min and male gender.<sup>387</sup>

### Cardiac Arrest (also see Chapter 87)

In a review of closed insurance claims, Caplan and associates<sup>388</sup> identified 14 cases of sudden cardiac arrest in healthy patients receiving spinal anesthesia. The etiology of sudden cardiac arrest after spinal anesthesia is not understood. Whether these catastrophic events represented lack of vigilant monitoring and treatment as opposed to some mysterious physiologic explanation is not known.<sup>389</sup> The latter notwithstanding, it is clear that hypoxemia and oversedation are complicit in the severe bradycardia and asystole that can occur suddenly during well-conducted spinal anesthesia.<sup>390,391</sup> Curiously, these rare events seem to be preferentially associated

with spinal anesthesia rather than epidural techniques. In their inaugural survey of French anesthesiologists, Auroy and colleagues reported the rate of cardiac arrest to be 6.4/10,000 after spinal anesthesia compared with 1/10,000 for all other neuraxial and peripheral regional anesthesia techniques combined.<sup>344</sup> In their larger follow-up survey of all anesthesiologists in France, Auroy and colleagues<sup>350</sup> reported 10 cases of cardiac arrest after 35,439 spinal anesthetics (2.5/10,000) and none after 5561 epidural techniques. Most recently, Cook and colleagues uncovered three cases of cardiovascular collapse among 707,425 neuraxial blocks (0.04/10,000) during their nationwide audit, two of which were during spinal anesthesia and one in the setting of CSE.<sup>323</sup>

## RESPIRATORY

Neuraxial opioids are commonly added to local anesthetic solutions to improve the quality and duration of neuraxial anesthesia and analgesia. The risk of respiratory depression associated with neuraxial opioids is dose dependent, with a reported frequency that approaches 3% after the administration of 0.8 mg of intrathecal morphine.<sup>392</sup> Respiratory depression may stem from rostral spread of opioids within the CSF to the chemosensitive respiratory centers in the brainstem.<sup>65</sup> With lipophilic anesthetics, respiratory depression is generally an early phenomenon occurring within the first 30 minutes; respiratory depression has never been described more than 2 hours after the administration of intrathecal fentanyl or sufentanil.<sup>225</sup> With intrathecal morphine, there is a risk of late respiratory depression, occurring as much as 24 hours after injection. Respiratory monitoring for the first 24 hours after the administration of intrathecal morphine is therefore advisable. Patients with sleep apnea can be especially sensitive to the potent respiratory-depressant effects of opioid medications and although definitive safety data evidence is lacking, the decision to administer neuraxial opioids to these patients is made with considerable caution.<sup>393,394</sup> Older patients also have a higher risk of respiratory depression, and the dose of neuraxial opioids should be reduced in this population (see [Chapter 65](#)). Coadministration of systemic sedatives also increases this risk.

## INFECTION

Bacterial meningitis and epidural abscess are rare, but potentially catastrophic, infectious complications of all neuraxial techniques. Sources of infection in neuraxial procedures include the equipment, the patient, or the practitioner. Staphylococcal infections arising from the patient's skin are one of the most common epidural-related infections, whereas oral bacteria such as *Streptococcus viridans* are a common cause of infection after spinal anesthesia, underscoring the need for the clinician to wear a facemask when performing neuraxial procedures. Other factors that may increase the likelihood of infection include the presence of a concomitant systemic infection, diabetes, immunocompromised states,<sup>90</sup> and prolonged maintenance of an epidural (or spinal) catheter. Large contemporary studies estimate the rate of serious neuraxial

infection to be less than 0.3/10,000<sup>341,348,350</sup> for spinal anesthesia, whereas infectious complications after epidural techniques may be at least twice as common.<sup>341,348,350,395-397</sup> Obstetric patients are less likely to develop deep infections related to epidural analgesia. The recent United Kingdom NHS audit reported no cases of meningitis and eight cases of epidural abscess after 707,455 neuraxial techniques, five of which occurred among 293,050 epidural techniques, two among 324,950 spinal anesthetics, and one among 47,550 caudal blocks.<sup>323</sup>

In 2017, the ASA and ASRA published a practice advisory regarding infectious complications associated with neuraxial anesthesia,<sup>229</sup> specifically addressing (1) prevention, (2) diagnosis, and (3) management. Previous publications have addressed infectious risks of neuraxial anesthesia in the febrile or infected patient,<sup>90</sup> the immunocompromised patient,<sup>398</sup> and in the setting of chronic pain treatments.<sup>399</sup>

Aseptic meningitis occurred mostly in the early 20th century, likely secondary to chemical contamination and detergents, which are no longer present in modern preservative-free preparations.

## BACKACHE

Back injury is perhaps the most feared complication of neuraxial anesthesia among patients. Evidence indicates that the incidence of back pain after spinal anesthesia is not different from general anesthesia.<sup>400</sup> Indeed, up to 25% of all surgical patients undergoing anesthesia, regardless of anesthetic technique, experience backache, the incidence of which increases to 50% when surgery lasts 4 to 5 hours.<sup>401</sup> There is also no association between epidural analgesia and new-onset back pain up to 6 months postpartum.<sup>402,403</sup> Preexisting back pain does appear to be a risk factor for persistent back pain after neuraxial anesthesia, although the severity of the pain does not appear to be worsened. Other risk factors include immobilization during surgery greater than 2.5 hours, lithotomy position, BMI greater than 32 kg/m<sup>2</sup>, and multiple attempts at block placement.<sup>400</sup>

## NAUSEA AND VOMITING

There are multiple possible mechanisms that contribute to nausea and vomiting in the setting of neuraxial anesthesia, including direct exposure of the chemoreceptive trigger zone in the brain to emetogenic drugs (e.g., opioids), as well as hypotension associated with generalized vasodilation and gastrointestinal hyperperistalsis secondary to unopposed parasympathetic activity (see also [Chapter 80](#)).<sup>404</sup> Although regional anesthesia is often recommended as an alternative to general anesthesia for patients at risk for postoperative nausea and vomiting, there are few studies that have primarily investigated the effects of neuraxial anesthesia on postoperative nausea and vomiting with sufficient statistical power. Factors associated with developing nausea or vomiting after spinal anesthesia include the addition of phenylephrine or epinephrine to the local anesthetic, peak block height greater than or equal to T5, baseline heart rate greater than 60 beats/min,

use of procaine, history of motion sickness, and the development of hypotension during spinal anesthesia. Among the opioids commonly added to intrathecal or epidural local anesthetics, morphine administration has the most frequent risk of nausea or vomiting, whereas fentanyl and sufentanil carry the least frequent risk.<sup>404</sup> Neuraxial opioid-related nausea and vomiting appears to be dose dependent. Using less than 0.1 mg morphine reduces the risk of nausea and vomiting, without compromising the analgesic effect.<sup>225</sup>

## URINARY RETENTION

Urinary retention can occur in as much as one third of patients after neuraxial anesthesia. Local anesthetic blockade of the S2, S3, and S4 nerve roots inhibits urinary function as the detrusor muscle is weakened. Neuraxial opioids can further complicate urinary function by suppressing detrusor contractility and reducing the sensation of urge.<sup>405</sup> Spontaneous return of normal bladder function is expected once the sensory level decreases to below S2-3.<sup>406</sup> Although male gender and age have been (albeit inconsistently) linked to urinary retention after neuraxial anesthesia, the administration of intrathecal morphine is strongly associated with this complication.<sup>405,407,408</sup>

## PRURITUS

Pruritus can be distressing to the patient. It is the most common side effect related to the intrathecal administration of opioids, with rates between 30% and 100%.<sup>225</sup> Pruritus actually occurs more commonly after intrathecal opioid administration than after intravenous opioid administration and is not dependent on the type or dose of opioid administered. Reducing the dose of intrathecal sufentanil from 5 µg to as little as 1.5 µg can reduce the likelihood of pruritus without compromising analgesia when added to hyperbaric bupivacaine for cesarean delivery (see Chapter 62).<sup>409</sup> The mechanism of pruritus is unclear but is likely related to the central opioid receptor activation rather than histamine release because naloxone, naltrexone, or the partial agonist nalbuphine can be used for treatment. Ondansetron and propofol are also useful therapies. Some antiinflammatories have been shown to reduce pruritus (e.g., diclofenac and tenoxicam), while mirtazapine, an antidepressant with 5HT<sub>3</sub> antagonism properties like ondansetron, may also be helpful if administered preoperatively.

## SHIVERING

The rate of shivering related to neuraxial anesthesia is as frequent as 55%.<sup>410</sup> The intensity of shivering is likely related more to epidural anesthesia than spinal.<sup>411</sup> Although there are multiple possible explanations for the difference in shivering intensity, this observation may simply be related to the inability to shiver because of the profound motor block associated with spinal anesthesia compared with epidural techniques. Another explanation may be the relatively cold temperature of the epidural injectate, which can affect the thermosensitive basal sinuses.<sup>410</sup> The addition of neuraxial opioids, specifically fentanyl and meperidine, reduces the

likelihood of shivering.<sup>410</sup> Recommended strategies to prevent shivering after neuraxial anesthesia include prewarming the patient with a forced air warmer for at least 15 minutes and avoiding the administration of cold epidural and intravenous fluids.

## WRONG ROUTE ADMINISTRATION

Wrong route administration refers to the infusion or injection of a drug into the wrong body compartment. In addition to epidural catheter migration or inadvertent intravascular placement (described below), an epidural infusion may be mistakenly connected to an intravascular device. Using less cardiotoxic local anesthetics may reduce the risk of harm if this does occur. Prevention is paramount and devices have been developed to make regional anesthesia and intravenous connections technically incompatible.

## COMPLICATIONS UNIQUE TO EPIDURAL ANESTHESIA

### Intravascular Injection

Epidural anesthesia can produce local anesthetic-induced systemic toxicity (see Chapter 29), primarily through the unintentional administration of drug into an epidural vein. The frequency of vascular puncture with the needle or cannulation with the catheter can reportedly approach 10%, with the highest rates seen in the obstetric population, where these vessels are relatively dilated and more vulnerable to entry.<sup>287,412</sup> The rate of seizures related to epidural anesthesia may be as frequent as 1%.<sup>294,344,350</sup> In obstetrics (see also Chapter 62), the likelihood of intravascular injection is decreased by placing the patient in the lateral (as opposed to the sitting) position during needle and catheter insertion, administering fluid through the epidural needle before catheter insertion, using a single-orifice type rather than a multi-orifice catheter or a wire-embedded polyurethane type compared with polyamide epidural catheter, and advancing the catheter less than 6 cm into the epidural space. The paramedian as opposed to the midline needle approach, and the use of a smaller-gauge epidural needle or catheter, does not reduce the risk of epidural vein cannulation.<sup>287</sup>

One of the most controversial issues related to epidural anesthesia has been the use of an epinephrine-containing test dose.<sup>413</sup> Epinephrine (15 µg) in 3 mL of local anesthetic remains the best pharmacologic method of detecting intravascular placement in nonpregnant adult patients.<sup>304</sup> However, controversy surrounds the use of epinephrine in obstetric patients, in whom uterine blood flow may be decreased by the intravascular injection, thereby putting the fetus at risk, and where the cardiovascular changes occurring in active labor may represent a false-positive response to epinephrine. Although epinephrine may place the fetus at risk in theory,<sup>414</sup> no such case has been described. The epidural epinephrine test dose can be unreliable in patients receiving β-adrenergic blockers<sup>415</sup> or if the test dose is administered during general anesthesia.<sup>416</sup> Because there is no fail-safe method of guaranteeing an extravascular location of an epidural local anesthetic, prevention of systemic toxicity should also involve aspiration of the catheter and incremental administration of the local anesthetic. The onset of

block, quality of the block, and block height are unaffected by administration of the epidural drug in 5-mL fractions.<sup>417</sup>

### Subdural Injection

Blomberg<sup>418</sup> used a fiberoptic technique to demonstrate that the subdural extra-arachnoid space is easily entered in 66% of autopsy attempts in humans. Despite this being an infrequent clinical problem with epidural anesthesia (<1%), it does allow a visual understanding of the subdural complications of epidural anesthesia.<sup>419</sup> This space, unlike the epidural space, also extends intracranially. When an epidural block is performed and a higher-than-expected block develops, but only after a delay of 15 to 30 minutes (unlike a total spinal), subdural placement of local anesthetic must be considered. With a subdural block, the motor block will be modest compared to the extent of the sensory block, and the sympathetic block may be exaggerated. The treatment is symptomatic.

### COMPLICATIONS UNIQUE TO COMBINED SPINAL-EPIDURALS

The risk of metal toxicity from abraded spinal needle particles using the needle-through-needle technique has not been confirmed.<sup>420</sup>

## Outcomes

Although the benefit of properly applied epidural anesthesia and analgesia as an excellent pain relief modality is unquestionable, its effect on postoperative morbidity and mortality is becoming more clear. Early meta-analysis showed a relative risk reduction in overall mortality in patients receiving neuraxial blockade, by as much as 30% in patients undergoing all types of surgery,<sup>421</sup> but these results included studies now over 40 years old, which may not reflect contemporary anesthetic practice. Recent work has focused on large prospective and retrospective database analyses as well as randomized controlled trials with some analyses including over 1 million patients.<sup>422</sup> Although these too must be treated with caution, there still appear to be benefits of neuraxial anesthesia beyond superior analgesia, particularly when neuraxial is used instead of, rather than combined with, general anesthesia.<sup>422a</sup> Furthermore, the specific surgical procedure may also influence outcome and it may be that any benefit is both procedure specific and technique specific (i.e., thoracic epidural may be more advantageous than lumbar epidural, and epidural local anesthetic may be more advantageous than epidural opioid).

As general anesthesia has become safer over the decades, demonstrating a mortality benefit is more challenging. Some large retrospective studies do show a reduction in mortality, but when present, the absolute difference is small. For cardiac surgery, meta-analyses have shown a reduced risk of mortality and myocardial infarction (composite endpoint); a reduced risk for acute renal failure, pulmonary complications, and supraventricular arrhythmia; and reduced duration of postoperative controlled ventilation in patients who received combined intraoperative general anesthesia and

TEA.<sup>74,423</sup> For major thoracic and abdominal surgery, thoracic epidural analgesia can reduce mortality, along with reductions in respiratory complications and opioid consumption, and improvements in cough and time to ambulation.<sup>422,424,425</sup> Conversely, there is now some evidence that myocardial infarction rates may be increased when epidural and general anesthesia are combined.<sup>422</sup>

Mortality and morbidity aside, there are other important advantages of neuraxial blockade. For bilateral total knee arthroplasty, neuraxial anesthesia decreases the rate of blood transfusion.<sup>426</sup> In patients undergoing major vascular and abdominal surgery, thoracic epidural local anesthetic infusion can reverse postoperative paralytic ileus associated with pain-induced sympathetic overactivity and systemic opioid.<sup>427</sup> Lumbar epidural infusion or thoracic epidural opioid infusion alone does not speed intestinal function recovery. For fast-track laparoscopic colon resection, thoracic epidural analgesia provides superior pain relief but fails to speed intestinal function recovery or hospital discharge time. In a recent meta-analysis, which compared neuraxial to general anesthesia for all major limb and truncal surgery combined, there was a reduction in length of stay in hospital, but this was measured in hours rather than days.<sup>422</sup>

What are the potential effects of neuraxial anesthesia on stress response, the immune system, and cancer recurrence?<sup>428-430a</sup> Functional cell-mediated immunity is required for monitoring and eradicating cancer cell growth. Lymphocytes, such as the natural killer (NK) cells and the cytotoxic T lymphocytes, can lyse the cancer cell through the perforin and granzyme pathway or through secretion of cytokines (e.g., interferons) to induce cancer cell apoptosis. In addition, the helper T cells control tumor angiogenesis through interferons, inhibit oncogenic signaling, and stimulate tumor destruction by engaging macrophages and granulocytes through interleukin production. There is an inverse relationship between NK cell activity at the time of surgery and the development of metastatic disease. Systemic cancer cell seeding happens during surgical dissection and manipulation. Unfortunately, this happens at a time of significant immunosuppression. Surgically induced stress hormone (e.g., corticosteroids), as well as inhaled volatile anesthetics and systemic opioids (morphine and fentanyl), can diminish NK cell function. Morphine also has proangiogenic properties that may promote dissemination of angiogenesis-dependent tumors. TEA and analgesia may be beneficial by virtue of its opioid and general anesthetic sparing and surgical stress-alleviating properties. Some encouraging data indicate a reduction of cancer recurrence associated with the use of perioperative epidural anesthesia and analgesia in patients undergoing retropubic prostatectomy,<sup>431,432</sup> rectal cancer,<sup>433</sup> and ovarian cancer resection.<sup>434,435</sup> Volatile, but not intravenous, anesthetics have also been shown to have a negative effect on immune function and cancer spread and therefore any benefit of regional anesthesia may simply be due to a reduction or avoidance in the use of volatile anesthetic drugs. In the same manner, this potential effect on the immune system may explain why surgical site infection has been shown to be reduced when using neuraxial compared general anesthesia in some, but not all, studies.<sup>422</sup>

## Recent Advances

### ULTRASOUND

There is now considerable evidence to support the role of ultrasound imaging for neuraxial blockade, and for lumbar techniques in particular.<sup>436</sup> Ultrasound can accurately identify the intervertebral levels, the midline spinous process, the midline interspinous window, and the paramedian interlaminar window (see also [Chapter 46](#)).<sup>233</sup> Bone does not permit ultrasound beam transmission, thus casting a hypoechoic (dark) shadow on the image. Conversely, passage of the ultrasound beam through the interspinous and interlaminar windows allows visualization of the hyperechoic dura (a bright line), the subarachnoid space, and the posterior aspect of the vertebral body. Visualization of the ligamentum flavum and epidural space is often more difficult. Successful transverse or longitudinal scan facilitates identification of the optimal location for proper needle insertion during neuraxial block and an estimation of the skin-to-dura distance. This is particularly useful in patients with difficult surface anatomic landmarks (e.g., obesity), spine pathology (e.g., scoliosis), and previous spine surgery (e.g., laminectomy).<sup>437</sup>

Ultrasound-facilitated neuraxial block involves preprocedure scanning of the spine to determine the best possible intervertebral level and window for needle insertion without actual real-time guidance (a highly challenging technique). Imaging of the lumbar spine is significantly easier than that of the thoracic spine, which has narrow interspinous and interlaminar windows, especially at T5-T8 levels.<sup>438</sup> Ultrasonography in the pediatric population is impressive because the vertebral column with limited ossification not only permits visualization of the spinal canal sonoanatomy, but the inserted needle and catheter tip, dural displacement, and the extent of cranial spread can be visualized during a fluid bolus injection in young infants and children (also see [Chapter 77](#)).<sup>439,440</sup> Several outcome studies have confirmed the utility of ultrasonography when neuraxial block is performed by the novice and in patients with difficult anatomic landmarks.<sup>441</sup>

### Acknowledgment

The authors thank Cyrus Tse for his assistance in preparing this chapter.

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## KEY POINTS

- Regional anesthesia is only successful when local anesthetic is inserted in close proximity to the targeted nerves. From the inception of regional anesthesia over a century ago, several techniques have been designed and available to facilitate the correct placement of local anesthetic, including the paresthesia-seeking approach, peripheral nerve stimulator, and most recently ultrasound guidance.
- There are no data to support the superiority of one nerve localization technique—paresthesia, nerve stimulation, ultrasound—over another with regard to reducing the risk of nerve injury.
- Ultrasound imaging can elucidate the structure of peripheral nerves and adjacent anatomic structures for regional block. Peripheral nerves have a characteristic honeycomb echotexture, formed by the internal pattern of connective tissue and nerve fibers.
- Ultrasound provides real-time imaging for needle tip placement and drug injection. Successful local anesthetic injections clarify the border of the nerve and track along the nerve path and its branches. Ultrasound guidance results in more consistent procedure times for peripheral nerve blocks and can be applied to many regional anesthesia procedures. Anatomic variation in nerve position and course, which is a potential source of block failure, can be directly visualized.
- Lipid emulsion bolus and infusion improve the success of resuscitation from cardiac arrest because of local anesthetic toxicity if given immediately after a local anesthetic overdose.
- Prior to regional blocks checklists are now being performed in an effort to make rare adverse events even less common, thereby improving patient safety.

## Introduction

Peripheral nerve blocks can be performed using a variety of guidance techniques. Recently, ultrasound has gained popularity for regional anesthesia because it allows direct imaging of peripheral nerves, the block needle, and injection distribution. This chapter is a focused update of two chapters on peripheral nerve blockade from the previous edition. The sections to follow contain a selective description of the more common peripheral nerve blocks utilized in clinical practice.

## Techniques for Localizing Neural Structures

### PARESTHESIA TECHNIQUES

The paresthesia-seeking technique has a long, successful history as a simple method that requires little specialized equipment. A paresthesia is elicited when a needle makes direct contact with a nerve. Paresthesia-seeking techniques are reliant on patient cooperation and participation to guide the needle and local anesthetic injection accurately; therefore only small doses of sedation medication are recommended. Paresthesia techniques have been criticized for

causing patient discomfort, although clinical studies have not shown a significant increase in neurologic complications with this technique.<sup>1</sup> Caution should be used when initiating the injection of local anesthetic to ensure that the needle is not intraneural. There is controversy in the literature regarding the use of B-bevel (blunt bevel or short bevel) needles versus sharp needles regarding the incidence and severity of nerve injury if the needle inadvertently punctures or pierces the nerve. Because B-bevel needles have a blunt tip, which is likely to push the nerve aside, they are much less likely to penetrate the nerve; however, when an injury does occur, it appears to be more severe. In contrast, sharp needles are more likely to penetrate the nerve, but the injury appears to be less destructive.<sup>2,3</sup> Success with the paresthesia technique is highly dependent on the skill of the practitioner and requires a thorough understanding of anatomy. This technique was slowly replaced in the 1980s when peripheral nerve stimulation was introduced. Currently, no single technique has been shown to be superior with respect to incidence of neurologic complications.

### PERIPHERAL NERVE STIMULATION

Peripheral nerve stimulators deliver small pulses of electric current to the end of a block needle to cause depolarization

and muscle contraction when the tip of the needle is in close proximity to a neural structure. This technique allows for localization of a specific peripheral nerve without requiring the elicitation of a paresthesia, thus allowing patients to be more sedated during block placement. It is necessary to attach the cathode (negative terminal) to the stimulating needle and the anode (positive terminal) to the surface of the patient because cathodal stimulation is more efficient than anodal stimulation. Most current-stimulating needles are coated with a thin layer of electrical insulation along the needle shaft with the exception of the tip. This allows for higher current density at the tip of the needle. Higher current output ( $>1.5$  mA) is more likely to stimulate neural structures through tissue or fascial planes and can be associated with painful, vigorous muscle contractions. After localization of the correct motor response, the current is gradually decreased to a current of 0.5 mA or less. A motor response at a current of approximately 0.5 mA is appropriate when used to facilitate the location for injection of local anesthetic or catheter placement.<sup>4</sup> Immediately following injection of local anesthetic or saline (ionic solutions), the current density at the needle tip will rapidly dissipate and the evoked motor response is eliminated (the Raj test).<sup>5</sup>

The stimulating current pulse can be modified to produce a sensory response. The short-duration impulse commonly used (0.1 ms) is effective in stimulating motor fibers, but a longer-duration pulse (0.3 ms) will also stimulate sensory fibers, a useful feature if a pure sensory nerve is being sought.

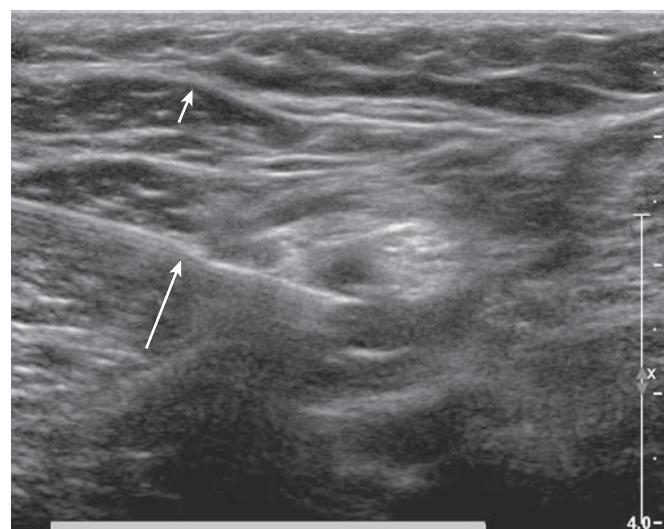
## Ultrasound Guidance

Ultrasound imaging allows direct visualization of peripheral nerves, the block needle tip, and local anesthetic distribution.<sup>6</sup> This imaging modality has proven highly useful for guiding targeted drug injections and catheter placement. This section describes the general principles of ultrasound imaging for regional blocks.

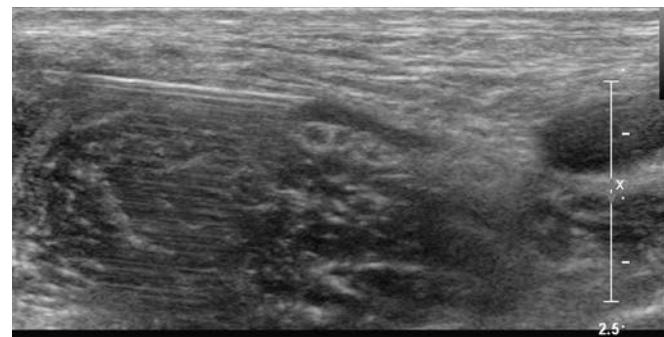
### FUNDAMENTAL ASSUMPTIONS AND ARTIFACTS

Ultrasound is sound with a frequency above the audible range ( $>20,000$  cycles per second). The frequencies used in clinical imaging are within the range of 1 to 20 MHz. High-frequency ultrasound beams are well collimated and therefore can provide high resolution. For most regional blocks, the highest frequency is selected that adequately penetrates the depth of field. Sound waves reflected at the interface of two tissues with different acoustic impedances generate echoes. Ambient lighting has a large effect on visual discrimination; therefore dim lighting without glare is especially useful for imaging low-contrast targets such as peripheral nerves.

Ultrasound imaging is predicated on several common assumptions.<sup>7</sup> First, the speed of sound through soft tissue is 1540 m/s, meaning 13  $\mu$ s elapse for each centimeter of soft tissue traversed back and forth for the total fly-back time of received echoes. This assumption allows interconversion of time and distance for echo ranging. Local heterogeneities in soft tissue can cause artifactual bending of the block needle on ultrasound scans, known as the bayonet artifact



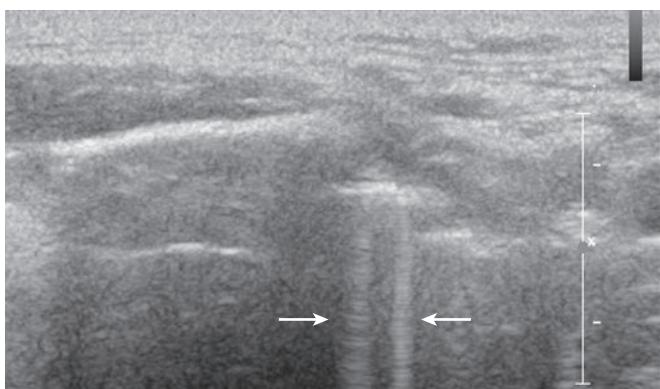
**Fig. 46.1 Bayonet artifact is observed during popliteal block of the sciatic nerve.** In this sonogram, the block needle appears to bend as it approaches the sciatic nerve in the popliteal fossa (long arrow). The slower speed of sound in the overlying adipose tissue, compared with the adjacent muscle (short arrow), produces this artifact.



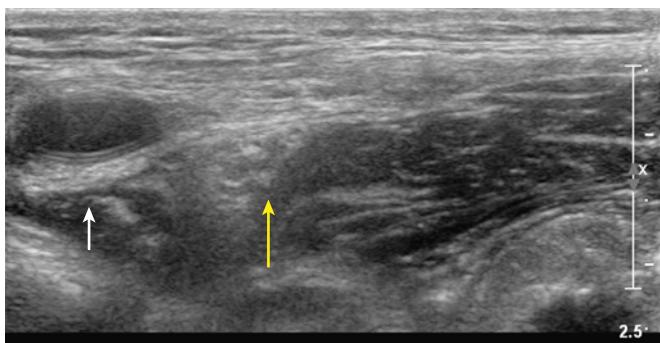
**Fig. 46.2 Reverberation artifact is observed during femoral nerve block.** Sound waves reverberate back and forth between the walls of the needle and then return later to the transducer. Because the sound waves return at a later time, they are displayed deep within the field of imaging. No reverberation artifact is observed from the needle tip because the bevel opening does not have opposing walls.

(Fig. 46.1).<sup>8,9</sup> Bayonet artifacts are commonly observed during the lateral in-plane approach to popliteal block (see Sciatic Nerve Blocks in the Popliteal Fossa) because more adipose tissue is present over the nerves near the posterior midline of the leg (adipose tissue has a slower speed of sound than the adjacent muscle). The speed of sound artifacts relate both to time-of-flight considerations and to refraction that occurs at the interface of tissues with different speeds of sound.

Second, ultrasound waves are assumed to take a straight path to and from tissue. When this does not occur, reverberation artifacts are displayed deep to the reflector. Reverberation artifacts are commonly observed from the block needle shaft at shallow angles of insertion because sound waves bounce back and forth between the walls of the needle before returning to the transducer (Fig. 46.2). Comet tail artifact is another type of reverberation artifact and helps identify strong reflectors such as the pleura during supraclavicular and intercostal blocks. At low receiver gain, the comet tail is seen as a tapering series of discrete echo bands just deep



**Fig. 46.3** Comet-tail artifact is observed during the scanning of the upper airway (arrows). Small collections of water near the air interface, which also are seen during scanning of the pleura, generate this artifact.

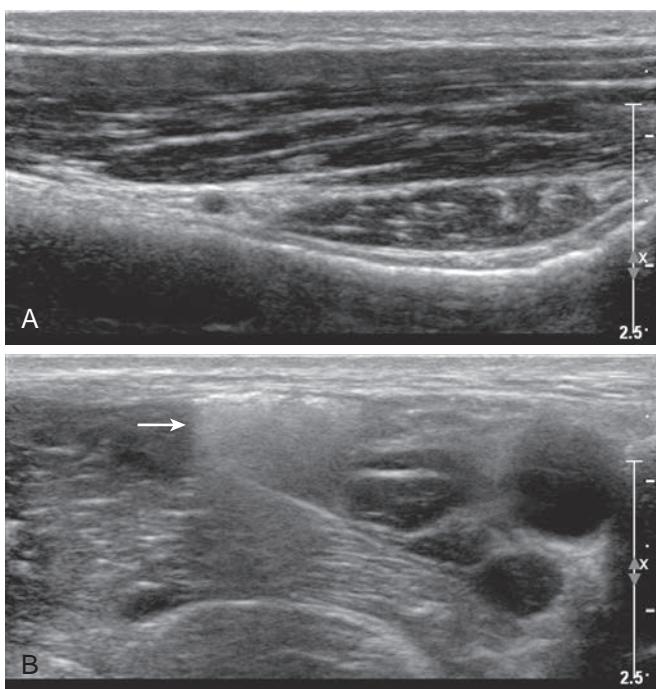


**Fig. 46.4** Posterior acoustic enhancement artifact is observed during femoral nerve block. The echoes deep to the femoral artery are enhanced (white arrow) and may be incorrectly identified as the femoral nerve (yellow arrow).

to a strongly reflecting structure. The spacing between the bands represents the distance between the anterior and posterior walls of the object.<sup>10</sup> Internal reverberations (arising from within the object) cause the comet tail artifact, most intensely observed when the anatomic object is perpendicular to the beam. Comet tail artifact from the pleura relates to lung water content, because small collections of lung water lined by the strongly reflecting pleura can allow the sound beam to enter and then return at varying times to the transducer (Fig. 46.3).

Third, all reflectors are assumed to be on the central ray of the transducer beam. When this assumption is not true, out-of-plane artifacts are observed (slice thickness artifacts). Definitive proof of out-of-plane artifacts requires multiple views, which are recommended when such ambiguities arise.

Unlike adjacent soft tissue, most biologic fluids do not significantly attenuate the sound beam and therefore cause acoustic enhancement (sometimes referred to as posterior acoustic enhancement or increased through-transmission). Acoustic enhancement artifacts deep to blood vessels can be erroneously interpreted as peripheral nerves (Fig. 46.4). For example, acoustic enhancement deep to the second part of the axillary artery in the axilla can be mistaken for the radial nerve. In the infraclavicular region, acoustic enhancement deep to the axillary artery can be mistaken for the posterior cord of the brachial plexus (and similarly,



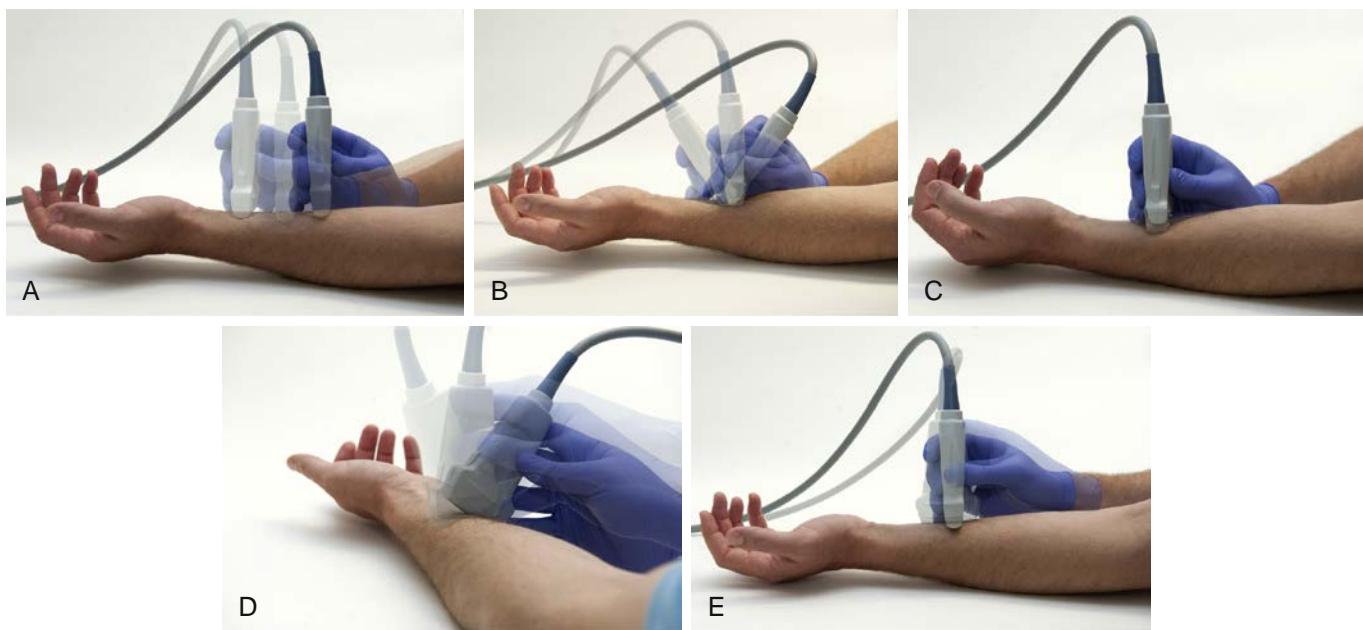
**Fig. 46.5** Acoustic shadowing occurs during regional blocks. (A) During block of the axillary nerve in the proximal arm, the cortical surface of the humerus reflects and absorbs sound waves, thereby producing acoustic shadowing deep to the bone surface. (B) During femoral nerve block, air inadvertently injected into the field layers produces strong reflection and acoustic shadowing (arrow).

for the femoral artery and the femoral nerve in the inguinal region).

Acoustic shadowing occurs deep to strong reflecting structures, such as the cortical surface of mature bone (Fig. 46.5). Acoustic shadows from refraction (also termed refractile shadowing or lateral edge shadowing) are often observed deep to the edges of blood vessels when the vessels are imaged in the short-axis view. Refractive edge shadows can be seen from the carotid artery during stellate ganglion block or from the second part of the axillary artery during infraclavicular block. Refraction artifacts (e.g., refractile shadowing) are less apparent when spatial compound imaging (for further information, see later in this chapter) is used to reduce angle-dependent artifacts.

## Transducer Selection, Manipulation, and Modes of Imaging

Ultrasound transducers consist of piezoelectric crystals that emit and receive high-frequency sound waves by interconverting electrical and mechanical energy. Transducer selection is important to the success of ultrasound-guided regional anesthesia procedures. High-frequency sound waves provide the best resolution but will not penetrate far into tissue. The frequency range is therefore chosen to be the highest that will allow adequate insonation of the entire depth of field. A low-frequency transducer can be used to image large nerves that lie deep, such as the cords of the



**Fig. 46.6 Transducer manipulation.** Sliding (A), tilting (B), compression (C), rocking (D), and rotation (E) of the transducer are shown.

brachial plexus that surround the second part of the axillary artery or the proximal sciatic nerve in the gluteal region.

The footprint size (i.e., the length of the active face transducer that contacts the skin) is chosen to provide a broad enough view of the structures of interest. As a general rule, the footprint should be at least as large as the anticipated depth of field. A square or landscape view is better than a keyhole view (i.e., depth greater than footprint) for guidance. As a rule of thumb, for in-plane technique (see Approaches to Regional Block With Ultrasound), every millimeter of the footprint is approximately a millimeter of guidance.

Linear-array transducers generally have a higher scan-line density than curved arrays and therefore produce the best image quality. Images from linear arrays are usually displayed in a rectangular format. When a linear transducer is needed but space at the site of block is limited by anatomic structures such as adjacent bone, a compact linear (hockey stick) transducer that has a smaller footprint can be very useful. Curved arrays provide a broad field of view for a given footprint size and are generally used when space is limited (e.g., infraclavicular region). Curved probes are easier to rock (see Infraclavicular Blocks) and produce images in sector format.

Universal precautions should be used when handling dirty equipment. External surface probes require disinfection between every use and after extended periods of non-use, per instructions of the manufacturer. Do NOT drop any ultrasound transducer, because the active face of the transducer is especially sensitive to contact with hard surfaces.

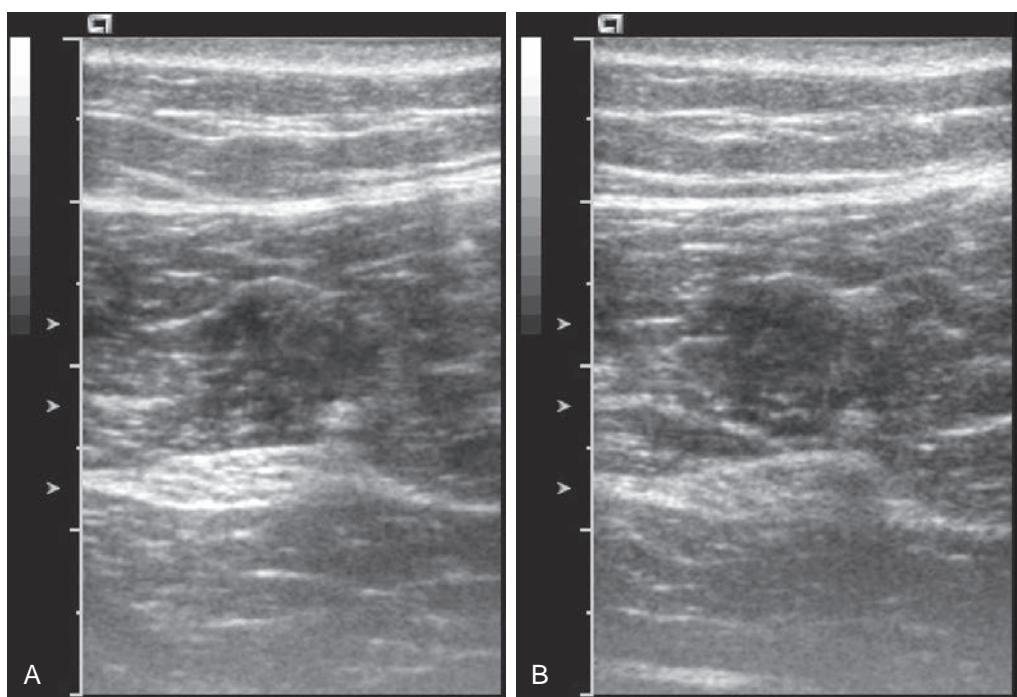
One of the essential skills to acquire for regional block with ultrasound is transducer manipulation (Fig. 46.6). For this reason, standardized nomenclature has been established<sup>11</sup>:

- Sliding (moving contact) the transducer along the known course of the nerve using a short-axis view often helps.
- Tilting (cross-plane, side-to-side) will vary the echo brightness of peripheral nerves. Optimizing this angle is critical to promote nerve visibility.

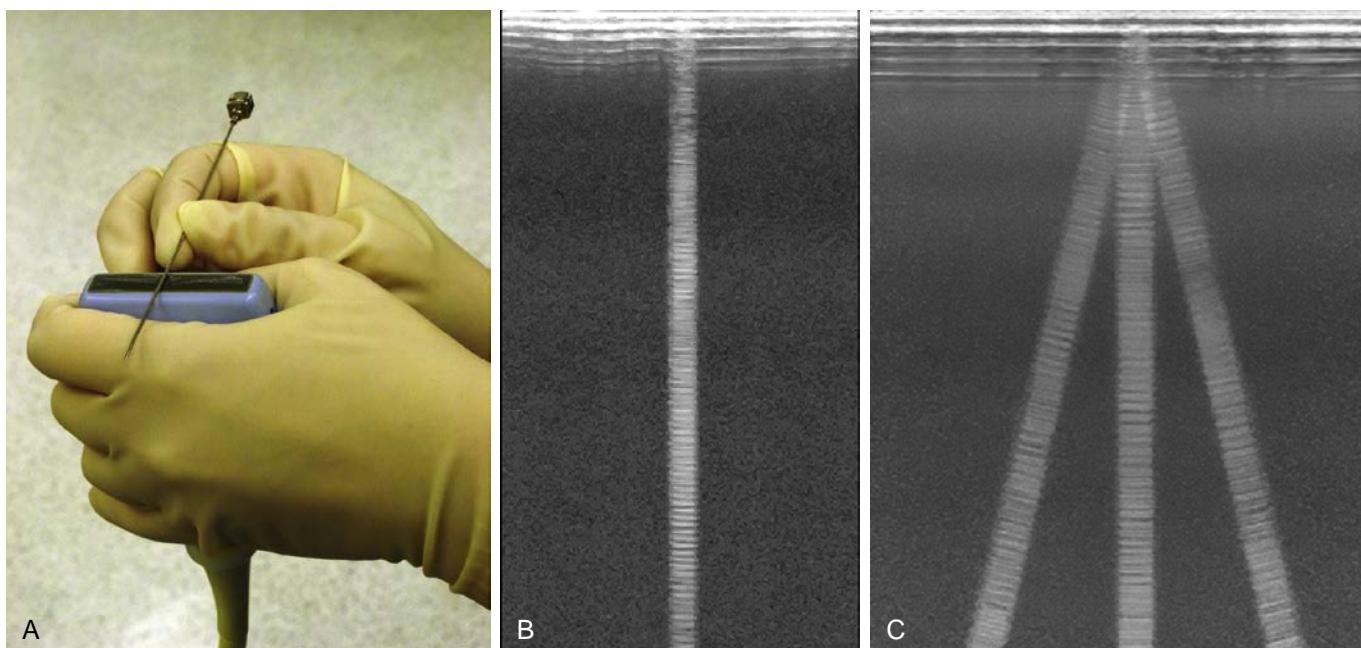
- Compression is often used to confirm venous structures. To improve imaging, compression not only provides better contact, but it also brings the structures closer to the surface of the transducer. Soft tissue is subject to compression; therefore estimates of tissue distances will vary.
- Rocking (in-plane, toward, or away from the indicator) is often necessary to improve visibility of the needle and anatomic structures when the working room is limited.
- Rotation of the probe will produce true short-axis views rather than oblique or long-axis views.

Anisotropy is the change in echogenicity with inclination of the transducer. In general, when objects are obliquely imaged, they appear less echogenic (Fig. 46.7). This relationship is most pronounced for tendons but also occurs for muscle and nerves.<sup>12</sup> Although the term anisotropy was first used to describe changes in received echoes when rocking the transducer with structures viewed in long axis, it has also been used for short-axis views when tilting the transducer. With experience, operators learn to rock and tilt the transducer naturally to fill in the received echoes from peripheral nerves. Sliding and rotating the transducer achieves needle tip localization after optimizing peripheral nerve echoes by tilting.

Spatial compound imaging steers ultrasound beams in different, predetermined angles, typically within approximately 20 degrees from the perpendicular (Fig. 46.8). These multiple lines of insonation are then combined to produce a single composite image. Spatial compound imaging appears to reduce angle-dependent artifacts, anisotropic effects, and acoustic shadows. Another advantage for regional block is that the definition of tissue planes and the detection of nerve borders can be improved. In the systems that have been tested, spatial compound imaging improves needle tip visibility over a limited range of needle insertion angles (<30 degrees). The stray lines of sight (i.e., those that travel off the field underneath the transducer) can be used to form a wider field of view in a trapezoidal format.



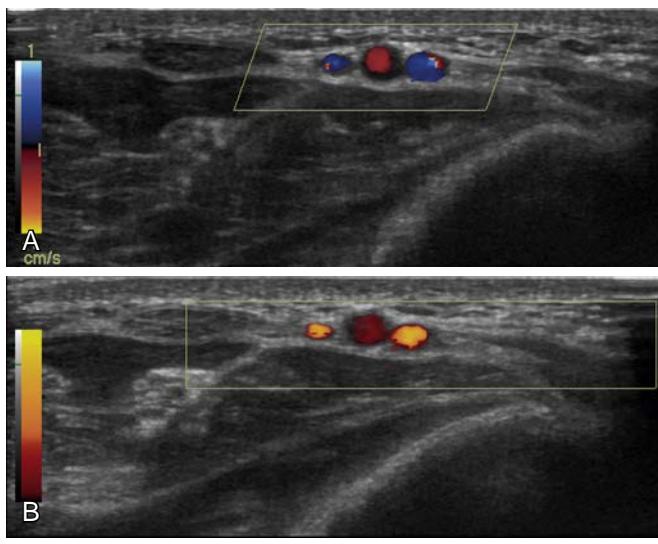
**Fig. 46.7** (A) Sciatic nerve imaging in the subgluteal region. (B) The amplitude of the received echoes diminishes when the angle of insonation is changed away from perpendicular to the nerve path, thereby demonstrating anisotropy.



**Fig. 46.8 Spatial compound imaging.** Some forms of ultrasound imaging use multiple lines of sight by electronically steering the beam to different angles. These sonograms were obtained by placing a linear array test tool (the solid metal stylet of a 17-gauge epidural needle) over the active face of the transducer to isolate a single element. (A) External photograph demonstrates the linear array test tool applied to the active face of the ultrasound transducer. (B) Single-beam imaging is demonstrated. (C) Three lines of sight are used to form a compound image. The test tool images do not display the beam itself, but rather the transmit and receive apertures.

A Doppler shift occurs when a wave source and receiver are moving relative to each other, which produces a change in frequency such that the frequencies of the transmitted and reflected sound waves are not the same. When a wave source and receiver are moving toward each other, the observed frequency is greater

than the source frequency; and when moving away from each other, the observed frequency is lower. The change in frequency is related to the velocity of moving reflectors and the angle of insonation. In clinical medicine, red blood cells are the primary reflectors that produce Doppler shifts.



**Fig. 46.9 Duplex sonograms illustrate the Doppler shift.** (A) In color Doppler, color encoding is based on the mean frequency shift. (B) In power Doppler, color encoding is based on the power spectrum.

### Box 46.1 Respective Advantages of Color and Power Doppler Imaging Modalities

#### Color Doppler

- Directional information
- Velocity estimates
- Less motion artifact (flash artifact)

#### Power Doppler

- More sensitive to detect the presence of flow (by a factor of 3-5 in some cases)
- Less angle dependent
- No aliasing

Doppler ultrasound imaging has different modes (Fig. 46.9). Traditional color Doppler encodes mean frequency shifts to provide directional velocity information; that is, conventional blue color indicates flow away from the transducer, whereas red color indicates flow toward the transducer. More recently, a more sensitive Doppler technology has been developed that encodes color based on the integration of the Doppler power spectrum.<sup>13</sup> Power Doppler is less angle dependent and not subject to aliasing. The disadvantages are that no directional information is provided and motion sensitivity (flash artifact) is high. Power Doppler is especially useful for detecting small arteries that accompany nerves (Box 46.1). Power Doppler can detect these small arteries and better delineate the course of tortuous vessels that have unfavorable angles to the ultrasound beam.

## Needle Tip Visibility

A large number of factors influence needle tip visibility in clinical practice. Metal needles are hyperechoic and can cause reverberation artifact. Needle tip visibility is best when the needle path is parallel to the active face of the

transducer. Under this condition, the needle is perpendicular to the sound beam; therefore strong specular reflections will be produced; that is, mirror-like reflections will be produced from a smooth surface. As the angle of incidence is increased, the mean brightness will decrease.<sup>14</sup> In this same study, the bevel angles were ground from 10 to 70 degrees but were found to have no effect on the needle tip echo. However, bevel orientation does influence the needle tip echo; visibility is best with the bevel either directly facing or averting the transducer.<sup>15</sup> Because needle diameters are smaller than the scan plane thickness, larger needles are more echogenic than finer ones.

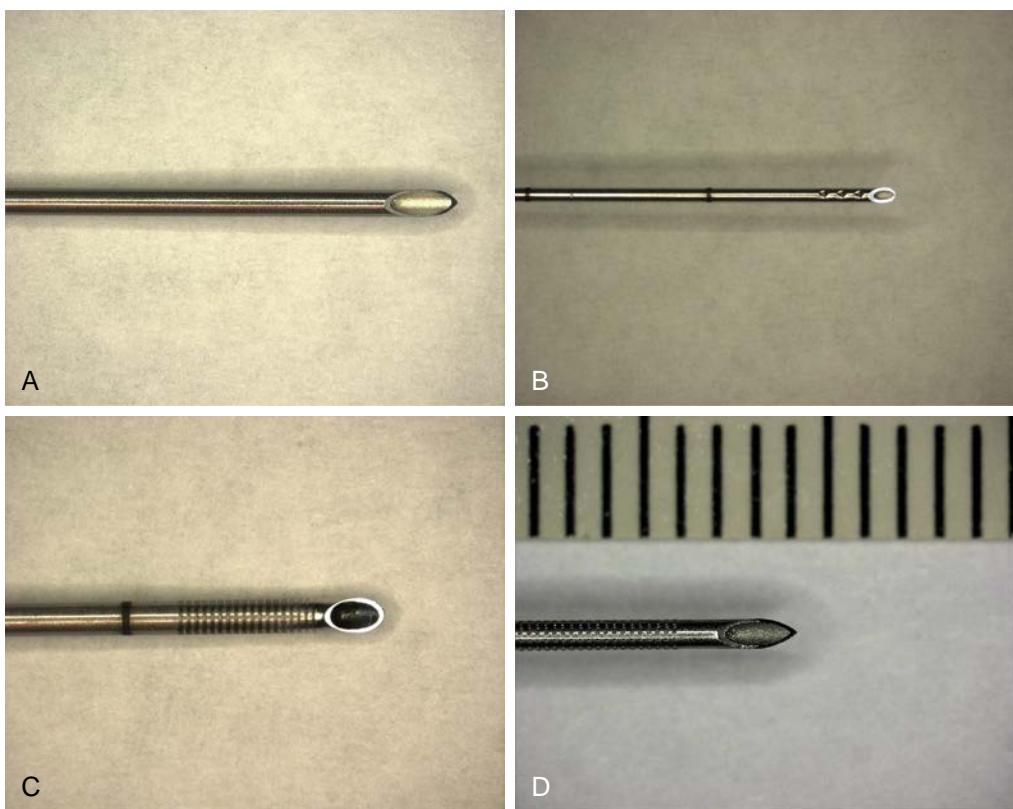
Visualization of needles in echogenic tissue is difficult, particularly in bright adipose tissue. A number of strategies have been proposed to improve needle tip visibility.<sup>16,17</sup> A low-receiver gain can improve the detection of the needle tip echo. Spatial compound imaging can help identify the needle tip when the needle path is at an angle with respect to the transducer. However, one limitation of this strategy is that only a small triangular section of the field of imaging receives all the lines of sight and is therefore fully compounded. In addition, the range of angles for spatial compound imaging is limited and is usually exceeded by the desired needle insertion path. Rocking back the transducer can improve the angle between the ultrasound beam and needle during in-plane technique (see Approaches to Regional Block with Ultrasound). Most practitioners orient the needle so that the needle bevel faces the transducer.

Among needles originally developed for use in regional anesthesia, Hustead bevels tended to be more visible than side port needles that lack cutting bevels. Needles with echogenic modifications are now commercially marketed for peripheral nerve blocks. One engineering strategy has been to texture the needle surface so that echoes return to the transducer source, regardless of the angle of insonation (Fig. 46.10). One potential limitation of these needle designs is the finite size of the needle texturing. Low-frequency transducers produce longer wavelengths that may be too large to reflect strongly back from the textured surface of the needle.

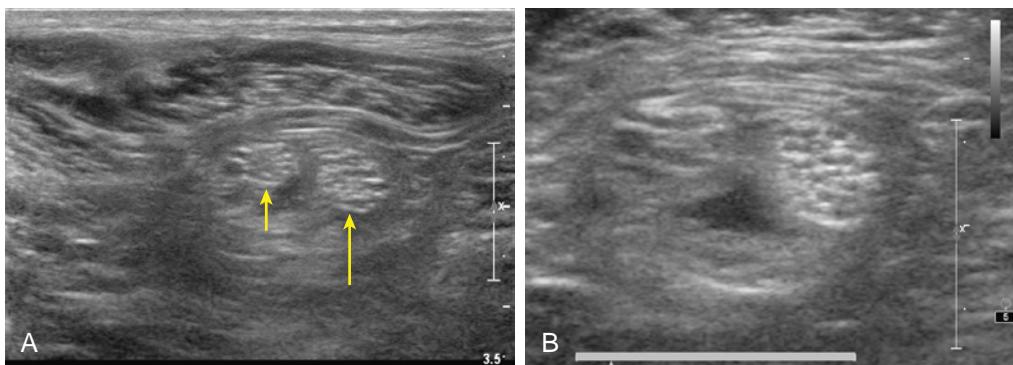
## Approaches to Regional Block With Ultrasound

Peripheral nerves can be directly detected with high-resolution ultrasound imaging.<sup>18</sup> The fascicular echotexture is the most distinguishing feature of nerves (honeycomb architecture) (Fig. 46.11). More central nerves, such as the cervical ventral rami, have fewer fascicles and can appear monofascicular on ultrasound scans. Ultrasound frequencies of 10 MHz or higher are required to distinguish tendons from nerves based on echotexture alone. One of the most powerful techniques to identify nerve fascicles is to slide a broad linear transducer over the known course of a peripheral nerve with the nerve viewed in short axis (transverse cross section).

Nerves can be round, oval, or triangular in shape. Although nerve shape can change along the nerve path, the cross-sectional nerve area is relatively constant in the absence of major branching (Fig. 46.12).<sup>19</sup> Peripheral



**Fig. 46.10 Photomicrographs of needles are used for regional block.** A plain conventional needle (A) and echogenic designs (B, C, D) are shown. A smooth needle may not generate a recordable echo because its rounded shaft reflects most incident sound away from the source. A variety of textured surfaces are manufactured and marketed to improve needle tip detection on acquired sonograms. (Modified from Gray AT. *Atlas of Ultrasound-Guided Regional Anesthesia*. 3rd ed. Philadelphia: Saunders; 2018.)

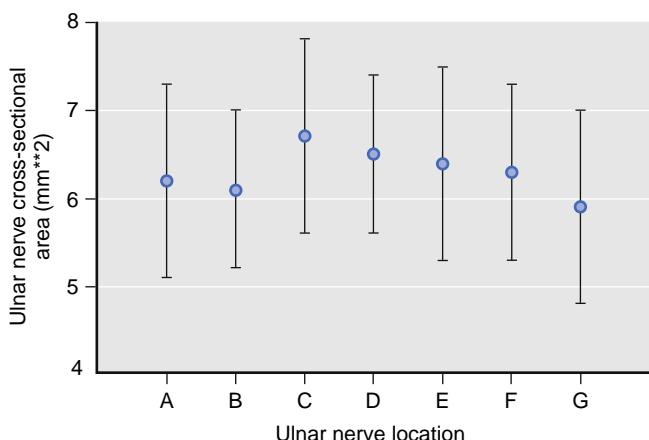


**Fig. 46.11 Nerve echotexture.** (A) Fascicles of the common peroneal (short yellow arrow) and tibial (long yellow arrow) nerves are visualized in the popliteal fossa. In this sonogram the honeycomb appearance of a polyfascicular peripheral nerve is observed. (B) Close-up view shows detailed echotexture of the two nerves.

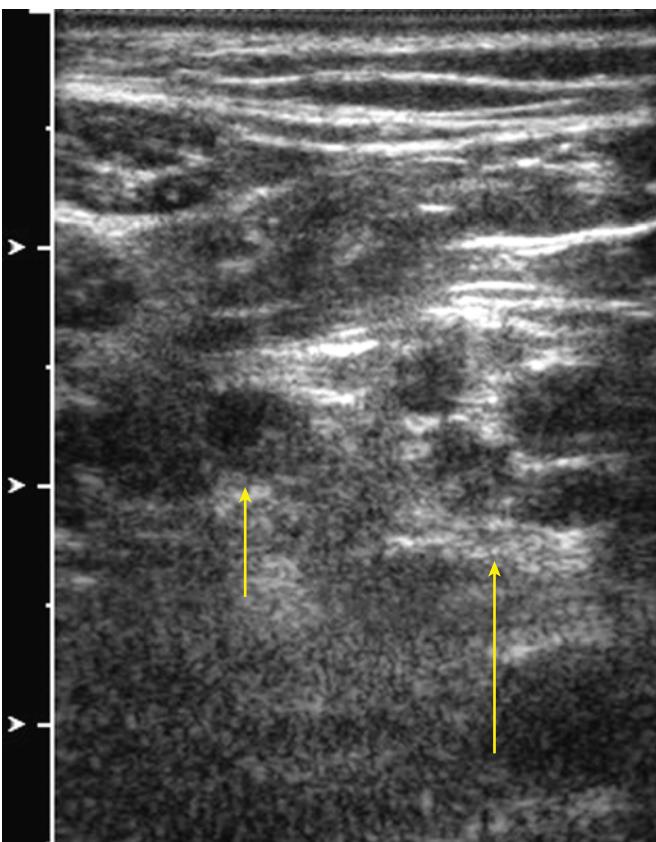
nerves are pathologically enlarged either by entrapment or in certain neuromuscular disorders, such as Charcot-Marie-Tooth, type 1A, disease (Fig. 46.13). Some evidence suggests that patients with diabetic neuropathy also have enlarged peripheral nerves.

Although direct nerve imaging has led to a phenomenal increase in ultrasound-guided regional anesthesia, the identification of other nearby anatomic structures, such as the fascia and other connective tissue, is also critical in this endeavor. These layers permit favorable distribution of local anesthetic, making nerve contact with the block needle unnecessary.

Many approaches to regional blocks with ultrasound are available (Table 46.1). Peripheral nerves are usually viewed in short axis rather than long axis. The needle can approach within the plane of imaging (in-plane technique) or cross the plane of imaging as an echogenic dot (out-of-plane technique). For some regional blocks, offline markings (skin markings before needle insertion) are used instead of online imaging (i.e., imaging during needle insertion and injection). Most studies have suggested that adequate visualization and correct identification of the relevant structures (e.g., peripheral nerve, needle tip, local anesthetic, adjacent anatomic structures) is more important than the



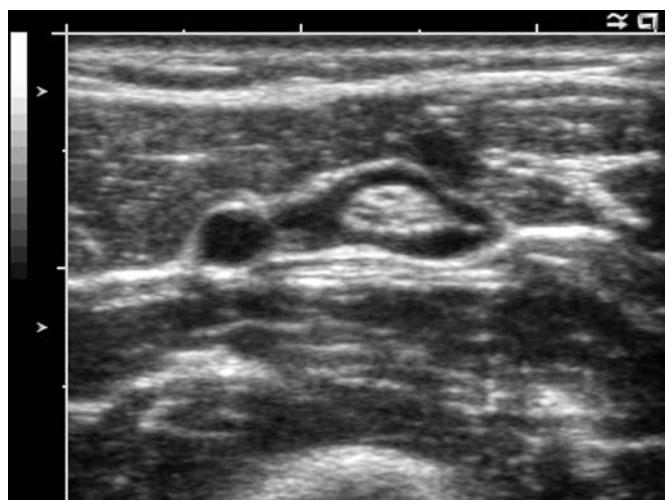
**Fig. 46.12 Cross-sectional area of a peripheral nerve as a function of nerve path length.** In this figure the cross-sectional area of the ulnar nerve is shown at various points in the upper extremity. Axilla (A); midhumerus (B); 2 cm proximal to medial epicondyle (C); medial epicondyle (D); 2 cm distal to medial epicondyle (E); arterial split (F); and wrist crease (G). Data are shown as mean values with standard deviations. Despite changes in shape that can occur, the cross-sectional area of nerves is relatively constant along the nerve path in the absence of major branching. (Modified from Cartwright MS, Shin HW, Passmore LV, Walker FO. Ultrasonographic findings of the normal ulnar nerve in adults. *Arch Phys Med Rehabil.* 288[3]:394-396, 2007.)



**Fig. 46.13 Sonogram demonstrates the popliteal fossa of a patient with Charcot-Marie-Tooth, type 1A, disorder.** The peripheral nerves are significantly enlarged because of the large fascicles (yellow arrows). Nerves of the symptomatic and asymptomatic sides can appear similar in these patients. Large tick marks are 10 mm apart.

**Table 46.1 Examples of Approaches to Regional Blocks With Ultrasound Guidance**

Approach	Examples of Regional Block
Short-axis view, in-plane	Almost any peripheral nerve block Almost any peripheral catheter placement
Short-axis view, out-of-plane	Shallow blocks Interscalene catheter Lateral femoral cutaneous nerve block Femoral nerve catheter placement
Long-axis view, in-plane	Proximal fascia iliaca block Proximal obturator block Anterior sciatic block
Long-axis view, out-of-plane	Epidural placement (longitudinal para-median view during midline approach) Transtracheal anesthesia



**Fig. 46.14 Local anesthetic injection for successful peripheral nerve block.** The ulnar nerve and ulnar artery are viewed in short axis in the forearm in this sonogram. The nerve is surrounded with anechoic local anesthetic.

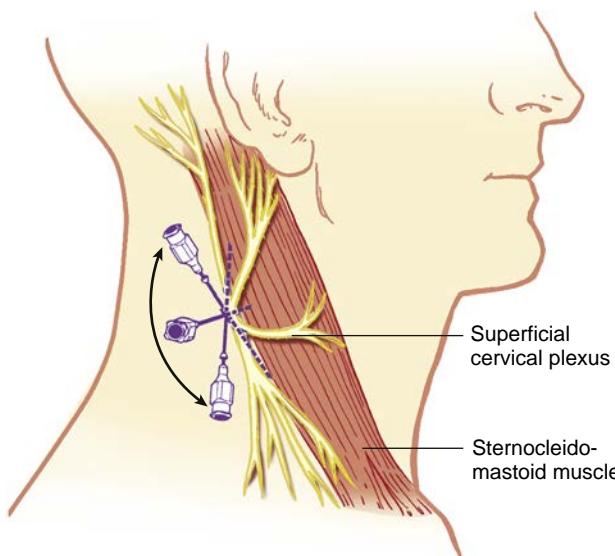
approach, per se, for outcomes after regional blocks. Nevertheless, consistent practice patterns are developing among institutions and illustrate the underlying principles.

Successful injection for peripheral nerve block has typical characteristics (Fig. 46.14). Injections should distribute around the nerve (clarifying the nerve border), travel along the nerve path and branches, and separate the nerve from common anatomic structures such as adjacent arteries that are wrapped together in common fascia and connective tissue. Because anechoic fluid is typically injected, echoes received from the peripheral nerve will also be enhanced by increased through transmission (but not necessarily a sign of block success).

## REGIONAL BLOCK TECHNIQUES

### Cervical Plexus Blocks

The cervical plexus is derived from the C1, C2, C3, and C4 spinal nerves and supplies branches to the prevertebral muscles, strap muscles of the neck, and phrenic nerve. The deep cervical plexus supplies the musculature of the neck.



**Fig. 46.15 Anatomic landmarks and method of needle placement for a superficial cervical plexus block.**

The superficial cervical plexus provides cutaneous sensation of the skin between the trigeminal innervation of the face and the T2 dermatome of the trunk.

### Clinical Applications

Blocks of the cervical plexus are easy to perform and provide anesthesia for surgical procedures in the distribution of C2 to C4, including lymph node dissections, plastic surgery repairs, and carotid endarterectomy.<sup>20,21</sup> The ability to continuously monitor the awake patient's neurologic status is an advantage of this anesthetic technique for the latter procedure and has resulted in an upsurge in the popularity of this technique. Bilateral blocks can be used for tracheostomy and thyroidectomy. A variety of approaches to cervical plexus block have been described, including some guided by ultrasound imaging.<sup>22,23</sup>

### Superficial Cervical Plexus

The superficial cervical plexus is blocked at the midpoint of the posterior border of the sternocleidomastoid muscle. A skin wheal is made at this point, and a 22-gauge, 4-cm needle is advanced, injecting 5 mL of solution along the posterior border and medial surface of the sternocleidomastoid muscle (Fig. 46.15). It is possible to block the accessory nerve with this injection, resulting in temporary ipsilateral trapezius muscle paralysis. Deep cervical plexus blocks also are possible but have been associated with a higher incidence of respiratory complications.<sup>24</sup>

## Brachial Plexus Blocks

### BRACHIAL PLEXUS ANATOMY

The brachial plexus is derived from the anterior primary rami of the fifth, sixth, seventh, and eighth cervical nerves and the first thoracic nerve, with variable contributions from the fourth cervical and second thoracic nerves. After leaving their intervertebral foramina, these nerves course

anterolaterally and inferiorly to lie between the anterior and middle scalene muscles, which arise from the anterior and posterior tubercles of the cervical vertebra, respectively. The anterior scalene muscle passes caudally and laterally to insert into the scalene tubercle of the first rib; the middle scalene muscle inserts on the first rib posterior to the subclavian artery, which passes between these two scalene muscles along the subclavian groove. The prevertebral fascia invests the anterior and middle scalene muscles, fusing laterally to enclose the brachial plexus in a fascial sheath.

Between the scalene muscles, these nerve roots unite to form three trunks, which emerge from the interscalene space to lie cephaloposterior to the subclavian artery as it courses along the upper surface of the first rib. The superior (C5 and C6), middle (C7), and inferior (C8 and T1) trunks are arranged accordingly and are not in a strict horizontal formation, as often depicted. At the lateral edge of the first rib, each trunk forms anterior and posterior divisions that pass posterior to the midportion of the clavicle to enter the axilla. Within the axilla, these divisions form the lateral, posterior, and medial cords, named for their relationship with the second part of the axillary artery. The superior divisions from the superior and middle trunks form the lateral cord, the inferior divisions from all three trunks form the posterior cord, and the anterior division of the inferior trunk continues as the medial cord.

At the lateral border of the pectoralis minor, the three cords divide into the peripheral nerves of the upper extremity. The lateral cord gives rise to the lateral head of the median nerve and the musculocutaneous nerve; the medial cord gives rise to the medial head of the median nerve, as well as the ulnar, the medial antebrachial, and the medial brachial cutaneous nerves; and the posterior cord divides into the axillary and radial nerves (Fig. 46.16).

Aside from the branches from the cords that form the peripheral nerves as described, several branches arise from the roots of the brachial plexus providing motor innervation to the rhomboid muscles (C5), the subclavian muscles (C5 and C6), and the serratus anterior muscle (C5, C6, and C7). The suprascapular nerve arises from C5 and C6, supplies the muscles of the dorsal aspect of the scapula, and makes a significant contribution to the sensory supply of the shoulder joint.

Sensory distributions of the cervical roots and the peripheral nerves are shown in Fig. 46.17.

Branches arising from the cervical roots were traditionally blocked with the interscalene approach to the brachial plexus. However, interscalene block has a well-documented risk of concomitant phrenic nerve block. This can result in symptomatic hemi-diaphragmatic paralysis and respiratory compromise, especially among those patients with obesity or moderate to severe obstructive pulmonary disease.<sup>25,26</sup> Recent evidence suggests diaphragm paresis may be avoidable with more distal "lung-sparing" block techniques that target the terminal nerves supplying the shoulder joint.

By design, brachial plexus blocks above the clavicle (e.g., interscalene and supraclavicular blocks) primarily target local anesthetic placement near the ventral rami, trunks, and divisions. Blocks below the clavicle (e.g., infraclavicular and axillary blocks) primarily target the cords and terminal nerves.

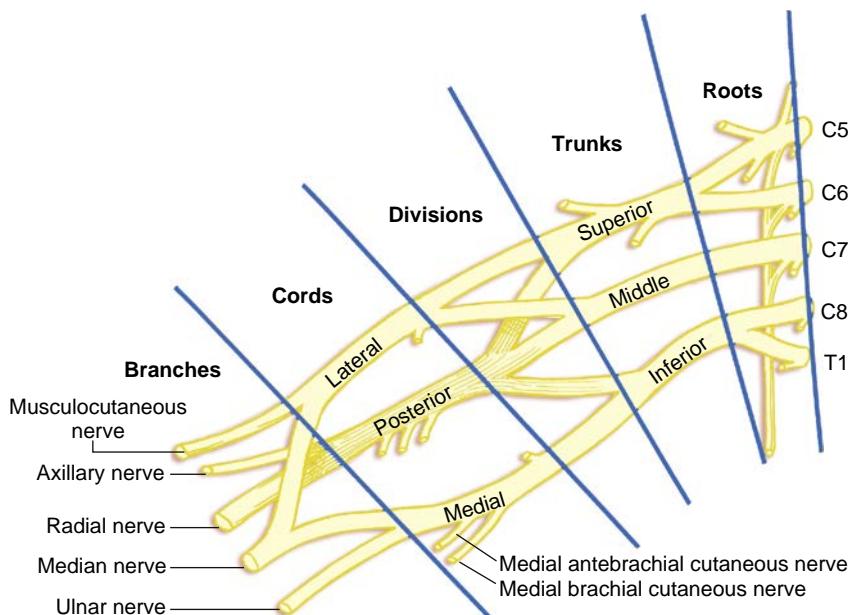


Fig. 46.16 Roots, trunks, divisions, cords, and branches of the brachial plexus.

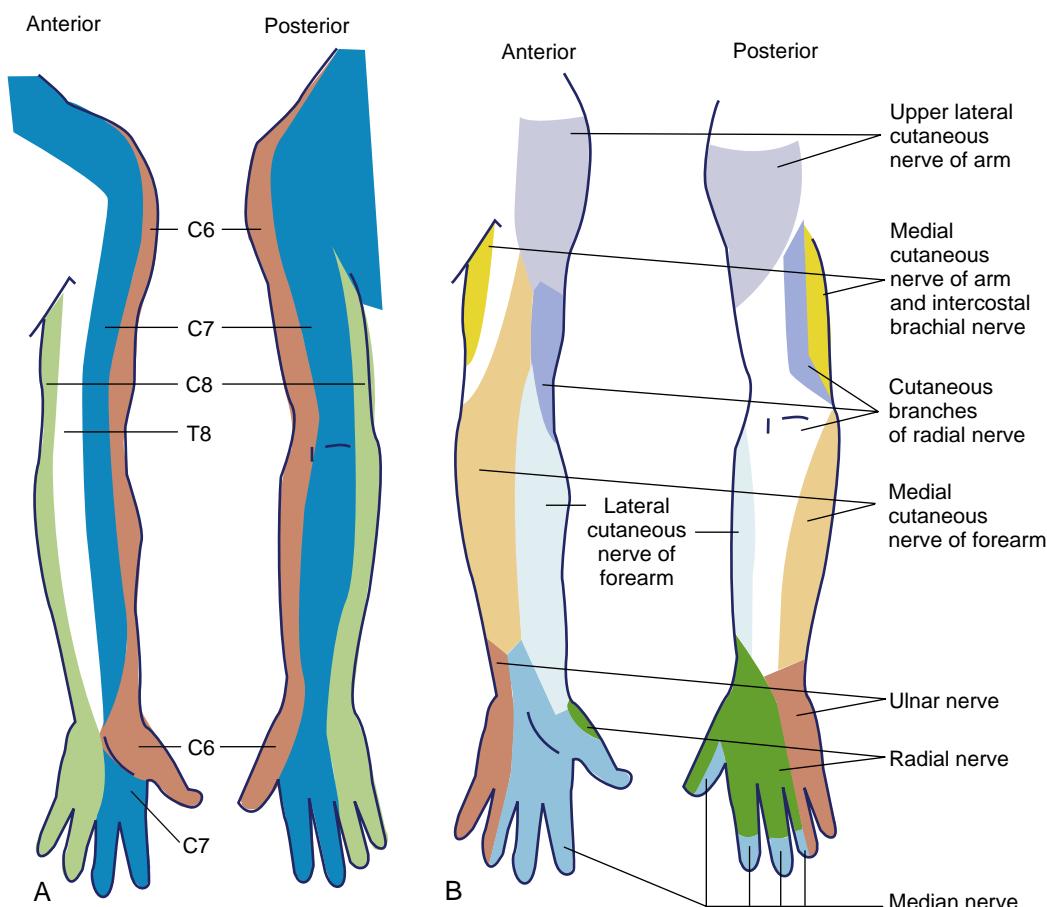
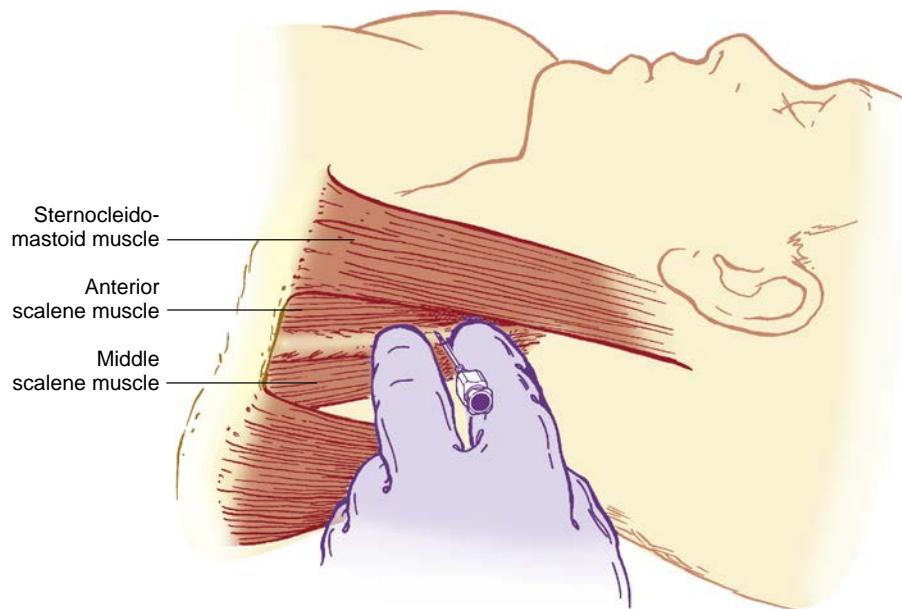


Fig. 46.17 (A) Cutaneous distribution of the cervical roots. (B) Cutaneous distribution of the peripheral nerves.

### Interscalene Blocks

The interscalene block is often chosen for regional anesthesia technique of the shoulder<sup>27</sup> in those patients without significant pulmonary disease. Blockade occurs at the level of the superior and middle trunks of the brachial plexus. Although this approach can be used for

forearm and hand surgery, blockade of the inferior trunk (C8 and T1) can be incomplete and may require supplementation of the ulnar nerve for adequate surgical anesthesia in that distribution.<sup>28</sup> Ultrasound guidance for interscalene block reduces the chance of inferior trunk sparing.<sup>29</sup>



**Fig. 46.18 Interscalene block guided by palpation.** The fingers palpate the interscalene groove, and the needle is inserted with a caudad and slightly posterior angle.

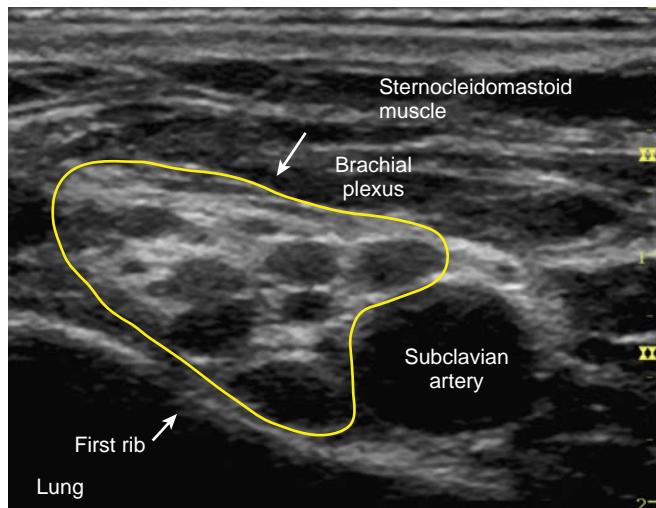
Several adjacent anatomic structures can serve as important landmarks for performance of interscalene block. The patient should be in the supine position, with the head turned away from the side to be blocked and the patient's arm in any comfortable position. The posterior border of the sternocleidomastoid muscle is readily palpated by having the patient briefly lift the head. The interscalene groove can be palpated by rolling the fingers posterolaterally away from this border over the belly of the anterior scalene muscle into the groove (Fig. 46.18). A line is extended laterally from the cricoid cartilage to intersect the interscalene groove, indicating the level of the transverse process of C6. Although the external jugular vein often overlies this point of intersection, it is not a consistent landmark.

### Ultrasound-Guided Technique

Traditional approaches to the interscalene block include paresthesia or peripheral nerve stimulation technique. However, this block is well suited to the use of ultrasound guidance. It is often easiest to obtain a supraclavicular view of the subclavian artery and brachial plexus (Fig. 46.19) and then trace the plexus up the neck with the ultrasound probe until the plexus trunks are visualized as hypoechoic structures between the anterior and medial scalene muscles (the "stoplight" sign<sup>30</sup>). The needle can then be advanced with either an in-plane or out-of-plane approach. After negative aspiration, a small test dose is administered, and local anesthetic spread around the brachial plexus confirms appropriate placement of the needle. Volumes as little as 5 mL may be successful and associated with a decreased frequency of diaphragmatic paresis.<sup>31</sup>

### Side Effects and Complications

At the traditional (C6) level of interscalene block, ipsilateral phrenic nerve block and resultant diaphragmatic paresis are inevitable. This effect probably results from the proximity of the phrenic nerve at this level<sup>32</sup> and may cause subjective symptoms of dyspnea. Respiratory compromise can



**Fig. 46.19 Ultrasound image of the brachial plexus at the level of the first rib.**

occur in patients with severe preexisting respiratory disease or contralateral phrenic nerve dysfunction.

Involvement of the vagus, recurrent laryngeal, and cervical sympathetic nerves is rarely significant if unilateral, but the patient experiencing symptoms related to these side effects may require reassurance. The risk of pneumothorax is small when the needle is correctly placed at the C5 or C6 level because of the distance from the dome of the pleura.

Severe hypotension and bradycardia (i.e., Bezold-Jarisch reflex) can occur in awake, sitting patients undergoing shoulder surgery under an interscalene block. The cause is presumed to be stimulation of intracardiac mechanoreceptors by decreased venous return, producing an abrupt withdrawal of sympathetic tone and enhanced parasympathetic output. This effect results in bradycardia, hypotension, and syncope. The frequency is decreased when prophylactic  $\beta$ -adrenergic blockers are administered.<sup>33</sup>

Epidural and intrathecal injections can occur with this block. The proximity of significant neurovascular structures may increase the risk of serious neurologic complications when interscalene block is performed in heavily sedated or anesthetized patients. Accordingly, interscalene blocks are usually placed under light sedation in adult patients.

**Supraclavicular Blocks.** Indications for supraclavicular blocks include operations on the elbow, forearm, and hand. Blockade occurs at the distal trunk–proximal division level of the brachial plexus. At this point, the brachial plexus is relatively compact, and a small volume of local anesthetic produces rapid onset of reliable blockade.

### Ultrasound-Guided Technique

The patient is placed in supine position, with the head turned away from the side to be blocked. The arm to be anesthetized is adducted against the side of the body. Similar to interscalene block, traditional approaches to the supraclavicular block include paresthesia or peripheral nerve stimulation. Given the widespread use and availability of ultrasound, this block is now more commonly performed with sonographic guidance. This allows the practitioner to visualize the brachial plexus, subclavian artery, pleura, and first rib. The inherent safety of this technique requires continuous visualization of the needle tip and adjacent anatomic structures during needle advancement.

A high-frequency (15-6 MHz) linear transducer is positioned just proximal to the supraclavicular fossa to obtain a supraclavicular view (see [Fig. 46.19](#)). The brachial plexus trunks and divisions are clustered vertically over the first rib on the lateral side of the subclavian artery. The first rib acts as a medial barrier to the needle reaching the pleural dome and is short, wide, and flat.

The needle can then be advanced under direct ultrasound guidance using an in-plane approach from lateral to medial.<sup>34,35</sup> The transducer rests near the clavicle so manipulation can be challenging. Thus advanced skills with needle control are required. After negative aspiration, a small test dose is administered, and local anesthetic spread around the brachial plexus confirms appropriate placement of the needle tip. Volumes as low as 15 to 30 mL may be successful.

### Side Effects and Complications

The prevalence of pneumothorax after supraclavicular block is 0.5% to 6% and diminishes with increased experience. Importantly, although the use of ultrasound may decrease the incidence of pneumothorax, the risk has not been eliminated.<sup>36</sup> When this occurs, the onset of symptoms is usually delayed, and it can take up to 24 hours to develop. Thus routine chest radiography after the block is not justified. The supraclavicular approach is best avoided when the patient is uncooperative or cannot tolerate any degree of respiratory compromise. Other complications include phrenic nerve block (as high as 40%-60%), Horner's syndrome, and neuropathy. The presence of phrenic or cervical sympathetic nerve block usually requires only reassurance. Although nerve damage can occur, it is uncommon and usually self-limited.

**Suprascapular Nerve Blocks.** Suprascapular nerve (SSN) block above the clavicle (anterior approach) is a viable alternative to interscalene block for analgesia of the shoulder region.<sup>37,38</sup> The advantage of this more peripheral approach is that the chance of concomitant phrenic nerve block is significantly reduced. In addition, if the block is semi-selective then other nerves that contribute articular branches to the shoulder joint (e.g., axillary nerve, lateral pectoral nerve) also can be blocked. The anterior approach to SSN block is more shallow (5-10 mm depth) than the more traditional block of the SSN block at the suprascapular notch (20-40 mm depth). Furthermore, the suprascapular notch has variable morphology and in some subjects this landmark is absent. The SSN is the primary sensory innervation of the shoulder joint<sup>39</sup> and is not blocked with approaches to the brachial plexus below the clavicle. Selective low-volume approaches to SSN block above the clavicle also may be useful for pain medicine and rehabilitation.<sup>40</sup>

### Indications

The SSN, a mixed-motor and sensory nerve originating from the superior trunk (C5 and C6 nerve roots and often C4 as well) makes a significant contribution to the sensory supply of the shoulder joint. The SSN root may be accessed from within the posterior cervical triangle of the neck where it passes underneath the omohyoid muscle toward the suprascapular notch. The SSN, unlike the suprascapular vessels that remain superficial, then passes deep to the superior transverse scapular ligament exiting through the scapular foramen into the supraspinous fossa finally providing nerve branches to muscles of the shoulder girdle.

### Ultrasound-Guided Technique

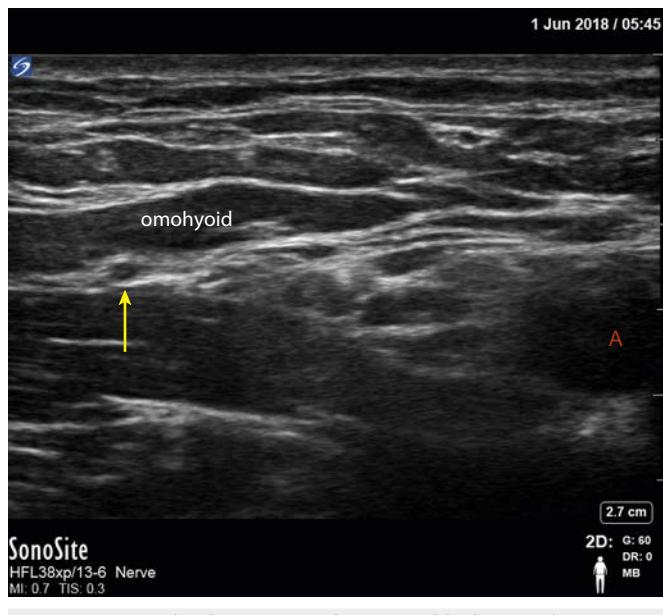
The anterior SSN block is performed in the supine position with head turned to the contralateral side when accessing the nerve within the posterior cervical triangle (similar positioning as the interscalene nerve block). Alternatively, the patient would be in a seated position to access the scapula for a more distal and posterior SSN block. In the seated position, ask the patient to place his/her hand over to the contralateral shoulder (full shoulder adduction) to move the target (nerve) and scapula lateral from the thorax. Ultrasound guidance is the preferred technique, although a landmark-based method with nerve stimulation for neurolocalization is an option.

**Proximal Suprascapular Nerve Block (Anterior Suprascapular Nerve Block).** The anterior SSN block technique has emerged as the preferred lung-sparing block alternative to interscalene nerve block.<sup>37,41</sup> A high-frequency linear transducer (15-6 MHz) probe is positioned just proximal to the supraclavicular fossa. Under dynamic scanning, the SSN can be visualized as a round hypoechoic structure deep to the inferior belly of the omohyoid muscle and lateral to the superior trunk in the posterior cervical triangle of the neck ([Fig. 46.20](#)) Consider tracing the SSN from its origin (nerve root C5) to facilitate identification. The nerve is then traced more posterior-lateral to a distance away from the superior trunk. A 22-gauge, 5-cm needle is most often selected with shallow 2- to 3-cm depths to the target. Through an out-of-plane or in-plane approach approximately 5 to 15

mL of local anesthetic is deposited deep into omohyoid muscle, but shallow to the prevertebral fascia (higher volumes could result in phrenic nerve blockade). Color Doppler use is advised as the superficial cervical artery and the suprascapular artery, also hypoechoic structures, are strong mimickers of the SSN within the posterior cervical triangle. Auyong and colleagues have shown the anterior SSN block technique provides noninferior, yet lung-sparing, analgesia compared to interscalene nerve block without need for additional terminal nerve block supplementation (e.g., axillary or SSN block).<sup>41</sup>

### Shoulder Block (Suprascapular Nerve Plus Axillary [Circumflex] Nerve Block)<sup>42</sup>

In contrast to the anterior suprascapular block, a more distal block of the SSN at the scapula requires the axillary (circumflex) nerve to be also blocked to be remotely comparable



**Fig. 46.20 Proximal suprascapular nerve block (anterior suprascapular nerve block).** The suprascapular nerve is featured as a round hypoechoic structure deep to the inferior belly of the omohyoid muscle lateral to the superior trunk of the brachial plexus within the posterior cervical triangle.

to more proximal brachial plexus blockade.<sup>43,44</sup> Unfortunately, the posterior SSN block even with the axillary (circumflex) nerve block will not provide complete anesthesia to the shoulder joint; therefore routinely general anesthesia with supplemental opioid medications would be expected for adequate analgesia.

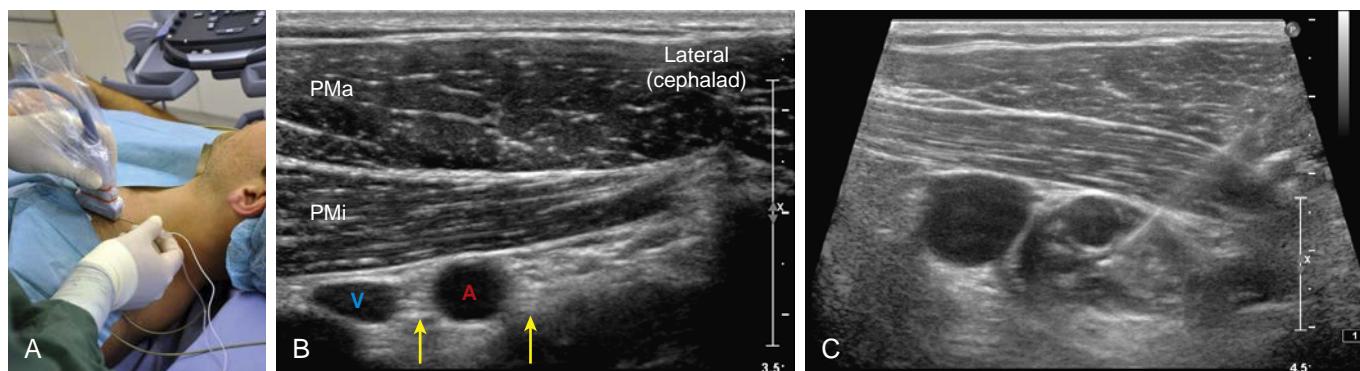
### Side Effects and Complications

Serious side effects and complications are primarily due to insertion complications and side effects from local anesthesia use.

Avoid directly targeting the SSN in the suprascapular notch because accidental anterior needle advancement can puncture the pleura. Also, avoid intramuscular placement whether it be avoiding deposit of local anesthesia within the omohyoid (anterior) or within the supraspinatus muscle (posterior), which may result in myotoxicity/myonecrosis. Additionally, the axillary (circumflex) nerve and posterior circumflex artery lie only 2 to 3 mm below the inferior capsule within the neurovascular quadrangular space. Thus a more proximal injection on the posterior upper arm carries a risk of entering the glenohumeral joint space with the block needle and higher local anesthesia volumes have been associated with spread to the posterior cord resulting in radial nerve blockade.

### INFRACLAVICULAR BLOCKS

The advantages of the infraclavicular block are that it usually results in complete brachial plexus anesthesia, it is a stable place for a catheter, and no manipulation of the arm is necessary.<sup>45-47</sup> The disadvantages are that the infraclavicular block is a deeper block; therefore needle or probe manipulations are necessary, along with steep angles of needle insertion that result in needle tip visibility issues. Although the arm can remain at the side of the patient, the block is easier when the arm is abducted to straighten the neurovascular bundle. The three arterial wall-hugging cords are named with respect to the second part of the axillary artery; therefore the expected positions are medial, lateral, and posterior. The artery is visualized in short-axis view deep to the pectoralis major and minor muscles (Fig. 46.21). Most practitioners use an in-plane approach from the head of the



**Fig. 46.21 Infraclavicular block with ultrasound imaging.** (A) External photograph of the setup for infraclavicular block shows the arm has been abducted in this case. (B) Sonogram of the cords of the brachial plexus (yellow arrows) are adjacent to the axillary artery (A) and vein (V). The neurovascular bundle lies deep to the pectoralis major (PMa) and pectoralis minor (PMi) muscles in this anatomic region. (C) Needle tip is in position for infraclavicular block and the resulting local anesthetic distribution.

**Table 46.2** Examples of Sonographic Landmarks for Infraclavicular Block

Proximal	Optimal Location	Distal
Cephalic vein	Pectoralis minor muscle (midportion)	Subscapular artery
Thoracoacromial artery	Brachial plexus cords surround axillary artery	Coracobrachialis muscle
Chest wall and pleura	Posterior (or medial) cord underneath axillary artery	Anterior circumflex artery Posterior circumflex artery

Infraclavicular block is usually performed at the level of the second part of the axillary artery (deep to the pectoralis minor muscle). Proximal and distal landmarks along the course of the axillary artery are listed.

### Box 46.2 Sonographic Signs Indicating Infraclavicular Block Success

- Reduction in axillary artery diameter during injection
- "U-shaped" distribution underneath the axillary artery
- Separation of cords from axillary artery
- *White wall* appearance to the axillary artery (free walls)
- *Dark layer* underneath the axillary artery (long-axis view)

Several studies of clinical block characteristics have validated the high predictive value of local anesthetic distribution underneath the axillary artery for three-cord anesthesia ("U-shaped" distribution).

table or side of the table. The ideal place for local anesthetic distribution to achieve complete infraclavicular block of the brachial plexus is posterior to the axillary artery for single-shot or catheter placement. Substantial evidence suggests that local anesthetic distribution posterior to the axillary artery produces complete brachial plexus block in the infraclavicular region (Table 46.2 and Box 46.2). The cords of the brachial plexus do not need to be directly visualized for successful block. Duplication of the axillary vein is one of the few anatomic variations in the infraclavicular region. The clinical problem is that the accessory vein lies adjacent to the lateral cord of the brachial plexus and near the usual desired position of the needle tip.

### AXILLARY BLOCKS

The axillary block is a versatile block for upper extremity anesthesia. Although relatively safe and effective with classical approaches, the cardinal weakness has been the failure to block the musculocutaneous nerve. With the advent of ultrasound imaging, this limitation can be overcome by directly visualizing the musculocutaneous nerve.

The axillary block provides surgical anesthesia of the elbow and more distal upper extremity. The shallow depth of the neurovascular bundle (a 20-mm field is typical) and the large amount of working room make this block relatively easy with ultrasound guidance (Table 46.3). Usually, three arterial wall-hugging branches (median, ulnar, and radial) and one branch with a characteristic medial-to-lateral course in the axilla (musculocutaneous) are visualized. In addition, the musculocutaneous nerve has a characteristic change in shape as it moves from adjacent to the artery (round) to within the coracobrachialis muscle (flat) and then exiting the muscle (triangular).

**Table 46.3** Comparison of the Infraclavicular and Axillary Approaches to Brachial Plexus Block

	Infraclavicular Block	Axillary Block
Depth	Deep (two overlying muscles)	Shallow
Onset	Slower	Faster
Tourniquet tolerance	Good	Fair
Catheter success	High	Low

Both in-plane (with needle approaching from the lateral side of the arm) and out-of-plane (with needle approaching from distal to proximal) techniques can be used (Figs. 46.22 and 46.23). The block is performed in the proximal axilla, with the transducer gently pressed against the chest wall to visualize the conjoint tendon of the latissimus dorsi and teres major.<sup>48</sup> A high-frequency linear probe with a small footprint (25–50 mm) with sterile cover can be used for axillary block. The ideal location for local anesthetic injection is between the nerves and the artery so that separation between the two structures occurs to ensure distribution within the neurovascular bundle. These injections result in excellent clinical sensory and motor blocks. The musculocutaneous nerve is usually blocked within the coracobrachialis, where its flat shape gives a large amount of surface area for rapid block. Duplication of the axillary artery and musculocutaneous-median nerve fusion (low-lying lateral cord) are common anatomic variations in the axilla.

## Trunk Blocks

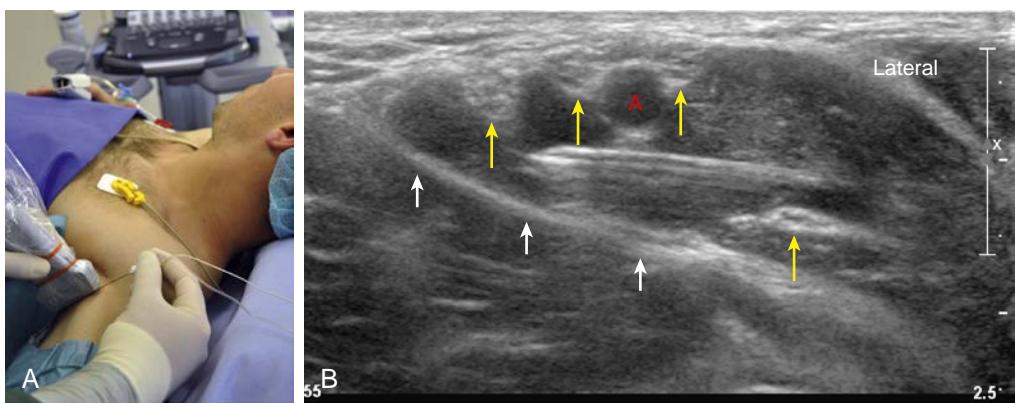
### INTERCOSTAL NERVE BLOCKS

The intercostal nerves are the primary rami of T1 through T11. T12 is technically the subcostal nerve, and it can communicate with the iliohypogastric and ilioinguinal nerves. Fibers from T1 contribute to the brachial plexus; T2 and T3 provide a few fibers to the formation of the intercostobrachial nerve, which supplies the skin of the medial aspect of the upper arm. Each intercostal nerve has four branches: the gray ramus communicans, which passes anteriorly to the sympathetic ganglion; the posterior cutaneous branch, supplying skin and muscle in the paravertebral area; the lateral cutaneous branch, arising just anterior to the midaxillary line and sending subcutaneous branches anteriorly and posteriorly; and the anterior cutaneous branch, which is the termination of the nerve.

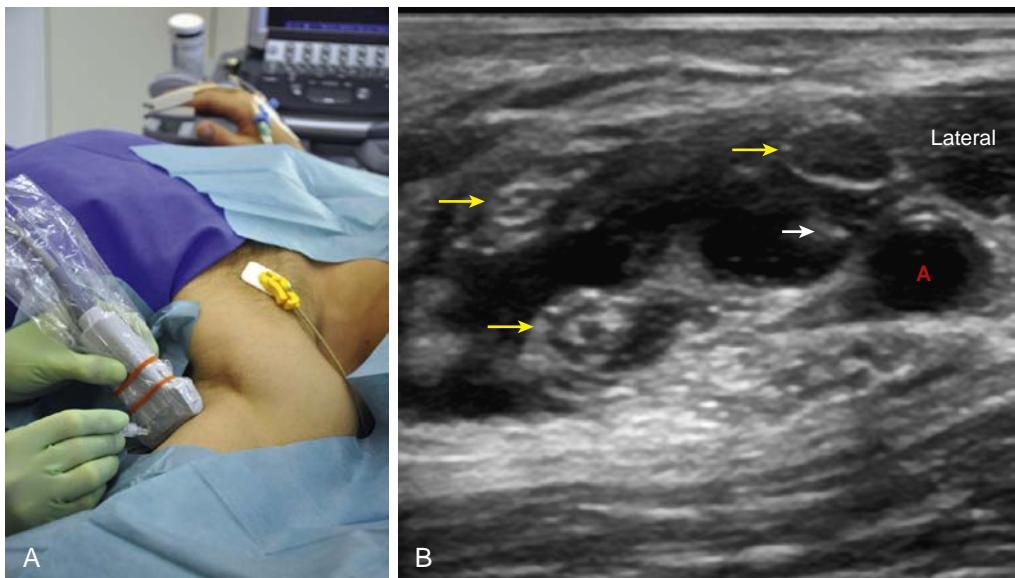
Medial to the posterior angles of the ribs, the intercostal nerves lie between the pleura and the internal intercostal fascia. At the posterior angle of the rib, the nerve lies in the costal groove accompanied by the intercostal vein and artery.

### Clinical Applications

Few surgical procedures can be performed with an intercostal block alone, and the application of these blocks in combination with other techniques has largely been supplanted by epidural blockade. However, in patients with contraindications to neuraxial blockade, these techniques can be used alone or combined with other blocks and light



**Fig. 46.22 Axillary block with ultrasound guidance.** (A) External photograph demonstrates the in-plane approach. (B) Sonogram of the neurovascular bundle in the short-axis view shows the needle tip in-plane after injection of the local anesthetic. The probe compression is just sufficient to coapt the walls of the satellite veins. The block is performed at the level of the conjoint tendon of the latissimus dorsi and teres major (white arrows), which lies under the neurovascular structures. The third part of the axillary artery (A) and nerves of the brachial plexus—radial, ulnar, median, and musculocutaneous—in order from medial to lateral (yellow arrows) are shown.



**Fig. 46.23 Axillary block with ultrasound guidance.** (A) External photograph demonstrates the out-of-plane approach. (B) Sonogram of the neurovascular bundle in the short-axis view shows the needle tip (white arrow) crossing the plane of imaging. The probe compression is just sufficient to coapt the walls of the satellite veins. The third part of the axillary artery (A) and nerves of the brachial plexus (yellow arrows) are shown.

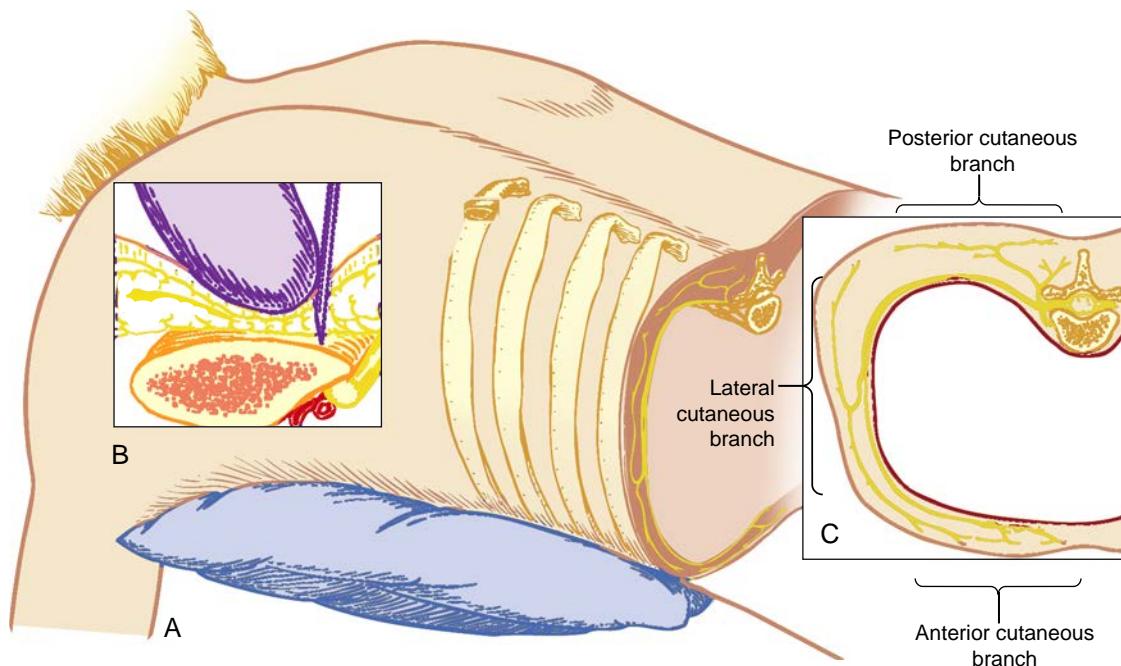
general anesthesia to provide excellent surgical conditions for intraabdominal procedures. Although surgical applications are possible, the majority of indications are for postoperative analgesia. Intercostal blocks provide a viable alternative to epidural and paravertebral blocks, with a similar safety and efficacy profile.<sup>49</sup>

### Intercostal Block Technique

The intercostal nerve can be blocked at the angle of the rib just lateral to the sacrospinalis muscle group. The patient is placed in the prone position with a pillow placed under the abdomen to reduce the lumbar curve (Fig. 46.24). A line is drawn along the posterior vertebral spines. Nearly parallel lines are drawn along the posterior angles of the rib, which can be palpated 6 to 8 cm from the midline. These lines angle medially at the upper levels to prevent overlying of the scapula. The inferior edge of each targeted rib is palpated and is marked on the line intersecting the posterior angle of the rib. After appropriate skin preparation, skin wheals

are injected at each of these points. A 22-gauge, short-bevel, 4-cm needle is attached to a 10-mL syringe. Beginning at the lowest marked rib, the index finger of the left hand displaces the skin up over the patient's rib. The needle is inserted at the tip of the finger until it rests on the rib. The fingers of the left hand are shifted to grasp the needle hub firmly. The left hand then walks the needle 3 to 5 mm off the lower rib edge, where 3 to 5 mL of local anesthetic are injected (see Fig. 46.24B and C). This process is repeated at each marked rib. Appropriate intravenous sedation providing analgesia and some degree of amnesia is desirable for the patient's comfort.

Alternatively, intercostal block can be performed in the supine patient at the midaxillary line. Theoretically, the lateral cutaneous branch of the nerve can be missed, but computed tomography studies show that injected solutions spread several centimeters along the costal groove. Further injection of 1 to 2 mL of local anesthetic as the needle is withdrawn blocks the subcutaneous branches.



**Fig. 46.24** (A) Patient positioning for an intercostal nerve block. (B) The index finger displaces the skin up over the rib. The needle is inserted at the tip of the finger and rests on the rib. The needle is walked off the lower rib edge and inserted 3 to 5 mm. (C) An intercostal nerve and its branches.

### Alternative Techniques

Intercostal blocks are possible with ultrasound imaging for guidance. However, the intercostal nerves and vessels are small (about 1-2 mm in diameter) and run in the costal groove and can therefore be difficult to directly image. Similarly, the innermost intercostal muscle, which separates the intercostal nerves and vessels from the internal and external intercostal muscles, is incomplete in the posterior thorax and can be difficult to image.<sup>50</sup> When detected, the innermost intercostal muscle is thin and hypoechoic on ultrasound scans.<sup>51</sup> Intercostal arteries are most visible medially before they enter the costal groove.<sup>52,53</sup> Intercostal arteries are more tortuous in elderly patients, and therefore more exposed and vulnerable to injury.<sup>54</sup>

Intercostal injections dent the pleura, similar to the displacement seen with paravertebral injections.<sup>55</sup> Injections of local anesthetic at the angle of the rib can track medially along the intercostal vessels within the costal groove toward the paravertebral space.<sup>56,57</sup> While variations on ultrasound-guided intercostal nerve blocks have been developed, including anterior approaches to intercostal branches in the serratus plane<sup>58,59</sup> and parasternal region,<sup>60</sup> new technologies are now being developed to improve ultrasound imaging of intercostal nerves and vessels.<sup>61</sup>

### Side Effects and Complications

The major complication with intercostal blockade is pneumothorax. The actual incidence, however, was as low as 0.07% in a large series performed by anesthesiologists at all levels of training. Routine postoperative chest radiographs showed an incidence of nonsymptomatic pneumothorax of 0.4% to 1.0%.<sup>62,63</sup> If this unusual complication occurs, treatment is usually limited to observation, administration of oxygen, or needle aspiration. Rarely, chest tube drainage is required.

The risk of systemic local anesthetic toxicity is present with multiple intercostal blocks because of the large volumes and rapid systemic absorption of the solutions. Use of epinephrine has been shown to decrease blood levels. Patients should be monitored and observed carefully during the block and for at least 20 to 30 minutes afterward. Patients with severe pulmonary disease who rely on their intercostal muscles can exhibit respiratory decompensation after bilateral intercostal blockade.

### TRANSVERSUS ABDOMINIS PLANE BLOCKS

Four peripheral nerves, the subcostal, ilioinguinal, iliohypogastric, and genitofemoral, primarily innervate the lower abdominal wall. The extended course of the first three nerves through the abdominal wall within the layer between the transversus abdominis and the internal oblique muscles makes this the desired anatomic location for regional block. For ultrasound-guided transversus abdominis plane (TAP) block, the patient is usually in the supine position (Fig. 46.25). The transducer is placed between the iliac crest and costal margin in the midaxillary line. In this location, the muscle layers of the lateral abdominal wall (external oblique, internal oblique, and transversus abdominis) are well defined.

Injection is in the fascial layer that separates the internal oblique and the transversus abdominis muscles. Direct visualization and proximity to the nerves is not critical if 15 to 20 mL of dilute local anesthetic is injected in this layer. The needle approach is in-plane from the anterior side and directed toward the posterolateral corner of the transversus abdominis muscle. The respiratory motion of the peritoneal cavity and influence of muscle contraction makes general anesthesia an appealing option for performing this block. The transversus abdominis muscle is relatively thin; therefore careful placement of the needle tip is necessary.



**Fig. 46.25 Transversus abdominis plane (TAP) block with ultrasound guidance.** (A) Abdominal wall image demonstrates the approach for TAP block. (B) In this sonogram the external oblique (EO), internal oblique (IO), and transversus abdominis (TA) muscles are identified (the three-layer-cake appearance). Nerves (yellow arrow) are seen entering the plane between the IO and TA muscles. (C) The needle approaches in-plane and is directed toward the posterolateral edge of the TA muscles. (D) The kayak sign demonstrates successful TAP injection. The fascia between the IO and TA muscles is split apart in the shape resembling a kayak.

## ILIOINGUINAL AND ILOHYPOGASTRIC NERVE BLOCKS

The ilioinguinal and iliohypogastric nerves arise from the first lumbar spinal root. They pierce the transversus abdominis muscle cephalad and medial to the anterior superior iliac spine to lie between the transversus abdominis and internal oblique muscles. After traveling a short distance caudally and medially, their ventral rami pierce the internal oblique muscle before giving off branches, which then pierce the external oblique and provide sensory fibers to the skin. The ilioinguinal nerve courses anteriorly and inferiorly to the inguinal ring, where it exits to supply the skin on the proximal, medial portion of the thigh. The iliohypogastric nerve supplies the skin of the inguinal region.

### Indications

Ilioinguinal and iliohypogastric blocks are used for analgesia following inguinal hernia repair and for lower abdominal procedures utilizing a Pfannenstiel incision. These blocks have been shown to reduce pain associated with herniorrhaphy significantly, although they do not provide visceral analgesia, and they cannot be used as the sole anesthetic during surgery. Despite the relatively simple technique, a failure rate as frequent as 10% to 25% has been reported.

**Landmark-Based Technique.** These blocks can be performed using a loss-of-resistance technique. The local anesthetic should be injected between the transversus abdominis and the internal oblique and between the internal and external oblique muscles.

The anterior superior iliac spine is located and a mark is made 2 cm cephalad and 2 cm medial. A blunt needle is inserted perpendicular to the skin through a small puncture site. Increased resistance is noted as the needle passes into the external oblique muscle. A loss of resistance is then observed as the needle passes through the external oblique muscle to lie between it and the internal oblique muscle. After negative aspiration, 2 mL of local anesthetic is injected. The needle is then inserted further until another loss of resistance is noted as the needle passes out of the internal oblique to lie between it and the transversus abdominis muscle where another 2 mL of local anesthetic is injected. The needle is withdrawn, and the same procedure is repeated two more times in a fan-like distribution between the internal and external oblique and then between the internal oblique and the transversus abdominis muscles. Typically, a total volume of approximately 12 mL of local anesthetic is used.

It is often difficult to appreciate the loss of resistance. Given the potential complications of advancing the needle too far, ultrasound guidance is often used for these

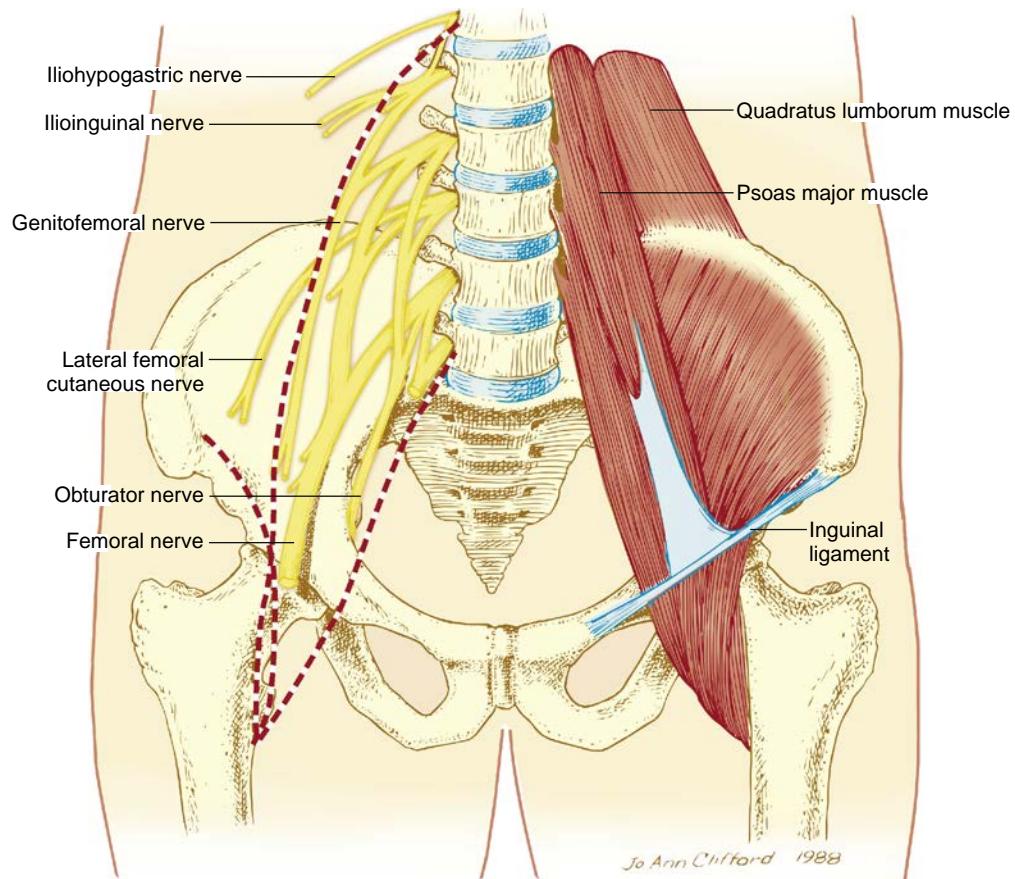


Fig. 46.26 The lumbar plexus lies in the psoas compartment between the psoas major and quadratus lumborum muscles.

blocks.<sup>64,65</sup> The ilioinguinal and iliohypogastric nerves cannot be selectively blocked, even if injection volumes of less than 1 mL are used.<sup>66</sup>

#### Side Effects and Complications

Blind injection can result in inadvertent injury to the intestine or blood vessels with perforation of the large and small bowel and pelvic hematoma. Lower extremity weakness owing to local anesthetic spread and subsequent femoral nerve blockade can also occur.<sup>66</sup>

## Lower Extremity Blocks

### LOWER EXTREMITY ANATOMY

The nerve supply to the lower extremity is derived from the lumbar and sacral plexuses. The lumbar plexus is formed by the anterior rami of the first four lumbar nerves, frequently including a branch from T12 and occasionally from L5 (Fig. 46.26). The plexus lies between the psoas major and quadratus lumborum muscles in the psoas compartment. The lower components of the plexus, L2, L3, and L4, primarily innervate the anterior and medial thigh. The anterior divisions of L2, L3, and L4 form the obturator nerve; the posterior divisions of the same components form the femoral nerve; and the lateral femoral cutaneous nerve is formed from posterior divisions of L2 and L3.

The sacral plexus gives off two nerves that are important for lower extremity surgery: the posterior cutaneous nerve of the thigh and the sciatic nerve. The posterior cutaneous nerve of the thigh and the sciatic nerve are derived from the first, second, and third sacral nerves plus branches from the anterior rami of L4 and L5, respectively. These nerves pass through the pelvis together and are blocked by the same technique. The sciatic nerve is a combination of two major nerve trunks, the tibial (i.e., ventral branches of the anterior rami of L4, L5, S1, S2, and S3) and the common peroneal (i.e., dorsal branches of the anterior rami of L4, L5, S1, S2, and S3), which form the sciatic nerve. The trunks separate at or above the popliteal fossa, with the tibial nerve passing medially and the common peroneal laterally. The cutaneous distributions of the lumbosacral and peripheral nerves are shown in Fig. 46.27.

### FEMORAL NERVE BLOCKS

The advantages of using ultrasound to guide femoral nerve block include a more complete block, local anesthetic volume sparing, and fewer side effects such as vascular punctures. The femoral nerve usually lies lateral to the femoral artery in the groove formed by the iliopsoas and psoas muscles. The nerve can be oval or triangular in cross-sectional shape with an anteroposterior diameter of approximately 3 mm and a mediolateral diameter of 10 mm. The best depiction of the femoral nerve is from 10 cm proximal to 5 cm distal to the inguinal ligament. According to the pelvic

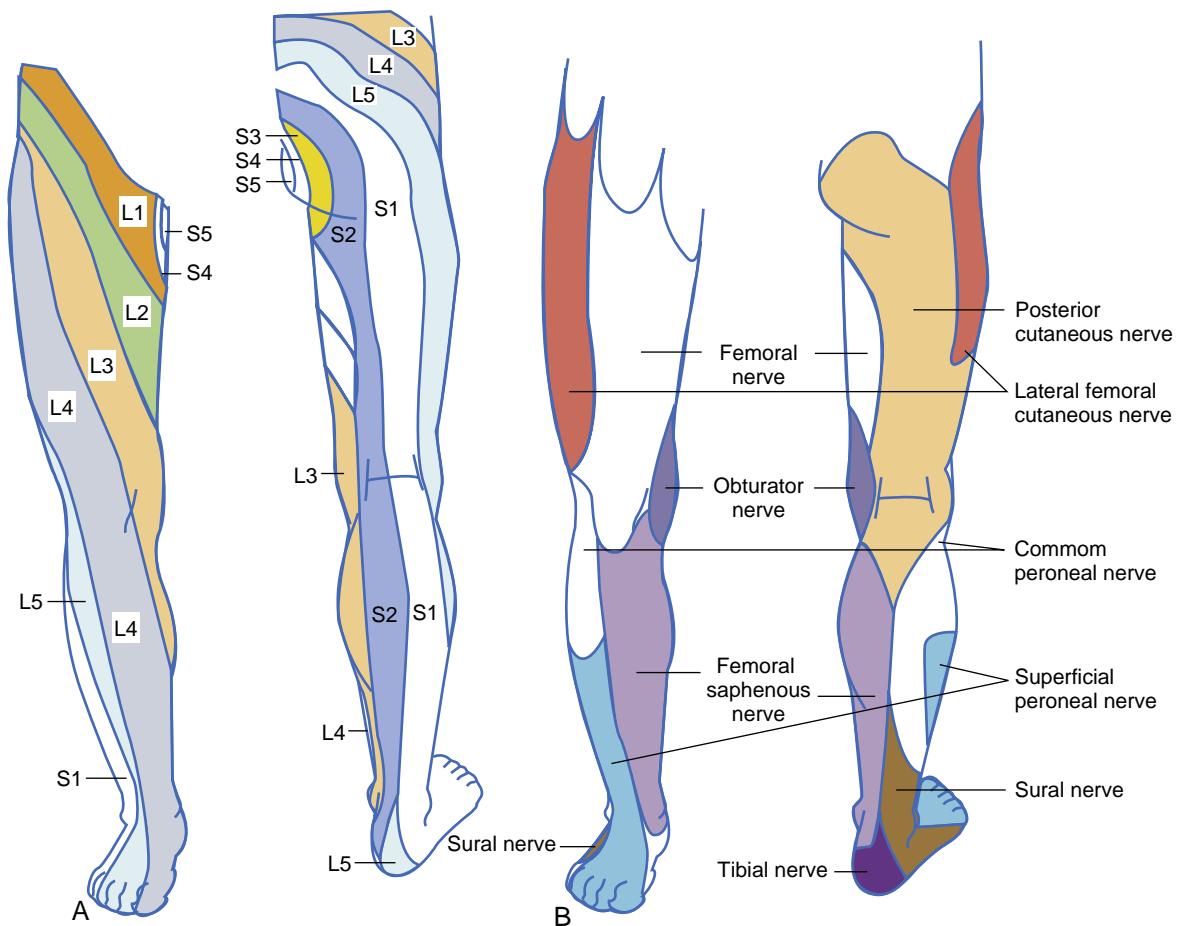


Fig. 46.27 (A) Cutaneous distribution of the lumbosacral nerves. (B) Cutaneous distribution of the peripheral nerves of the lower extremity.

inclination, some tilting of the ultrasound probe is necessary for the sound beam to meet the nerve perpendicularly for optimal scanning. In addition, the femoral nerve has a slight medial-to-lateral course; therefore some rotation of the probe is also necessary for the best view of the nerve. Because the femoral nerve is covered by echobright adipose tissue and fascia, the echogenic outer sheath of the nerve is difficult to establish. In some patients, the psoas tendon can appear similar to the femoral nerve. However, the psoas tendon lies deep within the muscle. If the profunda femoris artery (i.e., the deep branch of the femoral artery) is visualized, then the transducer is usually too distal for complete femoral nerve block. The femoral nerve is often identified as a slight indentation in the surface of the iliacus and psoas muscles.

For femoral nerve block, a broad (35-50 mm footprint) linear transducer is used (Fig. 46.28). Both in-plane (from lateral to medial) and out-of-plane (from distal to proximal) approaches can be used. The advantage of the in-plane approach is visualization of the approaching needle. The disadvantages are the longer needle path and a tendency of the needle to skim over the fascia iliaca by deforming it rather than puncturing it. The out-of-plane approach is often used for catheter placement.

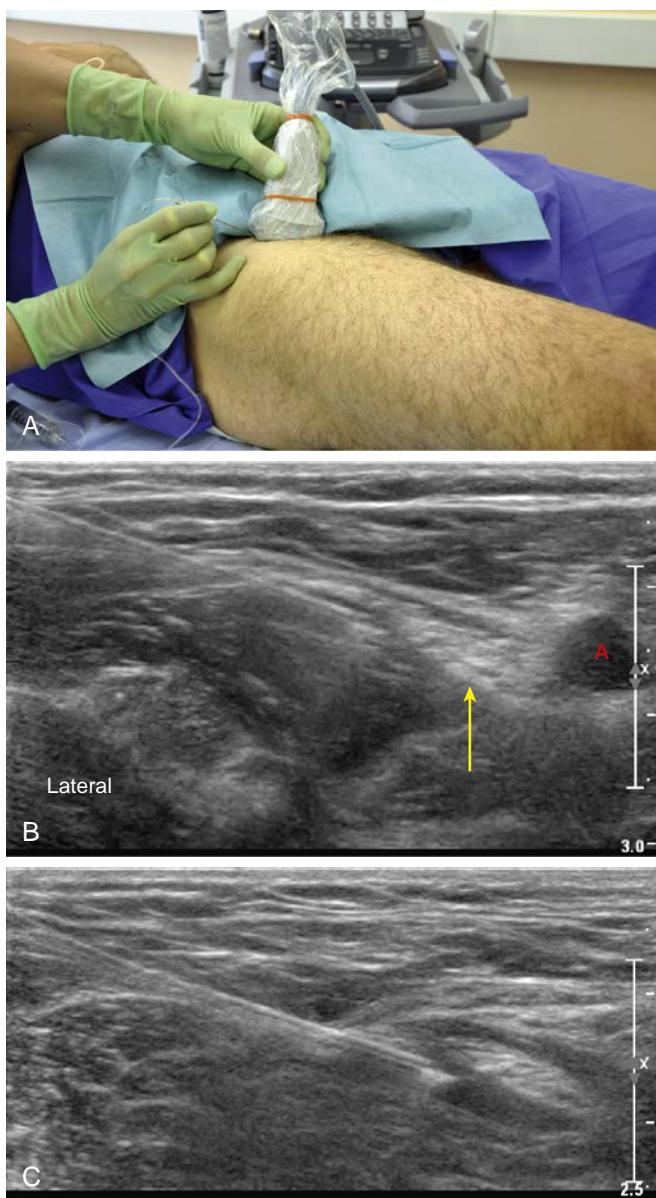
For either approach, the needle tip is positioned between the fascia iliaca and the iliopsoas muscle near the lateral corner of the femoral nerve to avoid the femoral vessels, similar to the method for fascia iliaca block.

The fascia iliaca has a characteristic mediolateral slant. The desired distribution is local anesthetic layering under or completely around the femoral nerve. When layering of local anesthetic is restricted over the nerve, the concern is that the fascia iliaca is intact and that block failure will result. In the obese patient, femoral nerve imaging is challenging and ultrasound can therefore be combined with nerve stimulation for successful block in these patients. After successful injection of a local anesthetic, distal branches of the femoral nerve can be appreciated by sliding the transducer along the known course of the nerve.

### Fascia Iliaca (Modified Femoral Nerve) Blocks

**Technique.** The fascia iliaca block was originally described in children and involved detection of a double pop sensation as the needle traverses the fascia lata and fascia iliaca of the thigh (see also Chapter 77).<sup>67</sup> Penetration of both layers of fascia is important for block success. To facilitate the appreciation of the “clicks” or “pops,” the use of a short-bevel or bullet-tipped needle has been advocated to provide more tactile feedback than with cutting needles.

Because the fascia iliaca invests the iliopsoas muscle and femoral nerve, high volumes of dilute long-acting local anesthetic can be injected to block nerves of the lumbar plexus via this anterior approach. The clinical applications for fascia iliaca block are similar as those for femoral nerve block.<sup>68</sup>



**Fig. 46.28 Femoral nerve block with ultrasound imaging (in-plane approach).** (A) External photograph shows the setup for femoral nerve block. (B) The needle tip is in position before injecting adjacent to the femoral nerve (yellow arrow). The femoral nerve lies lateral to the femoral artery (A). (C) Local anesthetic surrounds the femoral nerve after injection. (Modified from Gray AT. *Atlas of Ultrasound-Guided Regional Anesthesia*. 3rd ed. Philadelphia: Saunders; 2018.)

The needle entry site for the fascia iliaca block is determined by drawing a line between the pubic tubercle and the anterior superior iliac spine and dividing this line into thirds. The needle entry point is 1 cm caudal to the intersection of the medial two thirds and lateral one third along this line. This site is well away from the femoral artery, which is useful for patients in whom femoral artery puncture is contraindicated. Ultrasound can also be used to visualize the two fascial layers and monitor the spread of local anesthetic beneath the fascia iliaca.<sup>69,70</sup>

**Side Effects and Complications.** Intravascular injection and hematoma are possible because of the proximity of the femoral artery. Anatomically, the femoral nerve and artery are located in separate sheaths approximately 1 cm

apart. In most patients with normal anatomy, the femoral artery can be easily palpated, allowing correct, safe needle positioning lateral to the pulsation. The presence of femoral vascular grafts is a relative contraindication to these techniques, but these grafts are easily identified with ultrasound imaging in most cases. Because the injection is made between the femoral and lateral femoral cutaneous nerves, nerve damage is rare.

### SAPHENOUS NERVE BLOCKS ABOVE THE KNEE (INCLUDING ADDUCTOR CANAL BLOCK)

#### Indications

Several approaches to the saphenous nerve block have been described using an above-the-knee approach. When used in combination with multimodal analgesia, a saphenous nerve block at or near the mid-thigh can be as effective or in some studies preferable to a femoral nerve block following knee surgery because of reduced rates of quadriceps weakness.<sup>71-73</sup> The correct “adductor canal block” location is a source of active debate even though the putative anatomic targets may be separated by mere inches. The “true” adductor canal block may best be determined with ultrasound by identifying the medial border of the sartorius muscle converging with the medial border of the adductor longus muscle.<sup>74</sup> A double contour is appreciated on the roof of the canal, which denotes the vastoadductor membrane. This anatomic distinction holds importance as the nerve to the vastus medialis often lies outside the adductor canal in a distinct fascial sheath. Hence a too distal adductor canal block within the “true” adductor canal may miss the nerve to the vastus medialis, a major contributor to knee joint pain following total knee arthroplasty. Jaeger and colleagues advocate for a periarterial injection of local anesthesia lateral to the femoral artery under the sartorius muscle deep to the vastoadductor membrane midway between the anterior superior iliac spine and the patella where local anesthetic is likely to bathe both the saphenous nerve and the nerve to the vastus medialis.<sup>71</sup>

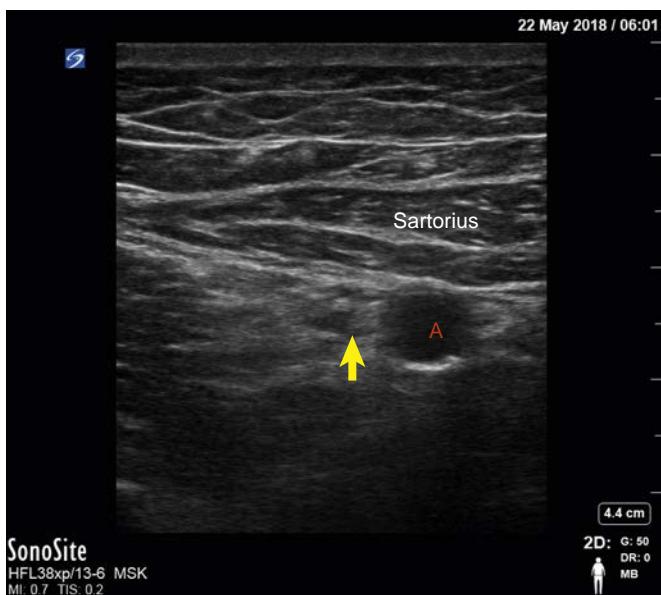
#### Anatomy

As the saphenous nerve is a terminal sensory branch of the femoral nerve above the knee, it supplies innervation to the infrapatellar branches to the knee joint. It pierces the fascia lata between the tendons of the sartorius and gracilis muscles before it runs in the adductor canal along the posterior border of the sartorius muscle. The nerve emerges and divides at the level of the knee before continuing distally along the medial border of the lower leg.

#### Technique

Adductor canal block is performed in the supine position with thigh positioned in slight external rotation with leg extended to expose the inner thigh. Ultrasound guidance is the preferred neurolocalization technique, although nerve stimulation would also be an option or both used in combination.

**Ultrasound-Guided Technique.** A high-frequency linear transducer (15-6 MHz) probe is positioned transverse on the anteromedial thigh, which is scanned in short-axis beginning at the junction between the middle and distal thirds of the thigh. The thick vastoadductor membrane



**Fig. 46.29 Proximal saphenous nerve block (adductor canal block).** Sonographically, the adductor canal block may best be determined by identifying the converging borders between the vastus medialis muscle (lateral), sartorius muscle (anterior), and femoral artery (most medial). Periarterial deposit of local anesthesia is desired lateral to the femoral artery midway between the anterior superior iliac spine and the patella.

defines the border between vastus medialis muscle (lateral), sartorius muscle (anterior), and femoral artery (most medial) (Fig. 46.29). A 22-gauge, 5-cm needle is most often selected with 2- to 3-cm depths to the target. Through an in-plane approach approximately 10 to 15 mL of local anesthetic (higher volumes may result in quadriceps paresis)<sup>75</sup> is injected lateral to the artery, deep to the sartorius muscle.

#### Side Effects and Complications

The risks of complications with this block are low, although the same theoretical risks with all regional anesthetic techniques apply to this block. Vascular injury leading to arterial pseudoaneurysm is possible. Intramuscular spread of local anesthetic should be avoided as cases of myonecrosis have been reported<sup>76</sup> and unexpected thigh weakness should prompt evaluation. Although adductor canal block is considered among the more selective “muscle-sparing” peripheral blocks of the lower extremity, caution is still advised and fall prevention strategies are important, including patient education on avoidance of unsupported ambulation.<sup>77</sup>

### SAPHENOUS NERVE BLOCKS BELOW THE KNEE

#### Indications

The saphenous nerve provides innervation to the medial aspect of the lower extremity from the knee to the medial malleolus. Saphenous nerve blocks are commonly combined with popliteal and ankle blockade. Several approaches to the saphenous nerve block have been described, including a paravenous (below the knee) approach. Ultrasound guidance can be used for this technique. The saphenous nerve can be blocked at the level of the ankle and can be combined with other injections for ankle block.

### Anatomy

The saphenous nerve emerges from the adductor canal hiatus and divides at the level of the knee before continuing distally along the medial border of the tibia, posterior to the great saphenous vein. The saphenous nerve is located approximately 1 cm medial and 1 cm posterior to the saphenous vein at the level of the tibial tuberosity.

#### Technique

The saphenous nerve at this point is purely sensory; therefore a field block technique is possible and likely equally effective to nerve stimulation. Ultrasound guidance has gained significant popularity as a tool to identify the neural and vascular structures that lie in close proximity to the saphenous nerve.

**Paravenous Approach.** At the level of the tibial tuberosity, approximately 5 to 10 mL of local anesthetic is infiltrated deep to the great saphenous vein.

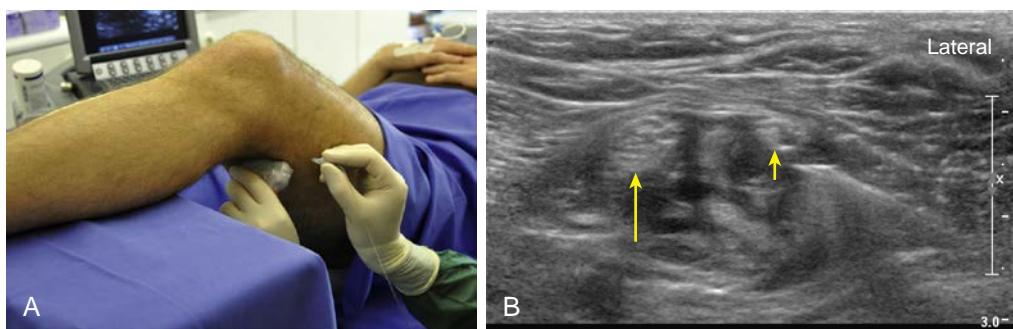
**Localized Field Block.** Approximately 5 to 10 mL of local anesthetic may be infiltrated from the medial condyle of the tibia anteriorly to the tibial tuberosity and posteriorly to the medial head of the gastrocnemius muscle. Success rates for this technique range from 33% to 65%.

#### Side Effects and Complications

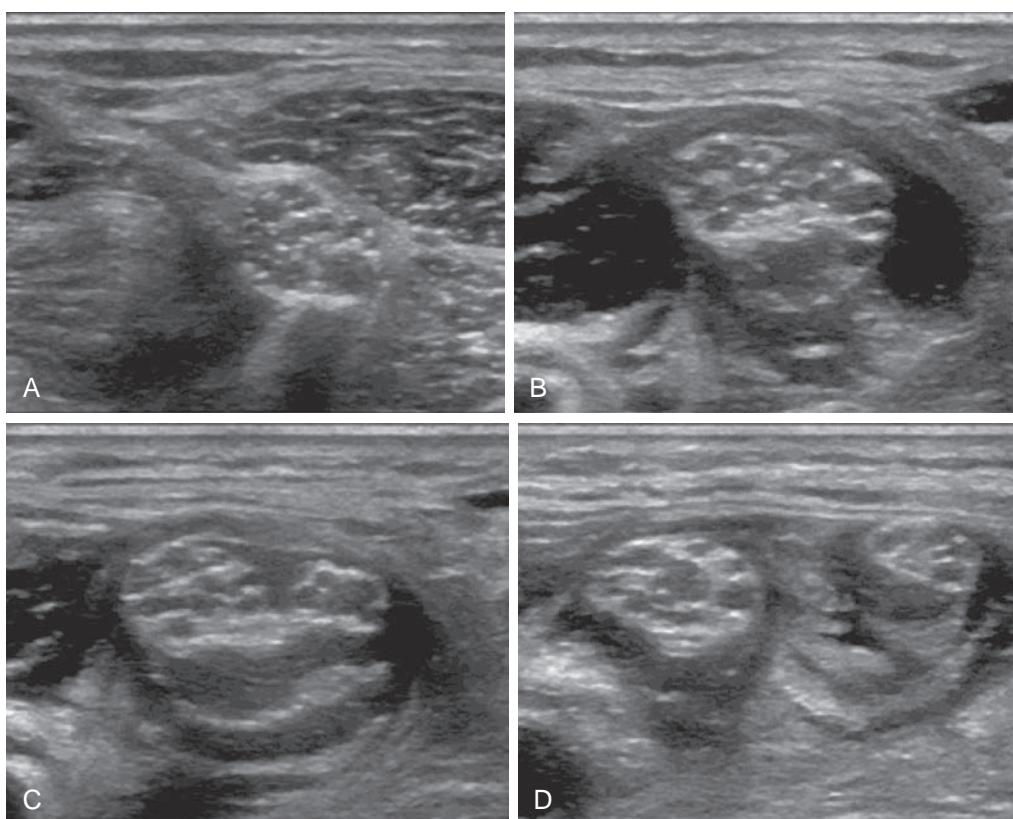
The risks of complications with this block are low, although the same risk pattern for all regional anesthetic techniques apply to this block; that is, nerve or tissue damage and vascular puncture with hematoma formation. Given that the great saphenous vein is used as a landmark for the field block technique, minor hematoma formation is not uncommon.

### SCIATIC NERVE BLOCKS IN THE POPLITEAL FOSSA

The sciatic nerve can be blocked anywhere along its course from the gluteal region to the popliteal fossa.<sup>78-80</sup> Many approaches have been described, including those from the anterior aspect of the thigh.<sup>81</sup> One of the most common approaches is to block the sciatic nerve in the popliteal fossa using a lateral approach in supine position with the leg elevated.<sup>82</sup> In this anatomic location, the block can be performed close to the skin surface. The division of the sciatic nerve provides a broad target with large surface area to promote clinical block characteristics. For this technique, the needle tip is positioned between the tibial and common peroneal components of the sciatic nerve near the division so that a single injection distributes to both nerves (Fig. 46.30). By sliding the transducer along the known course of the sciatic nerve, its characteristic division in the popliteal fossa can be identified. This method of sliding assessment is also important to verify the local anesthetic distribution after injection. The tibial nerve has a straighter course than the common peroneal nerve and has approximately twice the cross-sectional area. The tibial nerve lies posterior to the popliteal artery and vein at the popliteal crease, and this location can be a useful starting point when imaging is difficult. When the foot is moved, the nerves of the popliteal fossa have characteristic motions that can be helpful for nerve identification in some patients. The advantages of this



**Fig. 46.30 Popliteal block with ultrasound imaging (in-plane approach).** (A) External photograph shows the setup for popliteal nerve block in the supine position. The leg is elevated, and the transducer is applied to the posterior surface of the leg. (B) The needle approaches the bifurcation of the sciatic nerve in the plane of imaging from the lateral aspect of the leg. The needle tip is positioned between the tibial (long yellow arrow) and common peroneal (short yellow arrow) nerves.



**Fig. 46.31** Sciatic nerve imaging in the popliteal fossa before (A), during (B and C), and after (D) division into the tibial and common peroneal nerves. Local anesthetic tracks with both individual nerves, thereby confirming a successful block.

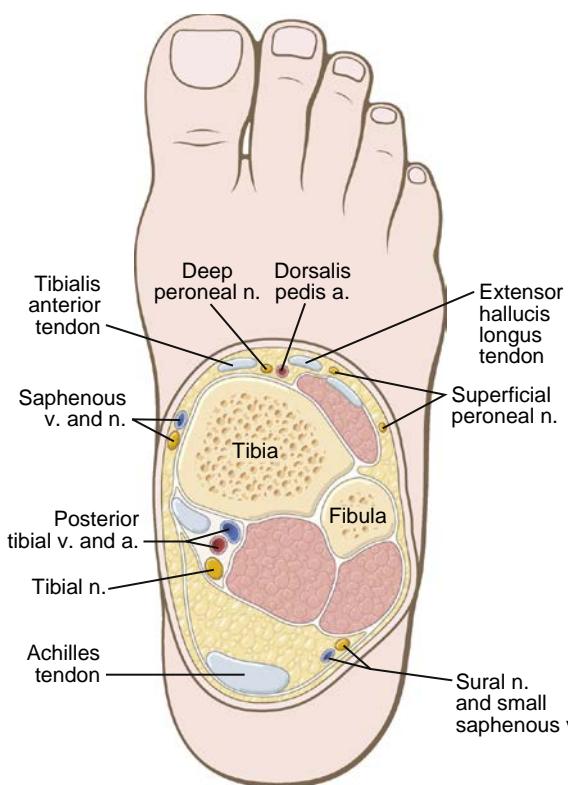
approach are the convenient position, the transducer position is remote from the site of needle entry, and the parallel in-plane approach of the block needle results in optimal needle tip visibility. After injection, following the local anesthetic distribution around and along the nerve path (Fig. 46.31) is relatively easy.

### ALTERNATIVE APPROACHES TO SCIATIC NERVE BLOCK

The sciatic nerve can be blocked anywhere along its course. However, approaches proximal to the popliteal fossa are usually more difficult because the nerve lies deeper from the skin surface. The sciatic nerve is a mobile structure with position and orientation varying with extremity

motion.<sup>83,84</sup> Because of the depth and variation in position, ultrasound guidance is useful for proximal sciatic nerve blocks in both adults and children.<sup>85</sup>

For procedures above the knee, the parasacral sciatic nerve block can provide an advantage over more distal approaches because the block of both the sciatic and posterior femoral cutaneous nerves is possible.<sup>86-89</sup> Alternatively, the posterior femoral cutaneous nerve can be blocked separately using ultrasound guidance.<sup>90</sup> The subgluteal approach to sciatic nerve block is useful when block of the hamstring muscles is indicated.<sup>91</sup> The anterior approach to sciatic nerve block is useful when the patient cannot be positioned for other approaches due to pain or leg traction.<sup>92-94</sup> These proximal approaches to sciatic nerve block may require multiple injections for rapid onset.<sup>91</sup> The



**Fig. 46.32 Cross-sectional anatomy for an ankle block.** An ankle block is performed by injecting local anesthetic solution at five separate nerve locations. The superficial peroneal nerve, sural nerve, and saphenous nerve are usually blocked by subcutaneous infiltration because they may have already branched as they cross the ankle joint. The tibial and deep peroneal nerves require deeper injection adjacent to the accompanying blood vessels (the posterior tibial and anterior tibial arteries, respectively). Because the block needle approaches the ankle from many angles, it is convenient to elevate the foot by supporting the calf. (Modified from Brown DL, Factor DA, eds. *Regional Anesthesia and Analgesia*. Philadelphia: WB Saunders; 1996.)

blood supply of the sciatic nerve in the gluteal region can be detected with ultrasound imaging, and this can help with nerve localization in some patients.<sup>95</sup>

### NERVE BLOCKS AT THE ANKLE

Ankle blocks are relatively simple to perform and offer adequate anesthesia for surgical procedures of the foot. These blocks are traditionally performed at the level of the malleoli and guided by surface landmarks.

Four of the five individual nerves that can be blocked at the ankle to provide anesthesia of the foot are terminal branches of the sciatic nerve: the tibial, sural, superficial peroneal, and deep peroneal branches (Fig. 46.32). The sciatic nerve divides at or above the apex of the popliteal fossa to form the common peroneal and tibial nerves. The common peroneal nerve descends laterally around the neck of the fibula, where it divides into the superficial and deep peroneal nerves. The sural nerve forms in the leg from both tibial and common peroneal nerve contributions.

The saphenous nerve is the major descending sensory branch of the femoral nerve. The territory of this nerve is the medial leg and can extend as far as the base of the great toe and is included as part of the ankle block.<sup>96</sup>

### Tibial Nerve Technique

The tibial nerve can be blocked with the patient in either the prone or the supine positions. The posterior tibial artery is palpated, and a 25-gauge, 3-cm needle is inserted postero-lateral to the artery at the level of the medial malleolus (Fig. 46.33A and B). A paresthesia is often elicited; however, it is not necessary for a successful block. If a paresthesia is obtained, 3 to 5 mL of local anesthetic should be injected. Otherwise, 7 to 10 mL of local anesthetic should be injected as the needle is slowly withdrawn from the posterior aspect of the tibia. Blockade of the tibial nerve provides anesthesia of the heel, plantar portion of the toes, and the sole of the foot, as well as some motor branches in the same area. Ultrasound imaging of the tibial nerve can shorten onset time (Fig. 46.34).<sup>97</sup>

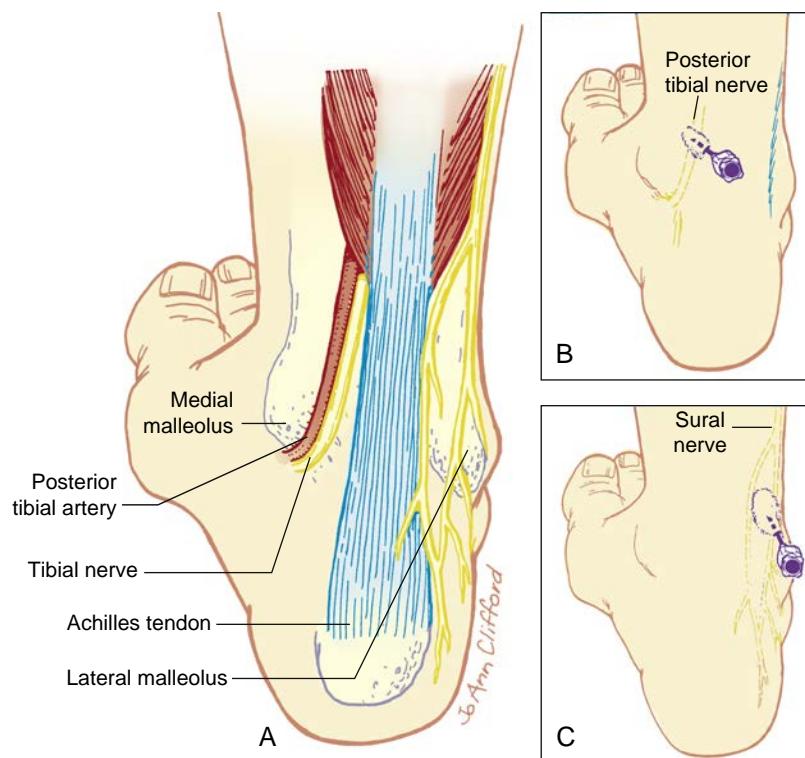
**Sural Nerve Technique.** The sural nerve is located superficially between the lateral malleolus and the Achilles tendon. A 25-gauge, 3-cm needle is inserted lateral to the tendon and is directed toward the malleolus as 5 to 10 mL of solution is injected subcutaneously (see Figs. 46.33 and 46.35). This block provides anesthesia of the lateral foot and the lateral aspects of the proximal sole of the foot.

**Deep Peroneal, Superficial Peroneal, and Saphenous Nerve Techniques.** The deep peroneal, superficial peroneal, and saphenous nerves can be blocked through a single needle entry site (see Fig. 46.35). A line is drawn across the dorsum of the foot connecting the malleoli. The extensor hallucis longus tendon is identified by having the patient dorsiflex the big toe. The anterior tibial artery lies between this structure and the tendon of the extensor digitorum longus muscle and is palpable at this level. A skin wheal is raised just lateral to the arterial pulsation between the two tendons on the intermalleolar line. A 25-gauge, 3-cm needle is advanced perpendicular to the skin entry site, and 3 to 5 mL of local anesthetic is injected deep to the extensor retinaculum to block the deep peroneal nerve. This technique anesthetizes the skin between the first and second toes and the short extensors of the toes.

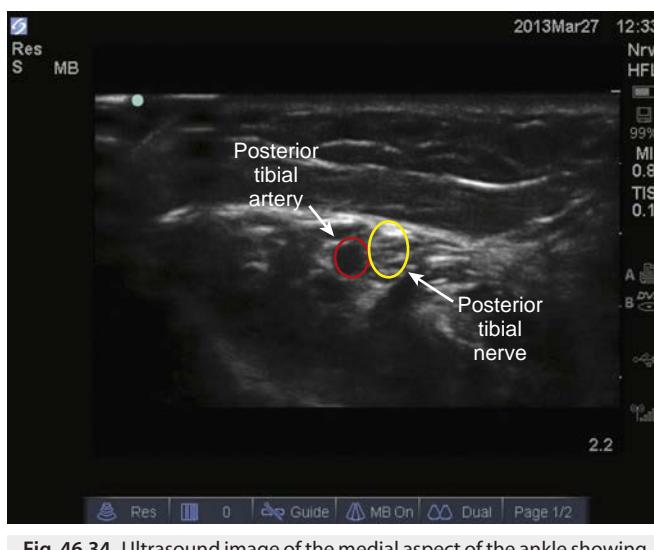
The needle is directed laterally through the same skin wheal while injecting 3 to 5 mL of local anesthetic subcutaneously, blocking the superficial peroneal nerve and resulting in anesthesia of the dorsum of the foot, excluding the first interdigital cleft. The same maneuver can be performed in the medial direction, thereby anesthetizing the saphenous nerve, a terminal branch of the femoral nerve that supplies a strip along the medial aspect of the foot.

### Side Effects and Complications

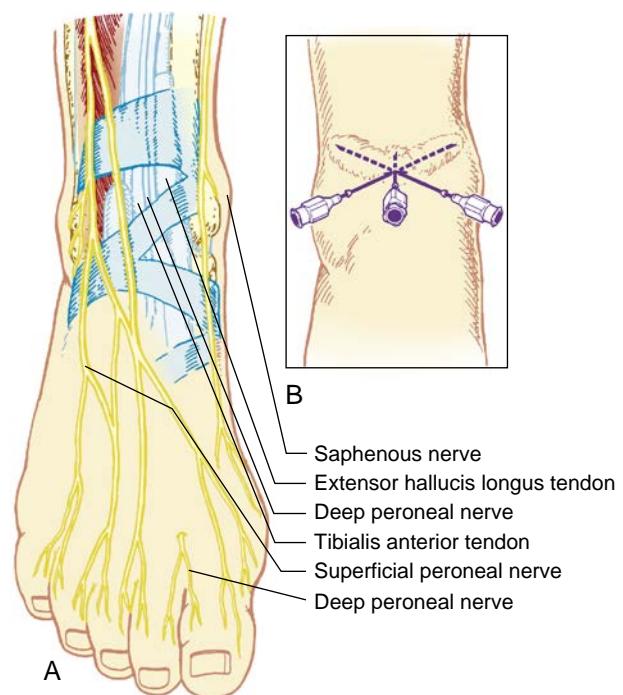
Multiple injections are required for this procedure, which can result in discomfort for the patient. Persistent paresthesias can occur, but they are generally self-limited. The presence of edema or induration in the area of the ankle block can make palpation of landmarks difficult. When this pathology is present, a more proximal block is usually performed (e.g., popliteal and saphenous nerves blocks in the distal thigh). Intravascular injection is possible but unlikely if aspiration for blood is negative.



**Fig. 46.33** (A) Anatomic landmarks for a block of the posterior tibial and sural nerves at the ankle. (B) Posterior tibial nerve and method of needle placement for a block at the ankle. (C) Sural nerve and method of needle placement for a block at the ankle.



**Fig. 46.34** Ultrasound image of the medial aspect of the ankle showing the posterior tibial artery (red) and the posterior tibial nerve (yellow).



**Fig. 46.35** (A) Anatomic landmarks for a block of the deep peroneal, superficial peroneal, and saphenous nerves at the ankle. (B) Method of needle placement for a block of the deep peroneal, superficial peroneal, and saphenous nerves through a single needle entry site.

## INTRAVENOUS REGIONAL ANESTHESIA (OR BIER BLOCK)

### Introduction and Clinical Applications

Intravenous regional blocks were first described in 1908 by the German surgeon, August Bier. The Bier block has multiple advantages, including ease of administration, rapid onset and recovery, muscular relaxation, and controllable duration of anesthesia. It is an excellent technique for short (<60 minutes) surgical procedures. Bier blocks are also used in the management of complex regional pain syndromes (for further details

on intravenous regional analgesia in pain syndromes, see [Chapter 51](#)). Most commonly IVRA is used for upper extremity procedures such as excision of soft tissue masses or carpal tunnel release. Lower extremity blocks are also possible.

## Technique (Upper Extremity)

With this technique blood is replaced with local anesthetic using a tourniquet to isolate the extremity from the central circulation. The duration of surgical anesthesia and analgesia for Bier block is essentially the time of tourniquet inflation. Contraindications to Bier block are the same as contraindications to tourniquet placement (limb ischemia, infection).

### Prerequisites

Place a thin intravenous catheter (20 or 22 gauge) in the operative extremity (to reduce the amount of bleeding when the catheter is removed). Use only a minimal amount of dressing to secure the catheter. The intravenous catheter is usually placed distal or near the surgical site (although it is not clear if this influences block quality). If intravenous access is difficult, the procedure may need to be aborted.

Importantly, the patient should also have an intravenous cannula in the nonoperative upper extremity for administration of fluids and other drugs. If antibiotics are indicated they should be administered before the block (to allow these drugs to effectively reach the surgical site before tourniquet inflation). Lipid emulsion should be immediately available in the event that local anesthetic systemic toxicity occurs (see Chapter 29 for more details).

### Extremity Exsanguination and Tourniquet Inflation

Raise the extremity above the level of the heart prior to exsanguination with an Esmarch bandage. This will passively drain venous blood from the extremity over one to two minutes (this can be done during the timeout). Stretch and wrap an Esmarch bandage around the extremity from distal to proximal in a spiral overlapping fashion, continuing until the cuff of the tourniquet is covered.

Following exsanguination with an Esmarch bandage, the tourniquet is typically inflated to 250 mm Hg or 100 mm Hg above systolic blood pressure. Therefore it is important that the patient be normotensive (systolic blood pressure 150 mm Hg or less) during the period of tourniquet inflation. If necessary, sedation or antihypertensive medications may be given. Another alternative is to increase the tourniquet inflation pressure to 275 mm Hg for brief tourniquet runs (usually <60 minutes for Bier blocks). For these reasons, it is important that blood pressure be carefully monitored and controlled during intravenous regional anesthesia. Both the surgical conditions and block quality are highly dependent on the exsanguination of the extremity.

Use of a single, wide cuff allows use of smaller inflation pressures during intravenous regional anesthesia. The postulated advantage is that the smaller pressures will decrease the incidence of neurologic complications related to high inflation pressures with the narrow double cuffs.<sup>98</sup>

Preservative free 2-chloroprocaine 0.5%, lidocaine 0.5%, or prilocaine 0.5% can be used for intravenous regional anesthesia (plain solution, without epinephrine).<sup>99-101</sup> For upper extremity anesthesia, an arm (about 0.6 mL/kg, maximum 50 mL) or forearm (about 0.4 mL/kg, maximum 25 mL) tourniquet can be used, depending on the surgical site.<sup>102</sup> Bupivacaine is not recommended for intravenous regional anesthesia because cases of severe local anesthetic toxicity have been reported.<sup>103</sup> However, dilute solutions of

long-acting amides (0.125% levobupivacaine or 0.2% ropivacaine) have successfully been used to prolong sensory block and analgesia after tourniquet deflation.<sup>104-106</sup>

An additional temporary tourniquet (used for intravenous placement) can be placed immediately proximal to the surgical site while the first 10 or 20 mL of local anesthetic is injected via the catheter (the second tourniquet is then released). This will confine local anesthetic to the distal extremity and promote block onset.<sup>107,108</sup> Inject slowly so that venous pressures remain low. If the injection is at a distal site the leakage under the tourniquet will be reduced. The onset of anesthesia is usually within 5 to 10 minutes. After injection, the intravenous catheter is typically removed (although repeat injections using an indwelling catheter have been described).

Because the Bier block does not result in prolonged analgesia, long-acting local anesthetic should be infiltrated into the surgical field prior to tourniquet deflation. In this manner the onset of infiltrative analgesia matches the offset of the Bier block.

### Tourniquet Deflation

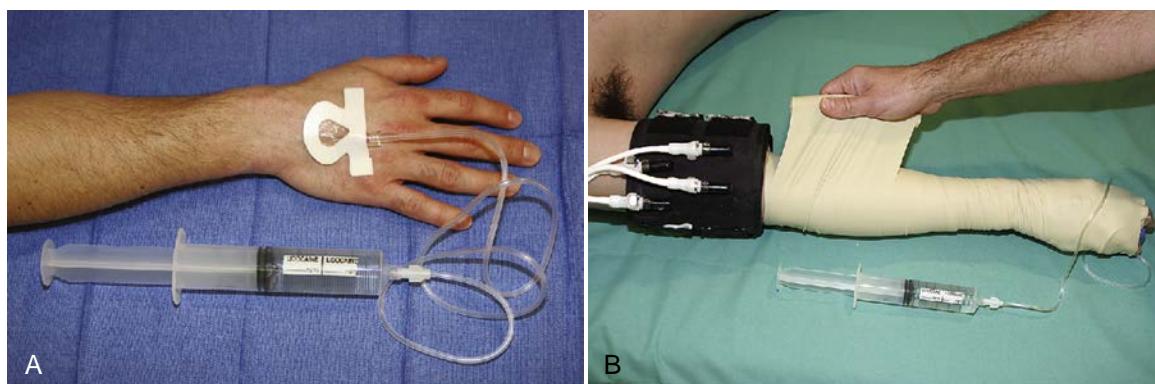
The tourniquet can be safely released after 25 minutes, but the patient should be closely observed for local anesthetic toxicity for several minutes after the tourniquet release. Shorter tourniquet times (<25 minutes) are possible with 2-chloroprocaine because this local anesthetic is rapidly degraded by plasma esterases when blood re-enters the extremity upon tourniquet deflation. Rare cases of systemic toxicity from 2-chloroprocaine have been reported in patients with atypical esterases.<sup>109</sup>

Systemic plasma levels of local anesthetic will increase with venous return from the extremity following tourniquet deflation. This occurs when the tourniquet inflation pressure is less than venous levels (nearly 0 mm Hg). Cyclic deflation of the tourniquet at 10-second intervals for two or three cycles increases the time to peak arterial lidocaine levels, which may decrease potential toxicity.<sup>110</sup> It is recommended to not raise the extremity immediately after the tourniquet is removed, as this will promote venous return containing local anesthetic. Reinflate the tourniquet if any signs of systemic toxicity occur.

### Comments

**Double-Cuff Tourniquets.** A double-cuff tourniquet can be used instead of a single-cuff tourniquet to extend the tourniquet tolerance time (Fig. 46.36). Both adjacent cuffs should have secure closures and reliable pressure gauges. After exsanguination of the arm, the proximal cuff is inflated to approximately 100 mm Hg greater than the systolic pressure, and absence of a radial pulse confirms adequate tourniquet pressure. When the patient complains of tourniquet pain, the distal tourniquet, which overlies anesthetized skin, is inflated, and the proximal tourniquet is released. However, if a long tourniquet time is anticipated it is usually best to choose other peripheral nerve block or provide a general anesthesia.

**Additives and Adjuncts.** Additives and adjuncts should be used with caution because prolonged exposure of these compounds to the venous endothelium during tourniquet



**Fig. 46.36** (A) Placement and securing of a small intravenous catheter. (B) Exsanguination of the arm with an Esmarch bandage before inflation of the tourniquet and injection of the local anesthetic solution through the catheter. In this figure a double-cuff tourniquet is shown.

inflation may result in phlebitis (even if the compounds are considered safe for routine intravenous use).

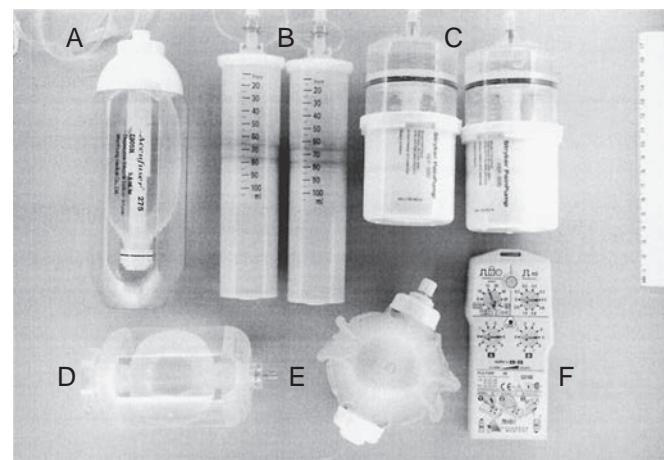
### Complications

Technical problems with this block include tourniquet discomfort, rapid resolution leading to postoperative pain, difficulty in providing a bloodless field, and the necessity of exsanguination in the case of a painful injury. Accidental or early deflation of the tourniquet or use of excessive doses of local anesthetics can result in systemic toxicity. Injection of the drug as distally as possible at a slow rate decreases blood levels and theoretically may increase safety. Nerve injury and compartment syndrome have been reported with long tourniquet times and high tourniquet inflation pressures. Hypertonic solutions can cause compartment syndrome and should never be used for intravenous regional anesthesia.<sup>111</sup>

## Continuous Catheter Techniques

The advantages cited for continuous nerve blockade include prolongation of surgical anesthesia, decreased risk of systemic toxicity because of lower incremental doses, postoperative pain relief, and sympathectomy. Catheter placement using over-needle and through-needle methods have been described. Advances in equipment technology, including the development of stimulating needles and catheters and portable pumps allowing local anesthetic infusion after hospital dismissal, have increased the success rate and popularity of continuous peripheral blockade (Fig. 46.37). Although concern regarding accurate catheter placement and maintenance still exists, the use of stimulating catheters and radiographic confirmation may further improve the functionality. Ultrasound guidance appears to produce more consistent times for catheter placement.<sup>112</sup> Overall, continuous peripheral nerve block provides superior analgesia compared with conventional opioid therapy. Minor technical problems such as catheter kinking, displacement or leakage, and bacterial colonization are frequent, with no adverse clinical consequences in the large majority of cases. Major neurologic and infectious adverse events are rare.

Methods of providing continuous brachial plexus anesthesia have been described since the 1940s. These methods frequently offer ingenious solutions for the placing and securing of the needle or catheter. This technique is especially applicable to patients with upper extremity or digit



**Fig. 46.37** Portable infusion pumps. (A) Accufuser (McKinley Medical, Wheat Ridge, Colo.). (B) Sgarlato (Sgarlato Labs, Los Gatos, Calif.). (C) Stryker PainPump (Stryker Instruments, Kalamazoo, Mich.). (D) MedFlo II (MPS Acacia, Brea, Calif.). (E) C-Bloc (I-Flow, Lake Forest, Calif.). (F) Microject PCA (Sorenson Medical, West Jordan, Utah). (From Ilfeld BM, Morey TE, Enneking FK. The delivery rate accuracy of portable infusion pumps used for continuous regional analgesia. *Anesth Analg*. 2002;95:1331–1336.)

replantation, total shoulder or elbow arthroplasty, or reflex sympathetic dystrophies, for which prolonged pain relief and sympathectomy are advantageous.

Continuous lower extremity techniques were also described decades ago, but until recently have remained underused compared with continuous upper extremity and neuraxial approaches. Reliable, improved success rates and the risk of spinal hematoma after neuraxial techniques led clinicians to reconsider continuous lower extremity blocks. Contemporary applications for continuous psoas compartment, sciatic, femoral, adductor canal, and popliteal fossa blockade have been reported. Compared with conventional systemic and neuraxial analgesic methods, continuous lower extremity blocks provide superior analgesia with fewer side effects, improve perioperative outcomes, and accelerate hospital dismissal after major joint replacement.

### TESTING THE CATHETER

Test injections of saline, local anesthetic, or air with real-time ultrasound imaging can be used to assess catheter

tip function. The overall success rate of peripheral nerve catheter placement with ultrasound guidance is high, so the additional value of these subsequent tests is still being established.<sup>113,114</sup>

## SECURING THE CATHETER

Catheter migration and dislodgement are clinically relevant issues. Catheter threading distances do not seem to correlate with the chance of dislodgement.<sup>115</sup> Excessively large threading distances (>5 cm) may result in catheter knotting. If ultrasound guidance is used for catheter placement, sterile dry gauze can be used to remove excess gel prior to securing the catheter. Skin adhesive applied to the catheter at the skin exit site may reduce catheter dislodgment, fluid leakage at the site, and chance of catheter related infection.<sup>116,117</sup> Application of skin adhesive at more than one site along the catheter may improve fixation.<sup>118</sup> A partial loop or coiling the catheter at the exit site will help reduce catheter dislodgement, and a variety of strain relief devices are now commercially available. Some practitioners elect to use tunnel catheters that are intended to remain in place for a prolonged period of time.

## Choice of Local Anesthetic

The choice of local anesthetic for a peripheral nerve block depends to some extent on the duration of the surgical procedure, although other factors are also important (see [Chapter 29](#)). Prolonged blockade for up to 24 hours often occurs with long-acting local anesthetics such as bupivacaine or ropivacaine. Although this feature often results in superb postoperative pain relief, it may be undesirable in some patients because of the possible risk of nerve or tissue injury in a partially blocked limb. A short- or medium-acting local anesthetic, such as lidocaine or mepivacaine, may be more appropriate for surgical anesthesia. Whatever drug is chosen, the total dosage should be calculated for each patient and should be kept within safe limits (see [Chapter 29](#) for details).

The highest concentrations of local anesthetic drugs are not appropriate for peripheral neural blockade; therefore 0.75% bupivacaine or ropivacaine, 2% lidocaine, 2% mepivacaine, and 3% 2-chloroprocaine are not recommended. The lowest concentrations of the same local anesthetics (i.e., 0.25% bupivacaine or ropivacaine and 0.5% mepivacaine or lidocaine) might not provide complete motor blockade.

Vasoconstrictors, usually epinephrine, can be added to the chosen local anesthetic to improve onset of action, to decrease drug uptake, and to prolong action. A concentration of 1:200,000 epinephrine is usually recommended. Ideally, the epinephrine should be added to the local anesthetic at the time the block is to be performed. Commercially prepared solutions with epinephrine have a lower pH than those in which it is freshly added, resulting in a higher percentage of ionized drug molecules. These ionized molecules do not readily cross the neural membrane, delaying the onset of drug action after injection. Epinephrine should not be added to the local anesthetic for blocks of the digits or penis because tissue ischemia can result. Various other

## Box 46.3 Recommendations: Needle Tip Location, Choice of Local Anesthetic, and Nerve Localization Techniques

### Needle Tip Location, Choice of Local Anesthetic, and Paresesthesia

- Intrafascicular needle insertion and injection should be avoided because it can cause histological and/or functional nerve injury.

### Nerve Localization Techniques

- There are no human data to support the superiority of one nerve localization technique over another with regard to reducing the likelihood of peripheral nerve injury.
- Peripheral Nerve Stimulation
  - Presence of an evoked motor response at a current of <0.5 (0.1 ms) indicates intimate needle-nerve relationship, needle-nerve contact, or an intraneuronal needle placement.
- Injection Pressure Monitoring
  - Animal data have linked high injection pressures to subsequent fascicular injury, but there are no human data that confirm or refute the effectiveness of injection pressure monitoring for limiting PNI.
- Ultrasound
  - Ultrasound can detect intraneuronal injection.
  - Current ultrasound technology does not have adequate resolution to discern between an interfascicular and intrafascicular injection.
  - Adequate images of needle-nerve interface are not consistently obtained by all operators and in all patients.

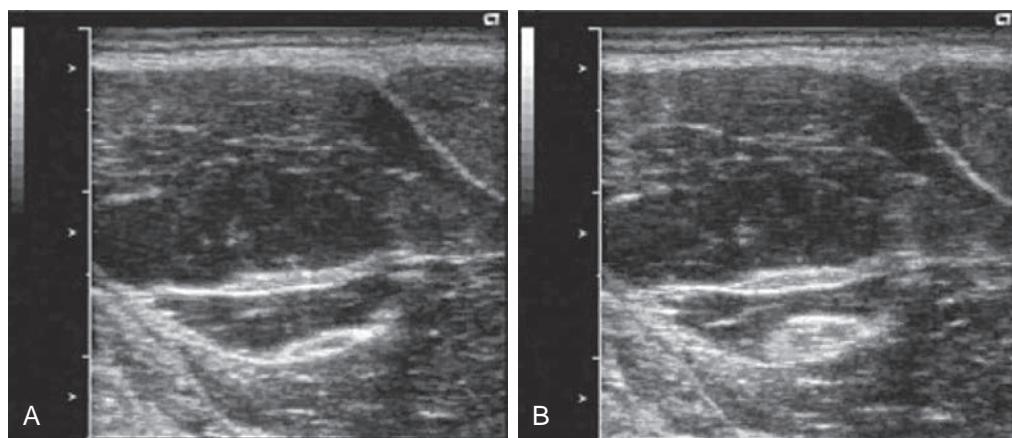
Modified from Neal JM, Barrington MJ, Brull R, et al. The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine: executive summary 2015. *Reg Anesth Pain Med*. 2015;40(5):401–430. PMID:26288034.

additives, including steroids, clonidine, dexmedetomidine, opioids, and ketamine have been reported to enhance or prolong local anesthetic peripheral nerve blockade. Liposomal bupivacaine, which slowly releases this local anesthetic, is now FDA approved for some peripheral nerve blocks.

## Complications and Safety

Nerve injury is a recognized complication of peripheral regional techniques ([Box 46.3](#)). Risk factors contributing to neurologic deficit after regional anesthesia include neural ischemia, traumatic injury to the nerves during needle or catheter placement, and infection. However, postoperative neurologic injury because of pressure from improper patient positioning, tightly applied casts or surgical dressings, and surgical trauma is often attributed to the regional anesthetic. Patient factors such as body habitus or a pre-existing neurologic dysfunction can also contribute.<sup>119–121</sup>

Although needle gauge, type (i.e., short vs. long bevel), and bevel configuration can influence the degree of nerve injury after peripheral nerve block, the findings are conflicting, and there are no confirmatory human studies. Theoretically, localization of neural structures with a nerve stimulator or ultrasound guidance would allow a high success rate without increasing the risk of neurologic complications, but this has not been established. Likewise, prolonged



**Fig. 46.38 Ultrasound image reveals intraneural injection.** These sonograms were obtained in the axilla before (A) and after (B) injection in the musculocutaneous nerve. Nerve expansion is detected but with preservation of the overall integrity of the nerve borders. No paresthesias were observed during or after the procedure. Neurologic outcome was favorable after this low-volume, low-pressure injection.

exposure, high dose, or high concentrations of local anesthetic solutions can also result in permanent neurologic deficits. In laboratory models, the addition of epinephrine increases the neurotoxicity of local anesthetic solutions and decreases nerve blood flow; however, the clinical relevance of these findings in humans remains unclear. Nerve damage caused by traumatic needle placement, local anesthetic neurotoxicity, and neural ischemia during the performance of a regional anesthetic can worsen neurologic outcome in the presence of an additional patient factor or surgical injury.

Hemorrhagic complications have been described with nearly every peripheral technique and range from localized bruising and tenderness to severe hematomas or hemorrhagic complications. The placement of peripheral nerve blocks in patients with a coagulopathy should be performed with caution, especially in a deep, noncompressible site where an expanding hematoma could go unnoticed (e.g., lumbar plexus) or in a location where a hematoma could compress the airway (e.g., interscalene).<sup>122</sup>

Prevention of neurologic complications begins during the preoperative visit with a careful evaluation of the patient's medical history and appropriate preoperative discussion of the risks and benefits of the available anesthetic techniques. It is imperative that all preoperative neurologic deficits are documented to allow early diagnosis of new or worsening neurologic dysfunction postoperatively. Postoperative sensory or motor deficits must also be distinguished from residual (prolonged) local anesthetic effect. Imaging techniques, such as computed tomography and magnetic resonance imaging, are useful in identifying infectious processes and expanding hematomas. Although most neurologic complications resolve completely within several days or weeks, significant neural injuries necessitate neurologic consultation to document the degree of involvement and coordinate further workup. Neurophysiologic testing, such as nerve conduction studies, evoked potentials, and electromyography, are often useful in establishing a diagnosis and prognosis.

Infectious complications can be caused by exogenous (contaminated medication or equipment) or endogenous sources. Infection at the site of needle placement is an

absolute contraindication to peripheral nerve blockade, although caution should be used in patients with nearby cellulitis or systemic blood infections (bacteremia or sepsis). Although bacterial colonization of peripheral nerve catheters is not uncommon, cellulitis, abscess, or bacteremia are extremely rare.<sup>123-125</sup>

Several large studies have established that severe systemic toxicity (seizures with or without cardiac arrest) occur on the order of 1:1000 for peripheral nerve blocks. Therefore practitioners of regional anesthesia must be familiar with the immediate detection and treatment of systemic local anesthetic toxicity. Systemic local anesthetic toxicity can occur immediately from an intravascular injection or it may be delayed because of rapid or excessive systemic absorption of local anesthetic. In addition to frequent aspiration during injection of local anesthetic, the addition of epinephrine can help alert the practitioner to potential intravascular injection. Attaching intravenous tubing to the needle allows immobility of the needle during injection. Typically, an assistant will aspirate with the syringe after each 5 mL injection of local anesthetic. Recent studies indicate that lipid emulsion rescue therapy improves success of resuscitation from cardiac arrest due to local anesthetic toxicity if given immediately after a local anesthetic overdose.<sup>126-130</sup>

For more details on treatment of local anesthesia toxicity, see [Chapter 29](#).

## Training

Interventional sonography is not without risks. Many studies have now demonstrated efficacy of ultrasound-guided regional blockade. Ultrasound has the potential to prevent and detect two important adverse events during peripheral nerve blocks: intravascular injection and intraneuronal injection of a local anesthetic.<sup>131,132</sup> The characteristic contrast from dissolved gas that is distributed within the vessel lumen can identify intravascular injection. The hallmark sign of intraneuronal injection is nerve expansion during injection (Fig. 46.38). Although ultrasound may have a profound impact on the safety of regional blockade,



**Fig. 46.39** Tissue equivalent phantom for training in ultrasound-guided interventions.

confirmatory studies of clinical practice are in progress. Many of these adverse events have only been recognized in retrospect by the review of recorded sonograms, which is a valuable training practice.

One of the original techniques developed for training novices in ultrasound-guided interventions was use of a tissue-equivalent phantom.<sup>133</sup> The phantom consisted of simulated tissue for needle placement practice (Fig. 46.39). To be realistic, the speed of sound must be similar as in soft tissue. In the first prototype, the phantom and container were clear; as a result, visual confirmation was possible. Several phantoms are now marketed for regional anesthesia purposes, and biologic tissue models that simulate nerve blocks have been developed.

A number of other effective teaching tools are being used. Cadavers have the advantage of realistic regional anatomic structures and can be used for simulated interventions.<sup>134</sup> The cost and use of specialized embalming methods that preserve nerve imaging and cadaver flexibility have limited this approach to a few specialized institutions. Most training studies have concluded that skills for ultrasound-guided procedures can be rapidly acquired.

One training study has identified common errors of novices while learning ultrasound-guided regional blocks.<sup>135</sup> These errors included advancing the needle when it was not visualized and unintentional probe movement. Novices often advance the needle even when it is not visualized, presumably because the natural inclination is to assume the needle has not reached the field of view. The potentially

quality-compromising behaviors were largely eliminated by the end of the study period, which ranged from 66 to 114 blocks per training participant.

## Summary and Conclusions

Peripheral nerve block techniques benefit the patient intraoperatively and postoperatively. Successfully mastering these techniques and applying them to the appropriate clinical situations add valuable options to the anesthetic care. Knowledge of regional anesthesia is also essential for the diagnosis and treatment of acute and chronic pain syndromes (see [Chapters 51](#) and [82](#)).

Ultrasound is a guidance tool that many people are electing to choose for regional anesthesia blocks. Once proficiency is established for a particular procedure, starting to use ultrasound for other interventional applications is relatively easy. Ultrasound imaging can prevent and detect critical events such as intravascular or intraneural injection that may improve safety during regional anesthesia procedures. However, if safety outcomes are to improve, then education and training play key roles in reducing these relatively uncommon adverse events.

## Acknowledgments

The authors would like to thank Ram Jagannathan, MD, MBBS, for his help with imaging. Additionally, we would like to acknowledge Dr. Adam B. Collins for providing figure 46.36.

This chapter contains content from two chapters in the 8th edition text. The editors, publisher, and returning contributors, Drs. Sandra L. Kopp and Andrew T. Gray, would like to thank Drs. Terese T. Horlocker and Denise J. Wedel for their contribution in the prior edition of this work. It has served as a foundation for the current chapter.

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## KEY POINTS

- Intravenous fluid therapy is a core part of perioperative practice, with the potential to influence patient outcomes.
- Water makes up approximately 60% of total body weight, varying widely with age and body composition. The ratio between the water volume within the intracellular and functional extracellular compartments is approximately 2:1.
- The endothelial glycocalyx forms a protein-poor intravascular fluid layer at the vessel perimeter; it has been integrated into a revised version of the Starling equation and updated model of capillary fluid movement.
- Sodium is the dominant extracellular cation and is responsible for much of extracellular fluid osmolality; dysnatremia is typically associated with disturbed extracellular fluid volume.
- Potassium is the dominant intracellular cation with a key role in the maintenance of transmembrane potentials; dyskalemia may be accompanied by impaired function of excitable tissues.
- Calcium is a key intracellular second messenger with roles in neuromuscular function, cell division, and oxidative pathways.
- Magnesium has a diverse range of physiologic effects, underlined by the increasing range of therapeutic applications of supplemental magnesium in the perioperative setting.
- Acid-base balance is relevant to fluid therapy because fluids containing supraphysiologic levels of chloride may cause an iatrogenic acidosis; the clinical relevance of this acidosis is debated.
- Intravenous fluids have a range of physiologic effects and should be considered drugs with indications, dose ranges, cautions, and side effects.
- The physiologic insult of the perioperative period may lead to a wide variety of disturbances in fluid and electrolyte balance.
- Clinical evidence to guide perioperative fluid therapy is lacking in many areas and cannot be directly extrapolated from general critical care trials.
- A balance must be found between inadequate fluid administration—allowing tissue hypoperfusion—and the adverse effects of excess intravenous fluids and toxicities related to fluid constituents.
- Goal-directed fluid therapy (GDT) may help in finding this balance for an individual patient in the perioperative setting, with evidence of reduced postoperative morbidity supporting its use in many surgical settings.
- No clear consensus exists on which intravenously administered fluid is associated with the best clinical outcomes in the perioperative setting. Comparisons of “balanced” with “unbalanced” and “crystalloid” with “colloid” fluids are being studied in many clinical settings; definitive conclusions are often lacking.
- The approach to fluid and electrolyte management may need adapting to numerous patient and surgical factors.

The administration of intravenous (IV) fluid is a core expertise for anesthesia providers and an area in which we have an important role in advising clinical colleagues. Alongside the traditional triad of maintenance of unconsciousness, pain relief, and neuromuscular relaxation, IV fluid therapy is a core element of the perioperative practice of anesthesia. The aims of perioperative fluid administration should be to avoid dehydration, maintain an effective circulating volume, and prevent inadequate tissue perfusion during a period when the patient is unable to achieve these goals through normal oral fluid intake.

Knowledge of the clinical effects of different fluids has increased substantially in recent years. The choice of fluid type in a variety of clinical situations can be rationally guided by an understanding of the physicochemical and biologic properties of the various crystalloid and colloid solutions available in combination with the available clinical trial data. Each clinical decision about fluid therapy has two key elements: which fluid to use and how much fluid to give. Recently, several clinical studies have changed our concepts regarding both these questions. However, we should be cautious about overinterpreting data from nonperioperative contexts. Despite recent high-quality “mega-trials” involving thousands of critically ill patients, key questions remain unresolved in the

perioperative setting. Goal-directed fluid therapy (GDT) is a good example of an intervention that is effective in the perioperative phase, but ineffective in established critical illness, and this should alert us to other possible similar distinctions. This chapter will review the physiology and pharmacology of IV fluid therapy in humans and discuss the impact of fluid and electrolyte management and alternative approaches on clinical outcomes.

## Physiology

### FLUID COMPARTMENTS

Water makes up approximately 60% of total body weight in the average adult, varying with age, gender, and body composition. Adipose tissue contains little water compared with other tissues, leading to marked variability in total body water (TBW) proportion between lean (75%) and obese (45%) individuals. Variation in adipose tissue also contributes to differences in TBW between adult males and females; these differences are reduced in old age as adipose tissue is reduced. The variations in body composition with age lead to a wide variation in TBW (Table 47.1). TBW is divided between anatomic and functional fluid compartments within the body, with the major division between intracellular fluid (ICF) and extracellular fluid (ECF). The size of these compartments and their widely differing composition are shown in Fig. 47.1 and Table 47.2. The ECF can be subdivided into the following compartments:

- Interstitial fluid (ISF): Lymphatic fluid and protein-poor fluid occupying cell spaces.
- Intravascular fluid: Plasma volume, including a proportion contained within the subglycocalyx (see later discussion).
- Transcellular fluid: Includes gastrointestinal (GI) tract fluid, bile, urine, cerebrospinal fluid, aqueous humor, joint fluid, and pleural, peritoneal, and pericardial fluid. These are functionally important fluids of widely varying composition contained within epithelial-lined spaces and regulated by active cellular transport (Table 47.3).
- Water in bone and dense connective tissue: Constitutes a substantial proportion of TBW but not part of the *functional* ECF because of slow kinetics of water distribution between this and other compartments.<sup>1</sup>

Total blood volume comprises extracellular (plasma and subglycocalyx compartments) and intracellular (blood cells) elements. With the nonfunctional ECF compartment (bone and connective tissue) excluded, the ratio between ICF and functional ECF is approximately 2:1 (ICF 55% of body weight to ECF 27.5% of body weight).

### PHYSICOCHEMICAL LAWS GOVERNING FLUID AND ELECTROLYTE MOVEMENT

The movement of water and solutes is governed by a variety of physicochemical and biologic processes, discussed in the following section.

#### Diffusion

Diffusion is the process by which solute particles fill the available solvent volume by motion from areas of high to low concentration. The speed of this equilibration is proportional to the square of the diffusion distance.

Diffusion also may occur across permeable membranes, according to Fick's law of diffusion:<sup>1</sup>

$$J = -DA \left( \frac{\Delta c}{\Delta x} \right)$$

where  $J$  is the net rate of diffusion,  $D$  is the diffusion coefficient,  $A$  is the cross-sectional area available for diffusion, and  $\Delta c/\Delta x$  is the concentration (chemical) gradient.

Diffusion may also be driven by the tendency of charged solutes to move down electrical gradients.

#### Osmosis

If a semipermeable membrane (one that is permeable to water but not a solute) separates pure water from water in which solute is dissolved, water molecules will diffuse across the membrane into the region of higher solute concentration. The hydrostatic pressure required to resist the movement of solvent molecules in this way is osmotic pressure. This is one of the fundamental colligative properties of a solution—that is, it depends on the number rather than the type of osmotically active particles in a solution, which may be complete molecules or dissociated ions.

Osmotic pressure in an ideal solution is affected by temperature and volume<sup>2</sup>:

$$P = \frac{nRT}{V}$$

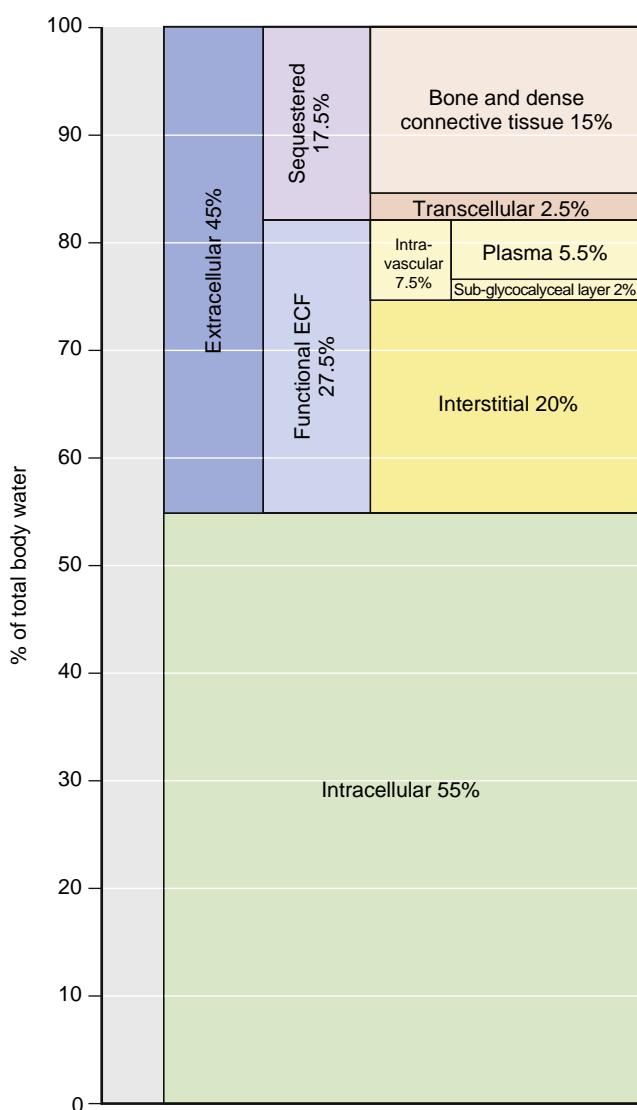
**TABLE 47.1** Age-Related Variation in Total Body Water and Extracellular Fluid as Percent of Body Weight (MULTIPLY by 10 for mL/kg)

Age	TBW (%)	ECF (%)	Blood Volume (%)
Neonate	80	45	9
6 months	70	35	
1 year	60	28	
5 years	65	25	8
Young adult (male)	60	22	7
Young adult (female)	50	20	7
Elderly	50	20	

In pregnancy, blood and plasma volumes increase by 45% and 50%, respectively, by term.

ECF, Extracellular fluid; TBW, total body water.

Data from Jones JG, Wardrop CA. Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth*. 2000;84(2):226–235; Chumlea WC, Guo SS, Zeller CM, et al. Total body water data for white adults 18 to 64 years of age: the Fels Longitudinal Study. *Kidney Int*. 1999;56(1):244–252; Baarsma R, Hof P, Zijlstra WG, et al. Measurement of total bodywater volume with deuterated water in newborn infants. *Biol Neonate*. 1992;62(2–3):108–112; and Ellis KJ, Shypailo RJ, Abrams SA, et al. The reference child and adolescent models of body composition. A contemporary comparison. *Ann NY Acad Sci*. 2000;904:374–382.



**Fig. 47.1 Distribution of total body water between fluid compartments.** “Sequestered” extracellular fluid (ECF) refers to water associated with bone and dense connective tissue or within the transcellular compartment and therefore not immediately available for equilibration with the other fluid compartments.

where  $P$  is the osmotic pressure,  $n$  is the number of particles,  $R$  is the gas constant,  $T$  the absolute temperature, and  $V$  the volume. The number of particles ( $n$ ) can be calculated by multiplying (mass of solute/molecular weight of solute) by the number of particles into which the solute dissociates. However, body fluids are not ideal solutions, because interionic interactions reduce the number of particles free to exert an osmotic effect. The total osmotic pressure of plasma is approximately 5545 mm Hg.

### Osmolality

Molality is the number of moles (each containing  $6 \times 10^{23}$  particles of a specific substance) present in 1 kg of solvent. Osmolality may be used to describe solutions containing many different types of particles and is the number of osmoles (each containing  $6 \times 10^{23}$  of any type of particle present) present in 1 kg of solvent. Normal body osmolality is

**TABLE 47.2** Composition of Intracellular and Extracellular Fluid Compartments (in mOsm/L Water)

	INTRACELLULAR	EXTRACELLULAR	
		INTRAVASCULAR	INTERSTITIAL
<b>CATIONS</b>			
Na <sup>+</sup>	10	142	145
K <sup>+</sup>	157	4	4
Ca <sup>2+</sup>	0.5*	2.5	2.5
Mg <sup>2+</sup>	20	0.8	0.7
<b>ANIONS</b>			
Cl <sup>-</sup>	10	103	117
HCO <sub>3</sub> <sup>-</sup>	7	25	27
HPO <sub>4</sub> <sup>2-</sup> /H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	11	2	2
SO <sub>4</sub> <sup>2-</sup>	1	0.5	0.5
Organic acids		6	6
Protein	4	1.2	0.2

Total intracellular Ca<sup>2+</sup> concentration may be as high as extracellular levels; however, this is largely sequestered or buffered, such that the cytoplasmic ionized Ca<sup>2+</sup> concentration is approximately 1000 times lower than extracellular fluid (0.3–2.6 μEq/L). The intracellular content of anions such as PO<sub>4</sub><sup>3-</sup> has been difficult to establish for similar reasons.

Data from Campbell I. Physiology of fluid balance. *Anaesth Intensive Care Med*. 2009;10(12):593–596; Hoffer LJ, Hamadeh MJ, Robitaille L, et al. Human sulfate kinetics. *Am J Physiol Regul Integr Comp Physiol*. 2005;289(5):R1372–R1380; and Hall JE. The body fluid compartments. In: Guyton and Hall Textbook of Medical Physiology. 12th ed. Philadelphia: WB Saunders; 2010:285–300.

285 to 290 mOsm/kg and is the same in intracellular and extracellular compartments because of the free movement of water between compartments that consequently prevents the development of any osmotic gradients. The largest contribution to plasma osmolality is made by sodium and its related anions chloride and bicarbonate.

It can be estimated by<sup>3</sup>:

$$\text{Serum osmolality} = (2 \times \text{Na}) + (\text{glucose}/18) + (\text{urea}/2.8)$$

where Na is the serum sodium concentration (mEq/L), glucose is the serum glucose concentration (mg/dL), urea is the blood urea nitrogen concentration (mg/dL), and the (2 × Na) component reflects both Na and its associated anions (predominantly Cl<sup>-</sup> and HCO<sub>3</sub><sup>-</sup>). Alternatively, osmolality can be measured by depression of plasma freezing point.

Osmolarity is the number of osmoles of solute per liter of solution; unlike osmolality, this may be affected by temperature changes as a result of the volume-expanding effect of increasing temperature.

### Tonicity

This is the *effective osmolality* of a solution with respect to a particular semipermeable membrane and takes into account solutes that do not exert an in vivo osmotic effect. For example, Na<sup>+</sup> and Cl<sup>-</sup> do not cross cell membranes freely and therefore exert an effective osmotic force across these membranes, whereas urea freely diffuses across cell

**TABLE 47.3** Composition of Transcellular Fluids (mEq/L Unless Stated)

Fluid	Daily Volume (L)	Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>2+</sup>	Mg <sup>2+</sup>	Cl <sup>-</sup>	HCO <sub>3</sub> <sup>-</sup>	pH
<b>Gastrointestinal tract</b>								
Saliva	1-1.5	30-90	20-40	2.5	0.6	15-35	10-40	6-7
Gastric	1.5-2.5	20-60	10-20			20-160	0	1-3.5
Bile	0.7-1.2	130-150	5-12	10-50		25-100	10-45	7-8
Pancreatic	1-1.5	125-150	5-10			30-110	40-115	8-8.3
Small bowel (concentrations from proximal to distal)	1.8	140-125	5-9			110-60	100-75	7-8
Large bowel	0.2 (lost in feces)	20-40	30-90			0-15	40	7-8
Sweat	0.1-0.5	45-60	5-10			45-60	0	5.2
Cerebrospinal fluid		140	2.8	2.1	1.7	120		7.33

Data from Grădinaru I, Ghiciuc C-M, Popescu E, et al. Blood plasma and saliva levels of magnesium and other bivalent cations in patients with parotid gland tumors. *Magnes Res*. 2007;20(4):254-258; Sewón LA, Karjalainen SM, Söderling E, et al. Associations between salivary calcium and oral health. *J Clin Periodontol*. 1998;25(11 Pt 1):915-919; and Lentner C. *Geigy Scientific Tables*. Vol. 1. *Units of Measurement, Body Fluids, Composition of the Body, Nutrition*. 8th ed. Basle: Ciba-Geigy Ltd; 1981.

membranes and therefore does not exert an osmotic effect here. Similarly, glucose is normally taken into cells by insulin-stimulated facilitated diffusion, so it is an ineffective osmole. Tonicity is important in determining in vivo distribution of fluids across a cell membrane and is sensed by the hypothalamic osmoreceptors. It can be estimated by subtracting urea and glucose concentrations from measured osmolality.

### Oncotic Pressure

Oncotic pressure is the component of total osmotic pressure that is due to the colloids, that is, large molecular-weight particles, predominantly proteins (albumin, globulins, fibrinogen). Of the total plasma osmotic pressure of 5545 mm Hg, 25 to 28 mm Hg is due to plasma oncotic pressure. The negative charge on proteins has the net effect of retaining a small excess of Na<sup>+</sup> ions within the plasma (the Gibbs-Donnan effect), which effectively increases the oncotic pressure above what would be predicted by calculations based purely on protein concentration. As the most abundant plasma protein, albumin is responsible for 65% to 75% of plasma oncotic pressure.

### FLUID COMPARTMENT BARRIERS AND DISTRIBUTION

The volume and composition of each fluid compartment depends on the barriers separating it from neighboring compartments.

#### Cell Membrane

The cell membrane separates the intracellular and extracellular compartments and as a lipid bilayer is impermeable to large hydrophilic molecules and charged particles such as free ions. Other than by passive diffusion of certain molecules, solutes may cross cell membranes in several ways.

### Carrier Proteins

**PRIMARY ACTIVE TRANSPORT.** Solute transport against a concentration gradient requires energy and is therefore directly coupled to adenosine triphosphate (ATP) hydrolysis—for example, by Na<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatases (ATPases). This is the fundamental mechanism by which ionic concentration gradients are maintained, which in turn drive a variety of biologic processes, including water and solute movement and electrical impulse transmission in excitable tissues.

**SECONDARY ACTIVE TRANSPORT.** The process of secondary active transport uses concentration gradients set up by ATPases to transport a solute driven by an ion moving down its concentration gradient, typically Na<sup>+</sup>. This process is termed cotransport when the solute is also moving down its concentration gradient or countertransport when the solute is being moved against its concentration gradient.

**Solute Channels.** The solute channels allow much faster transport of solutes than by ATPases or transmembrane diffusion. Examples include voltage-gated Na<sup>+</sup> channels and the glucose transporter GLUT1, which when inserted into the plasma membrane allows glucose to travel down its concentration gradient. This process is termed *facilitated diffusion*.

**Endocytosis and Exocytosis.** The processes of endocytosis and exocytosis are involved in the transport of large proteins and polypeptides across cell membranes.

#### Vascular Endothelium

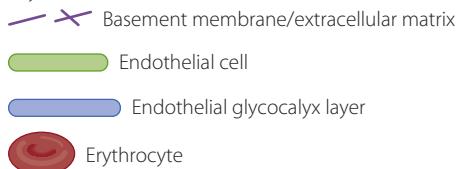
The barrier function of the vascular endothelium is particularly relevant perioperatively because of its key role in maintaining intravascular fluid volume. Surgical tissue trauma typically leads to loss of intravascular volume through surgical blood loss or inflammation-related shifts to other tissue compartments. The physiologic effect of IV fluid administered to overcome these losses and maintain adequate tissue oxygen delivery is highly dependent on

**TABLE 47.4** Capillary Characteristics

Capillary Type	Site	Large Pores	Basement Membrane	Glycocalyx Layer	Notes on Function
Nonfenestrated (continuous)	Muscle, connective tissue, lung, nervous tissue	None	Continuous	Continuous	Intercellular clefts are the main route for fluid filtration. These are partly occluded by junctional strands with multiple breaks. In the blood-brain barrier, these breaks are small (1 nm) and infrequent (zona occludens tight junctions), permitting passage of only the smallest non-lipid soluble molecules. In other tissues, the breaks are larger (5-8 nm) and more frequent (macula occludens loose junctions).
Fenestrated	Endocrine, gut mucosa, choroid plexus, lymph nodes Glomeruli	Pores within endothelial cells with covering diaphragm 6-12 nm size Endothelial pore size up to 65 nm	Continuous	Continuous	Fenestrations allow capillary reabsorption of fluid from ISF, in contrast to other capillary types.
Sinusoidal	Liver, spleen, bone marrow	Large intercellular gaps up to 120 nm	Discontinuous	No effective layer because of endothelial uptake of hyaluronic acid	Large fenestrations allow macromolecules (lipoproteins, chylomicrons) to pass between plasma and ISF; the result is no COP to oppose filtration, and the ISF in these tissues is effectively part of the plasma volume. Large volume filtration to the ISF here cannot be accommodated by tissue expansion because of fibrous capsules and is returned via lymphatics (e.g., liver lymph production accounts for 50% of total body lymph production)

COP, Colloid oncotic pressure; ISF, interstitial fluid.

Key:



Modified from Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth.* 2012;108:384.

fluid handling at the capillary level. Our understanding of this area has been refined by experimental physiologic models and techniques.

**Capillary Structure.** As shown in Table 47.4, the structure of capillaries varies depending on the underlying organ function. The most common capillary type is the nonfenestrated capillary, comprising continuous basement membrane and a single layer of endothelial cells joined by junctions that are punctuated by breaks. These intercellular clefts are the primary channel for transcapillary fluid flow. The intravascular aspect of the endothelial cells is covered by a continuous network of glycosaminoglycan (GAG) chains, including syndecan-1, hyaluronic acid, and glypcan, associated with membrane-bound proteoglycans; and glycoproteins, together forming the endothelial glycocalyx layer (EGL). The EGL covers fenestrations and intercellular

clefts and has a thickness of up to 1  $\mu$ m. In addition to its functions in preventing platelet and leukocyte adhesion, it has emerged as an important semipermeable layer contributing to endothelial barrier function.<sup>2</sup> Water and electrolytes can move freely across the vascular endothelial barrier through the EGL and then intercellular clefts or through fenestrations in the more specialized capillaries. Proteins were previously thought to be excluded from the ISF at the level of endothelial cells; however, it now appears that this occurs at the level of the glycocalyx. The subglycocalyx layer (SGL) therefore contains protein-poor fluid; slower protein transport into the ISF may occur across the endothelial cells by endocytosis and exocytosis and by transport through a small number of large pores, forming a gradient in protein concentration from SGL to ISF compartments. The volume of the SGL may be as much as 700 to 1000 mL; this volume therefore forms part of the intravascular volume and has an

electrolyte composition in equilibrium with the plasma but a much lower protein concentration because of the effective exclusion of larger molecules by the glycocalyx.

**Capillary Function.** The movement of fluid across the capillary membrane was initially described by Starling and then further refined. A hydrostatic pressure gradient at the arteriolar end of the capillary, greater than the inward oncotic pressure gradient, leads to net filtration of water into the ISF. Much of this water was previously thought to be reabsorbed into the vascular space toward the venular end of the capillary, where the outward hydrostatic pressure is lower and the inward oncotic pressure gradient is increased by exclusion of proteins from the capillary filtrate by the capillary endothelium. The water not reabsorbed by the capillary is removed from the ISF by the lymphatics.

More recent experimental and modeling techniques have integrated the role of the glycocalyx into a revised Starling equation and updated model of capillary fluid movement:<sup>4</sup>

$$J_v = K_f ([P_c - P_i] - \sigma [\pi_c - \pi_{sg}])$$

where  $J_v$  is the transcapillary flow,  $K_f$  is the filtration coefficient,  $P_c$  is capillary hydrostatic pressure,  $P_i$  is the interstitial hydrostatic pressure,  $\sigma$  is the reflection coefficient (the degree to which the tendency of a macromolecule to cross the endothelial barrier is resisted),  $\pi_c$  is the capillary oncotic pressure, and  $\pi_{sg}$  is the subglycocalyx oncotic pressure.

The key differences and their clinical relevance are as follows:<sup>3</sup>

- At steady state, continuous capillaries *do not* exhibit fluid reabsorption toward the venous end of the capillary (the “no-absorption” rule). However, overall measured capillary filtration ( $J_v$ ) is much less than predicted by the Starling principle, consistent with the larger colloid oncotic pressure (COP) gradient between SGL and capillary (opposing filtration) than between ISF and capillary. The smaller volume of filtrate is returned to the circulation by lymphatics.
- Plasma-SGL COP difference, not plasma-ISF COP difference, affects  $J_v$ . However, the no-absorption rule means that artificially raising COP (e.g., by albumin infusion) may reduce  $J_v$  but will not lead to reabsorption of fluid from the ISF into the plasma.
- An exception to the no-absorption rule occurs in acutely subnormal capillary pressures; a transient period of autotransfusion may occur, limited to approximately 500 mL. If subnormal pressures persist beyond this,  $J_v$  will approach zero, but ongoing reabsorption does not occur. Infusion of colloid in this setting will expand plasma volume, whereas infusion of crystalloid will expand total *intravascular* volume (plasma and EGL);  $J_v$  will remain close to zero in both cases until capillary pressure rises to normal or supranormal levels.
- At supranormal capillary pressures, COP difference is maintained and  $J_v$  is proportional to the hydrostatic pressure difference. In this setting, colloid infusion will maintain plasma COP but raise capillary pressure further and increase  $J_v$ . Crystalloid infusion will also increase capillary pressure but reduce plasma COP and therefore increase  $J_v$  to a greater extent than colloids.

The revised EGL model of fluid distribution, including the proposal that the intravascular volume effects of crystalloids and colloids are partly dependent on the preexisting capillary pressures (context sensitivity), helps explain some of the apparently conflicting findings in clinical fluid research.

**CRYSTALLOID VERSUS COLLOID INTRAVASCULAR VOLUME EFFECTS.** Infused crystalloid has been thought to distribute evenly throughout the extracellular compartments as a result of capillary filtration ( $J_v$ ), leaving approximately one fourth or one fifth of the original volume within the circulating blood volume, whereas colloids were presumed to initially remain largely within the intravascular volume. However, many studies of the effects of fluids on blood volume are based on red blood cell (RBC) dilution and changes in the hematocrit and do not account for the influence of the SGL volume, from which RBCs are excluded. Colloids are also excluded from the SGL; by remaining in the plasma volume, they will have a diluting effect on the hematocrit and appear to remain within the circulating volume. Crystalloids initially distribute throughout the plasma and SGL volumes. As a result, their RBC dilutional effects are less than those of colloids. This has previously been interpreted as crystalloid leaving the circulating compartment and entering the ISF; however, a proportion of the infused crystalloid will remain in the blood volume within the SGL. Furthermore, context sensitivity is responsible for the observation that clearance of crystalloid from its central compartment (the intravascular volume) is slower under anesthesia than in awake subjects.<sup>4</sup> It may also explain why the amount of crystalloid required to get intravascular volume effects similar to colloid is in the ratio 1.5:1 rather than the predicted 4:1.<sup>5-7</sup> The value of this ratio in the perioperative context is less clear and has been inferred from large clinical trials in critically ill patients. However, it is likely to be closer to the measured values in critical illness than the theoretic values traditionally used.

**FAILURE TO REDUCE EDEMA BY INCREASING CAPILLARY COLLOID ONCOTIC PRESSURE.** Hypoalbuminemia is well recognized as a marker of disease severity in critical illness. However, administering exogenous albumin or other colloids to increase capillary COP does not reduce peripheral or pulmonary edema, nor improve overall outcomes in sepsis. The no-absorption rule can provide a partial explanation, because even increasing COP gradient across the capillary wall by administration of albumin will not lead to reabsorption of fluid from edematous tissues. Again, previous studies showing apparent shifts of fluid from the interstitial to the intravascular compartment based on a reduced hematocrit after albumin infusion do not account for the potential role of compaction of the glycocalyx layer and transfer of fluid from the SGL to the plasma volume.

Finally, the importance of the endothelial glycocalyx is highlighted by studies showing that its degradation significantly impairs endothelial barrier function.<sup>8</sup> A range of physiologic insults may lead to glycocalyx injury and shedding, with the subsequent appearance of free heparin, chondroitin, and hyaluronic acid in the plasma. These include natriuretic peptides (which may be released in acute excessive increased intravascular volume),<sup>9</sup> hyperglycemia, and inflammatory mediators released during surgery, trauma,

and sepsis, such as C-reactive protein, bradykinin, and tumor necrosis factor (TNF).<sup>10</sup> Glycocalyx degradation may make an important contribution to the already well-characterized endothelial dysfunction seen in inflammation, in which phenotypic changes occur in endothelial cells. Here, an increase in the number of large pores, and a reduction in interstitial hydrostatic pressure favor  $J_v$ , with an increase in edema in compliant tissues such as the lung, muscles, and loose connective tissue. Impaired glycocalyx function will further favor  $J_v$  and lead to endothelial platelet aggregation and leukocyte adhesion. Maintenance of glycocalyx integrity is therefore gaining interest as a therapeutic target in perioperative fluid management.<sup>11</sup>

## PHYSIOLOGIC CONTROL OF OVERALL FLUID BALANCE

In health, 60% of daily water loss is through urinary excretion, although this proportion is less when sweating and insensible losses are increased. Integrated cardiovascular and renal neuroendocrine mechanisms attempt to maintain fluid volume homeostasis in response to perioperative challenges, such as reduced oral fluid intake, blood loss, and IV fluid administration.

TBW volume is controlled by a system of sensors, central control, and effectors. The sensors are (1) hypothalamic osmoreceptors that respond to changes in ECF tonicity, (2) low-pressure baroreceptors in the large veins and right atrium that sense central venous pressure (CVP), and (3) high-pressure baroreceptors in the carotid sinus and aortic arch that sense mean arterial pressure. The sensory inputs are integrated within the hypothalamus, which then triggers either increased water intake from thirst or increased water output via antidiuretic hormone (ADH, arginine vasopressin) secretion. Thirst and ADH release may be triggered by increased plasma tonicity, hypovolemia, hypotension, and angiotensin II. ADH release also may be stimulated by stress (including surgery and trauma) and certain drugs (e.g., barbiturates). Water intake does not usually depend on thirst because of social drinking behavior; thirst acts as a backup mechanism when the normal intake is inadequate. ADH, produced in the hypothalamus and released from the posterior pituitary, acts on the principal cells of the renal collecting ducts, which in the absence of ADH are relatively impermeable to water. ADH combines with the vasopressin 2 (V2) receptors on the basolateral membrane of the cells, triggering cyclic adenosine monophosphate (cAMP)-mediated insertion of aquaporin 2 water channels into the apical membrane. This results in water reabsorption down its osmotic gradient and formation of concentrated urine.

### Acute Disturbances in Circulating Volume

Acute variation in the intravascular volume leads to compensatory mechanisms over minutes to hours in an attempt to correct the acute abnormality. The homeostatic processes occurring in response to rapid blood loss are aimed at minimizing the change in effective blood volume (venoconstriction and mobilization of venous reservoirs, limited autotransfusion from ISF to plasma, reduced urine production) and maintenance of cardiac output and arterial pressure (tachycardia, increased inotropy, and vasoconstriction). The sensor organs for the acute change are

the low-pressure and high-pressure baroreceptors, and initial changes are mediated through increased sympathetic outflow. Renal vasoconstriction leads to a reduced volume of filtrate and activates the renin-angiotensin-aldosterone (RAA) axis. Renin is released from the juxtaglomerular cells and cleaves angiotensinogen to form angiotensin I, which is rapidly converted to angiotensin II. This induces further sympathetic activity, vasoconstriction, aldosterone release from the adrenal cortex, and hypothalamic ADH production. The overall result is increased renal salt and water retention, increased peripheral vascular resistance, and increased cardiac output. In the absence of ongoing loss, the delayed responses to major blood loss restore plasma volume within 12 to 72 hours, increase hepatic plasma protein synthesis, and restore RBC levels by erythropoiesis within 4 to 8 weeks.

Conversely, the rapid infusion of fluid to a normovolemic healthy adult leads to an initial rise in venous and arterial pressure and cardiac output. Several mechanisms act rapidly to bring these cardiovascular parameters toward normal, including pressure receptor-mediated venodilation and venous blood pooling and reduction in systemic vascular resistance. At a tissue level, autoregulatory responses lead to arteriolar vasoconstriction to maintain constant blood flow in the face of increased perfusion pressure. Multiple mechanisms then act to return circulating volume toward normal. A proportion of the infused fluid will be lost as a result of capillary filtration, particularly if the infused fluid reduces COP. Low-pressure baroreceptor stimulation leads to a decrease in pituitary ADH secretion, allowing diuresis, and atrial stretch leads to atrial natriuretic peptide (ANP) release, favoring natriuresis. Further ADH-independent renal mechanisms include glomerulotubular imbalance resulting from the marginal reduction in plasma COP; this rapidly increases the glomerular filtration rate (GFR) and reduces proximal tubule water and  $\text{Na}^+$  reabsorption, increasing urine volume. Finally, increased arterial blood pressure promotes the excretion of excess water and salt (i.e., pressure natriuresis and pressure diuresis). This is the pressure-volume control mechanism, one of the key mechanisms for the long-term maintenance of normal blood volume. However, arterial blood pressure is only slowly restored by cardiovascular reflexes after acute hypervolemia. It may take several days for a 20 mL/kg dose of isotonic salt solution to be fully excreted. Excretion of excess  $\text{Na}^+$  and water depends more on these passive processes and suppression of the RAA axis than on natriuretic peptide activity.<sup>12</sup> The contrast between this inefficiency and the rapid, effective mechanisms for dealing with reduced fluid volume and  $\text{Na}^+$  content reflects the evolution of physiology in an environment with a paucity of salt and variable water availability; excess  $\text{Na}^+$  intake is a feature of modern diets.

### Long-Term Control of Circulating Intravascular Volume

The Guyton-Coleman model is the archetypal representation of the circulation. Despite calls to refine the mathematical modeling of the long-term control of arterial blood pressure, it remains the most widely used model to explain the chronic control of blood volume and arterial pressure.<sup>13-15</sup> In health, short-term variations in blood volume

are very small and the cardiovascular system behaves as a closed system with arterial pressure a product of peripheral resistance, vascular compliance, and the Starling curve.<sup>16</sup> In the chronic setting or in acute alterations in blood volume, as described earlier, the circulating volume will vary and equality of input and output must be restored to avoid chronic fluid retention or dehydration; thus, the circulation acts as an open system. The kidneys are the primary organ regulating this equilibrium, largely through pressure natriuresis and diuresis. Indeed, in the chronic setting, arterial pressure subserves the renal requirement to excrete ingested  $\text{Na}^+$  and water rather than simply being a product of cardiac output, vascular compliance, and resistance. A recent interpretation integrates the Guyton-Coleman model with experimental observations (Fig. 47.2).<sup>16</sup> In health, the pressure-natriuresis curve is relatively flat, and excess intake of salt and water can be excreted without long-term rises in circulating volume or blood pressure. In many models of chronic hypertension, the renal excretion mechanism is reset such that natriuresis occurs only at higher arterial pressures and excessive exogenous water and salt results in higher blood pressure.

## ELECTROLYTE PHYSIOLOGY

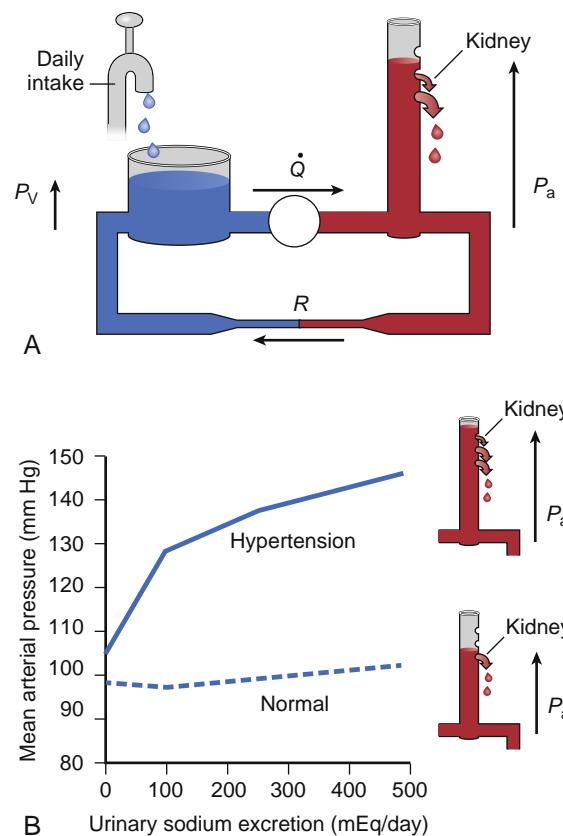
### Sodium Physiology

$\text{Na}^+$  is the dominant extracellular cation, and along with its associated anions accounts for nearly all the osmotically active solute in plasma and interstitial fluid. The relatively free movement of water throughout the fluid compartments means that  $\text{Na}^+$  is therefore the prime determinant of ECF volume. Total body  $\text{Na}^+$  content is approximately 4000 mmol, of which only 10% is intracellular. The concentration gradient between the intracellular and extracellular compartments (ratio 1:15) is maintained by ATPases and is vital for the function of excitable tissues, including action potentials and membrane potential, and for the handling of renal solute.

$\text{Na}^+$  intake is typically far in excess of minimum daily requirements, which are 2 to 3 mEq/kg/day at birth and decrease to 1 to 1.5 mEq/kg/day in adulthood.<sup>17,18</sup>  $\text{Na}^+$  is actively absorbed from the small intestine and colon under the influence of aldosterone and the presence of glucose in the gut lumen. Loss is predominantly by the renal route, with minor contributions from feces, sweat, and skin (10 mEq/day each).  $\text{Na}^+$  is freely filtered at the glomerulus, of which 99.5% is reabsorbed, mainly at the proximal convoluted tubule. Serum  $\text{Na}^+$  concentrations are maintained within a tight range (138–142 mEq/L) despite wide variation in water intake by the systems involved in the control of circulating volume outlined previously:

- hypothalamic osmoreceptor: ADH release
- atrial volume sensing: ANP release
- juxtaglomerular apparatus (renal arteriolar baroreceptor and filtrate  $\text{NaCl}$  content sensing): RAA activation

The excretion of total body excess  $\text{Na}^+$  relies on inefficient passive mechanisms, particularly the pressure-volume effect. Long-term ingestion of excess salt combined with low potassium ingestion contributes to hypertension, a condition not seen in populations with daily salt intake less than 50 mmol. The mechanism involves renal



**Fig. 47.2 Long-term control of blood volume in health and hypertension.** (A) Representation of the open circulation model. In the chronic setting, arterial pressure ( $P_a$ ) depends on daily water and sodium intake (dripping tap) and the renal pressure-natriuresis relationship (represented by the height of the holes in the arterial column) rather than cardiac output ( $Q$ ) and peripheral resistance ( $R$ ). (B) Experimental models of hypertension (e.g., long-term angiotensin II infusion) with controlled sodium intake (and therefore excretion) demonstrate a reset pressure-natriuresis curve in hypertension. This may be represented by kidney holes positioned further up the arterial column. Natriuresis occurs to a degree similar to that in normotension, so as to maintain a stable body water volume, but requires a higher arterial pressure to do so.  $P_v$ , Venous pressure. (A, Redrawn from Dorrington KL, Pandit JJ. The obligatory role of the kidney in long-term arterial blood pressure control: extending Guyton's model of the circulation. *Anaesthesia*. 2009;64:1218. B, Data from Hall JE. The kidney, hypertension, and obesity. *Hypertension*. 2003;41:625.)

salt retention and initial extracellular volume expansion (later mitigated by pressure natriuresis), with release of an endogenous digitalis-like factor and stimulation of renal  $\text{Na}^+$  pumps, furthering renal  $\text{Na}^+$  retention. Low  $\text{K}^+$  combined with the chronic action of digitalis-like factor inhibits vascular smooth muscle cell  $\text{Na}^+/\text{K}^+$  ATPases, resulting in excess intracellular  $\text{Na}^+$  content and reduced intracellular  $\text{K}^+$ , smooth muscle contraction, and increased peripheral vascular resistance.<sup>19</sup>

### Potassium Physiology

$\text{K}^+$  is the dominant intracellular cation in the body, with a total body content of approximately 4000 mmol, 98% of which is intracellular, particularly in muscle, liver, and RBCs. The ratio of ICF to ECF  $\text{K}^+$  balance is vital in the maintenance of cellular resting membrane potential, and  $\text{K}^+$  therefore has a key role in the behavior of all excitable tissues. Daily requirements reflect age and growth, with

more  $K^+$  required at higher metabolic rates. Term infants require 2 to 3 mEq/kg/day and adults 1 to 1.5 mEq/kg/day. Nearly all ingested  $K^+$  is absorbed by the intestine, and minimal amounts are excreted in feces. The acute and chronic handling of  $K^+$  must therefore maintain a stable plasma  $K^+$  concentration and resting membrane potential in the face of a daily  $K^+$  intake of a similar magnitude to the entire ECF  $K^+$  content. Transmembrane potentials particularly depend on  $K^+$  permeability, with  $K^+$  egress occurring through ion channels down its concentration gradient. This leaves behind intracellular anions, with a resultant negative transmembrane potential. The resting value of this potential is achieved when the tendency of  $K^+$  to move extracellularly as a result of its concentration gradient is matched by the tendency of  $K^+$  to move intracellularly because of the electrical gradient.

Acute  $K^+$  distribution involves shifts in  $K^+$  between the ECF and ICF, performed by ion transport systems under the influence of insulin, catecholamines, and ECF pH. The cell membrane  $Na^+/K^+$  ATPase exports three  $Na^+$  for every two  $K^+$  imported and is the means by which the gradients of these ions are maintained. Insulin, released after ingestion of  $K^+$ -containing food, stimulates the  $Na^+/H^+$  antiporter, increasing intracellular  $Na^+$ , which is then removed by  $Na^+/K^+$  ATPase with the net cellular uptake of  $K^+$ . Conversely, in the presence of hypokalemia, skeletal muscle expression of  $Na^+/K^+$  ATPase is reduced, allowing a “leak” of  $K^+$  from the ICF to ECF.<sup>20</sup> Catecholamines activate  $\beta_2$ -adrenoceptors, which ultimately stimulate  $Na^+/K^+$  ATPase activity, leading to increases in ICF  $K^+$ , a mechanism that counteracts the release of  $K^+$  from muscle cells during exercise.<sup>21</sup> ECF pH also has a bearing on  $K^+$  handling. The presence of mineral organic acids (where the acid anion is unable to diffuse into the cell) leads to increased cellular  $H^+$  uptake in exchange for  $K^+$  ions with consequent increases in ECF  $K^+$ . Organic acids (e.g., lactic acid and ketone bodies) are more able to diffuse across cellular membranes and  $H^+/K^+$  exchange is much less. Hyperkalemia may be observed in the setting of organic acidemia resulting from alternative mechanisms, such as insulin deficiency and osmotic drag in diabetic ketoacidosis or a failure of ATP production for  $Na^+/K^+$  ATPase in situations typified by anaerobic metabolism and lactic acidosis. Other factors that may influence ECF to ICF  $K^+$  balance include aldosterone (which at high levels may induce intracellular  $K^+$  shift, beyond its renal effects), hyperosmolar states (solvent drag of  $K^+$  along with water efflux), and digoxin (inactivates  $Na^+/K^+$  ATPase and may cause hyperkalemia).

Chronic  $K^+$  distribution involves renal mechanisms.  $K^+$  is freely filtered at the glomerulus, and undergoes extensive unregulated reabsorption along the proximal tubule, with only 10% to 15% reaching the distal nephron, where its reabsorption or secretion is tightly controlled. This occurs predominantly in two cell types found in the collecting ducts.

**Principal Cells.** The principal cells are able to secrete  $K^+$  under the electrochemical gradients set up by basal  $Na^+/K^+$  ATPases, which maintain low intracellular  $Na^+$  concentrations (aiding  $Na^+$  reabsorption from the tubule via  $Na^+$  channels) and high intracellular  $K^+$  concentrations (favoring  $K^+$  secretion into the tubule via  $K^+$  channels). Principal cell behavior is influenced by the following:

- Aldosterone, synthesized and released by the adrenal glands in response to raised  $K^+$  concentrations. This mineralocorticoid increases the synthesis and activity of both basal  $Na^+/K^+$  ATPases and luminal  $K^+$  channels to drive urinary  $K^+$  secretion.
- Tubular  $Na^+$  delivery. Increased distal tubular  $Na^+$  content leads to a steeper  $Na^+$  concentration gradient and increased principal cell reabsorption of  $Na^+$ . To maintain electroneutrality of the tubular fluid,  $K^+$  efflux into the tubule increases; this is partly responsible for the hypokalemia associated with diuretics that increase delivery of  $Na^+$  to the cortical collecting ducts (thiazides and loop diuretics). In contrast, amiloride blocks the principal cell luminal  $Na^+$  channel and therefore does not affect  $K^+$  efflux here.

**Intercalated Cells.** In addition to basal  $Na^+/K^+$  ATPases, these cells have luminal  $H^+/K^+$  ATPases that excrete one hydrogen into the tubule for every  $K^+$  reabsorbed. Low  $K^+$  settings lead to up-regulation of this luminal antiporter, reabsorbing more  $K^+$  at the expense of renal acid loss.

In addition to mechanisms involving aldosterone in a feedback loop, it is likely that feed-forward mechanisms also exist to rapidly modulate renal  $K^+$  handling when  $K^+$  is sensed in the GI system, even before plasma  $K^+$  levels rise.<sup>20</sup>

### Calcium Physiology

Beyond its role in bone structure, where 98% of body calcium ( $Ca^{2+}$ ) is stored,  $Ca^{2+}$  is one of the body's most important intracellular second messengers, playing a key role in muscular contraction, neuromuscular transmission, cell division and movement, and oxidative pathways. Intracellular  $Ca^{2+}$  entry may have direct effects in cardiac and skeletal muscle contraction—for example, leading to neurotransmitter release or inducing further large-scale release of  $Ca^{2+}$  from intracellular stores ( $Ca^{2+}$ -induced  $Ca^{2+}$  release). A large ECF-to-ICF gradient of ionized  $Ca^{2+}$  is maintained by ATPases, and cytoplasmic free  $Ca^{2+}$  levels are kept low by pumping into the sarcoplasmic reticulum. Increases in cytoplasmic  $Ca^{2+}$  concentration occurring as a result of cellular energetic failure and impaired  $Ca^{2+}$  transport are a key mediator of cell death pathways.<sup>22</sup>  $Ca^{2+}$  also plays a key role in coagulation by linking coagulation factors to the negatively charged plasma membrane of activated platelets.

Homeostatic mechanisms maintain serum  $Ca^{2+}$  concentrations between 4.5 and 5 mEq/L (8.5-10.5 mg/dL), largely under the influence of vitamin D and parathyroid hormone (PTH). Ionized  $Ca^{2+}$  is sensed by the extracellular domain of a G-coupled receptor expressed on parathyroid cells (the  $Ca^{2+}/Mg^{2+}$ -sensing receptor), inhibiting PTH release.<sup>23</sup> When ionized  $Ca^{2+}$  levels decrease, PTH is rapidly released with the following actions:

- Stimulates osteoclast bone resorption, releasing  $Ca^{2+}$  into the ECF
- Stimulates distal tubule calcium reabsorption
- Stimulates the renal conversion of 25-(OH)-vitamin D to 1,25-(OH)<sub>2</sub>-vitamin D (calcitriol, the most active vitamin D metabolite)

The manufacture of active vitamin D involves cholecalciferol formation in the skin during exposure to ultraviolet

**TABLE 47.5** Physiologic Roles of Magnesium

System	Effect	Mechanism and Clinical Relevance
Neurologic	Reduction in pain transmission	NMDA antagonism. Mg <sup>2+</sup> treatment provides effective perioperative analgesia. <sup>254</sup>
	Reduces neuromuscular transmission	Inhibition of neuronal Ca <sup>2+</sup> influx reduces neuromuscular junction ACh release (and motor end-plate sensitivity to ACh). Hypermagnesemia potentiates the effects of neuromuscular blockade.
	Sympatholysis	Inhibition of neuronal Ca <sup>2+</sup> influx reduces catecholamine release from adrenal medulla and adrenergic nerve endings. Pharmacologic use of Mg <sup>2+</sup> in obtunding pressor response to intubation or during surgery for pheochromocytoma.
	Anticonvulsant	Mechanism may relate to NMDA antagonism or cerebral arteriolar vasodilation, possible mechanisms for its efficacy in eclampsia, in which vasospasm has been observed. <sup>29</sup>
	Cortical depression at high levels	
Cardiovascular	Vasodilation	Predominantly arteriolar, because of inhibition of Ca <sup>2+</sup> influx-mediated vascular smooth muscle contraction. Mg <sup>2+</sup> administration typically leads to a minor reflex increase in inotropy despite the direct action of Mg <sup>2+</sup> on reducing cardiac contractility. <sup>255</sup>
	Antiarrhythmic effects	Mixed class IV (Ca <sup>2+</sup> channel inhibition) and weak class I (Na <sup>+</sup> channel inhibition) effects. Increases atrioventricular nodal conduction time and refractory periods, suppresses accessory pathway transmission, and inhibits early and delayed afterdepolarizations. Clinical use is in supraventricular tachycardias, atrial fibrillation rate control and postoperative prophylaxis, and tachyarrhythmias associated with dyskalemia, digoxin, bupivacaine, or amitriptyline. <sup>29</sup>
	Improved myocardial O <sub>2</sub> supply-to-demand ratio	Coronary vasodilation in combination with reductions in heart rate and contractility; however, no clear evidence of benefit in the setting of acute myocardial infarction.
Respiratory	Bronchodilation	Smooth muscle relaxation. Pharmacologic use of Mg <sup>2+</sup> is in acute bronchospasm.
Renal	Renal vasodilation and diuresis	Ca <sup>2+</sup> antagonism-related smooth muscle relaxation
Immune	Antiinflammatory	Pharmacologic doses of magnesium sulfate reduce monocyte inflammatory cytokine production. <sup>256</sup>
	Adaptive immunity	Mg <sup>2+</sup> is required as a second messenger during T-lymphocyte activation. <sup>257</sup>
Obstetric	Tocolysis	May be due to smooth muscle relaxation

ACh, Acetylcholine; NMDA, N-methyl-D-aspartate.

light, which then undergoes hepatic hydroxylation to 25-hydroxy-calciferol, then renal hydroxylation under the influence of PTH to 1,25-dihydroxy-calciferol (calcitriol). As with PTH, this stimulates osteoclastic bone resorption and additionally stimulates absorption of Ca<sup>2+</sup> from the GI tract.

Ca<sup>2+</sup> homeostasis is interlinked with that of other anions. In particular, magnesium is also able to modulate PTH levels, and hypocalcemia and hypomagnesemia frequently coexist. The homeostasis of phosphate (PO<sub>4</sub><sup>3-</sup>) is effectively the converse of Ca<sup>2+</sup> (e.g., renal hydroxylation of vitamin D is inhibited by hyperphosphatemia), and in health the (calcium × phosphate) product is kept relatively stable. An increase in the (calcium × phosphate) product may be seen in advanced chronic kidney disease and is associated with ectopic bone deposition.

Approximately 50% of circulating Ca<sup>2+</sup> is in the biologically active ionized form (the remaining 40% are bound to proteins, predominantly albumin and globulins, and 10% are complexed to anions such as HCO<sub>3</sub><sup>-</sup>, citrate, sulfate, PO<sub>4</sub><sup>3-</sup>, and lactate). Hypoalbuminemia decreases the total serum Ca<sup>2+</sup> but has less effect on the biologically important ionized form. To calculate the corrected total Ca<sup>2+</sup> concentration, 0.8 mg/dL is added per 1 g/dL decrease in albumin concentration below 4 g/dL. The degree of albumin-protein binding is affected by pH, with acidemia reducing protein binding and increasing the ionized fraction. Ionized Ca<sup>2+</sup> rises by approximately 0.1 mEq/L per 0.1 decrease in pH.<sup>26</sup> Given the approximate nature of corrected total Ca<sup>2+</sup>, biologically active ionized Ca<sup>2+</sup> should be measured when

possible. Specimens should ideally be taken without tourniquet (uncuffed), because local acidosis increases the ionized fraction.

### Magnesium Physiology

Mg<sup>2+</sup> has a diverse range of cellular actions, including modulation of ion channel activity and as an essential component of ATP production and hydrolysis. It is primarily an intracellular anion, although most is sequestered within organelles, bound to phospholipids, proteins, and nucleic acids. Free ionized Mg<sup>2+</sup> levels within the cytoplasm and ECF are therefore low (0.8–1.2 mM), and chemical concentration gradients are much less than for other anions. Of total body Mg<sup>2+</sup>, 50% is within bone, 20% within muscle, and the rest in liver, heart, and other tissues. Only 1% is within the ECF, and normal plasma levels may be maintained in the face of total body Mg<sup>2+</sup> depletion. Within the plasma, total Mg<sup>2+</sup> concentration is 1.5 to 2.1 mEq/L, of which approximately 25% is protein (mostly albumin) bound, 65% is in the biologically active ionized form, and the remainder is complexed to phosphates, citrates, and other anions.<sup>27</sup> Measurement of ionized Mg<sup>2+</sup> can be performed, although correction is required for interference from Ca<sup>2+</sup> ions.<sup>28</sup> The key roles of Mg<sup>2+</sup> (Table 47.5) highlight its diverse range of clinical applications when administered exogenously and stem from the following three main cellular actions:

1. Energy metabolism: Mg<sup>2+</sup> is required for ATP phosphorylation reactions, interacting with the outer two PO<sub>4</sub><sup>3-</sup>

- groups of ATP. Intracellular  $Mg^{2+}$  deficiency therefore impairs any enzyme systems using high-energy  $PO_4^{3-}$  bonds, such as glucose metabolism.<sup>27</sup>
2. Nucleotide and protein production:  $Mg^{2+}$  acts as a cofactor in every step of DNA transcription and replication and messenger RNA (mRNA) translation.
  3. Ion transport: by supporting the activity of ion-pumping ATPases,  $Mg^{2+}$  helps maintain normal transmembrane electrochemical gradients, effectively stabilizing cell membranes and organelles. In addition, effects on ion *channels* underlie one of the core functions of  $Mg^{2+}$ , namely physiologic competitive antagonism of  $Ca^{2+}$ . This is mediated through inhibition of L-type  $Ca^{2+}$  channels and extracellular local modification of membrane potential, preventing the intracytoplasmic influx of  $Ca^{2+}$  from both the ECF and intracellular sarcoplasmic reticulum stores.  $Mg^{2+}$  also effectively antagonizes N-methyl-D-aspartate (NMDA) receptors within the central nervous system, reducing  $Ca^{2+}$  entry by specific ion channels. These effects result in inhibition of a diverse array of excitable tissue cellular actions, including neurotransmitter release, muscular contraction, cardiac pacemaker and action potential activity, and pain signal transmission.

$Mg^{2+}$  is absorbed from the GI tract by a saturable transport system and passive diffusion, in quantities inversely proportional to the amount ingested. Excretion is via the GI tract (~60% of the ingested amount) and kidneys. Seventy-five percent is freely filtered at the glomerulus, and proximal tubule reabsorption is minimal, with 60% to 70% being reabsorbed at the thick ascending loop of Henle and 10% reabsorbed under regulation in the distal tubule. The regulation of total body  $Mg^{2+}$  levels by GI uptake and control of renal excretion is not under the control of a well-defined hormonal feedback loop. Although many factors can influence  $Mg^{2+}$  reabsorption (particularly PTH but also calcitonin, glucagon, acid-base balance,  $Ca^{2+}$  and  $K^+$  levels), the main determinant is the plasma  $Mg^{2+}$  concentration, sensed by  $Ca^{2+}/Mg^{2+}$ -sensor receptors present on the basal aspect of thick ascending loop cells. Other influences may alter the intracellular-extracellular balance of magnesium distribution. Catecholamines, acting by both  $\alpha$ - and  $\beta$ -adrenoreceptors, and glucagon lead to extrusion of magnesium from intracellular stores. Although experimental models have shown that adrenergic stimulation may increase serum  $Mg^{2+}$  concentrations, decreases in serum  $Mg^{2+}$  concentrations actually occur after stressors such as surgery, trauma, burns, and sepsis.<sup>27,29</sup> This may be due to a later phase of catecholamine-driven cellular uptake after the initial  $Mg^{2+}$  efflux.<sup>30</sup>

### Phosphate Physiology

$PO_4^{3-}$  is the most abundant intracellular anion and helps form some of the most important biologic molecules, including ATP, DNA, and RNA, membrane phospholipids, 2,3-diphosphoglycerate (2,3-DPG), and hydroxyapatite in bone.  $PO_4^{3-}$  is therefore required for energy metabolism, cellular signaling through phosphorylation reactions, cellular replication and protein synthesis, membrane integrity, and  $O_2$  delivery. In addition, the  $PO_4^{3-}$  buffer system is one of the key intracellular buffers. Of total body phosphorus, 80%

to 90% is stored in bone, with the remainder in the intracellular (soft tissues and erythrocytes) and extracellular fluid compartments.<sup>31</sup> Normal plasma inorganic phosphates are maintained at 3 to 5 mg/dL, and at normal pH, 80% exists in the divalent ( $HPO_4^{2-}$ ) rather than monovalent ( $H_2PO_4^-$ ) form. Plasma phosphates also include lipid phosphates and organic ester phosphates. Most intracellular  $PO_4^{3-}$  is organic.<sup>18</sup>

The typical daily intake of  $PO_4^{3-}$  (~1 g) outweighs metabolic requirements, yet 70% is absorbed, leading to post-prandial increases in serum  $PO_4^{3-}$  levels that are rapidly dealt with by increased renal excretion. GI uptake occurs predominantly by paracellular diffusion and is unregulated unless  $PO_4^{3-}$  ingestion is reduced, when vitamin D and PTH-stimulated active transport intervene.<sup>32,33</sup> Plasma inorganic  $PO_4^{3-}$  is freely filtered at the glomerulus, 80% of which is reabsorbed in the proximal tubule and a smaller amount in the distal tubule. Proximal tubule reabsorption is via  $Na^+$ -dependent cotransporters, the expression and activity of which are under the influence of PTH and  $PO_4^{3-}$  intake.

The regulation of normal  $PO_4^{3-}$  levels is mediated primarily by the PTH and vitamin D systems. Low plasma  $PO_4^{3-}$  levels stimulate 1-hydroxylase activity, with the formation of active vitamin D (1,25-dihydroxycholecalciferol), which increases GI and renal  $PO_4^{3-}$  absorption. Conversely, PTH release (stimulated by reduced plasma  $Ca^{2+}$ ) reduces renal  $PO_4^{3-}$  reabsorption.  $PO_4^{3-}$  plasma levels also may be reduced in the short term by cellular uptake in response to dopamine and adrenergic activity and alkalosis and intestinal factors (phosphatonins) released in response to increased intestinal luminal  $PO_4^{3-}$ .<sup>31</sup>

### Chloride Physiology

As the second most abundant electrolyte in the extracellular compartment, chloride ( $Cl^-$ ) has a key role in the maintenance of plasma osmolality, preservation of electrical neutrality, and acid-base status (explained by the Stewart model, see later discussion). Normal plasma values are 97 to 107 mEq/L;  $Cl^-$  is therefore responsible for nearly a third of plasma osmolality and two thirds of plasma negative charge.<sup>34</sup> Most  $Cl^-$  intake is derived from dietary  $NaCl$ , and the GI tract absorbs and secretes large amounts of  $Cl^-$ , primarily as gastric hydrochloric acid, but also throughout the intestinal lumen. This cellular  $Cl^-$  secretion leads to paracellular movement of  $Na^+$  into the lumen, with water moving down its osmotic gradient to form GI secretions.  $Cl^-$  excretion is primarily renal, largely in the proximal tubule by passive reabsorption or cotransport. More regulated control of  $Cl^-$  excretion is performed in the intercalated cells of the distal nephron under the influence of plasma acid-base balance by exchange of  $HCO_3^-$  for  $Cl^-$ .

### ACID-BASE DISTURBANCES AND FLUID THERAPY

Acid-base balance in general is discussed in Chapter 48; however, the two key areas in which intravascular fluid therapy may affect acid-base balance are iatrogenic acidosis caused by the administration of  $Cl^-$ -rich fluids and administration of sodium bicarbonate to correct acidosis. In summary, the interpretation of acid-base balance can be viewed in three main ways: by the Henderson-Hasselbach equation, by anion gap, or by Stewart's strong ion model.

The Henderson-Hasselbach equation represents the  $\text{HCO}_3^-$  buffer system and has plasma  $\text{HCO}_3^-$  concentration as an independent determinant of plasma pH. The anion gap model is consistent with the Henderson-Hasselbach equation, because it places changes in plasma  $\text{HCO}_3^-$  at the core of plasma acid-base balance. It represents a simple method for differentiating causes of metabolic acidosis and is defined as the difference between the most abundant *measured* cation and anion concentrations in the plasma ( $[\text{Na}^+] + [\text{K}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$ ). The normal anion gap is 4 to 11 mEq/L, and this difference is represented by “unmeasured” anions ( $\text{PO}_4^{3-}$ , sulfate, and anionic proteins). In the presence of excess organic acids (e.g., lactic acid or ketoacid), the accumulation of unmeasured anions is accompanied by a reduction in  $\text{HCO}_3^-$  to buffer the excess  $\text{H}^+$  ions, leading to an increase in the anion gap. In cases in which  $\text{Cl}^-$  is administered, even if  $\text{HCO}_3^-$  falls, the anion gap will remain normal.<sup>35</sup>

Stewart's model of acid-base balance has a different approach and proposes that plasma pH is dependent on the following three independent variables:

1.  $\text{pCO}_2$  (the plasma  $\text{CO}_2$  tension)
2.  $\text{A}_{\text{tot}}$ , the total plasma concentration of all nonvolatile buffers (albumin, globulins, and  $\text{PO}_4^{3-}$ )
3. Strong ion difference (SID), the difference between the total charge of plasma-strong cations ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ , and  $\text{Ca}^{2+}$ ) and strong anions ( $\text{Cl}^-$ , lactate, sulfate, and others). In a more simplified approach, apparent SID is defined as ( $[\text{Na}^+] + [\text{K}^+] - ([\text{Cl}^-] + [\text{lactate}])$ ). Normal plasma SID is approximately 42 mEq/L, and reductions in SID will lead to a fall in plasma pH.

The Stewart model has caused some controversy by representing  $\text{HCO}_3^-$  as a dependent variable,<sup>36</sup> but it has utility in explaining acid-base disturbances caused by fluid administration.<sup>37</sup>

### Hyperchloremic Acidosis

Administration of fluid with  $\text{Cl}^-$  concentration higher than that of plasma will in sufficient quantities (e.g., 30 mL/kg/h of 0.9% saline) cause a metabolic acidosis due to the  $\text{Cl}^-$  content.<sup>38</sup> This hyperchloremic acidosis may be explained by the Henderson-Hasselbach model of acidosis, where saline infusion causes dilution of bicarbonate and a resultant base deficit, or by the Stewart model. Here, the increasing plasma  $\text{Cl}^-$  concentration reduces apparent SID and therefore reduces plasma pH; the SID of completely ionized saline is zero, therefore its infusion progressively dilutes the normal plasma SID. Similar changes are not seen with solutions containing non- $\text{Cl}^-$  anions which are metabolized after infusion, such as lactated Ringer solution. Although in vitro as an electroneutral solution it also has an SID of zero, following administration, the lactate undergoes metabolism in patients with intact hepatic function, giving it an effective in vivo SID of approximately 29 mEq/L. This is slightly less than the plasma SID and is enough to counteract any alkalosis caused by dilution of  $\text{A}_{\text{tot}}$ .

Saline-induced hyperchloremic acidosis has a variety of potentially deleterious physiological effects. These include renal vasoconstriction, reduced GFR and reduced renin

activity in animal models,<sup>39-41</sup> and reduced renal cortical perfusion in healthy volunteers.<sup>42</sup> Coagulopathy and gastrointestinal dysfunction have also been suggested.<sup>43</sup> However, it is not clear that acidosis purely attributable to iatrogenic hyperchloremia leads to clinically important morbidity. A meta-analysis of studies comparing saline with balanced perioperative fluid regimes confirmed the presence of hyperchloremia and acidosis postoperatively in the saline groups, but typically these biochemical abnormalities were cleared by the first or second postoperative day.<sup>38</sup> There were no overall differences in markers of kidney injury or need for renal replacement therapy, nor in other morbidities such as clinically important coagulopathy or gastrointestinal symptoms. However, the available trials were relatively small, and higher-risk surgical groups (those with pre-existing impairment of acid-base status, emergency and major surgery) were under-represented. Interestingly, in one trial of patients undergoing renal transplant, saline administration was associated with significant hyperkalemia, presumably caused by cellular potassium extrusion due to extracellular acidosis.<sup>44</sup> It is therefore possible that the acidosis observed due to saline administration has a greater clinical effect on a selected high-risk group. Recent large trials in the emergency department and intensive care settings have shown an increase in a composite outcome of death or adverse renal event when patients are given saline rather than balanced crystalloid.<sup>45,46</sup> The effect seemed to be greatest in medical patients with sepsis. The difference in composite outcomes was small (15.4% in the saline group, 14.3% in the balanced group), but this should be taken in the context of the large number of hospitalized patients that receive intravenous fluids. Although these trials did not relate specifically to the perioperative setting, an increasingly cautious approach to saline administration seems appropriate.

### Bicarbonate Administration

The administration of IV  $\text{NaHCO}_3$  to treat metabolic acidosis should be reserved for the emergency treatment of select conditions, including severe hyperkalemia and arrhythmias associated with tricyclic antidepressant overdose. In many other situations, clinical benefit is not apparent, a finding that highlights an important pathophysiologic concept. Acidosis in itself may not be physiologically deleterious; indeed, it is a normal event during strenuous exercise, in which it may aid  $\text{O}_2$  offloading to tissues. Perhaps acidosis serves as a marker for the severity of underlying disease processes, such as hypoxia, ischemia, or mitochondrial dysfunction, which cause morbidity without adequate correction.<sup>43</sup>  $\text{HCO}_3^-$  administration also has the following negative effects:<sup>18</sup>

1. Carbon dioxide production. Most of the  $\text{HCO}_3^-$  administered is converted to  $\text{CO}_2$ , with two important consequences. First, excess  $\text{CO}_2$  requires excretion by hyperventilation. Converted  $\text{HCO}_3^-$  of 100 mEq represents an excess of 2.24 L of  $\text{CO}_2$  to be exhaled, which may present a significant physiologic challenge to critically ill patients with preexisting ventilatory impairment. Although this is disputed, the excess  $\text{CO}_2$  may also diffuse into the intracellular space, aggravating intracellular acidosis.<sup>18</sup>

- IV  $\text{HCO}_3^-$  brings a significant  $\text{Na}^+$  content and therefore osmotic load. This may lead to hyperosmolar hypernatremia, ECF expansion, and volume overload.
- If renal  $\text{HCO}_3^-$  distribution is impaired, there may be an “overshoot” toward metabolic alkalosis once the underlying disease process causing the initial acidosis is resolved.

In situations in which  $\text{HCO}_3^-$  administration is required, the total dose required to correct the base deficit can be calculated using the equation:<sup>5</sup>

$$\text{Dose (mEq)} = 0.3 \times \text{weight(kg)} \times \text{base deficit(mEq/L)}$$

Although half this dose is usually given, because of the problems outlined above, treatment should stop once the pH rises above 7.2.

## Fluid Pharmacology

Given the diverse range of physiologic effects of administered fluids, and the potentially large volumes which can be administered perioperatively, they should be considered as drugs with specific indications, cautions, and side effects. Many of the fluids available currently were developed several decades ago and entered clinical practice without rigorous analysis of their clinical benefits, or knowledge of their effects at an organ or cellular level. Newer colloid solutions have been approved by regulatory authorities and entered widespread clinical usage based on relatively small trials of efficacy. In some cases, safety concerns such as the impact of colloid-related renal dysfunction have only been highlighted by much later adequately powered trials.<sup>47</sup> The composition of available fluids is shown in Table 47.6, although not all fluids are available in all countries.

### CRYSTALLOIDS

Crystalloids are solutions of electrolytes in water. They may be classified by their tonicity after infusion or their overall composition. Crystalloids containing electrolytes found in plasma and a buffer such as lactate or acetate may be referred to as balanced solutions. Crystalloids are indicated for replacement of free water and electrolytes but also may be used for volume expansion. Conventional concepts of fluid compartments dictate that infused electrolytes will distribute freely throughout the ECF, water will follow down osmotic gradients, and the net result is a distribution of infused crystalloids throughout the entire ECF, with only 20% remaining in the intravascular compartment. This is challenged by large clinical trials and current knowledge of microvascular fluid handling (see the Vascular Endothelium section), which suggest that isotonic crystalloids may have a larger intravascular volume expanding effect than this, particularly in patients with low capillary hydrostatic pressures. The study of volume kinetics has quantified the redistribution of crystalloids from the central (intravascular) volume to the larger peripheral (total extracellular) volume. Perhaps up to 70% of a crystalloid infusion remains in the intravascular compartment at the end of a 20-minute

continuous infusion, decreasing to 50% after 30 minutes.<sup>4</sup> Nevertheless, more fluid will ultimately be filtered out of the capillary with crystalloids than with colloids, owing to colloids' effects on oncotic pressure. Patients resuscitated with crystalloids have a more positive fluid balance for the same volume expansion effect.<sup>51</sup> Tissue edema may increase in compliant tissues such as the lung, gut, and soft tissues, particularly when crystalloid solutions are infused into normovolemic subjects. Large-volume crystalloid infusions also may be associated with a hypercoagulable state caused by dilution of circulating anticoagulant factors; the clinical significance of this is not currently known.<sup>52</sup>

### Saline Solutions

**0.9% Sodium Chloride.** One of the most commonly administered crystalloids is 0.9% NaCl solution, yet it is not clear historically how it entered routine clinical practice. Although many of the crystalloids being examined for in vivo clinical usage during the 1800s had a composition much closer to that of plasma, Hamburger ascertained using in vitro red cell lysis experiments that 0.9% was the NaCl concentration that was isotonic with human plasma. Therefore, 0.9% saline was not initially developed with the aim of in vivo administration, yet has entered widespread clinical use despite having a  $\text{Na}^+$  and  $\text{Cl}^-$  concentration far in excess of that of plasma.<sup>53</sup> Its osmolarity, calculated as the sum of the solutes present, is slightly higher than that of plasma, although the osmolality (measured by freezing point depression) is 285 mOsm/kg, very similar to that of plasma. This discrepancy reflects the nonideal behavior of solutions. Both ions remain in the ECF after infusion, and it can be said to be isotonic—that is, of a similar *effective osmolarity* to that of plasma with respect to the cell membrane.

A 2-L infusion of 0.9% NaCl leads to an increase in ECF volume, dilutional decrease in hematocrit and albumin, increase in  $\text{Cl}^-$  and  $\text{K}^+$  concentrations, and decrease in plasma  $\text{HCO}_3^-$ .<sup>42</sup> The expansion of the ECF is more persistent than with balanced crystalloid solutions. Although both fluids induce diuresis, 0.9% NaCl has a later onset and the excess salt and water load may take multiple days for even a healthy subject to excrete.<sup>12</sup>

A 0.9% NaCl infusion leads to a hyperchloremic metabolic acidosis and reduced renal perfusion. Although important differences in clinical outcomes in the surgical populations are not clear,<sup>54</sup> in the wider critical care population an increased incidence of kidney injury and requirement for renal replacement therapy are seen when compared with the use of lower  $\text{Cl}^-$  solutions.<sup>46,55</sup> In healthy volunteers, large-volume (50 mL/kg) saline infusions lead to abdominal discomfort, nausea, and vomiting.

These side effects mean that the volume of saline administered perioperatively should be limited, unless there are compelling indications such as the following:

- Situations in which increased plasma  $\text{Na}^+$  may be beneficial, such as in the presence of cerebral edema.
- Preexisting  $\text{Na}^+$  or  $\text{Cl}^-$  total body depletion, such as gastric outlet obstruction (see later discussion). However, 0.9% NaCl is not suitable for the treatment of acute severe hyponatremia, because it has little effect on plasma  $\text{Na}^+$  levels in this situation.

**TABLE 47.6** Composition of Fluids Available for Intravenous Administration\*

Fluid	Sodium	Potassium	Chloride	Calcium	Magnesium	Bicarbonate	Lactate	Acetate	Glucuronate	Glucose (g/L) <sup>-1</sup>	Other	Osmolarity	Notes	pH (In Vitro)
Plasma	140	5	100	4.4	2	24	1	—	—	—	—	285	SID 42	7.4
0.9% NaCl	154	—	154	—	—	—	—	—	—	—	—	308	SID 0	6.0
1.8% NaCl	308	—	308	—	—	—	—	—	—	—	—	616		
0.45% NaCl	77	—	77	—	—	—	—	—	—	—	—	154		
5% dextrose	—	—	—	—	—	—	—	—	—	50	—	252		4.5
5% dextrose/0.45% NaCl	77	—	77	—	—	—	—	—	—	50	—	406		4.0
4% dextrose/0.18% NaCl	33	—	33	—	—	—	—	—	—	40	—	283		
Lactated Ringer solution (U.S. composition)	130	4	109	3	—	—	28	—	—	—	—	273		6.5
5% dextrose in lactated Ringer solution	130	4	109	3	—	—	28	—	—	50	—	525		5.0
Hartmann solution/compound Na <sup>+</sup> lactate	131	5	111	4	—	—	29	—	—	—	—	275	In vivo SID 27	6.5
Plasma-Lyte 148/ Normosol-R	140	5	98	—	3	—	—	27	23	—	—	294		4-6.5
Plasma-Lyte 56 and 5% dextrose/ Normosol M with 5% dextrose	40	13	40	—	3	—	—	16	—	50	—	389 / 363		3.5-6
Plasma-Lyte A pH 7.4	140	5	98	—	3	—	—	27	23	—	NaOH for pH	294		7.4
Sterofundin	140	4	127	5	2	—	—	24	—	—	Maleate 5	309		5.1-5.9
Plasma-Lyte R	140	10	103	5	3	—	8	47	—	—	—	312		
Hemosol	140	—	109.5	3.5	1	32	3	—	—	—	—	—	In vivo SID 33	
4%-5% albumin	†	—	†	—	—	—	—	—	—	—	Stabilizer: octanoate (caprylate)	†		7.4
20% albumin	†	—	†	—	—	—	—	—	—	—	Stabilizer: octanoate (caprylate)	†		
Plasmanate: Plasma protein fraction (human) 5%	145	0.25	100	—	—	—	—	—	—	—	88% human albumin, 12% α <sub>1</sub> -β <sub>1</sub> -globulins	COP 20 mm Hg	7.4	

Continued

**TABLE 47.6** Composition of Fluids Available for Intravenous Administration\*—cont'd

Fluid	Sodium	Potassium	Chloride	Calcium	Magnesium	Bicarbonate	Lactate	Acetate	Gluconate	Glucose (g/L) <sup>-1</sup>	Other	Osmolarity	Notes	pH (In Vitro)
Gelofusine (4%)	154	—	125	—	—	—	—	—	—	—	MWw 30 kDa		Succinylated gelatin	
Plasmion/Geloplasma (3%)	150	5	100	—	3	—	30	—	—	—	MWw 30 kDa		Succinylated gelatin	
Isoplex (4%)	145	4	105	—	1.8	—	25	—	—	—	MWw 30 kDa		Succinylated gelatin	
Gelaspan (4%)	151	4	103	2	2	—	—	24	—	—	MWw 30 kDa			
Haemaccel (poly-geline)	145	5.1	145	12.5	—	—	—	—	—	—	MWw 35 kDa			
Voluven: Waxy maize HES 6% (130/0.4)	154	—	154	—	—	—	—	—	—	—	—	308		
Venofundin: Potato HES 6% (130/0.42)	154	—	154	—	—	—	—	—	—	—	—			
Hetastarch: Waxy maize HES 6% (670/0.75)	154	—	154	—	—	—	—	—	—	—	—	309		5.5
Hextend: Waxy maize HES 6% (670/0.75)	143	3	124	5	1	—	28	—	—	—	—			
Pentaspan: Pentastarch 10%	154	—	154	—	—	—	—	—	—	—	MWw 264 kDa	326		5.0
Volulyte: Waxy maize HES 6% (130/0.4)	137	4	110	—	3	—	—	34	—	—	—	287		
Plasma volume: Potato HES 6% (130/0.42)	130	5.4	112	1.8	2	—	—	27	—	—	—			
Tetraspan: Potato HES 6% (130/0.42)	140	4	118	5	2	—	—	24	5	—	—			
10% Dextran 40	—	—	—	—	—	—	—	—	—	50	—	255		4.0

HES, Hydroxyethyl starch; MWw, weight-averaged mean molecular weight. Plasma-Lyte, PlasmaVolume, Baxter International, Deerfield, IL; Gelofusine, Gelaspan, Venofundin, Sterofundin, and Tetraspan, B Braun (Melsungen, Germany); Plasmion, Geloplasma, Voluven, and Volulyte, Fresenius-Kabi, Bad Homburg, Germany; Hextend, BioTime, Berkeley, Calif; Pentaspan from Bristol-Myers Squibb, Canada; Hemosol, Hospital, Rugby, United Kingdom.; Isoplex Beacon, Kent, United Kingdom; Normosol, Hospira, Lake Forest, IL.

\*Presented as mEq/L, except where stated.

<sup>†</sup>The NaCl content and osmolarity of albumin solutions varies dependent on formulation. Osmolarity values are calculated in vitro.

**Hypertonic Saline.** Solutions of 1.8%, 3%, and 7.5% NaCl are available. Their uses include:

Plasma volume expansion: The hypertonic nature of these solutions draws water out of the intracellular compartment and into the extracellular (including plasma) volume and may therefore achieve plasma volume expansion while minimizing the volume of fluid administered. Although it has not been studied extensively, use of hypertonic saline for trauma resuscitation, particularly in the prehospital phase, has not shown convincing benefit. In fact, one large trial showed no improvement in outcome and was stopped early.<sup>56</sup>

- Correction of hypoosmolar hyponatremia (see later discussion)
- Treatment of increased intracranial pressure: The increased plasma osmolality reduces cerebral edema and decreases intracranial pressure. Hypertonic saline may be superior to mannitol in this regard.<sup>57</sup> However, hypertonic saline used early in traumatic brain injury without knowledge of intracranial pressure has not been shown to be beneficial in clinical trials.<sup>58</sup>

At NaCl concentration greater than 7.5%, these solutions may cause endothelial damage; indeed, 11.7% NaCl may be used as a sclerosant agent and should therefore be administered into a central vein.

### Balanced Crystalloid Solutions

Intravenous crystalloid solutions were initially used clinically for the management of cholera in 1832 by O'Shaughnessy and Latta. The early solutions were more closely matched to physiologic plasma composition than NaCl solutions and contained 134 mEq/L Na<sup>+</sup>, 118 mEq/L Cl<sup>-</sup>, and 16 mEq/L HCO<sub>3</sub><sup>-</sup>.<sup>53</sup> However, clinical interest in more balanced solutions waned until Hartmann in 1932 used a lactated modification of Ringer solution for pediatric patients with acidosis associated with hypovolemia and liver and renal failure.<sup>59</sup> By this time, NaCl solutions were already in use for resuscitation from hemorrhage and trauma.<sup>53</sup>

Currently available balanced crystalloid solutions have lower overall osmolarity than 0.9% NaCl, with a lower Na<sup>+</sup> concentration and much lower Cl<sup>-</sup> concentration (see Table 47.6). The reduction in anionic content is compensated for by the addition of stable organic anionic buffers such as lactate, gluconate, or acetate. The measured osmolality of balanced solutions (265 mOsm/kg) is slightly lower than that of plasma, and they are therefore mildly hypotonic. Fluid compartment distribution of balanced solutions is resembles that of other crystalloids. After administration, the buffer is metabolized to produce HCO<sub>3</sub><sup>-</sup> in equimolar quantities by entry into the citric acid cycle. Lactate undergoes predominantly hepatic oxidation or gluconeogenesis to yield HCO<sub>3</sub><sup>-</sup> at a maximum rate of approximately 200 mmol/h.<sup>60</sup> Acetate is normally present in trace quantities in the plasma (0.2 mM), because it is rapidly oxidized by liver, muscle, and heart to yield HCO<sub>3</sub><sup>-</sup> at a maximum turnover of 300 mmol/h, beyond which zero-order kinetics intervene.<sup>61</sup> A small proportion may be converted to the acetoacetate. The metabolism of gluconate is less well characterized in terms of location and kinetics, but it is converted to glucose with subsequent entry into the citric

acid cycle.<sup>62</sup> Although balanced crystalloids can be constituted with HCO<sub>3</sub><sup>-</sup> as a main anion, this is limited by two factors. First, HCO<sub>3</sub><sup>-</sup> reacts with water to form CO<sub>2</sub>, which can diffuse out of most packaging materials. This has been addressed by some products, although availability is limited.<sup>63,64</sup> Second, the pH shift induced by the presence of HCO<sub>3</sub><sup>-</sup> can lead to precipitation of Ca<sup>2+</sup> (and Mg<sup>2+</sup>) if present.

The excretion of the excess water and electrolyte load with balanced crystalloids is more rapid than with isotonic saline.<sup>65</sup> This is due to the transient decrease in plasma tonicity after infusion, which suppresses ADH secretion and allows diuresis in response to the increased intravascular circulating volume. Balanced crystalloids do not reduce plasma SID to the same degree as NaCl solutions and therefore do not cause an acidosis; HCO<sub>3</sub><sup>-</sup> concentration is maintained or slightly elevated.

Some potential negative effects have been identified with balanced crystalloid solutions. Lactated Ringer solutions contain racemic (D- and L-) lactate, although D-lactate is only found in trace quantities in vivo. Concerns that large doses of D-lactate may be associated with encephalopathy and cardiac toxicity in patients with renal failure<sup>66,67</sup> have not been confirmed in human studies at plasma levels achievable with racemic lactated Ringer solution. The metabolism of D-lactate appears to be nearly as rapid as that of L-lactate.<sup>68</sup> The reliance on hepatic metabolism of most of the infused lactate means that lactated solutions should be avoided in severe liver failure. Concerns over the negative effects of excess exogenous acetate have been raised in patients receiving dialysis with an acetate-based dialysate. The proinflammatory, myocardial depressant, vaso-dilatory, and hypoxemia-promoting effects of high acetate levels manifest as nausea, vomiting, headaches, and cardiovascular instability and have led to the removal of acetate from contemporary dialysis fluids.<sup>61,69–73</sup> Acetate turnover is limited in patients with end-stage kidney disease and by the presence of other substrates for oxidation—for example, during lactic acidosis or proteolysis. It is therefore possible that critically ill patients or those with advanced kidney disease may exhibit biochemical acetate intolerance, although this possibility has not been explored in patients receiving acetate-based balanced crystalloids. Unlike acetate, much less is known about the effects of gluconate-containing fluids.<sup>74</sup> Indeed, this area requires investigation at a cellular, organ, and whole organism level, particularly because data in animal studies suggest poorer outcome and late increases in lactate in a hemorrhage model when acetate/gluconate-containing crystalloids are compared to lactated Ringer solution or isotonic saline for resuscitation.<sup>75</sup>

### Dextrose Solutions

Dextrose solutions have the following two main indications in the perioperative setting:

1. As a source of free water: An infusion of 5% dextrose effectively represents administration of free water. The in vitro osmolality resembles that of plasma so the infusion does not lead to hemolysis, but soon after administration, the dextrose is taken up into cells in the presence of insulin, leaving free water. These solutions are therefore hypotonic with respect to the cell membrane and

in excess can dilute plasma electrolytes and osmolality. They should therefore be used with care in the postoperative period, during which the relative syndrome of inappropriate secretion of antidiuretic hormone (SIADH) leads to water retention, increasing the risk for hyponatremia (see later discussion). Nevertheless, in carefully controlled volumes and with regular monitoring of serum electrolytes, they are a useful source of free water for maintenance requirements postoperatively, particularly if combined with a low concentration of NaCl. Dextrose solutions are less suitable for intravascular plasma volume expansion, because water can move between all fluid compartments, and a very small volume remains in the intravascular space.

2. Source of metabolic substrate: Although the caloric content of 5% dextrose is inadequate to maintain nutritional requirements, higher concentrations are adequate as a metabolic substrate, such as 4000 kCal/L for 50% glucose. Glucose solutions also may be coadministered with IV insulin to diabetic patients to reduce the risk for hypoglycemia, such as 10% dextrose at 75 mL/h.

## COLLOIDS

Colloid is defined as large molecules or ultramicroscopic particles of a homogeneous noncrystalline substance dispersed in a second substance, typically isotonic saline, or a balanced crystalloid. These particles cannot be separated out by filtration or centrifugation. Although not all solutions are available in all countries, those in production include semisynthetic colloids and human plasma derivatives. Semisynthetic colloids have a range of molecular sizes (polydispersed) in contrast to human albumin solution, which contains more than 95% albumin molecules of a uniform size (monodispersed). Colloid molecules above 70 kDa are too large to pass through the endothelial glycocalyx and are excluded from the subglycocalyx layer, so their initial volume of distribution is the plasma (rather than the entire intravascular) volume (see discussion of vascular endothelium). In contrast to pure electrolyte solutions, colloids have a higher COP and minimize transcapillary filtration, particularly at low capillary hydrostatic pressures. This maximizes their potential intravascular plasma volume expansion effect. However, at normal or supranormal capillary pressures, hydrostatic pressure will be increased and transcapillary filtration will occur.<sup>3</sup> In addition, colloid molecules may be lost from circulation in several ways—by filtration across capillaries whose barrier function is impaired by glycocalyx shedding or endothelial cell pore formation in inflammation or other stressors, by renal filtration of smaller colloid molecules, or by removal from the circulation by metabolism. Therefore, colloids have variable effective plasma half-lives, as outlined later. Colloids alter blood rheology, improving blood flow by hemodilution which leads to reductions in plasma viscosity and red cell aggregation.<sup>52</sup> In contrast to their beneficial effects, the introduction of a large dose of semisynthetic molecules (typically 40–60 g/L) to a complex physiologic system may bring a variety of undesired effects on the immune, coagulation, and renal systems. To limit these toxicities, maximum dosages are recommended for most colloids, but adverse effects may still occur with lower doses. As the potential

clinical relevance of toxicity is highlighted by large clinical trials, the use of colloids, at least in critical care, deserves increasing caution.<sup>76</sup> Whether these trials in critical care can be applied to the entire perioperative period has not been established. The evolving evidence base on the differential effects of isotonic saline or balanced crystalloid is also likely to focus more attention on the carrier solute used in colloids.

## Semisynthetic Colloids

**Gelatins.** Gelatins are derived from the hydrolysis of bovine collagen, with subsequent modification by succinylation (Gelofusine, B Braun, Bethlehem, PA; Geloplasma®, Fresenius, Waltham, MA) or urea-linkage to form polygeline (Haemaccel, Piramal, Orchard Park, NY). These forms have a similar molecular weight (MW), but the succinylated version undergoes conformational change as a result of increased negative charges, such that it is a larger molecule. The wide range of MWs means that much of an infused gelatin bolus will rapidly leave the circulation, predominantly by renal filtration. Despite this, a recent study suggests that 60 minutes after the end of infusion, 50% of the infused fluid volume remains in the intravascular space, similar to larger MW colloids.<sup>77</sup> Excretion is primarily by the renal route. In terms of negative effects, the gelatins have the least impact on clinically relevant hemostasis of all the semisynthetic colloids despite reductions in von Willebrand factor (vWF), factor VIIIc, and ex vivo clot strength,<sup>78</sup> but the highest estimated incidence of severe anaphylactic and anaphylactoid reactions (<0.35%).<sup>52</sup> The high Ca<sup>2+</sup> content of Haemaccel is a contraindication to coadministration of citrated blood products in the same infusion set. No known cases of variant Creutzfeldt-Jakob disease transmission have occurred involving pharmaceutical gelatin preparations. Gelatins are commonly used in perioperative practice in Europe but are not approved by the U.S. Food and Drug Administration.

**Hydroxyethyl Starches.** Hydroxyethyl starches (HESs) are modified natural polymers of amylopectin derived from maize or potato. Substitution of hydroxyethyl radicals onto glucose units prevents rapid in vivo hydrolysis by amylase, and the degree of substitution both in terms of hydroxyethyl substitutions per glucose unit (maximum three) and total number of glucose units with substitutions is a determinant of HES elimination kinetics. The degree of substitution (DS) is expressed as the number of substituted glucose molecules present divided by the total number of glucose molecules present. An alternative measure of substitution is the molar substitution (MS) ratio, calculated as the total number of hydroxyethyl groups present divided by the quantity of glucose molecules. MS is used to define starches as hetastarches (MS 0.7), hexastarches (MS 0.6), pentastarches (MS 0.5), or tetrastarches (MS 0.4). The pattern of substitution may vary because hydroxyethylation can occur at carbon positions 2, 3, or 6 of the glucose unit. The substitution type is defined by the C2/C6 hydroxyethylation ratio, and a higher ratio leads to slower starch metabolism. Starches are also classified by in vitro MW into high (450–480 kDa), medium (200 kDa), and low (70 kDa). However, HES solutions are very polydispersed and the MW quoted is an average. The size of starch molecule is responsible for both the therapeutic volume effects and adverse side effects. After administration,

smaller HES molecules (<50-60 kDa) are rapidly excreted and larger molecules are hydrolyzed to form a greater number of smaller molecules at a rate depending on the degree of substitution and C2/C6 hydroxyethylation ratio. The *in vivo* MW is therefore smaller and has a narrower distribution.<sup>79</sup> Ongoing renal excretion accounts for the elimination of smaller HES molecules, with medium-sized molecules being excreted in the bile and feces. A proportion of larger molecules, particularly those resistant to hydrolysis, is taken up by the mononuclear phagocyte (reticuloendothelial) system, where they may persist for several weeks or more.<sup>80</sup> The prolonged metabolism of HES means that their plasma volume effects typically last longer than those of gelatins or crystalloids. Larger MW starches can increase intravascular volume by approximately 70% to 80% of the infused dose even at 90 minutes.<sup>81</sup> Smaller MW starches with a low MS may have even larger volume effects as a result of the rapid initial metabolism with the formation of a large number of oncotically active molecules,<sup>82</sup> but studies in healthy human volunteers suggest only a similar volume effect to that of gelatins.<sup>77</sup>

For all fluids in this category, starch-related side effects have been associated with adverse outcomes in critical illness. Problems such as coagulopathy, accumulation, and renal dysfunction initially appeared to be related to larger MW starches, but now smaller tetrastarches are a concern as well. Despite this, study populations with critical illness, particularly sepsis, cannot be compared directly with elective perioperative patients. These trials should be interpreted with caution when considering the relevance of HES to surgical patients. Nevertheless, the official recommendations against the use of HES are clearly negative.

**Coagulation.** As with other synthetic colloids, HES products affect coagulation through dilutional effects in the circulation and MW-dependent reductions in vWF, factor VIII, and clot strength. The effect is most likely to occur with larger MW or slowly degraded medium MW (200 kDa/MS 0.62 or 200 kDa/MS 0.5/C2:C6 13) HES preparations and larger amounts of perioperative blood loss. This clinical effect is less marked with more rapidly degraded medium and small MW starches.<sup>52</sup> In patients with sepsis, even lower MW HES is associated with an increased risk of bleeding and blood transfusion, but it is unclear whether this also occurs in the perioperative setting.<sup>83,84</sup>

**Accumulation.** The accumulation of HES molecules in the mononuclear phagocyte system and skin, liver, muscle, and gut is a dose-dependent effect that gradually decreases over time. However, the accumulation may persist for several years, and larger amounts of tissue deposition are associated with pruritus.<sup>80</sup>

**Anaphylactoid Reactions.** The estimated incidence of severe anaphylactoid or anaphylactic reactions with HES products is less than with other colloids (<0.06%).<sup>52</sup>

**Renal Dysfunction.** HES products with medium-to-high MW are associated with oliguria, increased creatinine, and acute kidney injury in critically ill patients with preexisting renal impairment.<sup>6,85</sup> Although newer solutions with low MW (130 kDa/MS 0.4) were initially thought to be safer in

this respect, recent large-scale trials have shown a similar effect on the need for renal replacement therapy in severe sepsis, particularly when compared with balanced crystalloids.<sup>83,84</sup> A recent large trial in a mixed critical care population comparing HES with isotonic saline also reported an increase in renal replacement therapy with the starch solution. This study is more difficult to interpret, given the potential renal effects of saline, and, as with previous studies, the possibility that patients were given study fluids after partial resuscitation had already been achieved.<sup>51</sup> Currently, no similar data are available from large-scale studies on the intraoperative use of HES solutions, and a recent meta-analysis examining perioperative use of 6% HES concluded that although no increase in mortality or kidney injury was seen, the available evidence lacked statistical power to definitively answer this question.<sup>86</sup> Meanwhile, the use of starch-based colloids has been restricted or even completely suspended by regulatory authorities in both the United States and Europe.

**Dextran.** Dextran are highly branched polysaccharide molecules produced by the bacterium *Leuconostoc mesenteroides* after conversion of sucrose in the growth medium by bacterial dextran sucrase. The large-MW dextrans produced undergo acid hydrolysis to yield smaller MW molecules, which are then separated by fractionation to produce a solution with a restricted range of MWs. Available dextrans have an average MW of 40 kDa or 70 kDa. As with other colloids, the polydisperse nature of dextran solutions means that a proportion of smaller MW molecules are present that are rapidly filtered at the glomerulus; 70% of a dextran dose is renally excreted within 24 hours. Higher MW molecules are excreted into the GI tract or taken up into the mononuclear phagocyte system, where they are degraded by endogenous dextranases.<sup>52</sup> Dextrans have a plasma volume effect similar to that of starches, with a duration of 6 to 12 hours. In addition to their use in volume expansion, dextran 40 may be used in microvascular surgery, where its dilutional effects on blood viscosity and anticoagulant effects (see later discussion) favor flow in the microcirculation. Overall, the use of dextrans is limited by their range of toxicities.

**Antithrombotic effect:** This is particularly marked in lower MW dextrans and is mediated through a range of mechanisms, including red cell coating and inhibition of aggregation, factor VIIIc and vWF reductions, and impaired activity of factor VIII. Platelet aggregation is also inhibited. The result is clinically impaired hemostasis and increased perioperative blood loss.<sup>78</sup>

- **Blood cross-matching:** Dextrans coat the erythrocyte cell membrane and may interfere with blood type cross-matching.
- **Anaphylactoid reactions:** Dextrans have an intermediate risk for serious anaphylactic and anaphylactoid reactions (<0.28%). Preemptive treatment with dextran 1, a hapten inhibitor, may reduce this incidence to less than 0.0015%.<sup>52</sup>
- **Renal dysfunction:** Renal dysfunction resulting from osmotic nephrosis is recognized after low-MW dextran infusion,<sup>87</sup> although the true incidence of this phenomenon in perioperative patients is difficult to estimate

because of the limited use of dextrans in contemporary practice.

### Human Plasma Derivatives

The human plasma derivatives include human albumin solutions, plasma protein fractions, fresh frozen plasma, and immunoglobulin solution. Preparation techniques result in relatively purified solutions with the elimination of infective agents, although the theoretic risk for transmission of variant Creutzfeldt-Jakob disease and associated bovine spongiform encephalopathy remains. One U.K. case of presumed prion transmission has been described in association with factor VIII transfusion, although without clinical manifestation.<sup>88</sup> The ongoing transmission risk has been mitigated by sourcing many plasma derivatives from non-U.K. sources.

Solutions such as 5% albumin have a near-physiologic COP of 20 mm Hg and are used for volume expansion. Despite the association of hypoalbuminemia with worse outcomes from critical illness, the administration of exogenous albumin does not improve outcome in these situations. Early concerns that resuscitation with albumin may actually increase mortality in critical illness were not confirmed by a large controlled trial that found no difference in outcomes whether albumin or isotonic saline was used for resuscitation.<sup>5</sup> In this heterogeneous population, the albumin group required less fluid to attain similar endpoints (ratio 1:1.4), although in the subgroup of patients with trauma, and particularly brain injury, albumin may be associated with an increased incidence of mortality.<sup>5,89</sup> Conversely, in a subgroup analysis of patients with sepsis, albumin administration trended toward a decreased frequency of mortality that was supported by a subsequent meta-analysis.<sup>90</sup>

## Clinical Fluid and Electrolyte Management

### PATHOPHYSIOLOGIC FLUID ALTERATIONS IN THE PERIOPERATIVE PHASE

Before recommending practical approaches to administering fluid in the perioperative phase, it is important to consider the pathophysiologic processes, which affect not just the body's requirement for exogenous fluid and electrolytes but also the manner by which fluids are distributed by the body. The patient may enter the perioperative phase with abnormalities of intravascular fluid volume and distribution. Subsequent trauma (including surgery) induces a range of evolutionarily conserved neurohumoral and inflammatory changes, termed the stress response, which may have a significant impact on fluid and electrolyte responses and distribution. When the stress response is of an appropriate magnitude and duration, it can be a beneficial process for recovery from trauma; however, it could become pathologic if it is either exaggerated or prolonged or presents a physiologic burden to patients with limited baseline physiologic reserves.

#### Preoperative

Patients may enter the perioperative phase with established derangements of fluid and electrolyte balance. Hepatic, renal, and cardiac dysfunction are all associated with

disordered Na<sup>+</sup> distribution (see later discussion), which has profound secondary effects on ECF volume. Patients with end-stage renal disease depend on dialysis for fluid removal, and the timing of dialysis relative to surgery is critical. Chronic treatment with diuretics may also lead to electrolyte depletion. Depending on the treatment, hypertensive patients may have a volume-contracted circulation, making them prone to intraoperative hypovolemia.

The effects of preoperative fasting also should be considered, although its influence on fluid balance has perhaps been overstated. Modern perioperative practice mandates cessation of oral fluids only 2 hours before elective surgery, and overnight fasting usually does not result in changes to normal blood volume when measured using robust experimental techniques.<sup>91</sup> Conversely, bowel preparation can cause a weight loss of 1.5 to 1.7 kg<sup>92,93</sup> with a high water and K<sup>+</sup> content. The potentially deleterious effects of this should be limited by restricting bowel preparations when possible and compensating for fluid loss with simultaneous IV infusion of 1 to 2 L of crystalloid with K<sup>+</sup> supplementation, which can improve hemodynamics and lower serum creatinine.<sup>93</sup>

More severe disturbances of fluid and electrolyte balance can occur in patients presenting with acute disease requiring surgical intervention:

- Direct intravascular depletion from bleeding.
- Loss of fluid from the GI tract. This results in ECF depletion and loss of electrolytes, depending on the GI tract location. Excess gastric loss because of obstruction, vomiting, or excess nasogastric suction results in loss of Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, and acid. Loss of small bowel secretions results in high losses of Na<sup>+</sup>, Cl<sup>-</sup>, and HCO<sub>3</sub><sup>-</sup> with lesser K<sup>+</sup> losses. Large bowel losses, such as in diarrhea, deplete large quantities of K<sup>+</sup> with lesser losses of Na<sup>+</sup> and HCO<sub>3</sub><sup>-</sup>. Pathologic fluid sequestration within the bowel lumen may have similar effects without external signs of fluid loss.
- Inflammation-related redistribution from the intravascular to the extracellular compartment (see later discussion).
- Fluid sequestration in the physiologic third space, with edema, pleural effusions, and ascites.

#### Intraoperative

Many factors influence intraoperative fluid balance, such as:

- Altered distribution of intravascular volume. Anesthetic agents lead to vasodilation, which can affect both the venous and arterial systems and may reduce cardiac preload and afterload. This reduction may be exacerbated by sympathetic blockade caused by central neuraxial blockade, and cardiac output may also be decreased by the negative inotropic effect of anesthetic drugs. The distribution of blood within the vascular system is also influenced by the differential blunting of autoregulatory responses within organ beds caused by anesthesia. Microcirculatory dysfunction related to the effects of anesthesia and the inflammatory response to surgery may result in impaired functional matching of local O<sub>2</sub> delivery with tissue O<sub>2</sub> requirements, which may not be responsive to intravascular fluid therapy.

- Direct loss of intravascular volume from hemorrhage. The clinical manifestation of surgical blood loss may vary greatly depending on the volume and time course of the blood loss.
- Insensible losses. The opening of anatomic compartments leads to evaporative fluid loss from mucosal surfaces, although estimating the extent of this loss may be difficult. Humidity chamber studies indicate that the loss may be as little as 1 mL/kg/h even during a major laparotomy with extensive bowel exposure.<sup>94</sup>
- Inflammation-related redistribution. Major surgery induces an inflammatory response that redistributes fluid from the intravascular to the extracellular compartment. This typically manifests in the postoperative phase (see later discussion), although it may become clinically apparent intraoperatively during surgery of sufficient magnitude and duration.
- Renal output. The suppression of renal urine production is related to perioperative ADH secretion and may also be influenced by the effects of positive-pressure ventilation. Increased intrathoracic pressure reduces venous return and cardiac output, which combine with a variety of neurohumoral responses such as sympathetic activation and suppression of ANP release to decrease GFR and urine output.<sup>95</sup> As a result, intraoperative urine output may be low regardless of the volume of IV fluid administered.<sup>96</sup>

The early phase of the stress response is triggered during major surgery. Absolute or relative (redistributive) hypovolemia during the intraoperative phase invokes a range of conservative responses—described in the section on Acute Disturbances in Circulating Volume—that are aimed at redistributing blood away from the periphery and toward vital organs and maintaining circulating volume by retaining salt and water. The tissue trauma of surgery also triggers a well-described inflammatory and immune response, and together these changes may persist into the postoperative phase. The inflammatory response elicited by tissue trauma may be aggravated by periods of hypotension and tissue hypoperfusion.

### Postoperative

As a result of the preoperative and intraoperative factors outlined previously, patients may start the postoperative phase with significant derangements of intravascular volume and fluid compartment distribution. The stress response triggered by surgery may also have an ongoing influence on postoperative fluid balance.

**Inflammation and Immune Response.** Tissue injury leads to local vasodilation, increased endothelial permeability, and influx of leukocytes to the damaged area, with consequent production of proinflammatory cytokines for up to 72 hours, particularly interleukin-1 (IL-1), TNF- $\alpha$ , and IL-6. Cardiopulmonary bypass, extensive tissue trauma, or surgery in areas with subclinical preoperative inflammation, such as tumor or infection, may lead to a postoperative systemic inflammatory response syndrome (SIRS). An alternative trigger for SIRS is GI hypoperfusion. The physiologic response to hypovolemia is preservation of cardiac and brain perfusion at the expense of kidney, gut, and peripheral perfusion. The intestinal villi have a countercurrent blood supply that shunts blood away from the mucosa

in this situation, leading to mucosal necrosis and further impairment of gut barrier function by luminal digestive enzymes and bacteria. This allows gut bacterial endotoxin to translocate into the systemic circulation, acting as a potent trigger for systemic inflammation.<sup>97,98</sup> The reactive O<sub>2</sub> species released on reperfusion of compromised bowel further aggravate the inflammatory cascade.

Systemic inflammation impairs endothelial barrier function through changes in endothelial cell phenotype, increases in endothelial large pores, and degradation of the endothelial glycocalyx.<sup>2</sup> Hypervolemia caused by excessive fluid infusion leads to the release of cardiac natriuretic peptides, which may further degrade the endothelial glycocalyx.<sup>99</sup> In severe cases, inflammation-related endothelial dysfunction leads to a capillary leak syndrome, with loss of water, electrolytes, and proteins into the interstitial space causing edema in the lungs, bowel, and connective tissue. Reduced plasma oncotic pressure facilitates ongoing capillary fluid filtration into the extravascular space and consequent hypovolemia.

**Catabolic Metabolism.** The response to tissue injury requires an increase in energy substrate delivery, particularly to leukocytes involved in the acute inflammatory and immune reaction. This metabolic shift is mediated by catecholamine and cortisol release and involves muscle protein catabolism, with associated hepatic gluconeogenesis and acute phase protein production, and increased substrate delivery to damaged tissues. An increase in basal metabolic rate and adequate circulating volume are required to meet the needs of increased fuel mobilization, processing, and delivery.

**Regulation of Salt and Water Balance.** As described in the section on physiologic control of overall fluid balance, ADH release is induced during surgery, leading to postoperative retention of water. This may be a direct result of the acute stress response, and IL-6 has been proposed as a key mediator.<sup>100</sup> In addition, periods of hypovolemia and hypotension further stimulate ADH release and activate the RAA system with further water and salt retention and amplified ADH production. This may lead to a temporary period of oliguria despite a restored circulating volume and the risk for postoperative fluid overload and sodium fluctuations. Na<sup>+</sup> retention postoperatively is more pronounced in the hypercatabolic state after major surgery, as excess nitrogen competes with Na<sup>+</sup> for renal excretion.

In addition to these processes, fluid may be lost from the circulating volume as a result of reaccumulation into third spaces drained intraoperatively (ascites or pleural effusions), sequestration into the bowel lumen or removal through vomiting, nasogastric drainage, or stoma losses. Intravascular fluid distribution is also a dynamic situation postoperatively because of changes in vascular tone caused by rewarming, evolving epidural sympathetic blockade, or systemic inflammation.

### ASSESSMENT AND TREATMENT OF PERIOPERATIVE FLUID AND ELECTROLYTE IMBALANCE

#### Intravascular Volume

As a key variable influencing cardiac output (preload), and therefore tissue O<sub>2</sub> delivery, intravascular volume is at the

core of adequate tissue perfusion. Although the assessment of intravascular volume is an important part of perioperative fluid therapy, it may be challenging. Clinical history suggesting abnormal volume status should be sought (see earlier discussion) and accompanied by frequent clinical examinations, although many of the conventional markers of volume status are not reliable when taken in isolation. Obvious hypovolemia may manifest with tachycardia, reduced pulse pressure, hypotension, and increased capillary refill time, but the abnormalities of these individual physiologic variables may have numerous causes in the perioperative phase. Conversely, loss of up to 25% of blood volume may not be accompanied by significant hemodynamic alterations in healthy patients.<sup>101</sup> Urine output, frequently taken as a measure of adequate end-organ perfusion, may also be reduced postoperatively, even in the presence of normal circulating volume, as a result of ADH and RAA activation. More invasive measures of intravascular volume also have limitations. CVP is used as a marker of central venous volume, but it is also influenced by venous compliance. CVP may be normal or high in venoconstricted states even when the absolute vascular volume is reduced. Furthermore, the relationship between right-heart and left-heart filling pressures is not reliable in the presence of cardiopulmonary pathologic processes. Trends in CVP values over time may be a more useful marker, because static CVP readings are poorly predictive of subsequent responses to intravascular fluid challenges.<sup>102</sup> Stroke volume (SV) and cardiac output may be measured using a variety of techniques, and targeting these variables has been widely investigated in perioperative fluid management, as described later. Alternatively, the adequacy of tissue perfusion may be assessed at a whole organism level using blood lactate concentrations, which may also be elevated during reperfusion of ischemic tissue or in advanced liver failure, or mixed venous O<sub>2</sub> saturation, which identifies a mismatch between global O<sub>2</sub> delivery (DO<sub>2</sub>) and O<sub>2</sub> usage (VO<sub>2</sub>). Techniques used to assess the perfusion of individual organs have the potential to detect clinically occult hypovolemia affecting those tissue beds or surgical sites most at risk for hypoperfusion, such as the gut. These include near-infrared spectroscopy,<sup>103</sup> microdialysis,<sup>104</sup> and GI CO<sub>2</sub> and pH measurement. The latter technique is gastric tonometry and is based on the association between inadequate gut perfusion and mucosal hypercarbia and acidosis.<sup>105</sup> It may detect hypovolemia of a magnitude not detectable by changes in systemic blood lactate, SV, or other cardiovascular parameters<sup>101</sup> that is nevertheless associated with increased postoperative morbidity.<sup>106</sup> Despite some encouraging findings in early research studies, none of these monitors is currently in routine use for guiding perioperative hemodynamic therapy.

Both excessive and inadequate intravascular volume can have adverse physiologic effects and achieving the fine balance between the two is a key goal of perioperative fluid administration. This concept of the “sweet spot” of fluid volume is backed up by large clinical datasets showing associations between both under- and over-resuscitation and postoperative morbidity.<sup>107</sup> Modest hypovolemia, through its effects on gut perfusion and stimulation of protective neurohumoral reflexes, may exacerbate the inflammatory and antidiuretic aspects of the surgical stress response. More severe hypovolemia reduces preload, cardiac output, and therefore DO<sub>2</sub>. The result may be inadequate DO<sub>2</sub> to

meet metabolic demands, with an increase in O<sub>2</sub> extraction ratio (reflected in reduced mixed venous O<sub>2</sub> saturation), progressing to inefficient anaerobic ATP production if mitochondrial oxidative phosphorylation cannot be sustained. This situation may be aggravated by insufficient compensatory increases in cardiac output, impaired microvascular blood flow, or failure of cellular O<sub>2</sub> usage. Lactate is a by-product of anaerobic metabolism and its accumulation leads to a metabolic acidosis. ATP production may be inadequate to support normal cell functions in tissues with poor perfusion, leading to cell death and organ dysfunction in the most extreme circumstances. Inadequate global O<sub>2</sub> delivery has been associated with a range of postoperative morbidities and increased mortality and has been the target of numerous clinical trials. At an individual organ level, specific areas that have been manipulated surgically, such as tissue flaps and bowel anastomoses, may be susceptible to poor healing and failure when local perfusion is insufficient.

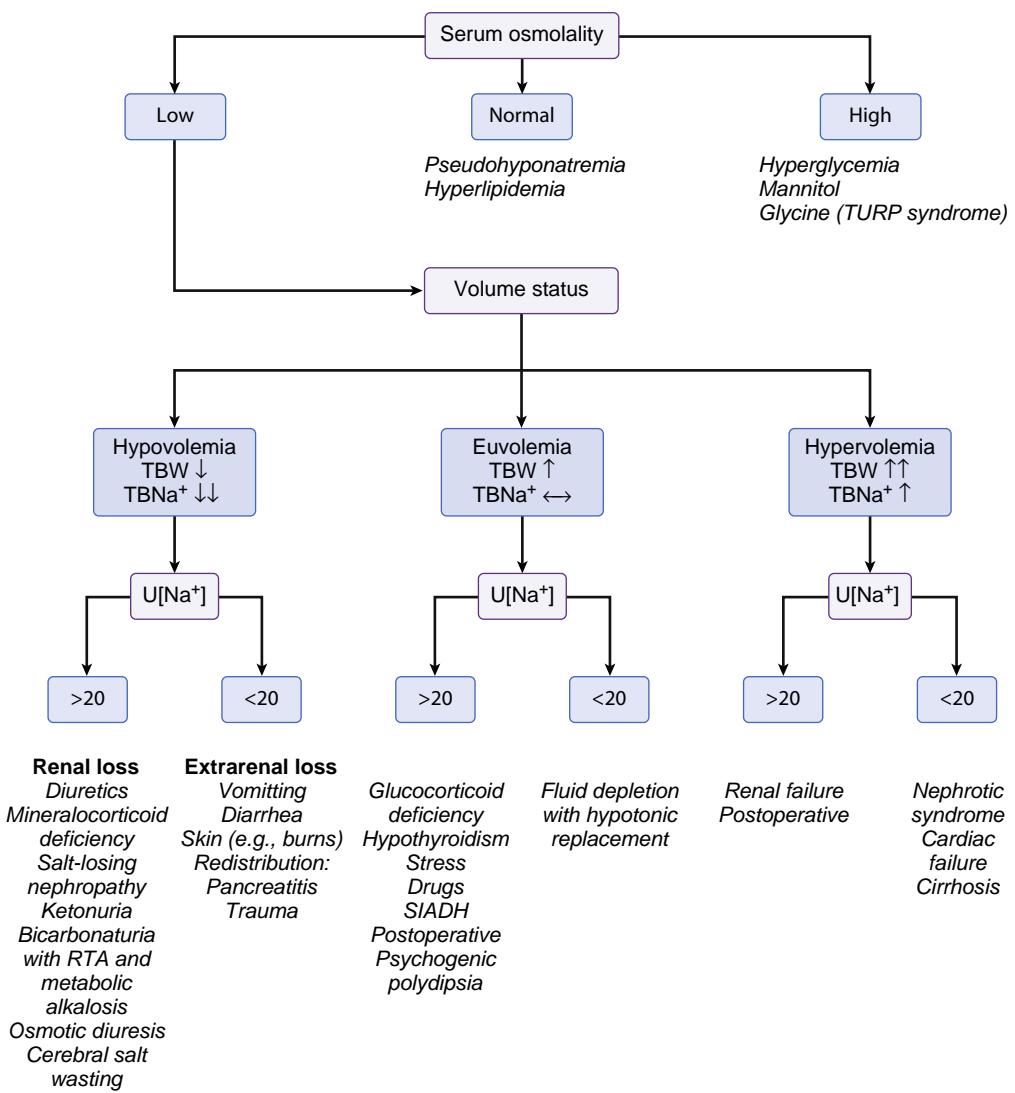
Hypervolemia also has adverse effects and is often an iatrogenic problem in the perioperative setting. Crystalloids or colloids administered when capillary hydrostatic pressures are normal or increased lead to increased capillary filtration of fluid into the interstitial space. If this exceeds the capacity of the lymphatics to return the excess fluid to the circulation, edema will develop in compliant tissues such as the lungs, muscle, and bowel. The effect is more pronounced if inflammation or deterioration of the glycocalyx reduces the endothelial barrier function opposing the passage of large molecules into the interstitium. The correction of salt and water overload is a slow process because of inefficient renal handling of excess Na<sup>+</sup> loads, and the effects of postoperative ADH secretion. Clinically significant edema contributes to postoperative GI dysfunction, although this is not well defined by small clinical trials.<sup>108,109</sup> Further potential effects of excessive intravascular fluid include reduced tissue oxygenation with impaired healing, pulmonary congestion predisposing to pulmonary infection, and increased myocardial work resulting from ventricular filling beyond the optimum portion of the Starling curve.<sup>110</sup> Side effects may occur that are attributable to the amount of fluid given, such as hypercoagulability or hypocoagulability, hyperchloremic acidosis, or renal dysfunction. A positive fluid balance and weight gain in the early perioperative period increases postoperative morbidity.<sup>111,112</sup>

## Electrolyte Imbalance

### Sodium Disorders

**HYPONATREMIA.** Hyponatremia may be present preoperatively, develop as a consequence of perioperative events, or both. It is classified as mild (130-134 mEq/L), moderate (120-130 mEq/L), or severe (<120 mEq/L). Moderate-to-severe hyponatremia, particularly of acute onset, is associated with significant perioperative morbidity.

**CAUSES.** Assessment of serum osmolality, TBW status, and urinary Na<sup>+</sup> concentration is vital for the accurate diagnosis of the underlying cause of hyponatremia.<sup>113,114</sup> A diagnostic algorithm with common causes is shown in Fig. 47.3. Na<sup>+</sup> is normally the key determinant of serum osmolality, and hyponatremia is usually observed in conjunction with reduced osmolality. In some situations, however, osmolality is normal or raised by the presence of solutes that induce cellular dehydration and translocation of water from cells to



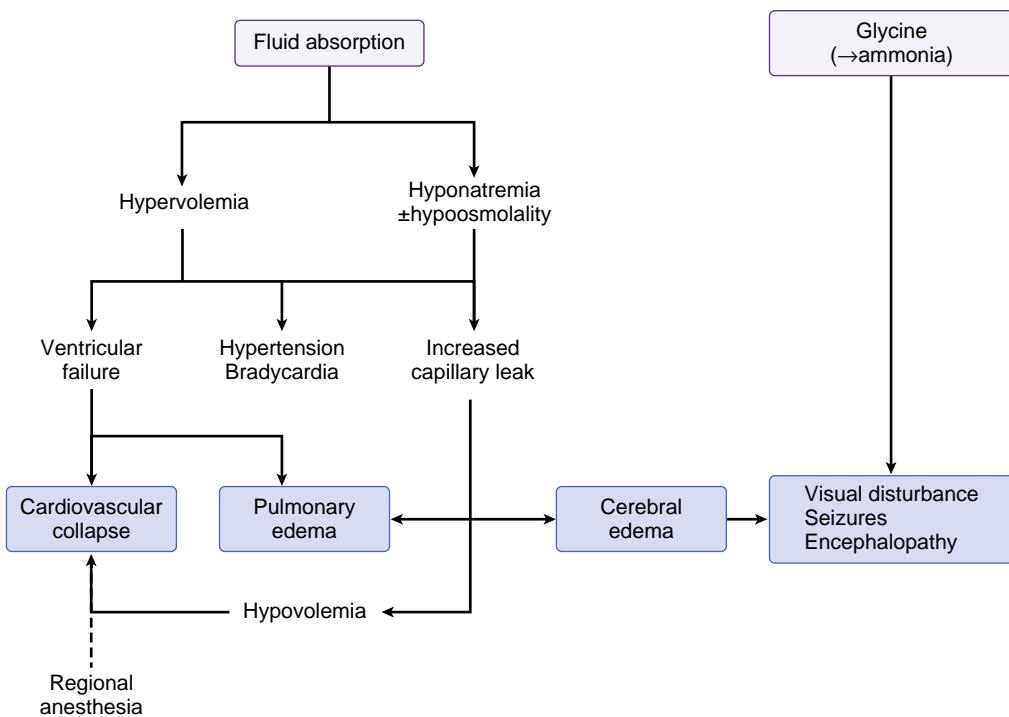
**Fig. 47.3 Causes and diagnostic algorithm for hyponatremia.** The diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH) include exclusion of adrenal, thyroid, and renal disease or diuretic usage, serum hypoosmolality ( $<270$  mOsmol/kg), clinical euvoolemia, increased urinary  $[Na^+]$  despite normal water and salt intake and inappropriate urinary concentration ( $>100$  mOsmol/kg). A characteristic response to water restriction occurs, with a 2- to 3-kg fall in weight accompanied by a reduction in salt wasting over 2 to 3 days. RTA, Renal tubular acidosis; TBW, total body water; TURP, transurethral resection of the prostate;  $U[Na^+]$ , urinary sodium concentration in mEq/L. (Modified from Kumar S, Berl T. Sodium. Lancet. 1998;352:220; and Tisdall M, Crocker M, Watkiss J, et al. Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J Neurosurg Anesthesiol. 2006;18:57.)

the ECF. These include glucose in the absence of adequate insulin, mannitol, maltose, and glycine. Alternatively, hyponatremia may be artifactual (pseudohyponatremia), caused by the presence of high lipid concentrations. In hypoosmolar hyponatremia, imbalanced gains or losses of TBW and  $Na^+$  occur such that serum  $Na^+$  concentration is reduced.

**PREOPERATIVE HYponatremia.** Hyponatremia may be an incidental finding during preoperative assessment, with the underlying pathologic mechanisms identified in Fig. 47.3. Even mild preoperative hyponatremia is associated with increased 30-day mortality, major cardiac events, wound infection, and pneumonia.<sup>115</sup> Whether hyponatremia is a direct causal mechanism in postoperative adverse events or a marker of underlying overt or subclinical pathologic processes, such as cardiac failure, is not clear, although excess risk is seen even in American Society of Anesthesiologists (ASA) class 1 and 2 patients undergoing elective surgery.

Interestingly, correcting preoperative hyponatremia does not clearly improve outcomes. The finding of preoperative hyponatremia should prompt a search for, and optimization of, potential underlying diseases. In moderate-to-severe hyponatremia, nonurgent surgery should probably be postponed to allow for gradual correction of hyponatremia (see later discussion).

**POSTOPERATIVE HYponatremia.** As previously discussed, the surgical stress response, aggravated by periods of hypotension and pain-related or physiologic stress-related sympathetic activity, can lead to a state of  $Na^+$  and water retention similar to SIADH. Avid water retention puts postoperative patients at risk for hyponatremia, particularly when administration of free water from IV dextrose-containing or other hypotonic solutions is ongoing. The incidence of postoperative hyponatremia is 1% to 5%, with children and premenopausal females at particularly high risk for neurologic



**Fig. 47.4 The transurethral resection of the prostate (TURP) syndrome.** Early hypervolemia-related hypertension may be followed by profound hypotension as a result of increased capillary filtration with hypovolemia, depressed cardiac function, and sympathetic blockade. Glycine itself may lead to seizures through allosteric activation of the *N*-methyl-*D*-aspartate receptor and is thought to cause the visual disturbance of the TURP syndrome. The hepatic deamination of glycine yields ammonia, which can further contribute to encephalopathy. (Modified from Gravenstein D. Transurethral resection of the prostate [TURP] syndrome: a review of the pathophysiology and management. *Anesth Analg*. 1997;84:438.)

symptoms. In these groups, symptoms and neurologic sequelae may occur at  $\text{Na}^+$  levels as high as 128 mEq/L. Elderly women typically do not become symptomatic until 120 mEq/L, unless the decrease is particularly rapid. The potential impact of postoperative hyponatremia is considerable; 8% of hyponatremic patients may develop encephalopathy, of whom 52% suffer permanent neurologic sequelae or death.<sup>116</sup> Failure to recognize hyponatremia as a cause of postoperative symptoms (see later discussion) or inadequate treatment based on fears of causing osmotic demyelination may contribute to these poor outcomes.<sup>117</sup> Prevention of postoperative hyponatremia should be a key goal of postoperative fluid therapy, based on limiting free water administration to pure maintenance requirements (1–1.2 mL/kg/h), replacing losses of  $\text{Na}^+$ -containing fluids (e.g., GI) with an appropriate isotonic salt solution, stopping IV therapy as soon as the oral route can be used, and daily (or more frequent in high-risk groups) monitoring of serum electrolytes.

**TRANSURETHRAL RESECTION OF THE PROSTATE SYNDROME.** The transurethral resection of the prostate (TURP) syndrome describes symptomatic hyponatremia, excessive intravascular volume, and edema resulting from IV absorption of hypotonic nonconductive (electrolyte-free) irrigation fluid during TURP or, rarely, transurethral resection of the bladder<sup>118</sup> or during ureteroscopic or hysteroscopic procedures. The syndrome may complicate 10% to 15% of TURP procedures, with onset between 15 minutes and 24 hours after the onset of resection.<sup>119</sup> Risk factors include increased intravesical pressure, prolonged resection, hypotonic irrigants, and open prostatic sinuses. The clinical features (Fig. 47.4) are related to intravascular volume changes,

hyponatremia, and absorption of irrigant solutes; the use of distilled water as an irrigant has largely been replaced by solutions of glycine, sorbitol, or mannitol because of the incidence of massive hemolysis. Hyponatremia resulting from free water absorption may lead to hypoosmolality, although the presence of glycine or other osmotically active solutes may maintain osmolality in the normal range. The following measures may help prevent the TURP syndrome:

- The use of conducting (isotonic saline) irrigant with bipolar diathermy.<sup>120</sup>
- Monitoring fluid absorption by comparing the amount instilled with the amount removed. Surgery should be halted if 750 mL (for females) or 1000 mL (for males) has been absorbed and the patient should be assessed for  $\text{Na}^+$  levels and neurologic status (if awake). Surgery should be terminated if 1000 to 1500 mL (for females) or more than 2000 mL (for males) has been absorbed. If saline irrigant is used, surgery should be terminated after 2500 mL has been absorbed. Although the risk for hypoosmolar hyponatremia is removed, the risk for excessive intravascular volume remains.<sup>121,122</sup>
- Limiting the duration of irrigation: irrigation should continue only for longer than 1 hour after careful assessment of the patient for possible TURP syndrome.
- Limiting intravesical pressure to less than 15 to 25 mm Hg or 70 mm Hg for endometrial procedures.
- Monitoring the patient's neurologic status by using regional anesthetic techniques. Symptoms in the awake patient include nausea and vomiting, visual disturbance, reduced level of consciousness, agitation, confusion, and seizures.

Treatment of the TURP syndrome should take into account the patient's intravascular volume status,  $\text{Na}^+$  level, and osmolality, but typically involves cessation of irrigation solutions and water restriction. A loop diuretic should be given to promote free water excretion if intravascular volume overload is present. In severe hypoosmolar hyponatremia with neurologic symptoms, hypertonic saline may be used. When osmolality is normal or marginally decreased, hemodialysis is preferred.<sup>123</sup>  $\text{Mg}^{2+}$  can be given for seizures, because its negative control of NMDA receptors counteracts dilutional hypomagnesemia and the excitatory effects of glycine.<sup>119</sup>

**PRESENTATION AND TREATMENT OF HYponatremia.** The symptoms of hyponatremia are related to cerebral edema and increased intracranial pressure and are highly dependent on how rapidly the hyponatremia occurred. In acute onset, symptoms typically occur when  $\text{Na}^+$  concentrations are as low as 120 to 125 mEq/L (higher in children and premenopausal females) with headache, confusion, agitation, vomiting, and lethargy. At  $\text{Na}^+$  concentrations less than 110 mEq/L, symptoms progress to seizures and coma. In the chronic setting, clinical features may be absent even at concentrations less than 120 mEq/L. In all cases of hyponatremia, potential underlying causes such as steroid deficiency, renal disease, and cardiac disease should be identified and treated. Treatment should be tailored to the patient's intravascular volume status, the chronicity of onset, and the presence of symptoms. Chronic hyponatremia (>48 hours or of unknown duration) should be treated cautiously because of cerebral compensation for the hypoosmolar state; sudden increases in osmolality lead to cerebral water loss and osmotic demyelination (e.g., central pontine myelinolysis). Treatment options for other scenarios are listed below:

- **Hypovolemic hyponatremia:** Symptoms are unusual because osmotic shifts in the brain are limited by the loss of both  $\text{Na}^+$  and water. ECF volume should be restored with isotonic saline, which will also reduce ongoing ADH release.
- **Hypervolemic hyponatremia:** In chronic cases, this should focus on restriction of water intake and optimization of the underlying disease state, such as improving cardiac output with angiotensin-converting enzyme (ACE) inhibitors to reduce the neurohumoral influence on water retention in cardiac failure. Loop diuretics (rather than thiazides, which impair urinary dilution) can be used to excrete free water once a negative  $\text{Na}^+$  balance has been achieved.
- **Chronic, asymptomatic hyponatremia:** No immediate correction of hyponatremia is required, and the underlying cause should be treated. Fluid restriction, ADH antagonists (lithium, demeclocycline), and loop diuretics may be used.
- **Symptomatic hyponatremia (typically euvolemic or hypervolemic):** In patients with moderate symptoms (confusion, lethargy, nausea, and vomiting), hypertonic 3% saline may be used at an initial rate of 1 mL/kg/h with the goal of increasing  $[\text{Na}^+]$  by 1 mEq/L/h for 3 to 4 hours, after which electrolytes should be rechecked. The infusion rate should be modified to ensure that  $[\text{Na}^+]$  is increased by no more than 10 mEq/L in the first

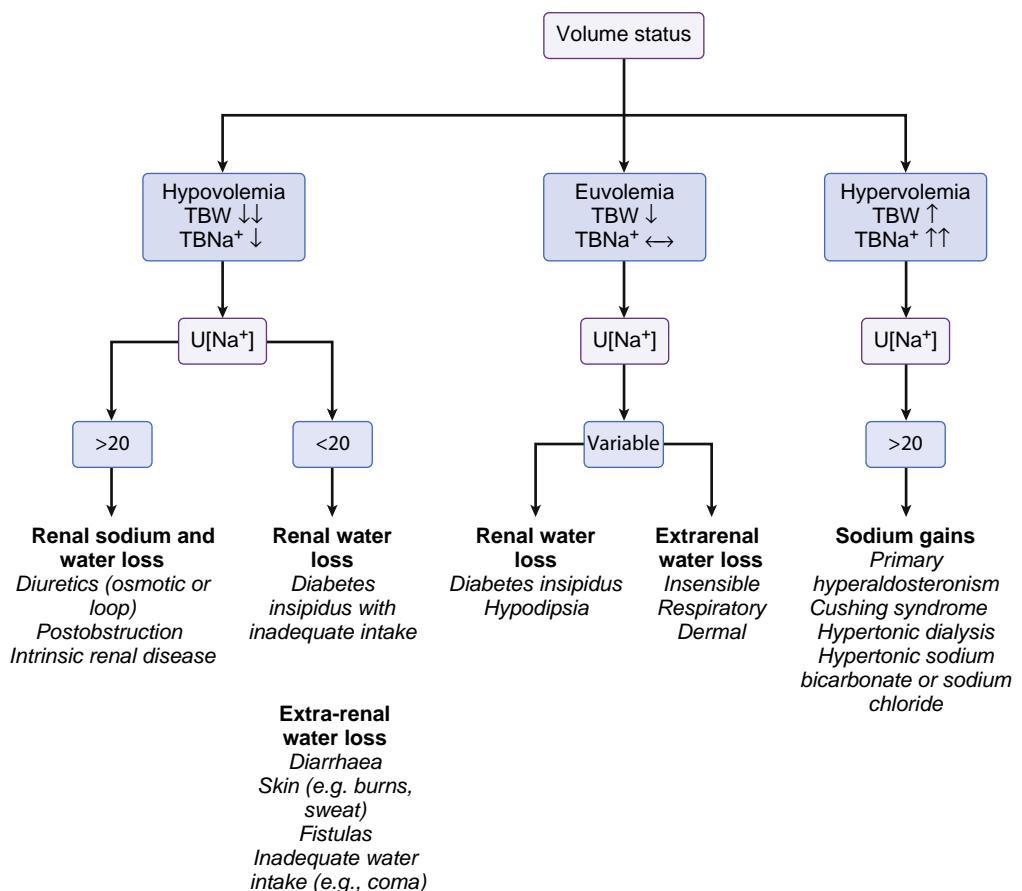
24 hours of treatment. Severely symptomatic hyponatremia (coma, seizures, often with  $[\text{Na}^+] < 120$  mEq/L) is typically of acute onset and the risks of undertreating are more than those of osmotic demyelination. A bolus of 100 mL of 3% saline should initially be given with the aim of acutely increasing  $[\text{Na}^+]$  by 2 to 3 mEq/L. If no improvement in neurologic status occurs, this approach may be repeated once or twice at 10-minute intervals. After this, treatment should continue as for moderately symptomatic patients, with a similar goal of increasing  $[\text{Na}^+]$  by no more than 10 mEq/L in the first 24 hours.<sup>124</sup> Electrolytes and osmolality should be rechecked every few hours, fluid balance should be carefully monitored, and patients reassessed regularly.

**HYPERNATREMIA.** Hypernatremia ( $[\text{Na}] > 145$  mEq/L) is less common than hyponatremia but may affect up to 10% of critically ill patients. If severe ( $[\text{Na}] > 160$  mEq/L), a 75% mortality may occur depending on the severity of the underlying disease process (Fig. 47.5).<sup>113,114</sup> The major mechanisms are excessive water loss with inadequate compensatory intake, lack of ADH, or administration of exogenous sodium. Diabetes insipidus (DI) is caused by a lack of ADH action as a result of impaired production or release (central DI) or reduced renal sensitivity to ADH (nephrogenic DI) with consequent failure to concentrate urine and excretion of large quantities of inappropriately dilute urine. If the patient is unable to accept compensatory fluid orally (e.g., because of coma or in the elderly with impaired thirst reflexes), they may rapidly become hypovolemic. Central DI is seen after pituitary surgery, subarachnoid hemorrhage, traumatic brain injury (particularly skull base fractures), and brainstem death. Nephrogenic DI may be due to renal disease, electrolyte disorders, or drugs (lithium, foscarnet, amphotericin B, demeclocycline).

Clinical features of hypernatremia include altered mental status, lethargy, irritability, seizures, hyperreflexia, and spasticity. Diagnosis is based on assessment of intravascular volume status, urinary osmolality, and  $\text{Na}^+$  concentration. In patients with persistent urine output of more than 100 mL/h and hypernatremia, DI should be considered. Diagnostic criteria include an inappropriately dilute urine (<300 mOsm/kg) in combination with hypernatremia and high serum osmolality (>305 mOsm/kg). Urine specific gravity (SG) may provide a rapid guide to urine osmolality where urgent treatment is being considered; urine SG less than 1.005 in the context of hypernatremia and a potential underlying cause is consistent with DI.

Treatment is tailored to the intravascular volume status, but as with hyponatremia, correction of the  $\text{Na}^+$  concentration should be no more rapid than 10 mEq/L/day unless the onset has been very acute.

- **Hypovolemic hypernatremia:** correction of the intravascular volume deficit with isotonic saline and correction of the underlying cause (e.g., insulin to reduce hyperglycemia), then correction of the water deficit with 0.45% saline, 5% dextrose, or enteral water to cover the deficit and ongoing losses.
- **Euvolemic hypernatremia:** use of 0.45% saline, 5% dextrose, or enteral water to replace the deficit and ongoing losses. In central DI, in which urine output is greater than 250 mL/h and risk exists for hypovolemia, titrated



**Fig. 47.5 Causes and diagnostic algorithm for hypernatremia.** TBW, Total body water;  $U[Na^+]$ , urinary sodium concentration in mEq/L. (Modified from Kumar S, Berl T. Sodium. *Lancet*. 1998;352:220.)

intravenous doses of desmopressin acetate 0.4 to 1  $\mu$ g (1-deamino-8-D-arginine vasopressin [DDAVP], an ADH analogue) should be given to reduce the urine output. Higher acute doses may have a prolonged effect with the risk for water intoxication.<sup>113,114</sup>

- Hypervolemic hypernatremia: stop administration of exogenous  $Na^+$ , give furosemide with 5% dextrose or enteral water. Dialysis may be indicated in the presence of renal failure.

**Potassium Disorders.** Because of the key role of  $K^+$  on excitable tissue resting membrane potential, dyskalemia can lead to life-threatening cardiac arrhythmias in the perioperative period. The normally predominant intracellular distribution of  $K^+$  means that abnormal plasma  $K^+$  levels may reflect abnormal ECF to ICF distribution, derangements of total body  $K^+$  content, or both. Sampling artifacts may be introduced into laboratory tests of  $K^+$ ; anticoagulated samples typically give results 0.4 to 0.5 mEq/L less than those from clotted samples because of erythrocyte  $K^+$  release during clotting. Hemolysis also artificially increases  $K^+$  levels and may be introduced by poor sampling technique or delayed processing of samples.

**HYPOKALEMIA.** Hypokalemia (<3.5 mEq/L) may be caused by the conditions outlined in Table 47.7. Moderate-to-severe

hypokalemia (2-2.5 mEq/L) leads to muscle weakness, electrocardiogram (ECG) abnormalities (ST segment depression, T wave depression, U wave elevation), and arrhythmias (atrial fibrillation and ventricular extrasystoles). All logic dictates that hypokalemia (e.g., as low as 2.6 mEq/L) should be associated with an increased rate of perioperative morbidity or mortality; however, no data support this conclusion.<sup>118</sup> Hypokalemia should be pragmatically corrected in the perioperative period to optimize neuromuscular function and reduce cardiac irritability. Such treatment is of prime importance when acute arrhythmias exist, and  $K^+$  should be maintained at greater than 4 to 4.5 mEq/L. The speed of the infusion should be slow enough to allow equilibration throughout the entire ECF, typically no faster than 0.5 mEq/kg/h.  $K^+$  solutions of concentration more than 40 mEq/L may be an irritant to veins and should be administered via a central venous catheter.

**HYPERTKALEMIA.** Hyperkalemia (>5.5 mEq/L) may result from excess intake, failure of excretion, or shift from the intracellular to extracellular compartment (Table 47.8). Failure of renal secretion is mediated through impaired principal cell function in the cortical collecting duct, which depends on aldosterone-stimulated  $Na^+/K^+$  exchange via basal  $Na^+/K^+$ ATPases and luminal  $Na^+$  and  $K^+$  channels. The features of hyperkalemia include muscle weakness, paralysis, and altered cardiac conduction (increased

**TABLE 47.7** Causes and Mechanisms of Hypokalemia

Mechanism	Cause	Notes
Inadequate intake	Anorexia nervosa Alcoholism Malnutrition	
Gastrointestinal loss	Vomiting Diarrhea Fistulas	Especially secretory diarrhea
Excess renal loss	Mineralocorticoid excess Glucocorticoid excess Diuretics Osmotic substances Hypomagnesemia Renal tubular acidosis Bartter and Gitelman syndromes	Primary and secondary hyperaldosteronism High concentration of cortisol overwhelms mineralocorticoid receptor despite lower affinity Loop or thiazide diuretics deliver increased $\text{Na}^+$ load to principal cells Glucose, urea, and mannitol also lead to increased collecting duct $\text{Na}^+$ delivery Impairs thick ascending limb $\text{Na}^+$ reabsorption; therefore, increased distal $\text{Na}^+$ delivery and $\text{K}^+$ loss via principal cells Failure of principal cell $\text{H}^+/\text{K}^+$ exchange Tubule ion transporter mutations mimicking loop or thiazide diuretic effect, respectively
Intracellular $\text{K}^+$ shift	$\beta_2$ -Agonists Insulin therapy Acute alkalosis Lithium overdose Hypokalemic periodic paralysis Vitamin $\text{B}_{12}$ therapy	Also seen in sympathetic activity

Modified from Kaye AD, Riopelle JM. Intravascular fluid and electrolyte physiology. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*. 7th ed. New York: Churchill Livingstone; 2009:1705.

automaticity and enhanced repolarization) with consequent ECG changes as  $\text{K}^+$  levels increase<sup>125</sup>:

- 5.5 to 6.5 mEq/L: tall, peaked T-waves
- 6.5 to 7.5 mEq/L: prolonged PR interval
- Greater than 7.5 mEq/L: widened QRS
- Greater than 9.0 mEq/L: sine wave pattern, bradycardia, ventricular tachycardia, increased risk for cardiac arrest

Chronically induced hyperkalemia (e.g., chronic renal failure) is better tolerated than acute increases in  $\text{K}^+$  concentrations. Ratios between intracellular and extracellular  $\text{K}^+$  concentrations may be very abnormal with acute hyperkalemia. With chronic hyperkalemia, these ratios are probably reestablished to normal. Acute hyperkalemia sufficient to induce electrocardiographic changes is a medical emergency that requires rapid treatment. The acute treatment of hyperkalemia involves shifting  $\text{K}^+$  from the ECF to ICF, antagonizing its cardiac toxicity with  $\text{Ca}^{2+}$ ,

**TABLE 47.8** Causes and Mechanisms of Hyperkalemia

Mechanism	Cause	Notes
Increased intake	Excessive $\text{K}^+$ treatment Blood transfusion Antibiotics containing $\text{K}^+$ salts	Typically in patients who also have impaired excretion (i.e., severe chronic kidney disease)
Failure of renal secretion	Mineralocorticoid deficiency Drugs causing mineralocorticoid blockade Collecting duct $\text{Na}^+$ channel blockade Tubulointerstitial nephritis Renal obstruction	Hypoaldosteronism Hyporeninemic, hypoadrenocortemic state (diabetic nephropathy, tubulointerstitial disease) Spironolactone (blocks mineralocorticoid receptor) ACE-I and ARBs (reduce aldosterone production) Heparin (selective hypoaldosteronism) Amiloride Trimethoprim Triamterene Pentamidine Cause damage or destruction of the cortical collecting duct
Extracellular $\text{K}^+$ shift	Succinylcholine Reperfusion of ischemic tissues Insulin deficiency Acute acidosis Malignant hyperpyrexia	Cellular ischemia reduces ATP production with failure of $\text{Na}^+/\text{K}^+$ ATPase activity and $\text{K}^+$ "leak" to the ECF. Cell lysis further releases $\text{K}^+$ . On reperfusion, excess ECF $\text{K}^+$ is rapidly delivered to the systemic circulation. During solid organ transplantation, this may be combined with residual perfusing solution used for ex vivo organ preservation, which contains a high $\text{K}^+$ content

ACE-I, Angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; ATP, adenosine triphosphate; ECF, extracellular fluid.

and increasing renal excretion. Elimination by GI resin exchange also may be used in more chronic cases (Table 47.9). Hyperkalemia greater than 6.5 mEq/L, in the context of anuric renal failure, is an indication for acute dialysis.

### Calcium Disorders

**HYPOCALCEMIA.** The causes of hypocalcemia are related to reduced PTH and/or vitamin D activity, increased bone deposition,  $\text{Ca}^{2+}$  chelation, or changes in binding protein concentration or ionized fraction (Table 47.10). The

**TABLE 47.9** Treatments for Hyperkalemia

Mechanism	Treatment	Indication	Notes
Antagonize cardiac toxicity	CaCl <sub>2</sub> 10% (10 mL) or Calcium gluconate	K <sup>+</sup> >6.5 mEq/L, particularly with ECG changes	Onset of action within a few minutes, duration 30-60 min
Intracellular potassium shift	Insulin 10-20 units (administered in 50 mL 50% glucose to avoid hypoglycemia) β <sub>2</sub> -Agonists (e.g., nebulized albuterol 2.5 mg) Hyperventilation  NaHCO <sub>3</sub> 1 mEq/kg	K <sup>+</sup> >6.0 mEq/L  K <sup>+</sup> >6.5 mEq/L	Onset within 10-20 min, duration 4-6 h  Induce K <sup>+</sup> uptake by increasing extracellular pH
Increase renal excretion	Furosemide 20-40 mg IV  Volume expansion with isotonic saline Fludrocortisone	Moderate-to-severe hyperkalemia	Increases Na <sup>+</sup> delivery to cortical collecting duct and exchange with K <sup>+</sup>  Mineralocorticoid effect
Other routes of K <sup>+</sup> elimination	Gastrointestinal resin exchange: sodium polystyrene sulfonate (Kayexalate) 15-30 g PO or per rectum  Hemodialysis	Any sustained hyperkalemia  Moderate-to-severe hyperkalemia with oliguria	

Hyperkalemia can be defined as mild (5.5-5.9 mEq/L), moderate (6.0-6.4 mEq/L) or severe (>6.5 mEq/L), with or without ECG changes.<sup>258</sup> *ECG, Electrocardiogram.*

**TABLE 47.10** Causes and Mechanisms of Hypocalcemia

Mechanism	Cause	Notes
Reduced regulatory hormones	Hypoparathyroidism  Pseudohypoparathyroidism Reduced vitamin D activity	Postparathyroid or thyroid surgery. May be acute effect of reduced PTH or more long-term hypocalcemia during remineralization of bone after surgery for hyperparathyroidism ("hungry bone syndrome") Hypomagnesemia (suppresses PTH secretion) Reduced receptor response to PTH Hyperphosphatemia (inhibits hydroxylation—e.g., in chronic kidney disease) Dietary/sunlight deficiency Anticonvulsants (increased turnover into inactive forms)
Ca <sup>2+</sup> chelation	Massive transfusion Cell lysis Pancreatitis	Caused by citrate in stored red blood cell solutions Phosphate release as a result of tumor lysis syndrome, trauma, or rhabdomyolysis Intraperitoneal free fatty acids formed by the action of released pancreatic lipase, which chelate Ca <sup>2+</sup> salts; further contributions from coexistent hypomagnesemia and hypoalbuminemia
Increased bone deposition	Prostate, breast cancer	Increased osteoclastic activity
Reduced ionized fraction	Alkalosis	For example, acute intraoperative hyperventilation
Reduced bound Ca <sup>2+</sup>	Hypoalbuminemia	Critical illness (where ionized Ca <sup>2+</sup> may be normal, and Ca <sup>2+</sup> replacement not required), poor nutrition
Unknown mechanism	Endotoxemic shock	

PTH, Parathyroid hormone.

following are characteristic symptoms, some of which will be absent in the anesthetized patient:

- Neuromuscular irritability
- Circumoral and peripheral paresthesia
- Chvostek sign (facial twitching induced by tapping on the facial nerve)
- Troussseau sign (forearm muscular spasm induced by inflating a pressure cuff)
- Muscle cramps
- Laryngospasm
- Tetany
- Seizures

- Cardiac
  - Impaired inotropy
  - Prolonged QT
  - Ventricular fibrillation
  - Heart block

After a rapid large volume transfusion of citrate-stored blood (>1.5 mL/kg/min) or fresh frozen plasma, ionized hypocalcemia may occur as a result of citrate chelation. This may be particularly severe and prolonged in patients with hepatic impairment, in whom citrate metabolism is reduced.<sup>126</sup> Citrate intoxication has been described for

**TABLE 47.11** Causes and Mechanisms of Hypercalcemia

Mechanism	Cause	Notes
Increased PTH	Primary hyperparathyroidism	The most common cause typically manifests with mild hypercalcemia resulting from an isolated parathyroid adenoma
	Secondary and tertiary hyperparathyroidism	The hypocalcemia of kidney disease-related hyperparathyroidism may progress to hypercalcemia with prolonged disease
Malignancy	PTH-related peptide secretion	PTH-rP may be secreted by most solid tumors; mimics PTH effects
	Osteolytic metastases	Breast, lung, lymphoma, thyroid, kidney, prostate, and multiple myeloma
	Calcitriol production	Typical in lymphoma
Excess vitamin D	Ectopic production Excess intake	Granulomatous disease (e.g., sarcoid), malignancy
Decreased renal excretion	Thiazide diuretics	
Increased bone turnover	Hyperthyroidism Immobilization	
Increased $\text{Ca}^{2+}$ intake	Milk-alkali syndrome	

PTH, Parathyroid hormone; PTH-rP, parathyroid hormone-related peptide.

many years but is rarely a clinical problem. Although  $\text{Ca}^{2+}$  plays an important role in coagulation, coagulopathy specifically attributable to hypocalcemia only occurs at ionized  $\text{Ca}^{2+}$  concentrations less than 1.2 mEq/L (0.625 mmol/L); rather, supplemental  $\text{Ca}^{2+}$  should be given in this situation to support cardiac inotropy and neuromuscular function, aiming for ionized  $\text{Ca}^{2+}$  more than 1.8 mEq/L (0.9 mmol/L).<sup>127</sup>  $\text{Ca}^{2+}$  also may be given during other situations in which myocardial contractility is impaired, such as during cardiac surgery, to optimize ventricular function. After parathyroidectomy,  $\text{Ca}^{2+}$  levels should be checked frequently until they have stabilized, because  $\text{Ca}^{2+}$  and vitamin D supplementation may be required in both the short and long term. In critical illness, total  $\text{Ca}^{2+}$  levels may be reduced because of hypoalbuminemia; however,  $\text{Ca}^{2+}$  supplementation should be required only if the ionized levels are low.  $\text{Ca}^{2+}$  may be given intravenously as 10% (weight/volume) calcium gluconate or 10% (weight/volume)  $\text{CaCl}_2$ . Although in these formulations calcium gluconate contains less elemental  $\text{Ca}^{2+}$  (0.45 mEq/mL vs. 1.36 mEq/mL for  $\text{CaCl}_2$ ), they are equally efficacious as long as the total Ca content given is equal. Calcium gluconate may be preferable for peripheral administration because the tissue injury from inadvertent extravasation is less severe than with  $\text{CaCl}_2$ .  $\text{Mg}^{2+}$  levels are often low during hypocalcemia and should also be corrected, particularly when hypocalcemia has been caused by infusion of isotonic saline or colloids in large volumes.

**HYPERCALCEMIA.** Hypercalcemia occurs when ECF  $\text{Ca}^{2+}$  influx from the GI tract and/or bone outweighs efflux to bone or excretion via the kidneys (Table 47.11). The symptoms are related to the severity and speed of onset of the abnormality, so mild chronic hypercalcemia is usually asymptomatic. More severe hypercalcemia manifests with neurologic symptoms (drowsiness, weakness, depression, lethargy, coma), GI symptoms (constipation, nausea, vomiting, anorexia, peptic ulcers), renal manifestations (nephrogenic diabetes insipidus—which may further aggravate hypercalcemia through dehydration—and renal stones),

electrocardiographic abnormalities (shortened QT interval, prolonged PR interval), and potentiation of digoxin toxicity. Treatment should address the underlying cause, including surgical parathyroidectomy in cases of severe hyperparathyroidism, or cessation of thiazide diuretics. In addition, the treatment of symptomatic hypercalcemia should aim to increase renal  $\text{Ca}^{2+}$  excretion by volume expansion with isotonic saline and possibly loop diuretics. This combination may reduce  $\text{Ca}^{2+}$  by 1 to 3 mg/dL in 1 to 2 days.<sup>26</sup> Bisphosphonates enhance osteoclastic bone deposition and are given if the hypercalcemia is severe or in milder cases in which response to hydration has been inadequate. A single IV dose of pamidronate 60 mg (moderate hypercalcemia, up to 13.5 mg/dL) or 90 mg (severe hypercalcemia) should return  $\text{Ca}^{2+}$  levels to normal within 7 days, and the effect may persist for up to 1 month. Zoledronic acid is a newer bisphosphonate that may be even more effective and is given intravenously at a dose of 4 mg.<sup>128</sup> Bisphosphonates should only be given when clinical dehydration has been treated to avoid calcium bisphosphonate precipitation and nephrotoxicity. Glucocorticoids may also be given for hypercalcemia associated with lymphoproliferative disease or ectopic vitamin D production.<sup>129</sup> Calcitonin increases renal  $\text{Ca}^{2+}$  excretion and reduces bone resorption for up to 48 hours when given intramuscularly or intravenously and may contribute to a mild reduction in  $\text{Ca}^{2+}$  levels during the rehydration phase.

### Magnesium Disorders

**HYPOMAGNESEMIA.** Serum  $\text{Mg}^{2+}$  concentration may be a poor indicator of total body content because of its large distribution in the intracellular compartment and slow equilibration with bone stores. Intraerythrocyte or intralymphocyte  $\text{Mg}^{2+}$  levels may give a better approximation of total body and tissue stores, but are more complex to process.<sup>130,131</sup> Both chronic and acute hypomagnesemia are associated with cardiovascular morbidity<sup>29</sup> and are particularly prevalent in diverse hospitalized patients (12% of general inpatients, 19% of preoperative cardiac surgery patients, 65% of critical care patients). The causes

**TABLE 47.12** Causes and Mechanisms of Hypomagnesemia

Mechanism	Cause
Inadequate gastrointestinal uptake	Malnutrition Prolonged vomiting or diarrhea Intestinal fistula Pancreatitis Prolonged nasogastric suction Malabsorption syndromes Small bowel syndrome Primary intestinal hypomagnesemia
Increased renal losses	Chronic parenteral fluid therapy Hypercalcemia and hypercalciuria Osmotic diuresis Drugs: Alcohol, loop and thiazide diuretics, aminoglycosides, cisplatin, amphotericin, cyclosporin, foscarnet Phosphate depletion Hungry bone syndrome Postobstructive nephropathy Renal transplantation Polyuric phase of acute kidney injury Primary hyperparathyroidism Bartter and Gitelman syndromes

are related to reduced  $Mg^{2+}$  intake from the GI tract or increased renal losses (Table 47.12), although relative depletion may occur in times of increased cell turnover and protein production (pregnancy, athletes, cold acclimatization). The clinical presentation of hypomagnesemia may be nonspecific; symptoms often relate to common coexisting hypocalcemia or hypokalemia<sup>32</sup>:

- Neuromuscular: Trousseau and Chvostek signs, vertigo, seizures, weakness
- Metabolic: Carbohydrate intolerance, hyperinsulinemia, atherosclerosis
- Cardiovascular: Wide QRS, prolonged PR, T-wave inversion, ventricular arrhythmias
- Musculoskeletal: Osteoporosis and osteomalacia

Treatment should be tailored to the severity of symptoms and degree of hypomagnesemia. Asymptomatic patients with moderate-severe hypomagnesemia should receive oral supplementation, as acute IV infusions will stimulate the renal  $Ca^{2+}/Mg^{2+}$ -sensing receptor, reducing  $Mg^{2+}$  reabsorption and leading to renal excretion of much of the acute dose. In the presence of symptoms or  $Mg^{2+}$  concentration of less than 1 mg/dL, IV  $Mg^{2+}$  should be administered (initial dose of 1-2 gm over 5 to 10 minutes in the presence of seizures or acute arrhythmias).<sup>32</sup> Coexistent hypocalcemia, hypokalemia, or both should also be treated, but they are unlikely to improve without replenishment of  $Mg^{2+}$ .  $Mg^{2+}$  has many other therapeutic indications, even in the absence of hypomagnesemia, as outlined earlier. A few of these patients are likely to have total body  $Mg^{2+}$  depletion that has not been detected by serum  $Mg^{2+}$  levels.

**HYPERMAGNESEMIA.** Limited GI absorption and efficient renal excretion mean that hypermagnesemia is typically iatrogenic. Symptoms reflect the effect of  $Mg^{2+}$  on neurologic and cardiac function and relate to the serum concentration<sup>18</sup>:

- 5 to 7 mg/dL: Therapeutic levels in the treatment of preeclampsia
- 5 to 10 mg/dL: Impaired cardiac conduction (widened QRS, long PR), nausea
- 20 to 34 mg/dL: Sedation, reduced neuromuscular transmission with hypoventilation, reduced tendon reflexes, and muscle weakness
- 24 to 48 mg/dL: Diffuse vasodilation with hypotension, bradycardia
- 48 to 72 mg/dL: Areflexia, coma, respiratory paralysis

$Mg^{2+}$  administration should therefore be performed with several important caveats. First, serum  $Mg^{2+}$  levels should be monitored closely during therapeutic administration. Second, because excretion is renal, doses should be decreased for patients with kidney disease. Third, it should be used with extreme caution in patients with a background impairment of neuromuscular transmission (myasthenia gravis, Lambert-Eaton myasthenic syndrome). Fourth, coadministration of neuromuscular blockers during anesthesia should be performed in reduced doses titrated to neuromuscular monitoring, because  $Mg^{2+}$  potentiates the effects of both depolarizing and nondepolarizing neuromuscular blockers. Treatment of acute hypermagnesemia includes promoting renal excretion by administration of fluids intravenously and diuresis. IV  $Ca^{2+}$  is given to temporarily antagonize  $Mg^{2+}$  and avoid diuretic-induced hypocalcemia. Definitive treatment, particularly in the presence of renal disease, may require dialysis.

### Phosphate Disorders

**HYPOPHOSPHATEMIA.** Hypophosphatemia may be related to impaired enteral uptake, increased renal excretion, or shifts to the cellular compartment or bone (Table 47.13). Symptoms of hypophosphatemia may be precipitated by hyperventilation in patients with chronic depletion. Refeeding syndrome may be observed on commencement of enteral or parenteral nutrition after a period of prolonged starvation and may manifest postoperatively. Insulin secretion is decreased during starvation. The consequent fat and protein catabolism results in intracellular electrolyte depletion despite normal plasma levels, particularly phosphate. On refeeding, a switch back occurs to carbohydrate metabolism, increased insulin secretion, and an increased cellular uptake of  $PO_4^{3-}$ , which may lead to profound hypophosphatemia. In the most severe forms (<1.5 mg/dL), features may include rhabdomyolysis, leukocyte dysfunction, cardiac and respiratory failure, seizures, hypotension, and coma. IV  $PO_4^{3-}$  replacement carries a risk for precipitating severe hypocalcemia, so should be reserved for moderate (<2.2 mg/dL) to severe or symptomatic cases and avoided in cases of ongoing hypocalcemia. Replacement protocols should be based on patient weight and serum  $PO_4^{3-}$ .<sup>132</sup>

**HYPERPHOSPHATEMIA.** The causes of hyperphosphatemia are shown in Table 47.13. The most common cause in clinical practice is renal failure, in which the filtered  $PO_4^{3-}$  load is reduced. This may be partly compensated for in mild chronic kidney disease by increased PTH secretion and inhibition of tubular  $PO_4^{3-}$  reabsorption, but in more severe kidney disease hyperphosphatemia must be controlled with

**TABLE 47.13** Causes and Mechanisms of Phosphate Abnormalities

HYPOPHOSPHATEMIA		HYPERPHOSPHATEMIA	
Mechanism	Cause	Mechanism	Cause
Internal redistribution	Respiratory alkalosis Refeeding Hormones (insulin, glucagon, epinephrine, cortisol) Sepsis Hungry bone syndrome		Increased endogenous load Tumor lysis syndrome Rhabdomyolysis Bowel infarction Malignant hyperthermia Hemolysis
Increased urinary excretion	Hyperparathyroidism Disorders of vitamin D metabolism Renal transplant Volume expansion Malabsorption Renal tubular defects Alcoholism Metabolic or respiratory acidosis	Increased exogenous load Reduced urinary excretion	Acidosis Intravenous infusion Oral supplementation Vitamin D intoxication Renal failure Hypoparathyroidism Acromegaly Tumor calcinosis
Decreased intestinal absorption	Dietary restriction Excess antacids Vitamin D deficiency Chronic diarrhea		Pseudohyperphosphatemia Bisphosphonate therapy Magnesium deficiency Multiple myeloma In vitro hemolysis Hypertriglyceridemia

Data from Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet*. 1998;352:391.

oral  $\text{PO}_4^{3-}$  binders. The features of hyperphosphatemia may be related to symptomatic hypocalcemia caused by an acute elevation in  $\text{PO}_4^{3-}$  levels. Hypocalcemia is mediated via  $\text{Ca}^+$  deposition in soft tissues when the calcium  $\times$  phosphate product is elevated, and by inhibition of renal 1 $\alpha$ -hydroxylase.<sup>32</sup>

**Chloride Disorders.** Disorders of  $\text{Cl}^-$  have the potential to affect acid-base balance, although this depends on the other constituents of the SID. As described, exogenous  $\text{Cl}^-$  administration from isotonic saline will increase the plasma  $\text{Cl}^-$  concentration with a lesser effect on  $\text{Na}^+$  concentration, thus reducing the plasma SID and therefore pH. Conversely, disease states exemplified by both hyperchloremia and hypernatremia or by hypochloremia and hyponatremia will not affect the SID and therefore not alter pH. Many of the causes of  $\text{Cl}^-$  abnormalities (Table 47.14) are pathologic processes that also affect  $\text{Na}^+$  levels. Investigation and treatment of these “matched” electrolyte imbalances should initially target the dysnatremia.

## PRACTICAL MANAGEMENT OF PERIOPERATIVE FLUID THERAPY

At each stage in the perioperative journey, the physician must decide how much and what type of IV fluid is required. Unfortunately, a robust evidence base with answers to these questions is not always available, so a pragmatic approach based on sound physiologic knowledge and the best available evidence is required. To make the process more complicated, fluid and electrolyte requirements are a dynamic situation with great inter-individual variability. Different fluid requirements are encountered in the preoperative, intraoperative, and postoperative phases, and these vary depending on patient factors, including weight and comorbidity, and on surgical factors, such as the magnitude and site of surgery. Furthermore, the goals of fluid

therapy vary depending on the severity of surgery and its associated morbidity. In “low-risk” minor surgery, fluid strategies may influence the incidence of relatively minor morbidity such as nausea and vomiting,<sup>133,134</sup> whereas in major surgery the focus is on the potential for fluid administration to affect postoperative morbidity, length of stay, and mortality.<sup>111,135,136</sup>

The goals of fluid therapy for major surgery are as follows:

- To ensure adequate circulating volume to support cellular  $\text{O}_2$  delivery and avoid the deleterious effects of hypoperfusion on cellular function and survival, inflammation, and neurohumoral responses. This may involve manipulation of not just circulating volume but also of cardiac output and vascular resistance.
- To avoid the iatrogenic side effects of fluid administration; excessive intravascular volume (which may not be readily apparent clinically), edema, excess  $\text{Na}^+$  or  $\text{Cl}^-$  load, toxicities related to synthetic compounds, or nonphysiologic quantities of anions (lactate, acetate, gluconate).

Large studies show that even during relatively standardized surgical procedures, there is a large variety in the volumes of fluid administered. This unexplained variability may be linked with postoperative morbidity, and regrettably appears to be more closely related to the approach of the individual anesthesia provider rather than justifiable patient or surgical factors.<sup>107,137</sup> A number of approaches are still being investigated in an effort to determine the optimum quantity and type of fluid that should be given in order to achieve these goals in perioperative care.

### Quantity of Fluid

IV fluid quantities may be given in two main ways: (1) by estimating the requirements based on patient weight, the phase of surgery, and nature of losses to estimate the

**TABLE 47.14** Causes and Mechanisms of Chloride Abnormalities

HYPOCHLOREMIC		HYPERCHLOREMIC	
Mechanism	Cause	Mechanism	Cause
Cl <sup>-</sup> loss	Diuretics Gastric drainage Vomiting Chronic respiratory acidosis	Cl <sup>-</sup> infusion Water loss	Cl <sup>-</sup> -rich fluids Parenteral nutrition Skin Fever Renal losses
Water balance in excess of Cl <sup>-</sup>	Congestive cardiac failure  Syndrome of inappropriate of antidiuretic hormone secretion Infusion of hypotonic fluids	Water loss exceeding Cl <sup>-</sup> loss (extrarenal)  Water loss exceeding Cl <sup>-</sup> loss (renal)  Increased tubular chloride reabsorption	Diabetes insipidus  Diarrhea  Burns Osmotic diuresis Postobstructive diuresis Intrinsic renal disease Renal tubular acidosis Recovery from diabetic ketoacidosis Early renal failure Acetazolamide Urteral diversion Posthypocapnia

Data from Yunos NM, Bellomo R, Story D, et al. Bench-to-bedside review: chloride in critical illness. *Crit Care*. 2010;14:226.

required dose, or (2) by direct measurement of an individual's physiologic variables and administering fluid in sufficient quantities to achieve an improvement in these physiologic variables, so-called goal-directed therapy.

**Targeting Overall Fluid Balance.** Traditional approaches to perioperative fluid administration are based on historical estimates of fluid requirements during fasting (e.g., using the "4-2-1" calculation; Table 47.15<sup>138</sup>) and during episodes of excess loss, such as when body cavities are open or bleeding occurs. The fluid volumes prescribed are then based on perceived knowledge of the movement of fluids between compartments—for example, crystalloid being used to replace blood loss in a 3:1 ratio to account for crystalloid movement into the extravascular compartment.<sup>18</sup> However, much of the physiologic basis of this management approach has been questioned recently.<sup>3,11</sup>

An extension of the milliliter-per-kilogram approach to fluid administration has been to examine whether higher (e.g., 12–18 mL/kg/h of intraoperative crystalloid) or lower (5–7 mL/kg/h) fluid doses in the immediate perioperative phase are associated with benefit after major surgery. Unfortunately, this work has been hampered by widely varying definitions of restrictive/conservative, standard, and liberal, differing fluid types (colloids/crystalloids), and different time courses over which the fluid strategy is applied. Despite these differences, a common theme is that when fluid is given based on a milliliter-per-kilogram protocol and on clinical assessment rather than to target defined physiologic endpoints, the administration of more than 3500 to 5000 mL of crystalloid solution in the immediate perioperative period is associated with increased postoperative morbidity in contrast

**TABLE 47.15** The 4-2-1 Estimation of Maintenance Water Requirements

Weight	Fluid Prescription
First 10 kg	4 mL/kg/h
Second 10 kg	2 mL/kg/h
All subsequent kilograms	1 mL/kg/h

Example: A 25-kg patient would require  $(4 \times 10) + (2 \times 10) + (1 \times 5) = 65$  mL/h "maintenance" water.

Data from Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19:823.

to administration of lower fluid volumes. This may be reflected in increased weight gain, cardiopulmonary dysfunction, impaired wound healing,<sup>111,133</sup> delayed GI function, and increased hospital length of stay.<sup>139,140</sup> One study gives apparently conflicting results,<sup>141</sup> although this may be partly accounted for by methodologic differences with the other studies here. In the recent pragmatic international RELIEF trial,<sup>142</sup> 3000 patients at increased risk for complications during major abdominal surgery were randomly assigned to receive a restrictive or liberal IV fluid regimen during and up to 24 hours after surgery. The restrictive group had a median IV fluid intake of 3.7 liters and a median weight gain of 0.3 kg as compared with 6.1 L and 1.6 kg in the liberal fluid group. There was no difference in the primary outcome of disability-free survival at 1 year, but the rates of surgical-site infection (16.5% vs. 13.6%) and renal-replacement therapy (0.9% vs. 0.3%) were increased in the restrictive group. This study provides an important warning of the consequences of excessive fluid restriction, a target for weight

change after surgery (+1.5 kg), and a useful benchmark recipe.

Very few studies have robustly examined the specific effects of postoperatively administered fluid volumes. Of those tackling this area, one showed an earlier return to gut function and hospital discharge when postoperative infusions were limited to 2000 mL of water and less than 100 mEq Na<sup>+</sup>/24 h,<sup>108</sup> whereas another showed no difference.<sup>143</sup> These represent very small studies with methodologic differences.

Although it seems likely that there exists an optimum fluid volume to be given to maximize perfusion while avoiding excessive intravascular volumes, the position of this curve likely varies widely across patients and in response to different insults. This is the rationale behind individualization of fluid therapy, where objective variables are measured and targeted with fluid therapy.

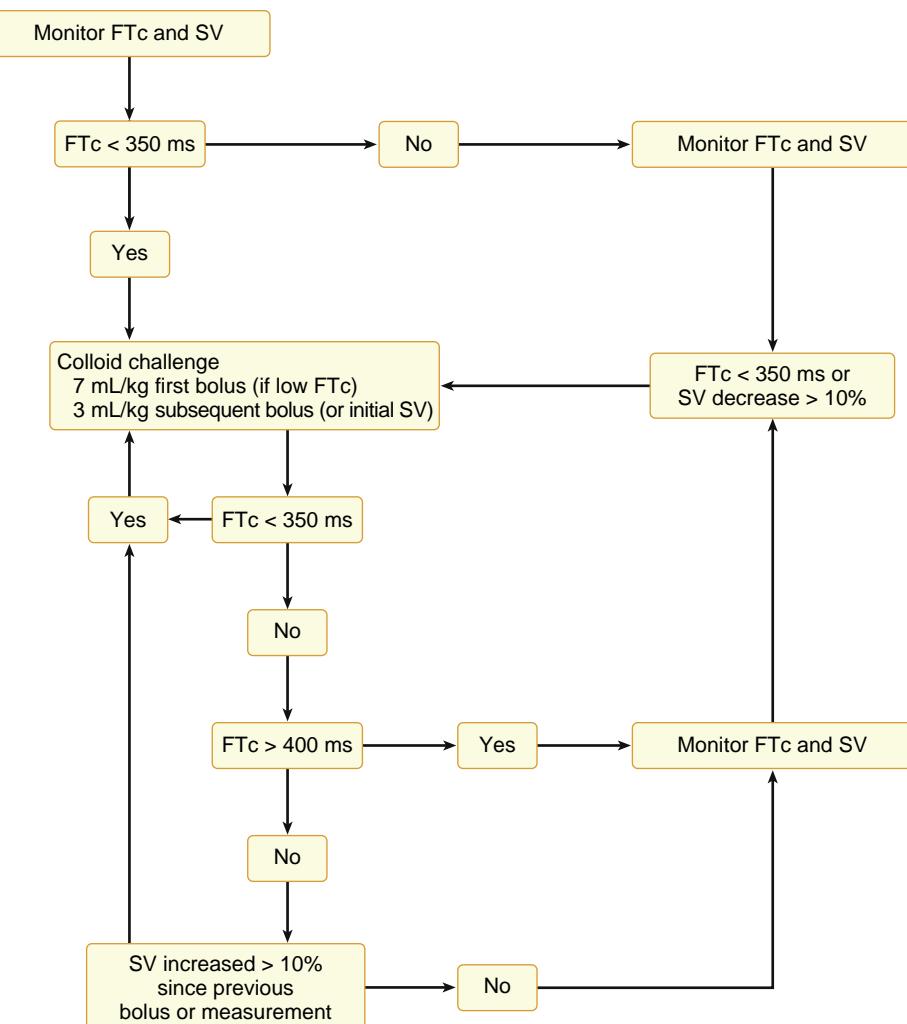
**Goal-Directed Therapy.** The practice of GDT is based on measuring key physiologic variables related to cardiac output or global O<sub>2</sub> delivery and administering fluids, and possibly inotropes, vasopressors, vasodilators, and RBCs to improved tissue perfusion and clinical outcome. This approach to fluid administration is a continuous dynamic process that targets defined physiologic endpoints rather than giving fluids without objective assessments of fluid status. GDT, used both in the perioperative and critical care setting, originated from observations that survivors of high-risk surgery achieved a particular elevation in global O<sub>2</sub> delivery and utilization in the perioperative period.<sup>144</sup> Subsequent trials used hemodynamic manipulation in an effort to replicate these supranormal “survivor values” in patients undergoing major surgery (cardiac index >4.5 L/min/m<sup>2</sup>, O<sub>2</sub> delivery index (DO<sub>2</sub>I) >600 mL/min/m<sup>2</sup>, O<sub>2</sub> consumption index >170 mL/min/m<sup>2</sup>).<sup>145,146</sup> The GDT approach has been studied in a wide variety of surgical settings and at various time points, including during preoperative optimization, intraoperative management, and the immediate postoperative period. Various tools to measure the physiologic targets of GDT are discussed below.

- **Pulmonary artery catheter (PAC).** Considered to be the gold standard hemodynamic monitor, providing measured and derived values for left-heart and right-heart filling pressures, mixed and central venous saturations, cardiac output, DO<sub>2</sub>, and VO<sub>2</sub> while allowing access to the central circulation. This was the tool used in the earlier GDT trials targeting increases in cardiac index and DO<sub>2</sub>I, but its use is declining because of concerns about catheter-associated morbidity, reduced expertise in insertion and data interpretation, and the availability of less invasive tools. In countries such as the United Kingdom, its use is typically restricted to cardiac, major liver, and transplant surgery.
- **Esophageal Doppler monitor (EDM).** This device uses transesophageal ultrasound measurement of descending aorta blood velocity, integrating this with estimated aortic cross-sectional area to derive SV. Other measurements include peak velocity, used as an indicator of ventricular contractility, and corrected flow time (FTc), and

the duration of systolic aortic blood flow corrected for heart rate. FTc may be reduced (<330 ms) by increased systemic vascular resistance (SVR), reduced SV, or both. SVR may be calculated by inputting CVP and mean arterial pressure (MAP), helping to identify whether a low FTc is due to inadequate preload or excessive afterload. Variation in SV with positive pressure ventilation (stroke volume variation, SVV) is also measured by the latest EDM models.

- **Arterial pressure and waveform analysis.** These monitors analyze the invasive arterial blood pressure, continuous non-invasive blood pressure from a finger cuff, or plethysmograph trace to yield two types of measurement. First, an estimate of SV (and therefore cardiac output and index) based on the principle that pulse pressure is proportional to SV when arterial compliance is constant. Interpatient variation in arterial compliance may be accounted for by regular calibration steps using lithium dilution (LiDCO Plus, LiDCO, Lake Villa, IL) or thermodilution (PiCCO, Phillips, Andover, MA) or ignored in uncalibrated monitors (LiDCO Rapid, LiDCO; FloTrac, Edwards, Washington, DC), which represent SV trends rather than absolute estimates. Second, SVV, a predictor of fluid responsiveness based on systolic pressure variation with intermittent positive-pressure ventilation, can be measured.
- **Thoracic bioimpedance,** relatively underexplored in perioperative interventional trials.
- **CVP:** Despite one study that demonstrated improved outcomes from hip fracture surgery when CVP response to intravascular fluid challenges was compared to unmonitored control,<sup>147</sup> CVP readings are clearly poorly predictive of intravascular blood volume and fluid responsiveness.<sup>148</sup>
- **Echocardiography:** This advanced technique is used for guiding fluid therapy and yielding information on cardiac performance and filling, but requires operator expertise and a transesophageal approach in the intraoperative setting.
- **Lactate:** A reduction in elevated blood lactate concentrations is used clinically as a marker of successful resuscitation.<sup>149</sup>
- **O<sub>2</sub> extraction and venous O<sub>2</sub> saturation (SvO<sub>2</sub>) or central venous saturation (ScvO<sub>2</sub>):** Inadequate tissue O<sub>2</sub> delivery may be signaled by increased O<sub>2</sub> extraction and the resultant mixed or central venous O<sub>2</sub> desaturation. Low ScvO<sub>2</sub> is associated with poor outcomes after high-risk surgery,<sup>150</sup> although it has been targeted in only one interventional study in major noncardiac surgery.<sup>151</sup>

A typical approach to GDT is to rapidly administer 250 mL boluses of colloid or crystalloid, aiming to increase SV by 10% or more each time. This process is continued until there is no further rise in SV, at which point ventricular filling is taken to be on the flatter part of the Starling curve. One example is in Fig. 47.6. Trials have varied in terms of the period during which this intervention is used (intraoperative or intra- and postoperative) and whether fluid loading is combined with protocolized inotrope infusion. Recent meta-analyses have highlighted the potential benefits of the GDT process. One meta-analysis with the most



**Fig. 47.6 Protocol for EDM-based intraoperative goal-directed fluid therapy.** *FTc*, Heart rate-corrected descending aorta flow time; *SV*, stroke volume. (Redrawn from Noblett SE, Snowden CP, Shenton BK, et al. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg*. 2006;93:1069.)

tightly defined patient group (surgery but not trauma or sepsis) and all time points (preoperative, intraoperative, and postoperative GDT) and GDT tools (PAC, EDM, and arterial waveform analysis), showed GDT to be associated with a reduction in postoperative morbidity and hospital length of stay.<sup>136</sup> Specifically, GDT leads to a reduction in the number of patients with postoperative renal impairment, respiratory failure, and postoperative wound infection. Many of the individual studies were not powered to detect a mortality difference; however, when analyzed rigorously in this Cochrane systematic review, excluding poorly controlled studies, hospital or 28-day mortality was reduced by GDT.<sup>136</sup>

The lack of more contemporary trials of adequate size to detect important outcome differences has been addressed in recent years. An increasing number of large, pragmatic clinical effectiveness trials using minimally invasive arterial waveform or Doppler devices have been completed or are in progress. Although the results of individual trials are mixed, most results appear to agree with the potential benefit of using these monitors in elective surgery suggested by

the previous Cochrane meta-analysis.<sup>152–154</sup> Large trials aiming to give a definitive answer on this intervention are currently underway in both elective and emergency gastrointestinal surgery.

A frequent finding in GDT studies is that the intervention group receives more fluid, typically an extra 500 mL of colloid, a finding that has raised questions, as follows:

- This fluid excess may seem to be at odds with the potential benefits of a conservative fluid strategy. However, it should be noted that the fluid excess in the liberal groups of fluid balance studies is typically of greater magnitude and different type (~1500 mL of excess crystalloid overall) and is indiscriminate, in comparison to the targeted administration to some patients based on specific physiologic variables in GDT. This difference may be partly responsible for the finding that overall outcomes in “liberal” groups are worse than those in GDT groups in their respective trials.<sup>112</sup>
- The potential benefit of the GDT process is underlined by a failure to replicate the improved outcomes when these

fluid balance differences are used as therapeutic targets. This was shown in a study in which the intervention group subjects were uniformly administered an extra 500 mL of colloid compared with the control group, with no improvement in postoperative outcomes.<sup>155</sup> This suggests that it is the individualization of therapy supported by monitored variables that may bring the clinical benefit.

- Even in GDT trials with few overall differences in intravascular fluid balance between the control and intervention groups, the individualization of patient fluid requirements may be reflected in the timing of intraoperative fluid administration. In one study, early intraoperative EDM-guided fluid administration in the first quarter of surgery increased cardiac output above that of the control group, a difference that was sustained until the end of surgery and reduced postoperative morbidity.<sup>156</sup>

Despite the apparent benefit of GDT in the studies performed so far, further research is still required in large-scale multicenter trials to address the following:

- Although most of the GDT studies have used boluses of a variety of colloids, it is not clear if one colloid is superior or whether crystalloids could be used for boluses instead. This is particularly relevant given the cost and potential toxicities of colloids when examined in sufficiently powered studies in critical care populations.<sup>51,84,157</sup>
- Hemodynamic monitors are currently under rapid development, and newer devices should be compared with existing ones for their utility in guiding GDT. Ultimately, as newer technologies are evaluated, the potential benefits of GDT may relate to the process of administering fluids based on rational physiologic endpoints rather than to the specific GDT tool used. As previous evaluations of monitoring devices have shown, no benefit is gained from using a device *per se*, but rather from the therapeutic intervention that the device allows.<sup>158</sup>

### Appropriate Fluid Selection

**Crystalloids or Colloids for Intravascular Plasma Volume Expansion.** Although crystalloids are the most rational choice of fluid for replacement of evaporative losses, maintenance fluid requirements, and expansion of the entire extracellular fluid volume, the choice of crystalloid or colloid for plasma volume replacement in the perioperative phase is not clear. This underlines the lack of adequately powered perioperative studies directly comparing the two fluid types when administered in a similar fashion. Although most GDT studies use colloid for their intravascular volume expansion, these studies are also comparisons of fluid administration guided by physiologic endpoints with nonguided therapy. Whether the same level of benefit can be achieved by crystalloid-based GDT merits further investigation. Crystalloid may be effective in plasma volume expansion (PVE) at amounts less than previously reported, although typically 40% to 50% more crystalloid than colloid must be administered to obtain the same clinical volume effect.<sup>3</sup> When combined with the increased propensity of crystalloid to filter across the capillary membrane, more extravascular volume expansion occurs, potentially causing tissue edema. When compared

with colloids, crystalloids may lead to increased GI mucosal edema<sup>159</sup> and the potential for delayed postoperative GI function and bacterial translocation. The differential effect of crystalloids when compared to colloids on tissue O<sub>2</sub> tension has no clear consensus.<sup>52</sup> The limited data comparing colloid with crystalloid for perioperative PVE may lead clinicians to extrapolate findings from studies in critical care. A Cochrane review highlighted the lack of improvement in all-cause mortality when colloids were used for intravascular volume expansion in unselected critical care populations.<sup>160</sup> In studies specific to patients with sepsis, starch-based colloids, including smaller MW versions, are associated with an increased requirement for renal replacement therapy, blood transfusion, and an increase in severe adverse events.<sup>83</sup> These data should be interpreted cautiously. First, some critical care studies compared starches with saline in the control group, which may itself be associated with renal problems.<sup>51</sup> Second, the surgical population has a different physiologic phenotype to those in critical care; meta-analysis suggests that starch is not associated with excess mortality or kidney injury in surgical patients, although the available trials are limited.<sup>86</sup> Despite these limitations, it is reasonable to avoid starch colloids in perioperative patients with severe sepsis or at increased risk of renal failure, pending the necessary large-scale trials assessing their safety in the perioperative setting. This is reflected in license restrictions for these fluids in the United States. In the United Kingdom, the use of starches has been suspended in all settings. The potential toxicities of colloids must be weighed against the potential fluid overloading effects of PVE using crystalloids until more data are available informing the debate on crystalloids versus colloids for perioperative PVE.

### Saline-Based or Balanced Solutions

**TYPICAL PRACTICAL APPROACH.** The following suggestions represent an assimilation of the physiology, fluid pharmacology, and available evidence presented in this chapter. However, in many areas of perioperative fluid management, the lack of robust evidence means that the choice of fluid and method of administration remains a clinician's choice informed by the balance of risks and benefits. The overall themes in prescribing fluids in moderate-to-major surgery are:

- The indication for giving a specific fluid should always be considered. Pure "maintenance" fluid should be given at a low fixed rate, with fluid required for replacement of losses or for resuscitation considered separately.
- Fluids administered should be individualized. This may be as simple as dosing postoperative maintenance fluids on a milliliter-per-kilogram basis or titrating intraoperative plasma volume expansion to objectively measured physiologic variables.
- Fluid status changes constantly throughout the perioperative period and should be frequently reassessed.
- The approach should be adapted to the patient and surgical factors outlined later.

**Preoperative.** In preparing for elective surgery, oral clear fluid intake should continue until 2 hours preoperatively and longer fasting discouraged. The use of preoperative

bowel preparation should be restricted to carefully selected cases, and in these cases an infusion of 1 to 2 L of balanced crystalloid with  $K^+$  supplementation should be given in the preoperative period. Chronic comorbidities should be assessed for their influence on fluid and electrolyte balance, as outlined later.

Emergency surgery patients are likely to have acute disturbances of fluid compartments. They require timely resuscitation guided by rational physiologic endpoints such as trends in blood pressure and heart rate, lactate, urine output, and mixed or central venous  $O_2$  saturations. Although preoperative fluid administration using cardiac output monitoring makes clinical sense, often logistical implications are involved with this approach and in some cases (ongoing blood loss or early surgical control of sepsis) surgery should not be delayed. A pragmatic approach is required to provide ongoing fluid resuscitation without compromising early surgical intervention. Upper GI losses should be quantified and replaced with isotonic saline, and lower GI losses (fistula, ileus, or obstruction) with balanced crystalloid.  $K^+$  should be supplemented as appropriate.

**Intraoperative.** A low background infusion (e.g., 1–1.5 mL/kg/h) of crystalloid should be used for maintenance requirements during surgery. Hypotension caused by general or regional anesthesia is related primarily to vasodilation and reduced inotropy, and unless the patient is hypovolemic because of preoperative factors, it is more rational to treat this with small doses of vaso-pressors and/or inotropes.<sup>11</sup> Fluid therapy in patients considered to be at higher risk should be guided by invasive pressure monitoring to allow for early recognition of overt hypovolemia and global tissue perfusion. Although no universally accepted definitions of a high-risk case exist,<sup>161</sup> factors such as major elective or emergency surgery, advanced age, comorbidities, and poor exercise tolerance, increase postoperative mortality risk to greater than 5%. In these cases and particularly in certain orthopedic and intraabdominal operations, where the evidence is strongest, cardiac output should be optimized by titrating boluses of a suitable colloid or balanced crystalloid to a measured variable such as SV and FTc, or cardiac output and  $O_2$  delivery. Stroke volume variation may also be measured, although its ability to accurately predict fluid responsiveness may be limited.<sup>162</sup> Blood loss should be replaced with colloid or blood products depending on the volume lost and variables suggesting inadequate tissue  $O_2$  delivery. Crystalloid may be used as an alternative for intravascular plasma volume expansion, but the increased volume required and potential for extravascular volume expansion should be considered. Overall, the goal should be to achieve euvoolemia by the end of surgery or the early postoperative period.

**Postoperative.** High-risk surgical patients may benefit from an ongoing period of GDT targeting  $O_2$  delivery in the early postoperative period.<sup>163</sup> In all other patients after major surgery, an assessment of fluid status should be made based on clinical examination and supporting physiologic measurements such as lactate, central or mixed venous saturations, and cardiac output variables,

if available. If patients are euvolemic and able to return to oral fluid intake, this is the best way of avoiding the iatrogenic effects of postoperative fluid administration. Early oral intake is typically well tolerated and safe, and early oral nutrition may reduce the incidence of postoperative complications.<sup>164</sup>

The following should be done in patients requiring ongoing IV therapy:

- Electrolytes should be checked at least daily to monitor for hyponatremia and other electrolyte derangements.
- Fluid requirements should be strictly divided into three categories for their ongoing assessment and treatment
  - **“Pure” maintenance requirements.** These should be salt-poor and contain a modest volume of free water to account for the postoperative state of salt and water retention. Infusions should therefore consist of the following<sup>164</sup>: (1) 1500 to 2500 mL in 24 hours, depending on weight, or 1 to 1.2 mL/kg/h. Given the relative reduction in TBW in obesity (see previous discussions on crystalloids, fluid compartments), consideration should be given to dosing this fluid requirement based on ideal body weight in this setting. (2) 50 to 100 mEq  $Na^+$  should be given in 24 hours, and (3) 40 to 80 mEq  $K^+$  should be given in 24 hours.
  - It is likely that part of this minimal maintenance volume should comprise hypotonic fluids such as 5% dextrose or 0.18% saline with 4% dextrose. Because of the risk for postoperative hyponatremia, this maintenance intravascular fluid volume should not be increased if suspicion for hypovolemia exists. Rather, the source of the ongoing loss should be identified and treated separately. As oral fluid intake increases, this maintenance fluid should be reduced proportionately.
- **Replacement of ongoing losses.** This fluid requirement requires frequent reassessment to appropriately titrate replacement fluids. Volumes given should reflect measured amounts lost and an assessment of intravascular volume status and adequacy of organ perfusion (mental state, lactate, hemodynamic trends). Losses from the GI tract (vomiting, nasogastric aspirates, stoma) should be replaced with an equal volume of isotonic saline or balanced crystalloid with  $K^+$  as appropriate. Losses to third spaces, such as reaccumulation of ascites, should be treated with a mixture of colloid and crystalloid, and blood loss replaced with colloid, blood, or blood products.
- **New requirements (resuscitation).** New requirements may relate to the development of postoperative complications such as hemorrhage (absolute hypovolemia) or acute sepsis (relative or absolute hypovolemia).

Postoperative oliguria should be interpreted cautiously, particularly in the first postoperative day. The patient should be carefully assessed for corroborative evidence of impaired end-organ perfusion and alternative causes of oliguria, including catheter obstruction and intraabdominal hypertension. In the absence of markers indicating hypovolemia and inadequate tissue perfusion, large volumes of fluid challenge are inappropriate and may aggravate

postoperative positive fluid and  $\text{Na}^+$  balance in the face of a normal surgical stress response.

## Special Considerations

### Patient Factors

**HEART FAILURE.** The diverse pathophysiologic effects of heart failure and their treatment may make perioperative fluid management particularly challenging. The hemodynamic effects of chronic heart failure are characterized by systolic and diastolic dysfunction of the left, right, or both ventricles with secondary maladaptive neurohumoral responses. These include persistent activation of the RAA axis, with consequent salt and water retention, and chronic sympathetic nervous system (SNS) activation, with persistent tachycardia and vasoconstriction. Under-treated patients may therefore present with edema in lungs and peripheral tissues and increased central blood volume in the face of poor myocardial function.

Treatments for heart failure attempt to correct many of the neurohumoral responses, and many have been shown to improve long-term prognosis in heart failure. In the perioperative phase, they may bring challenges to fluid management, including chronic volume depletion, blunting of normal sympathetic responses, and electrolyte disturbances. They include  $\beta$ -adrenoreceptor antagonists, diuretics, digoxin, and antagonists of aldosterone and angiotensin.

Perioperative fluid therapy in patients with heart failure has two goals. The first is to preserve cardiac output, bearing in mind the influence of preload, contractility, and afterload. The ventricles are typically poorly compliant and require adequate preload, which may be reflected in a relatively high CVP and adequate diastolic filling time to maintain good cardiac output. However, the flattened Starling curve of the failing heart means that excessive intravascular volume infusion and preload may lead to impaired contractility and worsening cardiac output. This leads to “forward failure,” manifested as inadequate organ perfusion, and “backward failure,” manifested as pulmonary and peripheral edema, particularly in the presence of aberrant salt and water excretion. The second goal is to minimize the cardiac work to avoid a vicious cycle of increased cardiac  $\text{O}_2$  demand, inadequate  $\text{O}_2$  supply, and worsening myocardial function. In particular, tachycardia triggered by hypovolemia and other stimuli should be avoided. Striking a balance between hypovolemia and hypervolemia is particularly important in patients with heart failure, but it may be difficult to assess clinically.

The practical approach to patients with heart failure involves careful preoperative assessment of fluid status and electrolytes and optimization of heart failure treatments when time allows. The complex cardiovascular situation often requires cardiac output monitoring for moderate or major surgery. Invasive modalities include transesophageal echocardiography or pulmonary artery catheterization,<sup>165</sup> although less invasive modalities may also be helpful. Measurement of cardiac filling and contractility is particularly important because the sources of intraoperative hypotension (reduced preload, contractility, or afterload) require different treatments. Infusion of large volumes of any fluid, including blood and products,

should be undertaken only with objective evidence of intravascular volume loss.

The effects of heart failure therapies should be evaluated carefully in the perioperative phase. Diuretics may leave patients in a chronically volume-contracted state that worsens anesthesia-related hypotension. Loop diuretics frequently cause hypokalemia and hypomagnesemia, whereas aldosterone antagonists cause hyperkalemia, which may be severe when combined with ACE-inhibitor treatment or chronic kidney disease. Normalization of electrolytes is particularly important in patients taking digoxin, in whom hypokalemia may potentiate digoxin toxicity. ACE-inhibitors or angiotensin receptor antagonists themselves lead to a blunted sympathetic and angiotensin response to anesthesia-related vasodilation. The hypotension caused by these should be treated appropriately by small doses of inotropes or vasopressors, which may include vasopressin analogs.<sup>165</sup>

**KIDNEY DISEASE.** Patients with dialysis-dependent chronic kidney disease have multiple pathologic features that must be considered in perioperative fluid therapy. Overall fluid balance may be disturbed by reduced or absent native urine production, with reliance on dialysis to achieve the target “dry” weight, representing estimated euvoolemia. Organ  $\text{O}_2$  delivery may be impaired by various factors, including chronic anemia, endothelial dysfunction, and microvascular perfusion abnormalities. The frequent coexistence of heart failure and systemic or pulmonary hypertension and the bleeding tendency caused by platelet dysfunction further increase the perioperative risk.<sup>166</sup>

Preoperative assessment should focus on the adequacy of chronic dialysis in attaining euvoolemia and estimating the normal volume of native urine output. Comorbidities should be assessed and optimized. Surgery should be undertaken in a facility where preoperative and postoperative dialysis or hemofiltration can be offered in case of intraoperative fluid overload or hyperkalemia. In elective surgery, preoperative dialysis should be timed such that the patient enters the intraoperative phase with a normal blood volume. Surgery in the presence of hypervolemia increases the risk for pulmonary and peripheral edema, hypertension, and poor wound healing, whereas hypovolemia increases the risk for anesthesia-related hypotension and inadequate tissue perfusion. Practically, this means performing dialysis the day before surgery to allow for equilibration of fluid and electrolyte compartments and time for dialysis anticoagulants to be metabolized. Electrolytes should be checked on the morning of surgery; sampling too soon after dialysis, before equilibration, may give an artificially low  $\text{K}^+$  result leading to unnecessary exogenous supplementation. Conversely, fasting may actually favor a hyperkalemic state as a result of the reduced presence of insulin; the ideal  $\text{K}^+$  value after dialysis is in the low-to-normal range. For emergency surgery, there may not be sufficient time to safely dialyze patients preoperatively. In this case, electrolyte abnormalities must be managed conservatively, with particular care paid to intraoperative fluid balance.

As with other major comorbidities with a critical impact on fluid and electrolyte balance, the importance of avoiding both hypovolemia and hypervolemia and the predisposition

to inadequate tissue perfusion mean that detailed monitoring of hemodynamic variables, including invasive central venous and arterial pressure and cardiac output, should be considered for moderate-to-major surgery. The amount of fluid administered intraoperatively should be titrated to objective physiologic measurements, although the type of fluid given is open to debate. Large volumes of isotonic saline should be avoided, because the induced acidosis favors extrusion of  $K^+$  from cells. In contrast,  $K^+$ -containing balanced crystalloids did not cause hyperkalemia in clinical trials.<sup>44,167</sup> An alternative crystalloid is a  $K^+$ -free  $HCO_3^-$ -buffered dialysis solution such as Hemosol. Colloids may be used for intravascular volume replacement, although owing to their predominantly renal excretion, the volume effect and potential toxicities may be exaggerated in these patients. Liaising with the nephrologist is important before considering blood transfusion; if the patient is awaiting renal transplantation, human leukocyte antigen-matched blood may be required to minimize antibody formation and future difficulties with blood and tissue matching.

**UPPER GASTROINTESTINAL LOSS.** Large volume gastric fluid loss may be caused by congenital or acquired gastric outlet obstruction and lead to a distinct pattern of fluid and acid-base abnormalities. Dehydration occurs as a result of water loss, reduced total body  $Cl^-$  content, and alkalosis caused by proton loss, with raised serum  $HCO_3^-$ . The initial renal response is formation of urine with low  $Cl^-$  and high  $HCO_3^-$  content. However, progressive dehydration leads to increased aldosterone secretion, aimed at retaining  $Na^+$  and water.  $Na^+$  is retained at the expense of  $K^+$  and  $H^+$  ions, leading to hypokalemia, and worsening metabolic alkalosis with a paradoxically acid urine. The alkalosis also reduces the circulating ionized fraction of  $Ca^{2+}$ .

Correction should include gradual rehydration with isotonic saline and  $K^+$  supplementation, changing to dextrose-containing saline solutions depending on electrolyte analysis. Any surgery required to treat gastric outlet obstruction should be scheduled after correction of the volume and acid-base status.

**SEPSIS AND ACUTE LUNG INJURY.** Patients with infection and sepsis syndromes may be encountered early in their presentations, as surgical source control of infection (drainage of abscesses, debridement of necrotic tissues, removal of infected devices) forms a key part of early sepsis therapy.<sup>168</sup> Cardiovascular instability may be a particular problem, contributed to by endothelial dysfunction and intravascular fluid loss, vasodilation with fluid maldistribution, sympathetic redistribution of blood volume away from the peripheral circulation, and impairment of cardiac function. Fluid resuscitation, with the goal of maintaining adequate end organ perfusion, has historically been a key part of the first six hours of sepsis treatment, which may represent the perioperative period for some patients. Early trials suggested that protocolized fluid resuscitation targeting central venous oxygen saturation was more effective than resuscitation guided by only CVP, MAP, and urine output targets in reducing mortality from sepsis.<sup>169</sup> However, more recent large international trials have shown that this approach has similar outcomes to resuscitation based on standard or protocolized care without targeting central venous oxygen saturations.<sup>170-172</sup> The following approach is suggested for septic patients with evidence of tissue hypoperfusion:<sup>173</sup>

- At least 30 mL/kg of crystalloid should be given within the first three hours of resuscitation.
- Further fluids should be guided by frequent reassessment of hemodynamic status. This assessment may incorporate more detailed measurements such as cardiac output, in addition to routinely available physiological variables (heart rate, blood pressure, urine output).
- Dynamic tests of fluid responsiveness such as passive leg raise or stroke volume response to a fluid challenge are recommended over static targets such as a fixed CVP value.
- Other resuscitation targets may include a MAP  $>65$  mm Hg in those requiring vasopressors, and normalization of lactate in patients with elevated levels.

These guidelines are based on a limited evidence base and further research is needed to refine this area. For example, some trials have suggested that a fluid bolus strategy may not be helpful in attaining hemodynamic targets<sup>174</sup> or may even be harmful in some settings.<sup>175</sup>

In established sepsis, fluid management becomes even more challenging due to the frequent presence of microvascular dysfunction, extravascular fluid overload, and disturbed neurohumoral responses to variations in intravascular volume.<sup>176</sup> There is uncoupling of the  $O_2$  delivery and consumption relationship as a result of cellular inability to use  $O_2$  (cytopathic hypoxia).<sup>177,178</sup> Because of this uncoupling, strategies to elevate global  $O_2$  delivery may be of little benefit while exposing patients to potential side effects of excessive fluid and catecholamine administration.<sup>179,180</sup> At this stage, a less positive overall fluid balance is associated with improved outcomes.<sup>181</sup>

Patients with established acute respiratory distress syndrome (ARDS) may also present for surgical procedures. Here the focus of fluid therapy is the fine balance between avoiding an increase in lung edema while maintaining adequate tissue perfusion. ARDS is typified by increased pulmonary endothelial permeability, with extravasation of water and protein. The consequences are interstitial and alveolar edema, reduced pulmonary compliance, increased pulmonary artery pressures, and hypoxemia. Meanwhile, organ perfusion may be impaired by increased intrathoracic pressures and reduced cardiac filling pressures. Observational studies have highlighted an association between overall positive fluid balance and mortality in ARDS,<sup>182</sup> backed by a large randomized controlled trial demonstrating a reduction in ventilator and intensive therapy unit days in patients treated with a conservative fluid administration strategy.<sup>183</sup> The findings were similar in a subgroup of patients from this trial who had undergone surgery and were treated with lower fluid volumes. There was also no increased kidney injury seen in the low fluid volume group.<sup>184</sup> Extravascular lung water (EVLW) seems to be important in predicting the worse outcomes associated with a more positive fluid balance. Thermodilution studies showed excess EVLW to have reasonable sensitivity and specificity in predicting ICU mortality in patients with ARDS.<sup>185</sup> Assuming global organ perfusion appears adequate, as demonstrated by normal lactate levels, intraoperative losses should be replaced but otherwise be conservative in the volumes of fluid given to patients with ARDS intraoperatively. There is a lack of adequately powered studies on the choice of

colloid or crystalloid for intravascular volume replacement in patients with ARDS.

**BURNS.** Extensive burns create a situation of copious fluid loss from the circulation combined with particular sensitivity to the effects of excess fluid administration. Thermal injury creates an area of necrotic tissue with surrounding ischemic areas. The combination of dead tissue with areas undergoing ischemia and subsequent reperfusion causes localized and systemic inflammatory reactions through histamine, prostaglandin, reactive  $O_2$  species, and cytokine release. Local impairment of endothelial barrier function leads to the loss of oncotically active plasma constituents, increased capillary filtration into the interstitial compartment, and evaporative transcutaneous fluid loss as a result of loss of skin integrity. Through similar mechanisms, extensive burns may lead to the systemic inflammatory response syndrome, with its well-recognized effects on fluid compartments outlined previously. The deleterious role of this inflammatory response is underlined by the reduction in mortality seen with early burn excision compared with conservative care.<sup>186</sup> IV fluid therapy is generally instituted for burns of greater than 15% total body surface area in adults and 10% total body surface area in children.<sup>187</sup> However, increasing uncertainty exists about the volume and type of fluid that should be given to patients with burns. Fluid administration is largely still based on formulas such as the Parkland formula (Box 47.1) or the Muir and Barclay versions. Although these have given a starting point for resuscitation volumes based on patient weight and extent of burn, myriad other patient and pathologic factors put such a recipe-based approach at odds with modern perioperative fluid therapy based on objective physiologic goals. Although the approaches based on these formulas advocate down-titration of administered fluid volumes if urine output is adequate (0.5–1 mL/kg/h),<sup>188</sup> in reality this appears not to be practiced. Indeed, large studies have shown that the majority of burn patients receive fluid volumes in excess of those predicted by the Parkland formula, with a mean of 6 mL/kg/% burn compared with 4 mL/kg/% burn in 24 hours predicted by the formula.<sup>189</sup> Conversely, patients with inhaled and other nonburn injuries, electrical burns, or delayed resuscitation are considered to need increased resuscitation intravascular volumes, yet this is not taken into account by the formulas.

Excessive fluid administration in burned patients (“fluid creep”) is not benign. As in all conditions typified by systemic inflammation, excess administered fluid will collect in compliant compartments. Pulmonary edema requiring ventilatory support, fasciotomies in muscle compartments, raised intraocular pressure, and conversion of superficial to deep burns have been observed and attributed to fluid resuscitation.<sup>187</sup> Intraabdominal hypertension and compartment syndrome are correlated to the volume of fluid administered, with a particular rise when more than 300 mL/kg is administered in 24 hours.<sup>190</sup> These concerns have led to renewed efforts to find the optimum regimen for burn resuscitation in terms of crystalloid versus colloid, newer formulas using lower volumes such as the Haifa formula, and targeting objective physiologic parameters such as SV or intrathoracic blood volume. Early trials have suggested that minimally invasive cardiac output monitoring may have a role, although there are no adequately sized trials to

### BOX 47.1 Parkland Burn Fluid Resuscitation Formula

First 8 h: 2 mL/kg × %TBSA (lactated Ringer solution)  
Next 16 h: 2 mL/kg × %TBSA (lactated Ringer solution)  
Next 24 h: 0.8 mL/kg × %TBSA (5% dextrose) + 0.015 mL/kg × %TBSA (5% albumin)

%TBSA, Burn size as % of total body surface area. Time periods refer to the time since the burn occurred.

Data from Baxter CR. Problems and complications of burn shock resuscitation. *Surg Clin North Am.* 1978;58:1313.

show whether this approach improves outcomes.<sup>191</sup> Pending a consensus from this ongoing work, burn resuscitation should be commenced with one of the currently accepted formulas, but actively down-titrated if a urine output of 0.5 to 1 mL/kg/h is obtained. A combination of crystalloids and colloids may be used to reduce the total fluid volume administered,<sup>192</sup> although the early use of colloids is controversial due to the perceived risk of extravasation of oncotically active molecules in the presence of severe capillary leak. In addition, patients with burns were included in recent license restrictions on the use of starches.<sup>191</sup> Intraabdominal pressure should be monitored, and consideration given to assessing resuscitation endpoints, such as lactate and cardiac output, in addition to urine output.

**PEDIATRICS.** Perioperative fluid therapy in pediatric patients has for many years been based on traditional approaches that are increasingly being reexamined. Holliday and Segar<sup>138</sup> proposed a quantity and composition of maintenance fluid in hospitalized children in 1957 based on water requirements to sustain average metabolic activity and the electrolyte composition of milk. This developed into the 4-2-1 volume calculation for maintenance fluid requirements aimed at replacing insensible and urinary losses with hypotonic crystalloids containing glucose to maintain isoosmolality. These concepts were translated into the perioperative phase and glucose-based solutions were administered intraoperatively to reduce the apparently high risk for preoperative hypoglycemia after prolonged fasting,<sup>193</sup> and postoperative maintenance fluids were prescribed based on the 4-2-1 calculation using hypotonic crystalloids. Furthermore, the pediatric population was thought to be at risk for clinically significant preoperative dehydration by fasting, as a result of limited urinary concentrating ability and ongoing insensible losses because of the relatively large body surface area. Intraoperative replenishment of these volumes using 25 mL/kg of isotonic salt solution for those 3 years of age and younger or 15 mL/kg for those 4 years of age and older has been recommended.<sup>194</sup>

Multiple factors have led to a reevaluation of this approach. First, the modern approach to preoperative fasting, such that children may take clear—and potentially carbohydrate-containing—fluids up to 2 hours before surgery, reduces the risk for hemodynamically significant preoperative dehydration.<sup>195</sup> Second, the incidence of preoperative hypoglycemia is infrequent (<2.5%) and related to inappropriately prolonged fasting or other risk factors, such as prematurity, small for gestational age, or poor nutritional status.<sup>196,197</sup> Surgery itself increases blood glucose concentration, and administering

glucose-containing solutions intraoperatively may cause hyperglycemia,<sup>198</sup> with the potential for osmotic diuresis and electrolyte abnormalities, or even adverse neurologic outcomes in the event of an ischemic or hypoxic event.<sup>197</sup> Glucose-free balanced crystalloid solutions should therefore be used intraoperatively, except in those at particularly high risk for hypoglycemia. Third, increasing awareness of the incidence and potentially disastrous neurologic outcomes from postoperative hyponatremia in pediatric populations has led to a reappraisal of postoperative hypotonic crystalloid maintenance fluids in 4-2-1 volumes. The effective SIADH induced by surgical stress and aggravated by the presence of pain and hypovolemia causes water retention and the risk for hypoosmolar hyponatremia if hypotonic solutions continue to be infused in significant volumes. Proposed strategies to avoid this include using one half to two thirds of the calculated 4-2-1 formula for maintenance fluids,<sup>195</sup> avoiding the most hypotonic fluids (4% dextrose with 0.18% NaCl),<sup>197</sup> using balanced isotonic crystalloids (containing glucose if available).<sup>199,200</sup> General measures that should be applied to all patients include:

- returning to oral fluids as early as possible
- ensuring euolemia to minimize the ADH response<sup>201</sup>
- clearly dividing *maintenance* requirements from the variable amounts of fluid required because of *ongoing losses* (e.g., GI or blood), which should typically be replaced by isotonic crystalloids, colloids, or blood
- checking electrolytes at least daily in those still receiving IV fluids

Although isotonic saline has been advocated as a “safer” fluid for postoperative maintenance, this brings the risk for Na<sup>+</sup> overload and hyperchloremic acidosis.

More recent developments in perioperative fluid management remain underexplored in pediatric populations. In particular, there is little data on whether colloid volume expansion is beneficial or harmful in pediatrics when compared with crystalloids, or whether goal-directed fluid therapy may confer the advantages that have been suggested in adult populations.

**HEPATIC FAILURE.** Progressive liver disease and cirrhosis cause a distinctive pattern of abnormal fluid balance. The combination of peripheral vasodilation and relative intravascular depletion can mimic a decrease in intravascular volume. Yet, total body Na<sup>+</sup> and water are retained with ascites and edema.<sup>202</sup>

The widely accepted pathophysiologic mechanisms are that progressive disruption of liver architecture combines with decreased hepatic nitric oxide (NO) bioavailability and increased vasoconstrictor production, leading to sinusoidal hypertension. Compensatory vasodilatory mechanisms, including NO overproduction, lead to splanchnic and systemic vasodilation, relative hypovolemia, and reduced systemic arterial pressure. This triggers baroreceptor-mediated activation of the RAA, SNS, and ADH release. Although cardiac output increases, reduced systemic vascular resistance persists despite these compensatory mechanisms. The state of hyperaldosteronism causes salt and water retention, but hyponatremia occurs because of a relative excess of water retention. Splanchnic vasodilation and vascular permeability combine with decreased lymphatic drainage to favor

the formation of ascites. The neurohumoral response also induces renal artery vasoconstriction, reducing renal blood flow and increasing the risk for hepatorenal syndrome. A range of therapies to maintain patients in a compensated state include: dietary fluid and salt restriction, diuretics (particularly spironolactone and loop diuretics), and intermittent or continuous drainage of ascites. However, the perioperative period presents considerable potential for disturbance of this fine balance. Excessive administration of isotonic saline will aggravate the preexisting salt and water overload, leading to further ascites and edema formation. Conversely, periods of hypovolemia are poorly tolerated, leading to a significant deficit in organ perfusion, further stimulation of the RAA, SNS, and ADH axes, and increasing risk for kidney injury. The approach should therefore be to assess volume status carefully, considering cardiac output monitoring, and to replace losses with appropriate volumes of isotonic crystalloid, colloid, or blood but to avoid salt and water overload. In instances of large-volume (>6 L) paracentesis, hemodynamic instability is a risk. Albumin appears to be a more effective prophylactic treatment for this than saline, abrogating the stimulated increase in plasma renin activity and maintaining more stable hemodynamics.<sup>203</sup> Lactate and other buffered fluids may be used in hepatic failure, although their metabolism may be slowed in advanced liver disease.

In decompensated liver disease with encephalopathy, raised intracranial pressure may be present and osmotherapy, such as hypertonic saline, should be used to bring plasma Na<sup>+</sup> into the high-normal range.<sup>204</sup> This is in contrast to chronic compensated liver disease, in which a degree of hyponatremia is well tolerated and does not require acute correction unless it is severe or symptomatic (see earlier discussion).

**OBSTETRICS: PREECLAMPSIA.** Preeclampsia is a multisystem disease of pregnancy characterized by hypertension, proteinuria, and multiorgan involvement that may affect the kidneys, liver, pulmonary, and central nervous systems. In contrast to the usual volume-expanded status in pregnancy, patients with preeclampsia have reduced plasma volume, combined with endothelial dysfunction and hypoalbuminemia. Previously IV volume expansion was thought to be beneficial in treating hypertension in preeclampsia; however, this has not been borne out by later studies.<sup>205,206</sup> Furthermore, a clear association exists between positive fluid balance and the incidence of pulmonary edema in this condition.<sup>207</sup> Acute pulmonary edema occurs in between 5% and 30% of cases of preeclampsia. It is associated with increased hospital length of stay and is a leading cause of death in preeclamptic patients. Most cases present in the postpartum period, perhaps reflecting the autotransfusion into a vasoconstricted circulation that occurs after delivery. Low COP also contributes.

Patients with preeclampsia should receive restricted volumes of IV crystalloid (80 mL/h, including that received as drug diluents<sup>208</sup>), and fluid balance should be observed carefully. Oliguria should not be treated by administration of large volumes of fluids in the presence of normal renal function. This conservative strategy has not been associated with an increase in kidney injury.<sup>209</sup> Any blood loss in the peripartum or perioperative period should be replaced with an appropriate volume of crystalloid, colloid, or blood,

depending on magnitude. Invasive monitoring should be used to direct fluid therapy in cases of severe preeclampsia.

### Surgical Factors

**NEUROSURGERY.** Multiple physiologic factors mean that fluid and electrolyte therapy are a key component in the perioperative management of intracranial pathology. This management may be complicated by disturbances of water and  $\text{Na}^+$  balance caused by neurosurgical diseases themselves. Much of the current fluid management in this area is based on knowledge of this physiology, experimental models, and gradual evolution of interventions investigated in small trials rather than large randomized studies.

The intact blood-brain barrier (BBB) excludes electrolytes and large molecules but allows passage of water. Extravascular brain water is therefore related to plasma osmolality, with cerebral edema a feature of hypoosmolar hyponatremic conditions. Intracranial diseases may compromise the integrity of the BBB, increasing the predisposition to edema. Cerebral perfusion also may be impaired if systemic blood pressure is inadequate in the face of increased intracranial pressure, particularly in pathologic conditions in which autoregulation is impaired. Rational management of fluids in neurosurgical patients should start with maintaining baseline blood volume and cerebral perfusion and avoiding significant decreases in serum  $\text{Na}^+$ , osmolality, and oncotic pressure. Several situations may require more specific management:

1. Increased intracranial pressure: Increasing serum osmolality may reduce total brain water and therefore intracranial pressure by creating brain-blood osmotic gradients. Mannitol and hypertonic saline given by bolus have been the pharmacologic mainstays in this area. The osmotic action of these drugs may be reduced if the BBB is disrupted by brain injury; however, they also have therapeutic benefits beyond simple osmotic effects.<sup>210</sup> A meta-analysis of the small studies available suggests that hypertonic saline may be superior to mannitol in reducing intracranial hypertension, but large-scale controlled studies are required to confirm this.<sup>57</sup> Conversely, using hypertonic saline in all patients with early traumatic brain injury without intracranial pressure monitoring has not been shown to improve outcomes.<sup>58</sup> Similarly, continuous infusion of hypertonic saline to induce persistent hypernatremia in the presence of cerebral edema also lacks evidence of benefit.<sup>211</sup> Restrictive fluid strategies have been advocated to minimize intracranial hypertension in severe traumatic brain injury. Although retrospective data analysis suggests that positive fluid balance is not associated with refractory intracranial hypertension, an association between hypervolemia and pulmonary edema was observed.<sup>212</sup>
2. Cerebral vasospasm: Manipulation of hemodynamics and hematocrit is traditionally used in the treatment of vasospasm after subarachnoid hemorrhage. This “triple-H” therapy (hypervolemia, hemodilution, hypertension) has entered practice based on small studies of efficacy rather than randomized trials.<sup>213,214</sup> Some workers, using extensive animal models, have advocated a hematocrit no lower than 30%, below which the benefits of reducing blood viscosity are outweighed by a reduction

in  $\text{O}_2$  delivery. They also caution against hypervolemia, both for its potentially injurious effects in the presence of a dysfunctional BBB and for the extracranial effects such as pulmonary edema.<sup>215</sup> “Prophylactic” hypervolemia aiming to prevent vasospasm is not recommended.<sup>216</sup>

3. An intracranial pathologic condition may itself be a cause of disturbances of both water and  $\text{Na}^+$  balance through diabetes insipidus, cerebral salt wasting, or SIADH. This should be assessed and treated as described in the section on electrolyte imbalance.

Clear comparisons of crystalloid and colloid in a variety of neurosurgical settings are lacking. Of the available evidence, albumin is associated with an increase in mortality in traumatic brain injury compared with isotonic saline.<sup>5</sup> In the absence of more robust evidence, a mixture of isotonic crystalloids and colloids is advocated in other neurosurgical settings.<sup>214,217</sup>

**TRAUMA.** In patients with evidence of major traumatic hemorrhage, the key goals are to avoid clot disruption until definitive control of bleeding, to treat the acute coagulopathy of trauma, to maximize tissue  $\text{O}_2$  delivery by the early use of packed red cell transfusion, and to avoid hypothermia and acidosis. This approach is termed hemostatic resuscitation. In the prehospital setting, restrictive fluid therapy may improve outcomes, particularly in penetrating trauma.<sup>218</sup> The approach should initially be one of permissive hypovolemia, with fluid administered to achieve cerebration rather than normotension in awake patients, systolic blood pressure of 70 to 80 mm Hg in penetrating trauma, or 90 mm Hg in blunt trauma.<sup>219</sup> The duration of organ hypoperfusion that may be involved with this approach should be minimized by rapid transfer for damage control intervention to stop bleeding, whether radiologic or surgical. Large volumes of IV crystalloids or colloids in early resuscitation will cause hemodilution and dilute clotting factors, and saline-based fluids may aggravate the acidosis associated with major blood loss. Rather, packed RBCs (PBCs), clotting factors (e.g., fresh frozen plasma [FFP]) and platelets should be replaced early. Limited evidence, particularly from military populations and retrospective analyses, suggests “high” ratios of FFP to PRBC (e.g., 1:1-1:2) are associated with the best outcomes in massive transfusion compared with lower ratios (e.g., 1:9).<sup>219,220</sup> Active warming should be used and clot stability improved with tranexamic acid.<sup>221</sup> Once hemostasis has been achieved, restoration of normal circulating volume and tissue perfusion is the goal, with ongoing blood, clotting factors, platelet, and fluid infusions targeting normalization of cardiac output and  $\text{O}_2$  delivery, lactate levels, and blood clotting (best checked using near-patient whole-blood tests of clotting, such as thromboelastography). A small number of trials support the practice of GDT in the immediate perioperative trauma setting, but larger controlled trials are required. After surgery and initial resuscitation, much of the evidence for ongoing fluid approaches is derived from unselected critical care populations. As outlined previously, the evidence suggests that in established critical illness, aggressive GDT may be harmful.<sup>218</sup>

Patients with traumatic brain injury in addition to major hemorrhage present a dilemma because the raised cerebral perfusion pressure required for adequate cerebral blood flow

in the face of raised intracranial pressure is at odds with the hypotensive resuscitation approach. In isolated head injuries, using fluids and vasopressors to achieve a mean arterial pressure *above* 90 mm Hg is recommended, with avoidance of hyponatremia and hypoosmolality to minimize cerebral edema.<sup>210,217</sup> Little evidence exists to inform resuscitation treatment in patients with mixed intracranial and extracranial trauma, so the strategy should be based on clinical judgment, prioritizing the requirements of the most severe injuries. Control of bleeding is particularly important to allow subsequent normalization of systemic blood pressure to meet the need for adequate cerebral perfusion. Even in general trauma, much of the evidence supporting current resuscitation approaches is derived from animal models and limited randomized trials, predominantly in young otherwise healthy subjects in the prehospital setting.<sup>218</sup> The needs of individual patients should therefore be taken into account, particularly because older patients with comorbidities may tolerate periods of hypoperfusion very poorly.

**FREE TISSUE FLAP SURGERY.** Free tissue flaps are frequently used during oncoplastic surgery, typically for breast reconstruction or after resection of head and neck tumors and involve the autologous transplantation of tissue to fill a defect, complete with arterial supply and venous drainage. Transplanted vessels are denervated and lack intrinsic sympathetic tone, but the feeding vessels are not; vasoconstriction in these feeding vessels related to cold and excessive doses of vasopressor must be avoided because it may threaten the perfusion of the flap. Flap blood flow depends on systemic blood pressure and blood viscosity, and hypovolemic hemodilution has traditionally been used to address these requirements. However, given the reduction in O<sub>2</sub> carrying capacity and potential for flap edema that this entails, a more conservative fluid strategy should be used, which may improve flap outcome.<sup>219</sup> The use of dextrans to improve blood flow is not currently favored, because no benefit has been demonstrated and the risks for medical complications is relatively high.<sup>220</sup> Free tissue flaps have disrupted lymphatics, which take several weeks to reconnect, making them particularly prone to interstitial edema. Large volumes of crystalloid—favoring increased capillary filtration—should be avoided and colloids used for blood volume expansion.<sup>221</sup>

**INTRATHORACIC PROCEDURES.** Any procedure within the thorax, including upper GI and thoracic surgery, can lead to postoperative respiratory problems, including ARDS and acute lung injury (ALI). The development of ARDS and ALI is partly due to the proinflammatory nature of one-lung ventilation,<sup>222,223</sup> modified by a host of other patient and surgical risk factors. In esophagogastrectomy, retrospective studies and case series have suggested reduced pulmonary complications with restrictive fluid strategies.<sup>224-227</sup> One retrospective observational study of esophagectomy patients found a cumulative fluid balance greater than 1900 mL from surgery to the second postoperative day to be an independent risk factor for other adverse outcomes, including death.<sup>228</sup> The use of diuretics to actively target fluid balance, degree of cardiovascular support, and presence or absence of epidurals was not explored in this study. More controlled trials of different fluid balance approaches are required in this population. However, the potential benefit of conservative fluid administration in this group is

consistent with the large randomized study of patients with ARDS demonstrating improved pulmonary outcomes in those treated with a restrictive rather than liberal fluid regimen.<sup>183</sup> While maintaining adequate tissue perfusion, a cautious approach to fluid administration is recommended, both to minimize pulmonary complications and to avoid anastomotic edema.

**HEPATIC RESECTION.** Blood loss during liver parenchymal resection, a risk factor for worse outcomes, is associated with high venous pressure and backflow of blood through the valveless hepatic veins. One study has shown that a CVP of 5 cm H<sub>2</sub>O or lower is associated with significantly lower blood loss and transfusion requirements.<sup>229</sup> Several techniques are used to maintain a low CVP, including conservative fluid management, at least until the hepatic resection is completed. Despite evidence that using a low CVP technique does not have adverse effects on renal or liver function,<sup>230</sup> a pragmatic compromise must be sought for each patient. Inducing hypovolemia during liver resection risks hemodynamic instability and end-organ hypoperfusion, increases the risk for air embolism, and reduces the physiologic reserve should massive blood loss occur. Once the liver resection is finished, a more generous fluid approach can be taken to ensure adequate circulating volume. This may be guided by invasive hemodynamic monitoring and minimally invasive cardiac output monitoring to provide a rational endpoint to fluid therapy in this phase.

**MAJOR INTRAABDOMINAL SURGERY.** Major intraabdominal operations, particularly those involving multiple organ resections for tumor, require careful perioperative fluid management. Major gynecologic operations such as pelvic exenteration or ovarian debulking and urologic procedures including cystectomy, radical nephrectomy, and major retroperitoneal lymph node dissection can involve dramatic fluid shifts in the perioperative period. Fluid losses during surgery are caused by prolonged peritoneal exposure, significant blood loss, and acute drainage of tumor-related ascites. The total volume lost is difficult to quantify, so cardiac output monitoring is valuable when combined with CVP and arterial pressure monitoring and serial blood gas analysis.<sup>231,232</sup> Intraoperative drainage of ascites is followed by fluid shift from the vascular space, as this reaccumulates postoperatively and may require large volumes to replace the ongoing loss. Another consequence of fluid redistribution is electrolyte abnormalities; hypokalemia and hypomagnesemia are frequently seen.

**RENAL TRANSPLANT.** The key goals of fluid therapy in the perioperative management of renal transplant are to ensure adequate renal perfusion to support early graft function and avoid fluid therapy side effects to which patients with impaired renal function may be susceptible. Traditionally, CVP-guided intraoperative fluid therapy has been advocated, using large volumes of crystalloid (up to 60-100 mL/kg) to achieve a CVP of 10 to 12 mm Hg or higher before reperfusion.<sup>233</sup> Recently, more conservative goals have been advocated, limiting crystalloid infusion to 15 mL/kg/h, aiming for a CVP of 7 to 9 mm Hg with no apparent increase in graft failure.<sup>234</sup> The role of alternative tools such as esophageal Doppler or pulse contour analysis to supplement or replace CVP-guided fluid therapy in this area also has been suggested, but so far only exploratory trials have been conducted.<sup>235,236</sup> Patients with renal failure may

develop acidosis-related hyperkalemia when isotonic saline is infused during transplant,<sup>44</sup> so balanced crystalloid solutions, or even K<sup>+</sup>-free, buffered dialysate solutions, should be used. The role of colloids in this population requires further study, although concerns over renal toxicity of starches may limit their use.<sup>235</sup> Postoperative fluid therapy should take into account the baseline maintenance requirements and the ongoing losses resulting from urine production.

**LIVER TRANSPLANT.** Liver transplantation involves a series of major physiologic disruptions that have direct relevance to fluid and electrolyte management.<sup>237</sup> Therapy should be guided by data from invasive monitoring, possibly including pulmonary artery catheterization. During phase I (pre-anhepatic), large volume blood loss and further fluid shifts resulting from drainage of ascites may occur. During phase II (anhepatic), a major reduction in venous return and therefore cardiac output may occur if a bicalaval approach is used. Crystalloid and colloid infusion may be required along with vasopressors to maintain arterial pressure during this phase, although excessive volume administration risks right heart failure after unclamping. Absent citrate and lactate metabolism during this phase contributes to acidosis, hypocalcemia, and hypomagnesemia. On reperfusion and unclamping, cold, acidotic, hyperkalemic fluid is released into the circulation. Preparation for this must include normalizing pH and maintaining plasma K<sup>+</sup> in the low-normal range during phase II. This may require Ca<sup>+</sup>, insulin-dextrose, hyperventilation, and even NaHCO<sub>3</sub> treatment. Phase III (reperfusion) leads to an acute rise in CVP, possibly with hepatic congestion and right heart strain. Systemic vasodilation and cardiac arrest may occur, leading to hypotension requiring vasopressor or inotrope support. If not given already, a bolus of CaCl<sub>2</sub> should be used to prevent hyperkalemia-related arrhythmias. Subsequent uptake of K<sup>+</sup> by a working graft may then require aggressive replacement. Ongoing infusion of fluids, red cells, and blood products should be guided by clinical blood loss. Other goals are to maintain a hematocrit of 26% to 32% and to correct the coagulopathy as guided by coagulation testing. There is increasing interest in the role of cardiac output-guided fluid in the perioperative care of patients undergoing liver transplantation.<sup>238</sup>

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

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