

subjects given atropine (177–212 minutes) compared with those administered glycopyrrolate (82–111 minutes). Similar effects have been observed in healthy patients undergoing general anesthesia reversed with neostigmine and anticholinergics.¹³⁴ Neuromuscular blockade was antagonized with neostigmine 50 µg/kg and either atropine 20 µg/kg or glycopyrrolate 8 µg/kg. Two hours after giving neostigmine, patients given atropine had persistent impairment of baroreflex sensitivity and high-frequency heart rate variability, whereas these variables had returned to baseline values in patients receiving glycopyrrolate. These investigations demonstrate that the parasympathetic nervous system control of heart rate is less impaired by glycopyrrolate than by atropine.

BRONCHOCONSTRICION. Bronchospasm can occur after the administration of neostigmine in surgical patients.^{135,136} Anticholinesterases (e.g., neostigmine) stimulate muscarinic receptors in airway smooth muscle; stimulation of these receptors can provoke bronchoconstriction. Neostigmine and pyridostigmine induce a phosphatidylinositol response (a reflection of smooth muscle contraction induced by a muscarinic agonist) in airway muscle, which can result in bronchoconstriction.¹³⁷ This response was inhibited in the presence of atropine, a direct bronchodilator. Edrophonium did not induce a phosphatidylinositol response. In patients with cervical spinal cord injuries, neostigmine alone caused bronchoconstriction, whereas neostigmine combined with glycopyrrolate caused bronchodilation.¹³⁸ The risk of perioperative bronchospasm appears low if anticholinesterases are administered concurrently with anticholinergics.

SUGAMMADEX REVERSAL OF NEUROMUSCULAR BLOCKADE

Sugammadex (Org 25969) is a modified γ -cyclodextrin and the first selective relaxant-binding agent based on an encapsulating principle for inactivation of a neuromuscular blocking drug (*su* refers to sugar, and *gammadex* refers to the structural molecule γ -cyclodextrin). This principle for reversal of rocuronium- and vecuronium-induced neuromuscular blockade was first introduced into clinical practice in 2008 and is now available for pediatric and adult anesthesia in most countries worldwide, including the United States and China. The complex formation of sugammadex and rocuronium or vecuronium occurs at all levels of neuromuscular blockade (profound through shallow) and results in a more fast-acting pharmacologic reversal when compared with anticholinesterase drugs. Consequently, sugammadex may markedly reduce postoperative residual neuromuscular blockade in the PACU.¹³⁹

Structure-Activity Relationships and Mechanism of Action

The three natural unmodified cyclodextrins consist of six, seven, and eight cyclic oligosaccharides (i.e., dextrose units joined through one to four glycosyl bonds) and are called α -, β -, and γ -cyclodextrins, respectively.^{140,141} Their three-dimensional structure resembles a hollow, truncated cone or a doughnut. The structure has a hydrophobic cavity and hydrophilic exterior because of the presence of polar hydroxyl groups. Hydrophobic interactions trap the lipophilic

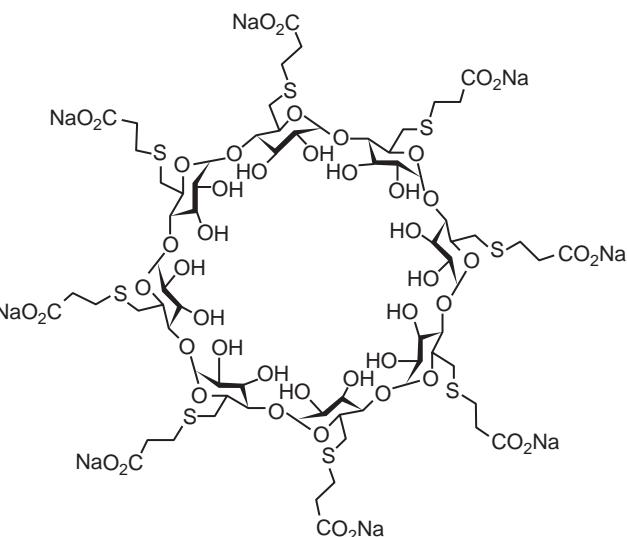


Fig. 28.15 Structure of the synthetic γ -cyclodextrin sugammadex (Org 25969). (From Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block. Chemical encapsulating of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem*. 2002;41:266–270.)

molecules in the cyclodextrin cavity, thereby resulting in the formation of a water-soluble guest-host complex. Sugammadex is built on this principle ring structure but is a modified γ -cyclodextrin. Although an unmodified γ -cyclodextrin possesses a larger lipophilic cavity (7.5–8.3 Å) than α - or β -cyclodextrins, it is still not deep enough to accommodate the larger rigid structure of the rocuronium molecule. Therefore the cavity is modified by adding eight side chains to extend it to 11 Å for better accommodation of the four hydrophobic steroid rings of rocuronium. Furthermore, at the end of these side chains, negatively charged carboxyl groups are added to enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium (Fig. 28.15).^{141,142} The stability of the rocuronium-sugammadex complex is a result of the combination of intermolecular forces (van der Waals forces), including thermodynamic (hydrogen bonds) and hydrophobic interactions.^{141–143} Sugammadex forms a rigid complex in a 1:1 ratio with steroid NMBDs (rocuronium and vecuronium) (Fig. 28.16).¹⁴¹ There is some binding affinity with pancuronium, but this interaction is too low to have a significant clinical effect. The molecular mass of the sugammadex-rocuronium complex is 2532 g/mol (sugammadex 2002 g/mol and rocuronium 530 g/mol), and that of the sugammadex-vecuronium complex is 2640 g/mol (vecuronium 638 g/mol).¹⁴¹ The rocuronium-sugammadex complex exists in an equilibrium with an association/dissociation rate of 1 molar concentration of sugammadex and rocuronium of 25,000,000:1, which means that sugammadex forms a very rigid complex and encapsulates rocuronium at 25 million times the rate that one molecule complex dissociates. The affinity of sugammadex toward vecuronium is 2.5 times smaller, but still high enough to form a tight complex.¹⁴¹ Rapid binding of rocuronium and sugammadex results in removal of free rocuronium molecules from the plasma. This creates a

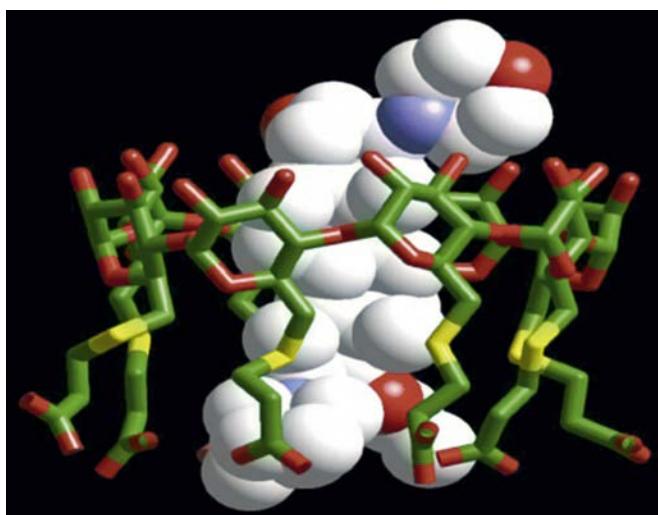


Fig. 28.16 The sugammadex-rocuronium complex. (From Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block. Chemical encapsulating of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem.* 2002;41:266–270.)

concentration gradient favoring movement of the remaining rocuronium molecules from the effect site at the neuromuscular junction into plasma, where the drug is encapsulated by free sugammadex molecules. Neuromuscular blockade is quickly reversed as rocuronium is removed from the binding sites at the neuromuscular junction. Sugammadex administration results in an increase in the total plasma concentration of rocuronium (free and that bound to sugammadex).¹⁴⁴ Because sugammadex acts as a selective binding agent and has no direct or indirect action on the molecular components of cholinergic transmission (cholinesterase, nicotinic receptors, or muscarinic receptors), the need for coadministration of anticholinergic drugs is eliminated.¹⁴⁵

Pharmacokinetics

The pharmacokinetic profile of sugammadex and rocuronium has been investigated in healthy volunteers and surgical patients.¹⁴⁶ Sugammadex, in a dose range of 0.1 to 8.0 mg/kg in healthy adult volunteers (without neuromuscular blockade), exhibited a dose-linear pharmacokinetic profile, a volume distribution of 18 L, an elimination half-life of 100 minutes, and a plasma clearance rate of 120 mL/min, with up to 80% of the dose being excreted in urine over 24 hours.¹⁴⁶ After encapsulation by sugammadex, rocuronium is less free to distribute to compartments other than those associated with the compartment in which sugammadex resides. During an infusion of rocuronium to maintain a stable depth of neuromuscular blockade, administration of sugammadex increased the measured plasma concentration of rocuronium; rocuronium redistributed from the effect compartment (including the neuromuscular junction) to the central compartment (mostly as the sugammadex complex) as it was encapsulated by sugammadex.¹⁴⁴ The volume of distribution of rocuronium decreases with increasing doses of sugammadex until the volume of distribution of rocuronium approaches the volume of distribution of sugammadex at higher doses.¹⁴⁴ Encapsulation changes the pharmacokinetics of rocuronium. In the absence of sugammadex, rocuronium is eliminated mainly by biliary excretion (>75%)

and to a lesser degree by renal excretion (10%-25%).¹⁴⁷ The main difference in the pharmacokinetic profile of sugammadex and rocuronium is that the clearance of sugammadex is approximately three times slower than that of rocuronium.¹⁴⁶ The rate and amount of urinary excretion of rocuronium when administered alone is slow and small, but when sugammadex (a dose of 2.0 mg/kg or more) is administered, the plasma clearance of rocuronium is decreased by a factor of more than two.¹⁴⁶ This decreased clearance occurs because the biliary route of excretion becomes unavailable for the rocuronium-sugammadex complex as the large size of this complex prohibits additional renal excretion. The clearance of rocuronium after binding by sugammadex decreases to a value approaching the glomerular filtration rate (120 mL/min).¹⁴⁷ However, the renal excretion of rocuronium is increased by more than 100% after administration of 4.0 to 8.0 mg/kg of sugammadex.¹⁴⁷ Following the administration of sugammadex, encapsulation of rocuronium in the plasma results in a rapid decrease in free rocuronium in this compartment, although the total plasma concentration of rocuronium (both free and bound by sugammadex) increases. This results in a concentration gradient between the relatively high level of free rocuronium in the effect compartment (the neuromuscular junction) and the low level in the plasma compartment.¹⁴⁴ As a result, free rocuronium molecules rapidly diffuse towards the plasma compartment and are encapsulated by sugammadex. Thus the increase in plasma levels of rocuronium after sugammadex administration illustrates the mechanism responsible for the rapid reversal of neuromuscular blockade by sugammadex.

Because renal excretion is the primary route for the elimination of sugammadex and the rocuronium-sugammadex complex, studies on elimination by dialysis have considerable relevance in clinical practice. In a small subset of patients with severe renal impairment, an investigation on dialysis showed that the clearance of sugammadex and rocuronium in blood was 78 and 89 mL/min, respectively. Therefore hemodialysis using a high-flux dialysis method is effective in removing sugammadex and the sugammadex-rocuronium complex in patients with severe renal impairment.¹⁴⁸

Pharmacodynamics

Clinical Use of Sugammadex in Healthy Patients

The first human exposure of sugammadex in male volunteers showed a large dose-dependent, more rapid recovery time from a rocuronium-induced neuromuscular blockade with sugammadex (0.1-8.0 mg/kg) as compared with placebo.¹⁴⁶ Administration of 8 mg/kg of sugammadex 3 minutes after a bolus dose of 0.6 mg/kg of rocuronium resulted in a recovery of the TOF ratio to 0.90 within 2 minutes compared with 52 minutes for placebo. Decreasing the dose of sugammadex to 4 mg/kg resulted in recovery of the TOF ratio to 0.90 in less than 4 minutes.¹⁴⁶ Similar recovery times were found in a study in which surgical patients received 0.6 mg/kg rocuronium, followed by different doses of sugammadex or placebo administered at a TOF count of 2.¹⁴⁹ Sugammadex reduced the median recovery time in a dose-dependent manner from 21 minutes in the placebo group to 1.1 minutes in the group receiving 4.0 mg/kg of sugammadex.¹⁴⁹ In another study, administration of sugammadex resulted in a more rapid and effective recovery from a rocuronium (0.6 mg/kg) or vecuronium

(0.1 mg/kg) neuromuscular blockade.¹⁵⁰ After a dose of 4.0 mg/kg of sugammadex, the mean recovery time to a TOF ratio of 0.90 was 1.1 minutes and 1.5 minutes after rocuronium and vecuronium, respectively (Figs. 28.17 and 28.18).¹⁵⁰ Reversal of neuromuscular blockade with larger doses of rocuronium (1.0–1.2 mg/kg) by different doses

of sugammadex (2.0–16.0 mg/kg) at different time points (3–15 minutes after rocuronium) showed a dose-dependent, rapid, and effective reversal compared with placebo.^{151–154}

Whereas anticholinesterase drugs, such as neostigmine, are unable to reverse deeper levels of neuromuscular blockade (e.g., posttetanic count of 1–2) because of a ceiling effect, sugammadex is effective in reversing profound neuromuscular blockade.^{152,155} Optimal doses of sugammadex of 4.0 mg/kg produced prompt recovery of the TOF ratio to 0.90 within minutes (Table 28.7).^{150–155} Therefore reversal of moderate and profound rocuronium and vecuronium neuromuscular blockades can be reliably achieved by administration of sugammadex, provided a dose of 2.0 and 4.0 mg/kg, respectively, is used. Because neostigmine has neuromuscular effects when given alone, some spontaneous recovery of the TOF should be evident before it is given. In contrast, sugammadex has no neuromuscular effects when given alone. Accordingly, sugammadex can be given even if there is no response to TOF stimulation. Sugammadex allows a profound neuromuscular blockade to continue until the end of surgery.

In contrast to the anticholinesterase drugs (e.g., neostigmine), intense neuromuscular blockade (no response to TOF and PTC stimulation) can be reversed by sugammadex immediately after the administration of rocuronium. In a multicenter investigation, patients were randomized to receive 1.2 mg/kg of rocuronium followed 3 minutes later by 16 mg/kg of sugammadex or a dose of 1.0 mg/kg of succinylcholine.¹⁵⁶ The mean time to 90% recovery of the first twitch (T1) from the start of sugammadex administration was 2.9 minutes and to a recovery of the TOF ratio to 0.90 was 2.2 minutes.¹⁵⁶ In contrast, the spontaneous recovery time from a succinylcholine neuromuscular blockade to 90% recovery of T1 was 10.9 minutes. Thus reversal of large doses of rocuronium with 16 mg/kg sugammadex was significantly faster than spontaneous recovery from succinylcholine (Fig. 28.19).¹⁵⁶ These findings were confirmed in a randomized trial that assessed how rapidly spontaneous ventilation could be reestablished after rapid sequence induction of anesthesia and intubation of the trachea, using either the combination of rocuronium (1.0 mg/kg)–sugammadex (16 mg/kg) or succinylcholine (1.0 mg/kg).¹⁵⁷ The median time from tracheal intubation to spontaneous ventilation was 406 seconds with succinylcholine and 216 seconds with rocuronium–sugammadex (Table 28.8).¹⁵⁷ These data demonstrated that sugammadex reversal of a large-dose rocuronium neuromuscular

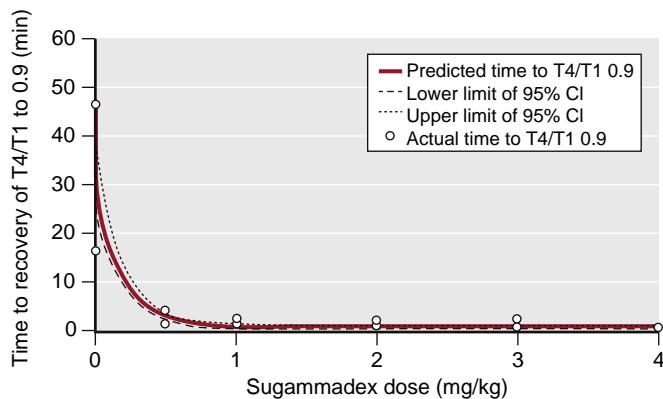


Fig. 28.17 The dose-response relation of sugammadex dose and time to recovery of the T4/T1 ratio to 0.9 with rocuronium 0.6 mg/kg. *T4/T1 ratio*, the degree of neuromuscular block. (From Suy K, Morias K, Cammu G, et al. Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *Anesthesiology*. 2007;106:283–288.)

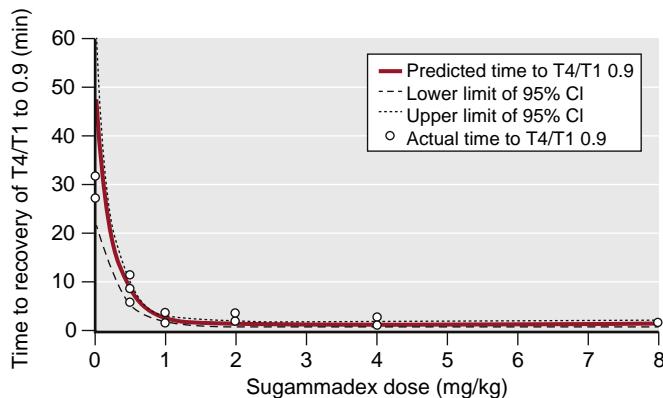


Fig. 28.18 The dose-response relation of sugammadex dose and time to recovery of the T4/T1 ratio to 0.9 with vecuronium 0.1 mg/kg. *T4/T1 ratio*, the degree of neuromuscular block. (From Suy K, Morias K, Cammu G, et al. Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *Anesthesiology*. 2007;106:283–288.)

TABLE 28.7 Recovery Times* of Reversal of a Rocuronium-Induced (1.2 mg/kg) Neuromuscular Blockade With Either Sugammadex or Placebo (NaCl 0.9%)

| | SUGAMMADEX | | | | | |
|-----------------|-------------------|-------------------|--------------------|--------------------|--------------------|-----------|
| Placebo (n = 4) | 2.0 mg/kg (n = 5) | 4.0 mg/kg (n = 5) | 8.0 mg/kg (n = 12) | 12.0 mg/kg (n = 7) | 16.0 mg/kg (n = 7) | |
| Mean (SD) | 122.1 (18.1) | 56.5 (5.4) | 15.8 (17.8) | 2.8 (0.6) | 1.4 (0.3) | 1.9 (2.2) |
| Median | 126.1 | 55.3 | 12.3 | 2.5 | 1.3 | 1.3 |
| Min-max | 96.8–139.4 | 50.5–65.1 | 3.3–46.6 | 2.2–3.7 | 1.0–1.9 | 0.7–6.9 |

*Recovery times (minutes) from the start of administration of sugammadex or placebo to recovery of the train-of-four ratio to 0.90. SD, Standard deviation.

From de Boer HD, Driessens JJ, Marcus MA, et al. Reversal of a rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex: a multicenter, dose-finding and safety study. *Anesthesiology*. 2007;107:239–244.

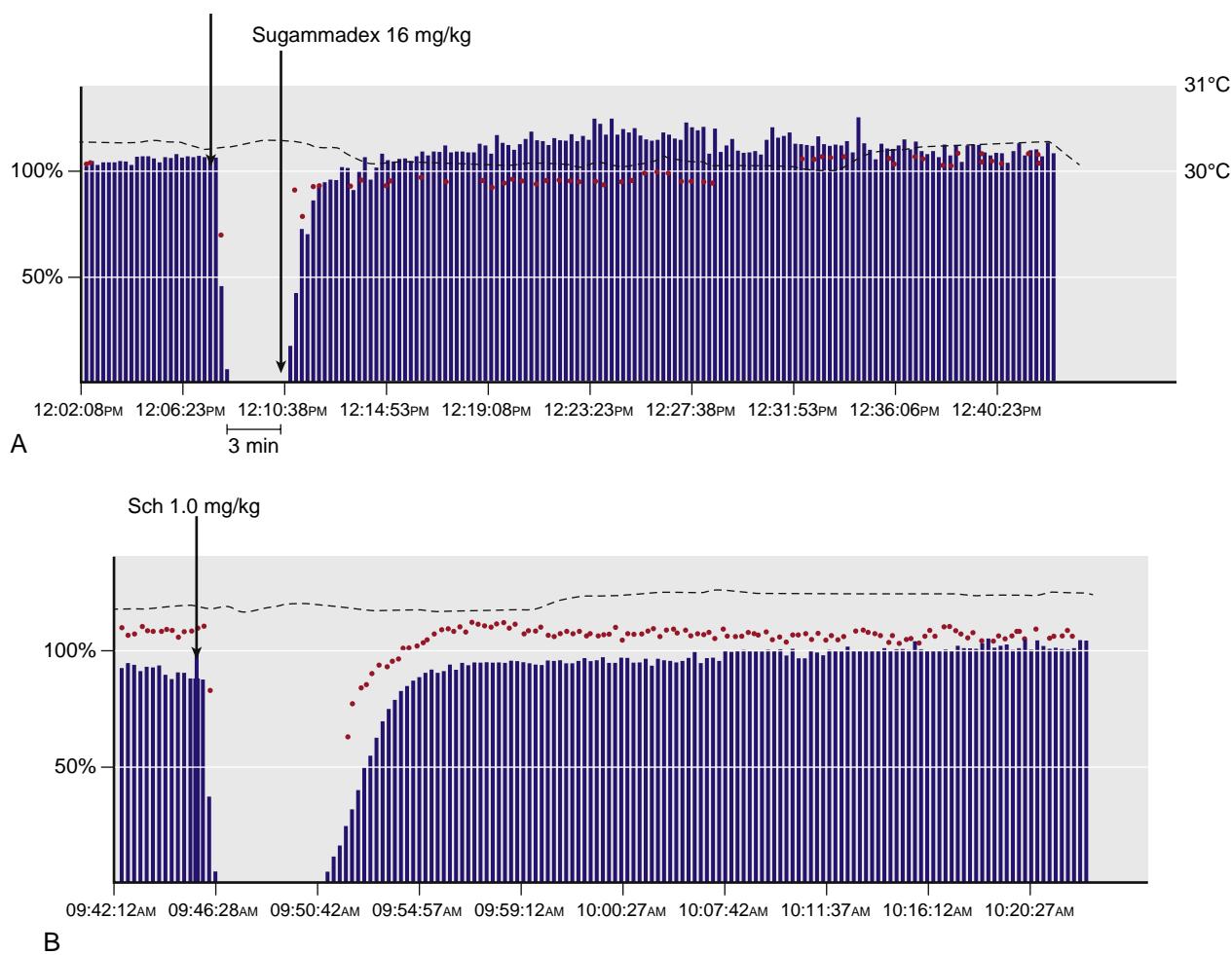


Fig. 28.19 (A) Recovery of T1 twitch height (blue tracings) and the train-of-four (TOF) ratio (red dots) after the administration of 1.2 mg/kg of rocuronium, followed 3 minutes later by 16 mg/kg of sugammadex, both given intravenously. Recovery to a first twitch height (T1) of 90% and a TOF ratio of 0.94 occurred 110 seconds later. The onset-offset time with this sequence (i.e., time from the end of the injection of rocuronium until T1 recovery to 90%) was 4 minutes, 47 seconds. (B) Effects of administering 1.0 mg/kg of succinylcholine (Sch) with spontaneous recovery to a T1 recovery to 90% occurring after 9 minutes, 23 seconds. Black dashed line represents hand skin temperature (°Celsius). (From Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg*. 2007;104:575–581.)

blockade was not only significantly faster than spontaneous recovery from succinylcholine, but that spontaneous ventilation could be restored more rapidly (i.e., this dose can be used to replace succinylcholine for endotracheal intubation). In clinical practice and during an unexpected difficult airway (cannot intubate, cannot ventilate scenario), a rocuronium neuromuscular blockade may be reversed by sugammadex immediately in order to restore spontaneous ventilation.

When sugammadex was compared with neostigmine or edrophonium, the time course of neuromuscular recovery was markedly different.^{158–160} In a clinical study, patients received 0.6 mg/kg of rocuronium after which neuromuscular blockade was sustained with supplemental boluses of rocuronium given at the reappearance of the second twitch (second response to TOF stimulation or T2).¹⁵⁸ Fifteen minutes after the last dose of rocuronium either 70 µg/kg of neostigmine, 1 mg/kg of edrophonium, or 4.0 mg/kg sugammadex was administered. The average time to achieve a TOF ratio of 0.90 was 10 times longer after the administration of neostigmine than it was after sugammadex (1044 seconds vs.

107 seconds) and 3 times longer after the administration of edrophonium (331 seconds). In another study by Blobner and associates, similar differences were found when comparing reversal of rocuronium at the reappearance of the second twitch in the TOF response using 2 mg/kg sugammadex versus neostigmine 50 µg/kg.¹⁵⁹ This was also confirmed in an investigation that assessed the efficacy of sugammadex versus neostigmine for reversal of profound rocuronium-induced neuromuscular blockade.¹⁶⁰ More than 97% of patients reversed with sugammadex (4.0 mg/kg) at a PTC of 1 to 2 recovered to a TOF ratio of 0.90 within 5 minutes. In contrast, 73% of the patients administered neostigmine (70 µg/kg) recovered between 30 and 60 minutes after administration, with 23% requiring more than 60 minutes to recover to a TOF ratio of 0.90 (Fig. 28.20).

A randomized trial compared the efficacy of sugammadex reversal of a rocuronium (0.6 mg/kg) neuromuscular blockade with that of neostigmine reversal of a cisatracurium (0.15 mg/kg) neuromuscular blockade.¹⁶¹ Time from the start of administration of reversal agent sugammadex 2.0 mg/kg or neostigmine 50 µg/kg to recovery of the TOF

TABLE 28.8 How Rapidly Can Spontaneous Ventilation Be Reestablished After a Rapid Sequence Induction and Intubation of Anesthesia Using Either Succinylcholine- or Rocuronium-Sugammadex

| | Succinylcholine (1 mg/kg) (n = 26) | Rocuronium (1 mg/kg) Sugammadex (16 mg/kg) (n = 29) | P-value |
|--|---------------------------------------|--|---------|
| Time from start of procedure to tracheal intubation (seconds) | 330 (313-351) | 324 (312-343) | .45 |
| Intubation conditions | | | .13 |
| Excellent | 20 (76%) | 27 (93%) | |
| Good | 6 (24%) | 2 (7%) | |
| Poor | 0 (0%) | 0 (0%) | |
| Intubation difficulty score | | | .23 |
| ≤5 | 24 (92%) | 28 (100%) | |
| >5 | 2 (8%) | 0 (0%) | |
| Time from tracheal intubation to spontaneous ventilation (seconds) | 406 (313-507) | 216 (132-425) | .002 |
| Time from tracheal intubation to T1 90% (seconds) | 518 (451-671) (n = 17) | 168 (122-201) (n = 27) | <.0001 |
| Time from injection of NMBD to T1 90% (seconds) | 719 (575-787) (n = 17) | 282 (242-319) (n = 27) | <.0001 |

*These data include tracheal intubation conditions, time to reappearance of spontaneous ventilation, and recovery of neuromuscular function from either succinylcholine or the combination of rocuronium-sugammadex.

From Sørensen MK, Bretlau C, Gätke MR, et al. Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine. A randomized trial. *Br J Anaesth.* 2012;108:682-689.

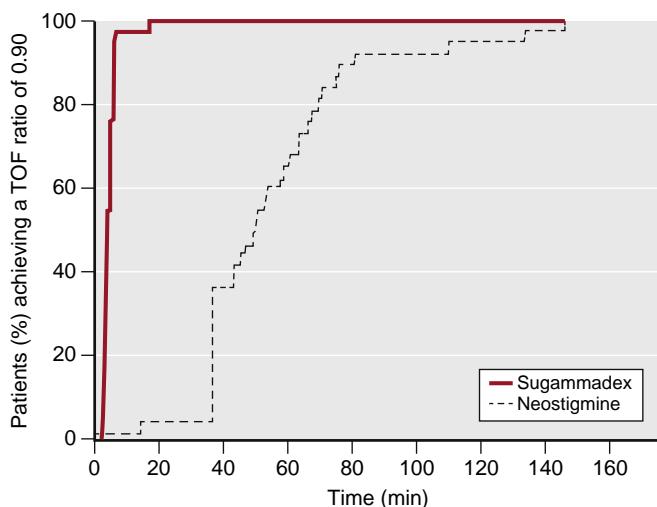


Fig. 28.20 Time to recovery of the train-of-four (TOF) ratio to 0.90 from profound rocuronium-induced neuromuscular blockade after administration of sugammadex 4 mg/kg or neostigmine 70 µg/kg. (From Jones RK, Caldwell JE, Brull SJ, et al. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology.* 2008;109:816-824.)

ratio to 0.90 was 4.7 times faster with sugammadex than with neostigmine, 1.9 versus 9.0 minutes, respectively.

Unlike with neostigmine or edrophonium, the choice of anesthetic (e.g., propofol vs. sevoflurane) does not influence the ability of sugammadex to reverse rocuronium-induced neuromuscular blockade.^{162,163} Provided that sugammadex is used in recommended dosages according to the level of neuromuscular blockade, a small risk exists of incomplete neuromuscular recovery or reoccurrence of neuromuscular blockade following surgery.

Clinical Use of Sugammadex in Pediatric and Older Adult Patients

PEDIATRICS. The use of sugammadex in pediatric patients was examined in a study enrolling 8 infants (28 days to 23 months), 24 children (2-11 years), and 31 adolescents (12-17 years).¹⁶⁴ Patients were anesthetized with propofol and opioids and received rocuronium 0.6 mg/kg. At the reappearance of T2 (second twitch), patients were given sugammadex 0.5, 1.0, 2.0, or 4.0 mg/kg or placebo. Recovery time to a TOF ratio of 0.90 decreased in a dose-dependent manner in all age groups. Residual neuromuscular blockade or recurarization was not observed, and no side effects were reported. In a more recent case report, sugammadex was used successfully in reversing a vecuronium-induced neuromuscular blockade in a 7-month-old infant.¹⁶⁵ Another case report described a 2-year-old patient who received readministration of rocuronium for reoperation after an initial successful reversal with sugammadex.¹⁶⁶ A recent systematic review showed that compared with neostigmine or placebo, sugammadex can reverse a rocuronium-induced neuromuscular blockade more rapidly with lower incidence of bradycardia.¹⁶⁷

While sugammadex can be used safely in children and adolescents (2-17 years old), information on the use of sugammadex in pediatric patients less than 2 years old is still limited.

OLDER ADULT PATIENTS. Reversal of neuromuscular blockade by sugammadex has been assessed in older patients. One hundred and fifty patients were divided into three groups: an adult group (18-64 years old), an older adult group (65-75 years old), and an oldest adult group (75 years or older).¹⁶⁸ Patients received an intubating dose of rocuronium 0.6 mg/kg with maintenance doses of 0.15 mg/kg as required. Sugammadex 2.0 mg/kg was administered after the last dose of rocuronium at the

TABLE 28.9 Rocuronium Recovery Time (min) from the Administration of Sugammadex (2 mg/kg at Appearance of T2) Until the Recovery of Train-of-Four Ratios as Indicated in Patients With and Without Renal Failure

| | PATIENT GROUP | | Anova |
|--------------------------------------|--|--|-------|
| | $CL_{CR} < 30 \text{ mL/min}$ (n = 15) | $CL_{CR} \geq 80 \text{ mL/min}$ (n = 14)* | |
| Recovery to TOF ratio 0.7, mean (SD) | 1.45 (0.47) | 1.17 (0.38) | NS |
| Recovery to TOF ratio 0.8, mean (SD) | 1.60 (0.57) | 1.32 (0.45) | NS |
| Recovery to TOF ratio 0.9, mean (SD) | 2.00 (0.72) | 1.65 (0.63) | NS |

ANOVA, Analysis of variance; CL_{CR} , total plasma creatinine clearance; NS, not significant; SD, standard deviation; TOF, train-of-four.

*One patient was excluded from the control group (normal renal function) because of unreliable TOF traces.

From Staals LM, Snoeck MM, Driessen JJ, et al. Multicenter, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function. *Br J Anaesth.* 2008;101:492–497.

reappearance of T2. Recovery of neuromuscular blockade by sugammadex was slightly (0.7 minutes) faster in patients younger than 65 years of age. In general, a prolonged circulation time secondary to a reduced cardiac output in older patients was anticipated to result in a longer recovery time from neuromuscular blockade after administration of sugammadex.^{169,170} However, based on these results, no dose adjustments are needed in older patients.¹⁶⁸ Yet, if it is necessary to achieve a fast recovery in a short period of time, a higher dose of sugammadex might be considered.¹⁷¹

Clinical Use of Sugammadex in Special Patient Populations

CARDIAC DISEASE. Studies evaluating the safety and efficacy of sugammadex in patients with underlying cardiovascular disease have not demonstrated an effect of sugammadex on electrocardiogram (no indication of a possible prolongation effect on the QTc interval).^{172,173} A study designed to evaluate the effects of sugammadex on QTc prolongation in healthy subjects (in doses up to 32 mg/kg, alone or in combination with rocuronium or vecuronium) revealed that the administration of sugammadex was not associated with QTc prolongation.¹⁷³ In a case report of a patient with long QT syndrome, a vecuronium neuromuscular blockade was reversed with sugammadex 2 mg/kg without adversely affecting the QT interval.¹⁷⁴ Based on current data, sugammadex reversal is not associated with cardiovascular side effects in healthy patients or in those with cardiovascular comorbidities (also see earlier section Complications Associated With Inhibitors of Acetylcholinesterase).

PULMONARY DISEASE. Patients with a history of pulmonary disease have an increased risk of postoperative pulmonary complications such as pneumonia, respiratory failure, and exacerbation of the underlying pulmonary disease.¹⁷⁵ Sugammadex has been studied in patients with pulmonary disease.¹⁷⁵ Seventy-seven surgical patients with a diagnosis or known history of pulmonary disorders received sugammadex in doses up to 4 mg/kg in order to reverse a rocuronium neuromuscular blockade. As in other adult patient groups, reversal of a rocuronium-induced neuromuscular blockade was rapid, and there were no signs of residual neuromuscular blockade or recurarization.¹⁷⁶ Of the 77 patients treated with sugammadex, 2 patients developed bronchospasm, 1

minute and 55 minutes respectively, after the administration of sugammadex. Both patients were asthmatic, and there was no evidence that these symptoms were related to sugammadex. In other subsets of high-risk pulmonary patients (cystic fibrosis and end-stage lung disease), the successful use of sugammadex has been reported.¹⁷⁷ Reversal of a neuromuscular blockade with sugammadex has potential advantages compared with anticholinesterase drugs (e.g., neostigmine) in patients with pulmonary disease because sugammadex lacks interactions with the muscarinic cholinergic system, and there is no need for coadministration of anticholinergic compounds (also see section, Complications Associated With Inhibitors of Acetylcholinesterase).

RENAL FAILURE. The use of sugammadex to reverse rocuronium neuromuscular blockade was investigated in 15 patients with severe renal impairment (creatinine clearance <30 mL/min) and compared with 15 patients with normal renal function (creatinine clearance >80 mL/min).¹⁷⁸ Sugammadex 2 mg/kg was administered at the reappearance of T2. There were no differences between groups in the recovery profile or the incidence of residual blockade after sugammadex (Table 28.9). In another study, the reversal of a rocuronium-induced deep neuromuscular blockade with sugammadex 4.0 mg/kg in patients with severe renal impairment (creatinine clearance <30 mL/min) showed a fast and stable reversal.¹⁷⁹ Sugammadex and sugammadex-rocuronium complex exposure is increased in patients with moderate and severe renal failure due to the decreased renal clearance.¹⁸⁰ The use of sugammadex in renal transplantation was described in two cases in which sugammadex was used for reversal of a rocuronium-induced neuromuscular block in pediatric patients and showed a fast and complete reversal without signs of residual neuromuscular blockade or recurarization.¹⁸¹ More recently, the long-term efficacy and safety of rocuronium and sugammadex in patients undergoing renal transplantation were described in 57 patients diagnosed with severe renal failure.¹⁸² Rocuronium and sugammadex appeared to be efficacious and safe in patients undergoing renal transplantation. Because complete elimination of the sugammadex-rocuronium complex remains poorly understood in renal impairment, sugammadex is at present not recommended for use in patients with severe renal failure. However, it can be used in patients with mild or moderate renal

dysfunction as its safety profile is similar to that of healthy patients.¹⁷⁸ Theoretically, because of the molecular mass of the rocuronium/vecuronium-sugammadex complex, it is possible to decrease the plasma levels of this complex by dialysis. Hemodialysis using a high-flux dialysis method has been demonstrated to be effective in removing sugammadex and the sugammadex-rocuronium complex in patients with severe renal impairment.¹⁴⁸

HEPATOBILIARY DISEASE. Sugammadex has not been studied in animal models or in patients with hepatic impairment. However, it is known that the biliary route of excretion becomes unavailable for either sugammadex or the rocuronium/vecuronium-sugammadex complex because the large size of this complex prohibits such excretion.¹⁸³ A population pharmacokinetic/pharmacodynamic (PK-PD) model was used to simulate the scenario of an immediate reversal, and reversal of a profound rocuronium-induced neuromuscular blockade in patients with hepatic impairment.¹⁸³ Under such study conditions, hepatic impairment had little effect on the reversal time when sugammadex (16 mg/kg) was administered 3 minutes after rocuronium (1.2 mg/kg). However, in other scenarios (sugammadex 2 mg/kg at reappearance of T2 and 4 mg/kg after 15 minutes), recovery from a rocuronium-induced (1.2 mg/kg) neuromuscular blockade was predicted to be longer than that seen in healthy patients.¹⁸³ In patients with hepatobiliary disease, the recovery of neuromuscular function after sugammadex administration will likely be faster than reversal with anticholinesterase drugs (but not be as rapid as patients without hepatobiliary disease). The explanation of the slower reversal is not yet fully understood and needs to be investigated in clinical studies. Based on limited available data, sugammadex should be used with caution in patients with hepatobiliary disease.

OBESITY. Patients with obesity, particularly morbid obesity (body mass index [BMI] > 40 kg/m²), are at risk for cardiovascular and respiratory complications perioperatively.¹⁸⁴ These patients are susceptible to critical respiratory events in the postoperative period, including hypoventilation, hypoxia, airway obstruction, and acute respiratory failure.^{38,68} The presence of postoperative residual neuromuscular blockade may further increase the risk for postoperative complications in these patients by producing impairment of the integrity of the upper airway and upper airway collapse.^{33,34} Therefore a rapid and complete reversal of neuromuscular blockade must be achieved before tracheal extubation is attempted. In this setting, sugammadex may have a more favorable recovery profile than traditional anticholinesterase drugs because it provides a more reliable recovery of neuromuscular functions and a less frequent risk of incomplete neuromuscular recovery.¹⁸⁴ A key issue is determining the appropriate dose of sugammadex to administer in a morbidly obese patient that is sufficient to capture remaining NMBD molecules. Whereas the dosing of NMBDs in obese patients should be based on lean/ideal body weight (because these drugs are hydrophilic and their volume of distribution is minimally affected by obesity), the dosing of sugammadex in obese patients is currently under debate. In order to ensure complete neuromuscular recovery, the dose of sugammadex must be sufficient to affect the gradient between the peripheral and central compartments and effectively encapsulate all rocuronium molecules. An

inadequate dose of sugammadex may be incapable of sustaining this redistribution of rocuronium and lead to reoccurrence of the neuromuscular blockade.

The current product monograph recommends calculating the sugammadex dose based on the patient's actual body weight. However, because the low volume of distribution at steady state (estimated at 0.16 L/kg) restricts distribution to the intravascular space, it might be relevant to determine the dose of sugammadex based on the lean/ideal body weight and not on the actual body weight.¹⁷⁸ However, in a recently published pooled analysis (27 trials) on the use of sugammadex in patients with obesity (BMI > 30 kg/m²), the authors concluded that the recommended dose on actual body weight provided rapid recovery from neuromuscular blockade in both obese and nonobese patients and that no dose adjustments should be undertaken in the obese patient.¹⁸⁵ Several studies have investigated the dosage of sugammadex based on lean or variations on the lean/ideal body weight.¹⁸⁶⁻¹⁸⁹ In one investigation, a sugammadex dose of 4 mg/kg based on a lean/ideal body weight calculation was administered to morbidly obese patients during a profound rocuronium neuromuscular blockade.¹⁸⁸ Approximately 40% of these patients were inadequately reversed with a lean/ideal body weight-based dose of sugammadex. In these patients, an additional dose of sugammadex 2 mg/kg based on lean/ideal body weight was required to achieve a TOF ratio 0.90. The conclusion of the authors was that a sugammadex dose calculated according to lean/ideal body weight was insufficient for reversing both profound and moderate blockade in a considerable number of morbidly obese patients.¹⁸⁸

In another study in morbidly obese patients, investigators examined reversal of a moderate level of a rocuronium neuromuscular blockade (at T1-T2) using a dose of sugammadex of 2.0 mg/kg.¹⁸⁷ Four different weight corrections were used: lean/ideal body weight, lean/ideal body weight +20%, lean/ideal body weight +40%, and actual body weight. This study demonstrated that a moderate rocuronium neuromuscular blockade could be effectively reversed with sugammadex 2.0 mg/kg using the calculation lean/ideal body weight + 40%.¹⁸⁷ In a more recent study, these findings were confirmed.¹⁹⁰ However, longer and larger interindividual variability of recovery times occur when dosing is based on lean/ideal body weight compared with dosing based on actual body weight.^{187,188} Additionally, reoccurrence of neuromuscular blockade after suboptimal dosing of sugammadex has been reported in a morbidly obese patient.¹⁸⁹ Hence until more data are available, the dose of sugammadex should be based on the actual body weight.

CESAREAN SECTION AND PREGNANT PATIENTS. Induction of general anesthesia in late pregnancy and for patients undergoing cesarean section typically involves a rapid sequence induction of anesthesia with either thiopental or propofol and a rapid-onset NMBD. For decades, succinylcholine has been the prototypic NMBD used in these procedures to produce optimal endotracheal intubation conditions.¹⁹¹ Rocuronium is an acceptable alternative to succinylcholine in rapid sequence induction of anesthesia procedures; rocuronium in doses larger than 1.0 mg/kg not only provides onset of action within 60 seconds, but also provides identical intubation conditions compared with succinylcholine.¹⁹² However, the duration of action of rocuronium

in dosages of 1.0 mg/kg or greater will result in a profound neuromuscular blockade of long duration (often more than 2 hours). Furthermore, the risk of failed intubation in the obstetric population is at least eight times higher compared with nonpregnant females.¹⁹³ In case of a failed endotracheal intubation scenario or a “cannot intubate, cannot ventilate” situation, rocuronium, even in dosages up to 1.2 mg/kg, can be immediately reversed with sugammadex 16 mg/kg.¹⁵⁶

Preclinical animal data demonstrated that uteroplacental transfer of sugammadex is very small (<2% to 6%). Sugammadex does not have negative effects on pregnancy or on embryonic, fetal, or postnatal development.^{191,194,195} Although no data are available about the excretion of sugammadex in human breast milk, excretion in breast milk is likely minimal, with insignificant clinical impact because oral absorption of cyclodextrins in general is small. Therefore sugammadex can be used in breastfeeding females. In two case series examining obstetric patients who received rocuronium and sugammadex (7 and 18 patients), no side effects were observed.^{194,195} The efficacy and safety of sugammadex in obstetric anesthesia have not been determined; yet serious adverse events for the mother or the neonate have not been reported after sugammadex.

NEUROMUSCULAR DISORDERS. Neuromuscular disorders are frequently associated with an increased incidence of perioperative respiratory complications due to muscle weakness.^{196,197} In these patient groups, administration of succinylcholine is often contraindicated and associated with potentially life-threatening side effects. The use of non-depolarizing NMBDs can on occasion be associated with prolonged spontaneous neuromuscular recovery, even after a single dose. Consequently, these patients have an increased risk for postoperative muscle weakness of multifactorial origin, one being residual neuromuscular blockade.^{196,197} Prompt recovery of neuromuscular function is essential to optimize patient safety and reduce the risk of pulmonary complications. However, reversal with anticholinesterase (e.g., neostigmine), especially in neuromuscular disorders, can be associated with postoperative complications.¹⁹⁷

Multiple case reports and case series describe the use of sugammadex in patients with various neuromuscular disorders such as myasthenia gravis, myotonic dystrophy, and spinal muscular atrophy (Fig. 28.21).¹⁹⁷⁻²⁰⁴ In general, dosing regimens for sugammadex were consistent with recommended doses adjusted to actual body weight and based on the level of neuromuscular blockade at the time of reversal. Sugammadex administration resulted

in prompt reversal of neuromuscular blockade with a similar recovery profile as observed in normal patients. Although no studies have been performed in patients with neuromuscular disorders, the reported cases indicate that sugammadex should be considered as an alternative reversal drug (e.g., instead of neostigmine) in this patient population. These observations need to be confirmed in a larger series of patient studies.

Side Effects and Drug Interactions

Sugammadex is contraindicated in patients with known hypersensitivity to the drug. The potential for hypersensitivity is reported in several case reports. Hypersensitivity is a concern; however, this is difficult to study because hypersensitivity reactions occur rarely. In a recent retrospective analysis, the incidence of potential sugammadex-induced anaphylaxis at a single center over a period of 3 years was investigated. The overall incidence of intraoperative hypersensitivity was 0.22% (95% CI, 0.17%–0.29%), and the incidence of anaphylaxis was 0.059% (95% CI, 0.032%–0.10%). In total 15,479 patients were exposed to sugammadex in the study period and the incidence of anaphylaxis associated with sugammadex administration was 0.039% ($n = 6$; 95% CI, 0.014%–0.084%).²⁰⁵ Prospective studies are needed to confirm the sugammadex anaphylaxis. Elevation of serum tryptase (positive predictive value of 93%, negative predictive value of 54%), skin testing (gold standard), and histamine levels in serum and urine are useful to confirm the diagnosis. Recently, a promising test, the basophil activation test, has been established to detect the causative compound of anaphylaxis with high specificity and sensitivity. However, more studies are needed to confirm this method to identify sugammadex-induced anaphylaxis.²⁰⁶

Other reported side effects include coughing, movement, parosmia (abnormal sense of smell), and elevated levels of *N*-acetyl-glucosaminidase in the urine.¹⁸³ Coughing and movement after the administration of sugammadex may have been due to the unmasking of inadequate anesthesia rather than a direct side effect of sugammadex. Initial studies showed a prolongation of activated partial thromboplastin and prothrombin time in healthy volunteers after sugammadex administration. However, in a more in-depth patient study that investigated the effect of sugammadex on postsurgical bleeding and coagulation variables, it was shown that sugammadex produced a limited, transient (<1 hour) increase in activated partial thromboplastin and

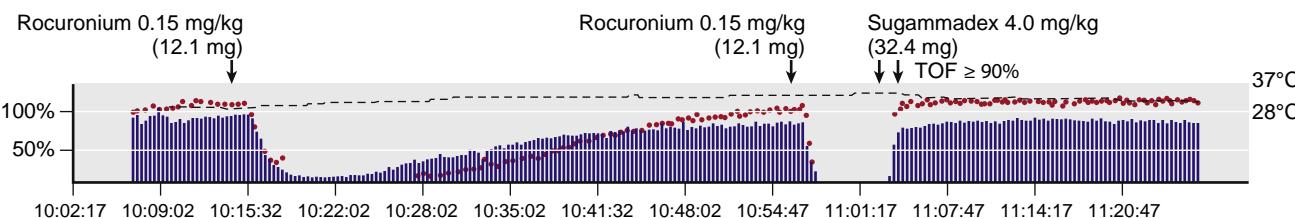


Fig. 28.21 Original tracing of sugammadex reversal in a patient with myasthenia gravis. The time to spontaneous recovery from the first profound rocuronium-induced neuromuscular blockade to a train-of-four (TOF) ratio was 36.5 minutes. The time from the start of the administration of sugammadex 4.0 mg/kg after the second dose of rocuronium to the recovery of the TOF ratio to 0.90 was 2.7 minutes. Blue tracings represent T1 recovery while red dots represent TOF ratio recovery. Black dashed line indicates hand skin temperature (degrees Celsius). (From de Boer HD, van Egmond J, Driessen JJ, et al. A new approach to anesthesia management in myasthenia gravis: reversal of neuromuscular blockade by sugammadex. *Rev Esp Anesthesiol Reanim*. 2010;57:81–84.)

prothrombin time but was not associated with increased risk of bleeding versus usual care.²⁰⁷

Cyclodextrins are a class of agents well known for their ability to form inclusion complexes with other compounds. Sugammadex forms a very tight complex with rocuronium or vecuronium in a 1:1 molecular ratio; however, because of its mechanism of action, it is possible that other relevant drug interactions may occur.²⁰⁸ Theoretically, two important drug interactions can take place. First, sugammadex is capable of encapsulating endogenous or pharmaceutical molecules other than steroid NMBDs, resulting in reduced efficacy of the encapsulated molecules. However, the ability to form complexes with steroid or nonsteroidal molecules such as cortisone, atropine, and verapamil is clinically insignificant because the affinity for sugammadex is 120 to 700 times less than that of rocuronium.²⁰⁸ In preclinical studies, an interaction of sugammadex with other steroid compounds could be excluded up to a dose of sugammadex of 500 mg/kg/day.²⁰⁹ Second, if the affinity of sugammadex for another molecule is very high, this molecule may displace rocuronium or vecuronium from the complex with sugammadex, resulting in reoccurrence of neuromuscular blockade. Both drug interactions may have potential clinical safety implications.²⁰⁸ A modeling approach has been developed to evaluate 300 compounds (including the most commonly used drugs in the perioperative period) for possible displacement interactions with sugammadex.²⁰⁸ In this screening, three compounds were identified as having possible displacement interactions: toremifene, fusidic acid, and flucloxacillin.²⁰⁸ However, no clinically relevant reoccurrence of neuromuscular blockade was identified when sugammadex was used in combination with these drugs.²⁰⁸ A clinical study reported that flucloxacillin did not cause reoccurrence of neuromuscular blockade after reversal with sugammadex; no clinically important displacement interaction was observed.²¹⁰

Special Considerations

Reintubation of the Trachea After Initial Reversal of Neuromuscular Blockade With Sugammadex. Patients receiving sugammadex before extubation of the trachea who need reintubation require special consideration because the remaining circulating sugammadex molecules may potentially interfere with readministration of rocuronium or vecuronium. In this setting, two alternate strategies can reestablish a neuromuscular blockade. Within 24 hours of sugammadex administration, it is currently recommended that a nonsteroidal NMBD be used instead of rocuronium or vecuronium. This conservative approach is based on the maximum clearance time for sugammadex. However, pre-clinical and clinical studies have shown that it is possible to safely reestablish neuromuscular blockade with rocuronium earlier than 24 hours.²¹¹ A modeling-based study in healthy volunteers revealed that high-dose rocuronium given 5 to 60 minutes after sugammadex reversal produced a complete neuromuscular blockade (T1 = 0%).²¹² Rocuronium (1.2 mg/kg) administered 5 minutes after sugammadex reversal produced a rapid onset of neuromuscular blockade (T1 = 0%), with a mean onset time of approximately 3 minutes. Thirty minutes after administration of sugammadex, an onset time of 1.5 minutes can be achieved with rocuronium

(1.2 mg/kg). Hence an inverse relationship exists between the onset time and the time interval between sugammadex and the repeat dose of rocuronium, and a direct relationship exists between the duration of neuromuscular blockade and the time interval between sugammadex and the repeat dose of rocuronium.

Based on dose calculations using a model in which the equilibrium is described in the common volume of distribution of rocuronium and sugammadex, even a second reversal is possible using sugammadex with large doses between 8 and 20 mg/kg.²¹¹

Incomplete Reversal of Neuromuscular Blockade.

Although sugammadex encapsulates rocuronium and vecuronium to form a rigid complex, case reports have described incomplete reversal of neuromuscular blockade.^{151,213} In a dose-finding study, a case was described in which a temporary decrease in the TOF response was observed in a healthy patient after reversal with 0.5 mg/kg sugammadex.²¹³ The TOF ratio initially reached 0.70 before decreasing to 0.30 and then gradually increasing to 0.90 (Fig. 28.22). The authors hypothesized that the decrease in TOF ratio occurred because of redistribution of unbound rocuronium from the peripheral compartments, with insufficient sugammadex available for additional encapsulation of rocuronium. Similarly, incomplete reversal was reported in two healthy patients given suboptimal doses of sugammadex (0.5 mg/kg) during profound rocuronium-induced neuromuscular blockade.¹⁵¹ In a study by Duvaldestin and associates, reversal of deep neuromuscular blockade with a low dose of sugammadex (0.5 and 1.0 mg/kg) found that five patients experienced recurrence of neuromuscular blockade.¹⁶³ In another study, both speed of reversal and effectiveness of sugammadex are dose-dependent; a single dose of 1.0 mg/kg of sugammadex ($n = 15$) administered at a deep neuromuscular blockade (PTC = 1) required

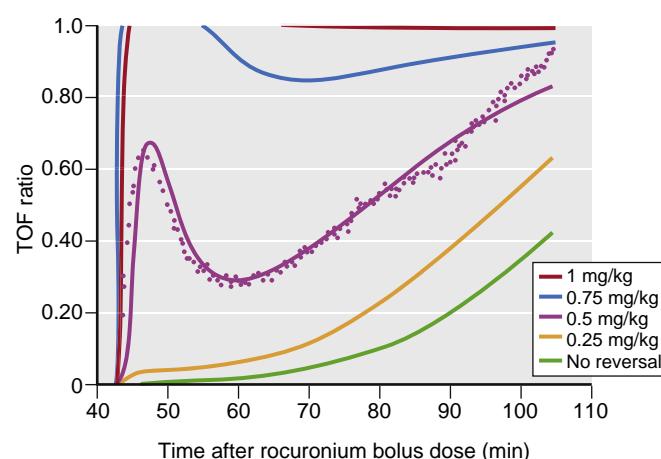


Fig. 28.22 The train-of-four data (dots) and the results of simulations (solid lines) of various sugammadex dosing amounts. Muscle relaxation rebound only occurs for sugammadex doses in a limited range. The simulations indicate that for this patient, doses larger than about 1 mg/kg are sufficient to achieve rapid muscle relaxation reversal and avoid muscle relaxation rebound. TOF, train-of-four. (From Eleveld DJ, Kuizenga K, Proost JH, et al. A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex. *Anesth Analg*. 2007;104:582–584.)

significantly longer time for reversal than a dose of 4.0 mg/kg ($n = 60$).²¹⁴ Interestingly, seven patients also exhibited residual ($n = 3$) and recurrence ($n = 4$) of neuromuscular blockade in the group of patients that received 1.0 mg/kg sugammadex. No patients who received the recommended dose of 4.0 mg/kg sugammadex had residual or reactivation of neuromuscular blockade. A similar pattern was observed with vecuronium-induced neuromuscular blockade. A longer reversal time and a higher incidence of residual and/or recurrence of neuromuscular blockade were noted in patients who received smaller (0.5 and 1.0 mg/kg) doses of sugammadex.²¹⁵ Therefore it is recommended that the dose be adjusted to the depth of neuromuscular blockade as underdosing of sugammadex is associated with an increased risk of residual neuromuscular blockade or recurrence of neuromuscular blockade.

Female Patients. Sugammadex may interact with hormonal contraceptive drugs. Possible capturing interactions, whereby unwanted encapsulation of a third drug by sugammadex reduces its clinical efficacy, have been investigated. In pharmacokinetic-pharmacodynamic simulations, it was predicted that 34% of (free) etonogestrel might be captured by 4 mg/kg sugammadex under very conservative modeling assumption conditions.²⁰⁹ The interaction with this bolus dose of sugammadex resulted in a decrease in etonogestrel exposure, which was similar to the decrease seen after one missed daily dose of an oral contraceptive. Patients using hormonal contraceptives should be informed about the possible reduced effectiveness of hormonal contraceptive drugs after the administration of sugammadex. The use of an additional nonhormonal contraceptive method for the next 7 days should be considered in this patient population.

Electroconvulsive Therapy. Electroconvulsive therapy is the transcutaneous application of small electrical stimuli to the brain for treatment of selected psychiatric disorders like major depression. The tonic-clonic convulsions associated with electroconvulsive therapy can result in injuries such as limb fractures and compression fractures of vertebral bodies. The introduction of anesthesia, especially neuromuscular blockade, can mitigate tonic-clonic motor activity and reduce the physiologic trauma associated with uncontrolled tetanic muscle contractions.²¹⁶ Succinylcholine is commonly used as a NMBD in these patients, and its use is associated with well-known unwanted side effects.²¹⁶ Rocuronium has similar efficacy as succinylcholine in electroconvulsive therapy, making it an appropriate alternative to succinylcholine.²¹⁷ However, the increased doses of rocuronium required to decrease the onset time are associated with a prolonged duration of neuromuscular blockade. Several reports have evaluated the use of sugammadex in electroconvulsive therapy. These investigations demonstrated that sugammadex produced a complete and rapid reversal of neuromuscular blockade induced by rocuronium, without signs of residual blockade or other safety concerns.²¹⁷⁻²²⁰ Therefore the combination of rocuronium and sugammadex may be an alternative to succinylcholine for electroconvulsive therapy. However, the required dose of sugammadex in this clinical situation is not well established.

Historically, an important strategy in anesthesia has been to ensure that neuromuscular blockade is sufficiently recovered to achieve adequate antagonism by neostigmine. Having an intense neuromuscular blockade at the end of surgery would more likely result in residual blockade. With the availability of sugammadex, a profound, or deep, neuromuscular blockade has been recommended for the entire duration of laparoscopy. A profound neuromuscular blockade increases surgical space with smaller pressures for the pneumoperitoneum.²²¹ It is even possible that reducing insufflation pressures may improve patient outcomes.²²¹ Furthermore, Staehr-Rye and associates²²² have postulated that a deep or profound neuromuscular blockade is associated with more optimal surgical conditions, which leads to less postoperative pain and nausea and vomiting. A recent review and metaanalysis has shown that deep neuromuscular blockade during laparoscopic surgical procedures allows lower insufflation pressure, thereby improving surgical conditions and reducing postoperative pain.²²³ Sugammadex, at doses of 2 to 8 mg/kg, was given to reverse the blockade when the TOF ratio was less than 0.90.

A recently published report describes the clinical experience in Japan.²²⁴ Notably, although neuromuscular blockade was not routinely monitored intraoperatively, the TOF ratio was determined after tracheal extubation. A total of 249 patients were studied in three separate groups. Patients with spontaneous recovery ($n = 23$) were compared with patients being reversed with either neostigmine ($n = 109$) or sugammadex 2.7 mg/kg ($n = 117$). Although the sugammadex group had the least frequent incidence of residual neuromuscular blockade, all three groups had a surprisingly frequent incidence of residual neuromuscular blockade.²²⁴

A scholarly editorial written by Naguib and associates²²⁵ placed prime emphasis on the dose of sugammadex used for reversal in combination with the lack of neuromuscular monitoring. Although proper monitoring is strongly advisable, an adequate dose of sugammadex is under current debate. Although the reversal effect of neostigmine is not improved by increasing the dose above the recommended dose interval, there are strong reasons to believe that sugammadex in doses larger than 2.7 mg/kg would be more effective for reversal. Others argue that a dose of sugammadex larger than 2.0 mg/kg would not be necessary if proper monitoring were used. Of course, another possibility exists. It would seem that a larger dose of sugammadex plus neuromuscular monitoring would be ideal.

In conclusion, sugammadex provides a novel concept in reversal of neuromuscular blockade. Although the expense of sugammadex continues to be an important factor that may limit its use, many institutions currently use sugammadex for routine reversal of neuromuscular blockade. We speculate whether, in the future, larger doses of sugammadex will likely be used and whether routine neuromuscular monitoring will finally be mandatory in anesthetic practice among countries worldwide.

CYSTEINE REVERSAL OF FUMARATE NEUROMUSCULAR BLOCKING DRUGS

A new class of nondepolarizing NMBDs called fumarates has been recently developed. These NMBDs are olefinic

(double-bonded) isoquinolinium diester compounds that differ from symmetric benzylisoquinolines such as mivacurium in their unique method of inactivation. The developed drugs (gantacurium [GW280430A, AV430A], CW002, and CW011) bind to L-cysteine to form less active degradation products (Fig. 28.23). The administration of L-cysteine can rapidly inactivate fumarate compounds and reverse neuromuscular blockade.

Gantacurium is an asymmetric α -chlorofumarate that was developed to be a replacement for succinylcholine.²²⁶ Gantacurium has a rapid onset and short duration of effect. The brief duration of gantacurium is primarily due to rapid reaction and subsequent inactivation of the drug with free cysteine in the plasma. The process of adduction of cysteine

to gantacurium occurs at the central fumarate double bond. The adduction changes the stereochemistry of gantacurium so that it can no longer bind to the nAChR at the neuromuscular junction. Degradation also occurs through a slower secondary route (pH-sensitive ester hydrolysis) that yields two products without neuromuscular blocking properties.^{226,227} CW 002 (a symmetrical fumarate) and CW 011 (an asymmetric maleate) are investigational NMBDs with no halogen (chlorine) substitution at the central double-bonded carbons. The absence of chlorine results in a slower adduction with cysteine; the inactivation of CW 002 and CW 011 is slower than gantacurium, resulting in a duration of action consistent with an intermediate-acting NMBD.

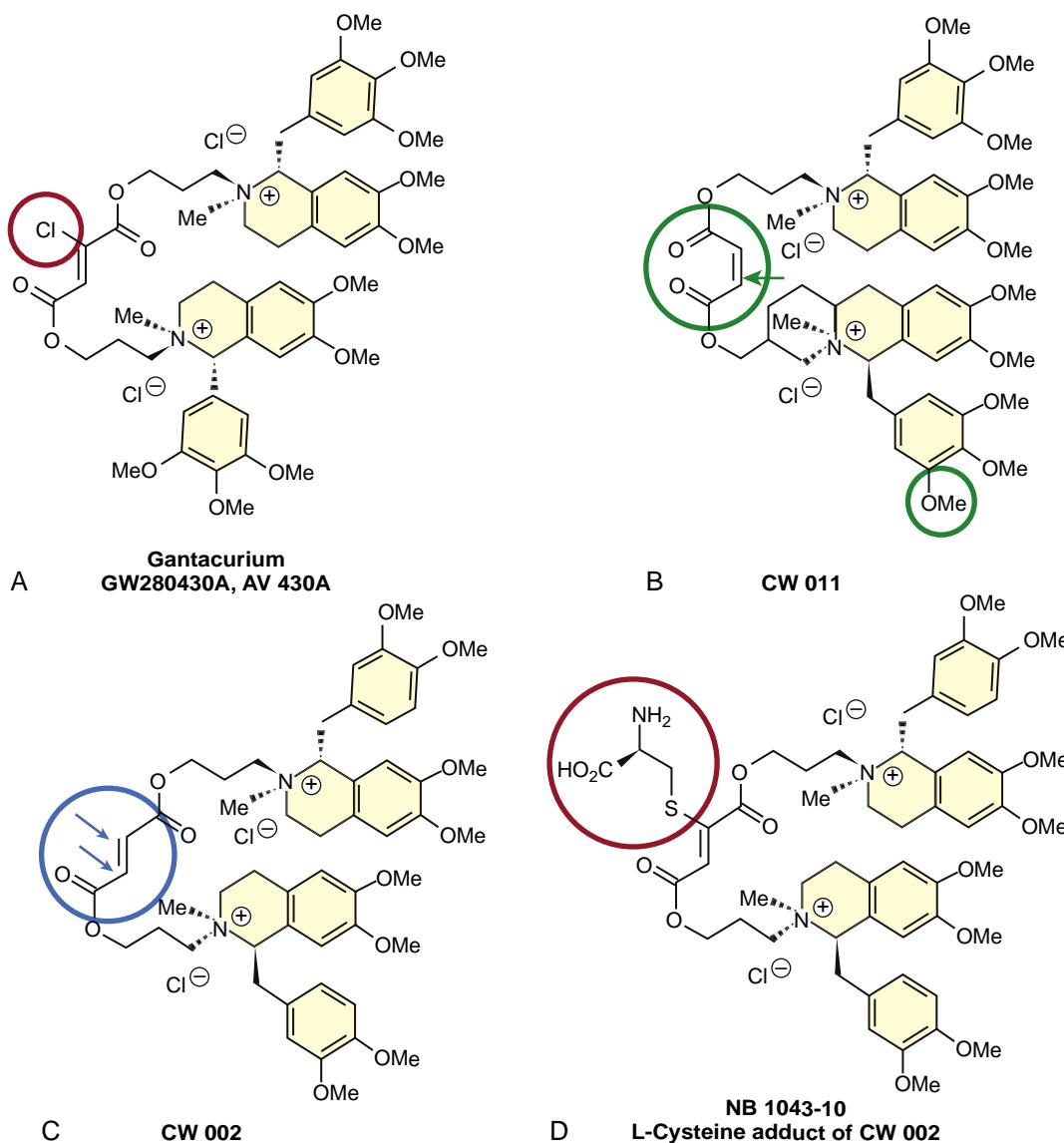


Fig. 28.23 The chemical formulas of gantacurium (A), CW 011 (B), and CW 002 (C). Chemical features are as follows. Chlorine substitution (red circle) on the olefinic double bond of gantacurium, a chlorofumarate, is designed to accelerate the L-cysteine adduction reaction. The fumarate CW 002 is symmetrical with no halogen (chlorine) substitutions and undergoes L-cysteine adduction more slowly than gantacurium, at either olefinic carbon (blue arrows), enabled by the adjacent α -carboxyl (ester) groups. The maleate CW 011 is asymmetric in that one isoquinolinium group contains an extra methoxy substitution (green circle). This may reduce access of L-cysteine to the olefin (green arrow) and may decrease the rate of the adduction reaction. The chemical formula of NB 1043-10, the L-cysteine adduct of CW 002, is also shown (D). The L-cysteine adduction is highlighted by the red circle. (From Savarese JJ, McGilvra JD, Sunaga H, et al. Rapid chemical antagonism of neuromuscular blockade by L-cysteine adduction to and inactivation of the olefinic (double-bonded) isoquinolinium diester compounds gantacurium (AV430A), CW 002, and CW 011. *Anesthesiology*. 2010;113:58-73.)

Cysteine is a nonessential endogenous amino acid derived from one molecule of serine and one molecule of methionine. It is composed of L- and D-enantiomers. L-Cysteine is a normal building block of protein and is a conditionally essential amino acid in infants.²²⁸ Several therapeutic applications of cysteine in medicine are common. It is often added to total parenteral nutrition solutions for pediatric patients in doses of approximately 80 mg/kg/day. An acetylated derivative of cysteine (N-acetyl L-cysteine) is approved for use in the treatment of acute acetaminophen toxicity. In the doses used clinically for these applications, there does not appear to be obvious toxicity. L-Cysteine has also been studied for reversal of the neuromuscular blockade for fumarate NMBDs. Several laboratory investigations have attempted to define the L-cysteine dose necessary to effectively reverse gantacurium, CW 002, and CW 011 neuromuscular blockade.

The first of the fumarate NMBDs studied was gantacurium. In monkeys, the total duration of action was one half to one third that of mivacurium at equipotent doses; at three times the ED₉₅ doses, the time until 95% twitch recovery was 8.5 ± 0.5 minutes versus 22.0 ± 2.6 minutes, respectively.²²⁷ The administration of edrophonium 0.5 mg/kg accelerated the recovery of blockade. In a human volunteer trial, the time from administration of 0.40 mg/kg of gantacurium (2 × ED₉₅) until a TOF ratio 0.90 or greater was achieved was studied during spontaneous recovery or reversal with edrophonium 0.5 mg/kg.²²⁹ Mean recovery time was significantly more rapid in the reversal group (3.8 minutes) compared with the spontaneous recovery group (14.3 minutes). The reversal of gantacurium with cysteine was investigated in monkeys.²²⁸ A bolus of L-cysteine (10 mg/kg) given 1 minute after gantacurium reduced

duration from 10.4 ± 3.1 minutes (spontaneous recovery) to 3.0 ± 1.0 minutes ($P < .001$). Antagonism of gantacurium was significantly faster at 1 minute with L-cysteine than edrophonium. These studies suggest that although gantacurium is a short-acting NMBD, recovery can be further enhanced by the administration of L-cysteine.

In contrast to gantacurium, CW 002 and CW 011 have a duration of action between a short-acting and intermediate-acting NMBD. In monkeys given four to five times the ED₉₅ of CW 002 and CW 011, the duration of blockade was three times longer than gantacurium (28.1 and 33.3 minutes vs. 10.4 minutes), but only half the duration of cisatracurium.²²⁸ The administration of neostigmine 1 minute after CW 002 did not accelerate neuromuscular recovery. Immediate reversal of CW 002 with cysteine (50 mg/kg), however, was highly effective in antagonizing neuromuscular blockade (95% of baseline twitch height within 2.2 ± 0.3 minutes and to a TOF ratio of 100% 1–2 minutes later) (Fig. 28.24).²²⁸ Similar findings were observed with CW 011 using this model. Larger doses of L-cysteine were needed to optimally reverse CW 002 and CW 011 (50 mg/kg) compared with gantacurium (10 mg/kg); this is likely related to the slower rate of adduction of L-cysteine to these compounds, as well as the greater potency of CW 002 and CW 011. L-Cysteine reversal of CW 002 has also been investigated in a dog model given a dose of 9 × ED₉₅.²³⁰ L-Cysteine (50 mg/kg) reduced the median duration of blockade from 70 minutes (spontaneous recovery) to less than 5 minutes. Doses of up to 200 mg/kg produced minimal hemodynamic changes and resulted in no anatomic, biochemical, or histologic evidence of organ toxicity.

In summary, fumarates are a new class of NMBDs that are inactivated primarily via adduction of cysteine to the double

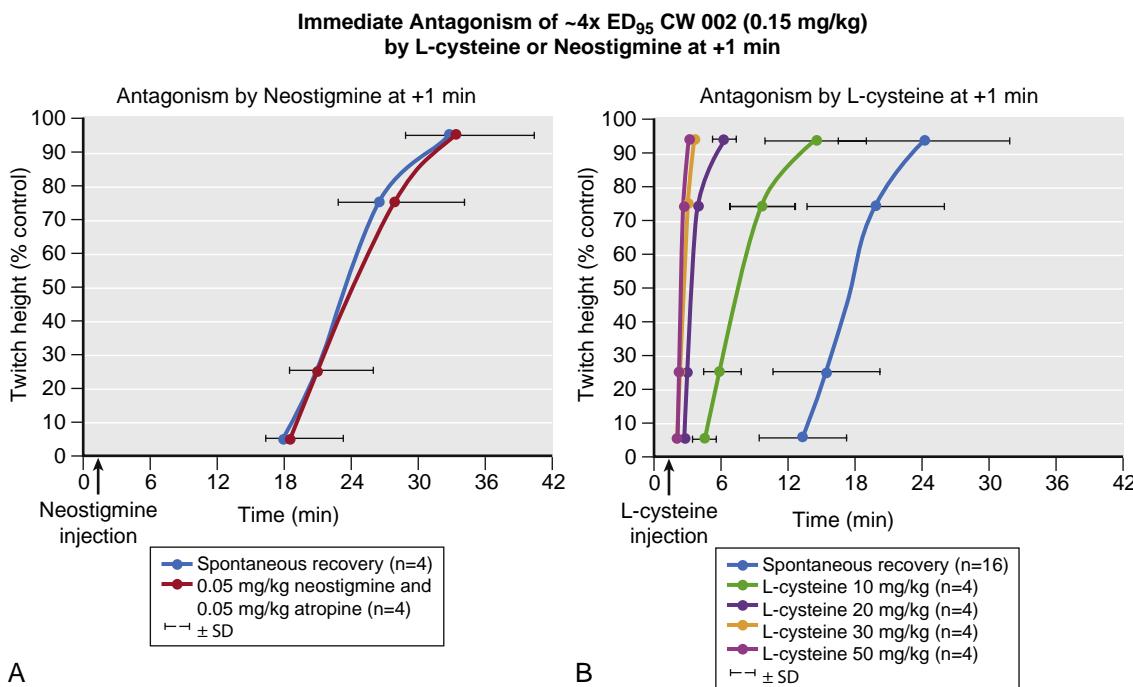


Fig. 28.24 Immediate antagonism of CW 002 blockade 1 minute after CW 002 dosage of 0.15 mg/kg, or $\approx 4 \times$ ED₉₅, injected at $t = 0$. Neostigmine (0.05 mg/kg + atropine 0.05 mg/kg) or L-cysteine (10, 20, 30, or 50 mg/kg) was given at +1 min. Neostigmine did not shorten recovery (A), whereas L-cysteine produced a dose-related acceleration of recovery (B), peaking at 50 mg/kg. Data were taken from anesthetized rhesus monkeys. (From Savarese JJ, McGilvra JD, Sunaga H, et al. Rapid chemical antagonism of neuromuscular blockade by L-cysteine adduction to and inactivation of the olefinic (double-bonded) isoquinolinium diester compounds gantacurium (AV430A), CW 002, and CW 011. *Anesthesiology*. 2010;113:58–73.)

bond of the compounds, resulting in breakdown products that do not bind to the neuromuscular junction. Initial laboratory studies have shown that the administration of exogenous L-cysteine results in complete reversal of deep neuromuscular blockade within 2 to 3 minutes. These studies suggest that chemical antagonism of fumarate NMBDs will allow clinicians to rapidly and completely antagonize neuromuscular blockade, even when large doses of an NMBD have been recently administered. Early clinical trials in human volunteers have examined the pharmacology of gantacurium, and investigations of CW 002 in volunteers are currently ongoing. The optimal dose of L-cysteine is 50 mg/kg in an animal model. The dosing of L-cysteine needed to reverse the effects of gantacurium, CW 002, and CW 011 in humans has not been established. Additional investigations are also needed to determine whether large doses of cysteine produce adverse effects in humans. If future studies are consistent with these early findings, fumarate NMBDs may allow clinicians to maintain profound neuromuscular blockade throughout the surgical procedure with little risk of postoperative residual paralysis.

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KEY POINTS

- Local anesthetics block voltage-gated sodium channels and thereby interrupt initiation and propagation of impulses in axons, but they have a wide variety of other biologic actions, desirable and undesirable.
- Currently available local anesthetics are of two chemical classes: aminoesters and aminoamides.
- The low potency and lack of specificity of available local anesthetics are due in part to the very weak structural constraints at their binding site on the sodium channel. Most of their features derive from the requirement for high solubility, rapidly reversible protonation, and rapid diffusion in both aqueous environments and in the lipid phases of biologic membranes.
- Reversible protonation of the tertiary amine group tends to make local anesthetics less charged at more basic pH and more charged at neutral or acidic pH; the neutral base forms are more soluble in lipid environments, whereas the charged acid forms, the more potent species, are more soluble in aqueous environments.
- Aminoesters are metabolized primarily by plasma esterases, and aminoamides are metabolized primarily by hepatic cytochrome P450-linked enzymes.
- The principal systemic toxicities of local anesthetics involve the heart (including atrioventricular conduction block, arrhythmias, myocardial depression, and cardiac arrest) and the brain (including agitation, lethargy, seizures, and generalized central nervous system depression). Hypoxemia and acidosis exacerbate these toxicities. Resuscitation after bupivacaine overdose is particularly difficult. Therefore prevention of intravascular injection or overdose is crucial, and major nerve blockade should involve incremental, fractionated dosing. Ultrasound can reduce the incidence of systemic toxicity and Intralipid can help in the resuscitation.
- Local anesthetics are directly toxic to nerve at the concentrations supplied in commercial solutions. Intraoperative concentrations during regional anesthesia are generally (but not always) below a threshold for toxicity because of spread of solutions through tissues and diffusion gradients from injection sites into nerve. Injection into a constrained tissue space increases the risk for local toxicity.
- Optimal use of local anesthetics in regional anesthesia requires an understanding of (1) the individual patient's clinical situation; (2) the location, intensity, and duration of regional anesthesia and analgesia required; (3) anatomic factors affecting deposition of drug near nerves; (4) proper drug selection and dosing; and (5) ongoing assessment of clinical effects after administration of a local anesthetic.
- Single-stereoisomer (as opposed to a racemic mixture) formulations have been developed in an effort to reduce systemic toxicity and improve sensory selectivity but true sensory selectivity has not been achieved with drugs currently available.
- The most important research avenues to improve local anesthetic action are slow release formulations, targeting of specific sodium channel subtypes, and targeting of nociceptive fibers.

Local anesthesia results from the blockade of nerve impulses to abolish sensation. All currently available, clinically useful agents are either aminoesters or aminoamides. These drugs, when applied in sufficient concentration at the site of action, prevent conduction of electrical impulses by the membranes of nerve and muscle. In addition to blockade of impulses, local anesthetics can inhibit various receptors, enhance release of glutamate, and depress the activity of certain intracellular signaling pathways. When local anesthetic agents are given systemically, the functions of

cardiac, skeletal, and smooth muscle, as well as transmission of impulses in the central and peripheral nervous systems and within the specialized conducting system of the heart, may all be altered. Local anesthetics may abolish sensation in various parts of the body by topical application, injection near peripheral nerve endings and major nerve trunks, or instillation within the epidural or subarachnoid spaces. Toxicity may be local or systemic. The central nervous and cardiovascular systems are most commonly involved in acute clinical toxicity.

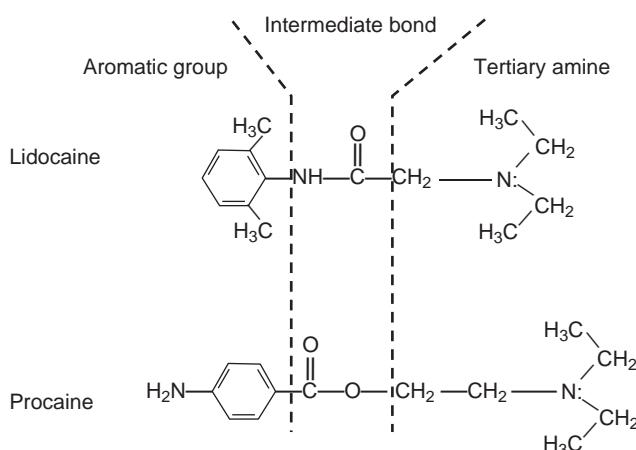


Fig. 29.1 Structures of two local anesthetics: the aminoamide lidocaine and the aminoester procaine. In both drugs, a hydrophobic aromatic group is joined to a more hydrophilic base, the tertiary amine, by an intermediate amide or ester bond.

Basic Pharmacology

CHEMISTRY

The Local Anesthetic Molecule

The typical local anesthetic molecule, exemplified by lidocaine and procaine (Fig. 29.1), contains a tertiary amine attached to a substituted aromatic ring by an intermediate chain that almost always contains either an ester (see Fig. 29.1) or an amide linkage (Fig. 29.2).

Local anesthetics may therefore be classified as aminoesters or aminoamide compounds. The aromatic ring system gives a lipophilic (membrane-loving) character to its portion of the molecule, whereas the tertiary amine end is relatively hydrophilic, particularly since it is partially protonated and thus bears some positive charge in the physiologic pH range (see Fig. 29.2). The structures of commonly administered local anesthetics are given in Table 29.1 and their physicochemical properties in Table 29.2.

STRUCTURE-ACTIVITY RELATIONSHIPS AND PHYSICOCHEMICAL PROPERTIES

The intrinsic potency and duration of action of local anesthetics are clearly dependent on certain features of the molecule.

Lipophilic-Hydrophilic Balance

The lipophilic versus hydrophilic character of a local anesthetic depends on the size of alkyl substituents on or near the tertiary amine and on the aromatic ring. “Lipophilicity” expresses the tendency of a compound to associate with membrane lipids, a property usually approximated by equilibrium partitioning into a hydrophobic solvent such as octanol.¹ Although octanol-buffer partition coefficients are comparable to membrane-buffer partition coefficients for the uncharged species of local anesthetics, they severely underestimate membrane partitioning for the charged, protonated species, octanol being a poor

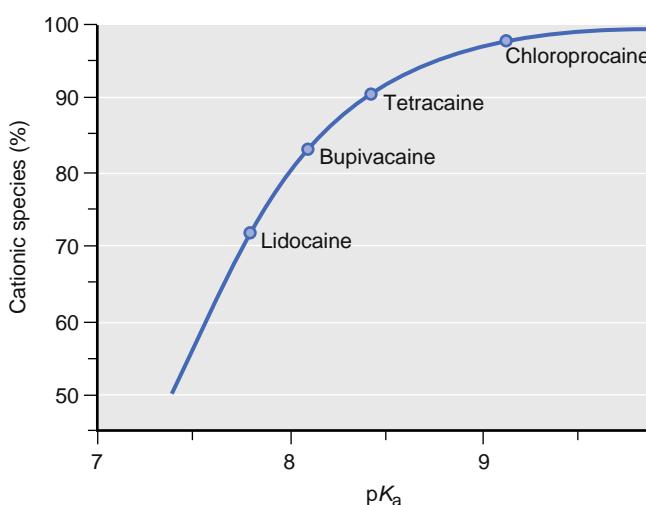


Fig. 29.2 Fraction of local anesthetic in the protonated, cationic form of an aqueous solution at physiologic pH (7.4) as a function of the pK_a of the drug. Lidocaine, the drug with the lowest pK_a , has the smallest fraction of its molecules protonated, the largest in the neutral form, and vice versa for chlorprocaine, the local anesthetic with the highest pK_a . Individual drug molecules become protonated and deprotonated in thousandths of a second in solution.

model for the polar regions near the membrane surface where local anesthetics are concentrated.² Here we use the term “hydrophobicity,” expressed as octanol-buffer partitioning, to describe a physicochemical property of local anesthetics.

Compounds with a more hydrophobic nature are obtained by increasing the size of the alkyl substituents. These agents are more potent and produce longer-lasting blocks than their less hydrophobic congeners do.³⁻⁵ For example, etidocaine, which has three more carbon atoms in the amine end of the molecule than lidocaine, is four times as potent and five times as long lasting when compared in the isolated sciatic nerve.

Hydrogen Ion Concentration

Local anesthetics in solution exist in a very rapid chemical equilibrium between the basic uncharged form (B) and the charged cationic form (BH^+). At a certain hydrogen ion concentration ($\log_{10}^{-1} [-pH]$) specific for each drug, the concentration of local anesthetic base in solution is equal to the concentration of charged cation. The logarithm of this hydrogen ion concentration is called pK_a . The relationship is defined by

$$\frac{[BH^+]}{[B]} = 10^{pK_a - pH}$$

pK_a values of local anesthetic agents in aqueous solution are listed in Table 29.2. The tendency to be protonated also depends on environmental factors, such as temperature and ionic strength, and on the medium surrounding the drug. In the relatively apolar milieu of a membrane, the average pK_a of local anesthetics is lower than in solution. This is chemically equivalent to saying that the membrane concentrates the base form of the local anesthetic

TABLE 29.1 Representative Local Anesthetics in Common Clinical Use

| Generic* and Common Proprietary Names | Chemical Structure | Approximate Year of Initial Clinical Use | Main Anesthetic Use | Representative Commercial Preparation |
|---------------------------------------|--------------------|--|---|--|
| Cocaine | | 1884 | Topical | 40-mg/mL solution |
| Benzocaine (Americaine) | | 1900 | Topical | 200 mg/mL |
| Procaine (Novocain) | | 1905 | Topical Infiltration Spinal | 200 mg/mL 10- and 20-mg/mL solutions 100-mg/mL solution |
| Dibucaine (Nupercaine) | | 1929 | Spinal | 0.667-, 2.5-, and 5-mg/mL solutions |
| Tetracaine (Pontocaine) | | 1930 | Spinal | Niphanoid crystals—20- and 10-mg/mL solutions |
| Lidocaine (Xylocaine) | | 1948 | Infiltration Peripheral nerve blockade Epidural Spinal Topical Topical | 5- and 10-mg/mL solutions 10-, 15-, and 20-mg/mL solutions 10-, 15-, and 20-mg/mL solutions 50-mg/mL solution 20-mg/mL jelly, viscous 25- and 50-mg/mL ointment |
| Chloroprocaine (Nesacaine) | | 1955 | Infiltration Peripheral nerve blockade Epidural | 10-mg/mL solution 10- and 20-mg/mL solutions 20- and 30-mg/mL solutions |
| Mepivacaine (Carbocaine) | | 1957 | Infiltration Peripheral nerve blockade Epidural | 10-mg/mL solution 10- and 20-mg/mL solutions 10-, 15-, and 20-mg/mL solutions |
| Prilocaine (Citanest) | | 1960 | Infiltration Peripheral nerve blockade Epidural | 10- and 20-mg/mL solutions 10-, 20-, and 30-mg/mL solutions 10-, 20-, and 30-mg/mL solutions |
| Bupivacaine (Marcaine) | | 1963 | Infiltration Peripheral nerve blockade Epidural Spinal | 2.5-mg/mL solution 2.5- and 5-mg/mL solutions 2.5-, 5-, and 7.5-mg/mL solutions 5- and 7.5-mg/mL solutions |
| Ropivacaine (Naropin) | | 1992 | Infiltration Peripheral nerve blockade Epidural | 2.5- and 5-mg/mL solutions 5- and 10-mg/mL solutions 5- and 7.5-mg/mL solutions |

*United States Pharmacopeia nomenclature.

From Covino B, Vassallo H. *Local Anesthetics: Mechanisms of Action and Clinical Use*. Orlando, FL: Grune and Stratton; 1976.

more than it concentrates the protonated cation form. The pH of the medium containing the local anesthetic influences drug activity by altering the relative percentage of the base and protonated forms. For example, in inflamed tissues the pH is lower than normal, and local anesthetics are more protonated than in normal tissue and thus penetrate the tissue relatively poorly (see later). The relationship between pK_a and the percentage of local anesthetic present in the cationic form is shown in Fig. 29.2. As described later, there are dual effects of pH on clinical effectiveness, depending on where the local anesthetic is injected and the importance of the base form for tissue penetration.

Anatomy of the Peripheral Nerve

Each peripheral nerve axon possesses its own cell membrane, the axolemma. Nonmyelinated nerves, such as autonomic postganglionic efferent and nociceptive afferent C fibers, contain many axons encased in a single Schwann cell sheath. In contrast, all large motor and sensory fibers are enclosed in many layers of myelin, which consists of the plasma membranes of specialized Schwann cells that wrap themselves around the axon during axonal outgrowth. Myelin greatly increases the speed of nerve conduction by insulating the axolemma from the surrounding conducting salt medium and forcing the “action current” generated by an impulse to flow through the axoplasm to the nodes of Ranvier, which are periodic interruptions in the myelin sheath where the active impulse is regenerated (Fig. 29.3). The Na^+ channels that serve generation and

propagation of impulses are highly concentrated at the nodes of Ranvier of myelinated fibers^{7a} but are distributed all along the axon of nonmyelinated fibers (see Fig. 29.3). A classification of peripheral nerves according to fiber size and physiologic properties is presented in Table 29.3. It is important to note that different fiber classes are not only distinguished by diameter and myelin thickness, but also by the structure of the neuronal membrane and ion channel composition.⁶

Each axon has its own connective tissue covering, the *endoneurium*. A typical peripheral nerve consists of several axon bundles, or fascicles. Each fascicle of many axons is encased by a second connective tissue layer, the epithelial-like *perineurium*, and the entire nerve is wrapped in a loose outer sheath called the *epineurium* (Fig. 29.4). To reach the nerve axon, a local anesthetic molecule must traverse any structures surrounding the nerve, such as the paraneurium of the distal sciatic nerve, the epineurium, the perineurium, and the endoneurium, as well as the neuronal plasma membrane. The main barrier to diffusion is the perineurium.^{7a} Further, nerves are composed of both neuronal tissues and non-neuronal tissues, such as connective or fatty tissues, and blood vessels. When performing a popliteal sciatic nerve block for example, it should be kept in mind that here, approximately 60% of the nerve cross-section is non-neuronal tissue.⁸

STRUCTURE OF THE AXONAL MEMBRANE

Biologic membranes consist of a molecular lipid bilayer containing proteins adsorbed on the surfaces, as well as embedded in or spanning the hydrocarbon core (Fig. 29.5). The

TABLE 29.2 Relative In Vitro Conduction-Blocking Potency and Physicochemical Properties of Local Anesthetic Drugs

| Drug | Relative Conduction-Blocking Potency* | PHYSICOCHEMICAL PROPERTIES | |
|-----------------------------|---------------------------------------|----------------------------|-----------------|
| | | pK_a † | Hydrophobicity† |
| LOW POTENCY | | | |
| Procaine | 1 | 8.9 | 100 |
| INTERMEDIATE POTENCY | | | |
| Mepivacaine | 1.5 | 7.7 | 136 |
| Prilocaine | 1.8 | 8.0‡ | 129 |
| Chloroprocaine | 3 | 9.1 | 810 |
| Lidocaine | 2 | 7.8 | 366 |
| HIGH POTENCY | | | |
| Tetracaine | 8 | 8.4 | 5822 |
| Bupivacaine | 8 | 8.1 | 3420 |
| Etidocaine | 8 | 7.9 | 7320 |

*Data derived from C fibers of isolated rabbit vagus and sciatic nerve.

† pK_a and hydrophobicity at 36°C; hydrophobicity equals the octanol/buffer partition coefficient of the base. Values are ratios of concentrations.

‡Values at 25°C.

From Strichartz GR, Sanchez V, Arthur GR, et al. Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficients and pK_a values of clinically used drugs. *Anesth Analg*. 1990;71:158–170.

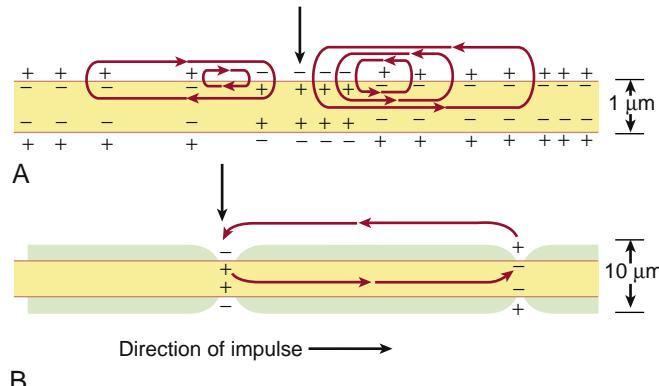


Fig. 29.3 Pattern of local circuit currents flowing during propagation of an impulse in a nonmyelinated C fiber's axon (A) and a myelinated axon (B). During propagation of impulses, from left to right, current entering the axon at the initial rising phase of the impulse (large vertical arrows) passes through the axoplasm (local circuit current) and depolarizes the adjacent membrane. Plus and minus signs adjacent to the axon membrane indicate the polarization state of the axon membrane: negative inside at rest, positive inside during active depolarization under the action potential, and less negative in regions where local circuit currents flow. This ionic current passes relatively uniformly across the nonmyelinated axon, but it is restricted in the myelinated axon to entry at the nodes of Ranvier, several of which are simultaneously depolarized during a single action potential.

character of the bilayer is determined by the phospholipids, which have long hydrophobic fatty acyl tails that lie in the center of the membrane, as well as by the polar hydrophilic head groups, which are usually composed of zwitterionic portions (containing positive and negative charges) that project into the cytoplasm or the extracellular fluid. Within the membrane there is both lateral and rotational diffusion, which allows lipids and certain proteins to migrate in a fluid mosaic, but most membrane proteins are fixed within specific regions of a membrane, anchored by connections to specific proteins of the cell's cytoskeleton.⁹ A dynamic interaction exists between the cell's membrane and cytoplasm.

Although we focus here on the channel-blocking actions of local anesthetics, it is noteworthy that many other cellular activities, including both metabolic and signal transduction pathways, are modulated by these drugs.

PHYSIOLOGY OF NERVE CONDUCTION

The neural membrane is able to maintain a voltage difference of -60 to -90 mV between the intracellular medium and the cell's outside, because at rest it is relatively impermeable to sodium ions (Na^+) but selectively permeable to potassium ions (K^+). The Na^+/K^+ pump, an

TABLE 29.3 Classification of Peripheral Nerves According to Anatomy, Physiology, and Function

| Fiber Class | Subclass | Myelin (μm) | Diameter | Conduction Velocity (m/sec) | Location | Function | Susceptibility to Local Anesthetic Block |
|-------------|----------|--------------------------|----------|-----------------------------|-------------------------------|--|--|
| A | α | + | 6-22 | 30-120 | Efferent to muscles | Motor | ++ |
| | β | + | 6-22 | 30-120 | Afferent from skin and joints | Tactile, proprioception | ++ |
| | δ | + | 3-6 | 15-35 | Efferent to muscle spindles | Muscle tone | ++++ |
| | | + | 1-4 | 5-25 | Afferent sensory nerves | Pain, cold temperature, touch | +++ |
| B | | + | <3 | 3-15 | Preganglionic sympathetic | Various autonomic functions | ++ |
| C | sC | - | 0.3-1.3 | 0.7-1.3 | Postganglionic sympathetic | Various autonomic functions | ++ |
| | dC | - | 0.4-1.2 | 0.1-2.0 | Afferent sensory nerves | Various autonomic functions Pain, warm temperature, touch | + |

From Bonica JJ. Principles and Practice of Obstetric Anesthesia and Analgesia. Philadelphia: FA Davis; 1967.

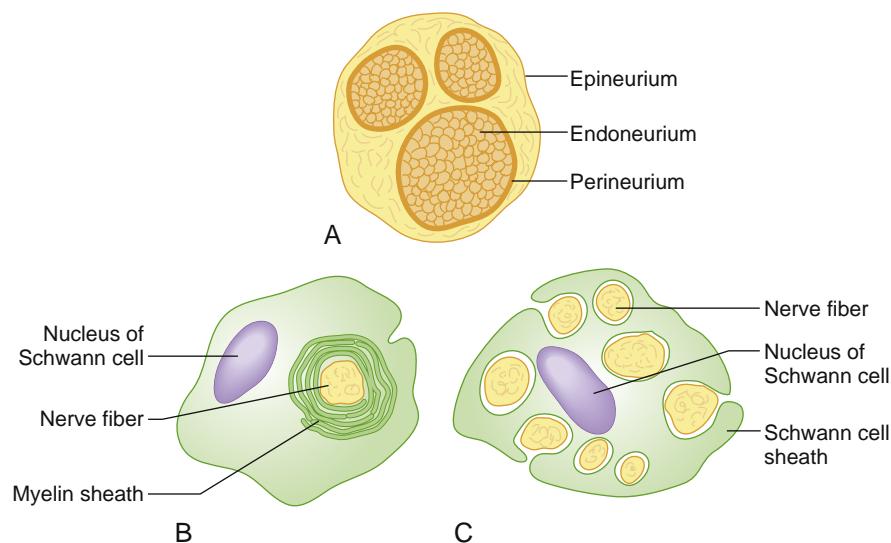


Fig. 29.4 (A) Transverse sections of a peripheral nerve showing the outermost epineurium; the inner perineurium, which collects nerve axons in fascicles; and the endoneurium, which surrounds each myelinated fiber. (B) Each myelinated axon is encased in the multiple membranous wrappings of myelin formed by one Schwann cell, each of which stretches longitudinally more than approximately 100 times the diameter of the axon. The narrow span of axon between these myelinated segments, the node of Ranvier, contains the ion channels that support action potentials. (C) Nonmyelinated fibers are enclosed in bundles of 5 to 10 axons by a chain of Schwann cells that tightly embrace each axon with but one layer of membrane.

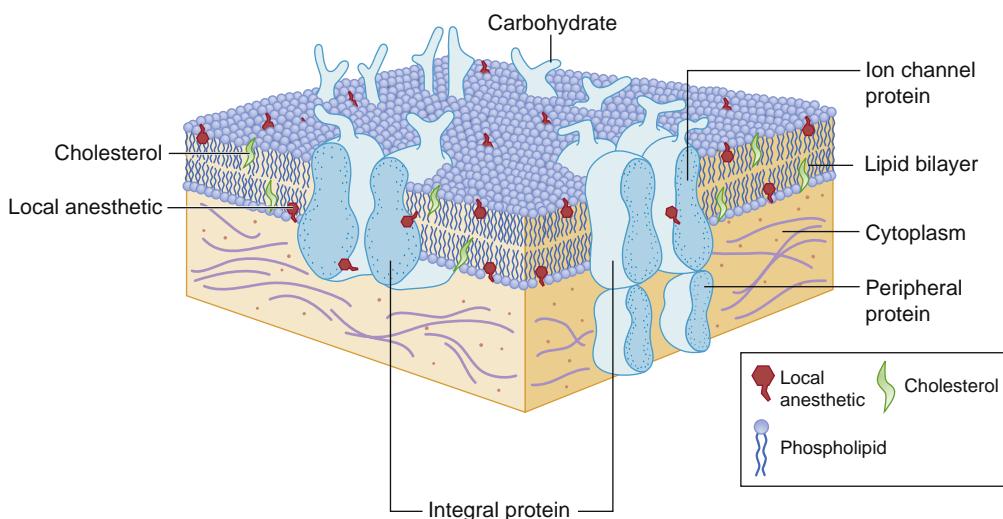


Fig. 29.5 A typical plasma membrane has at its core the lipid bilayer, composed of phospholipids and cholesterol molecules (in an approximately 5:1 ratio) embedding the membrane integral proteins, which are most often glycosylated by extracellular carbohydrates and include receptors and ion channels essential for intercellular communication. “Peripheral proteins” regulate the functions of membrane proteins, chaperone them to the plasma membrane, and stabilize them in the cell through interactions with both the cytoskeleton and the extracellular matrix. Probable membrane locations and protein sites for local anesthetics are also shown.

active, energy-dependent mechanism, sustains the ion gradients that drive this potential difference by constant extrusion of sodium from within the cell in exchange for a net uptake of potassium, with adenosine triphosphate used as an energy source. Although the membrane is relatively permeable to potassium ions, an intracellular-to-extracellular potassium ratio of 150 to 5 mM, or 30:1, is maintained by active removal of potassium as it leaks passively across the plasma membrane into the cell. The nerve at rest behaves largely as a “potassium electrode,” according to the Nernst equation:

$$E_m \approx E_K = \left(\frac{-RT}{F} \right) \ln \left(\frac{[K^+]_i}{[K^+]_o} \right)$$

where E_m is the membrane potential, E_K is the potassium equilibrium potential, R is the gas constant, T is temperature (kelvin), F is Faraday’s constant, and $[K^+]$ is the potassium ion concentration inside (i) and outside (o) the cell. For potassium, therefore,

$$E_K = -58 \log 30 \text{ or } -85.7 \text{ mV}$$

An opposite situation exists for Na^+ , which is at higher concentration outside the cell and has a Nernst potential, E_{Na} , of approximately +60 mV. During an action potential, the nerve membrane transiently switches its higher permeability from K^+ to Na^+ , thereby changing the membrane potential from negative to positive, and back again. The progress of this potential change and the underlying events are graphed in **Fig. 29.6**. They provide a basis for understanding local anesthetic conduction block.

Permeation of ions through membranes occurs via specialized proteins called ion channels.¹⁰ The conformation of these channels is often sensitive to the membrane potential; both Na^+ and K^+ channels in nerve membranes are activated to an “open” conformation by membrane

depolarization. Sodium channels, in addition, close to an “inactivated” conformation after their initial activation. A small membrane depolarization extending along an axon from a region of excited membrane, will begin to open both Na^+ and K^+ channels. The Na^+ channels open faster, and the inwardly directed Na^+ current (see **Fig. 29.6**) depolarizes the membrane further, thereby leading to opening of more Na^+ channels and increasing the inward Na^+ current even further (**Fig. 29.7**). This sequence of events continues during the *depolarizing phase* until some of the Na^+ channels have become inactivated and enough of the K^+ channels have opened to change the balance of current and result in a net outward current that produces membrane *repolarization* (see **Fig. 29.7**). After one action potential, the concentrations of Na^+ and K^+ have changed little for the large myelinated fibers but by as much as 10% for the small, nonmyelinated axons. The Na^+ ions entering and K^+ ions leaving the cell as a result of this process are restored by the Na^+/K^+ pump.

Depolarizations too weak to activate enough Na^+ channels to produce a net inward current are below the membrane’s excitability *threshold*. The precise value of the threshold varies in different regions of the cell and can change with time. Directly after an impulse, when some Na^+ channels are still inactivated and some K^+ channels are still activated, the threshold is above its “resting” value and the membrane is “refractory” to stimulation. Over time, as Na^+ inactivation decays and K^+ channels return to their closed conformation, the original resting threshold value is restored. The action potential is a wave of depolarization that is propagated along the axon by continuous coupling between excited and nonexcited regions of membrane. Ionic current (the action current) enters the axon in the excited, depolarized region and then flows down the axoplasm and exits through the surrounding membrane, thereby passively depolarizing this adjacent region (see **Fig. 29.3**).

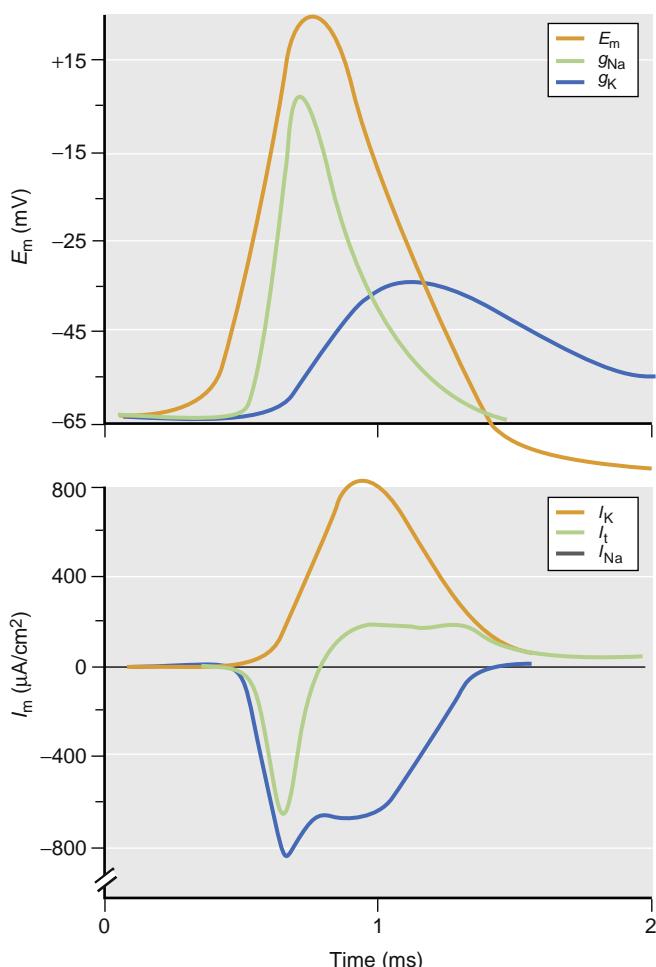


Fig. 29.6 Membrane potential (E_m) and the voltage-gated ionic conductance of sodium (g_{Na}) and potassium (g_K), which determine the corresponding membrane currents I_m (I_{Na} and I_K) during a propagated action potential. Modeled from the original studies of Hodgkin and Huxley on the squid giant axon (see Hodgkin^{7b}), these relationships hold for almost all invertebrate and vertebrate nerve fibers. The direction of the total ionic current (I_v), which is the sum of I_{Na} and I_K , is inward (negative values) for the depolarizing phase of the action potential and outward (positive values) for the repolarizing phase. (From Hodgkin A. *The Conduction of the Nervous Impulse*. Springfield, IL: Charles C. Thomas; 1964.)

Although this *local circuit current* spreads away from the excited zone in both directions, the region behind the impulse, having just been depolarized, is absolutely refractory, and propagation of impulses is thus unidirectional. The local circuit current spreads rapidly along a length of insulated internode in a myelinated axon (see Fig. 29.3), and many nodes of Ranvier in sequence are depolarized to threshold with little intervening delay. Single impulses do not jump from node to node as separate, discrete events; instead, active depolarization occurs simultaneously along several centimeters of the largest axons (see Fig. 29.3). Indeed, the local circuit current is so robust that it can skip past two completely nonexcitable nodes (e.g., blocked by local anesthetic) and successfully stimulate a third node. If excitability is partially reduced, such as by inhibition of some of the Na^+ channels, the amplitude of impulses in successive nodes falls accordingly, a process that can continue

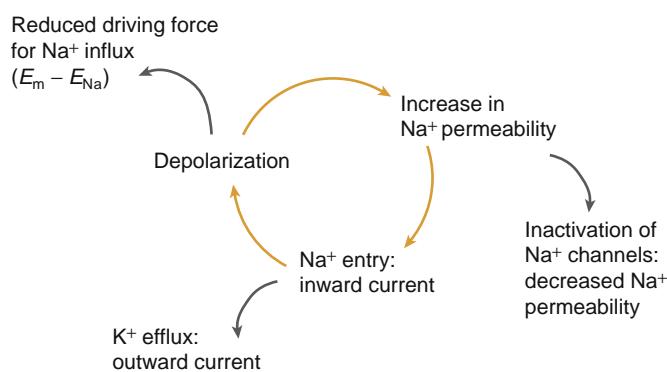


Fig. 29.7 The action potential can be understood in terms of the cyclic relationships between factors contributing to the regenerative, depolarizing phase and the passive, repolarizing phase. Positive factors (yellow arrows) increase the rate of depolarization in a positive-feedback loop, with each element in the cycle favoring the subsequent one. Negative factors (gray arrows) decrease the depolarization rate by reducing or opposing the related positive factor, with efflux of K^+ eventually dominating the ionic flow and repolarizing the membrane.

for many centimeters.¹¹ This situation probably occurs during certain phases of local anesthesia, as discussed later. When enough of the Na^+ channels are blocked, local circuit current fails to bring the adjacent resting region to threshold, and the impulse is fully extinguished.

Mechanism of Action of Local Anesthetics (Pharmacodynamics)

ACTIVE FORM

Local anesthetic bases are poorly to sparingly soluble in water but are quite soluble in relatively hydrophobic organic solvents. Therefore as a matter of chemistry (and to optimize shelf life), most of these drugs are formulated as hydrochloride salts. The pK_a of the drug and tissue pH determine the amount of drug that exists in solution as free base or as positively charged cation when injected into living tissue (see earlier). Furthermore, uptake of the drug by tissue, largely via lipophilic adsorption, will also alter its activity, both by shifting the effective pK_a downward, thereby favoring the neutral base form, and by limiting diffusion of the anesthetic away from the site of injection. Moderately hydrophobic local anesthetics block faster than either hydrophilic or highly hydrophobic ones, delivered at the same concentration, for the following reasons. Moderately hydrophilic local anesthetic block, such as lidocaine, are less bound to tissues than very hydrophobic drugs are (e.g., tetracaine) but are still more membrane permeant than very hydrophilic ones (e.g., 2-chloroprocaine). The highly hydrophobic local anesthetics, having higher intrinsic potencies (see Table 29.2), are therefore used in lower concentrations and their diffusion-controlled rate of onset is correspondingly reduced.

Which form of the local anesthetic, charged cation or neutral base, is actually responsible for blockade of impulses? More alkaline solutions of local anesthetics block nerve conduction more effectively. On sheath-free

nerves, the rate of inhibition by tertiary amine anesthetics is greater at alkaline than at neutral external pH¹² because membrane permeation, favored by the base over the cationic species, determines the rate of access to the binding site. Direct control of axoplasmic pH (or internal perfusion with permanently charged quaternary amine homologs) shows that the dominant potency derives from the cationic species acting from the cytoplasmic surface.^{13,14} The uncharged base also has intrinsic pharmacologic activity, however, which explains the effectiveness of benzocaine as a topical local anesthetic. The local anesthetic attaches to the binding site with its aromatic moiety, while the charged portion protrudes into the sodium channel's lumen.¹⁵

ELECTROPHYSIOLOGIC EFFECT OF LOCAL ANESTHETICS

The resting membrane potential of nerve is little affected by local anesthetics. As the concentration of local anesthetic applied to the nerve is increased, a decrease in the rate of depolarization and in the peak amplitude of the action potential occurs until the impulse is abolished. By using a "voltage-clamp" procedure, Na^+ currents and their inhibition by local anesthetics can be directly assayed (Fig. 29.8A). When the membrane of isolated neurons is rapidly depolarized to a constant value, the time course of ionic currents is observed. Sodium currents during one initial depolarization are reduced by subclinical doses of local anesthetic (e.g., 0.2 mM lidocaine) and totally abolished by clinical doses (e.g., 1% lidocaine \approx 40 mM). If the test depolarization is applied repeatedly at frequencies higher than 5 Hz (five pulses per second), the partially depressed (*tonically* inhibited) Na^+ current is further reduced incrementally for each pulse until a new steady-state level of inhibition is reached.^{13,16} This frequency-dependent inhibition, also called *phasic inhibition*, is reversed when stimulation is slowed or stopped, and currents return to the level of tonic inhibition observed in the resting nerve. Parallel to the phasic inhibition of Na^+ currents in voltage-clamped membranes is a "use-dependent" blockade of action potentials during normal physiologic function (see Fig. 29.8B).

Phasic actions are a manifestation of the selective affinity of local anesthetics for conformations of the Na^+ channel that result from depolarization. Both "open" and "inactivated" states of the channel bind local anesthetics more avidly than the resting state does. Repeated depolarization thus increases the fraction of drug-bound channels; dissociation of these bound drug molecules is usually a slower process than the normal recovery from inactivation (see earlier) and results in the use-dependent accumulation of channels in the blocked condition and the phenomenon of phasic block.

By its selective binding to a channel state, the local anesthetic stabilizes that state. During phasic block, therefore, more inactivated channels become drug bound, and reciprocally, less activation can occur. This relationship between state-dependent affinities and modification of transitions among states through drug binding is known as the "modulated receptor" model.¹⁷ Overall binding of anesthetic is increased by membrane depolarization for two reasons: *more binding sites become accessible* during activation

(the "guarded receptor" model) and drug *dissociation* from inactivated channels is *slower* than from resting channels (the modulated receptor model).

The potency of local anesthetics to produce tonic and phasic inhibition is similarly dependent on their structure, hydrophobicity, and pK_a . There appears to be a single, albeit complex, binding site for local anesthetics on the Na^+ channel, with a "tonic" affinity at rest and increased "phasic" affinity occurring as a result of depolarization. The sodium channel can be influenced by a number of drugs or toxins/venoms, and the different sites are numbered. The binding site for local anesthetics is referred to as Site 9, while the outer channel pore, binding site for tetrodotoxin (TTX) or saxitoxin (STX), is referred to as Site 1.

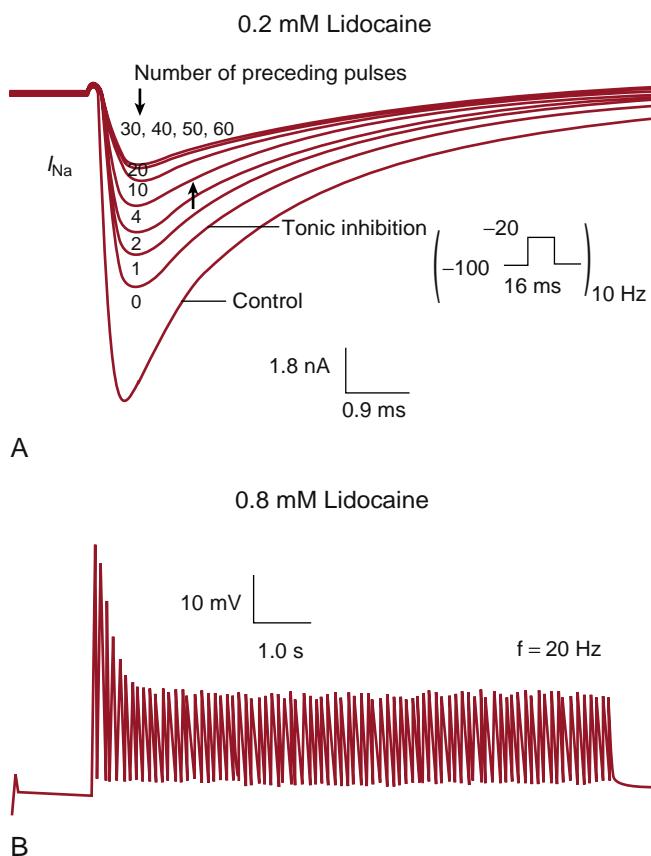


Fig. 29.8 Use-dependent actions of local anesthetics on excitable membrane properties. (A) Ionic Na^+ currents measured by a voltage-clamping technique are transiently activated by brief steps of depolarization applied infrequently (tonic test) or in a train at 10 times per second (phasic test, see E_m pattern in parentheses). After equilibration with 0.2 mM (0.005%) lidocaine, the currents measured tonically are reduced by approximately 30% from the control currents. Application of the phasic train of depolarizations results in a dynamic reduction of currents after each depolarization, with a steady-state value of phasic inhibition reached during the train of 75% of control currents. Recovery of currents to the tonic value occurs within a few seconds when phasic testing stops (not shown). (B) Action potentials are also inhibited in a phasic manner by local anesthetics. After equilibration with 0.8 mM lidocaine (0.02%), the action potential is tonically reduced by approximately 20% from its amplitude in drug-free solution (not shown). Stimulation by a train at 20 stimuli per second induces a phasic inhibition that further reduces the amplitude by about 70% from the control value. As with the ionic currents (A), phasic inhibition of the action potential recovers rapidly when high-frequency stimulation stops.

THE NATURE OF THE LOCAL ANESTHETIC

Binding Site

Intentional mutation of specific amino acids of the Na^+ channel has allowed definition of regions that interact directly with local anesthetics. The major functional protein of the Na^+ channel (the α -subunit) is composed of four homologous “domains” (D-1 to D-4), each of which contains six helical regions (S1 to S6) that span the core of the membrane (Fig. 29.9A). Each domain also has a loop, termed the “P region,” that links the extracellular ends of its S5 and S6 transmembrane segments; the P regions extend inward between the transmembrane regions such that when the α -subunit folds together, each P loop contributes a quarter of the cylindrical ion “selectivity pore,” the narrowest passage of an open channel (see Fig. 29.9B). Voltage sensitivity derives from the positive charges located on

S4 segments, which slide or swing “outward” in response to membrane depolarization. By linkages still unknown, this movement of S4 results in a conformational rearrangement of the S6 segments, which form the inner, cytoplasmic entry to the channel. Closed-to-open channel gating results from movement of the S6 segments, whereas inactivation gating results from binding of the cytoplasmic loop located between D-3 and D-4 to the cytoplasmic opening of the channel.

Local anesthetics bind in the “inner vestibule” of the closed Na^+ channel (see Fig. 29.9C). Amino acid mutations in the S6 segments of D-1, D-3, and D-4 all modify local anesthetic action, thus suggesting either that these regions form a “pharmacophore” small enough to simultaneously contact the drug at three surfaces or that the local anesthetic molecule moves rapidly among these three segments. The rate constant for binding of local anesthetic to

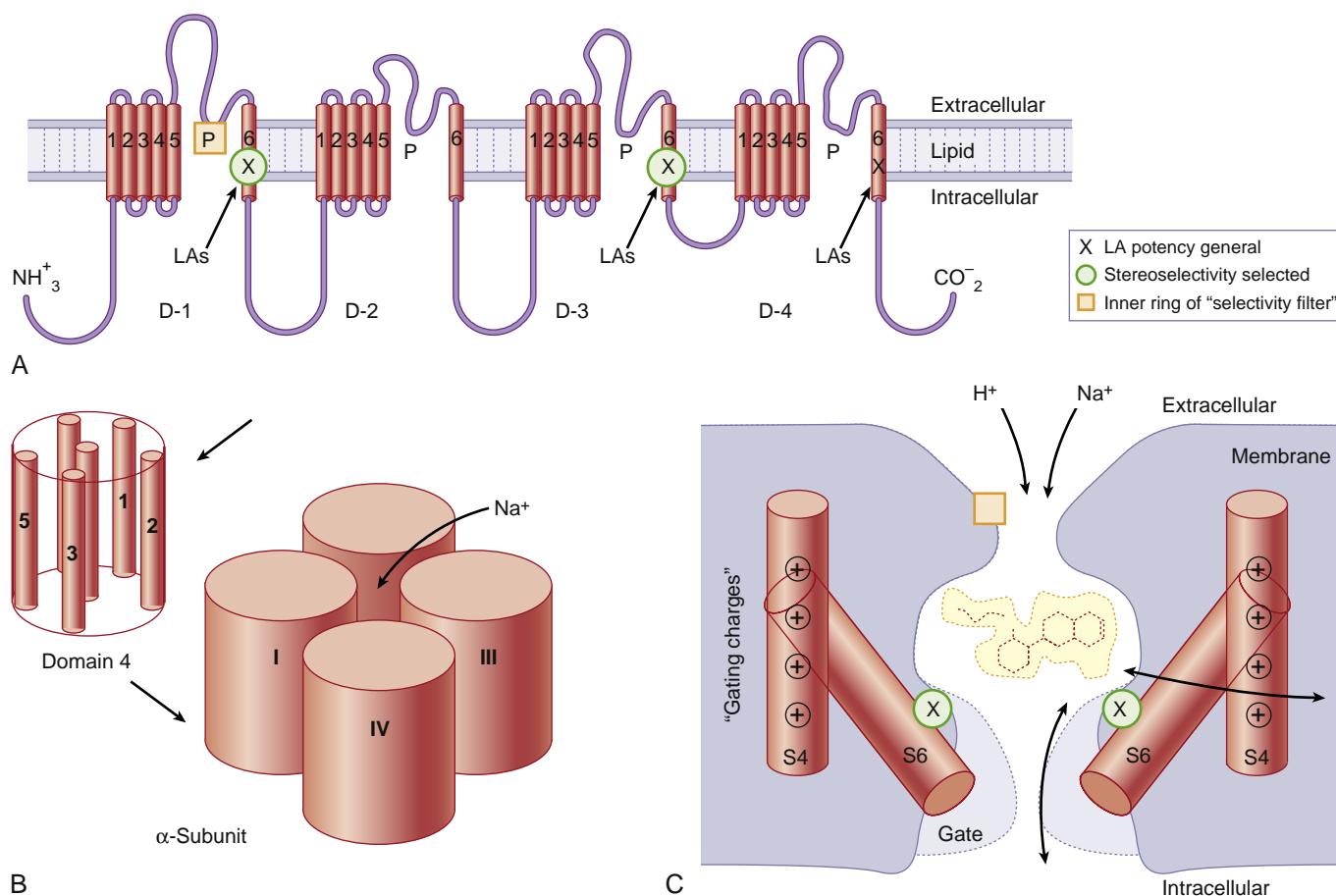


Fig. 29.9 Structural features of the Na^+ channel that determine local anesthetic (LA) interactions. (A) Consensus arrangement of the single peptide of the Na^+ channel α -subunit in a plasma membrane. Four domains with homologous sequences (D-1 through D-4) each contain six α -helical segments that span the membrane (S1 to S6). Each domain folds within itself to form one cylindrical bundle of segments, and these bundles converge to form the functional channel's quaternary structure (B). Activation gating leading to channel opening results from primary movement of the positively charged S4 segments in response to membrane depolarization (see panel C). Fast inactivation of the channel follows binding to the cytoplasmic end of the channel of part of the small loop that connects D-3 to D-4. Ions travel through an open channel along a pore defined at its narrowest dimension by the P region formed by partial membrane penetration of the four extracellular loops of protein connecting S5 and S6 in each domain. Intentional, directed mutations of different amino acids on the channel indicate residues that are involved in LA binding in the inner vestibule of the channel (X on S6 segments), at the interior regions of the ion-discriminating “selectivity filter” (square on the P region), and which are also known to influence stereoselectivity for phasic inhibition (circle, also on S6 segments). (C) Schematic cross section of the channel speculating on the manner in which S6 segments, forming a “gate,” may realign during activation to open the channel and allow entry and departure of a bupivacaine molecule by the “hydrophilic” pathway. The closed (inactivated) channel has a more intimate association with the LA molecule, whose favored pathway for dissociation is no longer between S6 segments (the former pore) but now, much more slowly, laterally between segments and then through the membrane, the “hydrophobic” pathway. Na^+ ions entering the pore will compete with the LA for a site in the channel, and H^+ ions, which pass very slowly through the pore, can enter and leave from the extracellular opening, thereby protonating and deprotonating a bound LA molecule and thus regulating its rate of dissociation from the channel.

the closed Na^+ channel is larger for the more hydrophobic molecules, which suggest that drug molecules can reach the binding site (and depart from it) through a “hydrophobic” pathway. The charged species of local anesthetics dissociates much more slowly from closed and inactivated Na^+ channels than the neutral form does, which suggests that an ionic bond may be involved in drug binding or that the charged molecule moves only slowly along the hydrophobic pathway. In brief, hydrophobicity delivers the drug to the receptor and charge keeps it there.

NEUROPHYSIOLOGIC ASPECTS OF PHASIC INHIBITION

Different fiber types in the nerve are affected differently during local anesthesia. At least part of this difference arises from pharmacokinetic factors. At the onset of and during recovery from clinical block, in particular, longitudinal and radial diffusion of drug will produce concentration variations within and along the nerve. This variation is superimposed on the dynamic use-dependent inhibition to provide variable propagation, which depends on a fiber’s geometry, position within the nerve, and functional as well as electrophysiologic properties.

Different fiber types are also differentially sensitive to local anesthetic blockade. *In vivo* experiments in which continuous superperfusion of peripheral nerve allows equilibration with drug, and experiments in which a drug bolus is delivered by percutaneous injection,¹⁸ analogous to clinical peripheral nerve block, show that small myelinated axons ($\text{A}\delta$ motor and $\text{A}\delta$ sensory fibers) are the most susceptible to impulse suppression. Next in order of block are the large myelinated ($\text{A}\alpha$ and $\text{A}\beta$) fibers, and the least susceptible are the small, nonmyelinated C fibers. In fact, in this last group, impulses in the slowest conducting population (conduction velocity of 0.5–0.8 m/s) are the most resistant to local anesthetic.¹⁸ Clinically, testing of block efficacy is often performed using methods that target $\text{A}\delta$ sensory fibers, so these findings suggest that loss of temperature or pin-prick discrimination does not guarantee complete and reliable block of all sensory modalities.

Selective Block of Na^+ Channel Isoforms

Nine different mammalian Na^+ channels have been physiologically identified and their genes have been sequenced. At least four of them are found in peripheral neurons, and some are exclusively associated with nociceptive afferents. Obviously, it would be clinically advantageous to selectively inhibit these channels and thus prevent or reduce pain while sparing other functions. Although selective channel blockade has been attained with naturally occurring small peptide toxins,¹⁹ relatively little selective blockade by local anesthetics has been reported,²⁰ probably because the local anesthetic pharmacophore is too similar among the different channel isoforms and the local anesthetic molecules themselves have several rotational axes, which makes them poor structural templates for selecting among static binding pockets. Selectively blocking different sodium channel isoforms can lead to distinct effects because they are not evenly distributed across the nerve and react differently to activation. Specifically, one of the main functions of the Nav1.7 isoform is to act as an amplifier in the terminals of primary

sensory neurons, while Nav1.8 is vital to the repetitive firing in these neurons, and Nav1.9 is able to generate persistent currents which can increase membrane excitability.²¹ Some recent advances which hold promise to improve nerve block properties of local anesthetics are summarized toward the end of this chapter.

Sodium Channel Isoforms and Their Contribution to Human Diseases Characterized by Pain or Pain Insensitivity

We now know several mutations in the prototypical neuronal sodium channels (Nav1.7, 1.8, and 1.9) which can lead to states of either spontaneous pain^{22,23} or profound and selective impairment of pain sensitivity.²⁴ This depends on the type of mutation and mode of inheritance. For example, mutations in Nav1.7 may lead to loss of channel function and, in the most extreme form, congenital insensitivity to pain. In contrast, activating mutations in the same channel can trigger erythromelalgia or paroxysmal extreme pain disorder.²¹ Molecular studies reveal that these disorders involve several distinct types of mutations in NaV1.7 sodium channels.^{22,23} When these channels are inserted into cells that lack sodium channels, they generate spontaneous, temperature-sensitive inward currents.²¹ Another recent finding was that certain preclinical models of visceral pain (e.g., cystitis) are not responsive to therapies specifically targeting the NaV1.7 channels, while block of NaV1.9 channels was effective.²⁵ Lastly, it is important to note that mutations in nonneuronal sodium channels can have profound clinical consequences as well. For example, mutations of the Nav1.4 sodium channel isoform in skeletal muscle can produce myotonia, periodic paralysis, and congenital myasthenia.²⁶

Aberrant impulses, which are often considered the hallmarks of various diseases of excitable membranes, such as abnormal repetitive firing in neuropathic pain or in certain types of inherited skeletal myotonia, are abolished by systemic lidocaine in doses that do not block normal propagating impulses. Conditions for the sensitivity of such impulses to local anesthetics, such as lidocaine, appear to result from the patterns of impulse spikes superimposed on slow membrane depolarizations caused by abnormal expression of Na^+ channels rather than from selective sensitivity of certain subtypes of channels to these drugs.²⁷

SUMMARY OF LOCAL ANESTHETIC MECHANISMS

Impulse blockade by local anesthetics may be summarized by the following chronology:

1. Solutions of local anesthetic are deposited near the nerve. Removal of free drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of aminoester anesthetics. The net result is penetration of the nerve sheath by the remaining free drug molecules.
2. Local anesthetic molecules then permeate the nerve’s axon membranes and reside there and in the axoplasm. The speed and extent of these processes depend on a particular drug’s pK_a and on the lipophilicity of its base and cation species.

3. Binding of local anesthetic to sites on voltage-gated Na^+ channels prevents opening of the channels by inhibiting the conformational changes that underlie channel activation.
4. During onset of and recovery from local anesthesia, impulse blockade is incomplete and partially blocked fibers are further inhibited by repetitive stimulation, which produces an additional, use-dependent binding to Na^+ channels.
5. One local anesthetic binding site on the Na^+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions.
6. The clinically observed rates of onset and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecules into and out of the whole nerve, not by their much faster binding and dissociation from ion channels. A clinically effective block that may last for hours can be accomplished with local anesthetic drugs that dissociate from Na^+ channels in a few seconds.

Clinical Pharmacology

Successful use of regional anesthesia requires knowledge of the pharmacologic properties of the various local anesthetic drugs, as well as technical skill in performance of the nerve block. Local anesthetic requirements vary considerably, depending on factors such as the type of block, surgical procedure, and physiologic status of the patient.

Commonly used aminoester local anesthetics include procaine, chloroprocaine, tetracaine, and the first true local anesthetic, cocaine. Commonly used aminoamides include lidocaine, mepivacaine, prilocaine, bupivacaine (the racemic form and its levoenantiomer), ropivacaine, and etidocaine. The ester and amide local anesthetics differ in their chemical stability, locus of biotransformation, and allergic potential. Amides are extremely stable, whereas esters are relatively unstable in solution. Aminoesters are hydrolyzed in plasma by cholinesterase enzymes, but the amides undergo enzymatic degradation in the liver. Two exceptions to this trend include cocaine, an ester that is metabolized predominantly by hepatic carboxylesterase, and articaine, an amide local anesthetic widely used in dentistry that is inactivated by plasma carboxylesterase-induced cleavage of a methyl ester on the aromatic ring.

p-Aminobenzoic acid is one of the metabolites of ester-type compounds that can induce allergic-type reactions in a small percentage of patients. The aminoamides are not metabolized to *p*-aminobenzoic acid, and reports of allergic reactions to these agents are extremely rare.

GENERAL CONSIDERATIONS

Clinically important properties of the various local anesthetics include potency, speed of onset, duration of anesthetic action, and differential sensory/motor blockade. As previously indicated, the profile of individual drugs is determined by their physicochemical characteristics (see Table 29.2).

Anesthetic Potency

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency⁵ because the anesthetic

molecule must penetrate into the nerve membrane and bind at a partially hydrophobic site on the Na^+ channel. Clinically, however, the correlation between hydrophobicity and anesthetic potency is not as precise as in an isolated nerve. Differences between *in vitro* and *in vivo* potency may be related to a number of factors, including local anesthetic charge and hydrophobicity (which influence partitioning into and transverse diffusion across biologic membranes) and vasodilator or vasoconstrictor properties (which influence the initial rate of vascular uptake from injection sites into the central circulation).

Onset of Action

The onset of conduction block in isolated nerves is related to the physicochemical properties of the individual agents. *In vivo* latency is also dependent on the dose or concentration of local anesthetic used. For example, 0.75% bupivacaine has more rapid onset than 0.25%. Chloroprocaine demonstrates a rapid onset of action in humans because its low systemic toxicity permits its use in high concentrations (3%).

Duration of Action

The duration of action of the various local anesthetics differs markedly. Procaine and chloroprocaine have a short duration of action. Lidocaine, mepivacaine, and prilocaine produce a moderate duration of anesthesia, whereas tetracaine, bupivacaine, ropivacaine, and etidocaine have the longest durations.

In humans, the duration of anesthesia is markedly influenced by the peripheral vascular effects of the local anesthetic drugs. Many local anesthetics have a biphasic effect on vascular smooth muscle; at low concentrations these agents tend to cause vasoconstriction, whereas at higher, clinically administered concentrations, they cause vasodilation.²⁸ However, differences exist in the degree of vasodilator activity of the various drugs. The effects of local anesthetics on vascular tone and regional blood flow are complex and vary according to concentration, time, and the particular vascular bed near the site of application. As a practical example, the topical local anesthetic formulation EMLA (eutectic mixture of the local anesthetics lidocaine and prilocaine) vasoconstricts cutaneous vessels initially and through most of the first hour of application, but vasodilation is observed after 2 or more hours of application.

Differential Sensory and Motor Blockade

Another important clinical consideration is the ability of local anesthetic agents to cause differential inhibition of sensory and motor activity. Bupivacaine became popular in the 1980s for epidural blocks because it was better than the previously available long-acting agents (e.g., etidocaine) in producing adequate antinociception without profound inhibition of motor activity, particularly when dilute solutions are used. Bupivacaine is widely used epidurally for obstetric analgesia and postoperative pain management because it can provide acceptable analgesia with only mild muscle weakness. Additional observations on the sensory selectivity of newer local anesthetics are detailed later in the section on chiral local anesthetics.

Traditional texts often state that small-diameter axons, such as C fibers, are more susceptible to local anesthetic

block than larger-diameter fibers. However, when careful measurements are made of single-impulse annihilation in individual nerve fibers, exactly the opposite differential susceptibility is noted (see earlier).^{29,30} Repetitive stimulation, such as occurs during propagation of trains of impulses, produces further, phasic inhibition of excitability, but it is not clear how this will affect a functionally selective failure of impulses. The length of drug-exposed nerve in the intrathecal space, imposed by anatomic restrictions, can perhaps explain clinically documented differential spinal or epidural blockade, with longer drug-exposed regions yielding block by lower concentrations of local anesthetic.³¹ However, this reasoning does not explain the functionally differential loss from peripheral nerve block. Other factors may include actual spread of the drug along the nerve or its selective ability to inhibit Na^+ channels over K^+ channels,³² which in itself can produce a differential block because these channels are present in very different proportions in different types of nerves. As a result of these confounding factors, conclusions about fiber-type involvement in chronic pain syndromes based on the dose or concentration requirement for pain relief in diagnostic nerve blockade should not be made.³³

FACTORS INFLUENCING ANESTHETIC ACTIVITY IN HUMANS

Dosage of Local Anesthetic

As the dosage of local anesthetic is increased, the probability and duration of satisfactory anesthesia increases and the time to onset of block is shortened. The dosage of local anesthetic can be increased by administering either a larger volume or a more concentrated solution. For example, increasing the concentration of epidurally administered bupivacaine from 0.125% to 0.5% while maintaining the same volume of injectate (10 mL) resulted in shorter latency, an improved incidence of satisfactory analgesia, and a longer duration of sensory analgesia.³⁴ The volume per se of anesthetic solution probably influences the spread of anesthesia. For example, 30 mL of 1% lidocaine administered into the epidural space produced a level of anesthesia that was 4.3 dermatomes higher than that achieved when 10 mL of 3% lidocaine was given.

In selecting the volume and concentration for a specific block in a particular patient, clinicians must balance the risk of adverse effects from excessive dosing (e.g., systemic toxicity, excessive motor or autonomic blockade) against the increased risk of block failure if an inadequate volume or concentration is chosen. The degree to which additional volume can compensate for imprecise needle placement varies among different blocks. With the advent of very precise needle placement using ultrasound-guided blockade, it has become clear that the median effective volume for obtaining successful blockade can be achieved with smaller volumes than have been recommended from some previous clinical series based on traditional methods of needle localization. For example, in a recent dose-finding randomized trial for femoral nerve blockade, the median volumes for 50% or 95% success in obtaining dense sensory and motor block at 30 minutes under ultrasound guidance were 57% and 54% of the corresponding volumes with the

use of nerve stimulation.³⁵ Interested readers will note the very wide confidence intervals found in this study and are encouraged to read recent work on some statistical design issues for dose-response studies involving all types of anesthetics.³⁶ As limited by toxicity considerations, the aim in most clinical situations should be to choose doses that provide high success rates; that is, an effective dose (ED) in 95% of patients (ED₉₅) is generally a more relevant guide to dose selection than an ED₅₀ dose. These considerations are especially salient when performing regional anesthesia for patients with chronic pain, hyperalgesia, or a history of previous failed regional anesthesia. Also, decreasing the dose substantially may provide a satisfactory block after 30 minutes (a common endpoint for clinical studies), but at the same time, the block may have a decreased duration of action. Duration of action is important such that the block will cover the intensely painful period after surgery, and if this period is longer than could be achieved using plain local anesthetics, and in cases where continuous techniques are not feasible, adjuvants/additives may help in prolonging the block.

Addition of Additives

Epinephrine. Vasoconstrictors, usually epinephrine, are frequently included in local anesthetic solutions to decrease the rate of vascular absorption, thereby allowing more anesthetic molecules to reach the nerve membrane and thus improve the depth and duration of anesthesia. The use of epinephrine as a marker for inadvertent intravascular injection continues to be sensible, even though false negatives and false positives can occur, such as difficulty in interpretation for specific patient groups as with parturients and patients under anesthesia or on β -blockers.³⁷ Clinically used solutions typically contain 5 $\mu\text{g}/\text{mL}$ or 1:200,000 of epinephrine, reflecting a balance between efficacy and vasoconstriction versus systemic side effects of epinephrine. The extent to which epinephrine prolongs the duration of anesthesia depends on the specific local anesthetic used and the site of injection. Epinephrine will significantly extend the duration of both infiltration anesthesia and peripheral nerve blockade with shorter-duration agents (e.g., lidocaine); epinephrine produces mild intensification of blockade but only most modest prolongation of epidural or peripheral blocks with bupivacaine.³⁶ Activation of α_2 -adrenergic receptors in the spinal cord may contribute to the beneficial effect of epidural epinephrine.

Clonidine and Dexmedetomidine. The α -2 agonist clonidine prolongs the action of local anesthetics by about 2 hours with wide variation between studies³⁸, and its conjectured mechanisms of action include actions on α -2 receptors and on hyperpolarization-induced currents.³⁹ However, there is a large number of negative studies, and adverse systemic events are of concern, including hypotension, bradycardia, and sedation, such that limiting the clonidine dose to 0.5 to 1 $\mu\text{g}/\text{kg}$ of ideal body weight has been proposed. Dexmedetomidine is a much more specific α -2 agonist, and prolongs both motor and sensory block by long-acting local anesthetics by approximately 4 hours.⁴⁰ Similar to clonidine, dexmedetomidine has also been shown to block the hyperpolarization-induced current.⁴¹

Nevertheless, risk of systemic adverse effects remains high, and optimal doses have not been determined. There seems to be no increased risk of neurotoxicity when clonidine or dexmedetomidine are used as nerve block adjuvants.

Buprenorphine. The partial μ -opiate receptor agonist, buprenorphine, intensifies blockade by two mechanisms, namely blockade of κ - and δ -opioid receptors, and blockade of voltage-gated sodium channel-blocking properties.⁴² Blockade by long-acting local anesthetics is prolonged by about 6 hours, but at the price of a high incidence of nausea and vomiting, such that the use of buprenorphine has largely been abandoned.⁴³ Buprenorphine is considered safe in terms of neurotoxicity.

Dexamethasone. The most effective adjuvant for prolonging block duration with minimal side effects currently available is dexamethasone, able to prolong duration of medium-acting local anesthetics by 2 to 3 hours, and the block of long-acting local anesthetics by up to 10 hours on average.⁴⁴ Blocks can be prolonged by intravenous or perineural administration of dexamethasone. Despite the fact that perineural administration of dexamethasone seems to be more effective than systemic use, many providers use systemic dexamethasone to avoid mixing drugs which were not designed to be administered together, circumvent the problem of off-label perineural use, and profit from the antiemetic effects of systemic dexamethasone. Doses between 4 and 10 mg have typically been used in adults.⁴⁵ The precise mechanism of action of dexamethasone is not understood and the potential for neurotoxic side effects has not been adequately studied.

Site of Injection

The most rapid onset but the shortest duration of action occurs after intrathecal or subcutaneous administration of local anesthetics. The longest latencies and durations are observed after conventional non-ultrasound-guided large-volume brachial plexus blocks. For example, intrathecal bupivacaine will usually produce anesthesia within 5 minutes that will persist for 3 to 4 hours. However, when bupivacaine is administered for brachial plexus blockade, the onset time is approximately 20 to 30 minutes, and the duration of anesthesia (or at least analgesia) averages 10 hours.⁴⁶ These differences in the onset and duration of anesthesia and analgesia are due in part to the particular anatomy of the area of injection, which will influence the rate of diffusion and vascular absorption and, in turn, affect the amount of drug used for various types of regional anesthesia. In the subarachnoid space, for example, the lack of a nerve sheath around the spinal cord and deposition of the local anesthetic solution in the immediate vicinity of the spinal cord are responsible for the rapid onset of action, whereas the relatively small amount of drug used for spinal anesthesia probably accounts for the short duration of conduction block.

In contrast, the onset of brachial plexus blockade is slow because the anesthetic agent is usually deposited at some distance from the nerve and must diffuse through various tissue barriers before reaching the nerve membrane. The prolonged block with brachial plexus blockade may

be related to several factors, including comparatively slow rates of vascular absorption from the brachial plexus sheath, larger doses of drug required for this regional anesthetic technique, and comparatively long segments of nerves exposed to local anesthetic.

Carbonation and pH Adjustment of Local Anesthetics

The addition of sodium bicarbonate to a solution of local anesthetic applied to an isolated nerve accelerates the onset and decreases the minimum concentration (C_m) required for conduction blockade by increasing pH and increasing the share of uncharged local anesthetic molecules that can more easily diffuse into the nerve cell.⁴⁷ Although the effect of carbon dioxide on local anesthetic activity is easily demonstrable in isolated nerve, controversy exists concerning the clinical utility of carbonated local anesthetic solutions⁴⁸ and the widespread introduction of ultrasound-guided nerve blockade with faster and more reliable block onset has decreased the relevance of carbonation, at least for peripheral nerve blockade.

Mixtures of Local Anesthetics

Mixtures of local anesthetics for regional anesthesia are sometimes used in an effort to compensate for the short duration of action of certain rapidly acting agents such as chloroprocaine and lidocaine, and the long latency of longer-acting agents such as tetracaine and bupivacaine. Mixtures of chloroprocaine and bupivacaine theoretically offer significant clinical advantages because of the rapid onset and low systemic toxicity of chloroprocaine and the long duration of action of bupivacaine; however, clinical results in studies of combinations have been mixed.⁴⁹ The use of catheter techniques for many forms of regional anesthesia makes it possible to begin with a rapid-onset local anesthetic such as lidocaine, mepivacaine, or chloroprocaine and then follow with an infusion of either a shorter-acting or longer-acting local anesthetic thereafter. Clinicians should be cautioned to not use maximum doses of two local anesthetics in combination in the mistaken belief that their toxicities are independent.⁵⁰ Toxicity in fact, is additive. Moreover, the use of ultrasound-guided nerve blockade has, in general, led to a decreased onset time and has made mixing local anesthetics less clinically relevant.

Pregnancy

The spread and depth of epidural and spinal anesthesia are greater in pregnant than in nonpregnant women. The effects of pregnancy on local anesthetic potency may reflect a combined effect of mechanical factors associated with pregnancy (i.e., dilated epidural veins decrease the volume of the epidural and subarachnoid spaces) and direct effects of hormones, especially progesterone, on the susceptibility of nerves to conduction blockade by local anesthetics.⁵¹ Hormonal alterations are probably the more important of these two factors because greater spread of epidural anesthesia is already observed during the first trimester of pregnancy,⁵² before any gross change in vascular dimensions within the epidural or subarachnoid spaces. The dosage of local anesthetics should probably be reduced in patients in all stages of pregnancy.

Choice of Local Anesthetic for Various Regional Anesthetic Procedures

On the basis of anatomic considerations, regional anesthesia may be divided into infiltration anesthesia, intravenous regional anesthesia (IVRA), peripheral nerve blockade (including plexus blockade), central neural blockade, and topical anesthesia. An additional method of local anesthetic injection, tumescent anesthesia, is included because it is widely used in office-based plastic surgery.

INFILTRATION ANESTHESIA

Any local anesthetic may be used for infiltration anesthesia. Onset of action is almost immediate for all agents after intradermal or subcutaneous administration; however, the duration of anesthesia varies (Table 29.4). Epinephrine will prolong the duration of infiltration anesthesia by all local anesthetic drugs, although this effect is most pronounced when epinephrine is added to lidocaine. The choice of a specific drug for infiltration anesthesia largely depends on the desired duration of action.

The dosage of local anesthetic required for adequate infiltration anesthesia depends on the extent of the area to be anesthetized and the expected duration of the surgical procedure. When large surface areas have to be anesthetized, large volumes of dilute anesthetic solutions should be used. These considerations are particularly important when performing infiltration anesthesia in infants and smaller children. As an example, consider a 4-kg infant receiving infiltration anesthesia with the maximum safe dose of lidocaine, 5 mg/kg. Dosing to 5 mg/kg permits 20 mg/4 kg, which is 1 mL of a 2% solution or 4 mL of a 0.5% solution. Lidocaine is effective for infiltration in concentrations as dilute as 0.3% to 0.5%, so the more dilute solution can be used more safely to anesthetize a larger area.

Patients frequently experience pain immediately after subcutaneous injection of local anesthetic solutions, in part because of the acidic nature of these solutions, and

in part because lidocaine briefly activates transient receptor potential vanilloid-1 (TRPV-1) and transient receptor potential ankyrin-1 (TRPA-1) channels, causing pain, before sodium channel block subsequently silences the neuron.⁵³ Alkalization of lidocaine solutions by the addition of sodium bicarbonate immediately before injection reduces pain on skin infiltration⁵⁴ and may improve onset (see earlier).

Infiltration analgesia and indwelling wound catheters are used increasingly as components of multimodal postoperative analgesia.⁵⁵⁻⁵⁷ In particular, sustained-release formulations such as Exparel have been introduced into clinical practice (see the section Development of Prolonged-Duration and Sensory- or Nociceptive-Selective Local Anesthetics).

INTRAVENOUS REGIONAL ANESTHESIA

IVRA (Bier's block) involves the intravenous administration of a local anesthetic into a tourniquet-occluded limb. The local anesthetic diffuses from the peripheral vascular bed to nonvascular tissue such as axons and nerve endings. Both the safety and the efficacy of this regional anesthetic procedure depend on interruption of blood flow to the involved limb and gradual release of the occluding tourniquet.

Lidocaine and prilocaine have been the drugs used most frequently for IVRA. Drugs with a high cardiotoxic potential such as bupivacaine should not be used for IVRA. One might suppose a safety advantage with the aminoester-linked compounds because of their hydrolysis in blood; however, thrombophlebitis has been reported with chloroprocaine. In general, approximately 3 mg/kg (40 mL of a 0.5% solution) of preservative-free lidocaine without epinephrine is used for upper extremity procedures. For surgical procedures on the lower limbs, 50 to 100 mL of a 0.25% lidocaine solution have been used. Even though the safety profile of IVRA is considered very good, seizures have been reported with lidocaine doses as low as 1.4 mg/kg of lidocaine, and cardiovascular collapse (CC) can occur.⁵⁸

TABLE 29.4 Infiltration Anesthesia

| Drug | PLAIN SOLUTION | | | EPINEPHRINE-CONTAINING SOLUTION | |
|--------------------------|-------------------|-------------------|----------------|---------------------------------|----------------|
| | Concentration (%) | Maximum Dose (mg) | Duration (min) | Maximum Dose (mg) | Duration (min) |
| SHORT DURATION | | | | | |
| Procaine | 1-2 | 500 | 20-30 | 600 | 30-45 |
| Chloroprocaine | 1-2 | 800 | 15-30 | 1000 | 30 |
| MODERATE DURATION | | | | | |
| Lidocaine | 0.5-1 | 300 | 30-60 | 500 | 120 |
| Mepivacaine | 0.5-1 | 300 | 45-90 | 500 | 120 |
| Prilocaine | 0.5-1 | 350 | 30-90 | 550 | 120 |
| LONG DURATION | | | | | |
| Bupivacaine | 0.25-0.5 | 175 | 120-240 | 200 | 180-240 |
| Ropivacaine | 0.2-0.5 | 200 | 120-240 | 250 | 180-240 |

PERIPHERAL AND TRUNCAL NERVE BLOCKADE

Regional anesthetic procedures that inhibit conduction in fibers of the peripheral nervous system can be classified together under the general category of peripheral nerve blockade. This form of regional anesthesia has been arbitrarily subdivided into minor and major nerve blocks. Minor nerve blocks are defined as procedures involving single nerve entities such as the ulnar or radial nerve, whereas major nerve blocks involve the blockade of two or more distinct nerves or a nerve plexus or the blockade of very large nerves at more proximal sites (i.e., the femoral and sciatic nerves).

Most local anesthetic drugs can be used for minor nerve blocks. The onset of blockade is rapid with most drugs, and the choice of drug is determined primarily by the required duration of anesthesia. A classification of the various drugs according to their duration of action is shown in **Table 29.5**. It has become possible to define the minimum local anesthetic volume for ultrasound-guided peripheral nerve blockade and across several nerves; the volume was approximately 0.1 mL per mm² of nerve cross-sectional area.^{59,60} However, as mentioned earlier, minimal volume to achieve sensory blockade 30 minutes after block may also mean decreased duration of the block as compared to “traditional” high volumes clinicians were accustomed to using during stimulator-guided regional anesthesia.

Brachial plexus blockade for upper limb surgery is the most common major peripheral nerve block technique,

but many lower extremity procedures are now carried out under peripheral nerve blocks for anesthesia or postoperative analgesia. A significant difference exists between the onset times of various agents when these blocks are used (**Table 29.6**). In general, agents of intermediate potency exhibit a more rapid onset than the more potent compounds do.

Next to surgeries on the upper and lower extremities, peripheral nerve blocks have become popular for treating pain after thoracic and abdominal procedures. In the case of superficial thoracic surgery such as breast surgery, field blocks such as the PECS-1 and PECS-2 and Serratus plane block have been successfully used. Proximal intercostal nerve blocks and paravertebral blocks are also employed for mastectomies and reconstructions by some institutions, but more research is needed to define efficacy, precise indications, and procedure-specific details of technique.⁶¹ Paravertebral and proximal intercostal techniques appear equally effective as epidural analgesia in treating pain after video-assisted thoracoscopic surgery (VATS) and thoracotomy and have fewer side effects.⁶²

PERINEURAL AND PLEXUS INFUSIONS

Local anesthetics are being administered by continuous infusion for several days after surgery^{56,63} or for periods of weeks to months for the treatment of chronic malignant and

TABLE 29.5 Minor Nerve Blocks

| Drug | Usual Concentration (%) | Usual Volume (mL) | Dose* (mg) | AVERAGE DURATION (MIN) | |
|----------------|-------------------------|-------------------|------------|------------------------|----------------------------------|
| | | | | Plain Solutions | Epinephrine-Containing Solutions |
| Procaine | 2 | 5-20 | 100-400 | 15-30 | 30-60 |
| Chloroprocaine | 2 | 5-20 | 100-400 | 15-30 | 30-60 |
| Lidocaine | 1 | 5-20 | 50-200 | 60-120 | 120-180 |
| Mepivacaine | 1 | 5-20 | 50-200 | 60-120 | 120-180 |
| Prilocaine | 1 | 5-20 | 50-200 | 60-120 | 120-180 |
| Bupivacaine | 0.25-0.5 | 5-20 | 12.5-100 | 180-360 | 240-420 |
| Ropivacaine | 0.2-0.5 | 5-20 | 10-100 | 180-360 | 240-420 |

*Doses are for a 70-kg adult. For pediatric doses, see **Chapter 76**.

TABLE 29.6 Major Nerve Blocks

| Drug | Usual Concentration (%) | Usual Volume (mL) | Maximum Dose (mg) Without/With Epinephrine | Onset (min) | Duration (min) |
|-----------------|-------------------------|-------------------|--|-------------|----------------|
| Lidocaine | 1-2 | 30-50 | 350/500 | 10-20 | 120-240 |
| Mepivacaine | 1-1.5 | 30-50 | 350/500 | 10-20 | 180-300 |
| Prilocaine | 1-2 | 30-50 | 400/600 | 10-20 | 180-300 |
| Bupivacaine | 0.25-0.5 | 30-50 | 175/225 | 20-30 | 360-720 |
| Levobupivacaine | 0.25-0.5 | 30-50 | 200/225 | 20-30 | 360-720 |
| Ropivacaine | 0.2-0.5 | 30-50 | 200/250 | 20-30 | 360-720 |

See also Chapter 46. Doses are for a 70-kg adult receiving epinephrine-containing solutions. Doses should be reduced for children, for patients with specific risk factors, and for blocks in specific locations (e.g., interscalene). When two or more blocks are performed together, the sum of the doses for each of the individual blocks should not exceed the max dose listed here.

nonmalignant pain. However, because of the poor sensory selectivity of contemporary local anesthetics, prolonged use of catheters at times conflicts with the paradigm of fast mobilization, especially as neuraxial and lower extremity techniques are concerned. With prolonged infusions there is a theoretical potential for delayed systemic accumulation and toxicity. However, the activation of the acute-phase response after trauma or surgery also leads to an increase in α -1 acidic glycoprotein, which is potent at binding free local anesthetics and decreases the risk of cumulation of free local anesthetic.⁶⁴

CENTRAL NEURAL BLOCKADE

Any of the local anesthetic drugs may be used for epidural anesthesia (Table 29.7), although procaine and tetracaine are rarely used because of their long onset times. Drugs of intermediate potency produce surgical anesthesia of 1 to 2 hours' duration, whereas long-acting drugs usually produce 3 to 4 hours of anesthesia. The duration of short- and intermediate-acting drugs is significantly prolonged by the addition of epinephrine (1:200,000), but the duration of long-acting drugs is only minimally affected by epinephrine. The onset of lumbar epidural anesthesia occurs within 5 to 15 minutes after the administration of chloroprocaine, lidocaine, mepivacaine, and prilocaine. Bupivacaine has a slower onset of action.

Bupivacaine epidural bolus doses at a concentration of 0.125% produce adequate postoperative analgesia in many clinical settings with only mild motor deficits.⁶⁵ Continuous epidural infusions of bupivacaine as dilute as 0.0625% to 0.1% are useful for labor epidural analgesia, especially when administered in combination with opioids and epinephrine. Bupivacaine 0.25% may be used for more intense analgesia (particularly during combined epidural-general anesthesia cases) with moderate degrees of motor block. Bupivacaine at concentrations of 0.5% to 0.75% is associated with a more profound degree of motor block, and surgical anesthesia. It should be emphasized that although high concentrations of local anesthetics may be appropriate for episodic bolus dosing for surgery, these concentrations (i.e., 0.25% for bupivacaine) should not be first choice for continuous epidural infusions. In some patients, increasing the local anesthetic dose or addition of adjuvants such as

epinephrine and lipophilic opioids is necessary to achieve adequate block intensity. Bolus injections produce much more cephalocaudad spread than continuous infusions do. When concentrated bupivacaine solutions are used for infusions, they have the potential for excessive local effect with an associated risk for unwanted and very prolonged motor blockade. Drugs available for subarachnoid administration are shown in Table 29.8. Bupivacaine is widely used as a spinal anesthetic, either as a hyperbaric solution at a concentration of 0.75% with 8.25% dextrose or by using the nearly isobaric (though slightly hypobaric) 0.5% solution. Intrathecal bupivacaine possesses anesthetic profile similar to that of tetracaine.⁶⁶

The addition of vasoconstrictors may prolong the duration of spinal anesthesia; for example, the addition of 0.2 to 0.3 mg of epinephrine to lidocaine, tetracaine, or bupivacaine solutions will produce a 50% or greater increase in duration.^{67,68} The duration of spinal anesthesia produced by tetracaine can also be increased to a similar extent by adding 1 to 5 μ g of phenylephrine. The addition of epinephrine to bupivacaine or lidocaine may be more effective in prolonging the duration of spinal anesthesia in lumbosacral segments than in thoracic segments.

TOPICAL ANESTHESIA

A number of local anesthetic formulations are available for topical anesthesia (Table 29.9), lidocaine, dibucaine, tetracaine, and benzocaine being the drugs used most commonly. In general, these preparations provide effective but relatively short durations of analgesia when applied to mucous membranes or abraded skin. Their efficacy is determined by drug form, melting point, concentration, and skin permeability.⁶⁹ Lidocaine and tetracaine sprays are commonly used for endotracheal anesthesia before intubation or for mucosal analgesia for bronchoscopy or esophagoscopy.

A variety of topical local anesthetic formulations have been developed to penetrate intact skin. EMLA, which is a eutectic mixture of 2.5% lidocaine base and 2.5% prilocaine base, is widely used for venipuncture, intravenous cannulation, skin grafting, and a range of other uses, including circumcision.⁷⁰ This preparation must be applied under an occlusive bandage for 45 to 60 minutes to obtain effective

TABLE 29.7 Epidural Anesthesia

| Drug With Epinephrine (1:200,000) | Usual Concentration (%) | Usual Volume (mL) | Maximum Dose (mg) | | |
|-----------------------------------|-------------------------|-------------------|--------------------------|-------------------|----------------------|
| | | | Without/With Epinephrine | Usual Onset (min) | Usual Duration (min) |
| Chloroprocaine | 2-3 | 15-30 | 700/900 | 5-15 | 30-90 |
| Lidocaine | 1-2 | 15-30 | 350/500 | 5-15 | |
| Mepivacaine | 1-2 | 15-30 | 350/500 | 5-15 | 60-180 |
| Prilocaine | 1-3 | 15-30 | 350/500 | 5-15 | |
| Bupivacaine | 0.25-0.5 | 15-30 | 175/225 | 15-20 | 180-350 |
| Levobupivacaine | 0.25-0.75 | 15-30 | 200/250 | 15-20 | 180-350 |
| Ropivacaine | 0.2-0.75 | 15-30 | 200/250 | 15-20 | 180-350 |

See also Chapter 45. Doses are for a 70-kg adult receiving epinephrine-containing solutions. Doses should be reduced for children, for patients with specific risk factors, and for specific catheter tip locations (e.g., upper thoracic).

TABLE 29.8 Spinal Anesthesia

| Drug | Usual Concentration (%) | Usual Volume (mL) | Total Dose (mg) | Baricity | Glucose Concentration (%) | Usual Duration (min) |
|-----------------|-------------------------|-------------------|-----------------|------------|---------------------------|----------------------|
| Procaine | 10.0 | 1-2 | 100-200 | Hyperbaric | 5.0 | 30-60 |
| Lidocaine | 1.5, 5.0 | 1-2 | 30-100 | Hyperbaric | 7.5 | 30-90 |
| Mepivacaine | 4.0 | 1-2 | 40-80 | Hyperbaric | 9.0 | 30-90 |
| Tetracaine | 0.25-1.0 | 1-4 | 5-20 | Hyperbaric | 5.0 | 90-200 |
| | 0.25 | 2-6 | 5-20 | Hypobaric | | 90-200 |
| | 1.0 | 1-2 | 5-20 | Isobaric | | 90-200 |
| Dibucaine | 0.25 | 1-2 | 2.5-5.0 | Hyperbaric | 5.0 | 90-200 |
| | 0.5 | 1-2 | 5-10 | Isobaric | | 90-200 |
| | 0.06 | 5-20 | 3-12 | Hypobaric | | 90-200 |
| Bupivacaine | 0.5 | 3-4 | 15-20 | Isobaric | | 90-200 |
| | 0.75 | 2-3 | 15-20 | Hyperbaric | 8.25 | 90-200 |
| Levobupivacaine | 0.5 | 3-4 | 15-20 | Isobaric | | 90-200 |
| | 0.75 | 2-3 | 15-20 | Hyperbaric | | 90-200 |
| Ropivacaine | 0.5 | 3-4 | 15-20 | Isobaric | | 90-200 |
| | 0.75 | 2-3 | 15-20 | Hyperbaric | | 90-200 |

Doses are for a 70-kg adult. Dosing may be reduced during pregnancy and with advancing age. Pediatric dosing is detailed in Chapter 76.

TABLE 29.9 Various Preparations Intended for Topical Anesthesia

| Anesthetic Ingredient | Concentration (%) | Pharmaceutical Application Form | Intended Area of Use |
|-----------------------|--|---------------------------------|--|
| Benzocaine | 1-5 | Cream | Skin and mucous membrane |
| | 20 | Ointment | Skin and mucous membrane |
| | 20 | Aerosol | Skin and mucous membrane |
| Cocaine | 4 | Solution | Ear, nose, throat |
| Dibucaine | 0.25-1 | Cream | Skin |
| | 0.25-1 | Ointment | Skin |
| | 0.25-1 | Aerosol | Skin |
| | 0.25 | Solution | Ear |
| | 2.5 | Suppositories | Rectum |
| Cyclomine | 0.5-1 | Solution | Skin, oropharynx, tracheobronchial tree, urethra, rectum |
| Lidocaine | 2-4 | Solution | Oropharynx, tracheobronchial tree, nose |
| | 2 | Jelly | Urethra |
| | 2.5-5 | Ointment | Skin, mucous membrane, rectum |
| | 2 | Viscous | Oropharynx |
| | 10 | Suppositories | Rectum |
| | 10 | Aerosol | Gingival mucosa |
| Tetracaine | 0.5-1 | Ointment | Skin, rectum, mucous membrane |
| | 0.5-1 | Cream | Skin, rectum, mucous membrane |
| | 0.25-1 | Solution | Nose, tracheobronchial tree |
| EMLA | Lidocaine, 2.5 Prilocaine, 2.5 | Cream | Intact skin |
| TAC | Tetracaine, 0.5 Epinephrine, 1:200,000 Cocaine, 11.8 | Solution | Cut skin |
| LET | Lidocaine, 4% Epinephrine, 1:20,000 Tetracaine, 0.5% | Solution | Cut skin |

EMLA, Eutectic mixture of lidocaine and prilocaine; LET, lidocaine-epinephrine-tetracaine; TAC, tetracaine-epinephrine-cocaine.
From Covino B, Vassallo H. *Local Anesthetics: Mechanisms of Action and Clinical Use*. Orlando, FL: Grune and Stratton; 1976.

cutaneous anesthesia; longer application times increase the depth and reliability of skin analgesia. EMLA appears to be quite safe in neonates, and methemoglobinemia with the use of prilocaine is exceedingly uncommon. EMLA is more effective for newborn circumcision than placebo is but less effective than dorsal penile nerve block.^{70,71} Several alternative topical local anesthetic formulations also are in use, including tetracaine gel⁷² and liposomal lidocaine.⁷³ Physical methods to accelerate local anesthetic transit across skin, including iontophoresis, local heating, electroporation, and a variety of forms of needleless pressure injection, may lead to more rapid onset of cutaneous analgesia.⁷⁴ Synera (originally studied as S-Caine) is a formulation of lidocaine and tetracaine that was developed with a heating element (activated by opening the package to initiate an oxygen-dependent exothermic reaction). This formulation has a rapid onset and evokes vasodilatation.⁷⁵

Topical anesthesia through cut skin is commonly used in pediatric emergency departments for liquid application into lacerations that require suturing. Historically, this had been provided by a mixture of tetracaine, epinephrine (adrenaline), and cocaine, known as TAC. TAC is ineffective through intact skin; in contrast, its rapid absorption from mucosal surfaces can lead to toxic, even fatal reactions. Another potential substance is ELA-max, a liposomal formulation of lidocaine which is useful for cuts or abrasions.⁷⁶ Lastly, Lidoderm patches have been in use for the topical treatment of postherpetic neuralgia.⁷⁷

Because of concerns regarding cocaine toxicity and the potential for diversion and abuse, cocaine-free topical preparations are strongly recommended, and alternatives such as the combination of an α_1 -adrenergic agonist (oxy-metazoline or phenylephrine) and a local anesthetic such as 2% to 4% lidocaine should be used, with more dilute solutions being recommended for infants and children.

TUMESCENT ANESTHESIA

A technique of local anesthesia most commonly used by plastic surgeons during liposuction procedures involves the subcutaneous injection of large volumes of dilute local anesthetic in combination with epinephrine and other agents. Total doses of lidocaine ranging from 35 to 55 mg/kg have been reported to produce safe plasma concentrations around or below 5 μ g/mL, but notably, these may only peak up to 20 hours after infusion, depending on the site of infiltration.⁷⁸ Despite these seemingly huge doses, very good safety outcomes have been reported in several case series.⁷⁹ Conversely, there have been several case series of cardiac arrest and death during plastic surgical procedures in patients with multiple risk factors. Here high local anesthetic concentrations and concomitant use of sedatives may have contributed to the patients' instability and deterioration.⁸⁰ Factors governing uptake and clearance from this method of local anesthetic delivery deserve further study.

SYSTEMIC LOCAL ANESTHETICS FOR POSTOPERATIVE PAIN AND NEUROPATHIC PAIN

Systemic lidocaine has been extensively investigated over the past 10 years for its potential to inhibit G protein-coupled

receptors, especially those of the Gq11 subfamily. Systemic local anesthetics have a strong antiinflammatory effect, but their application has only been shown to be of clinical significance in visceral surgery where they decrease inflammation and pain, and speed recovery when compared to placebo.⁸¹

A broad variety of local anesthetics, antiarrhythmics, anticonvulsants, and other Na^+ channel blockers are administered intravenously, orally, or both, to relieve a number of forms of chronic neuropathic pain.⁸² Clinical results are variable.⁸³ Although successful responses from intravenous lidocaine are often taken as a positive indication for oral mexiletine, some patients find mexiletine difficult to tolerate. When the signs of neuropathic pain are reversed by lidocaine infusion, normal nociception and other sensory modalities are unaffected, suggesting that the neurophysiologic correlate of the disease has an unusually high susceptibility to these drugs, present in plasma at concentrations 50 to 100 times lower than that required to block normal impulses in peripheral fibers. Laboratory studies suggest that ectopic impulse activity arising at a site of injury or elsewhere, such as the dorsal root ganglion, contributes to the neuropathic pain and that such impulses are particularly sensitive to use-dependent Na^+ channel blockers. It is noteworthy that relief of preexisting neuropathic pain, both clinically and in animal models,⁸⁴ can in some cases persist for days, weeks, or months after a single intravenous infusion of drug (e.g., lidocaine), far beyond the lifetime of the drug in vivo or any nerve block that it might affect. The mechanism of this remarkable action remains a mystery. Intuitively, this should be especially true for hereditary syndromes featuring gain-of-function mutations at the sodium channel, such as primary erythromelalgia and recent clinical experience and translational experiments have confirmed that mexiletine has the potential to normalize sodium currents in one specific mutation associated with erythromelalgia.⁸⁵

Pharmacokinetics

The concentration of local anesthetics in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution, and the rate of biotransformation and excretion of the specific drug.^{79,80} Patient-related factors such as age, cardiovascular status, and hepatic function influence the physiologic disposition and resultant blood concentration of local anesthetics.

ABSORPTION

The systemic absorption of local anesthetics is determined by the site of injection, dosage and volume, addition of a vasoconstrictor agent, and the pharmacologic profile of the agent itself.^{86,87} Comparison of the blood concentration of local anesthetics after various routes of administration reveals that the anesthetic drug level is highest after intercostal nerve blockade, followed in order of decreasing concentration by injection into the caudal epidural space, lumbar epidural space, brachial plexus, and subcutaneous tissue. When a local anesthetic solution is exposed to an area of greater vascularity, a greater rate and degree

of absorption occur. This relationship is of clinical significance because use of a fixed dose of a local anesthetic agent may be potentially toxic in one area of administration but not in others, and in one patient with specific physiology, but not in others. For example, the use of 400 mg of lidocaine without epinephrine for an intercostal nerve block results in an average peak venous plasma level of approximately 7 μ g/mL, which is sufficiently high to cause symptoms of central nervous system (CNS) toxicity in some patients. By comparison, this same dose of lidocaine used for a brachial plexus block yields a mean maximum blood level of approximately 3 μ g/mL, which is rarely associated with signs of toxicity.

The maximum blood concentration of local anesthetic drugs is related to the total dose of drug administered for any particular site of administration. For most drugs there is a proportionality between the amount of drug administered and the resultant peak anesthetic blood concentration. Epinephrine decreases the rate of vascular absorption of certain agents from various sites of administration and thus lowers their potential systemic toxicity. A 5- μ g/mL concentration of epinephrine (1:200,000) significantly reduces the peak blood levels of lidocaine and mepivacaine irrespective of the site of administration. Resorption of local anesthetics follows a biphasic pattern, with an initial fast peak reflecting the fluid phase and later a slower second peak corresponding to resorption from the lipid compartment.⁸⁸ The addition of epinephrine to local anesthetic solutions slows the first phase.⁸⁹ The net clinical effect is a more profound block, and lower systemic levels.⁹⁰

DISTRIBUTION

The systemic distribution of local anesthetics in many settings can be described sufficiently by a two-compartment model.⁹¹ The rapid disappearance phase is believed to be related to uptake by rapidly equilibrating tissues (i.e., tissues that have high vascular perfusion). The slower phase of disappearance from blood is mainly a function of the particular compound.⁸⁶ Local anesthetic drugs are distributed throughout all body tissues, but the relative concentration in different tissues varies. In general, more highly perfused organs show higher concentrations of local anesthetic drug than less well perfused organs do. The primary extraction takes place in the liver, but local anesthetics are also rapidly extracted by lung tissue.^{92,93}

BIOTRANSFORMATION AND EXCRETION

The pattern of metabolism of local anesthetic agents varies according to their chemical classification. The esters, or procaine-like drugs, undergo hydrolysis in plasma by the pseudocholinesterase enzymes; clearance of chloroprocaine is especially rapid.^{94,95} The aminoamide drugs undergo enzymatic degradation primarily in the liver. Lidocaine is metabolized somewhat more rapidly than mepivacaine, which in turn is more rapidly metabolized than bupivacaine.^{71,96,97} Excretion of the metabolites of amide-type local anesthetics occurs via the kidney. Less than 5% of the unchanged drug is excreted via the kidney into urine.

PHARMACOKINETIC ALTERATIONS BY PATIENT STATUS

Patient age may influence the physiologic disposition of local anesthetics. The half-life of lidocaine after intravenous administration averaged 80 minutes in human volunteers varying in age from 22 to 26 years, whereas volunteers 61 to 71 years of age demonstrated a significantly prolonged lidocaine half-life that averaged 138 minutes.⁹⁸

Newborn infants have immature hepatic enzyme systems and hence prolonged elimination of lidocaine, bupivacaine, and ropivacaine.⁹⁹ Bupivacaine, for example, has a terminal elimination half-life in adults that averages around 3.5 hours. In neonates and some younger infants, terminal elimination half-lives may be as long as 8 to 12 hours. Prolonged elimination is particularly an issue for continuous infusions of local anesthetics in infants, and seizures have been associated with high bupivacaine infusion rates.¹⁰⁰ Based on analysis of these cases, a maximum infusion rate of 0.4 mg/kg/h for prolonged bupivacaine infusions has been proposed for children and adults, whereas prolonged infusion rates for neonates and young infants should not exceed 0.2 mg/kg/h.¹⁰¹ Even at 0.2 mg/kg/h, plasma bupivacaine concentrations were found to be rising toward a toxic range in some younger infants after 48 hours.¹⁰² Similarly, prolonged lidocaine infusions in neonates should not exceed 0.8 mg/kg/h. The potential for toxicity with lidocaine infusions in neonates is also increased by the accumulation of its principal metabolite, monoethylglycinexylidide (MEGX), which can cause seizures. Chloroprocaine may offer unique advantages for epidural infusion in neonates because it is rapidly cleared from plasma, even in preterm neonates.¹⁰³

Decreased hepatic blood flow or impaired hepatic enzyme function can produce a substantial elevation of blood levels of the aminoamide local anesthetics. An average lidocaine half-life of 1.5 hours was reported in volunteers with normal hepatic function, whereas patients with liver disease demonstrated an average half-life of 5.0 hours. The rate of disappearance of lidocaine from blood has also been shown to be markedly prolonged in patients with congestive heart failure.¹⁰⁴

In some patients CNS depression is seen without a preceding excitatory phase, particularly if other CNS depressant drugs had been administered.

Toxicity

Local anesthetic drugs are relatively safe if administered in an appropriate dosage and in the correct anatomic location. However, systemic and localized toxic reactions can occur, usually as a result of accidental intravascular or intrathecal injection or administration of an excessive dose. In addition, specific adverse effects are associated with the use of certain drugs, such as allergic reactions to the aminoester drugs and methemoglobinemia after the use of prilocaine.

SYSTEMIC TOXICITY

Systemic reactions to local anesthetics primarily involve the CNS and the cardiovascular system. In general, the CNS is more susceptible to the actions of systemic local anesthetics

than the cardiovascular system, and thus the dose or blood level of local anesthetic required to produce CNS toxicity is usually lower than that resulting in circulatory collapse. However, a recent review of 93 cases showed that the symptoms encountered initially vary widely; and only 60% of patients actually exhibit the classic sequence of toxic events from minor CNS symptoms (e.g., perioral tingling, metallic taste, tinnitus), followed by major CNS symptoms (seizures) and cardiovascular collapse (CC).¹⁰⁵ Overall, the incidence of systemic toxicity following regional anesthesia is estimated at 1:1000 for nerve stimulator-guided blockade, and 1:1600 for ultrasound-guided regional anesthesia.¹⁰⁶

Central Nervous System Toxicity

The initial symptoms of local anesthetic-induced CNS toxicity are feelings of lightheadedness and dizziness followed frequently by visual and auditory disturbances such as difficulty focusing and tinnitus. Other subjective CNS symptoms include disorientation and occasional feelings of drowsiness. Objective signs of initial CNS toxicity are usually excitatory in nature and include shivering, muscular twitching, and tremors initially involving muscles of the face and distal parts of the extremities. Ultimately, generalized convulsions of a tonic-clonic nature occur. If a sufficiently large dose or rapid intravenous injection of a local anesthetic is administered, the initial signs of CNS excitation are rapidly followed by a state of generalized CNS depression. Seizure activity ceases, and respiratory depression and ultimately respiratory arrest may occur. CNS excitation may be the result of an initial blockade of inhibitory pathways in the cerebral cortex by local anesthetic drugs but can also result from the net stimulation of release of glutamate, an excitatory amino acid neurotransmitter. Blockade of inhibitory pathways allows facilitatory neurons to function in an unopposed fashion, which results in an increase in excitatory activity leading to convulsions. A further increase in the dose of local anesthetic leads to inhibition of activity of both the inhibitory and facilitatory circuits, which results in a generalized state of CNS depression.

In general, a correlation exists between potency of the local anesthetic and intravenous CNS toxicity.¹⁰⁷ Convulsions caused by an inadvertent intravenous bolus of local anesthetic can generally be terminated by small intravenous doses of a benzodiazepine, such as midazolam, or by small intravenous doses of propofol. While propofol is faster acting, large doses should be avoided, especially in patients with hemodynamic instability.¹⁰⁸ Respiratory or metabolic acidosis increases the risks for CNS toxicity from local anesthetics.¹⁰⁹ Elevated PaCO_2 enhances cerebral blood flow and thus the anesthetic is delivered more rapidly to the brain. In addition, diffusion of carbon dioxide into neuronal cells decreases intracellular pH, which facilitates conversion of the base form of the drugs to the cationic form. The cationic form does not diffuse well across the nerve membrane, so ion trapping will occur, which will increase the apparent CNS toxicity of local anesthetics. Hypercapnia and acidosis also decrease the plasma protein binding of local anesthetic agents.¹¹⁰ Accordingly, normocapnia should be targeted during episodes of local anesthetic systemic toxicity.

The clinical implication of this effect of hypercapnia and acidosis on toxicity deserves emphasis. Seizures produce hypoventilation and a combined respiratory and metabolic

acidosis, which further exacerbates the CNS toxicity. In the setting of local anesthetic toxic reactions, it is essential to provide prompt assisted ventilation and circulatory support as needed to prevent or correct hypercapnia and acidosis and to prevent or correct hypoxemia, which also exacerbates CNS toxicity. Based on the preceding discussion, it should be apparent that clinicians performing major conduction blockade should make a routine practice of having the following ready at hand: monitoring equipment; an oxygen tank or wall oxygen outlet; rescue airway equipment; and drugs to terminate convulsions, such as midazolam, thiopental, or propofol.

Cardiovascular System Toxicity

Local anesthetics can exert direct actions on both the heart and peripheral blood vessels, as well as indirect actions on the circulation by blockade of sympathetic or parasympathetic efferent activity.

Direct Cardiac Effects. The main mechanisms of local anesthetic toxicity are blockades of cardiac sodium channels leading to negative inotropy and arrhythmia. Local anesthetics act directly by decreasing the conduction in Purkinje fibers and cardiomyocytes by prolonging the recovery time. Other facets of local anesthetic toxicity include inhibition of fatty acid metabolism, interference with calcium homeostasis, and disruption of the mitochondrial respiratory chain.¹¹¹ The primary cardiac electrophysiologic effect of local anesthetics is a decrease in the rate of depolarization in the fast conducting tissues of Purkinje fibers and ventricular muscle.¹¹² This reduction in rate is believed to be due to a decrease in the availability of fast sodium channels in cardiac membranes. Action potential duration and the effective refractory period are also decreased by local anesthetics. However, this effect is dose-dependent and substance-specific. Specifically, electrophysiologic studies have shown that high blood levels of local anesthetics will prolong conduction time through various parts of the heart, as indicated on the electrocardiogram (ECG) by an increase in the PR interval and duration of the QRS complex. Extremely high concentrations of local anesthetics depress spontaneous pacemaker activity in the sinus node, thereby resulting in sinus bradycardia and sinus arrest. Also, the electrophysiologic effects of various agents differ qualitatively. Bupivacaine depresses the rapid phase of depolarization (V_{max}) in Purkinje fibers and ventricular muscle to a greater extent than lidocaine does. In addition, the rate of recovery from a use-dependent block is slower in bupivacaine-treated papillary muscles than in lidocaine-treated muscles. This slow rate of recovery results in incomplete restoration of Na^+ channel availability between action potentials, particularly at high heart rates. These differential effects of lidocaine and bupivacaine have been advanced as explanations of the antiarrhythmic properties of lidocaine versus the arrhythmogenic potential of bupivacaine. All local anesthetics exert dose-dependent negative inotropic action on cardiac muscle; the depression of cardiac contractility is roughly proportional to conduction blocking potency. Thus bupivacaine and tetracaine are more potent cardio depressants than is lidocaine. Local anesthetics may depress myocardial contractility by affecting calcium influx and triggered release from the sarcoplasmic reticulum,¹¹³ as well as by

inhibiting cardiac sarcolemmal Ca^{2+} currents and Na^+ currents. Lastly, mitochondrial metabolism is inhibited by bupivacaine, and, to a lesser extent, other long-acting local anesthetics such as ropivacaine,¹¹⁴ while the effect of lidocaine is smaller.

Direct Peripheral Vascular Effects. Local anesthetics exert biphasic effects on peripheral vascular smooth muscle.¹⁰³ Low concentrations of lidocaine and bupivacaine produced vasoconstriction in the cremaster muscle of rats, whereas high concentrations produced vasodilation in both isolated tissue models and *in vivo*. Cocaine is the only local anesthetic that consistently causes vasoconstriction at all concentrations because of its ability to inhibit the uptake of norepinephrine by premotor neurons and thus to potentiate neurogenic vasoconstriction.

COMPARATIVE CARDIOVASCULAR TOXICITY

All local anesthetics, but especially bupivacaine, can cause rapid and profound cardiovascular depression. The cardio-toxicity of bupivacaine appears to differ from that of lidocaine in the following manner:

1. The ratio of the dosage required for irreversible CC and the dosage that will produce CNS toxicity (convulsions; i.e., the CC/CNS ratio) is lower for bupivacaine and etidocaine than for lidocaine.¹¹⁵
2. Ventricular arrhythmias and fatal ventricular fibrillation may occur more often after the rapid intravenous administration of a large dose of bupivacaine but far less frequently with lidocaine. The CNS effects of local anesthetics may contribute to the generation of arrhythmias.
3. A pregnant patient may be more sensitive to the cardio-toxic effects of bupivacaine than a nonpregnant animal or patient.¹¹⁶ Consequently, the 0.75% solution of bupivacaine is no longer recommended for use in obstetric anesthesia in the United States.
4. Cardiac resuscitation is more difficult after bupivacaine-induced CC, and acidosis and hypoxia markedly potentiate the cardiotoxicity of bupivacaine.¹¹⁷ Conversely, Intralipid is believed to be most effective in bupivacaine-induced toxicity. Despite the experimental or clinical anecdotal use of many different resuscitation drugs in the setting of bupivacaine overdose, current guidelines focus on standard cardiopulmonary resuscitation, albeit with titration rather than fixed doses of epinephrine, early administration of lipid emulsion, and avoidance of propofol in settings of hemodynamic instability.¹⁰⁸ Bupivacaine-induced ventricular arrhythmias should not be treated with vasopressin, calcium channel blockers, β -blockers, or other local anesthetics with antiarrhythmic potential (such as lidocaine).¹¹⁸

Pharmacokinetic studies have estimated that Intralipid decreases cardiac bupivacaine concentration by 11% within 3 minutes of administration, and cerebral bupivacaine content by 18% within 15 minutes.¹¹⁹ Even though these findings are theoretical, they underline the notion that Intralipid should not be considered an antidote with full antagonistic properties. Rather, limited evidence suggests that it will considerably reduce the bupivacaine concentration in target organs, most likely improve metabolism,

and potentially have direct beneficial effects at the sodium channel. Intralipid is a valuable contribution to, but not a substitute for, careful and meticulous conduct of regional anesthesia.¹²⁰

The clinical implications for cardiac resuscitation after intravascular injection or overdose of local anesthetic are the following:

1. No medications are uniformly effective in facilitating resuscitation from bupivacaine-induced cardiac arrest or severe ventricular tachycardia (despite our recommendations regarding Intralipid later). Basic principles of cardiopulmonary resuscitation should be emphasized first, including attention to securing the airway, providing oxygenation and ventilation, and performing chest compressions as indicated.
2. Because resuscitation after local anesthetic-induced circulatory collapse is difficult, prevention of massive intravascular injection or excessive dosing is crucial.
3. Negative aspiration of the syringe does not always exclude intravascular placement. Incremental, fractionated dosing should be the rule for all patients undergoing major conduction blockade. Even though changes on the ECG are not present in all cases before circulatory collapse, they can often be seen, and continuous attention to the ECG (including changes in QRS and T-wave morphology, rate, rhythm, or ectopy) may be lifesaving by terminating injection before a cardiac arrest occurs.
4. Based on animal studies¹²¹ and a growing number of human case reports, hospitals and clinics that perform major conduction blockade or large volume infiltration blockade should keep available for emergency use a supply of lipid emulsion such as Intralipid 20%. If a patient experiences profound cardiovascular depression or circulatory arrest after the administration of bupivacaine, ropivacaine, or by extrapolation, other local anesthetics, then along with initiation of basic life support and the ACLS protocol, a rapid bolus of Intralipid 20%, 1.5 mL/kg (approximately 100 mL in adults) is recommended, followed if necessary by an infusion of 0.25 mL/kg/min over the next 10 minutes.

Chiral Local Anesthetics: Ropivacaine and Levobupivacaine

Commercial bupivacaine is a racemic mixture of (*R*)- and (*S*)-stereoisomers. In response to the problem of cardiovascular toxicity as a result of accidental intravenous injection of bupivacaine, single enantiomers were developed in the hope that they would be potentially safer. Ropivacaine (Naropin)¹²² and levo-(*S*)-bupivacaine (Chirocaine)¹²³ were formulated to exploit this stereoselectivity. Ropivacaine is a single (*S*)-stereoisomer that differs from levobupivacaine in the substitution of a propyl for the butyl group on the piperidine ring (see Fig. 29.2). With these designed changes in molecular structure, it was hoped that ropivacaine and levobupivacaine would be less intrinsically cardiotoxic. Conversely, it appears that the (*S*)-enantiomers of mepivacaine and bupivacaine are metabolized by the liver more slowly than the corresponding (*R*)-enantiomers, which would lead to somewhat greater systemic accumulation with prolonged infusions.

The very slow reversal of Na^+ channel blockade after a cardiac action potential, which is a hallmark of bupivacaine, is considerably faster with ropivacaine. In addition to these electrical differences, the negative inotropic potency of ropivacaine on isolated cardiac tissue appears to be considerably less than that of bupivacaine. Both electrical and mechanical differences in the toxic profiles may arise from the selective inhibition of Ca^{2+} currents by bupivacaine.

Do the data support the claim of a greater therapeutic index for ropivacaine than bupivacaine, particularly with regard to cardiotoxicity? In clinical studies comparing potencies of ropivacaine and bupivacaine administered for brachial plexus¹²⁴ or lumbar epidural block,¹²⁵ the anesthetic profiles of the drugs were almost identical. A third exemplary study comparing lumbar epidural 0.5% bupivacaine with 0.75% ropivacaine also found no significant differences in motor or sensory effects between the drugs at these different concentrations.¹²⁶ Overall, it appears that ropivacaine is slightly less potent than bupivacaine (1:1.3 to 1:1.5) for regional anesthesia. In some laboratory animal studies and in some human studies, ropivacaine also produced blocks of shorter duration than those induced by bupivacaine. Other studies in animals and humans have found equal durations of sensory and motor block for the two drugs.

At the projected equipotent doses for nerve block, are the drugs equally toxic? The overall impression is that ropivacaine is less cardiotoxic than bupivacaine. Studies in animals have generally found that bupivacaine more readily produces conduction disturbances, cardiac collapse, or ventricular fibrillation than ropivacaine does and that aggressive cardiac resuscitation after an intentional intravenous bolus in dogs leads to effective reversal of the toxic effects far more frequently with ropivacaine than with bupivacaine.¹²⁷

The greater safety of ropivacaine than bupivacaine may be related both to the reduced toxicity of the single (*S*)-isomer and to the difference between the propyl- and butyl-*N*-piperidine substituent. In contrast to bupivacaine, the cardiotoxic profile of ropivacaine in pregnant ewes is the same as the corresponding profile in nonpregnant ewes.¹²⁸

Levobupivacaine has been studied in a range of clinical settings and sites of administration. Although a number of publications have compared levobupivacaine with racemic bupivacaine and ropivacaine,^{129,130} conclusions differ among studies regarding the relative potency and duration of block of these three drugs at different sites of administration with respect to sensory and motor end points. Clinicians should note that levobupivacaine is formulated as a weight percentage with regard to its free base content, whereas the weight percentage of most other local anesthetics is calculated on the basis of the hydrochloride salt.¹³¹

Acidosis and Hypoxia

As with CNS toxicity, hypercapnia, acidosis, and hypoxia potentiate the negative chronotropic and inotropic actions of lidocaine and bupivacaine in isolated cardiac tissue, and the combination of hypoxia and acidosis markedly potentiates the cardiodepressant effects of bupivacaine.¹³² Hypoxia and acidosis also increased the frequency of cardiac arrhythmias and the mortality rate in sheep after the intravenous administration of bupivacaine. Hypercapnia,

acidosis, and hypoxia occur very rapidly in some patients after seizure activity caused by the rapid accidental intravascular injection of local anesthetic agents.¹³³ Thus the cardiovascular depression observed in some patients after the accidental intravenous injection of bupivacaine may be related in part to the effect of seizures producing acidosis and hypoxia and thereby leading to an exacerbation of bupivacaine's intrinsic cardiotoxicity.

Indirect Cardiovascular Effects

High levels of spinal or epidural blockade can produce severe hypotension. A follow-up study of closed claims of patients who suffered perioperative cardiac arrest confirmed previous reports of a series of cardiac arrests involving generally healthy patients undergoing spinal or epidural anesthesia.¹³⁴ These events frequently occurred in conjunction with high dermatomal levels of blockade, liberal use of sedatives, and progression to cardiac arrest after a period of hypotension accompanied by bradycardia, often involving delays in recognition of the problem, delays in instituting airway support (particularly in sedated patients), and delays in administration of direct-acting combined α - and β -adrenergic agonists, such as epinephrine. Whereas mild to moderate degrees of hypotension generally respond well to indirect-acting sympathomimetics such as ephedrine or incremental dosing of phenylephrine, the combination of severe hypotension and severe bradycardia under spinal anesthesia should in most clinical settings be treated promptly with incremental dosing of epinephrine, initially at doses of 0.1 to 1 $\mu\text{g}/\text{kg}$.

METHEMOGLOBINEMIA

A unique systemic side effect associated with a specific local anesthetic is the development of methemoglobinemia after the administration of large doses of prilocaine.¹³⁵ In general, 600-mg doses are required for the development of clinically significant levels of methemoglobinemia in adults. Hepatic metabolism of prilocaine generates *O*-toluidine, which oxidizes hemoglobin to methemoglobin. Methemoglobinemia, if severe, may be treated by the intravenous administration of methylene blue. Standard dosing of the topical local anesthetic EMLA (a mixture of lidocaine and prilocaine) in term newborns produced minimal amounts of methemoglobin, and EMLA, if dosed appropriately, should be regarded as very safe in the great majority of newborns. Risk may be increased in newborns with rare metabolic disorders or after the concomitant administration of other drugs that impair reduction of methemoglobin.

ALLERGIES

Even though patients receiving local anesthetics may experience a range of local and systemic symptoms, prospective studies indicate that very few of these reactions are truly confirmed as allergic reactions.^{136,137} Aminoester drugs such as procaine may produce allergic-type reactions more commonly than do the aminoamides, although even with aminoesters, the vast majority of reactions are not allergic. Aminoesters, unlike aminoamides, are derivatives of *p*-aminobenzoic acid, which is known to be allergenic. Some aminoamide solutions may contain a preservative,

methylparaben, whose chemical structure is similar to that of *p*-aminobenzoic acid, but for most aminoamides, preservative-free solutions are available.¹³⁸ Contamination of vials with latex antigen has been suspected in some allergic reactions, although it has been difficult to confirm. In the very rare patient for whom confirmed allergy to both aminoamides and aminoesters precludes their use for spinal anesthesia, meperidine can be considered as an alternative.¹²⁸

LOCAL TISSUE TOXICITY

All the clinically used aminoamide and aminoester local anesthetics can produce direct toxicity to nerves if they achieve sufficiently high intraneuronal concentrations.¹³⁹ Conversely, in the great majority of clinical applications, no damage to nerves occurs. Although local anesthetics are usually packaged and injected at concentrations well above their physiologically effective range, in the process of delivery they are generally diluted sufficiently that no harm is done. If such dilution does not occur, however, long-term or permanent neural deficits do result. Thus the application of 5% (200 mM) lidocaine in viscous, dense solutions through narrow intrathecal catheters had been associated with a high frequency of transient or longer-term radicular symptoms or even cauda equina syndrome.¹⁴⁰ Laboratory investigations have shown that such high concentrations of local anesthetics alone applied directly to bare nerve fibers produce an irreversible conduction block in less than 5 minutes.¹⁴¹ Clinicians should be aware that the concentrations of formulated local anesthetic solutions are neurotoxic per se and that their "natural" dilution, which occurs *in situ* or in tissue, is essential for safe use.

If cauda equina syndrome was considered one catastrophic end of the spectrum, the opposite side would be transient neurologic syndrome, a temporary radicular irritation thought to be caused by local anesthetic application and influenced by patient positioning.¹⁴² Single-shot spinal anesthesia with commonly recommended doses and concentrations of many different local anesthetics can produce more limited and transient neurologic symptoms (back pain, paresthesias, radicular pain, or hypesthesia).¹⁴³ Some studies and systematic reviews have found that mepivacaine and lidocaine at a range of dilutions cause more frequent symptoms than do bupivacaine and prilocaine.¹⁴⁴ The risk of transient neurologic symptoms after spinal anesthesia was not diminished by dilution of lidocaine from 5% to either 1% or 2%. Differences in study design, method of questioning, and criteria for inclusion may be partially responsible for differences in the prevalence of radicular sequelae in various studies. Despite these differences in study design, a meta-analysis concluded that the pooled relative risk for transient neurologic symptoms after spinal anesthesia with lidocaine was 6.7-fold higher than with bupivacaine and 5.5-fold higher than with prilocaine.¹⁴⁴ The addition of vasoconstrictors to local anesthetic solutions has been reported to potentially increase risk,¹⁴⁵ but within the limits of current dosing, neuraxial administration of vasoconstrictors as an adjuvant seems to be safe.¹⁴⁶ Neurotoxicity appears to be unrelated to conduction block per se, because STX, neosaxitoxin, and tetrodotoxin, highly potent blockers of sodium channels, can produce intense

conduction blockade without histologic or behavioral signs of nerve injury.¹⁴⁷

Skeletal muscle changes have been observed after the injection of local anesthetic agents such as lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine.¹⁴⁸ In general, the more potent, longer-acting agents bupivacaine and etidocaine appear to cause more localized skeletal muscle damage than do the less potent, shorter-acting agents lidocaine and prilocaine. This effect on skeletal muscle, to the best of our current knowledge, is reversible due to the regenerative potential of skeletal muscle and the comparatively small area of the muscle affected, which is why it is often clinically inapparent.

Development of Prolonged-Duration and Sensory- or Nociceptive-Selective Local Anesthetics

Several methods for producing long-duration nerve blockade are under investigation. First, there have been efforts to use readily available drugs such as tricyclic antidepressants^{149,150} or quaternary local anesthetic derivatives as novel local anesthetics,¹⁵¹ but these efforts have consistently been hampered by concerns over neurotoxicity.

SLOW-RELEASE FORMULATIONS

Liposomal encapsulation can prolong nerve blockade, depending on the dose and the physical properties of the liposome (surface charge, size, lamellar structure).¹⁴¹⁻¹⁴³ This mode of action has been investigated for decades but the clinical introduction has only been recent. Liposomal bupivacaine (Exparel) has been licensed for infiltration analgesia¹⁵² but its dose-response for blockade of peripheral nerves is less clear.¹⁵³ A recent study showed potential benefits when combining Exparel with bupivacaine for interscalene block,¹⁵⁴ and the Food and Drug Administration has moved to expand Exparel licensing to select nerve block indications. Despite strong basic science data, the clinical benefit of these formulations, especially for nerve blockade, and when compared to plain long-acting local anesthetics, is not as convincing as one would hope. Other modes of slow-release are embedding in bone wax, polylactic acid, polyglycolic acid, fatty-acid-based biodegradable polymers, and proliposomal formulations.⁷ Finally, another variant of slow-release formulations is photo-triggered on-demand release.

SITE 1 BLOCKERS

Prolonged-duration local anesthesia also appears to be feasible with the use of site 1 sodium channel blockers.¹⁴⁸ The site 1 blocker neosaxitoxin has been used in humans in phase 1 and phase 2 clinical trials.¹⁴⁹⁻¹⁵¹ A combination of site 1 toxins with either local anesthetics or adrenergics results in prolongation of blockade and improvement in the therapeutic index.¹⁵⁵ Theoretically attractive features of site 1 toxins include their apparent lack of local tissue toxicity on nerves¹³⁷ or muscles¹⁵² and their minimal cardiotoxicity.¹⁵³

TARGETING OF SPECIFIC SODIUM CHANNEL ISOFORMS

Coming back to the nine different subtypes of sodium channels, research efforts have been directed at blocking specific isoforms thought to be of particular relevance for defined pain conditions. The Nav1.7 subtype, for example, has been linked to somatic pain, and to hereditary syndromes of hyperalgesia¹⁵⁶ or insensitivity to pain.¹⁵⁷ A monoclonal antibody has been described which is 1000 times more potent at blocking sodium currents through Nav1.7 than those of other isoforms.¹⁵⁸ Importantly, animal models of visceral pain suggest a substantial role of Nav1.9 in these syndromes.²⁵

TARGETING OF NOCICEPTIVE FIBERS

High hopes had been raised by reports of sensory-selective blockade of peripheral nerves when a quaternary derivative of lidocaine was targeted into nociceptors using activation of TRPV-1 channels by lidocaine or capsaicin. TRPV channels are preferentially located in small sensory fibers.¹⁵⁹ After several promising studies, concerns over neurotoxicity¹⁵¹ prevented this combination from entering clinical practice. Yet, the concept of targeting specific variants of local anesthetic drugs into specific fibers has been confirmed, and if a combination of drugs is found which can provide these effects with decreased neurotoxicity, the strategy as such may hold promise. Whether any quaternary derivatives of local anesthetics have less neurotoxicity than their parent compounds remains as of yet unanswered.

To summarize, several avenues of research may lead to new local anesthetics or new modes of application, but only liposomal bupivacaine has been introduced into clinical practice. Potentially, these new strategies may move us closer to the holy grail of regional anesthesia, where patients benefit from a tailored surgical block followed by prolonged periods of reliable sensory (or even nociceptive) block without impairment in motor function.

Biologic Mechanisms of Local Anesthetic Failure: Inflammation, Hyperalgesia, Tachyphylaxis, and Genetic Variants

Failure of local anesthesia is commonly ascribed to technical failure of delivery, insufficient volume or concentration of drug, or erroneous clinical decisions in selection of techniques. However, there are a number of clinical situations in which biologic processes contribute to failed local anesthesia, even with proper technique and drug selection.

For example, in patients going to the dentist with infections such as a tooth abscess or severe pulpitis, failure rates of standard doses of local anesthetic have been reported to be as high as 70%. Local anesthetic failure at a site of inflammation appears to reflect a combination of pharmacokinetic factors and pharmacodynamic factors. Pharmacokinetic factors include (1) increased local blood flow leading to

accelerated removal of drug from perineural injection compartments; (2) local tissue acidosis leading to a greater proportion of the drug in the hydrochloride form, which diffuses more poorly across biologic membranes; and (3) local tissue edema, which increases diffusion distances for drug into nerves. Pharmacodynamic factors include the effects of inflammation on both peripheral sensitization of nerves and central sensitization.¹²⁰ It is noteworthy that in the setting of an infected mandibular tooth, inferior alveolar nerve block (performed proximally at a site presumably remote from the infected area) also has an unexpectedly high failure rate. Increasing the concentration of local anesthetic can still result in satisfactory, albeit shorter, blockade. In clinical practice, these patients require a higher local anesthetic dose to achieve sufficient analgesia. Inflamed tissue is more difficult, but not impossible, to anesthetize.

Apparent reductions in the effectiveness of local anesthetic infusions over time may be due to a number of causes unrelated to tolerance per se, including dislodgement of catheters and changes in the dermatomal origin or intensity of nociceptive input. In obstetric patients receiving epidural bolus injections, recurrence of pain before the next injection resulted in a reduction in the intensity and duration of blockade, whereas repeat injection before the return of pain prevented this rapidly occurring form of tolerance, or tachyphylaxis.¹⁶⁰ In postoperative patients, co-administration of systemic opioids prevented regression of segmental block in patients receiving thoracic epidural bupivacaine infusions.¹⁶¹ Studies in rats suggest that both pharmacokinetic and pharmacodynamic mechanisms are involved. In a rat model, tachyphylaxis was linked to the development of hyperalgesia,¹⁶² and drugs that inhibit hyperalgesia, including *N*-methyl-D-aspartate receptor antagonists and nitric oxide synthase inhibitors,¹⁶³ also prevented tachyphylaxis. Conversely, repeated sciatic injections of lidocaine resulted in reduced intraneuronal lidocaine content along with reduced duration of block.¹⁶⁴ The exact mechanism, however, has not been determined, and the clinical relevance with continuous use of long-acting local anesthetics is unclear.

Occasionally patients report that “local anesthetics don’t work for me.” Although this claim may reflect previous technical failures or a variety of other processes and patient- or procedure-specific factors, it is possible that in some cases these failures may involve genetic or acquired variation in local anesthetic responsiveness. Several mutations in the transmembrane segment IIIS6 of the rat brain α -subunit have been shown to decrease the affinity between sodium channels and local anesthetics and anticonvulsants¹⁶⁵ and similar investigations have also been carried out in sodium channel subtypes Nav1.7¹⁶⁶ or Nav1.5.¹⁶⁷ Of note, different mutations at specific points in the local anesthetic binding site led to differential response of these channels to sodium channel blockers, suggesting that the binding of local anesthetics to the “receptor” is a more dynamic, fluid, and structure-dependent process than commonly assumed. This is supported by a clinical study which showed that some percent of persons reporting inefficient regional anesthesia really did demonstrate partial resistance when tested in standardized manner, and some patients had selective resistance against specific local anesthetics.¹⁶⁸ While Clendenen and colleagues published the genetic workup of a family with inherited local

anesthetic resistance,¹⁶⁷ there are preliminary hints that local anesthetic resistance may also be acquired. Interesting case reports suggest that repeated exposure to scorpion bites can elicit acquired resistance to local anesthetics.¹⁶⁹ Elements of scorpion toxin are known to interact with sodium channels, albeit at other sites (Site 3 and 4) than local anesthetics (which bind to Site 9),¹⁷⁰ and therefore the sustained modulation of sodium channel function by toxins is yet another fascinating potential facet of sodium channel and local anesthetic pharmacology.

Conclusions

Local anesthetics have been a central pillar in perioperative management of patients for more than a century, and continued research will assure that we know as much as possible about these drugs, and how we can use them as optimally as possible for the benefit of the patients whose care has been entrusted to us.

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KEY POINTS

- Perioperative risk is multifactorial and may occur as a result of anesthesia-, surgery-, and/or patient-specific factors.
- Anesthesia-related (and surgery-related) risk is typically defined as morbidity and mortality occurring within 30 days of surgery, although events that occur at later points may still be related to anesthesia and/or surgery.
- The overall risk of anesthesia relates to both specific, organ-based complications and the rapidity with which they are managed (i.e., rescued).
- In the literature on anesthesia-related risk, the rates of morbidity and mortality reported across studies show a substantial variability in part attributable to the wide variety of definitions used in these studies.
- Historical studies of anesthesia-related risk identified anesthesia-related respiratory depression as the major cause of death and coma totally attributable to anesthesia. This finding prompted the creation of postanesthesia care units (PACUs).
- Research into anesthesia-related cardiac arrest has found it to be attributable to medication administration, airway management, and technical problems of central venous access.
- Multivariate modeling can be used to determine specific factors associated with an increased likelihood of adverse postoperative events, and it has been used to define a range of clinical risk indices to predict postoperative outcomes.
- Surveys of maternal mortality suggest that although the absolute rate of complications attributable to anesthesia has not decreased over time, the increased use of regional anesthesia may have led to improvements in outcome.
- Medication-related and cardiovascular events were the most common causes of cardiac arrest in the Pediatric Perioperative Cardiac Arrest (POCA) Registry.
- Growth in the number and variety of surgical procedures performed in hospital outpatient departments, ambulatory surgery centers, and physician offices creates novel challenges for assessing and managing perioperative risk.
- Initiatives established over time by the Anesthesia Patient Safety Foundation, the American Society of Anesthesiologists (ASA), and others have sought to decrease the potential risks of anesthesia through systems-level improvements, standardization of care processes, human-factors engineering, and simulation-based training.
- Emerging evidence suggests that the choice of anesthetic drugs, ventilator strategies, or technique may impact patient outcomes.

Introduction

Since the beginning of its modern history, the administration of anesthesia has been recognized as a hazardous enterprise,¹ with distinct risks to the patient and occupational risks to anesthesia providers. From the perspective of public health, understanding both the nature and the magnitude of these risks is important on multiple levels. For individual patients, receiving accurate information on the probability of specific perioperative complications is a prerequisite for informed decision making related to anesthesia and surgery. More broadly, understanding the extent to which rates of perioperative morbidity and mortality

vary across patients, physicians, and hospitals provides an important opportunity for assessing and improving quality in healthcare.

Efforts to determine the risks of anesthesia are complicated by many potential perspectives from which such risks can be defined. The use of alternate periods of observation for morbidity and mortality—the intraoperative period alone, the first 48 hours after surgery, the duration of the hospital stay, or the first 30 days or longer after surgery—complicates simple conclusions about the risks faced by any individual patient undergoing anesthesia and surgery and at what point after surgery the likelihood of further adverse events has returned to baseline (Table 30.1). For example,

TABLE 30.1 Time Perspective of Anesthetic Morbidity and Mortality Studies

| Study | Study Year | Time Perspective |
|--------------------|------------|---|
| Beecher and Todd | 1954 | All deaths on the surgical services |
| Dornette and Orth | 1956 | Deaths in the surgical unit or after failure to regain consciousness |
| Clifton and Hotten | 1963 | Any death under or attributable to anesthesia or without return of consciousness after anesthesia |
| Harrison | 1978 | Death within 24 h |
| Marx et al. | 1973 | Death within 5 days |
| Hovi-Viander | 1980 | Death within 3 days |
| Lunn and Mushin | 1982 | Death within 6 days |
| Tiret and Hatton | 1986 | Complications within 24 h |
| Mangano et al. | 1992 | Death within 2 years |
| Monk et al. | 2005 | Death within 1 year |

Modified from Derrington MC, Smith G. A review of studies of anaesthetic risk, morbidity, and mortality. *Br J Anaesth.* 1987;59(7):815–833.

patients undergoing ambulatory surgery have the lowest risk of death the day of surgery as opposed to 1 month later.² At the opposite end of the spectrum, asymptomatic release of cardiac enzymes in the perioperative period can have implications for months to years.^{3–5} Divergent conclusions would also be expected from studies that consider adverse events that are solely attributable to the administration of anesthesia versus those that examine the overall rates of morbidity and mortality after surgery, which anesthesia care may modify. Studies exclusively focusing on the intraoperative period have characterized contemporary anesthesia care as a patient safety “success story” as a result of the low rates of death directly attributable to anesthesia care. As a result, anesthesia has been hailed by the National Academy of Medicine as “an area in which very impressive improvements have been made” in terms of patient safety.⁶

Nonetheless, a broader perspective on perioperative outcomes presents a more complicated story. For example, in the case of a patient with established coronary artery disease who sustains a myocardial infarction after experiencing tachycardia during high-risk surgery, the cause of the patient’s adverse outcome could arguably be attributed to both the patient’s underlying coronary artery disease and to the absence of intraoperative heart rate control. In this situation, the decision to view the perioperative infarction primarily as a consequence of patient disease or as an event that could be prevented by anesthesia care carries vastly different implications for efforts to define and reduce the risks of anesthesia.

Finally, the diverse array of outcomes considered as hazards of anesthesia complicate the interpretation of the literature on the risks of anesthesia. Traditionally, investigators have focused on issues of death and major morbidity such as myocardial infarction, pneumonia, and renal failure. More recently, however, this view has been broadened to include economic outcomes, as well

TABLE 30.2 Examples of Common Outcome Measures

| Outcome | Example |
|---|---|
| Mortality Failure-to-rescue | Mortality after a postoperative complication |
| Morbidity Major | Myocardial infarction Pneumonia Pulmonary embolism Renal failure or insufficiency Postoperative cognitive dysfunction |
| Minor | Nausea Vomiting Readmission |
| Patient satisfaction Quality of life | |

as patient-centered outcomes such as functional independence, quality of life, and satisfaction (Table 30.2). For example, unanticipated rehospitalization after ambulatory surgery or a delay in discharge as a result of postoperative nausea and vomiting are both potentially important from the perspectives of the patient’s quality of life, as well as economics.

In this chapter, current theories regarding the underlying causes of adverse events in the perioperative period are reviewed, and the historical and contemporary literature regarding the nature and magnitude of risk related to both intraoperative anesthesia care and perioperative care are examined. Next, historical and recent efforts to characterize the patient-, provider-, and facility-level determinants of anesthetic and perioperative risk are reviewed through statistical risk indices, and clinically based approaches to patient classification, and available literature on the determinants of risk unique to the obstetric, pediatric, and geriatric populations are discussed. Finally, future directions in research and clinical care related to anesthetic risk are discussed, with a focus on the health policy implications of changing knowledge regarding the hazards of anesthesia.

Framework of Perioperative Risk

Perioperative risk is multifactorial and depends on the interaction of anesthesia-, patient-, and surgery-specific factors (Fig. 30.1). With respect to anesthesia, the selection and effects of medications, including volatile and intravenous anesthetic drugs, and the skills of the practitioner are important. Similarly, the surgeon’s skills and the surgical procedure itself also affect perioperative risk. Further, practitioners may influence outcomes at multiple points in the postoperative course. Although the incidence of specific local or organ-based complications, such as perioperative myocardial infarction or central line–related bloodstream infection, may be modified by anesthetic or surgical care, variations in the adequacy of care delivered to patients who have already experienced a complication (i.e., failure to rescue) may largely explain hospital-to-hospital differences in surgical outcomes.^{7–9} Notably, although past investigators have pointed to volume-outcome relationships as potentially mitigating these hospital-to-hospital outcome

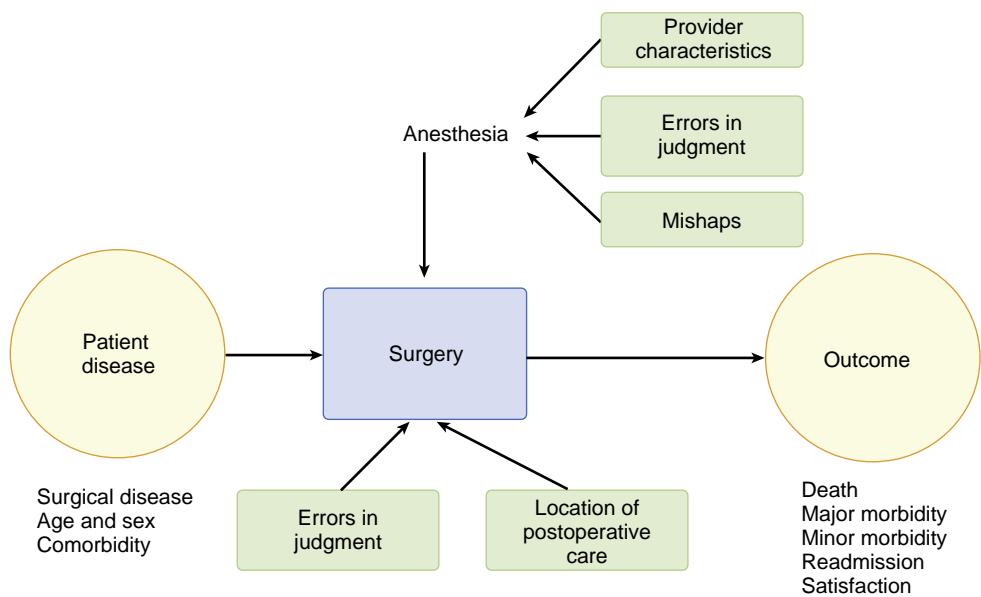


Fig. 30.1 Representation of the influences of various components on poor perioperative outcomes. Surgical, anesthetic, and patient characteristics all contribute to outcome. Anesthesia-related contributions can include issues of judgment and mishaps, as well as characteristics of the provider. The surgical procedure itself affects outcome, as does the location of intraoperative and postoperative care.

differences,^{10,11} more recent data have suggested that local quality-improvement efforts, rather than large-scale efforts, at regionalization of care for elective surgeries hold the greatest potential to yield meaningful improvements in operative outcomes.¹²

The potential for anesthetic care to influence the overall hazard of surgery at multiple time points highlights both the complexity of measuring the risks of anesthesia and surgery, and the range of potential opportunities that may exist to reduce such risks. Given these challenges and opportunities, the goal of the next section is to summarize the current state of knowledge in this area, including the relative strengths and weaknesses of randomized and nonrandomized (i.e., observational) study designs used in efforts to understand patterns of outcomes after surgery and anesthesia.

Issues Related to Study Design

TYPES OF STUDIES

To interpret the literature related to anesthetic and perioperative risk, the strengths and limitations of various study designs must be understood. *Prospective cohort studies* involve the identification of a group of subjects who are monitored over time for the occurrence of an outcome of interest. The goal is to identify patients in whom the outcome develops. For studies of perioperative mortality, individual cases can be reviewed to determine the cause of mortality. Alternatively, data on all patients in the cohort study can be obtained, and discrete factors associated with the development of morbidity or mortality can be determined, often using multivariate regression techniques. An example of a prospective cohort study to identify factors associated with perioperative cardiac morbidity and mortality is that of Goldman and colleagues,¹³ which led to development of the Cardiac Risk Index.

Although prospective cohort studies have important value in identifying risk factors for perioperative outcomes, they also have significant limitations. The range of patients enrolled in the cohort study, both in terms of baseline characteristics and the care they receive, may impact the generalizability of the study findings. Additional biases may be introduced by loss of patients to follow-up. Failure to anticipate the potential impact of some variables and collect data on them may limit the insights gained from a cohort study. Similarly, the inability to collect data on all potential confounders of the relationship between a putative risk factor and a given outcome limits the extent to which cohort studies can support causal inferences.

Randomized clinical trials offer stronger evidence of causality than do observational cohort studies. In a randomized trial, subjects are assigned by random allocation to one of two or more treatments (potentially including a placebo) and are observed for the development of a particular outcome. In the context of perioperative risk, randomized trials may be used to determine the efficacy of an intervention or anesthetic regimen intended to improve postoperative outcomes. For example, hypothermia in the perioperative period has been associated with an increased incidence of perioperative ischemia, a surrogate marker for morbidity.¹⁴ In a randomized clinical trial, the use of forced-air warming to maintain normothermia was associated with a significantly less frequent incidence of perioperative morbid cardiac events.¹⁵ Randomized clinical trials often build on hypotheses generated in cohort studies regarding the determinants of outcomes by testing interventions directed at a specific risk factor associated with adverse outcomes.

Randomized clinical trials derive their strength from their high degree of internal validity; the randomization scheme and the use of placebo (or accepted alternative treatments) provide strong evidence that the results are related to the intervention. Importantly, these trials may have a lower degree of external validity because the intervention tested

in a particular trial may not work as well or in the same manner as when it is diffused into a more heterogeneous population. Further, as a result of sample size limitations, clinical trials may often be unable to detect subtle differences in outcomes among study groups or differences in rare events.

Retrospective studies involve the identification of patients who have sustained an outcome and definition of risk factors associated with the outcome. An example of a retrospective design is a case-control study. *Case-control studies* identify patients with the outcome of interest. Frequently, these patients are included as part of a prospective cohort study. The prevalence of a risk factor in patients with the outcome (i.e., cases) is compared with the prevalence of the risk factor in matched control participants to maximize the efficiency and power of the results. The ratio of cases to control participants can be varied to yield greater power with an increasing number of controls. An alternative retrospective design involves the systematic review of identifiable adverse events for patterns of error. For example, Cheney and colleagues¹⁶ developed the American Society of Anesthesiologists' Closed Claims Project (ASA-CCP) to assess the risks associated with anesthesia care. By obtaining the records of major events that led to legal litigation, they were able to identify factors that contributed to bad outcomes. With this methodology, selected morbidities that led to litigation can be identified. The limitation of this methodology is that the actual rates of complications in the overall population are not known; only the number of closed legal claims is identified. Cases that do not result in litigation are not included in the database.

PROBLEMS INHERENT IN STUDYING ANESTHESIA-RELATED RISK

Studying anesthesia-related risk involves a range of methodologic challenges. On the most basic level, multiple definitions exist for key outcomes, such as perioperative mortality. In particular, the timeframe in which a death can be attributed to the surgery or the delivery of anesthesia or both varies. Notably, many events related to surgery may occur after discharge when monitoring of outcomes becomes more challenging. For this reason, the National Surgical Quality Improvement Program (NSQIP), a large, prospectively collected U.S. registry of surgical care and outcomes, requires 30-day follow-up on all patients to allow for consistent assessments of outcomes for all patients.

A second major challenge in any study of postoperative outcomes is the low observed rate of many key outcomes in the population of interest. Although some recent writers have called into question the safety of contemporary anesthesia care,¹⁷ anesthesia-related death remains relatively uncommon in absolute terms. For example, the rate of anesthesia-related mortality described in the Confidential Enquiry into Perioperative Deaths (CEPOD) of 1987 was 1 in 185,000 patients as opposed to the 1 in 2680 cases reported by Beecher and Todd approximately 30 years earlier.^{18,19} As a result, efforts to identify the range of factors that now contribute to anesthetic mortality are likely to require large patient cohort studies available either from administrative sources or collected over several years from multiple institutions. Several attempts have been made to

establish large epidemiologic databases to address this challenge. One example of such an approach has been the work of Dennis Mangano and the Multicenter Study of Perioperative Ischemia Research Group with regard to cardiac surgery. This group used its database to evaluate issues such as the rate and importance of atrial fibrillation after cardiac surgery and the association of perioperative use of aspirin with cardiac surgical outcomes.^{20,21} Other approaches include the development of cardiac surgery databases by the Society of Thoracic Surgeons, the U.S. Veterans Administration NSQIP, and the Northern New England Cardiovascular Disease Study Group.²²⁻²⁵ These databases are used to define risk factors for poor outcome, to compare local with national complication rates, and as educational tools. In the United States, the Multicenter Perioperative Outcomes Group has undertaken such an enterprise by pooling electronically collected intraoperative and postoperative data.²⁶ Although these databases may provide extremely important information to improve care, the ability to generalize results to centers that do not have sufficient infrastructure to participate in such projects (e.g., smaller hospitals) is unknown.

Variations in care and outcomes across institutions may further complicate efforts to develop meaningful estimates of perioperative risk for use in clinical decision making by individual patients. Beyond the impact of patient illness, type of surgery, or anesthetic approach, hospital-level differences in postoperative care may have a profound impact on outcome. For example, the incidence of pulmonary embolism may be related to nursing care and the frequency of patient ambulation after surgery²⁷; similarly, the presence of an intensivist who makes daily rounds and higher nurse staffing ratios may also affect outcome.²⁸

Finally, issues of risk adjustment complicate efforts to determine changes in anesthesia risk over time. Common endpoints, such as mortality, are influenced by patient factors as well as by anesthesia and surgical care; as such, temporal trends in patient acuity may influence the apparent adverse outcomes associated with anesthesia and surgery in a given period. With appropriate risk adjustment, changes in mortality rates over short periods may provide some indication of changes in the quality of anesthesia or surgical care. When viewed over longer periods, however, it may be more difficult to reach firm conclusions regarding temporal changes in the safety of anesthesia or surgery based on differences in mortality rates over time. For example, if improvements in anesthetic technology have allowed for older and sicker patients to undergo surgery, then the safety of anesthesia may have improved without any apparent change in mortality rates because a sicker patient population is now offered surgery that, in the past, would have been avoided. Similarly, the rapid adoption of new but relatively high-risk procedures complicates simple comparisons of anesthesia-related complications over time.

STUDIES OF ANESTHESIA-RELATED MORTALITY

Efforts to understand the specific risks imposed by anesthesia care, above and beyond the surgical procedure itself, have represented an important dimension of research in anesthesia since the early 20th century. Although more recent trends in anesthesia research have emphasized a

TABLE 30.3 Estimates of the Incidence of Mortality Related to Anesthesia Before 1980

| Study | Year | Number of Anesthetics | Primary Cause | Primary and Associated Causes |
|--------------------|------|-----------------------|---------------|-------------------------------|
| Beecher and Todd | 1954 | 599,548 | 1:2680 | 1:1560 |
| Dornette and Orth | 1956 | 63,105 | 1:2427 | 1:1343 |
| Schapira et al. | 1960 | 22,177 | 1:1232 | 1:821 |
| Phillips et al. | 1960 | — | 1:7692 | 1:2500 |
| Dripps et al. | 1961 | 33,224 | 1:852 | 1:415 |
| Clifton and Hotton | 1963 | 205,640 | 1:6048 | 1:3955 |
| Memery | 1965 | 114,866 | 1:3145 | 1:1082 |
| Gebbie | 1966 | 129,336 | — | 1:6158 |
| Minuck | 1967 | 121,786 | 1:6766 | 1:3291 |
| Marx et al. | 1973 | 34,145 | — | 1:1265 |
| Bodlander | 1975 | 211,130 | 1:14,075 | 1:1703 |
| Harrison | 1978 | 240,483 | — | 1:4537 |
| Hovi-Viander | 1980 | 338,934 | 1:5059 | 1:1412 |

From Ross AF, Tinker JH. Anesthesia risk. In: Miller RD, ed. *Anesthesia*, ed 3. New York, NY: Churchill Livingstone; 1990;722.

broad view of perioperative outcomes not strictly limited to events primarily caused by anesthesia care,³⁰ the history of efforts to determine the safety of anesthesia management represents an important chapter in the development of modern perioperative medicine. This history also serves as important background for understanding current research and practice.

Research performed before 1980 demonstrated wide variation in reported rates of anesthesia-related mortality (Table 30.3). Beecher and Todd's 1954 report of anesthesia-related deaths at 10 institutions represents the earliest published major analysis of anesthesia outcomes.¹⁸ Their study included 599,548 anesthesia procedures and found a rate of all-cause mortality of 1 per 75 cases (1.3%). In 1 out of every 2680 procedures, anesthesia represented the primary cause of mortality, and it was a primary or contributory cause of mortality in 1 of 1560 procedures. The work of Dornette and Orth³¹ investigating perioperative deaths over a 12-year period at their institution corroborated these findings: they reported a mortality rate attributable to anesthesia in 1 in 2427 cases, and totally or partially attributable to anesthesia in 1 in 1343 cases. In contrast, Dripps and colleagues found the anesthesia-attributable mortality rate to be 1 in 852 in a similar single-institution longitudinal study.³² These differences may be partially explained by Dripps' observation of 30-day, rather than intraoperative or 48-hour mortality, or differences in patient severity across studies.

Multiple additional studies on anesthetic mortality appeared between 1960 and 1980.³³ In the United States, these included the Baltimore Anesthesia Study Committee,³⁴ which reviewed 1024 deaths occurring on the day of or the day after a surgical procedure, and several single-institution studies.^{35,36} Overall, the rate of anesthesia-related mortality in these studies varied

TABLE 30.4 Incidence of Complications Partially or Totally Related to Anesthesia

| Complications | Partially Related | Totally Related | Total* |
|-------------------|-------------------|-----------------|--------|
| All complications | 1:1887 | 1:1215 | 1:739 |
| Death | 1:3810 | 1:13,207 | 1:1957 |
| Death and coma | 1:3415 | 1:7924 | 1:2387 |

*Total number of anesthetics: 198,103. From Tiret L, Desmonts JM, Hatton F, Vourc'h G. Complications associated with anaesthesia—a prospective survey in France. *Can Anaesth Soc J*. 1986;33:336–344.

widely, ranging from 1 in 1232 cases in a study by Schapira et al³⁵ to 1 in 7692 cases in the Baltimore Anesthesia Study Committee report. Results from the international community during that period were similarly heterogeneous in methodology and findings.^{37–40}

Studies of anesthetic risk published before 1980 varied widely in the definitions used for anesthesia-related mortality and in the mortality rates they reported; however, they suggested that death related solely to anesthesia was a relatively uncommon event. Moreover, an overall trend toward lower rates of anesthesia-related mortality across studies over time suggested potential improvements in anesthesia safety.

Studies since 1980 have generally been performed on a regional or national basis with a particular emphasis on documenting changes over time in anesthesia-related mortality. For example, Holland⁴¹ reported deaths occurring within 24 hours after anesthesia in New South Wales, Australia. The incidence of anesthesia-attributable deaths decreased from 1 in 5500 procedures performed in 1960 to 1 in 26,000 in 1984. Based on these estimates, the investigators asserted that for all patients receiving surgery, it was more than five times safer to undergo anesthesia in 1984 than it was in 1960.⁴²

Under the direction of the French Ministry of Health, Tiret and colleagues⁴³ carried out a prospective survey of complications associated with anesthesia in France between 1978 and 1982 from a representative sample of 198,103 anesthesia procedures from hospitals throughout the country. Death was solely related to anesthesia in 1 in 13,207 procedures and partially related in 1 in 3810 (Table 30.4). The French survey confirmed previous findings that major complications occur more frequently in older patients, those undergoing emergency surgical procedures, and those with more extensive comorbid conditions as measured by ASA physical status classification. More notably, the investigators found that postanesthesia respiratory depression was the leading principal cause among cases of death and coma that were solely attributable to anesthesia. Moreover, almost all the patients who had had respiratory depression leading to a major complication had received narcotics, as well as neuromuscular blocking drugs, but they had not received anticholinesterase medications for reversal of the agents.

Despite these observations, the low rates of anesthesia-attributable mortality documented in the French study offered compelling evidence of improvements in anesthesia safety. Such findings were reinforced by other, concurrent work in Finland⁴⁴ and in the United Kingdom,⁴⁵ resulting in the development of the United Kingdom CEPD, which

TABLE 30.5 Death Totally Attributable to Each Component of Risk in the Confidential Enquiry into Perioperative Deaths

| Component | Mortality Rate Contribution |
|------------|-----------------------------|
| Patient | 1:870 |
| Operation | 1:2860 |
| Anesthetic | 1:185,056 |

Modified from Buck N, Devlin HB, Lunn JL. Report of a confidential enquiry into perioperative deaths. Nuffield Provincial Hospitals Trust, The King's Fund Publishing House, London, 1987.

TABLE 30.6 Most Common Clinical Causes of Death in the Confidential Enquiry into Perioperative Deaths

| Cause of Death | Percent of Total |
|--------------------------|------------------|
| Bronchopneumonia | 13.5 |
| Congestive heart failure | 10.8 |
| Myocardial infarction | 8.4 |
| Pulmonary embolism | 7.8 |
| Respiratory failure | 6.5 |

Modified from Buck N, Devlin HB, Lunn JL. Report of a confidential enquiry into perioperative deaths. Nuffield Provincial Hospitals Trust, The King's Fund Publishing House, London, 1987.

assessed almost 1 million anesthetics during a 1-year period in 1987 in three large regions of the United Kingdom.

Beyond confirming earlier work, CEPOD's findings suggested that anesthesia care was far safer than had been found in prior studies. Examining deaths within 30 days of surgery, CEPOD investigators observed 4034 deaths in an estimated 485,850 surgeries for a crude mortality rate of 0.7% to 0.8%. Anesthesia was considered the sole cause of death in only three individuals, for a rate of 1 in 185,000 cases, and anesthesia was contributory in 410 deaths, for a rate of 7 in 10,000 cases (Table 30.5).¹⁹ The five most common causes of death in the CEPOD cohort study are shown in Table 30.6. Notably, of the 410 perioperative deaths, gastric aspiration was identified in 9 cases and cardiac arrest in 18 cases. Ultimately, CEPOD researchers concluded that avoidable factors were present in approximately 20% of the perioperative deaths. Contributing factors for anesthesiologists and surgeons tended to be failure to act appropriately with existing knowledge (rather than a lack of knowledge), equipment malfunction, fatigue, and inadequate supervision of trainees, particularly in off-hours shifts (Table 30.7).

Large national studies performed since the 1987 CEPOD report vary in the extent to which their findings agree with those of the CEPOD investigators. In a prospective study of 7306 anesthesia procedures in Denmark, Pedersen and colleagues⁴⁶ found complications attributable to anesthesia in 43 patients (1 in 170) and 3 deaths (1 in 2500), an incidence far higher than that documented by the CEPOD investigators. Complications in the 43 patients, in order of incidence, included cardiovascular collapse in 16 (37%), severe postoperative headache after regional anesthesia in 9 (21%), and awareness under anesthesia in 8 (19%).

TABLE 30.7 Grade of Physician According to Time of Surgery in the Confidential Enquiry into Perioperative Deaths

| Grade | ANESTHETIST | | SURGEON | |
|------------|-------------|--------|---------|--------|
| | Day* | Night† | Day* | Night† |
| Consultant | 50 | 25 | 45 | 34 |
| Others | 50 | 75 | 55 | 66 |

*Represents Monday through Friday, 9 AM to 7 PM.

†Represents Monday through Friday, 7 PM to 9 AM, and Saturday and Sunday.

Modified from Buck N, Devlin HB, Lunn JL. Report of a confidential enquiry into perioperative deaths. Nuffield Provincial Hospitals Trust, The King's Fund Publishing House, London, 1987.

In the United States, Li and colleagues⁴⁷ conducted a population-level study to estimate epidemiologic patterns of anesthesia-related deaths, using International Classification of Diseases (ICD) codes listed in the United States multiple-cause-of-death data files for the years 1999 through 2005. Although the interpretation of Li's study is complicated by questions surrounding the sensitivity of ICD codes for anesthesia-related mortality,⁴⁸ their findings are in accord with those of the CEPOD report in presenting anesthesia-related mortality to be an extremely rare cause of death at the population level. The authors found anesthesia to be the underlying cause of death in 34 patients each year in the United States and a contributing factor in another 281 deaths annually, resulting in a 97% decrease in anesthesia-related death rates since the 1940s.

Recent European studies have taken a broader focus beyond anesthesia-related events to examine perioperative outcomes more generally, particularly among high-risk patients who Lagasse and others previously observed to account for the majority of postoperative deaths.¹⁷ In a 2011 report, NCEPOD investigators prospectively collected data on all patients undergoing inpatient surgery, excluding obstetric, cardiac, transplant, or neurosurgery cases, in United Kingdom National Health Service facilities over a 1-week period.⁴⁹ In addition to prospectively collected patient-level data on clinical care and outcomes, the authors conducted a detailed institution-level survey of resources and practices. Although the authors observed an overall 30-day mortality rate of 1.6%, a subset of high-risk patients—approximately 20% of the full cohort—experienced a disproportionate share of adverse outcomes, accounting for 79% of all perioperative deaths. Notably, the authors identified important gaps in the perioperative management of these patients. A minority of the high-risk patients were monitored using an arterial line, a central line, or cardiac output monitoring; still more concerning was their observation that 48% of all high-risk patients who died were never admitted to a critical care unit for postoperative management. Similar findings were obtained in another study of surgical outcomes conducted across 28 European countries between April 4 and April 11, 2011.⁵⁰ Such patterns, which the authors describe as a “systematic failure in the process of allocation of critical care resources” in Europe, highlight the potential importance of “rescue”—the prevention of mortality among patients who experience postoperative complications—in determining the outcomes of surgical care. Further, to the extent that critical

care use among patients who die after surgery is higher in the United States than in the United Kingdom,⁵¹ such differences may offer insight into potential reasons for earlier observations of lower risk-adjusted postoperative mortality among American versus British surgical patients.⁵²

In the United States, Whitlock and colleagues^{52a} retrospectively analyzed 2,948,842 cases logged in the National Anesthesia Clinical Outcomes Registry between 2010 and 2014. They documented a mortality rate of 33 per 100,000. Increasing ASA physical status, emergency case status, time of day, and age less than 1 year or greater than 65 years were independently associated with perioperative mortality. After adjustment for confounding factors, mortality remained greater for cases started after 6 PM, suggesting that certain factors influencing perioperative mortality might be modifiable. The most common concurrent outcomes in patients who died within 48 hours of anesthesia were hemodynamic instability (35.0%) and respiratory complications (8.1%). Notably, due to data limitations, the authors did not comment on the number of deaths that were anesthesia associated.

In summary, research on anesthesia-related mortality offers a complex and still incomplete picture regarding the risks of anesthesia. Taken from the perspective of the 1987 CEPID report or the findings of Li and colleagues, modern operative anesthesia could be characterized as an exceedingly safe enterprise with bad outcomes occurring as truly rare events; however, other studies have disputed these findings. More recent work has sought to go beyond efforts to quantify the contribution of anesthesia per se to overall operative risk to explore how anesthesia providers might be able to improve outcomes among high-risk patients—in essence asking not “how safe is anesthesia?” but instead “how can anesthesia providers help make surgery safer?” Ultimately, these studies’ differing messages emphasize not only the dynamic nature of anesthesia risk over time, but also highlight important changes in how anesthetic risk has been defined across different periods and how alternate approaches to evaluating, describing, and mitigating such risk may be more or less relevant at a given moment in time.

ANALYSIS OF INTRAOPERATIVE CARDIAC ARREST

In an alternative approach to evaluating perioperative mortality specific to anesthesia, several studies have evaluated intraoperative fatal and nonfatal cardiac arrest. In contrast to efforts to estimate the mortality attributable to anesthesia per se, studies of intraoperative cardiac arrest may offer a broader picture of the potential hazards of anesthesia by examining an adverse outcome that is far more common than mortality yet remains highly consequential for long-term outcomes.

These studies offer a range of perspectives on the incidence of intraoperative cardiac arrest and the causes of such events. For example, Keenan and Boyan⁵³ studied the incidence and causes of cardiac arrest related to anesthesia at the Medical College of Virginia between 1969 and 1983. A total of 27 cardiac arrests occurred during 163,240 procedures, for an incidence of 1.7 per 10,000 cases. Pediatric patients had a threefold higher risk of cardiac arrest

TABLE 30.8 Selected Cardiac Arrest Series When the Denominator Is Greater Than 40,000 Anesthetics

| Study | Years | Total Number of Anesthetics | Rate of Arrest |
|------------------|------------|-----------------------------|----------------|
| Hanks and Papper | 1947-1950 | 49,728 | 1:2,162 |
| Ehrenhaft et al. | 1942-1951 | 71,000 | 1:2,840 |
| Bonica | 1945-1952 | 90,000 | 1:6,000 |
| Blades | 1948-1952 | 42,636 | 1:21,318 |
| Hewlett et al. | 1950-1954 | 56,033 | 1:2,061 |
| Briggs et al. | 1945-1954 | 103,777 | 1:1,038 |
| Keenan and Boyan | 1969-1978 | 107,257 | 1:6,704 (P) |
| Cohen et al. | 1975-1983 | 112,721 | 1:1,427 (C) |
| Tiret et al. | 1978-1982 | 198,103 | 1:3,358 (C) |
| Tiret et al. | 1978-1982 | 198,103 | 1:11,653 (P) |
| Keenan and Boyan | 1979-1988* | 134,677 | 1:9,620 (P) |
| Newland et al. | 1989-1999 | 72,959 | 1:14,493 (P) |
| Newland et al. | 1989-1999 | 72,959 | 1:7,299 (C) |
| Olsson et al. | 1967-1984 | 250,543 | 1:33,000 |
| Biboulet et al. | 1989-1995 | 101,769 | 1:7,828 |
| Kawashima et al. | 1994-1998 | 2,363,038 | 1:10,000 (P) |
| Sprung et al. | 1990-2000 | 518,294 | 1:20,000 (P) |
| Braz et al. | 1996-2005 | 53,718 | 1:9:10,000 (P) |

*Since pulse oximetry was introduced in 1984, no preventable respiratory cardiac arrests have occurred.

C, Contributory cause; P, primary cause.

Modified from Brown DL. Anesthesia risk: a historical perspective. In: Brown DL, ed. *Risk and Outcome in Anesthesia*. 2nd ed. Philadelphia, PA: Lippincott; 1992:14.

than did adults, and emergency cases had a sixfold greater risk. Importantly, specific errors in anesthesia management could be identified in 75% of the cases; most common among these were inadequate ventilation and overdose of an inhaled anesthetic. Notably, the investigators identified progressive bradycardia preceding all but one arrest, suggesting that early identification and treatment may prevent complications.

Similar findings were reported by Olsson and Hallen,⁵⁴ who studied the incidence of intraoperative cardiac arrest at the Karolinska Hospital in Stockholm, Sweden, from 1967 to 1984. A total of 170 arrests occurred in 250,543 anesthesia procedures performed. Sixty patients died, for a mortality rate of 2.4 per 10,000 procedures. After eliminating cases of inevitable death (e.g., rupture of a cerebral aneurysm, trauma), the rate of mortality caused by anesthesia was 0.3 per 10,000 procedures. The most common causes of anesthesia-related cardiac arrest were inadequate ventilation (27 patients), asystole after succinylcholine (23 patients), and postinduction hypotension (14 patients). The incidence of cardiac arrest was highest in the patients with significant comorbid disease, as assessed by the ASA physical status classification. Notable is the finding that the incidence of cardiac arrest decreased over the study period. These findings were reproduced in other studies, including that of Biboulet and colleagues⁵⁵ and Newland and associates.⁵⁶

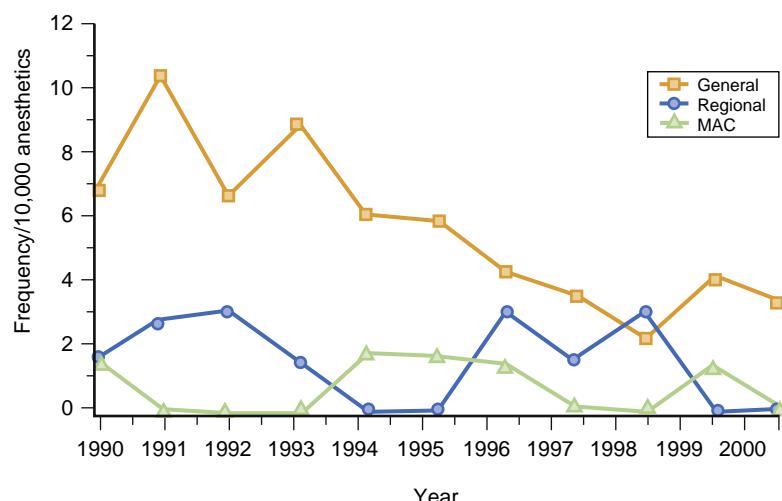


Fig. 30.2 Frequency of cardiac arrest by calendar year and type of anesthesia. MAC, Monitored anesthesia care. (From Sprung J, Warner ME, Contreras MG, et al. Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: a study of 518,294 patients at a tertiary referral center. *Anesthesiology*. 2003;99:259–269.)

TABLE 30.9 Cardiac Arrest Totally Attributable to Anesthesia During Anesthesia and Surgery and Its Outcomes, 1994 to 1998

| | Number of Arrests | OUTCOMES | | | | |
|----------------------|-------------------|---------------------|------------------------|---------------------|------------------|------------|
| | | Uneventful Recovery | Death in Surgical Unit | Death Within 7 Days | Vegetative State | Others |
| 5-year total | 237 | 185 | 13 | 15 | 9 | 15 |
| Incidence per 10,000 | 1.00 | 0.78 | 0.05 | 0.08 | 0.04 | 0.06 |
| 95% CI | 0.88-≈1.12 | 0.66-≈0.89 | 0.2-≈0.08 | 0.02-≈0.13 | 0.03-≈0.05 | 0.02-≈0.10 |
| Ratio | 100% | 78.1% | 5.5% | 6.3% | 3.8% | 6.3% |
| 95% CI | | 55.3-≈100 | 1.7-≈9.3 | 3.0-≈9.7 | 2.5-≈5.3 | 1.7-≈11.0 |

N = 2,363,038. CI, Confidence interval.

Reproduced with permission from Kawashima Y, Takahashi S, Suzuki M, et al. Anesthesia-related mortality and morbidity over a 5-year period in 2,363,038 patients in Japan. *Acta Anaesthesiol Scand*. 2003;47:809–817.

Sprung and colleagues⁵⁷ demonstrated similar findings with regard to incidence and outcome of cardiac arrest during 72,529 procedures between 1989 and 1999 in a teaching hospital in the United States. They also found that the frequency of arrest in patients receiving general anesthesia decreased over time (7.8 per 10,000 during 1990-1992; 3.2 per 10,000 during 1998-2000). The frequency of arrest during regional anesthesia (1.5 per 10,000) and monitored anesthesia care (MAC) (0.7 per 10,000) remained the same during the study period (Fig. 30.2). More recently, Ellis and group^{57a} used an institutional quality improvement database to identify all instances of cardiac arrest occurring within a 24-hour perioperative period between 1999 and 2009. They identified 161 arrests in 217,365 anesthetics, 14 of which were found to be anesthesia-attributable (0.6 per 10,000 anesthetics) and 23 that were anesthesia-contributory (1.1 per 10,000). Of anesthesia-attributable events, the majority (64%) were caused by airway complications during induction or emergence. The mortality associated with these events was 29%.

Kawashima and colleagues identified even lower rates of cardiac arrest attributable to anesthesia in a survey-based study conducted in Japan from 1994 through 1998.⁵⁸ The average yearly incidence of cardiac arrest during surgery

that was totally attributable to anesthesia was 1 per 10,000 cases (95% CI, 0.88-1.12). The average mortality per year in the surgical unit or within seven postoperative days that was totally attributable to anesthesia was 0.21 (0.15-0.27) per 10,000 cases. The two principal causes of cardiac arrest solely attributable to anesthesia were drug overdose or selection error (15.3%) and serious arrhythmia (13.9%). Preventable human errors caused 53.2% of cardiac arrests and 22.2% of deaths in the surgical unit that were totally attributable to anesthesia. The outcomes of cardiac arrests totally attributable to anesthesia are shown in Table 30.9.

Kheterpal and colleagues at the University of Michigan examined predictors of cardiac adverse events—including cardiac arrest, myocardial infarction, and clinically significant arrhythmia—among 7700 patients undergoing noncardiac surgery. Eighty-three patients (1.1%) experienced an adverse event. The authors identified nine independent predictors of an adverse event: (1) age 68 years or older, (2) body mass index of 30 or greater, (3) emergency surgery, (4) previous coronary intervention or cardiac surgery, (5) active congestive heart failure, (6) cerebrovascular disease, (7) hypertension, (8) operative time of 3.8 hours or longer, and (9) the intraoperative administration of one or more units of packed red blood cells.⁶⁰

In summary, perioperative cardiac arrest is a relatively rare event whose incidence may be decreasing over time. Further, research in this area has highlighted the role of both patient factors and intraoperative care as contributing to the risk of intraoperative and postoperative cardiac arrest and emphasized the management of ventilation and the selection and dosing of anesthetic medications as key areas of focus for the prevention of such events.

PERIOPERATIVE MORTALITY AND MORBIDITY IN OUTPATIENT SURGERY

In the United States, an estimated 60% of all surgical procedures are performed on an outpatient basis, and this percentage is increasing annually. The type and extent of surgical procedures performed in an outpatient setting are constantly changing, and more complicated procedures associated with greater perioperative risk are increasingly being performed on an outpatient basis.

Notably, early research on the safety of two ambulatory surgical procedures—tonsillectomy and simple mastectomy—presented a negative view of the hazards of surgery in the outpatient setting. One of the first procedures advocated to be performed on an ambulatory basis was tonsillectomy. Although a 1968 case series of 40,000 outpatient tonsillectomies reported no deaths,⁶¹ details on patient selection and length of postoperative monitoring were vague. Based on insurance company and state mandates, performance of tonsillectomy on an outpatient basis became routine.⁶² Beginning in the mid-1980s and continuing in the 1990s, a number of articles evaluated outcomes with early discharge after tonsillectomy. For example, Carithers and colleagues⁶³ in 1987 at Ohio State University reported on 3000 tonsillectomies and argued that early discharge might be hazardous and economically unwarranted. The rate of readmission for active bleeding between 5 and 24 hours after surgery was reported to be between 0.2% and 0.5%.⁶⁴⁻⁶⁷ More recently, Cote and his co-investigators in the Society for Pediatric Anesthesia^{67a} used a survey instrument as well as analysis of the ASA-CCP to investigate adverse events associated with tonsillectomy in children. They identified a total of 111 events occurring between 1999 and 2010. Death was the most common outcome (66%), followed by neurologic injury (11%) and prolonged hospital stay (10%). Events in children at risk for obstructive sleep apnea (OSA) were more frequently attributed to apnea, whereas children not at risk for OSA were more likely to experience adverse events secondary to hemorrhage. Fifty percent of patients with postoperative events had received postoperative opioids, including 61% of those children who experienced apneic events in the next 24 hours. Events occurred in multiple locations (the operating room, postanesthesia care unit [PACU], and after discharge). In spite of the limitations in the largely self-reported data, these findings clearly suggest that tonsillectomy remains a procedure with significant associated risk, even in the ambulatory setting.

Mastectomy represents a second important case study in the development of surgery as an outpatient procedure. An analysis of Medicare claims demonstrated that the rate of outpatient mastectomy increased from a negligible proportion of all mastectomies in 1986 to 10.8% of

all mastectomies performed among Medicare beneficiaries in 1995.⁶⁸ Within this population, simple mastectomies performed on an outpatient basis had a significantly higher rate of readmission than did those undergoing a 1-day hospital stay, with an adjusted odds ratio of 1.84. Additionally, rates of readmission after 1-day stays were significantly lower for infection (4.1 vs. 1.8 per 1000 cases), nausea and vomiting (1.1 vs. 0 per 1000 cases), and pulmonary embolism or deep venous thrombosis (1.1 vs. 0 per 1000 cases).

More recent research suggests that, for some procedures, mere exposure to anesthesia in the outpatient setting may present an increased risk for complications. In 2013, Cooper and colleagues^{68a} reviewed outcomes for a sample of cancer-free Medicare beneficiaries in the Surveillance, Epidemiology, and End Results database undergoing outpatient colonoscopy without polypectomy, and compared outcomes including hospitalization and aspiration pneumonia for those undergoing procedures with or without deep sedation (anesthesia services). The researchers identified 35,128 (21.2%) procedures with anesthesia services in a total of 100,359 patients; overall complications were more common in patients who had received anesthesia (0.22% vs. 0.16%, $P < .001$). Aspiration was also more common in the anesthesia group (0.14% vs. 0.1%, $P = .02$). Multivariate analysis also demonstrated an increased risk of complications associated with use of anesthesia (odds ratio 1.46, 95% CI 1.09-1.94).

In contrast to these procedure-specific studies, the 1993 publication of Warner and colleagues⁶⁹ on major morbidity and mortality within 1 month of ambulatory surgery strongly argued for the safety and feasibility of surgery in the outpatient setting. Among the 38,598 patients included in Warner's study, four died. Of these four deaths, two were due to myocardial infarctions occurring more than 1 week after surgery; the other two deaths occurred in automobile accidents (Fig. 30.3). Partially as a result of these findings, the use of ambulatory surgery has dramatically grown between the early 1990s and the present, with a concurrent increase in the number and type of sites for ambulatory surgery. Such sites now include not only freestanding ambulatory surgery centers (ASCs) and physician's offices, but they also include interventional radiology units and other diagnostic and therapeutic sites not affiliated with any other healthcare facility.

In the context of such growth, investigators have sought to examine the relative safety of similar procedures performed across different outpatient settings. Fleisher and co-workers² performed a claims analysis of patients undergoing 16 different surgical procedures in a nationally representative (5%) sample of Medicare beneficiaries for the years 1994 through 1999. A total of 564,267 procedures were studied, with 360,780 in an outpatient hospital, 175,288 in an ASC, and 28,199 in a physician's office. On the day of surgery, no deaths occurred in the office, but four deaths occurred in the ASC (2.3 per 100,000) and nine deaths occurred in the outpatient hospital (2.5 per 100,000). The 7-day mortality rate was 35 per 100,000 in the office setting, 25 per 100,000 in the ASC, and 50 per 100,000 in the outpatient hospital. The rate of admission to an inpatient hospital within 7 days was 9.08 per 1000 in the office, 8.41 per 1000 in the ASC,

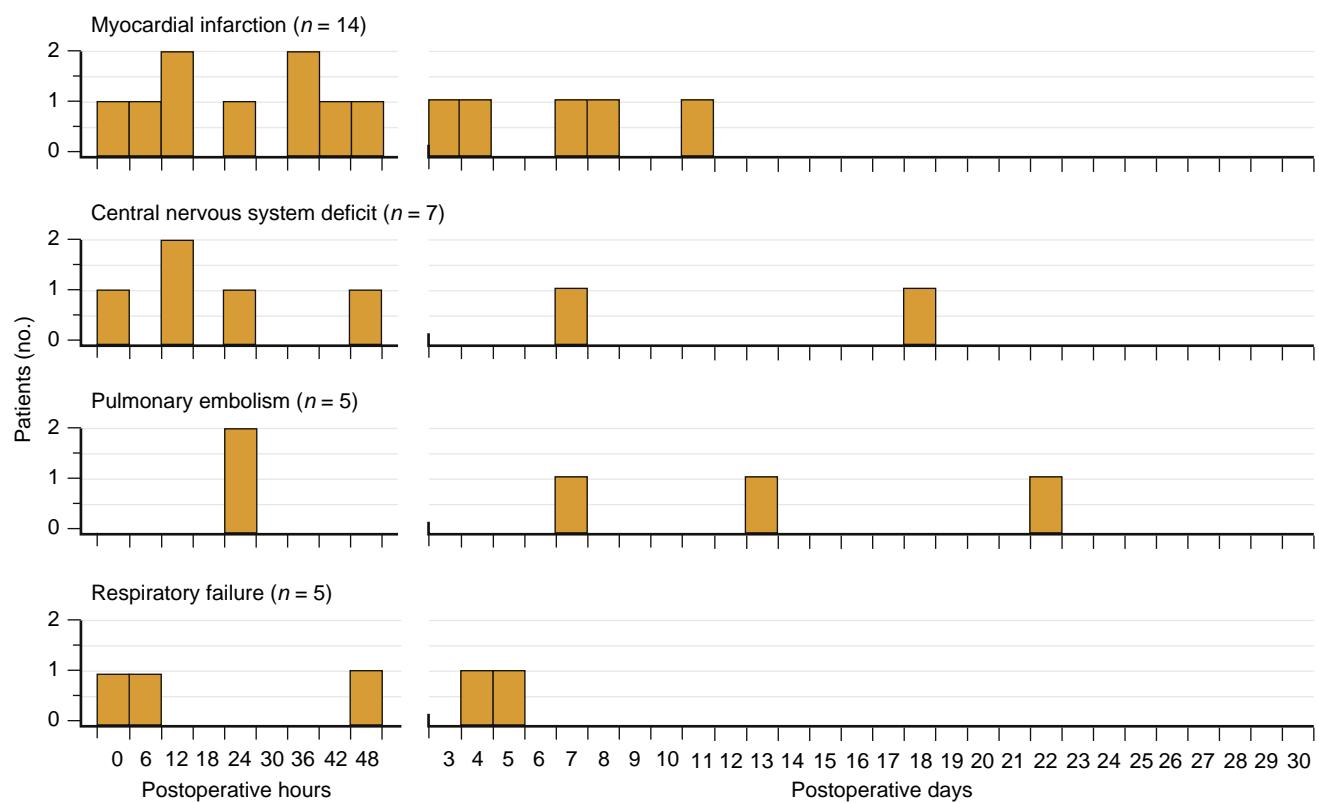


Fig. 30.3 Timing of perioperative events in patients undergoing ambulatory surgery. Many of the events occurring within the first 48 hours are probably related to the stress of surgery. A subset of events occurring after this period may be related to background event rates. The overall rate of morbidity was lower than expected for a similar cohort of age-matched nonsurgical patients. (From Warner MA, Shields SE, Chute CG. Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. *JAMA*. 1993;270(12):1437–1441.)

and 21 per 1000 in the outpatient hospital. Notably, the inferences of this study are limited by an inability to distinguish fully whether these differences in outcomes are related to the differences in the types of patients selected to have surgery in each setting versus the differences in the care patients received in each setting.

Subsequent work by Chukmaitov and colleagues compared quality outcomes between ASCs and hospital-based outpatient departments in the state of Florida between the years 1997 and 2004.⁷¹ Although their conclusions were limited by differences in the data available for patients treated in each setting, they postulated that the difference in outcomes between the two locations may be related to variations in organizational structure, processes, and strategies.

In contrast to the growing literature on the safety of anesthesia and surgery in ASCs, limited information exists to quantify the incidence of complications in office-based settings. The American Association for Ambulatory Plastic Surgery Facilities mailed a survey to their members to determine the incidence of complications occurring in office facilities.⁷² The overall response rate was 57%. The findings showed that 0.47% of patients had at least one complication, including bleeding, hypertension, infection, and hypotension, and 1 in 57,000 patients died. Although low in absolute terms, the observation of a rate of mortality after minor outpatient procedures that is three times the current estimate for anesthesia-related complications is concerning in this context.

Vila and colleagues reviewed all adverse incident reports to the Florida Board of Medicine for procedures dated April 1, 2000, to April 1, 2002.⁷³ Adverse incidents occurred at a rate of 66 and 5.3 per 100,000 procedures in offices and ASCs, respectively. The death rate per 100,000 procedures performed was 9.2 in offices and 0.78 in ASCs. The relative risk (RR) for injury and death for procedures performed in offices versus ASCs was 12.4 (95% CI, 9.5–16.2) and 11.8 (95% CI, 5.8–24.1), respectively. As a result, the authors concluded that if all office procedures had been performed in ASCs, approximately 43 injuries and 6 deaths per year could have been prevented. However, several other groups have also analyzed the Florida data and have been unable to document the increased risk in the office setting.^{74–76}

In summary, although early research on ambulatory surgery placed an emphasis on the undue risks created by premature discharge, more recent analyses confirm that a range of surgeries can be safely performed in properly selected patients. Although some variations in outcomes have been observed across settings (i.e., hospital outpatient department vs. ASC), available literature suggests that, given proper patient selection, outpatient surgeries can be performed with a low rate of adverse events in multiple practice environments. Given the gradual expansion of outpatient surgery over time to include patients with greater burdens of comorbid disease and more extensive procedures, ongoing evaluations will be essential to characterize the dynamic, evolving nature of anesthetic risk in the ambulatory setting.

USE OF ANESTHESIA INFORMATION MANAGEMENT SYSTEMS

Over the past four decades, the use of computerized databases has enhanced the ability to assess perioperative risk and complications.

In one of the earliest computer analyses of postanesthesia deaths, Marx and associates³⁶ identified 645 individuals who died within 7 days after surgery out of a total cohort of 34,145 consecutive surgical patients. More recently, the growth of electronic anesthesia record systems has allowed for better insights into the causes of anesthesia-related events within the surgical unit, and, when used in combination with other data sources, on postoperative outcomes. An early example of such an analysis was that of Sanborn and colleagues,⁷⁷ who used a computer anesthesia record to identify intraoperative incidents. They were able to demonstrate that perioperative deaths occurred more frequently in patients who sustained an intraoperative incident of any type than in those who did not. Reich and colleagues similarly used computerized anesthesia records to evaluate hemodynamic variables and their relationship to risk.⁷⁸ They identified pulmonary hypertension, hypotension during cardiopulmonary bypass, and post-cardiopulmonary bypass pulmonary diastolic hypertension as independent predictors associated with mortality, stroke, and perioperative myocardial infarction over and above the effects of other preoperative risk factors.

More recently, data from the University of Michigan anesthesia information management system have been used to identify predictors of perioperative risk, including that of inadequate mask ventilation and of postoperative acute kidney injury. In the former evaluation of 22,660 patients,⁷⁹ limited or severely limited mandibular protrusion, abnormal neck anatomy, sleep apnea, snoring, and a body mass index of 30 kg/m² or greater were independent predictors of grade 3 or 4 mask ventilation and difficult intubation. Review of 15,102 patients who had a normal preoperative creatinine clearance and underwent noncardiac surgery⁸⁰ demonstrated that acute renal failure developed in 121 patients (0.8%), with 14 requiring renal replacement therapy (0.1%). Seven independent preoperative predictors were identified: age, emergency surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. Acute renal failure was associated with increased mortality from any cause at 30 days, 60 days, and 1 year.

In an effort to expand upon the insights gained from single-institution studies, two major efforts have since been initiated to pool electronic data on anesthesia care from multiple sites as a means of more effectively comparing outcomes and defining risk factors related to outcomes after anesthesia. The first of these, the Multicenter Perioperative Outcomes Group, was initiated in 2008 under the leadership of investigators at the University of Michigan. This project currently collects electronic anesthesia data from over 50 participating anesthesia departments in two countries. To date, the group has released a series of observational studies, including a report on the risks and outcomes of epidural hematomas after perioperative and obstetric epidural catheterization²⁶ and a subsequent report evaluating

the risk of epidural hematoma after neuraxial anesthesia in thrombocytopenic parturients.^{80a} Other projects have evaluated predictors of difficult mask ventilation and intubation via direct laryngoscopy,^{80b} as well as the success of a variety of rescue intubation techniques following direct laryngoscopy.^{80c} The Multicenter Perioperative Outcomes Group recently established Initiative for Multicenter Perioperative Clinical Trials, an arm dedicated to clinical and translational research.

The second group, the National Anesthesia Clinical Outcomes Registry, is maintained by the Anesthesia Quality Institute, a nonprofit organization established by the ASA. This large-scale data warehouse collects paper and electronic anesthesia case data used to review anesthesia practices with the intent of optimizing local efforts to assess both the risk and the quality of care, and for research purposes for the specialty as a whole. The Registry has released data related to perioperative mortality (cited earlier).

OTHER APPROACHES TO DISCERN THE ROOT CAUSE OF MORBIDITY AND MORTALITY

Although mortality directly attributable to anesthesia appears to have declined over time, the exact causes of this decline remain unclear. Numerous factors have been implicated in the improved outcome, including new monitoring modalities, new anesthetic drugs, and changes in the anesthesia workforce. However, relating the reduced risk to any one factor on the basis of available epidemiologic data is difficult. Further, although the use of newer monitoring modalities, particularly pulse oximetry, would be expected to improve outcomes, no randomized trial has been able to document such a conclusion. This limitation supports the need for continued monitoring of complications and their root cause through a number of approaches.

Initiated by the Professional Liability Committee of the ASA, the ASA-CCP represents one important approach to understanding the root causes of important complications of anesthesia care. The ASA-CCP constitutes an ongoing, nationwide survey of closed insurance claims for major anesthesia-related adverse events. In an early publication based on data collected by the ASA-CCP, Caplan and colleagues reviewed both fatal and nonfatal outcomes resulting in claims against anesthesia providers. Among the fatal events, unexpected cardiac arrest during spinal anesthesia was observed in 14 healthy patients from the initial 900 claims.⁸¹ These cases were analyzed in detail to identify patterns of care that might have led to the event. Two patterns were identified: oversedation leading to respiratory insufficiency and inappropriate resuscitation of high spinal sympathetic blockade.

Tinker and co-workers⁸² queried the ASA-CCP to determine the role of monitoring devices in the prevention of anesthesia mishaps. They reviewed 1097 anesthesia-related claims and determined that 31.5% of the negative outcomes could have been prevented by the use of additional monitors, primarily pulse oximetry and capnography. Injuries that were deemed preventable with additional monitoring resulted in dramatically more severe injury and cost of settlement than did those judged to be nonpreventable with additional monitoring. These findings were reinforced by a subsequent study of intraoperative respiratory

events by Caplan and colleagues (Table 30.10).⁸³ These claims represented the single largest class of injury (34%), with death or brain damage occurring in 85% of cases. They identified inadequate ventilation, esophageal intubation, and difficult tracheal intubation as the primary causes of respiratory events. The investigators believed most of the outcomes to be preventable with better monitoring, such as pulse oximetry or capnography (Fig. 30.4).⁸⁴ In more recent evaluations of MAC using the ASA-CCP, more than 40% of 121 claims associated with MAC involved death or permanent brain damage. Respiratory depression, after an absolute or relative overdose of sedative or opioid drugs, was the most common (21%, $n = 25$) of the complications.

A similar registry was developed by the Danish Patient Insurance Association.⁸⁵ For the years of 1996 through 2004, 1256 files were related to anesthesia, and 24 deaths were considered to be a result of the anesthetic procedure: 4 deaths were related to airway management, 2 to ventilation management, 4 to central venous catheter placement, 4 as a result of medication errors, 4 from infusion pump problems, and 4 after complications from regional blockade. Severe hemorrhage caused one death, and the cause was uncertain in one case.

TABLE 30.10 Distribution of Adverse Respiratory Events in the American Society of Anesthesiologists' Anesthesia Closed Claims Study

| Event | Number of Cases | Percent of 522 Respiratory Claims |
|--|-----------------|-----------------------------------|
| Inadequate ventilation | 196 | 38 |
| Esophageal intubation | 94 | 18 |
| Difficult tracheal intubation | 87 | 17 |
| Inadequate inspired oxygen concentration | 11 | 2 |

From Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. *Anesthesiology*. 1998;68(1):5-11.

Cooper and colleagues^{86,87} took an alternate approach to examining perioperative mortality through the study of critical incidents, which were defined as those that were potentially preventable and could lead to undesirable outcomes. This definition included events that led to no harm or only transient effects. The investigation involved collecting data on anesthesia-related human errors and equipment failures from anesthesiologists, residents, and certified registered nurse anesthetists (CRNAs). In a series of reports, the authors identified frequent incidents, such as disconnections in breathing circuits, and causes of discovery of errors, such as intraoperative relief. They confirmed that equipment failure was a small cause of anesthesia mishaps (4%), whereas human error was a predominant factor. They suggested that future studies of anesthesia-related mortality and morbidity should classify events according to a strategy for prevention rather than outcome alone.

Other countries have developed similar databases, such as the Australian Incident Monitoring Study. Data from this database have been used to evaluate problems with ventilation, with vascular access, and in the PACU.^{88,89}

ISSUES ASSOCIATED WITH ANESTHESIA-RELATED MORTALITY

The studies detailed in the preceding text focus on intraoperative or in-hospital deaths directly attributable to anesthesia care; nonetheless, perioperative complications may contribute to the risk of mortality beyond the immediate postoperative period. For example, a perioperative stroke or myocardial infarction may lead to death after the period of analysis. Notably, recent research has suggested that even small myocardial infarctions or unstable angina during the perioperative period have been associated with worsened long-term survival.⁹¹ Should these *late* deaths be attributed to anesthesia complications for the purpose of such analyses? The answer depends on the outcome and its relationship to anesthesia management.

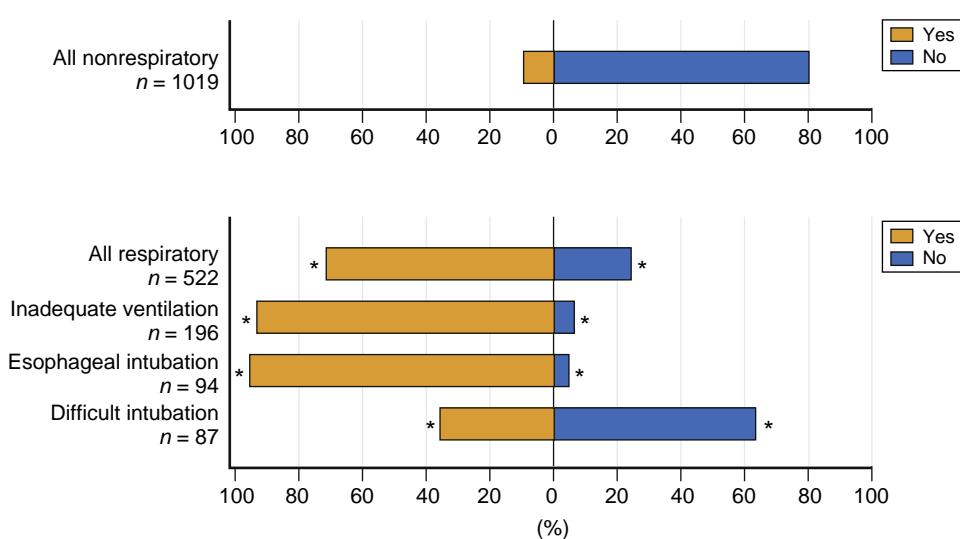


Fig. 30.4 Relationship between adverse events in the American Society of Anesthesiologists' Anesthesia Closed Claims Project and preventable complications. Preventable events related to respiratory complications were significantly more common than those related to all nonrespiratory complications. Of the respiratory complications, difficult intubation had the least number of preventable complications (* $P < .05$ vs. nonrespiratory claims). (From Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: a closed claims analysis. *Anesthesiology*. 1990;72(5):828-833.)

The potential effects of anesthesia on long-term survival were suggested by Monk and colleagues.⁹² Using multivariate Cox proportional hazards models, these investigators identified three variables as significant independent predictors of mortality: patient comorbidity (RR, 16.116), cumulative deep hypnotic time (bispectral index < 45) (RR, 1.244/h), and intraoperative systolic hypotension (RR, 1.036/min). Further work is required to determine whether these results reflect a true pathophysiologic link between perioperative (anesthesia) management and long-term outcome or a simple statistical association. This study and others, however, emphasize the importance of evaluating all aspects of anesthesia care and short- and long-term outcomes to try to optimize both long- and short-term patient outcomes.

Risks Related to Patient Characteristics

Multiple studies have demonstrated that perioperative morbidity and mortality are increased in the presence of coexisting medical diseases. The ASA physical status classification system, originally proposed in 1941,⁹³ represents a widely used method of classifying the severity of coexisting disease among surgical patients. Since its introduction, this classification system has established a standardized terminology for anesthesia practice and has aided in developing valid statistical comparisons of outcomes among sites.⁹⁴

The correlation between ASA physical status and mortality offers a simple illustration of the link between comorbidities and adverse operative outcomes. In 1961, Dripps and co-workers demonstrated that mortality increased as the severity of comorbid disease increased, as assessed by the ASA physical status classification.³² Several investigators have reevaluated the relationship between operative mortality and ASA physical status and demonstrated similar findings.^{43,46,95}

In Canada, Cohen and colleagues⁹⁶ analyzed 100,000 anesthesia procedures and determined mortality within 7 days of surgery by using governmental vital statistics mortality data between the years 1975 and 1984. For each patient, information was collected on age, preoperative conditions, ASA physical status, anesthetic technique, monitors, and other factors. The overall 7-day mortality rate was 71.04 deaths per 10,000 procedures. Risk markers for mortality are detailed in Table 30.11.

One of the limitations of the ASA physical status classification system is that the ranking is determined by individual anesthesia providers; as such, there may be variance between providers, as demonstrated by Owens and co-workers.⁹⁷ In light of these limitations, other studies have attempted to define the specific patient characteristics that are most strongly associated with perioperative adverse events related to a particular organ system. In evaluating the risk directly related to the patient's condition, the limitations of the methodology must be understood. All such studies evaluate the predictive value of a clinical or laboratory risk factor for a defined perioperative complication. In this approach, a cohort of individuals of interest is defined. Ideally, the study is performed prospectively, and the outcome of interest is assessed in a rigorous, blinded fashion. Despite

TABLE 30.11 Risk Factors Associated With Increased Odds of Dying Within 7 Days For All Cases

| Variable | All Procedures: Relative Odds of Dying Within 7 Days | 95% Confidence Limits |
|---|--|-----------------------------|
| PATIENT RELATED | | |
| Age (yr) | | |
| 60-79 vs. < 60 | 2.32 | 1.70-3.17 |
| 80+ vs. < 60 | 3.29 | 2.18-4.96 |
| Sex (female vs. male) | 0.77 | 0.59-1.00 |
| ASA physical status classification (3-5 vs. 1-2) | 10.65 | 7.59-14.85 |
| SURGERY RELATED | | |
| Major vs. minor | 3.82 | 2.50-5.93 |
| Intermediate vs. minor | 1.76 | 1.24-2.5 |
| Length of anesthesia (≤ 2 h vs. < 2 h) | 1.08 4.44 | 0.77-1.50 3.38-5.83 |
| Emergency vs. elective | | |
| OTHER FACTORS | | |
| Year of surgery (1975-1979 vs. 1980-1984) | 1.75 | 1.32-2.31 |
| Complication in the surgical or recovery unit (yes vs. no) | 1.42 | 1.06-1.89 |
| ANESTHESIA RELATED* | | |
| Experience of the anesthetist (>600 procedures for ≥ 8 years vs. <600 procedures for <8 years) | 1.06 | 0.82-1.37 |
| Inhalation with narcotic vs. inhalation alone | 0.76 | 0.51-1.15 |
| Narcotic alone vs. inhalation alone | 1.41 | 1.01-2.00 |
| Narcotic with inhalation vs. inhalation alone | 0.79 | 0.47-1.32 |
| Spinal vs. inhalation alone | 0.53 | 0.29-0.98 |
| Number of anesthetic drugs (1-2 vs. 3) | 2.94 | 2.20-3.84 |

*All cases performed with the five most frequently used anesthetic techniques.

Modified from Cohen MM, Duncan PG, Tate RB. Does anesthesia contribute to operative mortality? *JAMA*. 1988;260(19):2859-2863.

this, many available studies of perioperative risk factors focus on selected patients and include a retrospective design, methods that greatly limit their generalizability and validity. Many studies use multivariate modeling to determine the factors associated with increased risk. A major limitation in the use of multivariate modeling for this purpose is the assumption that the intraoperative period is a *black box* and that care is not modified by the knowledge of the risk factor (Fig. 30.5). However, anesthesiologists modify intraoperative care of high-risk patients in an attempt to minimize the likelihood of complications. Changes in medical care over time and better knowledge about high-risk patients should result in a reduction of the risk related to specified clinical factors. Such considerations make it difficult to design and complete formal investigations to validate individual management strategies in the context of current practice.

One common approach taken in past efforts to quantify operative risk has been to examine the relationship between a single risk factor and a broad range of adverse perioperative outcomes. For example, numerous studies have evaluated the importance of hypertension on perioperative risk. Goldman

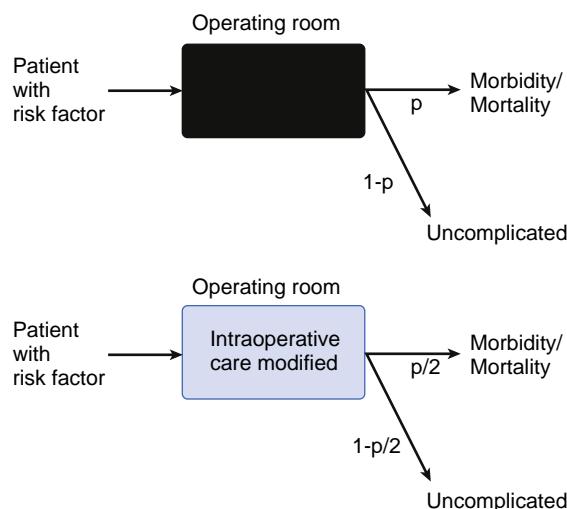


Fig. 30.5 The concept of the black box for risk indices. In developing a risk index, patients with a specific risk factor enter the operating room and have a complication at a rate p . If the anesthesiologist is aware of the importance of the risk factor and can modify care to reduce such risk ($p/2$), then the risk factor may no longer be significant. If the risk factor is ignored, then complications may again occur in such patients.

and Caldera⁹⁸ evaluated a cohort of patients undergoing noncardiac surgery under general anesthesia. Hypertension was not associated with increased perioperative risk, although the number of patients with diastolic blood pressure greater than 110 mm Hg was too small to draw any statistically significant conclusions. In contrast, Hollenberg and co-workers⁹⁹ identified hypertension and the presence of left ventricular hypertrophy as predictors of perioperative ischemia, but they did not consider their independent relationship to perioperative major morbidity. More recently, Baron and colleagues^{99a} analyzed data from a prospective study examining perioperative care across 28 European countries to evaluate the impact of hemoglobin levels on in-hospital mortality. Patients with severe (hemoglobin < 8 g/dL) or moderate (8-11 g/dL) levels were found to have higher rates of in-hospital mortality as well as longer length of stay and a higher likelihood of postoperative admission to the intensive care unit.

An alternative to examining the impact of a single risk factor on perioperative outcomes involves a more general effort to identify multiple risk factors for one or more adverse perioperative outcomes. Multiple researchers have undertaken prospective and retrospective cohort studies with the goal of identifying patients at greatest risk for fatal and nonfatal myocardial infarction. One of the earliest attempts to define cardiac risk was performed by Goldman and colleagues at the Massachusetts General Hospital.¹³ They studied 1001 patients older than 45 years of age who were undergoing noncardiac surgery. Using multivariate logistic regression, they demonstrated nine clinical factors associated with increased morbidity and mortality. Each risk factor was weighted in the logistic regression equation and converted into points in the index. An increasing number of points was associated with increasing perioperative cardiac morbidity or mortality.

Several attempts have been made to validate the Goldman Cardiac Risk Index in the surgical population.^{100,101} The validity of the Cardiac Risk Index is more controversial for patients undergoing vascular surgery. Several

groups¹⁰²⁻¹⁰⁴ were able to demonstrate a similar, if not identical, pattern of increasing cardiac complication rate with increasing cardiac risk. Several other studies, however, were unable to demonstrate any relationship between the Cardiac Risk Index and perioperative cardiac complications, with a high incidence of complications found in patients with a Cardiac Risk Index of I or II.^{105,106} When the ASA physical status classification system was compared with the Goldman Cardiac Risk Index in a cohort of 16,277 patients undergoing noncardiac surgery,¹⁰⁶ both indices demonstrated predictive value, although the objective Goldman Cardiac Risk Index provided little additional value over the more subjective ASA physical status classification.

Since the introduction of the Goldman Cardiac Risk Index, other investigators have put forward alternative risk indices for cardiac events after noncardiac surgery, such as the Detsky Modified Risk Index,¹⁰⁷ which confirms many of the factors identified by Goldman and allows calculation of a pretest probability of complications based on the type of surgery, after which the Detsky Modified Risk Index is applied with the use of a nomogram. The Detsky Modified Risk Index was advocated as the starting point for risk stratification in the American College of Physicians guidelines on preoperative evaluation.¹⁰⁸ Lee and colleagues¹⁰⁹ created a Revised Cardiac Risk Index (RCRI) incorporating six additional risk factors identified in a single-institution study: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine level higher than 2.0 mg/dL. The rate of major cardiac complications increased with the number of risk factors. The performance of the RCRI was examined in a metaanalysis conducted by Ford and colleagues,¹¹⁰ who found that although the RCRI showed moderate discrimination for patients at low versus high risk for cardiac events after noncardiac surgery, it did not perform well at predicting death or at predicting cardiac events after vascular surgery.

Gupta and colleagues¹¹¹ used data collected by the NSQIP to evaluate the risk for cardiovascular events after noncardiac surgery. This model, which included five variables—type of surgery, dependent functional status, abnormal creatinine level, ASA physical status, and increasing age—demonstrated improved discrimination over the RCRI, which did not improve with the addition of the RCRI score to the model.

Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study (VISION) is a multinational cohort group actively investigating major perioperative vascular events and their impact on mortality. In a 2016 study of over 15,000 patients in 12 countries, Berwanger and colleagues^{111a} noted a reduction in risk of a composite outcome of all-cause mortality, myocardial injury after noncardiac surgery (MINS), and stroke at 30 days (RR = 0.83, 95% CI 0.40-0.83, $P = .007$) associated with preoperative statin use. Perioperative statin use was also associated with a reduction in all-cause mortality, cardiovascular mortality, and MINS; however, there was no statistically significant difference in risk of myocardial infarction or stroke in statin users or non-users.

In a secondary analysis of the same patient cohort, Abbot and group^{111b} investigated the association between

elevated heart rate preoperatively and MINS within 30 days of surgery. Preoperative heart rate was stratified by deciles. The results showed that 7.9% of participants had sustained MINS, 2.8% myocardial infarction, and 2.0% died. After adjusting for confounders, the highest heart rate decile (preoperative heart rate more than 96 beats/min) was associated with increased risk of perioperative MINS (odds ratio 1.48, $P < .01$), MI (odds ratio 1.71, $P < .01$), and mortality (odds ratio 3.16, $P < .01$). Heart rates in the lowest decile (<60 beats/min) were independently associated with reduced mortality (odds ratio 0.05, $P = .02$). In a second subgroup analysis, preoperative hypercoagulability was associated with a higher risk of MINS.^{111c}

Beyond the efforts at identifying those patients most at risk of postoperative cardiovascular events, recent research has sought to develop statistical models for a range of other organ-based preoperative outcomes. These have included risk models for acute kidney injury in cardiac¹¹² and non-cardiac surgery patients,⁶⁰ postoperative respiratory failure,^{113,114} and stroke after cardiac surgery¹¹⁵ and carotid endarterectomy.¹¹⁶

In contrast to the efforts to determine risk factors for specific organ-based complications, other investigators have sought to develop risk-prediction models to identify those patients at risk of death from any cause in the immediate postoperative period. For example, Glance and colleagues from the University of Rochester used data from the NSQIP to derive and validate a predictive score for 30-day all-cause mortality for noncardiac surgery. They identified three factors that were highly predictive of death at 30 days after surgery: (1) ASA physical status, (2) emergency status, and (3) surgery type. Patients with ASA physical status I, II, III, IV, or V were assigned 0, 2, 4, 5, or 6 points, respectively; intermediate- or high-risk procedures were assigned 1 or 2 points, respectively; and emergency procedures were assigned 1 point. Patients with risk scores less than 5 had a predicted risk of mortality less than 0.5%, whereas patients with a risk score of 5 to 6 had a risk of mortality between 1.5% and 4%. Patients with a risk score greater than 6 had risk of mortality more than 10%.¹¹⁷

Beyond their clinical applicability, such risk indices have become important in the context of health policy by allowing for comparisons of risk-adjusted mortality rates across hospitals and physicians providing cardiac surgery. For example, the state of New York annually publishes data on mortality rates associated with coronary bypass grafting by surgeon and by hospital.¹¹⁸⁻¹²⁰ For comparison of rates across institutions, institutional mortality rates are typically risk-adjusted so that high-performing institutions that treat a high percentage of medically complex patients are not spuriously categorized as *poor performers* simply because of the features of their patient mix.

Beyond identifying clinical indicators of perioperative risk, historic and current research has focused on the role of genetics and genomics on the outcomes of major surgical procedures. Notably, the impact of genotype on perioperative risk has been well known since elucidation of the inheritance pattern of malignant hyperthermia. With malignant hyperthermia, a clear link exists between the autosomal dominant disease and an adverse outcome after administration of an anesthetic.¹²¹ Interest in evaluating the impact of genetic polymorphism on overall perioperative outcome is

increasing, even if the link to anesthesia is less well defined. For example, apolipoprotein E4 has been shown to modulate neurologic injury and recovery after a variety of acute ischemic insults, including coronary artery bypass grafting.¹²² Polymorphism of the glycoprotein IIIa constituent of the platelet integrin receptor has also been correlated with postoperative cognitive decline.^{123,124} Further research will be required to determine specific genetic profiles that will impact anesthetic management strategies, drug selection, and other aspects of care.

Special Patient Groups

OBSTETRICS

Anesthesia for the obstetric patient carries unique challenges, since both the mother and the fetus are potentially at risk for complications. Fortunately, maternal mortality is rare, and the anesthesia-related component of maternal delivery represents only a small fraction of all maternal deaths. As a result, studies of peripartum complications require a large number of patients from a diversity of clinical settings.

In parallel to the early efforts to determine the overall risk of anesthesia for surgery, a series of studies were performed between 1974 and 1985 that sought to determine the rate of obstetric complications in the United States and England, and to assess the contribution of anesthesia per se to the risk of adverse events in this group. Kaunitz and coauthors¹²⁵ reported an anesthesia-related death rate of 0.6 per 100,000 births with data from all 50 states. Endler and co-workers¹²⁶ studied births in Michigan between 1972 and 1984 and found a rate of 0.82 anesthesia-related deaths per 100,000 live births. Eleven of the 15 deaths were associated with cesarean section. Obesity and emergency surgery were risk factors in many patients. Complications related to regional anesthesia were identified as a problem in the earlier years of the study, whereas failure to secure a patent airway was the primary cause of mortality in the later years. No anesthesia-related maternal deaths occurred in the final 2 years of the study. Rochat and colleagues¹²⁷ studied 19 areas of the United States between 1980 and 1985 and reported 0.98 anesthesia-related deaths per 100,000 live births. They observed that maternal mortality did not decrease over the time of the study.

The Confidential Enquiry into Maternal Deaths in England and Wales has been assessing maternal deaths since 1952.¹²⁸ Morgan¹²⁸ reported the maternal deaths from anesthesia between 1952 and 1981 (Table 30.12). The total maternal mortality rate decreased over time, but the percentage of deaths related to anesthesia increased, although the absolute number of deaths associated with anesthesia decreased. Later reports identified technical difficulties with intubation as a major risk factor. The other major finding of this study was that the experience of the anesthesia provider in obstetric anesthesia was the most important factor in anesthesia-related maternal mortality.

More recent investigations have confirmed ongoing decreases over time in the hazards of obstetric anesthesia. Hawkins and associates¹²⁹ obtained data from the ongoing National Pregnancy Mortality Surveillance System of the

Centers for Disease Control and Prevention on births and fetal deaths from 1979 through 1990 to determine the possible risk related to anesthesia for obstetrics. They identified a total of 129 women who died of anesthesia-related causes during the study period. Most (82%) of the deaths occurred during cesarean section, and the incidence of anesthesia-related maternal mortality decreased over time (Table 30.13), possibly the result of a trend toward a greater use of neuraxial techniques. Importantly, among maternal deaths that occurred in the context of general anesthesia for cesarean delivery, 73% were related to airway problems.

In a subsequent study, Panchal and colleagues¹³⁰ conducted a retrospective case-control study using patients' records from a state-maintained anonymous database of deliveries between 1984 and 1997. Of the 822,591 hospital admissions for delivery during the 14-year study period, 135 maternal deaths occurred. The most common diagnoses associated with mortality during hospital admission for delivery were preeclampsia or eclampsia (22.2%), postpartum hemorrhage or obstetric shock (22.2%), pulmonary complications (14%), blood clot or amniotic embolism or both (8.1%), and anesthesia-related complications (5.2%). Notably, Panchal's study recorded differences by race in the rate of maternal

death per 100,000 live births per year (Fig. 30.6). Although the potential causes of this difference remain to be elucidated, Panchal's findings also suggested potential improvements over time in both the overall risk of maternal mortality, as well as the degree to which such risk differed by race.

More recent studies have continued to portray maternal mortality related to anesthesia as an important, although exceedingly rare event. Importantly, contemporary analyses of adverse maternal outcomes of anesthesia emphasize the particular risks associated with airway management in this population.^{131,132} In 2004, the Society for Obstetric Anesthesia and Perinatology established the Serious Complication Repository Project to better capture the incidence of serious complications related to obstetric anesthesia. D'Angelo and colleagues^{132A} collected outcomes of over 257,000 anesthetics at 30 institutions over a 5-year period. They identified a total of 157 serious complications, 85 of which were anesthesia-related (1 major complication per 3000 anesthetics). Maternal death occurred in 30 cases, but none were determined to be anesthesia-related. Complications frequently attributable to anesthesia included high neuraxial block, respiratory arrest, and unrecognized intrathecal catheter (Table 30.14).

In summary, extensive past research has indicated that the risks of major morbidity and mortality attributable to obstetric anesthesia care have decreased over time; nonetheless, recent research indicates that adverse outcomes continue to occur and may be of particular concern for patients receiving general anesthesia for cesarean delivery. As these risks are quantified with increasing precision using large databases, further research will be needed to validate these findings and identify the impact of variable care delivery (including the use of differing anesthetic techniques) and the maternal outcomes across institutions and practice environments.

PEDIATRICS

There are few studies of anesthesia-related risk in the pediatric population. Several themes emerge from these studies: very young infants are at increased risk of mortality, and anesthesia-related risk is reduced in centers with specialized pediatric anesthesia facilities. More recently, attempts have been made to define the neurocognitive risks presented by exposure to anesthesia at a young age.

In Beecher and Todd's classic 1954 study on anesthesia outcomes,¹⁸ a "disproportionate number" of anesthesia-related deaths occurred in children younger than 10 years of age. Similarly, Graff and colleagues¹³³ from the Baltimore Anesthesia Study Committee reported 335 operative deaths

TABLE 30.12 Maternal Mortality Figures Obtained from the Confidential Enquiry into Maternal Deaths in England and Wales

| Years | Maternal Mortality Per 1000 Total Births | Number of Deaths from Anesthesia | Percent of True Maternal Deaths from Anesthesia | Percent With Avoidable Factors |
|-----------|--|----------------------------------|---|--------------------------------|
| 1952-1954 | 0.53 | 49 | 4.5 | — |
| 1955-1957 | 0.43 | 31 | 3.6 | 77 |
| 1958-1960 | 0.33 | 30 | 4.0 | 80 |
| 1961-1963 | 0.26 | 28 | 4.0 | 50 |
| 1964-1966 | 0.20 | 50 | 8.7 | 48 |
| 1967-1969 | 0.16 | 50 | 10.9 | 68 |
| 1970-1972 | 0.13 | 37 | 10.4 | 76 |
| 1973-1975 | 0.11 | 31 | 13.2 | 90 |
| 1976-1978 | 0.11 | 30 | 13.2 | 93 |
| 1979-1981 | 0.11 | 22 | 12.2 | 100 |

From Morgan M. Anaesthetic contribution to maternal mortality. *Br J Anaesth.* 1987;59(7):842-855.

TABLE 30.13 Numbers, Case Fatality Rates, and Risk Ratios of Anesthesia-Related Deaths During Cesarean Section Delivery by Type of Anesthesia in the United States, 1979 to 1984 and 1985 to 1990

| Population | NUMBER OF DEATHS | | CASE-FATALITY RATE | | RISK RATIO | |
|------------|------------------|-----------|---------------------------|---------------------------|-----------------------|--------------------------|
| | 1979-1984 | 1985-1990 | 1979-1984 | 1985-1990 | 1979-1984 | 1985-1990 |
| General | 33 | 32 | 20.0* (95% CI, 17.7-22.7) | 32.3* (95% CI, 25.9-49.3) | 2.3 (95% CI, 1.9-2.9) | 16.7 (95% CI, 12.9-21.8) |
| Regional | 19 | 9 | 8.6† (95% CI, 1.8-9.4) | 1.9† (95% CI, 1.8-2) | Referent | Referent |

*Per million general anesthetics for cesarean section.

†Per million regional anesthetics for cesarean section.

CI, Confidence interval.

Modified from Hawkins JL, Gibbs CP, Orleans M, et al. Obstetric anesthesia work force survey, 1981 versus 1992. *Anesthesiology.* 1997;87(1):135-143.

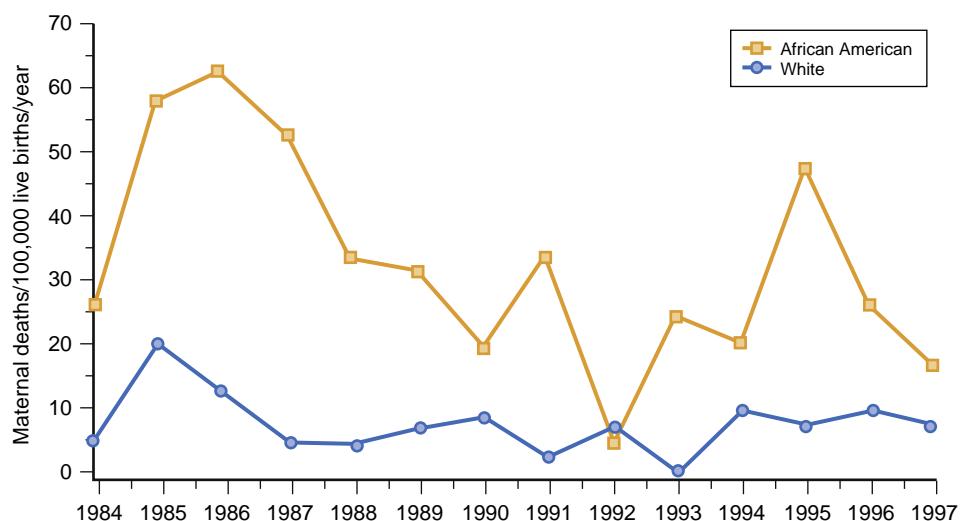


Fig. 30.6 Delivery mortality ratios by race in Maryland, from 1984 to 1997, according to discharge summaries. (From Panchal S, Arria AM, Labhsetwar SA. Maternal mortality during hospital admission for delivery: a retrospective analysis using a state-maintained database. *Anesth Analg*. 2001;93(1):134–141.)

TABLE 30.14 Incidence of Serious Complications Associated With Obstetric Anesthesia

| Serious Complication | Totals | Incidence (95% CI) | Anesthesia Related | Incidence (95% CI) |
|-----------------------------------|--------|----------------------------------|--------------------|-----------------------------------|
| Maternal death | 30 | 1:10,250 (1:7,180-1:15,192) | 0 | |
| Cardiac arrest | 43* | 1:7,151 (1:5,319-1:9,615) | 2 | 1:128,398 (1:35,544-1:1,060,218) |
| Myocardial infarction | 2 | 1:153,758 (1:42,562-1:1,269,541) | 2 | 1:128,398 (1:35,544-1:1,060,218) |
| Epidural abscess/meningitis | 4 | | 4 | 1:62,866 (1:25,074-1:235,620) |
| Epidural hematoma | 1 | | 1 | 1:251,463 (1:46,090-1:10,142,861) |
| Serious neurological injury | 27 | 1:11,389 (1:7,828-1:17,281) | 7 | 1:35,923 (1:17,805-1:91,244) |
| Aspiration | 0 | | 0 | |
| Failed intubation | 10 | | 10 | 1:533 (1:290-1:971) |
| High neuraxial block | 58 | | 58† | 1:4366 (1:3356-1:5587) |
| Anaphylaxis | 5‡ | 1:61,499 (1:26,353-1:189-403) | 0 | |
| Respiratory arrest in labor suite | 25 | 1:8,455 (1:5,714-1:12,500) | 16 | 1:10,042 (1:6,172-1:16,131) |
| Unrecognized spinal catheter | 14 | | 14 | 1:15,435 (1:9,176-1:25,634) |
| Total | 157§ | 1:1,959 (1:1,675-1:2,294) | 85¶ | 1:3,021 (1:2,443-1:3,782) |

*Fourteen cardiac arrests did not result in maternal death.

†Also includes high blocks on labor and delivery that resulted in respiratory arrest from local anesthetic administration.

‡The medications associated with anaphylaxis were administered by anesthesia personnel but were not anesthesia medications.

§There were 157 total serious complications; however, some complications are listed in more than one category.

¶There were 85 anesthesia-related complications; however, some complications are listed in more than one category.

Modified from D'Angelo R, Smiley RM, Riley ET, Segal S. Serious complications related to obstetric anesthesia: the serious complication repository project of the society for obstetric anesthesia and perinatology. *Anesthesiology*. 2014;120(6):1505–1512.

in the pediatric age group. Of these, 58 were thought to be primarily or partially attributable to anesthesia. The percentage of operative deaths attributable to anesthesia was relatively constant among age groups at 16.6% to 21.7%. The studies that followed those of Beecher and Todd and the Baltimore Anesthesia Study Committee provided further detail on the risks associated with pediatric anesthesia over time. Tiret and coauthors¹³⁴ prospectively studied major anesthesia-related complications in pediatric patients in 440 hospitals in France between 1978 and 1982. There were 27 major complications in 40,240 cases, which included 12 cardiac arrests and 1 death. The incidence of

major complications and cardiac arrest was significantly higher in infants than in older children. Most complications in infants involved the respiratory system and predominantly consisted of airway problems and aspiration. Older children experienced respiratory and cardiac complications, which occurred most frequently during induction and recovery.

Cohen and colleagues¹³⁵ studied 29,220 anesthesia procedures at the Winnipeg Children's Hospital in the 1980s. Data on patients' coexisting medical conditions and postoperative follow-up were obtained within 72 hours. Complications included death, cardiac arrest, drug reactions, airway

TABLE 30.15 Summary of Perioperative Events by Age Group

| | <1 Month (n = 361) | 1-12 Months (n = 2,544) | 1-5 Years (n = 13,484) | 6-10 Years (n = 7,184) | 11+ Years (n = 5,647) |
|--------------------------|--------------------|-------------------------|------------------------|------------------------|-----------------------|
| Any intraoperative event | 14.96 | 7.31 | 7.10 | 12.22 | 9.69 |
| Any recovery room event | 16.61 | 7.23 | 12.20 | 14.88 | 15.23 |
| Any postoperative event | 13.57 | 10.30 | 20.32 | 31.49 | 32.44 |
| Minor event* | 23.82 | 7.51 | 3.26 | 3.37 | 3.33 |
| Major event† | | | | | |
| Any event‡ | 48.89 | 25.92 | 37.50 | 50.52 | 51.33 |
| Among patients seen | 41.55 | 23.47 | 33.16 | 45.04 | 45.78 |
| Among all patients | | | | | |

*Includes nausea and vomiting, sore throat, muscle pain, headache, dental conditions, positional conditions, conditions involving extremities, eye conditions, croup, temperature, behavioral problems, thrombophlebitis, arterial line problem, awareness, and "other" problems.

†Includes "other respiratory" conditions, cardiovascular disorders, nerve palsy, hepatic disorders, renal disorders, seizures, surgical complications, and death.

‡Percentage of total anesthetics in which at least one event occurred in the intraoperative unit, recovery unit, or later during the postoperative period.

All figures are given as the percentage of events per total anesthetics.

Modified from Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. *Anesth Analg*. 1990;70(2):160-167.

obstruction, and minor complications such as nausea and vomiting, arrhythmias, and sore throat. Neonates underwent a higher percentage of major vascular or cardiac and intraabdominal procedures, and older children had a higher incidence of extremity procedures. Intraoperative cardiac arrest occurred most frequently in patients younger than 1 year of age (4 in 2901 procedures). Postoperatively, minor events such as nausea and vomiting were more common in older children, whereas respiratory events were more common in infants and younger children (Table 30.15). When compared with adult patients, children experienced different complications, which frequently extended well into the postoperative period. In a comparison of 2-year periods between 1982 and 1987, rates of intraoperative events were found to be stable, and the rate of postoperative complications decreased.

More recently, van der Griend and colleagues reported on 24-hour and 30-day mortality associated with 101,885 anesthetics administered to 56,263 children at the Royal Children's Hospital in Melbourne, Australia. They noted a rate of all-cause 24-hour mortality of 13.4 per 10,000 anesthetics and a 30-day all-cause mortality of 34.5 per 10,000 anesthetics. The incidence of deaths related to anesthesia was far lower, occurring at a rate of 1 in 10,188 or 0.98 cases per 10,000 anesthetics performed. In all of the 10 anesthetic-related deaths that the authors observed, preexisting medical conditions were assessed to have been a significant contributing factor.¹³⁶

In contrast to efforts to determine the incidence and predictors of mortality among pediatric surgical patients, a number of investigators have focused on cardiac arrest in the context of pediatric anesthesia. For example, Flick and associates¹³⁷ studied patients younger than 18 years of age who underwent surgery at the Mayo Clinic and experienced perioperative cardiac arrest between November 1, 1988 and June 30, 2005. A total of 92,881 anesthetics were administered during the study period, 4242 (5%) of which were for the repair of congenital heart malformations. The incidence of perioperative cardiac arrest during noncardiac procedures was 2.9 per 10,000, and the incidence during cardiac procedures was 127 per 10,000. The incidence of perioperative cardiac arrest attributable to anesthesia was 0.65 per 10,000 anesthetics. The incidence of cardiac

arrest and mortality was highest in neonates (0 to 30 days of life) undergoing cardiac procedures (incidence, 435 per 10,000; mortality, 389 per 10,000).

Investigators at the Children's Hospital of Boston conducted a registry study to evaluate rates of arrest in patients undergoing surgery for congenital heart disease.¹³⁸ Over a 5-year period, 41 cardiac arrests occurred in 40 patients during 5213 anesthetics for an overall frequency of 0.79%. Eleven cardiac arrests (26.8%) were classified as either likely (n = 6) or possibly related (n = 5) to anesthesia (21.1 per 10,000 anesthetics) but with no mortality.

Efforts to understand the causes and outcomes of cardiac arrest in pediatric anesthesia patients have been aided by the development of large-scale clinical registries for research and quality improvement. In 1994, the Pediatric Perioperative Cardiac Arrest (POCA) Registry¹³⁹ was formed to determine the clinical factors and outcomes associated with cardiac arrest in anesthetized children. A total of 289 cardiac arrests occurred in the 63 institutions in the database during the first 4 years of the registry, 150 of which were judged to be related to anesthesia (1.4 per 10,000 anesthesia procedures), with a 26% mortality rate. Medication-related causes and cardiovascular causes of cardiac arrest were most common. Anesthesia-related cardiac arrest occurred most often in patients younger than age 1 year and in patients with severe underlying disease. In 2007, an update from the POCA registry was published.¹⁴⁰ From 1998 through 2004, 193 arrests (49%) were related to anesthesia. Cardiovascular causes of cardiac arrest (41%) were the most common, with hypovolemia from blood loss and hyperkalemia from transfusion of stored blood being the most common identifiable cardiovascular causes (Fig. 30.7). In contrast to the earlier study, medication-related arrests only accounted for 18% of all arrests.

In 2010, POCA investigators reported on anesthesia-related cardiac arrest in children with preexisting cardiac disease, comparing 245 cardiac arrests in children without heart disease with 127 cardiac arrests in children with cardiac conditions. Compared with children without cardiac disease, children with cardiac conditions were more often ASA physical status III, IV, or V and more often arrested from cardiovascular causes. Mortality was higher in children with heart disease than among children without heart

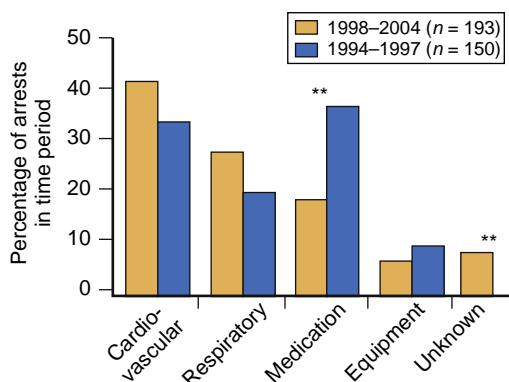


Fig. 30.7 Causes of anesthesia-related cardiac arrest in the Pediatric Perioperative Cardiac Arrest (POCA) Registry from 1998 to 2004 versus 1994 to 1997. (**P < .01 1998–2004 vs 1994–1997 by Z test). (From Bhananker SM, Ramamoorthy C, Geiduschek JM, et al. Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry. *Anesth Analg*. 2007;105(2):344–350.)

disease (33% vs. 23%) but did not differ when adjusted for ASA physical status classification.¹⁴¹

In recent years, researchers have become increasingly interested in how anesthetic exposure in young children impacts neurocognitive development. In 2016, Sun and group^{141a} published a sibling-matched cohort study conducted over 4 years at four university hospitals in the United States. They enrolled a total of 105 sibling pairs, one of whom had been exposed to inhalational anesthetics for an inguinal hernia repair before 36 months of age. Neurocognitive testing performed on both siblings did not demonstrate a statistically significant difference in intelligence quotient. Another group (Ing and colleagues)^{141b} analyzed data from the Western Australia Pregnancy Cohort to evaluate the relationship between anesthetic exposure in children younger than 3 years of age and neuropsychological, academic, and behavioral outcomes in a cohort of 2868 children. They identified discrepancies in neuropsychological test and ICD-9 coded clinical outcomes, but did not identify any differences in academic achievement, and suggest that the unique attributes of specific tests may explain the variation in cognitive outcomes described in different studies. In another cohort study, Backeljauw and colleagues^{141c} matched 5- to 18-year-old participants in a language development study who had undergone surgery with anesthesia before age 4 with unexposed peers. They found that exposed subjects had statistically significantly lower scores in listening comprehension and performance intelligence quotient, and that these changes were associated with lower gray matter density in key brain regions (occipital cortex and cerebellum). Given these conflicting results, further research is clearly needed to evaluate and quantify this impact in more detail.

OLDER ADULTS

The relationship of age to operative risk has been a subject of scientific and clinical debate since the early days of modern surgery. The nature of operative and anesthetic risk in older patients remains a vital area of inquiry particularly as the proportion of U.S. adults 65 years of age and older is anticipated to increase rapidly over the next three decades.

A key issue in research on the safety of surgery and anesthesia among older adults is the determination of what constitutes *old age* from the perspective of perioperative risk. Multiple definitions have been used for advanced age, including age older than 65, 70, 80, or 90 years. Denney and Denson¹⁴² evaluated risk associated with surgery in patients older than 90 years of age. They reported 272 patients undergoing 301 operations at the University of Southern California Medical Center, finding a high perioperative mortality rate among older patients with serious bowel obstruction (63%). Taking a slightly different approach, Djokovic and Hedley-Whyte¹⁴³ studied outcome after surgery in 500 patients older than 80 years of age. They found that mortality was predicted by ASA physical status classification, with greater comorbid conditions associated with increasing risk. Myocardial infarction was the leading cause of postoperative death. Patients without significant comorbid diseases (ASA I classification) had a mortality rate of less than 1%.

Del Guercio and Cohn¹⁴⁴ investigated the value of preoperative invasive monitoring in obtaining hemodynamic and cardiopulmonary variables for predicting operative risk in the older adult. Among 148 consecutive patients older than 65 years of age who were treated in a surgical ICU, only 13.5% had normal physiologic measurements. Advanced and uncorrectable functional deficits were found in 63% of patients, and all in this group who underwent the planned surgery died.

Del Guerico and Cohn's work represented one of several studies that emphasized coexisting diseases, rather than aging itself, as the cause of apparently increased perioperative mortality among older adults. More recently, a growing body of literature has focused on the importance of functional disability and chronic geriatric syndromes, such as frailty and dementia, as determinants of postoperative outcomes among older individuals. Robinson and colleagues examined a cohort of 110 surgical patients with a mean age of 74 years, finding a 15% 6-month rate of mortality. Statistically significant predictors of 6-month mortality included impaired cognition, a recent fall, hypoalbuminemia, anemia, functional dependence, and comorbidity. Notably, functional dependence was the strongest predictor of 6-month mortality. Four or more markers in any one patient effectively predicted 6-month mortality (sensitivity, 81%; specificity, 86%).¹⁴⁵ Finlayson and colleagues observed high rates of mortality after major gastrointestinal surgery among older nursing home residents versus the overall Medicare population; the high rates of mortality were likely attributable to high rates of comorbidity and functional disability within this population.¹⁴⁶

In this context, research on the risks of surgery and anesthesia in the older adult now focuses on broader definitions of *risk* that include functional outcomes and quality of life, in addition to traditional morbidity and mortality outcomes. Finlayson and colleagues examined 6822 older nursing home residents undergoing intestinal resections for colon cancer, noting a 53% 1-year mortality rate and a 24% rate of sustained decline in functional independence in activities of daily living among survivors. In multivariate regression, age older than 80 years, hospital readmission after surgical discharge, surgical complications, and functional decline before surgery all predicted functional decline at 1 year.¹⁴⁷

As the older population continues to grow, researchers have recently begun to evaluate the neurocognitive impact of anesthesia on the elderly.

The measures of outcome relative to patient goals of care are becoming increasingly important in determining optimal strategies for perioperative management of the geriatric population. The ASA recently instituted a Perioperative Brain Health Initiative (Fleisher)^{147a} dedicated to exploring the potential relationship between anesthetic exposure and postoperative cognitive function and delirium. This topic is discussed in more detail in [Chapter 83](#).

Risks Directly Related to the Anesthetic Drug

Numerous studies have evaluated the influence of the choice of anesthetic on outcome, a question that is discussed throughout this book. From a global perspective, there does not appear to be a single best anesthesia technique for a particular surgery or group of surgeries, although emerging evidence begs for more research on this subject. In a multivariate analysis by Cohen and co-workers⁹⁶ of 100,000 anesthesia procedures performed in Canada, the choice of drug did not provide any additional prognostic information for predicting mortality beyond that of patient disease and the surgical procedure. In univariate analysis, MAC appeared to be associated with worse outcomes; however, this association was attributable to the use of MAC in sicker patients (see [Table 30.11](#)).

One question that has persisted within the anesthesia literature is the issue of whether anesthetic medications carry inherent toxicity. For example, numerous discussions have focused on the potential toxicity of halothane and sevoflurane. In the case of halothane, concern focused on the potential for fulminant, potentially fatal, hepatic necrosis with this medication. After several case reports of hepatic necrosis after halothane anesthesia, a large retrospective study of 856,500 anesthesia procedures at 34 institutions was undertaken.¹⁴⁸⁻¹⁵⁰ In all but seven cases, hepatic necrosis could be explained by other causes. Halothane could be associated with hepatitis and hepatic failure, but the incidence was very low.

In the case of sevoflurane, concern has centered on the potential nephrotoxicity of its metabolite compound A. Although some laboratory studies have supported the contention that sevoflurane reacts with soda lime to form compound A and that this metabolite can lead to renal toxicity,^{151,152} clinical studies have been unable to confirm this potentially detrimental effect^{153,154} in the United States.

Some research groups have recently sought to identify and quantify other anesthesia-attributable effects. In 2016, Wigmore and colleagues^{154a} published the results of a retrospective cohort study evaluating survival and recurrence outcomes in propensity-matched patients undergoing primary resection of malignancy with inhaled versus intravenous anesthetics in over 7000 patients in the United Kingdom. After adjusting for confounders, the investigators demonstrated a hazard ratio of 1.46 for death in patients receiving volatile anesthetic versus those receiving inhalational agents, a result which demands further prospective investigation.

In 2008, the GALA investigators^{154b} published results of a randomized controlled trial comparing outcomes following carotid endarterectomy with local versus general anesthesia in 3526 patients with asymptomatic or symptomatic carotid stenosis. Primary outcomes included stroke, myocardial reinfarction, and 30-day mortality. Of the patients undergoing general anesthesia 4.8% experienced events, as compared to 4.5% of patients who were managed with local anesthetics (3 events preventable per 1000 treated). The investigators were not able to identify a statistically significant benefit to local or general anesthesia for individual primary outcomes, or for 30-day quality of life, hospital length of stay, or surgical duration. In a retrospective cohort study published in 2015, van den Berg and colleagues^{154c} investigated outcomes of intraarterial treatment of patients with acute ischemic stroke with or without general anesthesia. Cases without general anesthesia were associated with good clinical outcome in a higher proportion than those treated with general anesthesia (26% vs. 14%), although there were notable distinctions between the two groups. They also found a nonsignificant mortality benefit in the non-general anesthesia group. The authors speculated that anesthetics might alter autoregulation of cerebral blood flow; however, their results were confounded by the determination that arterial recanalization was delayed by up to 20 minutes in patients undergoing interventions with general anesthesia.

Numerous studies have attempted to define the *safest* anesthetic for high-risk patients. In the late 1980s, there was concern that isoflurane caused coronary steal in patients with coronary stenosis and collaterals and that this could result in myocardial ischemia.^{155,156} A series of studies were conducted to evaluate the rate of perioperative cardiac morbidity and mortality in patients undergoing coronary artery bypass grafting to determine the importance of the agent used for general anesthesia.¹⁵⁷⁻¹⁶⁰ Taken together, these studies demonstrated negligible differences in outcome, thus supporting the contention that multiple safe approaches to general anesthesia may exist for an individual context. Other studies have focused on the relative safety of general anesthesia versus neuraxial or regional techniques (Basques et al.).^{161,162,162a} For lower extremity and pelvic surgery, regional anesthesia was associated with a lower incidence of graft thrombosis and deep venous thrombosis, as well as decreased bleeding, decreased length of stay (Neuman et al.),^{162b} reduced risk of surgical site infection, and risk of prolonged hospitalization (Helwani et al.).^{162c} Regional anesthesia has also been specifically associated with lower major complication rates in patients with OSA (Memtsoudis et al.).^{162d} In a more recent meta-analysis published by O'Donnell and colleagues,^{162e} the findings were less favorable. Although they were able to determine a small difference in hospital length of stay attributable to regional anesthesia, the discrepancies in outcome reporting among the different studies were such that they were not able to identify definitively any other differences between the two approaches. The investigators of two randomized controlled trials currently underway, REGAIN (Neuman et al.)^{162f} and RAGA-delirium, (Li et al.)^{162g} are attempting to quantify the impact of anesthetic choice on morbidity, mortality, and cognitive outcomes in patients undergoing hip fracture surgery.

For patients undergoing vascular surgery, the primary finding favoring regional anesthesia was a lower incidence of graft thrombosis and the need for reoperation in patients undergoing infrainguinal bypass surgery; however, the largest of these studies was unable to demonstrate any difference in outcome based on anesthesia technique.¹⁶³⁻¹⁶⁵ The rate of this complication was low in the total cohort in the largest trial, which made it impossible to detect any difference based on technique. Summarizing findings from several of these studies, Rodgers and co-workers¹⁶² published an influential meta-analysis of regional versus general anesthesia. Neuraxial blockade was found to reduce postoperative mortality and other serious complications. As such, the magnitude of some of these benefits remained uncertain. Discussion of regional versus general anesthesia is presented in [Chapters 45 and 46](#).

The impact of perioperative ventilation modality has also recently come under investigation: in 2015, Ladha's group^{165a} published a hospital-based registry study examining outcomes of 69,239 patients undergoing noncardiac surgery requiring endotracheal intubation. Roughly 50% of patients received a protective ventilation strategy (reduced tidal volume and high positive end-expiratory pressure [PEEP]) versus standard care. Protective ventilation, defined as a PEEP of 5 cm H₂O and a plateau pressure of 16 cm H₂O or less, was associated with a reduced risk of postoperative respiratory complications. High driving pressure and plateau pressure were associated with an increased risk of respiratory complications. Severgnini and colleagues^{165b} randomized 56 patients undergoing elective open abdominal surgery to a standard mechanical ventilation strategy (tidal volume of 9 mL/kg, ideal body weight [IBW], and zero PEEP), or "lung protective" ventilation (7 mL/kg, IBW, PEEP of 10 cm H₂O, recruitment maneuvers). Patients receiving protective ventilation demonstrated respiratory function and reduced Clinical Pulmonary Infection Score for several days postoperatively. Length of stay did not differ between groups.

Risks Related to Surgery

The surgical procedure itself significantly influences perioperative risk. In virtually every study performed, emergency surgery is associated with additional risk.⁹⁸ In some cases, the risk related to surgery is a function of the underlying disease processes and the stress related to the surgical procedure. As a category of surgical procedures, cardiovascular surgery has historically been associated with the highest risk of mortality and major morbidity. (The risks related to anesthesia for cardiac surgical procedures are reviewed in [Chapter 54](#).) Vascular surgery is among the highest-risk group of noncardiac procedures. Although aortic reconstructive surgery has traditionally been considered the procedure with the highest risk, infrainguinal procedures have shown a similar rate of cardiac morbidity in several studies, possibly due to a higher burden of coronary artery disease in this population.^{166,167} Other high-risk vascular procedures include amputation.¹⁶⁸ Intraabdominal, thoracic, and orthopedic procedures have also been associated with increased risk.^{13,168}

Eagle and associates¹⁷⁰ evaluated perioperative cardiac morbidity and mortality among patients who had been treated for coronary artery disease and subsequently underwent major noncardiac surgery. Among these patients, major vascular surgery was associated with the highest risk of myocardial infarction or death, with a combined incidence of morbidity and mortality greater than 5%. Procedures associated with a combined complication rate of 1% to 5% included intraabdominal, thoracic, and head and neck surgical procedures. Low-risk procedures included breast, skin, urologic, and orthopedic surgeries. Ultimately, these groupings of surgical procedures came to form the basis for the definitions of surgical risk published in the American College of Cardiology/American Heart Association joint guidelines on perioperative cardiovascular evaluation for noncardiac surgery.¹⁷¹ More recent statistical modeling efforts, such as those of Gupta¹¹¹ and Glance,¹¹⁷ aimed at predicting postoperative outcomes have reinforced the important contribution of the type of surgical procedure to the overall operative risk.

Studies of the perioperative complication rate related to superficial procedures are generally reassuring. Backer and associates¹⁷² evaluated the rate of perioperative myocardial reinfarction in patients who have a history of preexisting coronary artery disease and who underwent ophthalmologic surgery. They demonstrated that the rate of perioperative cardiac morbidity after ophthalmologic surgery was extremely low, even in patients with a recent myocardial infarction. Similar findings have been reported by multiple other investigators.^{69,173}

More recent work suggests that surgical duration may also affect perioperative risk. Kim and group^{173a} reviewed a cohort of over 1 million patients undergoing surgery under general anesthesia between 2005 and 2011 and demonstrated an association between surgery duration and the risk of development of venous thromboembolism. These results were preserved in analysis of individual procedures and classes of procedure by specialty.

Risks Related to the Location of Surgery and Postoperative Monitoring

Perioperative risk varies among hospitals for major procedures such as coronary artery bypass grafting and abdominal aortic aneurysm repair.^{9,10,174} Multiple studies have documented a relationship between surgical volume and mortality. Although surgical skill most certainly plays a role in the rate of complications and mortality, local factors may also play an important role. For example, low surgical volume may lead to less skilled anesthesia and postoperative care. The influence of each of these factors on overall morbidity and mortality is unknown.

Although the value of postoperative monitoring and care in an ICU has never been documented in a randomized clinical trial, many investigators have suggested that such care is one of the primary reasons for the improved morbidity and mortality in recent years. For patients undergoing major vascular surgery, several investigators have suggested that more intense postoperative monitoring could

obviate the need for preoperative cardiac testing and revascularization.¹⁷¹ One potential value of risk assessment is the identification of patients who could benefit from referral to clinical centers with more extensive perioperative resources. Patients with a low probability of perioperative morbidity and mortality could have surgery performed locally, and individuals at higher risk could receive benefit from transfer to a center with high surgical volume.

Risks Related to the Anesthesia Provider

Over the past decade a great deal of attention has been paid to the role and skill of the anesthesia provider on patient outcome. Historically, anesthesia has been administered by a diverse group of providers with variable levels of supervision. The extent to which the skills and training of the individual anesthesia provider may affect outcomes has been assessed in a number of studies. In a now-classic paper, Slogoff and Keats¹⁷⁵ studied the association of perioperative myocardial ischemia and cardiac morbidity in patients undergoing coronary artery bypass grafting across multiple anesthesiologists working in a single practice. Notably, the rate of perioperative ischemia and infarction varied by anesthesiologist, and the authors concluded that operator technique and experience may affect risk. Subsequent work has moved beyond efforts to demonstrate variability in anesthesia outcomes at the level of the individual practitioner to examine whether outcomes might vary across different models of anesthesia care. Arbous and coauthors reported a case-control study over 1 year in the Netherlands,¹⁷⁶ in which they found that practice-level independent variables associated with a decreased risk for coma and death in 24 hours were (1) anesthesia equipment check performed with a checklist; (2) direct availability of an anesthesiologist by telephone, beeper, or walkie-talkie during maintenance anesthesia; (3) no change of anesthesiologist during the case; (4) presence of a full-time nurse anesthetist versus a part-time anesthetist during maintenance anesthesia; and (5) presence of two providers versus one person during emergence. This study was one of very few that attempted to identify practice characteristics rather than specific drugs or techniques that have an impact on anesthesia outcomes, and the results are striking, in spite of numerous issues with data reporting and matching. The finding that practitioner characteristics affect outcomes warrants further follow-up.

Attention has recently turned to the impact of handoffs of anesthesia care on patient outcomes. In 2018, Jones and colleagues^{176a} published a retrospective cohort study evaluating outcomes including all-cause mortality, hospital readmission, and major postoperative complications in 313,066 patients undergoing major surgery. They identified an association between complete anesthesia handoffs (i.e., when one provider or team leaves the case permanently and is replaced by another) and increased incidence of primary outcomes, as well as with increased rates of ICU admission and hospital length of stay. The study design was limited by the inability to control for the career experience of the replacement anesthesiologist and surgeon as well as by the sole use of billing codes to determine exposure to a transition in anesthesia care.

Several studies have attempted to evaluate the complication rates and risks associated with various care provider models. Bechtoldt,¹⁷⁷ as a member of the North Carolina Anesthesia Study Committee, evaluated 900 perioperative deaths that occurred in an estimated 2 million anesthesia procedures performed in North Carolina between 1969 and 1976. The lowest rate of anesthesia-related deaths (1 per 28,166 procedures) occurred in patients who received anesthesia from an anesthesia care team (physician anesthesiologist and CRNA), and the highest rate (1 per 11,432 procedures) was associated with anesthesia administered by a dentist; the rate for the nurse anesthetist-only cohort was intermediate (1 per 20,723). A study by the Stanford Center for Health Care Research¹⁷⁸ demonstrated similar outcomes: the investigators reported that death plus severe morbidity was 11% higher than predicted in patients who received their care in a nurse anesthetist-only setting, 3% lower than predicted for physician-only care, and 20% lower than predicted for an anesthesia care team environment. Both studies demonstrated significant methodologic limitations.

The impact of specific provider types may be greatest in particular situations: for example, patients with significant comorbid diseases and those who sustain perioperative complications may benefit from providers with specific skill sets. One way to study such issues is to evaluate the rate of survival after complications. Silber and colleagues⁷ at the University of Pennsylvania studied the medical records of 5972 surgical patients randomly selected from 531 hospitals. They evaluated patient and hospital characteristics, including the number and type of physicians, board certification status, and ratio of care providers. The 30-day mortality rate correlated with patient characteristics. Failure to rescue (i.e., failure to prevent death) after an adverse event was inversely associated with the proportion of board-certified anesthesiologists on staff in each facility. Improved perioperative survival was significantly associated with the presence of an increased number of board-certified anesthesiologists. These findings were corroborated in follow-up studies by the same group,^{179,181} wherein analysis was again limited by database characteristics.¹⁸¹ By contrast, Pine and co-workers evaluated mortality after eight specific surgical procedures¹⁸² and used stepwise logistic regression to derive procedure-specific risk adjustment models. They found hospitals without anesthesiologists had results similar to those facilities in which anesthesiologists provided or directed anesthesia care. The authors did not evaluate failure to rescue or cause of mortality.

More recently, work by Needleman and Minnick compared obstetric outcomes in facilities with different obstetric anesthesia staffing patterns.¹⁸³ Although the authors observed consistent differences in maternal mortality and other quality indicators at facilities where nurse anesthetists practiced with minimal or no supervision by anesthesiologists versus anesthesiologist-only facilities, questions regarding risk adjustment and study design limit definitive interpretations of this work for policy making.¹⁸⁴ Similarly, a 2010 study by Dulisse and Cromwell suggested no changes in overall surgical patient outcomes in states that had enacted laws allowing nurse anesthetists to practice independently versus states that required anesthesiologist supervision.¹⁸⁵ However, as such new

BOX 30.1 Proposed Definitions from the 1984 International Symposium on Preventable Anesthesia Morbidity and Mortality

| | |
|---------------------|---|
| Outcome | |
| Normal | |
| Abandoned procedure | |
| Morbidity | |
| Death | |
| Morbidity | Unplanned, unwanted, undesirable consequence of anesthesia |
| Mortality | Death that occurs before recovery from the effects of a drug or drugs given to facilitate a procedure |
| | Death that occurs during an attempt to relieve the pain of a condition |
| | Death that results from an incident that occurs while the drugs are effective |

Modified from Pierce EC Jr. The 34th Rovenstine Lecture. 40 years behind the mask: safety revisited. *Anesthesiology*. 1996;84(4):965–975.

legislation was not associated with major changes in the number or types of surgery conducted without anesthesiologist supervision, Dulisse and Cromwell's work does not speak directly to the question of the gains or losses in safety associated with any specific provider type for a given type of surgery.

Ultimately, as concluded by Smith and associates¹⁸⁶ in a review of available published studies through 2004 on the influence of anesthesia providers, the relationship of patient outcomes to the type of anesthesia provider has not yet been conclusively demonstrated. Nurse anesthetists and other nonphysician providers are vital to the delivery of anesthesia care in the United States and elsewhere, and determining the optimal scope of practice for such providers remains an ongoing area of academic research and political debate.

Improving Anesthesia Safety

Over the past several decades, major improvements to the safety of anesthesia have been initiated. In 1984, Cooper, Kitz, and Pierce hosted a landmark International Symposium on Preventable Anesthesia Mortality and Morbidity in Boston. Approximately 50 anesthesiologists from around the world attended the meeting and, after much debate, established a series of definitions of outcome, morbidity, and mortality (Box 30.1). Beyond its specific conclusions, however, the symposium remains an event of major historical importance as a seminal early event in the movement to improve patient safety and as the context out of which the Anesthesia Patient Safety Foundation (APSF) was established. After its formal incorporation in October 1985, the APSF has since actively promoted a range of initiatives focused on fulfilling its mission to continually improve the safety of patients during anesthesia care by encouraging and conducting: (1) safety research and education, (2) patient safety programs and campaigns, and (3) national and international exchange of information and ideas. To

BOX 30.2 Selected Areas of Focus of the Anesthesia Patient Safety Foundation, 1985 to 2012

- Use of anesthesia simulators for training and evaluation
- Improvement of standards for intraoperative monitoring
- Application of patient safety checklists to intraoperative care
- Promotion of standardized approaches to difficult airway management
- Prevention of medication-related adverse events
- Reuse and attempted resterilization of disposable anesthesia equipment
- Risks of outdated anesthesia machines without modern safety features
- Aiding the development of practice standards by the World Federated Societies of Anesthesiologists
- Surgery department crisis management, including teamwork, team training, and resource management
- *Production pressure*, causing dangerous omissions and cutting corners
- Intravenous procedural sedation by nonanesthesia personnel
- Contamination of medical gases and disruption of pipeline flow
- Contamination of intravenous medications
- Special risks of office-based anesthesia
- Patients with obstructive sleep apnea and their postoperative care
- Postoperative cognitive dysfunction (particularly in older adults)
- Possible long-term increase in morbidity and mortality after extensive general anesthesia
- Postoperative vision loss, especially in extensive prone spine surgery
- Wrong-site surgery
- Residual neuromuscular blockade and postoperative complications
- Protocols for assessing and managing adverse events
- Persistence of deaths from malignant hyperthermia
- Dangers and challenges in patients with coronary artery stents
- Maintenance of current protocols for the anesthesia machine checkout
- Possible impact of anesthesia management on cancer recurrence
- Persistence of surgical unit fires

Modified from Eichhorn JH. The Anesthesia Patient Safety Foundation at 25: a pioneering success in safety, 25th anniversary provokes reflection, anticipation. *Anesth Analg*. 2012;114(4):791–800.

this end, the APSF has focused on promoting research, practice improvement, and knowledge dissemination across a range of priority areas (Box 30.2). Overall, these efforts have stressed the potential for systems-level improvements, standardization of care processes, human-factors engineering, and simulation-based training to limit harms caused by preventable adverse events and errors in crisis management in the context of anesthesia care. Through this work, the APSF has come to serve as a leader in patient safety, not only in the context of anesthesia and perioperative care, but also more generally within medicine by establishing *patient safety* as a formal concept, discipline in medical care, and serving as a model for other organizations such as the U.S. National Patient Safety Foundation.¹⁹⁷

Alongside the efforts of the APSF, other prominent organizations, such as the ASA, have sought to improve the safety of anesthesia care through the creation and dissemination of standards and guidelines for clinical practice.

In general, both standards and guidelines represent summations by clinicians of the available evidence about the benefits and risks of particular approaches to treatment. Typically, a practice standard implies that a therapy or practice should be performed for patients with a particular condition. Standards are approved only if an assessment of the probabilities and utilities of the group indicate that the decision to choose the treatment or a strategy would be virtually unanimous. At present, the ASA has established one set of practice standards for anesthesia care, which outline basic requirements for intraoperative monitoring.¹⁹⁸

In contrast to practice standards, guidelines are intended to be more flexible than standards, but they should be followed in most cases. Depending on the patient, setting, and other factors, guidelines can and should be tailored to fit individual needs. Similar to standards, guidelines should be cost-effective methods. Specific guidelines have been created by the ASA for diverse issues such as a difficult airway,¹⁹⁹ the use of the pulmonary artery catheter,²⁰⁰ and the use of blood components²⁰¹ with the goal of defining the evidence on which optimal practice can be based. In a similar vein, the World Health Organization has recently placed an emphasis on the potential for a simple preoperative checklist, modeled on the processes used in other high-risk industries such as aviation, to reduce the rates of adverse events in the perioperative period.²⁰² Driven in part by the findings of improved outcomes with checklist use in a multicenter, international study by Haynes and co-authors,²⁰³ such expanding interest in the use of standardized safety checks offers new potential opportunities to decrease the risk of anesthesia further.

Applying further insights gained from the aviation industry to anesthesia care, the APSF and other organizations have focused on developing simulation-based approaches to train anesthesia providers and to evaluate their decision-making capabilities in crisis situations.²⁰⁴⁻²⁰⁸ To date, an extensive array of standardized scenarios have been developed for making comparisons among individuals, and research is ongoing to examine how best to use this technology in anesthesia training and recertification. Ultimately, such efforts, combined with improved monitoring of adverse outcomes through large outcomes databases and those now being assembled by the Multicenter Perioperative Outcomes Group and the Anesthesia Quality Institute, hold potential to improve the safety of anesthesia care continually on both a national and an international level.

Summary

The risks related to anesthesia appear to have dramatically decreased over the past several decades. Clearly, death solely attributable to anesthesia is rare; rather, underlying patient disease and the nature and extent of surgery have a greater effect on overall outcome than do risks attributable to the anesthetic per se. Although these changes in the risk attributable to anesthesia could justifiably be considered a major achievement on the part of anesthesia providers over time, they also present a novel challenge to anesthesia providers to identify new opportunities to aid in more broadly decreasing both the morbidity and the mortality of surgical procedures and to aid in aligning the results of surgical

interventions with individual patients' goals of care. At the same time, vigilance must be continued to maintain high standards of basic anesthesia care across both hospital- and nonhospital-based settings. Finally, anesthesia providers should play a role in systems-based thinking to improve perioperative care and the short- and long-term outcomes of patients undergoing surgery and anesthesia.

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KEY POINTS

- The anesthesia preoperative evaluation, which is the clinical foundation for guiding perioperative patient management, reduces perioperative morbidity and enhances patient outcome.
- The fundamental purpose of preoperative evaluation is to obtain pertinent information regarding the patient's medical history, formulate an assessment of the patient's perioperative risk, and develop a plan for any requisite clinical optimization.
- The preanesthesia evaluation should include a focused clinical examination, documentation of comorbid illness, reduction of patients' anxiety through education, assurance that preexisting medical conditions are optimally managed, selective referrals to medical specialists, ordering of preoperative investigations, initiation of interventions intended to decrease risk, discussion of aspects of perioperative care, arrangements for appropriate postoperative care, and recommendations to delay or cancel the surgical procedure, if deemed appropriate.
- Comorbid medical diseases can influence anesthesia and perioperative management, thus requiring the anesthesiologist to be knowledgeable in many aspects of internal medicine.
- Patients require appropriate preoperative diagnostic and laboratory studies consistent with their medical history and the proposed surgical procedure. Routine preoperative testing cannot be justified because it is costly and often clinically inappropriate.
- The anesthesiologist-led preoperative evaluation outpatient clinic can enhance operating room efficiency, decrease day-of-surgery cancellations or delays, reduce hospital costs, and enhance the quality of patient care.
- New and updated preoperative evaluation consensus and evidence-based guidelines published by multiple medical specialties have important influences on the preparation of patients for anesthesia and surgery.
- Anesthesiologists must be aware of, and be compliant with, increasing regulatory and reporting requirements involving preoperative issues by healthcare agencies.
- The anesthesiologist is the perioperative medical specialist and thus is uniquely positioned to evaluate the risks associated with anesthesia or surgery, discuss these risks with the patient, and manage them perioperatively in collaboration with the surgical team, referring physician, and other medical specialists.

Preoperative evaluation is required prior to the administration of any anesthetic. Its practice and scope have changed dramatically. Initial changes were driven by a rapid transformation in practice from hospital admission of patients the night before surgical procedures to admission on the morning of surgery. More recently, preanesthesia evaluation has become integral to the Perioperative Surgical Home model that aims to develop an integrated model for managing the entire perioperative episode of care.¹ This evolution in practice has led to a new approach to preoperative evaluation, which is a vital role of the perioperative physician. Accordingly, many anesthesiologists have expanded their responsibilities from providers of intraoperative anesthesia care to *perioperative medical specialists* who use their unique knowledge and experience to manage medical complexities related to surgery.² This expanded role entails that anesthesiologists assume the leadership role in the assessment and optimization of patients who are scheduled for surgery.³ This chapter provides a comprehensive discussion of the practice of preoperative evaluation, as well as a review of related concepts, current evidence, and consensus-based clinical practice guidelines.

Evolution of Preanesthesia Evaluation

All patients requiring anesthesia for surgery must undergo a preoperative evaluation by their anesthesia provider. The conduct of this evaluation has changed substantially. Historically, anesthesiologists assessed their patients for the first time either just before the surgical procedure or on the preceding day, with the remainder of preoperative evaluation and preparation being the responsibility of the surgeon, primary care provider, or other specialist. In some countries, this approach remains the usual clinical practice. Nonetheless, in many countries, anesthesiologists have increasingly taken on a leadership role in preoperative evaluation and preparation, well in advance of the scheduled procedure. This is particularly true for high-risk patients or those undergoing high-risk procedures.

Several factors explain this change. First, considerably fewer patients are admitted to the hospital prior to the

day of surgery. In many countries, there is little financial justification for the previous model of admitting patients prior to the day of surgery. For example, most surgical procedures in the United States are performed on an outpatient or same-day admission basis, including major neurosurgical, cardiac, and cancer resection procedures. Second, surgical patients are increasingly likely to be older frail individuals with significant burdens of medical comorbidity.⁴ For such patients, sufficient time is needed between the preanesthesia evaluation and the planned surgery to facilitate testing, interventions, and medical optimization. In the case of patients with very high-risk medical comorbidity, preoperative consultation by an anesthesiologist can help inform a shared decision-making process for proceeding with surgery (see section on “Frailty, Geriatric Conditions, and the Older Surgical Patient”). Third, anesthesia care increasingly extends beyond the operating room alone. Preoperative evaluation is an integral component of the anesthesiologists’ role as perioperative physicians who are involved in integrated medical care before, during, and after surgery. The specialty is uniquely positioned for this role given its expertise in the management of medical complexities related to anesthesia and surgery. This view of preoperative evaluation as a key component of the integrated management of the entire perioperative episode of care is essential to the Perioperative Surgical Home model.¹

Outpatient preoperative assessment clinics have been instrumental in facilitating greater involvement of anesthesiologists in preoperative evaluation. These clinics also impose new clinical and organizational challenges. In an institution where most surgical patients are evaluated in the preoperative assessment clinic, anesthesiologists may have less time to evaluate medically complex patients. Consequently, anesthesiologists must achieve a high level of efficiency and accuracy in the assessment of a patient’s history, physical examination, and differential diagnosis, as well as in the planning of perioperative management. Conversely, in a hospital where only the highest-risk patients are referred for consultation at a preoperative assessment clinic, the anesthesia department must interact with surgical departments to establish general protocols that ensure capture of the information needed to perform anesthesia safely, as well as the appropriate selection of individuals who require preoperative anesthesia consultation. In addition to changes in the scope and timing of the preanesthesia evaluation, this assessment has increasingly been influenced and governed by practice guidelines. For example, in the United States, The Joint Commission mandates documentation of a history and physical examination for any surgical patient within 30 days before the planned procedure, as well as reassessment within the 48-hour period immediately preceding the surgical procedure. The American Society of Anesthesiologists (ASA) and European Society of Anaesthesiology (ESA) have published specific guidelines for preoperative anesthesia evaluation.^{5,6} In addition, several other specialty societies published practice guidelines specifically relating to the preoperative management of medical issues in surgical patients.⁷⁻¹²

Goals and Benefits of Preanesthesia Evaluation

Preoperative evaluations help influence and improve perioperative care (Fig. 31.1). Indeed, inadequate preoperative evaluation was a contributing factor in 3% of perioperative adverse events in the Australian Incident Monitoring Study database.¹³ The overarching goals of preanesthesia evaluation are to (1) ensure that the patient can safely tolerate anesthesia for the planned surgery; and (2) mitigate perioperative risks such as pulmonary or cardiovascular complications. In pursuit of these goals, preanesthesia evaluations offer opportunities to perform focused clinical examinations, better document comorbid illness, reduce the patient’s (and family’s) anxiety through education, optimize preexisting medical conditions, make selective referrals to medical specialists (e.g., cardiologists), order specialized investigations (e.g., cardiac stress tests), initiate interventions intended to decrease risk, discuss aspects of perioperative care (e.g., anticipated risks, fasting guidelines), and arrange appropriate levels of postoperative care (e.g., critical care unit). If a patient is deemed to be at very high risk for adverse perioperative outcomes, the anesthesiologist may also recommend consideration of a nonoperative or less invasive treatment. Such a recommendation helps inform shared decision making for surgery (see Clinical Examination During Preoperative Evaluation section). In some cases, preanesthesia evaluation can identify a previously unrecognized medical condition (e.g., hypertension) that may not significantly affect perioperative risks, but warrants longer-term follow-up by appropriate healthcare professionals.

Compared to preoperative evaluations performed by surgeons or primary care physicians alone, anesthesiologist-led preoperative evaluation is associated with more selective ordering of laboratory tests and referral to specialists, thereby leading to reduced healthcare costs.¹⁴⁻¹⁷ Within the context of an anesthesiologist-led preoperative evaluation clinic, preanesthesia evaluations also associated with reduced anxiety,¹⁸ improved acceptance of regional anesthesia,¹⁹ fewer day-of-surgery case cancellations,^{14,20-22} shorter hospital length-of-stay,^{19,21,22} and lower hospital costs.²¹

Clinical Examination During Preoperative Evaluation

The *clinical examination*, consisting of the history and physical examination, is a fundamental component of preoperative evaluation by anesthesiologists. This information helps identify the underlying basis for the planned surgery, clarify the extent of comorbidities with specific perioperative relevance, identify opportunities for preoperative optimization, and select any appropriate preoperative testing. The consistency and quality of preoperative examinations are enhanced through standardization. Specifically, the baseline clinical examination of all surgical patients should include a consistent

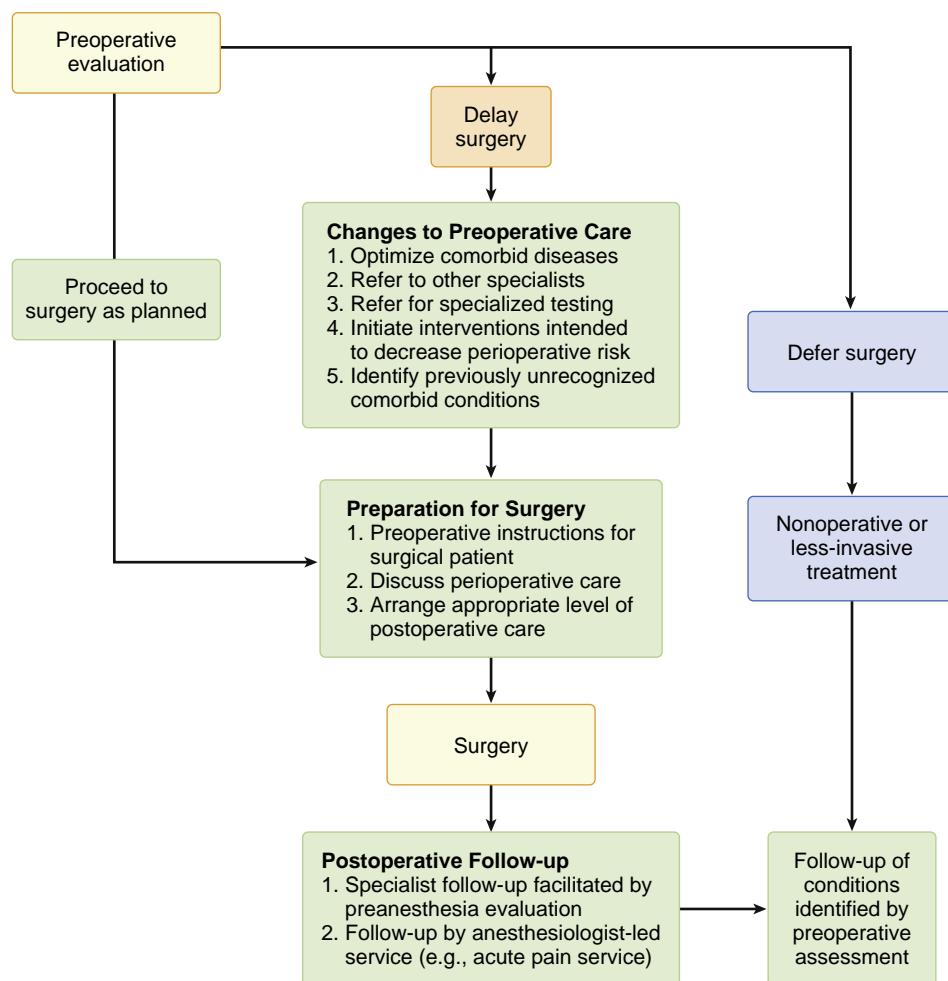


Fig. 31.1 Mechanisms by which preoperative evaluation can help influence and improve perioperative care.

set of components,²³ with opportunities for more detailed examination of one or more of these components (e.g., cardiovascular system) based on the findings from the standardized initial examination. Computer-based preoperative evaluation tools offer a mechanism for improving the standardization of high-quality preoperative assessments,^{24,25} and are recommended in the 2018 ASA guidelines on preoperative evaluation.⁶ The quality of the preoperative physical examination is further enhanced by appropriately considering evidence-based implications of different findings.²⁶

COMPONENTS OF THE MEDICAL HISTORY

The important components of the anesthesia history are presented in the sample preoperative history form in Fig. 31.2. This information can be documented, either on paper or an electronic form, by anesthesia staff during an in-person or telephone interview with the patient. Alternatively, the patient can complete a form capturing the required information, either in person or remotely through a web-based program. The preanesthesia evaluation starts with the planned surgery and its indication. The development of the underlying condition

necessitating surgery (e.g., cancer) and any prior related therapies need to be evident. Current known medical problems, past medical issues, previous surgeries, anesthesia types, and anesthesia-related complications must be noted. A simple notation of diseases or symptoms such as hypertension, diabetes mellitus, ischemic heart disease, shortness of breath, or chest pain is not sufficient. Rather, their associated severity, stability, associated activity limitations, exacerbations (current or recent), prior treatments, and planned interventions should be clearly documented. All related diagnostic test results, interventions, and names of treating physicians should be reviewed. The patient's responses to these initial questions may elicit further inquiry to establish a complete history.

Prescription and over-the-counter medications (including supplements and herbal medications) should be documented, along with their dosages and schedules. This information should include any recently interrupted medications with perioperative implications (e.g., recent corticosteroid therapy). The anesthesiologist should list any allergies to medications and other substances (e.g., latex, radiographic dye), with special emphasis on the patient's response to the exposure.

| | | | |
|--|---|---------------------|---------------------------|
| Patient's name _____ | Age _____ | Sex _____ | Date of surgery _____ |
| Planned operation _____ | Surgeon _____ | | |
| Primary care doctor/phone # _____ | Other physicians/phone #s _____ | | |
| 1. Please list all operations (and approximate dates) | | | |
| a. _____ | d. _____ | | |
| b. _____ | e. _____ | | |
| c. _____ | f. _____ | | |
| 2. Please list any allergies to medicines, latex, or other (and your reactions to them) | | | |
| a. _____ | c. _____ | | |
| b. _____ | d. _____ | | |
| 3. Please list all medications you have taken in the last month (include over-the-counter drugs, inhalers, herbals, dietary supplements, and aspirin) | | | |
| Name of Drug | Dose and How Often | Name of Drug | Dose and How Often |
| a. _____ | _____ | f. _____ | _____ |
| b. _____ | _____ | g. _____ | _____ |
| c. _____ | _____ | h. _____ | _____ |
| d. _____ | _____ | i. _____ | _____ |
| e. _____ | _____ | j. _____ | _____ |
| (Please check YES or NO and circle specific problems) | | | |
| 4. Have you taken steroids (prednisone or cortisone) in the last year? | <input type="checkbox"/> <input type="checkbox"/> | | |
| 5. Have you ever smoked? (Quantify in _____ packs/day for _____ years) | <input type="checkbox"/> <input type="checkbox"/> | | |
| Do you still smoke? | <input type="checkbox"/> <input type="checkbox"/> | | |
| Do you drink alcohol? (If so, how much?) _____ | <input type="checkbox"/> <input type="checkbox"/> | | |
| Do you use or have you ever used any illegal drugs? (we need to know for your safety) | <input type="checkbox"/> <input type="checkbox"/> | | |
| 6. Can you walk up one flight of stairs without stopping? | <input type="checkbox"/> <input type="checkbox"/> | | |
| 7. Have you had any problems with your heart? (circle) (chest pain or pressure, heart attack, abnormal ECG, skipped beats, heart murmur, palpitation, heart failure [fluid in the lungs], require antibiotics before routine dental care) | <input type="checkbox"/> <input type="checkbox"/> | | |
| 8. Do you have high blood pressure? | <input type="checkbox"/> <input type="checkbox"/> | | |
| 9. Have you had any problems with your lungs or your chest? (circle) (shortness of breath, emphysema, bronchitis, asthma, TB, abnormal chest x-ray) | <input type="checkbox"/> <input type="checkbox"/> | | |
| 10. Are you ill now or were you recently ill with a cold, fever, chills, flu or productive cough? | <input type="checkbox"/> <input type="checkbox"/> | | |
| Describe recent changes _____ | | | |

A

Fig. 31.2 (A and B) Sample patient preoperative history form. (ECG, Electrocardiogram; TB, tuberculosis; TMJ, temporomandibular joint.)

Patients often claim an “allergy” to a substance when, in reality, the reaction was an expected side effect (e.g., nausea or vomiting with narcotics). Tobacco, alcohol, or illicit drug use must be documented. Tobacco exposure is best quantified using pack-years (number of packs of cigarettes smoked per day, multiplied by the number of years of smoking); as an example, an individual who smoked two packs of cigarettes daily for the prior 10 years is deemed to have a 20 pack-year history of tobacco use. A personal or family history of pseudocholinesterase deficiency and malignant hyperthermia (including a suggestive history such as hyperthermia or rigidity during anesthesia) must be clearly documented

to facilitate appropriate planning before the day of surgery. Information from previous anesthetic records may clarify an uncertain history.

A standardized general review of all organ systems should then be performed. For example, patients should be asked whether they ever had problems with their heart, lungs, kidneys, liver, and nervous system. In addition, they should be asked about any history of cancer, anemia, bleeding problems, or prior hospitalization for any reason. The principal emphasis should be on airway abnormalities, anesthesia-related adverse events (personal or family history), as well as symptoms of cardiovascular, pulmonary, hepatic, renal, endocrine, or

| (Please check YES or NO and circle specific problems) | | YES | NO |
|---|--------------------------|--------------------------|----|
| 11. Have you or anyone in your family had serious bleeding problems? (circle) (prolonged bleeding from nosebleed, gums, tooth extractions, or surgery) | <input type="checkbox"/> | <input type="checkbox"/> | |
| 12. Have you had any problems with your blood (anemia, leukemia, sickle cell disease, blood clots, transfusions)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 13. Have you ever had problems with your: (circle) | <input type="checkbox"/> | <input type="checkbox"/> | |
| Liver (cirrhosis, hepatitis, jaundice)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Kidney (stones, failure, dialysis)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Digestive system (frequent heartburn, hiatus hernia, stomach ulcer)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Back, neck or jaws (TMJ, rheumatoid arthritis)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Thyroid gland (underactive or overactive)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 14. Have you ever had: (circle) | <input type="checkbox"/> | <input type="checkbox"/> | |
| Seizures, epilepsy, or fits? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Stroke, facial, leg or arm weakness, difficulty speaking? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Cramping pain in your legs with walking? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Problems with hearing, vision or memory? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 15. Have you ever been treated for cancer with chemotherapy or radiation therapy? (circle) | <input type="checkbox"/> | <input type="checkbox"/> | |
| 16. Women: Could you be pregnant? | <input type="checkbox"/> | <input type="checkbox"/> | |
| Last menstrual period began: _____ | | | |
| 17. Have you ever had problems with anesthesia or surgery? (circle) (severe nausea or vomiting, malignant hyperthermia [in blood relatives or self], prolonged drowsiness, anxiety, breathing difficulties, or problems during placement of a breathing tube) | <input type="checkbox"/> | <input type="checkbox"/> | |
| 18. Do you have any chipped or loose teeth, dentures, caps, bridgework, braces, problems opening your mouth, swallowing or choking? (circle) | <input type="checkbox"/> | <input type="checkbox"/> | |
| 19. Do your physical abilities limit your daily activities? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 20. Do you snore? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 21. Please list any medical illnesses not noted above: | <hr/> <hr/> <hr/> <hr/> | | |
| 22. Additional comments or questions for nurse or anesthesiologist? | <hr/> <hr/> <hr/> | | |

B

Fig. 31.2, cont'd.

neurologic disease. For example, a report of a patient who has experienced excessive sore throat, dental injuries, or “the need to have a small tube” with previous anesthetic cases may be an indication of previous difficulty with airway management. A history of snoring and daytime somnolence may suggest undiagnosed sleep apnea (see later section on “Obstructive Sleep Apnea”). Any history of chest discomfort (including its duration, precipitating factors, associated symptoms, and relieving factors) could be important. Similarly, a list of previous surgical procedures should be obtained and can help complete the medical history. Finally, records from primary care physicians, specialists, or inpatient admissions may reveal any issues the patient did not recall.

ASSESSMENT OF FUNCTIONAL CAPACITY

The assessment of the patient’s cardiopulmonary fitness or functional capacity is an integral component of the preoperative clinical examination. This information is typically used to estimate a patient’s risk for major postoperative morbidity or mortality, and to determine whether further preoperative testing is required.⁷ Importantly, suboptimal functional capacity is common in many economically advanced countries. For example, only one-fifth of American adults meet federal guidelines for recommended levels of aerobic and strengthening activity.²⁷ Poor exercise capacity and cardiopulmonary disease have a bidirectional relationship. Specifically, lack of exercise may increase the risk of developing

cardiopulmonary disease but preexisting cardiopulmonary disease can also prevent an individual from exercising. For example, patients with peripheral artery disease (PAD) may be limited by intermittent claudication, and patients with ischemic heart disease may be limited by exertional chest discomfort. There is a reasonable body of evidence demonstrating an association between poor preoperative functional capacity and increased perioperative risk. Most of these studies involved objective assessment of preoperative functional capacity using either exercise testing or cardiopulmonary exercise testing (CPET).²⁸⁻³¹ Several other large studies have demonstrated association between very significant preoperative functional impairment (i.e., difficulty or inability to perform activities of daily living) and increased risks of postoperative mortality,³² cardiovascular complications,³³ and pulmonary complications,^{34,35}

The challenge with assessment of preoperative functional capacity pertains to how best to assess it in usual clinical practice. Typically, the anesthesiologist will inquire about a patient's general activity levels during the preoperative interview, and on that basis, make a *subjective assessment* of the patient's functional capacity. Functional capacity is typically quantified in using the metabolic equivalent of task (MET), where one MET is approximately the rate of energy consumption at rest (3.5 mL/kg/min). A proposed scheme for estimating METs based on information from the preoperative interview is presented in Table 31.1. There are important limitations to the usual clinical approach for this integral component of the preoperative evaluation. First, subjective assessment does not accurately estimate the patient's true exercise capacity. In a multicenter prospective cohort study of 1401 patients undergoing major noncardiac surgery, anesthesiologists' subjective assessment had only 19% sensitivity and 95% specificity for identifying patients' inability to attain 4 or more METs during formal exercise testing.³⁶ In addition, subjective assessment has poor correlation with standardized questionnaires that have been validated for measuring functional capacity.^{37,38} Second, subjective assessment has generally shown poor performance in predicting postoperative morbidity and mortality. In a single-center cohort study of 600 surgical patients, patients' self-reported poor exercise capacity (defined as inability to walk four blocks and climb two flights of stairs) was associated with increased risk of serious perioperative complications,³⁹ but the magnitude of the association was relatively weak (positive likelihood ratio of 1.3 and negative likelihood ratio of 0.6). For context, positive test results should have likelihood ratios greater than 2 to provide clinically meaningful information, whereas negative test results should have likelihood ratios of less than 0.5.⁴⁰ Furthermore, in both a multicenter prospective cohort study and single-center retrospective cohort study, subjective assessment was a poor predictor of postoperative mortality and morbidity.^{36,41}

To improve preoperative evaluation of functional capacity, anesthesiologists should consider instead using structured questionnaires, such as the Duke Activity Status Index (DASI) (Table 31.2).⁴² This 12-item self-administered questionnaire

TABLE 31.1 Metabolic Equivalents* of Functional Capacity

| METs | Equivalent Level of Exercise |
|------|--|
| 1 | Eating, working at computer, or dressing |
| 2 | Walking down stairs or in your house, or cooking |
| 3 | Walking 1 or 2 blocks on level ground |
| 4 | Raking leaves, gardening |
| 5 | Climbing 1 flight of stairs, dancing, or bicycling |
| 6 | Playing golf, or carrying clubs |
| 7 | Playing singles tennis |
| 8 | Rapidly climbing stairs, or jogging slowly |
| 9 | Jumping rope slowly, or moderate cycling |
| 10 | Swimming quickly, running or jogging briskly |
| 11 | Skiing cross country, or playing full-court basketball |
| 12 | Running rapidly for moderate to long distances |

*One metabolic equivalent of task (MET) is the amount of oxygen consumed while sitting at rest, and is equivalent to an oxygen consumption of 3.5 mL/min/kg body weight.

Modified from Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13:555-565.

about activities of daily living has demonstrated correlation with gold-standard measures of functional capacity in surgical patients.^{36,43} Furthermore, DASI scores have been shown to improve prediction of postoperative cardiac complications following noncardiac surgery.³⁶ While there is some varying opinion as to how DASI scores should be converted to METs, the original formula is presented below:

$$\text{Estimated METS} = \frac{(0.43 \times \text{DASI score}) + 9.6}{3.5}$$

Other alternatives for estimating functional capacity include simple exercise tests (e.g., 6-minute walk test, incremental shuttle walk test),⁴⁴ exercise testing (e.g., electrocardiogram [ECG] exercise testing), or CPET. If using a standard exercise test (i.e., not CPET), extrapolation from the total treadmill time on a Bruce protocol exercise test results in overestimation of true exercise capacity. More importantly, resting left ventricular ejection fraction should not be used as a proxy measure of functional capacity.^{45,46}

PHYSICAL EXAMINATION

At a minimum, the preanesthetic examination should include vital signs (i.e., arterial blood pressure, heart rate, respiratory rate, oxygen saturation), height, and

TABLE 31.2 Duke Activity Specific Index questionnaire

| Can You | Points |
|--|--------|
| 1. Take care of yourself, that is, eat dress, bathe, or use the toilet? | 2.75 |
| 2. Walk indoors, such as around your house? | 1.75 |
| 3. Walk 200 yards on level ground? | 2.75 |
| 4. Climb a flight of stairs or walk up a hill? | 5.50 |
| 5. Run a short distance? | 8.00 |
| 6. Do light work around the house like dusting or washing dishes? | 2.70 |
| 7. Do moderate work around the house like vacuuming, sweeping floors, or carrying groceries? | 3.50 |
| 8. Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture? | 8.00 |
| 9. Do yard work like raking leaves, weeding, or pushing a power mower? | 4.50 |
| 10. Have sexual relations? | 5.25 |
| 11. Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a ball? | 6.00 |
| 12. Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing? | 7.50 |
| Total score: | |

From Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol*. 1989;64:651–654.

weight. Body mass index (BMI), which is calculated based on height and weight, is more informative than weight alone in establishing obesity. A scheme for classifying children and adults based on BMI is presented in **Table 31.3**. Information pertaining to BMI can help identify individuals at risk for difficulties with airway management, and some chronic diseases (e.g., heart disease, diabetes mellitus, obstructive sleep apnea [OSA]). An ideal body weight should also be calculated,⁴⁷ using available formulae such as the Devine equation.⁴⁸ Information on ideal body weight can better inform dose selection for some anesthesia-related medications, and settings for positive pressure ventilation. Readily available online calculators can be used to quickly determine both BMI and ideal body weight. Patients often have increased arterial blood pressure during the preoperative visit, even without a prior history of hypertension. This finding may be caused by anxiety, or patients having forgotten to take their usual dose of antihypertensive

TABLE 31.3 Classification Scheme for Body Mass Index

| Body Mass Index | Weight Status |
|--|-----------------------|
| ADULTS OVER 20 YEARS OLD | |
| BMI < 18.5 | Underweight |
| BMI 18.5–24.9 | Normal |
| BMI 25.0–29.9 | Overweight |
| BMI 30.0 and above | Obese |
| FOR CHILDREN AND TEENS | |
| BMI-for-age < 5th percentile | Underweight |
| BMI-for-age 5th percentile to < 85th percentile | Normal |
| BMI-for-age 85th percentile to < 95th percentile | At risk of overweight |
| BMI-for-age ≥ 95th percentile | Overweight |

BMI, Body mass index.

From Centers for Disease Control and Prevention. <http://www.cdc.gov>.

BOX 31.1 Components of the Airway Examination

- Length of upper incisors (concerning if relatively long)
- Condition of the teeth
- Relationship of maxillary incisors to mandibular incisors (concerning if there is prominent overbite)
- Ability to advance mandibular incisors in front of maxillary incisors (concerning if unable to do this)
- Interincisor or intergum (if edentulous) distance (concerning if < 3 cm)
- Visibility of the uvula (concerning if Mallampati class is 3 or more)
- Shape of uvula (concerning if highly arched or very narrow)
- Presence of heavy facial hair
- Compliance of the mandibular space (concerning if it is stiff, indurated, occupied by mass, or nonresilient)
- Thyromental distance (concerning if < 6 cm)
- Length of the neck
- Thickness or circumference of the neck
- Range of motion of the head and neck (concerning if unable to touch tip of chin to chest or cannot extend neck)

From: Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118:251–270.

medication. Thus, a single reading during the preoperative evaluation may not reflect the patient's usual blood pressure control. Repeating the blood pressure measurement or obtaining previous readings, either by obtaining medical records (including prior ambulatory blood pressure testing) or asking patients about their "usual" blood pressure measurements are informative. Ideally, the referral documentation from the patient's primary care physician or surgeon should include information on the patient's usual blood pressure readings.⁴⁹

From an anesthesiologist's perspective, inspection of the airway may be the most important component of the physical examination (see **Chapter 44**). The components of the airway examination are presented in **Box 31.1**.⁵⁰

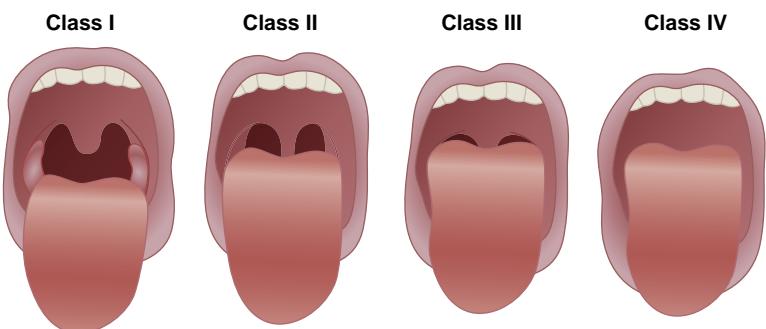


Fig. 31.3 Mallampati classification: class I, soft palate, fauces, entire uvula, pillars; class II, soft palate, fauces, portion of uvula; class III, soft palate, base of uvula; class IV, hard palate only. (From Bair AE, Caravelli R, Tyler K, et al. Feasibility of the preoperative Mallampati airway assessment in emergency department patients. *J Emerg Med*. 2010;38:677-680.)

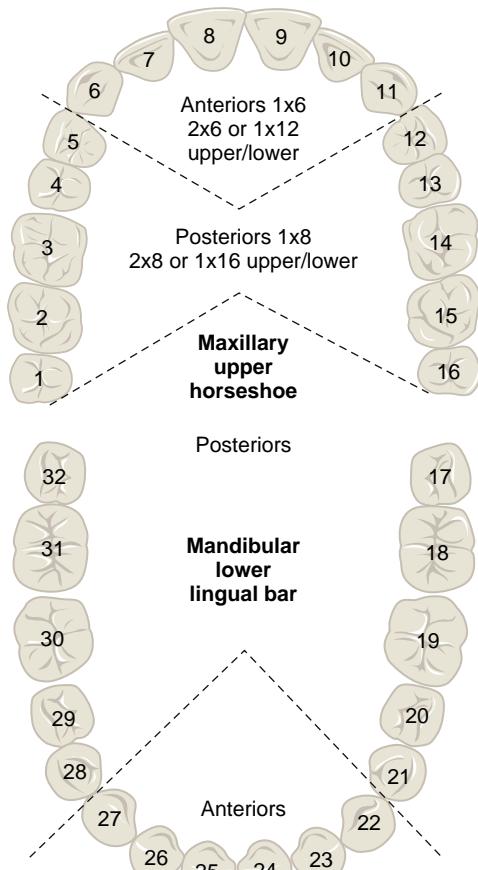


Fig. 31.4 Tooth numbering.

Documentation of an airway examination includes the Mallampati score (Fig. 31.3),⁵¹ status of teeth, degree of neck mobility (especially extension), neck circumference (increased size predicts difficulty with laryngoscopy), thyromental distance, body habitus, and pertinent deformities. Because of the potential for dental injuries during anesthesia, any preexisting tooth abnormalities should be documented (Fig. 31.4). In a French prospective cohort study of 1501 patients, the following characteristics were identified as independent predictors of

difficult bag-mask ventilation: age more than 55 years, BMI more than 26 kg/m^2 , absence of teeth, presence of a beard, and a history of snoring.⁵² These risk factors are largely consistent with those identified in an American retrospective cohort study of 22,660 patients: age 57 years or more, BMI 30 kg/m^2 or greater, presence of a beard, Mallampati classification III or IV, severely limited mandibular protraction, and a history of snoring.⁵³ Other possible risk factors for difficult ventilation include an increased neck circumference, face and neck deformities (i.e., prior surgery, prior radiation, prior trauma, congenital abnormalities), rheumatoid arthritis, Trisomy 21 (Down syndrome), scleroderma, cervical spine disease, or previous cervical spine surgery. The physical examination must be supplemented by examination of previous anesthetic records, especially when there are indications of a potentially difficult airway. Patients with known difficult airways should be encouraged to obtain medical alert identification. When challenging airways are identified, advance planning ensures that necessary equipment and skilled personnel are available on the day of surgery. An evaluation of the heart, lungs, and skin is necessary, as well as further focus on organ systems involved with diseases reported by the patient. This evaluation should include cardiac auscultation, as well as inspection of arterial pulses, veins (peripheral and central), jugular venous distention, ascites, hepatomegaly, and peripheral edema. Inspection of peripheral veins can also help assess the ease of intravenous access. The auscultatory examination should assess for murmurs, abnormal heart sounds (e.g., third or fourth heart sounds), and pulmonary rales. If intravenous access sites are limited, possible central line placement can be discussed with the patient, or arrangements can be made for assistance from interventional radiology. Auscultation for carotid bruits is also important, especially in patients with a history of stroke, transient ischemic attacks (TIAs), or head and neck irradiation. The presence of a carotid bruit significantly increases the likelihood of an important lesion (i.e., 70%-99% stenosis) in both symptomatic or asymptomatic patients, but the absence of a bruit does not rule out carotid stenosis.²⁶ Examination of the pulmonary system should include both auscultation (i.e., wheezing, decreased breath sounds, abnormal

breath sounds) and inspection (i.e., cyanosis, clubbing, accessory muscle use, respiratory effort). A basic screening neurologic examination should document deficits in mental status, speech, gait, cranial nerve function, motor nerve function, and sensory nerve function. For selected patients (e.g., those with deficits, or scheduled to undergo neurosurgery), a more extensive or focused neurologic examination should document preexisting abnormalities that may aid in diagnosis or interfere with positioning. In addition, the definition of a baseline preoperative neurologic state helps determine whether any postoperative deficits represent new deficits versus preexisting abnormalities.

Frailty, Geriatric Conditions, and the Older Surgical Patient

As patients age, the accumulation of comorbid conditions puts them at increased risk for adverse outcomes after surgery.⁵⁴ In addition, geriatric-specific risk factors such as functional and cognitive impairment are associated with poor postoperative outcomes.⁵⁴ These clinical conditions, which do not fit into discrete disease categories, are often overlooked in routine preoperative assessments. In order to (1) accurately inform patients of their surgical risk and (2) identify targets for preoperative optimization, assessment of geriatric vulnerabilities is essential before surgery. The American College of Surgeons (ACS) and the American Geriatrics Society (AGS) have established best practice guidelines to guide the preoperative assessment of older surgical patients.⁵⁵

GERIATRIC-FOCUSED ASSESSMENT IN THE OLDER SURGICAL PATIENT

Function and Mobility

Preoperative functional decline is associated with morbidity, mortality, and loss of function after surgery.⁵⁴ Assessment of function prior to surgery is consequently essential for risk stratification and postdischarge planning in older surgical patients. Activities-of-daily-living (ADLs) assess the ability to perform basic tasks of selfcare, such as dressing, bathing, toileting, movement, continence, and eating. Instrumental ADLs determine an individual's ability to live independently by the ability to complete shopping, laundry, transportation, finances, medications, food preparation, and housekeeping. To determine additional functional vulnerabilities, determination of vision deficits, hearing deficits, and swallowing difficulties should be routine. Mobility impairment can be efficiently screened by enquiring about a history of falls, determining fall risk, and performing a Timed-Up-And-Go test.⁵⁶ The Timed-Up-And-Go test involves timing patients while they perform the following tasks in sequence:

1. Stand up from a chair (without using arm rests if possible)
2. Walk 10 feet
3. Turn around and walk back to chair
4. Sit down in chair

In a prospective cohort of older surgical patients, Timed-Up-And-Go test times were associated with risks of postoperative complications and 1-year mortality in a stepwise fashion.⁵⁷

Cognition

Preoperative cognitive impairment is strongly linked to delirium, complications, functional decline, and death after surgery.⁵⁴ The Mini-Cog test (available at <https://minicog.com>), which consists of a three-item recall test and clock draw test, is an efficient tool to screen for preoperative cognitive impairment. Additional information about potential cognitive deficits should be elicited from someone who knows the patient well. Importantly, mild cognitive impairment that is not clinically apparent may have a critical impact on decision-making capacity. Patients should be able to describe, in their own words, the essential elements of the consent discussion—including the surgical condition, indications for surgery, risks, benefits, and alternatives to surgery. It is important to note the four legal criteria for medical decision-making capacity, namely that the patient can (1) clearly indicate his/her treatment choice; (2) understand the relevant information communicated by the physician; (3) acknowledge his/her medical condition, treatment options, and expected outcomes; and (4) engage in a rational discussion about treatment options.⁵⁵

Nutrition

In general, most surgeons and anesthesiologists are keenly aware of the role nutritional status plays in recovery after surgery for all surgical patients. The most common adverse events related to poor nutritional status are infectious complications (i.e., surgical site infections, pneumonia, urinary tract infections), wound complications (i.e., dehiscence, anastomotic leaks), and increased length of stay.⁵⁴ The ACS National Surgical Quality Improvement Program (NSQIP) and AGS Best Practice Guidelines recommend the following steps to screen for poor nutritional status (older adults with limited material resources are at particular risk for food insecurity).⁵⁵

1. Document height, weight, and BMI

A BMI value less than 18.5 kg/m² places an individual at elevated risk and should prompt referral for nutritional assessment.

2. Measure baseline serum albumin and prealbumin concentrations

Serum albumin concentration less than 30 g/L (in the absence of hepatic or renal dysfunction) should prompt referral for nutritional assessment.

3. Inquire about unintentional weight loss in the last year

Unintentional weight loss exceeding 10% to 15% of baseline weight within the prior 6 months is associated with severe nutritional risk and should prompt referral for nutritional assessment.

Frailty

Frailty, which is defined as a state of increased vulnerability to physiologic stressors, is associated with adverse health outcomes after medical and surgical interventions and

TABLE 31.4 Preoperative Assessment and Optimization in the Older Surgical Patient

| Domain | Assessment | Preoperative Optimization |
|-----------|---|---|
| Cognition | <ul style="list-style-type: none"> ■ Mini-Cog Test ■ Visual and hearing ■ Impairment ■ Alcohol abuse ■ Medication review | <ul style="list-style-type: none"> ■ Formal assessment by geriatrician for patient identified to have cognitive impairment on screening ■ Remind patient to bring all assistive devices (glasses, hearing aids) to hospital ■ Limit use of sedating or psychotropic medications preoperatively |
| Function | <ul style="list-style-type: none"> ■ Evaluate ability to perform activities of daily living and instrumental activities of daily living ■ Obtain history of falls ■ Timed up and go test | <ul style="list-style-type: none"> ■ Refer patients with functional deficiencies or history of falls for formal evaluation by a physical therapist before surgery ■ Exercise education ■ Obtain assistive devices ■ Plan for in-hospital and postdischarge rehabilitation therapy |
| Nutrition | <ul style="list-style-type: none"> ■ Document body mass index ■ Measure albumin and prealbumin ■ Query unintentional weight loss | <ul style="list-style-type: none"> ■ Patients at severe malnutritional deficit should be referred to dietician for formal assessment ■ Preoperative nutritional supplementation and nutrition education |

From Oresanya LB, Lyons WL, Finlayson E. Preoperative assessment of the older patient: a narrative review. *JAMA*. 2014;311:2110–2120.

limited life expectancy.⁵⁸ Numerous validated instruments measuring frailty are in current use in research and clinical practice. There are two primary models of frailty—the frailty phenotype and the deficit accumulation model. The frailty phenotype described by Fried and colleagues is based on the identification of traits associated with the occurrence of disease, hospitalization, falls, disability, and death in a large prospective cohort study.⁵⁹ This study defined the determinants of frailty as weight loss, exhaustion, physical activity, walk time, and grip strength. The deficit accumulation model of aging (based on data from the Canadian Study of Health and Aging) identified 92 signs, symptoms, functional impairments, and laboratory abnormalities that are proportionally weighted into a frailty index for predicting mortality.⁶⁰

While numerous studies have demonstrated the association of patient frailty with adverse surgical outcomes,^{54,61–64} the incorporation of a patient's level of frailty into routine clinical practice has not been broadly implemented. Many frailty instruments require special training, input of laboratory values or clinical data, and a fair amount of time to complete; hence, they are impractical in a busy clinical setting. A recent survey of surgical oncologists reported that although most surgeons expressed interest in preoperative optimization for older patients, only 6% currently perform geriatric assessments in their older patients.⁶⁵ Factors contributing to the low level of adoption include perceptions regarding the amount of time required to assess for vulnerabilities, and lack of specific programs designed to address them within typical clinical practices. To address this gap, several investigators have validated efficient strategies to measure frailty in clinical practice. Robinson and colleagues developed two alternative frailty assessment definitions for surgical patients,^{66,67} which were

- Mini-Cog score of 3 or less, serum albumin concentration of 30 g/L or less, one or more falls in the prior 6 months, and hematocrit under 35%.
- Timed-Up-And-Go test 15 or more seconds, activity-of-daily-living dependence, and Charlson comorbidity index score 3 or greater.⁶⁸

Frailty identified with the Edmonton Frail Scale (EFS) has been shown to be associated with adverse outcomes after surgery.⁶¹ The EFS can be administered by an individual with no formal medical education, and has been validated in comparison to the geriatric specialist's comprehensive geriatric assessment.⁶⁹

Additional Considerations

Anxiety, depression, substance abuse, and social isolation are common underdiagnosed conditions in older adults. Careful screening can identify these potential barriers to recovery, safe discharge after surgery, and maintenance of independence. Up to 11% of the population 71 years of age or more in the United States suffer from depression.⁷⁰ The Patient Health Questionnaire-2 is an efficient instrument to screen for depression that includes only two questions: “*In the past 12 months, have you ever had a time when you felt sad, blue, depressed, or down for most of the time for at least two weeks?*” and “*In the past 12 months, have you ever had a time, lasting at least two weeks, when you didn't care about the things that you usually care about or when you didn't enjoy the things that you usually enjoy?*” Among individuals aged 65 years or more, 13% of males and 8% of females consume at least two alcoholic drinks per day.⁷¹ Alcohol and substance abuse are associated with increased rates of postoperative mortality and complications including pneumonia, sepsis, wound infection and disruption, and prolonged length of stay.⁷² Consequently, the ACS NSQIP and AGS recommend screening for alcohol and substance abuse among older individuals with the modified CAGE (acronym of four clinical interview questions: cutting down, annoyance by criticism, guilty feeling, and eye-openers) questionnaire (see section on “Patients With a History of Substance Abuse”).

PREOPERATIVE OPTIMIZATION FOR FRAIL GERIATRIC PATIENTS (TABLE 31.4)

One goal of the preoperative assessment of elderly surgical patients is to identify potentially modifiable risk factors—such as malnutrition, poor physical function, anxiety, and social isolation—in order to optimize surgical outcomes. Several recent geriatric *prehabilitation* models have emerged

to help meet this need, with some demonstrating promising results. One of the first of such programs was the Proactive Care of Older People undergoing surgery (POPS) before-and-after study in United Kingdom.⁷³ The overarching aim of this project was to decrease complications and hospital length of stay among at-risk older adults undergoing elective surgery. The authors performed a structured geriatric team intervention that identified at-risk patients, and then facilitated coordinated multidisciplinary optimization of geriatric vulnerabilities. The interventions included preoperative home visits by occupational and physical therapists, social worker inputs, nutrition education, and relaxation techniques. In addition to preoperative optimization, interdisciplinary teams participated in daily inpatient rounds, weekly multidisciplinary meetings, and bi-weekly ward rounds led by a consultant or clinical nurse specialist. Compared to historical controls, surgical patients who received the POPS intervention experienced fewer postoperative complications (e.g., pneumonia, delirium), improved pain control, lower rates of delayed mobilization, lower rates of inappropriate urinary catheter use, and shorter hospital length of stay.

Similar findings were observed in the more recently reported Perioperative Optimization of Senior Health study, which was another before-and-after study.⁷⁴ This preoperative interdisciplinary clinic evaluated at-risk patients (either aged age ≥ 80 years, or aged ≥ 65 years with concurrent geriatric vulnerability) and designed targeted optimization. Compared to historical controls, the combination of geriatric prehabilitation and inpatient geriatric comanagement were associated with reduced hospital length of stay, reduced readmission rates, and increased rates of discharge to home with self-care. Another example of a promising prehabilitation program is the Michigan Surgical Home and Optimization Program,⁷⁵ which is a structured home-based preoperative training program with physical, nutritional, and psychological interventions. The intervention included (1) a home-based walking program with daily reminders and feedback; (2) incentive spirometry instructions starting 1 week prior to surgery; (3) education on nutrition, stress management, and care planning; and (4) resources for smoking cessation, when appropriate. Compared to matched historical controls, patients enrolled in the program experienced reductions in both hospital length of stay and healthcare costs. While promising, these studies do have methodological weakness as before-and-after studies, as opposed to methodologically more robust parallel arm randomized trials, cluster randomized trials, or stepped-wedge trials (see Chapter 90). Nonetheless, the consistency in findings across the studies is supportive of the notion that attention to preoperative and perioperative assessment in the older population can result in improved postoperative outcomes that benefit patients, hospitals, and healthcare systems.

DECISION MAKING FOR SURGERY IN OLDER ADULTS

The critical initial step in surgical decision making for the older patient is an assessment of the patient's decision-making capacity. Among older adults, only about 3% lack medical decision-making capacity. However, among older adults with mild cognitive impairment, this proportion is

as high as 20%.⁷⁶ A Mini-Cog exam (see section on "Cognition") is an efficient way to screen for cognitive impairment in the surgical setting. If the patient does not have capacity, treatment goals and choices should be discussed with the patient's surrogate, with patient involvement as appropriate. Even cognitively intact patients may have difficulty grasping the risks and tradeoffs involved in decisions for surgery. The "teach-back" method (i.e., asking patients to communicate back information about their diagnosis, treatment plan, and potential risks of treatment) may be useful to confirm that the risks, expected benefits, and alternatives to surgery are fully understood. Various resources are available to aid in using the teach-back method (e.g., <http://www.teachbacktraining.org>).

Collaborative decision making is essential in older adults with limited life expectancy. Rather than a traditional conversation that focuses on the process of correcting the underlying surgical condition, the conversation should be driven by a focus on the older adult's overarching health goals. Using open-ended questions, physicians elicit the patient's global healthcare goals that may prioritize (1) life prolongation; (2) function and independence; (3) maintenance of cognition; or (4) comfort. Further discussion should be framed by the patient's most important health goal. A frank, realistic, and granular conversation about the ability of surgery to satisfy healthcare goals and priorities is essential. Invasive treatments should only be considered if there is a realistic possibility that overarching health goals can be achieved. These goals, however, are often dynamic and must be revisited as conditions change. Often, primary physicians who have longitudinal relationships with patients can provide important insight into their patient's health goals and should be included in this important deliberation. To assist in high-risk surgical decision making, preoperative palliative care consultation should be considered in individuals with poor prognoses who are electing to undergo surgery, particularly if they have a life expectancy of less than 6 months.

Preoperative Evaluation of Patients With Coexisting Disease

For some conditions commonly seen in the preanesthetic assessment clinic, preoperative optimization, testing, and intervention may be important (see also Chapter 32). Identification of these comorbid conditions might be an opportunity for the anesthesiologist to intervene to decrease perioperative risk. These conditions are best managed before the day of surgery, thus allowing ample time for thoughtful evaluation, consultation, and planning.

CARDIOVASCULAR DISEASE

Cardiovascular complications are serious perioperative adverse events that account for about 45% of all deaths within 30 days after major noncardiac surgery.⁷⁷ These events occur relatively frequently. For example, the multicenter Vascular Events in Noncardiac Surgery Patients Cohort Evaluation prospective cohort study found a 4% risk of myocardial infarction, 17% risk of prognostically important

myocardial injury, and 0.7% risk of acute heart failure during the 30 days following major noncardiac surgery.⁷⁸ Evidence-based preoperative cardiovascular assessment guidelines have now been published in several countries, including the 2014 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines,⁷ 2014 European Society of Cardiology (ESC) and ESA guidelines,⁹ 2017 Canadian Cardiovascular Society (CCS) guidelines,⁸ 2017 Brazilian Society of Cardiology guidelines,⁷⁹ and 2014 Japanese Circulation Society guidelines.⁸⁰ While the guidelines provide generally similar guidance, there are some important differences that will be highlighted in the sections below.

Hypertension

Based on revised 2017 ACC/AHA guidelines, hypertension is defined as a blood pressure greater than 130/80 based on appropriately measured arterial blood pressure.⁸¹ About 45% of adults in the United States have hypertension,⁸² with a similar prevalence in other countries. While most individuals with hypertension have primary (or essential) hypertension, there are several important causes of secondary hypertension, including primary renal disease, OSA, pheochromocytoma, renovascular hypertension, Cushing syndrome, hyperthyroidism, and coarctation of the aorta. Hypertension leads to significantly increased risks of left ventricular hypertrophy (LVH), heart failure, ischemic heart disease, chronic kidney disease (CKD), ischemic stroke, intracerebral hemorrhage, and PAD. The duration and severity of hypertension are highly correlated with subsequent end-organ damage, morbidity, and mortality. These risks appear to increase once blood pressure exceeds 117/75, with each subsequent 20 mm Hg increase in systolic blood pressure and 10 mm Hg increase in diastolic blood pressure being associated with a two-fold increase in the risk of stroke and cardiovascular death.⁸³ In the perioperative setting, hypertension is associated with increased risks of postoperative death and myocardial infarction, but the magnitude of this association is relatively weak (odds ratio 1.35; 95% confidence limits, 1.17–1.56).⁸⁴

In patients with hypertension, the goals of preoperative evaluation are to identify any secondary causes of hypertension, presence of other cardiovascular risk factors (e.g., smoking, diabetes mellitus), and evidence of end-organ damage. For example, paroxysmal hypertension or hypertension in young individuals should prompt a search for hyperthyroidism, illicit drug use (e.g., cocaine, anabolic steroids), and coarctation of the aorta. Similarly, a history of paroxysmal hypertension associated with episodic tachycardia and palpitations should raise suspicions about an underlying pheochromocytoma (see next section). The physical examination should focus on vital signs (including blood pressure measured in both arms), thyroid gland, peripheral pulses, and cardiovascular system (including bruits and signs of intravascular volume overload). Additional specialized testing is directed by the initial clinical evaluation. For example, patients with long-standing, severe, or poorly controlled hypertension should undergo an ECG and blood sampling to measure creatinine concentration. Individuals on diuretic antihypertensives (e.g., chlorthalidone, hydrochlorothiazide) may require evaluation of electrolytes. Patients with suspected hyperthyroidism will require thyroid function tests.

While preoperative hypertension is associated with an increased risk of cardiovascular complication,⁸⁴ this association is generally not evident for systolic blood pressure values less than 180 mm Hg or diastolic blood pressure values less than 110 mm Hg. Additionally, there is no compelling data that delaying surgery to optimize blood pressure control will result in improved outcomes. Accordingly, some international practice guidelines support proceeding with surgery if the systolic blood pressure is less than 180 mm Hg and diastolic blood pressure is less than 110 mm Hg.^{9,49} Usual antihypertensive medication treatment should be continued in these patients during the perioperative period. For patients with severe hypertension (i.e., diastolic blood pressure > 110 mm Hg or systolic blood pressure > 180 mm Hg), anesthesiologists should weigh the potential benefits of delaying surgery to optimize antihypertensive treatment against the risks of delaying the procedure. In general, all long-term antihypertensive treatment should be continued up to the day of surgery, with the possible exception of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Administration of these medications within 24 hours before surgery is consistently associated with increased risks of intraoperative hypotension,⁸⁵ and possibly associated with elevated risks of postoperative myocardial injury.⁸⁶ Accordingly, it is reasonable to withhold these medications for 24 hours before surgery, provided that they are restarted postoperatively once patients are hemodynamically stable. Importantly, failure to resume ACEI and ARB therapy postoperatively is itself associated with adverse outcomes.^{87,88}

Even if surgery is not necessarily delayed to facilitate improved blood pressure control, the preanesthesia evaluation should also be viewed as an excellent opportunity to alter long-term consequences of diseases. Thus, appropriate postsurgery referrals should be made to facilitate improved long-term management of hypertension.

Ischemic Heart Disease

Ischemic heart disease (IHD) afflicts about 16.5 million adults in the United States, and 111 million people worldwide.²⁷ It also accounts for about 13% of all deaths, both in the United States and worldwide (<http://www.who.int/mediacentre/factsheets/fs317/en/>).²⁷ While death rates attributable to IHD are declining in many high-income countries,⁸⁹ other regions continue to experience high or increasing rates of IHD mortality. IHD mediates adverse effects because of its immediate impact (e.g., myocardial infarction, sudden cardiac death) and related diseases (e.g., heart failure, atrial fibrillation). Therapy for IHD includes antiplatelet therapy (e.g., aspirin, adenosine diphosphate receptor [P2Y₁₂] inhibitor), renin angiotensin system inhibitors (e.g., ACEI, ARB), β -adrenergic blockers, other antianginal therapies (e.g., calcium channel blocker, nitrates), lipid reducing agents (e.g., statins), and coronary revascularization with either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Based on recent randomized controlled trials, several newer types of medical therapy for IHD may be increasingly used, including novel antiinflammatory therapy (e.g., canakinumab),⁹⁰ low-dose direct oral anticoagulant (DOAC) therapy,⁹¹ and antibody-based lipid-lowering agents.⁹² Coronary revascularization—specifically with CABG—improves survival

compared to medical therapy (pooled relative risk 0.80, 95% limits 0.70-0.91) in several high-risk IHD states,⁹³ namely left main coronary artery stenosis, triple-vessel coronary artery disease, and two-vessel coronary artery disease with proximal left anterior descending artery stenosis.⁹⁴ When PCI is used instead for these high-risk states, PCI with a newer generation drug eluting stent (DES) may also confer a survival benefit, albeit with marginal statistical significance.⁹³ In patients who meet indications for revascularization, CABG improves survival more than PCI in multivessel disease that is associated with either diabetes mellitus or higher coronary artery lesion complexity.⁹⁵ Notably, aside from these high-risk states (e.g., triple vessel coronary artery disease), PCI has not been shown to convincingly improve survival in stable IHD.⁹⁶

In the perioperative setting, IHD is a risk factor for myocardial infarction and a prognostically important myocardial injury after surgery.^{97,98} It is also associated with elevated risks of 30-day postoperative mortality,⁹⁹ especially if a patient had experienced a myocardial infarction, acute coronary syndrome, or severe angina (i.e., occurring at effort levels less than walking one to two blocks or climbing one flight of stairs) within the 6 months preceding surgery.^{77,78} Surgical patients with IHD may also have important comorbidities with important perioperative implications, such as heart failure and atrial fibrillation (see sections of “Heart Failure” and “Atrial Fibrillation”). The goals of preoperative evaluation are to (1) ascertain whether the patient has previously undiagnosed significant IHD; (2) characterize any known IHD with respect to severity, functional limitations, therapy, and prior investigations; (3) determine whether additional preoperative specialized testing or consultations are warranted; and (4) identify opportunities for reducing perioperative risk related to IHD. In the case of patients without known IHD, evaluation of traditional risk factors for IHD (i.e., smoking, hypertension, increased age, male sex, hyperlipidemia, family history) is important when significance of suspicious symptoms (e.g., chest discomfort, dyspnea) or abnormal ECG. In patients with known IHD, the anesthesiologist should characterize any history of chest discomfort (i.e., pain, pressure, tightness) with respect to its duration, precipitating factors, associated symptoms, and relieving factors. Exertional dyspnea may represent an angina equivalent but is also a nonspecific finding that might be related to physical deconditioning, pulmonary disease, or heart failure. It is useful to classify any angina based on the CCS grading scale:

- CCS class I: Ordinary physical activity (e.g., walking, climbing stairs) does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation
- CCS class II: Slight limitation of ordinary activity. No angina is precipitated by walking more than two blocks on level ground or climbing more than one flight of stairs at a normal pace and in normal conditions. Angina is only precipitated by walking or climbing stairs rapidly, walking uphill, and walking or stair climbing under challenging conditions (e.g., after meals, in cold, in wind, under emotional stress, during the few hours after awakening).
- CCS class III: Marked limitation of ordinary physical activity. Angina precipitated by walking one or two

blocks on level ground and climbing one flight of stairs in normal conditions and at normal pace.

- CCS class IV: Inability to carry on any physical activity without discomfort. Angina may be present at rest.

Patients with risk factors for IHD or suspicious symptoms may require an ECG, especially before intermediate-risk or high-risk surgical procedures.⁹ Routine preoperative ECGs are not indicated (Box 31.2), especially in asymptomatic patients without known cardiovascular disease or risk factors.⁷ While specific preoperative abnormalities are associated with increased perioperative cardiac risk (e.g., bundle branch blocks [BBBs]), these abnormalities do not enable clinicians to identify patients with increased perioperative cardiac risk more accurately when considered in combination with known clinical risk factors.¹⁰⁰ Establishing a baseline for postoperative comparison is often the most important reason to obtain a preoperative ECG; however, this decision should be based on the patient’s likely risk of postoperative cardiovascular complications. Thus, a baseline ECG is unlikely to be helpful in an individual at very low risk for postoperative cardiac events. If a previous ECG is available from the previous 3 months and there has been no intervening change in clinical status, a repeat ECG is likely not needed.⁷ Other typical preoperative laboratory tests that may be considered for patients with known or suspected IHD include creatinine and hemoglobin concentrations. Both chronic renal insufficiency and anemia are risk factors for perioperative cardiac complications.^{97,101,102} In addition, anemia can modify the effects of β -adrenergic blockade in surgical patients, with evidence of increased harm when used in patients with perioperative anemia or significant bleeding.^{103,104}

BOX 31.2 Recommendations for Preoperative Resting 12-Lead Electrocardiogram

Class IIa Recommendation: It Is Reasonable to Perform the Procedure

Preoperative resting 12-lead ECG is reasonable for patients with known IHD, significant arrhythmia, PAD, CVD, or other significant structural heart disease (except if undergoing low-risk surgical procedures).

Class IIb Recommendation: The Procedure May Be Considered

Preoperative resting 12-lead ECG may be considered for asymptomatic patients without known coronary heart disease, except for those undergoing low-risk surgical procedures.

Class III Recommendation: The Procedure Should Not Be Performed Because It Is Not Helpful

Routine preoperative resting 12-lead ECG is not useful for asymptomatic patients undergoing low-risk surgical procedures.

CVD, Cerebrovascular disease; *ECG*, electrocardiogram; *IHD*, ischemic heart disease; *PAD*, peripheral artery disease.

From Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e278–e333.

Preoperative cardiac risk assessment algorithms have been proposed by several practice guidelines, including the ACC/AHA guidelines (Fig. 31.5)⁷ and the CCS guidelines (Fig. 31.6).⁸ These algorithms have somewhat differing target populations. The ACC/AHA algorithm encompasses patients with known IHD or associated risk factors who are having noncardiac surgery. The CCS guidelines focus on adults (≥ 18 years old) having inpatient surgery who are either 45 years or older, or who have significant cardiovascular disease (i.e., IHD, cerebrovascular disease [CVD], PAD, heart failure, severe pulmonary hypertension, severe obstructive cardiac valvular disease). While the algorithms have many fundamental similarities, they also have several key differences, which will be discussed below. Importantly, the algorithms should always be viewed as flexible guidance frameworks that should be tailored, as needed, to individual patients. The initial step in these risk assessment algorithms is consideration of the urgency of the planned surgery. The 2014 ACC/AHA guidelines define an *emergency* procedure

as one where life or limb would be threatened if surgery did not proceed within 6 hours or less; an *urgent* procedure as one where life or limb would be threatened if surgery did not proceed within 6 to 24 hours; and a *time-sensitive* procedure as one where delays exceeding 1 to 6 weeks would adversely affect outcomes (e.g., most oncology surgery).⁷ Based on this classification scheme, patients should proceed directly to any required emergency surgery without further preoperative cardiac assessment.^{7,8} For these individuals, the focus should be on surveillance (e.g., serial cardiac enzymes, hemodynamic monitoring, serial ECGs) and early treatment of any postoperative cardiovascular complications.

In the second step, active cardiac conditions—such as acute coronary syndromes, decompensated heart failure, severe valvular disease (e.g., critical aortic stenosis), suspected significant pulmonary hypertension, or significant arrhythmias (e.g., atrial fibrillation with rapid ventricular rate, sustained ventricular tachycardia)—should be ruled

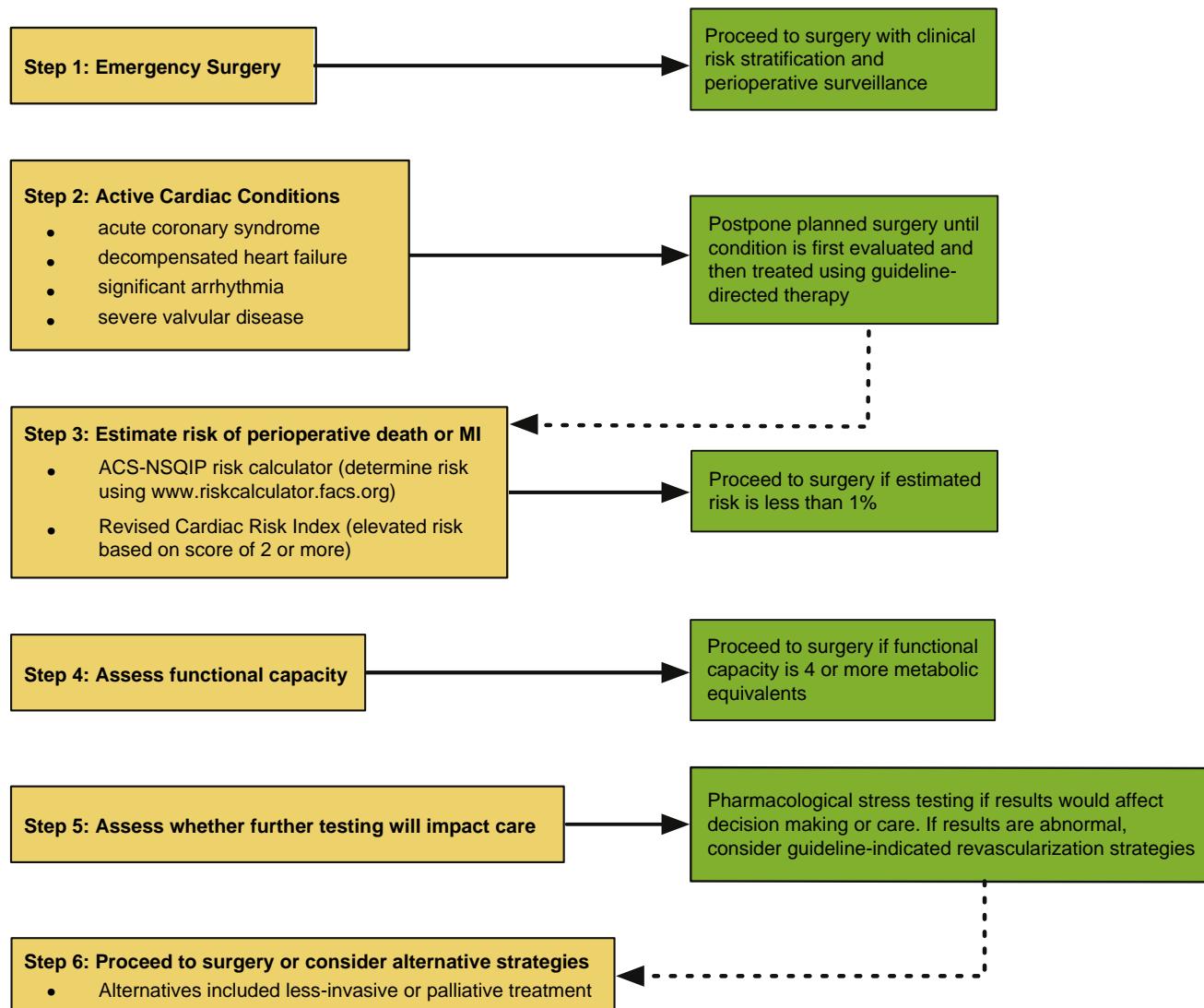


Fig. 31.5 Simplified cardiac evaluation algorithm for noncardiac surgery proposed by the 2014 American Heart Association and American College of Cardiology guidelines. ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; MI, myocardial infarction. (From Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e278–e333.)

out in patients not requiring emergency surgery.⁷ If any of these conditions are present, they must be initially treated, after which the original planned surgery can be reconsidered based on its risk-benefit balance. When assessing whether a patient has an active cardiac condition, the anesthesiologist should inquire about any recent myocardial infarction. In a study of about 560,000 patients who underwent major noncardiac surgery in the United States,¹⁰⁵ the risk of 30-day postoperative myocardial infarction or death was significantly elevated when surgery was performed within 60 days after a prior myocardial infarction. Thus, the 2014 ACC/AHA guidelines recommend deferring nonurgent surgery until 60 days after a recent myocardial infarction.⁷

In the third step, perioperative cardiac risk should be estimated based on readily available clinical information that encompasses both patient-level (e.g., comorbidities) and surgery-level (e.g., procedure type) characteristics. The 2014 ACC/AHA guidelines and 2014 ESC/ESA guidelines recommend using clinical risk indices, namely the Revised Cardiac Risk Index (RCRI) (Table 31.5),⁹⁷ ACS NSQIP surgical risk calculator (<https://riskcalculator.facs.org/RiskCalculator>),³² or NSQIP Myocardial Infarction and Cardiac Arrest risk calculator.³³ If these indices find the estimated risk of postoperative myocardial infarction or death to be less than 1% (consistent with RCRI ≤ 1), the ACC/AHA

guidelines recommend that patients simply proceed directly to surgery.⁷ The 2017 CCS guidelines suggest using the RCRI, as opposed to the NSQIP risk calculators, largely because the NSQIP-risk models were developed using a database without routine postoperative troponin surveillance, implying that the predicted absolute myocardial infarction rate might underestimate the true rate by three-fold,⁹⁸ and have not been externally validated.⁸ In addition, the NSQIP risk calculators have largely not been externally validated. By comparison, the RCRI was derived in a cohort study with standardized cardiac biomarker surveillance,⁹⁷ and also has undergone extensive external validation.¹⁰⁶ Nonetheless, the RCRI has limitations, especially with respect to inadequate consideration of variations in cardiac risk across different surgical procedures.¹⁰⁷ The CCS guidelines recommend that patients proceed directly to surgery if they meet all the following criteria: age over 65 years, RCRI score of 1 or greater, and no history of significant cardiovascular disease (i.e., coronary artery disease, CVD, PAD, heart failure, pulmonary hypertension, or severe obstructive cardiac valvular disease).

In the fourth and subsequent steps, there are substantial differences between the American versus Canadian preoperative risk assessment algorithms. The ACC/AHA algorithm recommends that a patient with a functional capacity

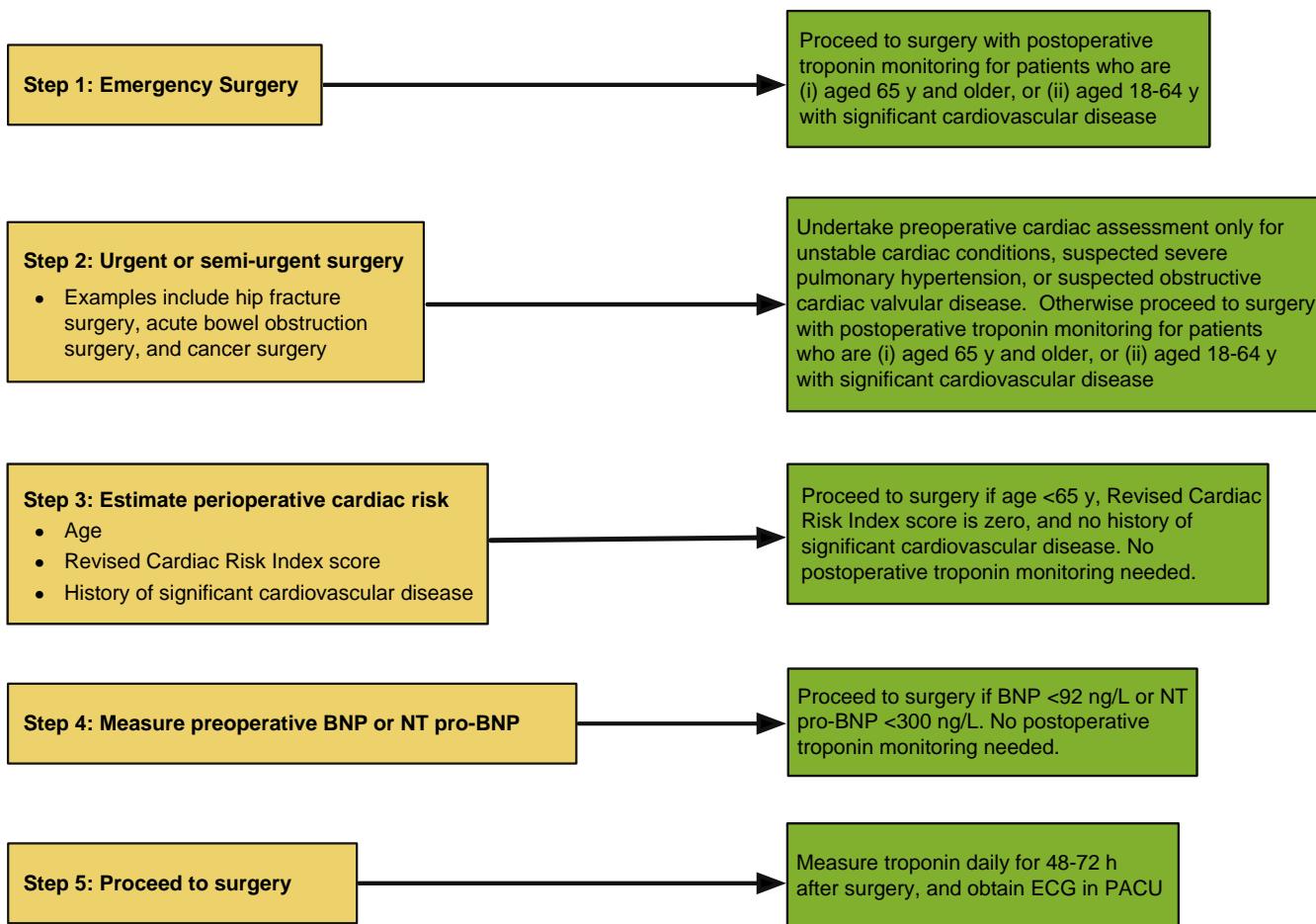


Fig. 31.6 Simplified cardiac evaluation algorithm for noncardiac surgery proposed by the 2017 Canadian Cardiovascular Society guidelines. BNP, Brain natriuretic peptide; ECG, electrocardiogram; NT pro-BNP, N-terminal-pro-BNP; PACU, postanesthesia care unit. (From Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol.* 2017;33:17-32.)

of 4 or more METs should proceed directly to surgery.⁷ This guidance is largely based on older studies of preoperative exercise testing,^{30,31} and more recent studies of preoperative CPET,^{108,109} which found an association between poor functional capacity and elevated perioperative cardiac risk. The major clinical challenge with this recommendation pertains to how best to estimate patients' preoperative functional capacity in clinical practice (see earlier section on "Assessment of Functional Capacity"). Simple subjective assessment of functional capacity based on the usual preoperative history does not accurately estimate true exercise capacity,³⁶ and does not accurately predict postoperative cardiovascular complications.^{36,41} Thus, in clinical practice, anesthesiologists should generally use a structured questionnaire, especially the DASI (see Table 31.2),⁴² with

TABLE 31.5 Components of the Revised Cardiac Risk Index and Expected Cardiac Event Risk

| Components of Revised Cardiac Risk Index* | Points Assigned |
|---|-----------------|
| High-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedure) | 1 |
| Ischemic heart disease (by any diagnostic criteria) | 1 |
| History of congestive heart failure | 1 |
| History of cerebrovascular disease | 1 |
| Diabetes mellitus requiring insulin | 1 |
| Creatinine > 2.0 mg/dL (176 µmol/L) | 1 |
| Revised Cardiac Risk Index Score | |
| Risk of Major Cardiac Events†‡ | |
| 0 | 0.4% |
| 1 | 1.0% |
| 2 | 2.4% |
| ≥3 | 5.4% |

*Data from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.

†Data from Devereaux OJ, Goldman L, Cook DJ, et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ*. 2005;173:627–634.

‡Defined as cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest.

consideration of formal exercise testing if the results would alter management. Notably, DASI scores improve the accuracy of prediction of cardiac complications following noncardiac surgery beyond that achieved with the RCRI alone.³⁶

If a patient is deemed to have either low (i.e., < 4 METs) or uncertain functional capacity, the AHA/ACC guidelines recommend consideration of exercise or pharmacologic cardiac stress testing, if the results could plausibly inform decision making or clinical care. Patients with high-risk abnormal test results can be considered for subsequent coronary angiography, and possibly revascularization (if usual nonoperative indications for coronary revascularization are met). Importantly, the ACC/AHA guidelines emphasize the importance of considering alternative less invasive or nonsurgical treatment for the underlying condition, especially in patients found to be at very high cardiac risk.

As opposed to assessing functional capacity, the CCS guidelines recommend preoperative risk assessment with cardiac biomarkers,⁸ specifically brain natriuretic peptide (BNP) or N-terminal-pro-BNP (NT pro-BNP). These neurohormones are secreted by the cardiac ventricles in response to stretch or ischemia of the atrial and ventricular walls. In the nonoperative setting, elevated natriuretic peptide concentrations are powerful markers of cardiovascular risk in individuals with IHD or associated risk factors, as well as in individuals with heart failure.¹¹⁰ Interestingly, there is only slight-to-fair correlation between plasma levels of these biomarkers and measures of exercise capacity,³⁶ suggesting that natriuretic peptides measure a different patient characteristic. An individual patient data meta-analysis of 18 studies in noncardiac surgery found that preoperative natriuretic peptide concentrations can differentiate patients based on their perioperative cardiac risk (Table 31.6).¹¹¹ In general, BNP concentrations less than 100 ng/L or NT pro-BNP concentrations less than 300 ng/L are indicative of a patient at very low perioperative cardiac risk. Conversely, BNP concentrations above 300 ng/L or NT pro-BNP concentrations above 900 ng/L are indicative of a patient at high cardiac risk. Importantly, natriuretic peptides also improve the accuracy of risk estimation beyond that achieved with traditional clinical risk factors alone.¹¹¹ The CCS guidelines recommend that preoperative BNP or NT pro-BNP testing be used to inform the required level of postoperative surveillance. Specifically, they recommend

TABLE 31.6 Risk of Death or Myocardial Infarction After Noncardiac Surgery Based on Preoperative Brain Natriuretic Peptide or N-Terminal-Pro-Brain Natriuretic Peptide Concentrations

| Preoperative BNP Concentration (ng/L) | Likelihood Ratio* for Death or MI | Preoperative NT pro-BNP Concentration (ng/L) | Likelihood Ratio* for Death or MI |
|---------------------------------------|-----------------------------------|--|-----------------------------------|
| 0–99 | 0.6 | 0–300 | 0.4 |
| 100–250 | 1.4 | 301–900 | 1.5 |
| >250 | 3.9 | 901–3000 | 2.7 |
| | | >3000 | 5.0 |

*Positive test results should have likelihood ratios > 2 to provide clinically meaningful information, whereas negative test results should have likelihood ratios of < 0.5. BNP, Brain natriuretic peptide; MI, myocardial infarction; NT pro-BNP, N-terminal-pro-BNP.

From Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery. B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. *J Am Coll Cardiol*. 2014;63:170–180.

routine troponin surveillance for 48 to 72 hours after surgery in patients with elevated preoperative BNP (≥ 92 ng/L) or NT pro-BNP (≥ 300 ng/L) concentrations. No other preoperative testing or intervention is recommended based on the results of preoperative cardiac biomarker testing.

Although current evidence pertaining to risk assessment with preoperative natriuretic peptides is promising, there are also some important limitations. First, the event rate for death or myocardial infarction in this individual patient data meta-analysis was about 11%, which is considerably higher than would be expected in usual clinical practice. This high event rate is explained, in part, by the intermediate-to-high risk characteristics of the study sample, and by two large included studies that defined cardiovascular complications based on elevated troponin concentrations alone (as opposed to less frequent myocardial infarction events).^{112,113} Therefore, further research remains needed to determine biomarker threshold levels and prognostic accuracy in generalizable study samples. Second, while elevated natriuretic peptide concentrations are indicative of elevated perioperative cardiac risk, they do not indicate underlying pathophysiological mechanism. Aside from ischemia and heart failure, other prognostically important conditions can cause elevated natriuretic peptide concentrations, including right ventricular dysfunction, cardiac valvular disease, and atrial fibrillation. Thus, further specialized testing (e.g., echocardiography) may be helpful in some patients with high preoperative BNP or NT pro-BNP concentrations, if the results might inform clinical care or decision making. Third, nonoperative data suggest natriuretic peptides have limitations as prognostic biomarkers in certain disease states, including obesity and chronic renal kidney.

The anesthesiologist has several other avenues for further investigating or optimizing known or suspected IHD before surgery—including consultations, biomarkers, stress testing, coronary angiography, coronary revascularization, and medical therapy. When considering the need for additional consultations before surgery, an initial phone call to the primary care physician or cardiologist often yields important information that obviates the need for further consultation. Any specialist consultation (e.g., cardiologist) initiated by the anesthesiologist should seek specific advice regarding the diagnosis, treatment, or further optimization of the patient's condition. It is preferable to ask specific questions, such as *“Does this patient have IHD?”* or *“Is this patient optimized for planned radical nephrectomy?”*, to avoid unhelpful consultation reports that simply state that a patient is *“cleared for surgery.”*

Aside from BNP and NT pro-BNP, several other preoperative biomarkers have shown promise, with the most compelling data pertaining to high-sensitivity troponin assays. In the nonoperative setting, these high-sensitivity assays have demonstrated subtle resting elevations in cardiac troponin concentrations in an important segment of the population without any acute coronary syndrome. These individuals have significantly elevated risks of death, as well as progression to IHD or heart failure.^{114,115} Perhaps unsurprisingly, many otherwise stable surgical patients may have elevated troponin concentrations even before surgery. For example, in a cohort study of 325 patients undergoing major inpatient noncardiac surgery, about 20% had a preoperative

high-sensitivity troponin T concentration exceeding the 99th percentile for the assay.¹¹⁶ Thus, especially in patients for whom postoperative troponin surveillance is planned, a preoperative troponin measurement is integral to determining whether any elevated postoperative concentration reflects acute injury versus chronic long-term elevation. Two large cohort studies have also shown that these preoperative troponin elevations may aid in risk stratification for noncardiac surgery.¹¹⁷⁻¹¹⁹ Specifically, a preoperative high-sensitivity troponin T concentration above 14 ng/L is associated with increased risks of death and cardiovascular complications after major noncardiac surgery. Furthermore, addition of preoperative high-sensitivity troponin T appears to improve the accuracy of risk estimation beyond that achieved with traditional clinical risk factors and natriuretic peptides.^{117,118} Further research remains needed to confirm these initial results, establish ideal screening thresholds, and replicate these analyses using other high-sensitivity troponin assays. Importantly, prognostically important conditions other than myocardial ischemia can cause elevated troponin concentrations, including right ventricular dysfunction, cardiac valvular disease, and atrial fibrillation.

When supplementing preoperative evaluation, cardiac stress testing can help diagnose IHD, assess its severity, and estimate perioperative cardiac risk. The tests therefore address both *diagnosis* and *prognosis*. Several stress tests are available that differ based on the stress modality (i.e., exercise, pharmacologic) and ischemia monitoring method (i.e., ECG, perfusion imaging, echocardiography). An exercise stress test is a preferred option for a patient who is capable of exercising and likely to achieve an adequate heart rate response during exercise. Exercise stress testing also allows for an objective measurement of functional capacity. An adequate test result is obtained when patients can exercise to 85% of their target heart rate (i.e., 220 minus age). Pharmacologic stress modalities (e.g., dobutamine, dipyridamole, adenosine, regadenoson) are indicated for an individual who cannot exercise or is unlikely to achieve an adequate heart rate response because of pacemakers, significant bradycardia, or high-dose negative chronotropic drugs (e.g., β -adrenergic blockers). The choice of pharmacologic stress modality is generally immaterial, but there are some exceptions. For example, since dobutamine uncovers ischemia by increasing contractility, heart rate, and blood pressure, it may not be the best choice in patients with pacemakers, significant bradycardia, aortic aneurysms, cerebral aneurysms, or poorly controlled hypertension. While adenosine and dipyridamole rely on their vasodilatory properties and do not depend on a heart rate response, they may exacerbate bronchospasm in patients taking theophylline. In addition, these drugs may cause dangerous reductions in preload in the presence of severe stenotic valvular heart disease.

An exercise ECG stress test is a reasonable option for a patient with a relatively normal baseline ECG who is capable of exercising with an adequate heart rate response. An imaging monitoring method (i.e., echocardiography, myocardial perfusion imaging) can be used instead if a patient has significant ECG abnormalities (e.g., left bundle branch block [LBBB], LVH with strain pattern) that may interfere with electrocardiographic detection of ischemia. Nonetheless, exercise myocardial perfusion imaging may still be

problematic in patients with LBBB, because of false-positive results related to septal perfusion defects.⁷ Stress echocardiography assesses for wall motion abnormalities both at rest and under stress conditions (i.e., exercise, dobutamine). Resting abnormalities indicate scar tissue from a prior infarction, while new abnormalities under stress conditions (i.e., inducible wall motion abnormalities) indicate limited blood due to stenotic coronary lesions. Nuclear myocardial perfusion imaging detects ischemia by comparing radioisotope uptake by viable myocardium under resting and stress conditions. Perfusion defects at rest are indicative of a prior infarction. Since normal coronary arteries vasodilate with exercise or specific pharmacologic stressors (i.e., adenosine, dipyridamole), normal myocardium maintains normal radioisotope uptake in stress conditions. By comparison, stenotic vessels are maximally vasodilated at rest, and unable to further vasodilate under stress conditions. Thus, myocardium with flow-limiting lesions has normal radioisotope uptake at rest, but decreased uptake under stress conditions (i.e., reversible perfusion defects). In general, the choice of test should be informed by patient factors (e.g., ability to exercise) and local expertise in cardiac stress testing.

Cardiac stress tests can also help predict whether patients are likely to experience perioperative cardiac complications. Since these events occur relatively infrequently, the prognostic performance of these tests should not be evaluated based on positive or negative predictive values. It is preferable to use positive likelihood ratio and negative likelihood ratio values, which can be readily calculated using sensitivity and specificity values.

$$\text{Positive likelihood ratio} = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

$$\text{Negative likelihood ratio} = \frac{1 - \text{sensitivity}}{\text{specificity}}$$

There are relatively few data on the prognostic performance of preoperative exercise ECG stress testing. In a meta-analysis of studies in vascular surgery, exercise ECG stress testing had a positive likelihood ratio of 2.4 and negative likelihood ratio of 0.4 for predicting postoperative cardiac death or myocardial infarction.¹²⁰ Conversely, ECG stress testing had diminished predictive performance (positive likelihood ratio 1.8 and negative likelihood ratio 0.8) in a cohort study of 200 patients undergoing mixed noncardiac surgery.³⁰ Considerably more research has been published pertaining to the prognostic accuracy of preoperative stress testing based on myocardial perfusion imaging or echocardiography. In a meta-analysis in noncardiac surgery, stress echocardiography has a positive likelihood ratio of 4.1 and a negative likelihood ratio of 0.2 for predicting postoperative death or myocardial infarction. In the case of myocardial perfusion imaging, the positive likelihood ratio was 1.8 and negative likelihood ratio was 0.4.¹²¹ The prognostic value of myocardial perfusion imaging might be further improved by considering the extent of reversible defects. In another meta-analysis in vascular surgery, reversible defects on preoperative myocardial perfusion imaging were associated with significantly increased cardiac risk only

when the extent of reversibility exceeded 20% of the myocardium.¹²² Notably, isolated fixed defects (i.e., no associated reversible defects) were not associated with elevated cardiac risk.¹²² While available evidence does suggest that stress echocardiography has better prognostic accuracy, these data should be interpreted cautiously since they are older, heterogeneous, and do not account for varying local expertise in stress testing modalities. In addition, it remains unclear as to whether cardiac stress tests provide *incremental* prognostic information in patients who have already been assessed using clinical risk factors.

Some patients with high-risk findings on initial cardiac stress testing may require subsequent evaluation of coronary anatomy using either noninvasive computed tomography coronary angiography (CTCA) or invasive coronary angiography. These tests can diagnose IHD, assess its severity, and help assess perioperative cardiac risk. Using contemporary imaging technology, CTCA has reasonably high accuracy for detecting clinically significant coronary artery stenosis.^{123,124} An initial retrospective cohort study found CTCA to improve prediction of cardiac complications after intermediate-risk noncardiac surgery, as compared to using the RCRI alone.¹²⁵ Conversely, a larger multicenter prospective cohort study found that the addition of CTCA to the RCRI was five times more likely to overestimate risk in low-risk individuals than correctly identify a previously misclassified high-risk individual.¹²⁶ Thus, CTCA does not appear to be an appropriate first-line test to supplement clinical risk stratification. Nonetheless, it may be a reasonable follow-up option in patients with high-risk cardiac stress test results.

Invasive coronary angiography is the gold standard for diagnosing IHD and may also be a follow-up option for patients with high-risk cardiac stress test results. Two Italian randomized trials in vascular surgery patients have suggested that routine preoperative invasive coronary angiography—followed by revascularization of any critical stenosis—reduces risks of postoperative myocardial ischemia,¹²⁷ and long-term mortality.^{128,129} Although interesting, these findings still do not support a clinical shift to this invasive assessment strategy, largely because any patient-relevant benefits were seen over long-term follow-up, not the immediate postoperative period. Any merit for an invasive coronary artery assessment strategy is highly related to whether coronary revascularization before noncardiac surgery is beneficial. This issue remains controversial. The most relevant study is the Coronary Artery Revascularization Prophylaxis trial.¹³⁰ In the multicenter randomized controlled trial of 510 vascular surgery patients with known significant IHD, preoperative revascularization using CABG or PCI with bare metal stents (BMSs) did not reduce the risk of postoperative myocardial infarction or long-term mortality. Notably, the trial excluded patients with left main coronary artery stenosis, which is the only subgroup where revascularization was associated with improved survival in a related cohort study.¹³¹ At present, both American and European guidelines only recommend consideration for revascularization in patients who meet usual nonoperative indications (e.g., left main coronary artery stenosis, triple-vessel coronary artery disease),^{7,9} while the CCS guidelines recommend against preoperative revascularization in any patient with stable IHD.⁸

In general, randomized controlled trials have also *not* shown benefit from *de novo* medical therapy to decrease perioperative cardiac risk, including β -adrenergic blockers,^{132,133} α_2 -adrenergic agonists,^{134,135} and low-dose aspirin.¹³⁶ Despite initial promising data on perioperative β -adrenergic blockade,¹³⁷ these benefits were not replicated in larger multicenter randomized trials, such as the Perioperative Ischemic Evaluation Study-1 (POISE-1) trial. Current randomized trial evidence shows that perioperative β -adrenergic blockade reduces the risk of postoperative myocardial infarction, but at the cost of increased risks of acute stroke, hypotension, and death.¹³³ Although it is possible that these risks are mitigated by starting β -adrenergic blockers several days before surgery,^{138,139} and titrating therapy to a reasonable target heart rate without precipitating hypotension, there are no compelling data showing the efficacy and safety of this approach.¹⁴⁰ Caution should especially be exercised when using β -adrenergic blockers in individuals with known CVD because of the risks of perioperative stroke.^{132,133}

Conversely, most *long-term* cardiovascular medications in patients with IHD should be continued up to surgery, including β -adrenergic blockers, statins, and most other antihypertensive medications. Nonetheless, there are some exceptions. Since ACEI and ARB administration within 24 hours before surgery is associated with increased risks of hypotension⁸⁵ and myocardial injury,⁸⁶ it is reasonable to withhold these medications for 24 hours before surgery, provided that they are restarted postoperatively (see section on “Hypertension”).^{87,88} Despite theoretical benefits,¹⁴¹ randomized controlled trials to date have not shown benefits from routinely continuing aspirin before noncardiac surgery. For example, in the POISE-2 trial, continuing low-dose aspirin (100 mg/day) did not prevent cardiac complications but increased risks of major bleeding.¹³⁶ The lack of clear benefit may be explained, in part, by acute thrombosis being a relatively infrequent contributor to perioperative myocardial infarction.^{142,143} Nonetheless, since only one third of participants in the POISE-2 trial had diagnosed vascular disease, it is possible that continuation of aspirin benefits some very high-risk subgroups. Consistent with this possibility, a relatively small post-hoc subgroup analysis from the POISE-2 trial found that perioperative aspirin reduced the risk of death or myocardial infarction in patients with prior PCI.¹⁴⁴ Based on these data, a reasonable strategy is to only continue aspirin *selectively* in patients where the risk of cardiac events is felt to exceed the risk of major bleeding. Other medications that should generally be withdrawn before surgery include P2Y₁₂ inhibitors (e.g., clopidogrel, ticagrelor, prasugrel) and DOACs (see sections on “Atrial Fibrillation” and “Preoperative Antiplatelet Therapy”).

Coronary Stents

Following PCI with stent implantation, patients require an initial period of dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor (e.g., clopidogrel, ticagrelor, prasugrel), after which they can be transitioned to aspirin monotherapy. The purpose of DAPT is to prevent potentially catastrophic stent thrombosis during the vulnerable period preceding stent reendothelialization. Temporary preoperative discontinuation of DAPT during this vulnerable period predisposes patients to cardiovascular complications,

especially given the prothrombotic state triggered by surgical stress. Based on emerging evidence and improved DES technology, recommendations pertaining to minimum duration of DAPT before elective noncardiac surgery continue to evolve—as reflected in updated 2016 guidelines published by the ACC/AHA.¹⁴⁵ These guidelines recommend that elective noncardiac surgery should be delayed for 30 days or more after BMS implantation. In the case of DES, the ideal recommended minimum delay is 6 months, which is consistent with several cohort studies showing relatively low perioperative cardiac risk when elective noncardiac surgery was performed 6 months or more after DES implantation.^{146,147} Based on expert opinion, the guidelines also indicate that elective noncardiac surgery can sometimes be performed from 3 to 6 months after DES implantation (particularly with new generation stents), if the risk of stent thrombosis is judged to be less than the risk of further delaying surgery.¹⁴⁵ When DAPT is temporarily interrupted before noncardiac surgery, the guidelines strongly recommend that aspirin be continued, and P2Y₁₂ inhibitor therapy be restarted as soon as possible after surgery.¹⁴⁵

Although not explicitly indicated in the 2016 ACC/AHA guidelines, factors other than stent type and time interval since PCI should also inform judgments on the safety of performing elective noncardiac surgery in patients with coronary stents. For example, a large retrospective cohort study of about 26,600 patients found that the risks of noncardiac surgery early after stent implantation were increased when PCI had been performed for acute myocardial infarction, as opposed to unstable angina or non-acute coronary syndrome indications.¹⁴⁸ As a consequence, it may be particularly important to delay noncardiac surgery for 6 months when the indication for DES was treatment of an acute myocardial infarction.

During preoperative evaluation, the anesthesiologist should determine the presence, type (drug-eluting vs. bare-metal), location, and original indication of any coronary stent. Given the complex issues related to these patients, subsequent management should be performed in collaboration with a cardiologist and the responsible surgeon, especially for patients receiving DAPT.¹⁴⁵ Whenever possible, surgical procedures should be performed following critical time windows (i.e., 30 days after BMS, or 3–6 months after DES), aspirin should be continued throughout the perioperative period, and any P2Y₁₂ inhibitor therapy should be restarted as soon as possible after surgery. The importance of continuing aspirin perioperatively is supported by the substudy of the POISE-2 randomized trial.¹⁴⁴ In this subgroup analysis of 470 patients with prior PCI, aspirin reduced the risk of death or myocardial infarction (hazard ratio, 0.50; 95% confidence limits, 0.26–0.95) without any significantly increased bleeding risk. Unfractionated heparin and low-molecular-weight heparin (LMWH) should not be used to “bridge” patients who have been withdrawn from antiplatelet therapy, especially since heparin can paradoxically increase platelet aggregation.¹⁴⁹ Following surgery, close monitoring for myocardial injury (i.e., serial troponin measurement) should be strongly considered, with any suspected stent thrombosis treated using PCI. High-risk patients are thus ideally best managed in facilities with immediate access to interventional cardiology.

Heart Failure

Heart failure has been defined as a clinical syndrome resulting from impaired diastolic filling or systolic ejection of the cardiac ventricles.¹⁵⁰ Its major clinical manifestations are dyspnea, fatigue, and fluid retention. Although prevalence estimates are affected by differences in diagnostic criteria, recent estimates suggest that heart failure afflicts more than 6.5 million individuals in the United States,²⁷ and more than 23 million worldwide.¹⁵¹ Heart failure is the sequelae of a broad array of underlying pathology, including ischemic heart disease (i.e., ischemic cardiomyopathy), hypertension, valvular heart disease, myocarditis, infiltrative disorder (e.g., sarcoidosis, amyloidosis), and peripartum cardiomyopathy. In addition, many affected individuals have no identifiable underlying cause (i.e., idiopathic dilated cardiomyopathy). Several approaches can be used to classify heart failure, including the presence versus absence of associated signs or symptoms (i.e., compensated vs. decompensated heart failure), and the extent of functional limitation. In heart failure patients, functional status is typically classified based on New York Heart Association (NYHA) categories:

- NYHA class I: no limitation of physical activity; ordinary activity not a cause of fatigue, palpitations, or syncope
- NYHA class II: slight limitation of physical activity; ordinary activity resulting in fatigue, palpitations, or syncope
- NYHA class III: marked limitation of physical activity; less than ordinary activity resulting in fatigue, palpitations, or syncope; comfort at rest
- NYHA class IV: inability to do any physical activity without discomfort; symptoms at rest

Heart failure can also be classified based on the severity of ventricular systolic dysfunction, namely as heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved ejection fraction (HFpEF).¹⁵² Individuals with HFpEF (or diastolic heart failure) have normal left ventricular ejection fraction ($\geq 50\%$), normal left ventricular end-diastolic volume, and abnormal diastolic function. By comparison, HFrEF (or systolic heart failure) is characterized by more significant left ventricular systolic dysfunction (i.e., ejection fraction $\leq 40\%$). Individuals with borderline left ventricular systolic function (i.e., ejection fraction 41%-49%) are classified as borderline HFpEF. They tend to have characteristics and outcomes similar to patients with HFpEF.¹⁵² Among patients with heart failure, about half have HFpEF.¹⁵³ Although they have a high mortality risk (10%-20% at 1-year),^{154,155} patients with HFpEF have lower adjusted risks of death (adjusted hazard ratio 0.68) over long-term follow-up than patients with HFrEF.¹⁵⁵ Most medical therapy for improving morbidity and mortality in heart failure (i.e., ACEI, ARB, aldosterone antagonist, β -adrenergic blocker, ivabradine) has only demonstrated efficacy in HFrEF.¹⁵⁶ In contrast, medical therapy for HFpEF is largely aimed at symptoms and underlying conditions (e.g., hypertension). Other heart failure-related treatments include diuretics (for volume overload), anticoagulants (for atrial fibrillation or left ventricular thrombus), implantable cardioverter-defibrillators (ICDs), or cardiac resynchronization therapy (CRT).

In the perioperative setting, heart failure is a recognized risk factor for mortality and morbidity after major surgery. *Symptomatic* heart failure has been consistently identified

as a risk factor for adverse perioperative outcomes in multiple studies. For example, in a retrospective cohort study of about 159,000 Medicare beneficiaries in the United States, heart failure was associated with significantly higher risks of 30-day mortality (adjusted hazard ratio 1.63) after noncardiac surgery.¹⁵⁷ Similarly, a more recent matched cohort study using the NSQIP registry showed new or worsened heart failure within 30 days before surgery to be associated with increased risks of 30-day mortality (adjusted relative risk 2.08) or major morbidity (adjusted relative risk 1.54).¹⁵⁸ Symptomatic heart failure is also a component of the Revised Cardiac Index, which is commonly used for estimating perioperative cardiac risk cardiovascular complications. Among patients with heart failure, perioperative risk may be higher in patients with HFrEF versus HFpEF. Specifically, in a cohort study of 174 heart failure patients undergoing noncardiac surgery, an ejection fraction less than 30% was associated with much higher adjusted risks (adjusted odds ratio 4.88) of postoperative death, myocardial infarction, or heart failure exacerbation.¹⁵⁹ Nonetheless, HFpEF may still be prognostically important in the perioperative setting, as evidenced by a meta-analysis that found diastolic dysfunction to be associated with a doubling (pooled adjusted odds ratio 2.03) in the risk of postoperative adverse cardiac events.¹⁶⁰ Although symptomatic HF is a clear indicator of increased perioperative risk, the prognostic importance of *asymptomatic* systolic dysfunction is less clear. For example, in a cohort study of 339 individuals undergoing noncardiac surgery, a reduced ejection fraction was associated with increased cardiac morbidity, but this information did not improve risk prediction beyond that achieved with clinical risk factors.¹⁶¹ Similarly, in another cohort study of 570 individuals undergoing noncardiac surgery, a reduced ejection only had prognostic importance within the subgroup with RCRI scores of 2 or greater.¹⁶² Consistent with these data, the current ACC/AHA guidelines discourage routine preoperative assessment of ventricular function (Box 31.3).⁷

The clinical stability of heart failure symptoms prior to surgery is another important determinant of perioperative risk, as evidenced by a single-center retrospective cohort study from the United States.¹⁶³ After examination at a hospitalist-run preoperative evaluation clinic, clinically stable heart failure patients had relatively low risks of 30-day mortality (1.3%) after noncardiac surgery, albeit with longer hospital length of stay and higher readmission rates relative to matched controls. Consistent with these data, the ESC/ESA guidelines recommend that elective intermediate-risk and high-risk noncardiac procedures be deferred for at least 3 months after initiation of medical therapy in patients with newly diagnosed heart failure.⁹

The preoperative history pertaining to heart failure should clarify its type, etiology, severity, stability (including prior exacerbations), recent investigations (e.g., echocardiograms), and current therapy (medical and device-based). The anesthesiologist should inquire about recent weight gain, fatigue, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, peripheral edema, hospitalizations, and recent changes in medical management. The patient's functional status should be classified according to the NYHA categories. It is especially important to determine if the signs and symptoms of heart failure are