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By Howard H. Bernstein and Jerome You

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Anesthetic Considerations for Nonobstetric Surgery During Pregnancy

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Anesthesia for nonobstetric surgery in patients who are pregnant presents unique challenges and concerns for anesthesiologists. Each year in the United States, more than 75,000 women undergo nonobstetric surgery during pregnancy [1]. The maternal physiologic adaptation to pregnancy alters the volume of distribution, amount of free unbound drug, sensitivity to anesthetics, maternal oxygen consumption, risk for aspiration, blood pressure and cardiac output in the supine position, risk for thrombosis and embolism, and the function of all other organ systems. In addition, anesthesiologists have a second unseen patient, the fetus, who also may be affected directly or indirectly by an anesthetic administered to the mother. This article reviews the implications of pregnancy on anesthetic management by presenting and analyzing the management of five patients undergoing various surgical procedures during pregnancy.

CASE 1

This is a 32-year-old gravida (G) 1 para (P) 0 at 25 weeks gestational age who had acute cholecystitis and cholelithiasis. She presented to her physician complaining of right upper quadrant pain and fever. Her white blood cell count was elevated to 22,000, with a leftward shift in the differential count. Antibiotic therapy was started with little improvement, and an increase in liver function studies was noted. Ultrasound evaluation of the fetus demonstrated a healthy fetus with growth consistent with a gestational age of 25 weeks. No evidence of premature labor was noted. Because of her lack of improvement, the decision was made to proceed to a laparoscopic-assisted cholecystectomy.

During the preoperative interview, the patient asked if the drugs used could harm her child.

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TERATOGENIC RISK OF ANESTHESIA

Teratogenicity may be induced at any stage of gestation of the fetus. To produce a defect, the agent must be given in a significant dosage, at a particular stage of development at which the fetus is susceptible, and, possibly, for a minimal period of exposure [2].

Organ development occurs at specific stages during fetal development. Although early effects may lead to major malformations or death of the fetus, later interference with development generally leads to minor malformations or functional defects [3].

The teratogenic risk of anesthetic medications is difficult to assess in patients who are pregnant. Patients who are pregnant and require surgery often have infection or fever. In addition, the hemodynamic changes and metabolic disturbances related to surgery itself may play a role. Finally, in the age of balanced anesthetic techniques involving multiple medications, it becomes more difficult to identify individual teratogens because of pharmacologic interactions. Animal studies may be designed to test the teratogenic potential of individual agents. Unfortunately, teratogenesis may be species specific, making it difficult to extrapolate from an animal model to humans.

Thus far, only one large epidemiologic study exists reporting the reproductive outcome of pregnant women undergoing anesthesia and surgery. The Collaborative Perinatal Project [4], however, reports the data as individual agents, although most anesthetics involved more than one agent. In addition, patients were grouped together regardless of gestational age or level of criticality.

Inhaled anesthetic agents

Nitrous oxide

There is some controversy regarding the teratogenic effects of nitrous oxide. Nitrous oxide inactivates vitamin B₁₂, an essential cofactor for methionine synthetase, and may interfere with DNA synthesis. Although no increase in the risk for congenital defects was observed in the Collaborative Perinatal Project [4], several animal studies did observe an increased frequency of anomalies and growth restriction [5–7]. Other animal studies find no such increase [8,9]. Although studies raise some concern over the use of nitrous oxide, there does not seem to be a high risk for teratogenicity with its use in humans.

Other inhaled anesthetic agents

With halothane, there was no significant increase in the frequency of congenital abnormalities in children of pregnant women [4]. Animal studies, however, show mixed data regarding halothane. Although fetal anomalies were found in some studies [10–12], other studies find no teratogenic effects observed after exposure [13,14]. There are no human epidemiologic studies involving enflurane or isoflurane; however, animal studies show some evidence of increased risk for congenital anomalies [15,16]. The clinical relevance of these findings is uncertain. Sevoflurane and desflurane are classified as class B drugs by the Food and Drug Administration (FDA). Animal studies report no teratogenic
effects, but first-trimester studies in humans have not been performed [17]. It is believed that all the potent halogenated agents are safe in pregnancy.

**Intravenous anesthetics**

Human studies show no increase in congenital anomalies in infants exposed to thiopental and methohexital in utero [4]. Human epidemiologic studies have not been conducted for etomidate or ketamine; however, animal studies using higher doses than used in clinical practice fail to demonstrate teratogenic effects [18,19]. Although propofol has not been studied in patients who are pregnant, animal studies do not show any evidence of teratogenicity [20].

**Narcotics**

Methadone, morphine, and meperidine are teratogenic in the hamster model [21]. The maternal administration of narcotic antagonists prevented teratogenesis. It is hypothesized that narcotic-induced respiratory depression and hypercarbia and not the narcotic itself may be the teratogen. In a rat model, fentanyl was administered by a technique allowing for high dose and no respiratory depression. No teratogenicity was observed [22]. It is important, when administering narcotics during early pregnancy, to avoid respiratory depression and hypercarbia.

**Sedatives**

The use of sedatives, in particular benzodiazepines, in the first trimester of pregnancy is controversial. \( \gamma \)-Aminobutyric acid (GABA) is shown to inhibit palate shelf reorientation, leading to cleft palate formation; because diazepam mimics GABA, it also may predispose to cleft palate formation [23]. The teratogenic potential of GABA and diazepam is species specific. In studies of women giving birth to infants who have congenital anomalies, diazepam consumption was seen more commonly in mothers of infants born with cleft palate than with other anomalies [24,25]. The study states that this association may have appeared only by chance [25]. Other studies do not confirm these early findings [26,27]. One study finds a possible association between the use of lorazepam and anal atresia, although no association between any benzodiazepine and cleft lip and palate was noted [27]. As the use of a benzodiazepine is not absolutely necessary, the FDA recommends avoiding its administration during early pregnancy. Benzodiazepines are used routinely to sedate the fetus during second and third trimester fetal procedures.

Preoperative evaluation revealed a gravid woman in no acute distress. Pregnancy had been normal to date. Past medical history was unremarkable. Physical examination revealed a blood pressure of 100/60 with a pulse of 100 beats per minute (BPM). Weight was 65 kg. Airway examination revealed a Mallampati class I airway. Dentition was intact. There were no dentures or caps. Evaluation of the lungs demonstrated clear lungs. Heart examination revealed a grade II/VI midsystolic murmur at the left sternal boarder. The rest of the examination was unremarkable.
The patient was brought to the operating room, was placed on the operating room table, and assumed the left lateral position. Blood pressure cuff, electrocardiogram, and pulse oximeter were placed. An electronic external fetal heart rate (FHR) monitor also was placed. FHR initially was 150 BPM. She was moved from the left lateral position to a supine position. She complained feeling as if she were fainting. Blood pressure was 70/30 with a pulse of 120 BPM. No change in FHR was noted. A wedge was placed under her left hip with alleviation of her symptoms. Blood pressure returned to her normal pressure of 110/60 with a pulse of 100 BPM.

Maternal cardiovascular adaptation to pregnancy (Table 1) begins at approximately 6 weeks’ gestational age with an increase in blood volume [28] leading to an increase in cardiac output. Cardiac output increases by 30% to 50% because of a 30% to 50% increase in stroke volume and a 17% increase in heart rate [28,29]. Central venous pressure and pulmonary artery occlusion pressure

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Physiologic changes during pregnancy</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong> → ← ↑ ↓</td>
</tr>
<tr>
<td>Cardiac output</td>
</tr>
<tr>
<td>Stroke volume</td>
</tr>
<tr>
<td>Heart rate</td>
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<td>Systemic vascular resistance</td>
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<tr>
<td>Mean arterial pressure</td>
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<tr>
<td>Central venous pressure</td>
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<tr>
<td><strong>Respiratory</strong></td>
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<td>Minute ventilation</td>
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<tr>
<td>Tidal volume</td>
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<tr>
<td>Respiratory rate</td>
</tr>
<tr>
<td>Functional reserve capacity</td>
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<tr>
<td>Expiratory reserve volume</td>
</tr>
<tr>
<td>Residual volume</td>
</tr>
<tr>
<td>Inspiratory capacity</td>
</tr>
<tr>
<td>Total lung capacity</td>
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<tr>
<td>Airway resistance</td>
</tr>
<tr>
<td>$\text{PaCO}_2$</td>
</tr>
<tr>
<td>$\text{HCO}_3^-$</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>esophageal peristalsis</td>
</tr>
<tr>
<td>gastric emptying (labor)</td>
</tr>
<tr>
<td>small bowel motility</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>Renal blood flow</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
</tr>
<tr>
<td>Maternal blood volume</td>
</tr>
<tr>
<td>Red blood cell mass</td>
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Abbreviations: ↑, increases; ↓, decreases; → ←, no change. Data from Refs. [29,53,88,184,185].
undergo no significant changes. Despite the increased intravascular volume and cardiac output, there is little change in arterial blood pressure because of a decrease in systemic and pulmonary vascular resistance [29].

Significant remodeling of the heart also occurs, resulting in enlargement of all chambers of the heart [30]. Enlargement of the left atrium makes the heart more susceptible to developing supraventricular arrhythmias. Grade I to II/VI early to midsystolic murmurs commonly are heard as a result of tricuspid annular enlargement leading to regurgitation. These murmurs rarely are of clinical significance [30].

Body position also plays a significant role in determining maternal blood pressure. By the time the uterus reaches the level of the umbilicus, at approximately 20 weeks’ gestational age, supine position may result in significant compression of the inferior vena cava and infrarenal aorta [31,32]. This uterine compression may result in a decrease in ejection fraction of 20% to 30% [28] resulting in hypotension, the supine hypotensive syndrome, that may be avoided with left uterine tilt.

Changes in maternal blood pressure may affect uterine blood flow (UBF) and, ultimately, exchange across the placenta. UBF is not autoregulated. A decrease in maternal blood pressure or increase in uterine vascular resistance may decrease UBF and blood supply to the maternal side of the placenta, leading to fetal hypoxemia and, ultimately, acidosis. In the presence of a normally functioning placenta, transient decreases in UBF are well tolerated by the fetus. In contrast, in the presence of a poorly functioning placenta, such as in post dates pregnancy, impaired oxygen exchange already may have occurred. Further reductions in UBF and oxygen exchange across the placenta may lead to severe fetal hypoxia and death or neurologic dysfunction.

As the uterine vascular resistance may affect UBF, the use of pressors with significant \(\alpha\)-agonism has been of concern. In animal studies, the use of \(\alpha\)-agonists results in a rise in maternal blood pressure accompanied by a decrease in UBF [33,34]. The use of \(\beta\)-agonists results in a rise in maternal blood pressure and UBF [33,34]. In humans, the use of phenylephrine, an \(\alpha\)-agonist, in clinically relevant doses, does not have an adverse effect on fetal outcome [35]. Both \(\alpha\)- and \(\beta\)-agonists may be administered to correct maternal hypotension.

Debate exists as to whether or not ephedrine or phenylephrine is the preferred pressor to treat epidural or spinal anesthesia–induced maternal hypotension. In studies comparing ephedrine, a mixed \(\alpha\)- and \(\beta\)-agonist, and phenylephrine, a pure \(\alpha\)-agonist, both resulted in correction of maternal hypotension during spinal anesthesia [35,36]. Umbilical artery pH was lower in the newborns of mothers treated with ephedrine compared to phenylephrine [37,38]. The reason is not certain. In the fetal lamb, \(\beta\)-adrenergic stimulation may lead to an increase in fetal metabolic rate, oxygen demand, and, ultimately, anaerobic metabolism and metabolic acidosis [39,40].

Pregnancy results in changes in the normal electrocardiogram [41]. Heart rate is increased, with the greatest change noted in the third trimester, a 21% increase over the nonpregnant state. QRS axis is shifted to the right in the first
trimester and to the left in the third trimester, although great individual variability is noted. No significant changes are noted in cardiac rhythm. Depression of the ST segment and T-wave flattening may be noted [42] and large Q wave in lead III [43]. None of these changes are of clinical significance (Table 2).

Prior to entering the operating room, the patient was administered a non-particulate antacid containing 30 mL of 0.3 M sodium citrate. As the patient was at increased risk for aspiration during induction a rapid sequence induction of general anesthesia was planned.

In 1946, Mendelson [44] published his classic study of the pathophysiology of the aspiration of gastric contents in the anesthetized patient. He reported two distinct types of aspiration: aspiration of solid food, leading to complete mechanical airway obstruction, and aspiration of liquid gastric contents, leading to a chemical pneumonitis. Aspiration of liquid contents and solid contents may occur simultaneously. In Mendelson’s report, tracheal obstruction with solid food led to the asphyxial death of two parturients in the delivery room. Aspiration of liquid contents led to the development of a chemical pneumonitis and varying degrees of acute pulmonary failure. He also created an animal model comparing the aspiration of hydrochloric acid, unneutralized human emesis, saline, and neutralized human emesis. He demonstrated that the acute pneumonitis was the result of the acid content of human emesis. Aspiration of hydrochloric acid and human emesis led to the same pulmonary findings seen in women aspirating gastric contents under general anesthesia. Aspiration of normal saline or neutralized human emesis led to temporary pulmonary symptoms without the development of the syndrome of aspiration pneumonia. Mendelson’s syndrome became synonymous with pulmonary aspiration pneumonitis.

Gastric emptying of solids is impaired during labor but not antepartum [45–49]; however, narcotic administration may slow gastric emptying time [50–52].

Table 2
Changes in the electrocardiogram during pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Increased in all trimesters, 21% increase in third trimester</td>
</tr>
<tr>
<td>QRS axis</td>
<td>First trimester: right deviation</td>
</tr>
<tr>
<td></td>
<td>Second trimester: no change from antepartum</td>
</tr>
<tr>
<td></td>
<td>Third trimester: left deviation</td>
</tr>
<tr>
<td>QRS duration and amplitude</td>
<td>No significant change</td>
</tr>
<tr>
<td>Q–T interval</td>
<td>No significant change</td>
</tr>
<tr>
<td>P–R interval</td>
<td>No significant change</td>
</tr>
<tr>
<td>T wave: duration and amplitude</td>
<td>No significant change</td>
</tr>
<tr>
<td>T wave: axis</td>
<td>Left shift, greatest in third trimester</td>
</tr>
</tbody>
</table>

Esophageal reflux occurs in approximately 30% to 50% of pregnant women [53]. Decreased esophageal sphincter tone, resulting from increased progesterone, incompetence of the lower esophageal sphincter, and impaired esophageal peristalsis, predisposes patients who are pregnant to reflux disease. Although this patient is not in labor, she still should be considered at increased risk for passive regurgitation and aspiration during the induction of and emergence from general anesthesia, and a rapid sequence induction with cricoid pressure is indicated.

All patients who are pregnant prior to the induction of general anesthesia should receive a nonparticulate antacid, such as 0.3 M sodium citrate, for neutralization of stomach acid [54,55]. The aspiration of a particulate antacid is shown to induce severe pulmonary damage and, therefore, should be avoided [56–58]. The use of ranitidine and an H₂ receptor blocker, alone or in combination with a nonparticulate antacid, raises gastric pH and lowers gastric volume [59,60]. Metoclopramide also is shown to decrease gastric emptying time [61].

As a rapid sequence induction of general anesthesia with endotracheal intubation was planned, the patient was preoxygenated with 100% oxygen administered by facemask. General anesthesia was induced with propofol, and intubation was facilitated by succinylcholine. Initial laryngoscopy failed to visualize the vocal cords. The patient was repositioned and direct laryngoscopy was performed again. During the second laryngoscopy, the SpO₂ decreased to 60%. Intubation with a 6.0-mm endotracheal tube was successful. Bilateral breath sounds and end-tidal CO₂ (ETCO₂) were identified. With manual ventilation, the oxygen saturation rapidly returned to 100%.

**INTRAVENOUS ANESTHETICS**

Thiopental, ketamine, etomidate, and propofol all are used for the induction of general anesthesia in patients who are pregnant. All drugs cross the placenta after induction [62–67]. All are used successfully with no difference in neonatal effects, such as respiratory depression, umbilical cord pH, and Apgar scores [68–73]. Etomidate is shown to depress neonatal cortisol production. This effect is of unknown clinical significance [74]. There is no definite clinical advantage of one agent over the others. Choice of induction agent should be based on patients’ clinical condition and general state of health.

The maternal sensitivity to thiopental is increased in pregnancy. The induction dose needed for thiopental decreases by approximately 18% to 35% in early pregnancy and at term, respectively [75,76]. In contrast, no change in sensitivity to propofol is demonstrated in early pregnancy [77]. Maternal recovery after propofol is faster than after thiopental. The reason for the increased sensitivity to thiopental is unknown.

Narcotics, such as morphine, fentanyl, and sufentanil, all cross the placenta [78,79] and may induce neonatal respiratory depression when administered prior to delivery. This rarely is a problem in nonobstetric surgery during
pregnancy as the fetus is unlikely to be delivered. Maternal narcotic administration may lead to a decrease in FHR variability.

Theoretic concern regarding high-dose administration of narcotics exists. It is shown that maternally administered morphine sulfate, 10 to 15 mg intramuscularly, may result in a decrease in fetal breathing movements and FHR accelerations, possibly a result of placental vasoconstriction [79]. Prolonged maternal exposure to intravenous (IV) morphine is reported to cause fetal and placental vasoconstriction [80]. In this case report [79], fetal status improved after switching to fentanyl. Two animal studies demonstrate adverse fetal effects of high-dose fentanyl (approximately 50 μg/kg estimated fetal weight) [81,82]. These studies demonstrate a rise in FHR [81,82], lactate, and cortisol levels [81]; a fall in fetal pH and fetal PaO₂ [81,82]; and a rise in PaCO₂ [82]. These studies may be species specific as no human studies show a similar rise in FHR after fentanyl administration, although smaller fentanyl doses were administered [83,84]. Further human investigation is needed before any changes in anesthetic protocols can be recommended.

AIRWAY ANATOMY
Management of the airway in patients who are pregnant may be more difficult than in women who are not pregnant. There are many anatomic and physiologic changes that occur, placing patients at risk for developing complex airway issues.

In an assessment of malpractice claims, difficult endotracheal intubation and esophageal intubation represented 23% of damaging events during obstetric general anesthesia [85].

The parturient undergoes an average weight gain of 20 kg during pregnancy. Weight gain is the result of increasing size of the uterus and fetus, increased blood and fluid volumes, increased fat deposition, and increased breast size. These changes may make positioning for intubation more difficult.

Increases in interstitial fluid and blood volume and increased estrogen during pregnancy lead to capillary engorgement and swelling in the upper airway. In addition, changes in colloid pressure resulting from protein leakage and edema may lead to increased tongue size, pharyngeal edema, and decreased neck mobility. These changes may increase the difficulty of intubation [85].

Mallampati score increases as gestation progresses from first to late third trimester [86]. At term, the incidence of Mallampati class IV airway increases by 34% because of pharyngeal edema [86]. During pregnancy, an increase in Mallampati classification score from II to IV is shown to increase the risk for difficult intubation significantly: class II (relative risk [RR] 3.2), class III (RR 7.58), and class IV (RR 11.3) [87]. In addition, other factors are found to have increased relative risk for difficult intubation: short neck (RR 5.01), protruding maxillary incisors (RR 8.0), and receding mandible (RR 9.71) [87].

PULMONARY FUNCTION
Early in pregnancy, hormonal alterations affect pulmonary function. Minute ventilation increases approximately 50%, mostly secondary to the increase in progesterone, although mechanical changes in breathing and metabolic changes
also are involved. Progesterone stimulates central respiratory drive directly and enhances the response to alveolar CO₂, resulting in increased tidal volume of approximately 40%, with little to no increase in respiratory rate.

The mechanical changes that occur during pregnancy include increased lower chest wall circumference, elevation of the diaphragm approximately 4 to 5 cm, and a widening of the costal angle of approximately 50% [30]. The changes result in decreased expiratory reserve volume of 15% to 20%, residual volume of 20% to 25%, and functional residual capacity (FRC) of 20%. Other lung volumes experience minor changes, including a 5% to 10% increase in inspiratory capacity and minimal change in total lung capacity and vital capacity.

Lung function does not seem to be altered significantly. Spirometry and flow-volume loops remain basically unchanged. Total airway resistance decreases approximately 50% during pregnancy. Lung compliance does not seem to change, although chest wall compliance decreases. The decreased compliance is greater than the decrease in airway resistance, resulting in an increased work of breathing of approximately 50% [88]. Studies of diffusion capacity during pregnancy show inconsistent results.

Arterial blood gas studies reflect the changes in ventilation. The respiratory alkalosis secondary to hyperventilation results in a PaCO₂ of 28 to 32 mm Hg, with renal compensation leading to serum bicarbonate levels of 18 to 21 mEq/L. Resulting arterial pH is between 7.40 and 7.47. The decrease in arterial CO₂ partial pressure results in an increase in arterial and alveolar oxygen partial pressures.

Dyspnea during pregnancy is a common complaint beginning early in pregnancy. The sensation is secondary to the central effects of progesterone and stimulation of chest wall proprioceptors as mechanical changes of breathing take place [89]. It affects as many as 70% of healthy pregnant women toward term, although the sensation generally is mild and improves toward term. If symptoms worsen or affect a patient’s ability to function, however, the patient should have heart and lung function assessed to rule out disease.

Oxygen consumption increases from 182 mL/min, before conception, to 256 mL/min by 8 to 11 weeks, to a peak of 300 mL/min at 32 weeks’ gestational age [90]. Increased oxygen consumption primarily is the result of the metabolic needs of the fetus, uterus, and placenta. Also, a significant decrease in FRC occurs during pregnancy (discussed previously). Because of the increased oxygen consumption and decreased FRC, it is not surprising that maternal PaO₂ falls rapidly during periods of apnea, such as during induction of general anesthesia in pregnant women (Fig. 1) [91].

The patient was placed on a ventilator and ETCO₂ was maintained at 32%. Muscle relaxation was maintained with vecuronium and anesthesia maintained with isoflurane and fentanyl; nitrous oxide was not used per request of the surgeon.

Maintaining normal maternal PaCO₂ is necessary to ensure normal fetal acid base status and oxygenation. Maternal PaCO₂ and fetal PaCO₂ equilibrate
rapidly; therefore, maternal hypercapnia rapidly causes fetal hypercapnia. Fetal hypercapnia leads to increased fetal breathing movements, increased oxygen extraction and consumption, and a lowering of the fetal PaCO2 [92]. Also, severe fetal hypercapnia and acidosis may lead to fetal myocardial depression and hypotension [93].

Maternal hyperventilation leading to a respiratory alkalosis may lead to a decrease in fetal PaO2 [94], fetal tachycardia, and acidosis [95]. Maternal alkalosis is shown to cause vasospasm of the umbilical artery [96] and vein [95], leading to decreased maternal-to-fetal oxygen transfer. Also, because of the Bohr effect, maternal hyperventilation may lead to a left shift of the maternal oxyhemoglobin dissociation curve, further impairing fetal-to-maternal oxygen transfer [93]. Positive pressure ventilation, independent of maternal PaCO2, may result in decreased maternal cardiac output and UBF [93].

Pregnancy increases sensitivity to inhaled anesthetics. This effect is believed the result of increased progesterone and circulating endogenous opioids. The end effect on minimal alveolar concentration (MAC) is a decrease of 25% to 40% [97]. Careful titration of dose is needed to avoid decreased maternal cardiac output and, therefore, UBF.

Fetal effects of maternal inhalation of the volatile halogenated agents have been studied in animal models and in humans undergoing cesarean section. High concentrations of halothane and isoflurane may cause a decrease in maternal blood pressure and UBF, leading to fetal bradycardia and hypotension [98–100]. In ewes, administration of moderate doses of halothane or isoflurane (less than 1.5 MAC) was associated with little fetal effect and maintenance of UBF [100,101]. In clinically relevant doses in humans (1 MAC or less), all the volatile halogenated agents have been used successfully to maintain general anesthesia for cesarean section with no clear advantage of one over the other [102–104].

Transplacental transfer of all muscle relaxants is demonstrated [105,106]. Transfer of the nondepolarizing muscle relaxants is minimal; no cases of

![Fig. 1. Oxygen tension during apnea. (Adapted from Archer GW Jr, Marx GF. Arterial oxygen tension during apnoea in parturient women. Br J Anaesth 1974;46:358–60.)](image-url)
neonatal respiratory depression are reported [107,108]. Fetal concentrations are proportional to the maternal dose injected [109]. Transient respiratory depression of the fetus in mothers homozygous for the atypical allele for serum pseudocholinesterase is reported [110,111]. This is a rare event but underlines the importance of taking a thorough maternal history.

The volume of distribution of atracurium, vecuronium, and pancuronium are unchanged during pregnancy [109]. The clearance of atracurium and its clinical duration are unchanged during pregnancy [109]. The clinical duration of vecuronium at term is twice as long as in the nonpregnant state [109]. Despite the decrease in pseudocholinesterase levels during pregnancy, the clinical duration of succinylcholine is unchanged.

The patient underwent an open laparoscopic-assisted cholecystectomy.

The most common indications for nonobstetric surgery during pregnancy are appendicitis, cholelithiasis, ovarian cyst, and adnexal torsion [112,113]. Maternal mortality is reported at 0.006% to 0.4% [113,114]. Cohen-Kerem and co-workers [114] report an overall rate of fetal loss of 2.5% and rate of premature labor after surgical intervention of 3.5% with an increase to 4.6% after appendectomy. Acute appendicitis is associated with a postoperative spontaneous abortion rate of 13.0% [115]. The incidence of major malformations was not increased as compared to the general population [114].

**LAPAROSCOPIC SURGERY**

Laparoscopic surgery, in general, offers advantages over open procedures, especially in patients who are pregnant. Advantages include smaller incisions and, thus, less pain leading to less use of narcotics and earlier ambulation and recovery, leading to shorter hospital stays [116]. There also is faster wound healing and lower risk for infection. Laparoscopy during pregnancy is complicated by impaired visualization resulting from the gravid uterus and the changes in physiology that accompany insufflation of the abdomen with CO₂. Although the majority of studies indicate that laparoscopic surgery is safe during pregnancy [114], there are reports of fetal death, premature labor, and spontaneous abortion [117].

Intraperitoneal insufflation of carbon dioxide leads to an increase in intra-abdominal pressure. Increased intra-abdominal pressure decreases dynamic lung compliance, increases peak inspiratory pressure, and decreases minute ventilation [118,119]. These changes result in a lower arterial pH and elevated PaCO₂, reversed by desufflation [118,119]. Alveolar–arterial oxygen gradient and PaO₂ do not change significantly [119].

Concerns regarding respiratory acidosis during laparoscopic procedures in pregnant women were brought about when found to be associated with preterm labor, spontaneous abortion, and fetal death [117], suggesting the importance of maintaining normocarbia. Several animal studies find that ETCO₂ measurements underestimate PaCO₂ levels by as much as 20 mm Hg [120,121], raising
concerns about the reliability of ETCO2 monitoring. Human studies do not find a significant difference in PaCO2 to ETCO2 [122]. Although these studies find significant changes in PaCO2, only one animal study finds significant fetal hypoxemia and acidosis associated with insufflation of the abdomen [123].

The hemodynamic changes during laparoscopy are brought about by the pneumoperitoneum, increased intra-abdominal pressure, and hypercapnia from absorbed CO2 and patient position. These changes are reviewed by Sharma and coworkers [124]. Insufflation pressures above 10 mm Hg are associated with decreased cardiac output and increases in arterial pressure, heart rate, and systemic and pulmonary vascular resistance. These changes are exaggerated by the head-up position and corrected by the Trendelenburg position. Hemodynamic changes are similar in patients who are pregnant and in women who are not pregnant [125].

Recently, several centers have begun using gasless laparoscopic techniques in an attempt to avoid insufflation with CO2. This technique avoids the complications induced by producing a pneumoperitoneum. This technique had been used successfully in pregnancy without adverse fetal outcome [126,127].

Rizzo reports a long-term follow-up of children born to mothers who underwent laparoscopic procedures during pregnancy [128]. The investigator finds no increase in the incidence of fetal demise, major medical problems, or failure to thrive in the resultant children.

The Society of American Gastrointestinal Endoscopic Surgeons (SAGES), in 1998, released guidelines to enhance the safety of mother and fetus during laparoscopic procedures. These include (1) deferment of surgery until the second trimester; (2) use of pneumatic compression devices on the lower extremities; (3) fetal and maternal status monitoring, including ETCO2 and arterial blood gas monitoring; (4) use of a lead shield over the uterus and selective use of fluoroscopy; (5) abdominal access using an open technique; (6) dependent positioning to decrease pressure on the vena cava; (7) minimizing pneumoperitoneum pressures to 8 to 12 mm Hg to a maximum of 15 mm Hg; and (8) preoperative obstetric consultation [129].

Rollins and colleagues [130] at LDH Hospital in Salt Lake City, Utah, report their experience with laparoscopic appendectomy and cholecystectomy during pregnancy. Their published guidelines differ from SAGES guidelines in several points: (1) using FHR monitoring only pre- and postoperatively; (2) using appropriate surgical criteria; no need for deferring surgery to the second trimester; (3) allowing a higher pneumoperitoneum pressure (10 to 15 mm Hg); (4) monitoring ETCO2 and not arterial blood gases; (5) using open or Veress technique; and (6) recommending therapeutic and not prophylactic use of tocolytic agents (Table 3).

**APPENDECTOMY**

Acute appendicitis occurs during pregnancy at a rate of 0.5 to 1.0 per 1000 pregnancies, making appendectomy the most common nonobstetric procedure performed during pregnancy [131,132]. Early diagnosis is essential in acute
appendicitis, as delay may risk perforation. Ruptured appendicitis and peritonitis may cause premature labor and preterm delivery in up to 40% of cases and is associated with a neonatal mortality rate of up to 35% [131–133].

Is laparoscopic appendectomy preferable to open appendectomy in pregnancy? In patients who are not pregnant, retrospective and prospective studies fail to demonstrate a significant advantage to laparoscopic versus open appendectomy [134,135]. The Cochrane Database of Systemic Reviews identifies several advantages to laparoscopic appendectomy: fewer wound infections, less pain on the first day after surgery, slightly shorter hospital stay, and more rapid return to work and normal activity [136]. As laparoscopic surgery has become more popular, its use in pregnancy has increased [130]. Many studies are published establishing the safety of laparoscopic appendectomy in pregnancy [130,137–140]. These studies show no significant difference in maternal, fetal, or neonatal outcome after laparoscopic appendectomy compared to open appendectomy. The final determination of which approach to surgery (ie, open versus laparoscopic) must be determined by surgeons based on severity of disease, previous abdominal surgery, and surgical expertise in technique and must consider the physiologic effects of insufflation of the abdomen to mother and fetus. At the authors’ institution and at others’ [130], laparoscopic appendectomy has become the standard of care; an understanding of the physiologic changes of pregnancy and how they are complicated by laparoscopic surgery and abdominal insufflation is necessary in order to provide anesthesia safely to pregnant women who have acute appendicitis.

**CHOLECYSTECTOMY**

Biliary tract disease is the second most common surgical issue in the pregnant population. Gallstones are present in 5% of patients who are pregnant and frequently are symptomatic [132,141]. Initial management generally is medical.

<table>
<thead>
<tr>
<th>LDS Hospital</th>
<th>SAGES</th>
<th>LDS Hospital and SAGES</th>
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<tbody>
<tr>
<td>Pre- and postoperative monitoring of fetus and uterus</td>
<td>Intraoperative fetal and uterine monitoring</td>
<td>Pneumatic compression devices</td>
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<td>Appropriate criteria for all trimesters</td>
<td>Second-trimester deferment</td>
<td>Lead shield with selective fluoroscopy</td>
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<td>Pneumoperitoneum 10–15 mm Hg</td>
<td>Pneumoperitoneum 9–12 mm Hg</td>
<td>Dependent positioning</td>
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<td>Maintain ET$\text{CO}_2$ 30–40 mm Hg</td>
<td>Serial arterial blood gas analysis/ET$\text{CO}_2$ monitoring</td>
<td>Obstetrics consultation</td>
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<td>Open (Hasson) or Veress technique</td>
<td>Open (Hasson) technique</td>
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<td>Tocolytics usages for uterine irritability (not prophylactically)</td>
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**Table 3**

Recommendations for laparoscopic surgery during pregnancy
Approximately 41%, however, fail medical therapy and require cholecystectomy. Other indications include acute cholecystitis, peritonitis, and gallstone pancreatitis. Approximately 1 in 2000 pregnant women requires cholecystectomy [141].

Maternal and fetal outcome after laparoscopic cholecystectomy has been studied. In a review of laparoscopic cholecystectomies, there was only one maternal death 15 days postoperatively secondary to hemorrhage, with no other serious maternal complications [137]. As with other surgeries, the risk for fetal loss is greatest in the first trimester at 12%, decreasing with gestational age [142]. The risk for premature labor increases with increasing gestational age, reaching approximately 40% in the third trimester [142]. The risk for spontaneous abortion or preterm labor was the same for open versus laparoscopic cholecystectomy [141].

**ADNEXAL SURGERY**

With ultrasonography, adnexal masses may be diagnosed in up to 4% of pregnancies [143,144]. The majority found in the first trimester resolve spontaneously and probably represent corpus luteum cysts [143]. Large persistent masses, greater than 5 cm, are less common and occur in less than 0.1% of pregnancies [145]. Of these masses, the majority, 40%, are dermoid cysts and approximately 8% are malignant tumors [145].

Most investigators recommend conservative management for adnexal masses less than 6 cm because smaller masses are less likely to be malignant or undergo torsion [145,146]. Planned surgical intervention for adnexal masses is not without fetal risk. In one study, 3% had spontaneous abortions, 12% had preterm delivery, and there were three fetal deaths [147,148]. As fetal loss, after adnexal surgery, is greatest in the first trimester, surgery should be postponed, if safe, to later pregnancy or the postpartum period.

Laparoscopic adnexal surgery is used with increasing frequency and seems safe in the pregnant population. In one study, there were no cases of spontaneous abortion or preterm delivery [149]. It reports one case of fetal death found to be unrelated to surgery.

> After completion of the surgical procedure, residual muscle relaxation was antagonized with neostigmine andglycopyrrolate. The inhalation agents were discontinued and the patient was placed on 100% oxygen. Spontaneous breathing returned and the patient was extubated.

For reversal of residual neuromuscular blockade, an anticholinesterase, neostigmine, routinely is administered. An anticholinergic, atropine or glycopyrrolate, is administered with the neostigmine for its antimuscarinic effects. Tertiary ammonium salts, such as atropine, cross the placenta readily, resulting in a maternal-fetal serum ratio at equilibrium of 1.0 [150,151]. In animal and human studies, the dose of atropine used during reversal does not lead to a change in FHR or variability [152]. Glycopyrrolate, a quaternary ammonium salt,
leads to a maternal-fetal serum ratio of between 0.13 and 0.4, indicating partial transfer [150,151]. The fetal-maternal serum concentrations of neostigmine, after maternal administration, have not been reported; however, as neostigmine is a quaternary ammonium, only partial transfer is expected.

Despite the expected limited transfer of neostigmine across the placenta, at least two cases of fetal bradycardia are reported after reversal of neuromuscular blockade with neostigmine and glycopyrrolate [153,154]. The author also has witnessed a fetal bradycardia after reversal with neostigmine and glycopyrrolate. These events suggest that the transfer of neostigmine across the placenta is greater than that of glycopyrrolate. It is for this reason that the authors believe it is prudent to antagonize the muscarinic stimulatory effects of neostigmine with atropine rather than glycopyrrolate in patients who are pregnant.

CASE 2

A 35-year-old G3P2 at 34 weeks presented to the emergency department after a motor vehicle accident. Examination revealed a gravid woman with size equal to dates. Her pregnancy was uneventful to date. Examination revealed evidence of a fractured right hip. There was no clinical evidence of abdominal or thoracic trauma. Ultrasound of the abdomen was unremarkable. Ultrasound evaluation of the uterus revealed a live fetus at 34 weeks with no evidence of a placental abruption or fetal compromise. Nonstress test was reactive. The patient was in good general health with no significant past medical history.

Trauma occurs in 5% of pregnancies, with 55% secondary to motor vehicle accidents, 22% secondary to assault, and 22% from falls [155]. Maternal trauma may lead to fetal demise. Most common causes of trauma leading to fetal death are motor vehicle accidents, gunshot wounds, and falls [156]. Motor vehicle accidents are responsible for a fetal loss rate of 2.3 per 100,000 live births [156]. Predictors for fetal loss include high severity of injury, low Glasgow Coma Scale score, shock as indicated by large base deficit, vaginal bleeding as an indicator of placental abruption, and abdominal injury or pain [157].

Patients should be evaluated for maternal and fetal injury. Trauma to the maternal abdomen may lead to placental abruption. Ultrasound evaluation of the placenta for evidence of abruption is mandatory. Fetal biophysical profile and nonstress test should be performed to assess fetal well-being. Trauma ultrasound or focused abdominal sonography for trauma (FAST) is effective in assessing the abdomen for injury in patients who are pregnant [158].

Aggressive management of intravascular volume is recommended to maximize uterine artery blood perfusion. Significant maternal hypovolemia may lead to decreased UBF and fetal compromise. Transfusion should not be avoided in the face of maternal hemorrhage. Adequate maternal blood volume and oxygen carrying capacity are necessary to maximize maternal and fetal outcome.
As the planned surgery would not interfere with FHR monitoring and the fetus was viable, intraoperative FHR monitoring was planned.

The purpose of FHR monitoring is to assess fetal oxygenation. In order to accomplish this, the FHR tracing is analyzed for its baseline rate, degree of variability, and presence of FHR accelerations or FHR decelerations. In 1997, the National Institute of Child Health and Human Development Research Planning Workshop published definitions of FHR patterns (Table 4) [159]. A normal FHR at term is between 110 and 160 BPM. Fetal bradycardia is a FHR baseline less than 110 BPM; fetal tachycardia is a FHR baseline greater than 160 BPM. FHR variability is quantitated as the amplitude of peak-to-trough in BPM. Normal, moderate, amplitude range is 6 to 25 BPM. Accelerations are defined as a visible increase in heart rate, from baseline, occurring in less than 30 seconds. Duration of the acceleration is defined as time from onset to return to baseline. At 32 weeks’ gestation, the acceleration has a peak of 15 BPM or more lasting at least 15 seconds but less than 2 minutes. Prior to 32 weeks, the acceleration has an acme of 10 BPM or more above baseline, lasting for at least 10 seconds but less than 2 minutes. Periodic FHR decelerations are referred to as early, late, or variable. As early and late decelerations occur in association with a uterine contraction, they are not seen during nonobstetric surgery unless uterine contractions begin. Variable deceleration is defined as an abrupt decrease in FHR, time to nadir less than 30 seconds, at least 15 BPM below baseline, and lasting at least 15 seconds but less than 2 minutes. A prolonged deceleration is defined as a decrease in FHR of at least 15 BPM lasting greater than 2 minutes (Fig. 2).

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Fetal heart rate monitoring</th>
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<tr>
<td>Normal fetal heart rate</td>
<td>110 BPM to 160 BPM</td>
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<tr>
<td>Fetal tachycardia</td>
<td>&gt;160 BPM</td>
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<td>Fetal bradycardia</td>
<td>&lt;110 BPM</td>
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<tr>
<td>FHR variability</td>
<td>Amplitude of peak to trough in BPM</td>
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<tr>
<td>Normal</td>
<td>6–25 BPM</td>
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<tr>
<td>Decreased</td>
<td>1–5 BPM</td>
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<tr>
<td>Absent</td>
<td>0 BPM</td>
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<tr>
<td>Increased</td>
<td>&gt;25 BPM</td>
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<tr>
<td>Acceleration</td>
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<tr>
<td>32 weeks and later</td>
<td>Peak at 15 BPM or more lasting 15 seconds to 2 minutes</td>
</tr>
<tr>
<td>Before 32 weeks</td>
<td>Peak at 10 BPM or more lasting 15 seconds to 2 minutes</td>
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<tr>
<td>Prolonged deceleration</td>
<td>Decrease in FHR of at least 15 BPM lasting greater than 2 minutes</td>
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Fetal monitoring was instituted prior to establishment of spinal anesthesia. Baseline FHR was 140 BPM with normal variability; FHR accelerations were noted. The mother was complaining of pain and anxiety; fentanyl (100 mcg) and midazolam (2 mg, IV) in divided doses were administered. Several minutes later, she was feeling more comfortable. The FHR tracing showed minimal variability and no accelerations (Fig. 3).

Normal FHR variability, amplitude range of 6 to 25 BPM, generally is associated with normal fetal oxygenation and pH [160]. Maternal administration of narcotics, IV morphine, meperidine, or nalbuphine is shown to decrease FHR variability and FHR accelerations [161–165]. General anesthesia also is
associated with the loss of FHR variability and accelerations [166,167]. FHR variability monitoring, therefore, is not a useful parameter in predicting fetal oxygenation in nonobstetric surgery performed under general anesthesia or with heavy sedation. It is important to understand the effects of general anesthesia and narcotic analgesia on FHR variability in order to avoid unnecessary cesarean section during nonobstetric surgery [168].

Spinal anesthesia with isobaric bupivacaine, 10 mg, was administered at the L3-4 interspace. A T10 level of anesthesia was achieved. The patient was positioned on the fracture table in the left lateral position and surgery was started. FHR tracing continued to demonstrate minimal variability, with no FHR decelerations noted. Approximately 45 minutes into the procedure, maternal blood loss was estimated at 1000 mL and blood pressure decreased from 110/60 to 80/40 mm Hg. A prolonged FHR deceleration to 70 BPM was noted. The mother was treated with IV phenylephrine, 50 mcg, and a 1000 mL bolus of balanced salt solution. The maternal blood pressure returned to baseline value with a return of the FHR to normal. Maternal hematocrit was noted to be 20% and transfusion of 3 units packed red blood cells was performed. The procedure proceeded uneventfully. There were no further episodes of FHR deceleration (Fig. 4).

Although FHR variability may not be useful as an indicator of fetal hypoxemia, a prolonged deceleration is significant. When the FHR is 60 BPM or less, the fetal cardiac output is minimal and fetal hypoxia may develop. Prompt treatment is needed. In this case, the cause most likely is maternal hypotension resulting from blood loss. Immediate treatment with pressors, crystalloid, and red blood cell transfusion is necessary. The FHR is expected to return to baseline as UBF returns to normal with a rise in the maternal blood pressure. In the absence of prolonged maternal shock, it is unlikely that the fetus will sustain hypoxic injury [169].

Fig. 4. FHR tracing showing prolonged deceleration with recovery.
The value of continuous electronic FHR monitoring of the fetus during non-obstetric surgery in patients who are pregnant is not clear. In a literature review, no cases of fetal hypoxic mortality or morbidity were identified without the occurrence of maternal hypoxic complications regardless of the use of FHR monitoring or whether or not alterations of the FHR tracing were noted [170]. A committee opinion of the American College of Obstetricians and Gynecologists made no specific recommendations regarding the use of intraoperative FHR monitoring. They recommend the decision to monitor the fetus be individualized and, if used, based on fetal gestational age, type of surgery, and available facilities [170].

CASE 3

A 37-year-old G3P2 at 18 weeks presents for an excision of a suspicious breast mass. The pregnancy has been uneventful to date. She is in good health with an unremarkable past medical history. Biopsy is planned under local anesthesia with IV sedation. FHR immediately before the procedure was 155 BPM. As the fetus was not viable and local anesthesia was planned, FHR monitoring was not performed.

Pregnancy-associated breast cancer occurs in approximately 1 in 5000 pregnancies [171]. Although it was feared that the hormonal changes of pregnancy may worsen the prognosis, recent studies find this to be untrue [158]. Biopsy or excision of the mass poses no increased risk to mother and fetus.

Diagnosis and surgery should not be delayed because of pregnancy. Although no large studies have been completed, several case series involving mastectomy, breast-conserving surgery, and axillary surgery suggest that these surgeries can be performed without significant risk to mother and fetus [172]. The safety of sentinel lymph node biopsy during pregnancy is not established, as multicenter trials generally exclude patients who are pregnant. Currently, either technicium 99m or isosulfan blue dye is used for lymphatic mapping. Isosulfan blue dye, however, is a class C drug and not recommended for use in patients who are pregnant [158].

CASE 4

A 23-year-old G1P0 at 22 weeks' gestational presented to the emergency department complaining of the worst headache of her life. MRI of her brain revealed an arteriovenous malformation. A neurosurgical procedure was planned under general anesthesia.

The risk for cerebral infarction or intracerebral hemorrhage is unchanged during pregnancy but increased significantly in the postpartum period [173]. The incidence of brain tumors during pregnancy does not seem to differ from the general population [174]. Specific concerns regarding neurosurgical intervention include controlled hypotension, hypothermia, hyperventilation, and diuresis. The decision for surgical intervention is made independent of a patient’s pregnancy.
Controlled hypotension can be induced with volatile anesthetic, nitroglycerin, and nitroprusside. As UBF is proportional to blood pressure, controlled hypotension may lead to decreased UBF and fetal asphyxia. Prolonged use of nitroprusside may lead to cyanide accumulation in the fetus. Induced maternal hypothermia may lead to fetal bradycardia. Controlled maternal hyperventilation may lead to a respiratory alkalosis, resulting in decreased UBF and impaired delivery of oxygen from the maternal circulation to the placenta. Diuresis should be administered carefully, as maternal hypovolemia may lead to decreased UBF. Although no controlled studies have been performed, neonatal outcome does not seem to be affected by the neurosurgical procedure [174].

The use of intraoperative FHR monitoring is controversial. Successful outcomes are achieved with and without fetal monitoring [175–177]. In all cases, careful attention is placed on maintaining maternal hemodynamics to maximize UBF. As during other surgical procedures performed under general anesthesia, loss of FHR variability is reported during neurologic surgery [178].

CASE 5

A 36-year-old G1P0 was scheduled for emergency mitral valve replacement, at 32 weeks, after developing severe mitral regurgitation after acute bacterial endocarditis. Her past medical history was significant for mitral valve prolapse. The course of her pregnancy was uneventful, with normal fetal growth and health. Mitral valve replacement was performed under general anesthesia with high flow nonpulsatile cardiopulmonary bypass. FHR monitoring was used. Fetal bradycardia was noted after the establishment of bypass. The FHR improved when flow was increased. The procedure and recovery were uneventful. She delivered a healthy newborn at 38 weeks gestational age.

Cardiac disease complicates up to 4% pregnancies in the United States [179,180]. Cardiac surgery in these patients generally is not indicated unless severe impairment of cardiac function exists. In general, it is recommended to delay surgery until the second trimester to avoid any potential teratogenesis associated with the surgery or anesthesia. Arnoni and colleagues do not find an association between gestation age and fetal or maternal mortality [181].

Pomini and colleagues reviewed the literature regarding cardiopulmonary bypass during pregnancy from 1958 to 1991 [182]. Maternal mortality after heart surgery with cardiopulmonary bypass is not different from that in women who are not pregnant. Fetal mortality is reported to be from 12% to 20%. Hypothermia is associated with a 24% fetal mortality, whereas no fetal deaths have occurred after normothermic bypass. They recommend high-flow, normothermic bypass be used to maximize fetal outcome. Their recommendations are in agreement with other investigators’ [181,183].
References
[34] Ralston DH, Shnider SM, deLormier AA. Effects of equipotent ephedrine metaraminol, mephenteramine and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;70:354–70.


It is estimated that between 500,000 and 2 million thromboembolic events occur annually in the United States [1], including deep venous thromboses, myocardial infarctions, thromboembolic strokes, and pulmonary emboli. Although major thrombi often can be lysed with fibrinolytic agents or sometimes can be removed surgically, pharmacologic prevention of thrombus formation in susceptible patients and high-risk situations is clearly preferable. Thus, anticoagulants and antiplatelet agents play a critical role in preventing thrombus formation associated with a variety of disease states, pathologic processes, and clinical situations (eg, thrombus formation on a prosthetic heart valve or in the left atrium of a patient who has atrial fibrillation; deep venous thrombosis [DVT] in the perioperative period after hip arthroplasty or knee replacement).

Although effective for routine purposes, most currently available agents were discovered serendipitously more than a half-century ago and were adopted for widespread clinical use with only a rudimentary understanding of their mechanisms of action and before their potential side effects were fully appreciated. Advances in the knowledge of the physiology of in vivo hemostasis and the pathophysiology of specific disease states have revealed that many of time-honored agents have significant limitations and potentially serious side effects.

One of the biggest problems with the standard agents heparin and warfarin is that they impair hemostasis at a very gross level in the coagulation mechanism. This action sometimes is problematic, because key individual differences exist that result in variable efficacy of therapy and duration of action, mandating close monitoring to ensure therapeutic activity while avoiding hemorrhagic complications.

New agents have been developed that specifically target critical enzymes, receptors, and steps of the coagulation mechanism and that have predictable pharmacodynamics and minimal interindividual variability. Such characteristics often obviate the need for routine monitoring during therapy. These
new agents are classified according to either their specific target of inhibition (eg, factor Xa) or their mechanism of action with respect to thrombin inhibition (direct or indirect; with “indirect” implying a mechanism of action that depends on activation of antithrombin). This article provides a perspective on the limitations and problems of the currently available anticoagulants and antiplatelet agents and reviews the current status of newly developed agents now in human clinical trials.

**THE CURRENT UNDERSTANDING OF COAGULATION: A CELL-BASED MODEL**

The mechanisms affecting normal in vivo hemostasis are complex, with many interrelated pathways and component factors affected by a variety of cellular elements and the endothelium itself. Although the classic intrinsic and extrinsic coagulation pathways do lead to the formation and activation of thrombin (and hence the amplification of coagulation), the traditional model of coagulation as cascades occurring in association with each other and with platelet activation does not account for the critical contributions of cellular components of hemostasis currently believed to take place in vivo. Additionally, an appreciation of the important role played by thrombin in the coagulation cascade is key to an understanding of why the success of any anticoagulation strategy depends on thrombin inhibition.

Cellular hemostasis is thought to occur in three stages: initiation, amplification, and propagation. The initiation stage takes place on tissue-factor–bearing cells (eg, monocytes, which can bind tissue-factor and present it to a ligand) that come into play when endothelial injury occurs and tissue factor is exposed [2]. The initiation stage is characterized by presentation of tissue factor to its ligand, factor VII, and the subsequent activation of factors IX and X on the tissue-factor–bearing cell [3]. The activation of factor X to Xa causes thrombin production and activation. Once generated, thrombin feeds back to activate factors VIII, V, and platelets. Fig. 1 demonstrates these critical zymogen interactions.

![Fig. 1. Classic serine protease interactions leading to the generation of thrombin (factor IIa). Ca, calcium; PK, prekallikrein; Plt, platelet; XL, crosslinked.](image-url)
The amplification stage then occurs on the surface of the activated platelet, which exposes surface phospholipids that act as receptors for the activated factors VIIIa and IXa. The platelet surface allows further thrombin formation and hence the amplification of coagulation. Continued generation and activation of thrombin causes further positive feedback mechanisms to occur that ultimately ensure the formation of a stable clot. These mechanisms include cleavage of fibrinogen to fibrin, release and activation of factor XIII for fibrin cross-linkage [4], and the release of a fibrinolysis inhibitor that can be activated by thrombin. Thrombin also is a potent stimulus for platelet aggregation and causes vasoconstriction. Specific details regarding the critical roles of platelet activation and aggregation are discussed in detail in the later section on antiplatelet agents.

Normally, vascular endothelium provides a surface that prevents platelet adhesion and clotting through several interrelated mechanisms that limit the generation and activity of thrombin. Such mechanisms include

- Endothelial expression of thrombomodulin which, when bound to thrombin, limits thrombin’s ability to activate platelets, factor V, factor VIII, and fibrinogen [2]. Thrombomodulin also binds factor Xa (indirectly inhibiting prothrombinase activity) [5] and facilitates the activation of the anticoagulant protein C [6].
- Endothelial synthesis of protein S, an important cofactor, which enhances protein C activity [7]
- Endothelial expression of tissue factor pathway inhibitor, which binds to factor Xa in the tissue factor/VIIa/Xa complex [8]
- Components of the subendothelial matrix, which promote the localized activity of antithrombin III (e.g., heparan sulfate and glycosaminoglycans) [9] and heparin cofactor II (e.g., dermatan sulfate) [10]
- Release of molecules/substances that tend to inhibit platelet function (e.g., prostaglandin I2 and nitric oxide)

Although the previous discussion merely highlights some of the important concepts governing in vivo hemostasis, it demonstrates the extremely complex and highly regulated balance struck between endogenous anticoagulant and procoagulant activities of a variety of cellular, soluble, and endothelial components. Controlling such a complicated system in the management of patients at risk for thromboembolic complications is challenging and is limited by individual genetic differences and by inherent limitations of the agents used.

**LIMITATIONS OF THE STANDARD AGENTS HEPARIN AND WARFARIN**

Heparin
From its original discovery by Howell in 1922 and its introduction to clinical use in 1937, heparin (named for its abundance in the liver) has been the standard parenteral anticoagulant in the management of venous and arterial thrombotic disease. Although heparin is highly effective, inexpensive, and easily reversible, this time-honored anticoagulant has significant limitations.
The synthesis of heparin from intestine was described in 1933 by Bourin and Lindahl, but heparin actually is an unfractionated assortment of molecules with molecular weights ranging from 5 to 30 kd [11]. Common to these molecules is a pentasaccharide sequence that binds to antithrombin (produced by the liver and naturally present in plasma), greatly potentiating its natural ability to inactivate the serine protease factors IXa, Xa, and IIa (thrombin). An unpredictable dose response occurs with unfractionated heparin, however, because of the variable number of molecules in any given preparation that actually possess the necessary pentasaccharide sequence to bind antithrombin. Additionally, factor Xa and thrombin already bound to platelets are not inactivated, and platelet factor 4 (PF4, released from the α-granule of platelets upon activation) interferes with heparin–antithrombin binding locally [11], neutralizing its anticoagulant effect.

Heparin can be used as an anticoagulant in a variety of clinical situations, but the route of administration tends to differ by indication and is dictated at least partially by convenience. Intravenous administration is routinely used for therapeutic anticoagulation during cardiac and vascular surgery and in hospitalized patients at high risk of vascular thrombosis. Subcutaneous administration is generally used to prevent DVT in high-risk patients (eg, patients who have undergone hip arthroplasty, have cancer, or are immobile). Unfortunately, an oral formulation of heparin is not used because of its intrinsic instability under acidic conditions and poor absorption by the gastrointestinal mucosa. The impossibility of oral administration significantly limits prophylactic outpatient use of heparin, because parenteral administration is often inconvenient, uncomfortable, and relatively expensive. Although formulations employing specialized delivery systems and penetration enhancers are under development [12], none are routinely available at this time. Subcutaneously administered DVT prophylaxis during pregnancy is one of the few common outpatient uses of heparin (because of the contraindication to warfarin during pregnancy, as discussed later).

Heparin must be cleared from the plasma by the reticuloendothelial system, metabolized by the liver, and excreted by the kidneys. The duration of action of heparin is related directly to the dose administered (eg, 100 U/kg and 400 U/kg intravenous doses are cleared with half-lives of 1 and 2.5 hours, respectively) [11], assuming normal reticuloendothelial system, hepatic, and renal function.

The anticoagulant activity of heparin is most commonly monitored by its prolongation of the activated partial thromboplastin time (aPTT); a value 1.5 to 2.5 times normal is considered therapeutic. Determination of the activated clotting time (ACT) and plasma heparin concentration are of value in certain clinical situations (eg, cardiac surgery). It also is possible to monitor the antithrombotic activity of heparin by monitoring anti-Xa activity, although this assay is not performed routinely in most clinical care settings. As previously mentioned, interindividual differences exist, and the precise dose of heparin required to produce a desired therapeutic elevation of the aPTT varies
because of differences in concentrations of plasma heparin-binding proteins (eg, vitronectin, and PF4) that may competitively inhibit heparin binding to antithrombin [11]. When a desired aPTT elevation fails to occur despite appropriate heparin administration, different assays may be necessary to differentiate between true and apparent heparin resistance. True resistance stems from inherited or acquired deficiencies of antithrombin (eg, in cirrhosis or nephrotic syndrome), from rapid clearance of the drug, or potentially from nonspecific heparin binding to white blood cells, vascular endothelial cells, and acute-phase proteins [1]. Apparent resistance (often caused by elevated factor VIII levels [1]) is a phenomenon caused by a limitation of aPTT monitoring, because ostensibly therapeutic concentrations of heparin may be present in the plasma as determined by anti-Xa assay or protamine sulfate titration. Although the use of very high or repeated bolus doses of heparin ultimately may produce a desired aPTT in this situation, the risk of bleeding is increased dramatically.

Hemostatic competence can be restored after heparin administration with the administration of protamine sulfate. Classically, 1 mg of protamine sulfate is administered intravenously to reverse 100 U of heparin. Protamine administration is not benign in all patients, however. Potential adverse effects often are related to the rate of administration (eg, vasodilatory hypotension, increased pulmonary vascular resistance with potential right ventricular failure) but also include anaphylactic and anaphylactoid reactions.

A major problem with heparin is its undesirable effect on platelets. Heparin is known to activate platelets, causing aggregation and mild consumptive thrombocytopenia (although the lower molecular weight fractions tend to have less pro-aggregatory properties) [13,14]. This effect often leads to the clinical syndrome of heparin-induced thrombocytopenia type I (HIT I). This fairly benign process usually occurs early in the course of heparin exposure and is characterized by a mildly reduced platelet count. Platelet counts below 100,000 mm$^3$ may be expected in 1% to 5% of patients within 7 to 14 days after initiation of full or low-dose therapy [15]. This thrombocytopenia generally resolves with discontinuation of heparin therapy.

In certain patients, however, the binding of heparin to PF4 generates an immune response with production of antibodies against PF4. Although IgG, IgM, and IgA antibody subtypes all have been demonstrated to be produced, the IgG subtypes seem to be most pathogenic [16–18]. The IgG subtypes strongly activate platelets by binding through their Fc receptors, resulting in severe thrombocytopenia [19,20] and a procoagulant state [21,22]. In addition, the PF4 released from activated platelets binds to heparin-like glycosaminoglycans on the surface of endothelial cells in vascular beds. HIT-IgG antibodies subsequently bind to the endothelium-bound PF4, resulting in complement-mediated endothelial damage that exposes tissue factor, triggering hemostasis locally and predisposing the patient to intravascular thrombosis [23,24].

This potentially serious syndrome is heparin-induced thrombocytopenia type II (HIT II). The overall risk of HIT-associated thrombosis is about 75%, ranging from a low of 50% in patients who have mild thrombocytopenia
(platelet nadir 100,000/μL), to a high of 90% in patients who have more severe thrombocytopenia (platelet nadir 30,000/μL) [25]. Both venous and arterial thromboses are observed in patients who have HIT II, and the risk is not always negated by cessation of heparin therapy [26]. Venous thrombosis is most common, especially DVT of the legs and pulmonary embolism [25,27,28]. DVT in the arms is strongly associated with the presence of upper body central venous access. Arterial thrombosis occurs most often in the legs, followed by thromboembolic stroke and myocardial infarction [25]. Mortality in patients who have HIT-associated thromboses approaches 50%.

Warfarin
The history of warfarin began in 1924 with a previously unknown hemorrhagic disorder in cattle that had ingested partially fermented sweet clover in their feed [11]. The cause eventually was identified in 1939 by Campbell and Link as bishydroxycoumarin. By 1948, this identification was parlayed into a very effective rat poison named “warfarin” (an acronym derived from the name of the patent holder, the Wisconsin Alumni Research Foundation, with “arin” taken from coumarin). Although it was realized in the medical community that this agent could be effective in treating thromboembolic disease in humans, fear of excessive hemorrhage prevented its adoption for use. This attitude changed in 1951, however, when an unhappy military draftee survived an attempted suicide with the rat poison. Since that time, warfarin sodium has been the cornerstone of oral anticoagulation therapy, but the concern for bleeding complications remains.

Warfarin sodium is a member of a family of compounds that act as vitamin K antagonists. Hepatic vitamin K activity allows the production of biologically active forms of the coagulation factors II, VII, IX, and X as well as the regulatory proteins C and S. In the presence of vitamin K, carboxylation of glutamic acid residues in the amino terminus of these proteins confers calcium-binding properties that are essential to their respective functions in hemostasis. Warfarin therapy decreases the production of biologically active forms of the vitamin K–dependent proteins, but those produced before the onset of therapy remain active until they are cleared from the circulation, resulting in a variable delay from initiation of therapy to achievement of therapeutic anticoagulation. The reported half-lives for the vitamin K–dependent factors are 6 hours for factor VII, 8 hours for protein C, 24 hours for factor IX, 30 hours for protein S, 36 hours for factor X, and 50 hours for factor II [11]. Thus, achieving anticoagulation with warfarin generally takes several days. Additionally, functional levels of protein C fall significantly earlier than levels of factors X and II, potentially resulting in a short-lived prothrombotic state. The protein C/S complex is an important regulator of coagulation, limiting thrombin formation and promoting clot dissolution. Clearly, potential hypercoagulability in a patient who requires anticoagulation is clinically counterproductive, and often maintenance anticoagulation with another agent (eg, unfractionated heparin
[UFH], low molecular weight heparin [LMWH]) is initiated during this interval.

Once an adequate level of anticoagulation is achieved, chronic anticoagulation with warfarin is administered orally with a dosing schedule (e.g., daily, every other day, or some other schedule) determined by the patient’s response to the compound. Warfarin, however, has a narrow therapeutic index with significant potential for bleeding complications; one of the significant limitations of warfarin is the need for frequent monitoring of the level of anticoagulation to maintain adequate anticoagulation while avoiding bleeding. The need for frequent phlebotomy is inconvenient and uncomfortable for patients, and the monitoring tests themselves have limitations, as described here.

Warfarin therapy is monitored by the prothrombin time (PT) in conjunction with the international normalized ratio (INR). The PT is prolonged if functional levels of factors V, VII, X, II, or fibrinogen are decreased, but the assay itself is most affected by levels of factors VII and X and much less so by factor II levels [29]. Additionally, the amount of prolongation can vary considerably among individuals and laboratories. This potential variation has several origins, including the manner in which laboratories collect, handle, and store the samples, but a major issue is the source of thromboplastin used to perform the assay, because not all sources of thromboplastin provide adequate sensitivity to detect small changes in factor activity levels. Laboratories primarily using rabbit-derived thromboplastin may underdetect small decreases in factor activity levels, potentially resulting in overdosing of warfarin [11]. Thus, the INR was adopted.

The INR is a ratio of the patient PT to a reference PT (established by using a standardized World Health Organization source of human thromboplastin). An INR above 1.2 is expected to occur when levels of factor VII are reduced to 55% of baseline. A further decrease in these levels to 40% of baseline correlates with an INR of 1.5 [11]. The target INR for warfarin therapy typically is in the range of 2.0 to 3.0 (unless the patient has a prosthetic heart valve, in which case the INR is maintained in the range of 2.5–3.5). Attaining an appropriate PT prolongation while avoiding overshoot is critical, because the severity of bleeding complications correlates directly with the intensity of warfarin anticoagulation [30–33]. Although all bleeding complications are potentially serious, the risk of intracranial hemorrhage has been shown to increase dramatically with an INR above 4.

The PT/INR must be monitored carefully during the initiation of anticoagulation and frequently thereafter for the duration of maintenance therapy, with adjustments to warfarin dose and dosing schedule based on individual response. Additionally, there are numerous drug interactions, coexisting medical problems, concomitantly administered medications (especially certain antibiotics), and other factors that can alter plasma levels of warfarin rapidly as a result of competition for cytochrome P-450 metabolism of warfarin, displacement of warfarin from albumin, and (in the specific case of antibiotics) an alteration of normal colonic flora (a usual source of endogenous vitamin K).
A review by Hylek and colleagues [34] identified several risk factors associated with developing an INR of 6.0 or greater during outpatient warfarin therapy:

- Acetaminophen intake (taking the equivalent of 325 mg/d for 1 week increased the risk 10-fold)
- Acute diarrheal illness
- Coexisting advanced malignancy
- Decreased oral intake, changes in prescribed warfarin dose
- Moderate alcohol consumption (defined as the range of one drink every other day to two drinks per day)
- Excessive actual warfarin intake

Factors found to limit the risk of developing an excessive INR included increased intake of vitamin K and alcohol use that was either minimal (1–2 drinks per week) or excessive (> 2 drinks per day or binge drinking).

Just as with initiation of therapy, the rate of normalization of the INR with cessation of warfarin therapy is highly variable [35,36]. This unfortunate reality often creates problems in the perioperative period, especially when a regional anesthetic technique is planned. Current recommendations are to discontinue warfarin therapy 4 or 5 days before a planned procedure, but not all patients will have restored hemostatic competence after this time. Measurement of the INR is helpful to assure readiness for surgery (or a regional anesthetic). Soon after cessation of warfarin administration, the INR begins to normalize, primarily because of return of factor VII levels, but adequate levels of factors X and II take longer to return. Although most practitioners accept an INR below 1.4 as sufficient, full hemostatic competence cannot be assumed until the INR is fully normalized (< 1.2). Although vitamin K (phytonadione) can be administered safely to hasten INR recovery [29], recovery will take a few days. When necessary, fresh-frozen plasma can be infused preoperatively or intraoperatively to normalize the INR more rapidly by replacing biologically active forms of the vitamin K–dependent proteins.

Current recommendations from the American Society of Regional Anesthesia (ASRA) [37] urge caution when performing neuraxial anesthesia in patients who have recently discontinued warfarin therapy. Among the numerous specific recommendations in their consensus statement is a reminder regarding the potential synergy between warfarin and other commonly used anticoagulants and antiplatelet agents. Hemostatic defects can exist despite a normal value of a given, single coagulation assay (eg, the PT/INR). These cautions are echoed in a recent review by Tai and colleagues [38]. Although (as discussed later) they reported a complication of hypercoagulability during warfarin therapy in a patient receiving concurrent LMWH therapy, this case serves as a reminder that, by themselves, common measures of anticoagulation (eg, PT, aPTT) do not give a full picture of coagulability.

Pregnancy is characterized by a well-recognized prothrombotic state often requiring anticoagulant therapy. DVT with pulmonary embolism is a major
cause of morbidity and mortality during this time, reportedly complicating as many as 1:1000 pregnancies [39], although there is some indication that the true incidence may be much higher [40]. Pregnant women who have prosthetic heart valves are at especially high risk for thrombotic complications. Unfortunately, warfarin cannot be used safely during pregnancy because of warfarin embryopathy. This syndrome consists primarily of nasal hypoplasia and epiphyseal stippling in the developing fetus, with intermittently associated abnormalities of the central nervous system and eyes; however, there also is a risk of fetal demise [41,42]. The risk may be greatest between weeks 6 and 12 of gestation and may reflect the effect of warfarin on a vitamin K–dependent bone matrix protein, osteocalcin. Most practitioners therefore prescribe subcutaneous UFH for pregnant women who are at high risk of or who have documented DVT, although there are data suggesting that this prophylaxis may be suboptimal in the presence of a prosthetic heart valve [43,44].

In addition to the numerous issues already discussed, a range of adverse dermatologic manifestations occur with warfarin therapy, typically ranging from relatively benign ecchymoses and purpura to vesicular urticarial eruptions. Warfarin-induced skin necrosis is an uncommon but potentially serious complication, typically occurring within 3 to 6 days of initiation of warfarin therapy, although there are cases reported after a few weeks [45]. Since its initial description by Flood and colleagues [46] in 1943, only a few hundred cases have been reported. The proposed mechanism is based on the early decline of protein C levels with initiation of warfarin therapy (especially in patients who have protein S deficiency), although inherited and acquired deficiencies of protein C, protein S, and antithrombin III have all been associated with this occasionally devastating hypercoagulable complication [47–49]. Factor V Leiden (a common inherited cause of hypercoagulability) has not been associated with warfarin-induced skin necrosis [50]. The “purple-toe syndrome” is an uncommon syndrome described in patients receiving warfarin who have underlying atherosclerotic vascular disease [51].

Thus, although warfarin is a highly efficacious agent, its use is associated with unpredictable pharmacokinetics and pharmacodynamics, multiple interactions with concurrent medications, food, and alcohol, a narrow therapeutic index, and the need for INR monitoring and dose adjustments throughout therapy. Additionally, there are common states in which it is needed but contraindicated (eg, pregnancy), and there are potentially serious adverse reactions.

**ALTERNATIVES TO HEPARIN AND WARFARIN**

For all the reasons discussed in the previous section, alternative agents that more specifically inhibit various steps of the coagulation mechanism have been developed. These alternatives include both parenteral and oral antithrombotic and antiplatelet agents. As knowledge of in vivo hemostasis and vascular physiology has grown, it has become clear that effective prevention of thrombosis depends on the vascular bed in which it may occur. Antiplatelet agents
play a major role in the management of arterial thromboses, whereas venous thrombi often can be prevented by the use of agents that inhibit generation of thrombin and fibrin. The following sections discuss both currently available and recently developed agents. Many of the new agents are still being investigated in human clinical trials, and experience with these agents remains somewhat limited.

**ANTITHROMBOTIC AGENTS**

Low molecular weight heparins

LMWHs are a mixture of molecules with molecular weights of 1 to 10 kd derived from UFH. As such, not all LMWH preparations are composed of the same fractions of heparin molecules, and therefore different preparations have somewhat different properties (including different propensities to cause bleeding). Although they bind antithrombin through the same pentasaccharide sequence as UFH, LMWHs exert their anticoagulant activity primarily through their anti-factor Xa activity [11]. Peak anti-Xa activity occurs 3 to 4 hours after a subcutaneous LMWH injection, and significant anti-Xa activity persists up to 12 hours later.

In comparison with UFH (which has an anti-factor Xa:antithrombin activity ratio of 1:1), first-generation LMWHs (eg, enoxaparin, dalteparin) have reported ratios in the range of 2:1 to 4:1 [1], and a recently developed second-generation LMWH (bemiparin) has a reported ratio of nearly 8:1 [52]. The efficacy and safety of bemiparin is currently the subject of human clinical trials [53]. Additionally, in comparison with UFH, LMWHs have greater bioavailability [54,55] a decreased incidence of bleeding complications [56–59], less nonspecific binding [54,60], and longer, non–dose-dependent half-lives making once- or twice-daily dosing based on body weight possible without the need for routine laboratory monitoring [61,62].

Monitoring of anti-Xa activity may be prudent in certain situations because, despite their demonstrated advantages, LMWHs retain some of the limitations of their parent class of UFH. For example, LMWHs are cleared through the kidneys, mandating caution in patients who have renal insufficiency [63]. If reversal of anticoagulant activity is required, LMWHs are only partially neutralized by protamine sulfate [64,65]. Protamine reverses the anti-IIa effect of LMWHs but not the anti-Xa effect. Further, given the inherent differences between different LMWH preparations, the degree of actual reversal achieved with protamine is variable and seems to correlate with the degree of sulfation of the LMWH preparation [66,67]. Idiosyncratic and autoimmune thrombocytopenia can still occur with LMWHs [68], although the incidence is reportedly less than with UFH [69–71].

Since their introduction to clinical practice in the United States in 1993, a major use of LMWHs has been prophylaxis against DVT in the surgical population. When prophylactic anticoagulation is not provided, DVT may develop in 40% to 80% of patients after total knee replacement and in 40% to 60% after hip replacement. The thrombosis is proximal in as many as 20% of these
patients [72]. Upwards of 7% suffer pulmonary embolism [73,74], and that embolism is fatal in approximately 0.2% to 0.7% [75–77]. Clinical trials have demonstrated that LMWHs prevent DVT [78] and actually are more efficacious than UFH, with lower rates of bleeding complications [56–59]. LMWHs also are more effective than warfarin in decreasing the incidence of DVT but at a cost of increased bleeding complication rates [79–82]. Thus, as discussed by Conduah and colleagues [54], there must be a balance between efficacy and safety when choosing an agent for DVT prophylaxis.

Although the lack of a need for routine monitoring makes LMWHs appealing, the timing of the administration of these agents must be carefully planned. The benefits of epidural and/or spinal anesthesia for patients undergoing vascular surgery [83], orthopedic surgery [84], general abdominal surgery [85], and labor analgesia are well described, but LMWHs have been associated with central neuraxial bleeding in the perioperative period when epidural and/or spinal anesthetics were employed [86]. Clearly, anticoagulation with UFH and warfarin also has the potential to cause neuraxial bleeding, but their anticoagulant activity is generally monitored in the perioperative period, facilitating the timing of the initiation of central neuraxial blockade and also the timing of removal of an epidural catheter, an important risk factor for epidural bleeding [87,88]. As reviewed by Horlocker [88], both the dose and the dosing regimen (eg, daily versus twice-daily administration) may account for the relatively higher number of central neuraxial hematomas associated with LMWHs observed in the United States as compared with the European experience. Although the true incidence of neurologic dysfunction resulting from such bleeding complications is unknown, the literature reports the incidence as less than 1 per 150,000 epidural and less than 1 per 220,000 spinal anesthetics [89].

Current ASRA recommendations regarding the perioperative use of LMWHs in the setting of central neuraxial blockade are as follows [37]:

1. The smallest effective dose of LMWH should be administered perioperatively.
2. Initiation of LMWH therapy should be delayed for 24 hours postoperatively when blood is present during needle and catheter placement.
3. In the setting of twice-daily dosing of a LMWH, indwelling catheters should be removed before initiation of LMWH thromboprophylaxis, with the first dose of LMWH administered at least 2 hours after catheter removal.
4. In the setting of single daily dosing, indwelling catheters can be safely maintained, but the catheter should be removed no sooner than 10 to 12 hours after the last dose of LMWH.

Pentasaccharides—selective factor Xa inhibitors

As discussed previously, the mechanism of action of UFH and the LMWHs involves binding of a pentasaccharide sequence to antithrombin, greatly potentiating its natural inhibition of thrombin as well as of factors IXa and Xa. Although LMWHs act primarily through anti-Xa activity, their action is not selective. In contrast, fondaparinux (Arixtra, GlaxoSmithKline, Philadelphia, PA, USA) is a recently approved synthetic pentasaccharide that causes
antithrombin-mediated selective inhibition of factor Xa. Fondaparinux does not inhibit thrombin or affect platelet function. This agent has a bioavailability of 100% and a half-life of 15 hours after subcutaneous injection [90]. The major route of elimination is urinary excretion of unchanged drug. According to the manufacturer, patients who have renal impairment exhibit prolonged clearance in proportion to their decrease in creatinine clearance. Prolonged elimination is also seen in patients older than 75 years and weighing less than 50 kg. Predictable pharmacokinetics and low inter- and intraindividual variability allow once-daily dosing and make monitoring unnecessary [91].

Fondaparinux does not bind to PF4 and does not seem to elicit or interact with HIT antibodies; therefore it may result in less HIT than UFH and LMWH [92]. Although it is not yet approved for use as an alternative anticoagulant in patients who have HIT, there is a small experience with this agent for this purpose [93]. Additionally, the synthetic nature of this type of agent may address theoretical concerns regarding the transmission of animal diseases to humans (potentially possible with UFH and LMWHs). Idraparinux, a metabolite of pentasaccharide, is currently the subject of human clinical trials. This agent has a half-life of 130 hours, which may facilitate once-weekly dosing for primary or secondary prevention of thromboembolic events [94].

Fondaparinux is approved currently in the United States for perioperative DVT prophylaxis after major orthopedic surgery (eg, hip or knee replacement, hip fractures) and in the treatment of DVT and pulmonary embolism. Clinical trials have demonstrated that fondaparinux is more effective than enoxaparin for the prevention of perioperative venous thromboembolism in patients undergoing orthopedic surgery [95–99]. A recently conducted trial of 2048 high-risk patients undergoing major abdominal surgery found similar efficacy of postoperative fondaparinux and perioperative dalteparin in the prevention of perioperative DVT [100]. Although a trend toward higher rates of bleeding was noted in the fondaparinux group, this trend did not reach statistical significance. Fondaparinux was also demonstrated to be “noninferior” to enoxaparin and UFH for the treatment of patients who had DVT and pulmonary embolism, respectively [101,102]. The Michelangelo Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial currently assigns patients randomly to receive either fondaparinux or enoxaparin in the management of acute coronary syndromes [103].

The risk of fondaparinux regarding neuraxial hematoma in the setting of regional anesthesia is unknown at this time because of limited clinical experience with the agent. There is a black box warning (Fig. 2) in the package insert similar to that of the LMWHs and heparinoids [104]. Current ASRA recommendations regarding the perioperative use of fondaparinux in the setting of central neuraxial blockade are as follows [37]:

Until further clinical experience is available, performance of neuraxial techniques should occur under conditions utilized in clinical trials (single needle pass, atraumatic needle placement, avoidance of indwelling neuraxial
Catheters). If this is not feasible, an alternate method of [DVT] prophylaxis should be considered.

Heparinoids

Heparinoids were among the first heparin alternatives available but are infrequently used in clinical practice. Dermatan sulfate acts as an anticoagulant by activating heparin cofactor II. Danaparoid is a glycosaminoglycan mixture derived from porcine intestinal mucosa composed of heparan sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate (4%). Danaparoid has an anti-factor Xa:antithrombin activity ratio higher than 22:1. The use of danaparoid has been limited, however, by its long half-life, difficulty in monitoring anticoagulant levels, and its potential to cross-react with HIT antibody (5%–20%) [105]. Interest in these compounds as potential antimetastasis and antirestenosis agents has resurfaced recently [106].

Direct thrombin inhibitors

Direct thrombin inhibitors (DTI) are perhaps the most promising alternatives to UFH because of their highly specific mechanism of action. There are three sites on the thrombin molecule on which antithrombin agents can potentially act to inhibit thrombin function: the active (catalytic) site, exosite-1 (which ensures proper alignment and orientation of substrate molecules), and exosite-2 (the binding site for indirectly acting thrombin inhibitors, such as the heparin/antithrombin-III complex) [107–109]. Available DTIs bind either to the

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**Fig. 2.** Black box warning included in the Arixtra package insert. (From ARIXTRA: A black box warning. Available at: www.fda.gov/medwatch/SAFETY/2004/may_PI/Arixtra_PI.pdf. Accessed January 30, 2006.)
active site (eg, argatroban, melagatran) or to both the active site and exosite-1 (hirudin, lepirudin, bivalirudin). Unlike heparin, which acts to inhibit only free (fluid-phase) thrombin, DTIs inhibit both free and fibrin-bound thrombin. This activity is advantageous because in addition to inhibiting thrombin-mediated fibrin formation, DTIs also indirectly inhibit the activation of cofactors V, VII, and XIII, as well as thrombin-mediated platelet activation [110].

**Argatroban**

Argatroban (GlaxoSmithKline, Philadelphia, PA, USA) is a DTI approved for use as an alternative anticoagulant to heparin for patients who have HIT. This agent is a synthetic derivative of arginine that binds the catalytic site of thrombin, inhibiting both free and fibrin-bound forms. The half-life is approximately 40 minutes, and the agent is metabolized in the liver with biliary elimination. Thus, argatroban may be an advantageous agent in the patient who has renal insufficiency. Argatroban therapy is initiated (with or without a loading dose) with an intravenous infusion at 2 \( \mu \text{g/kg/min} \) (0.5 \( \mu \text{g/kg/min} \) if there is hepatic insufficiency), and the dose is then adjusted to maintain the aPTT 1.5 to 3 times normal (although the ACT also may be used to guide therapy). Hemostatic competence is restored within 2 to 4 hours after discontinuation of argatroban infusion [111,112].

Although the main indication for argatroban is as an alternative anticoagulant to heparin for patients who have HIT, its use has been well described in patients undergoing interventional cardiology procedures, and it has been investigated as a heparin alternative in patients who have acute coronary syndromes, unstable angina, and thromboembolic stroke. In general, such investigations have found an efficacy similar to heparin, although some have reported a tendency to fewer bleeding complications [113–116].

**Hirudin and lepirudin**

Hirudin, a DTI isolated from the salivary glands of the medicinal leech *Hirudo medicinalis*, was the first parenteral anticoagulant used in humans (1909) [117] and the first anticoagulant used for hemodialysis (1926) [118]. Unlike heparin, hirudin directly inhibits clot-bound thrombin as well as fluid-phase thrombin, does not require a cofactor (eg, antithrombin) and is not susceptible to neutralization by PF4. These characteristics would seem beneficial for patients in whom platelet activation and thrombosis is a hallmark of the disease of HIT [119]. Hirudin is a small molecule (7 kd) that is eliminated by the kidney and can be filtered or dialyzed easily.

Monitoring the effects of hirudin and other DTIs is reportedly accurate using the ecarin clotting time. This clotting time was a modified test used in a clot-based platform of testing that is no longer manufactured or commercially available [120]. Thus, point-of-care monitoring of thrombin inhibition has not been aggressively studied [121,122]. Plasma drug levels can be obtained but are not available with rapid turnaround times. Hirudin is prepared as a recombinant product (r-hirudin) called lepirudin (Refludan, Sanofi-Aventis, Paris, France).
Like argatroban, the main use of lepirudin is as an alternative anticoagulant to heparin for patients who have HIT syndromes. This indication was established by two multicenter trials with historical controls [123,124]. Lepirudin has a short half-life (1.5 hours), is renally cleared, and may be monitored by the aPTT. Current lepirudin dosing recommendations for acute HIT management are 0.4 mg/kg as an intravenous bolus followed by 0.15 mg/kg/h (up to 110 kg). The target aPTT is 1.5 to 2.5 times the median value for the normal range.

Lepirudin has been used as an anticoagulant during cardiopulmonary bypass for patients who have HIT. An algorithm for lepirudin use in this setting was devised by Pöttsch and Madlener [125]. Outpatient subcutaneous lepirudin has been used to treat patients who have HIT and patients refractory to other anticoagulant therapy. Lepirudin also has demonstrated utility as a primary anticoagulant in the settings of acute coronary syndromes without ST elevation [126–128] and acute myocardial infarction [129–133].

Major clinical issues with lepirudin treatment include the lack of an antidote, exaggerated effects in patients who have renal insufficiency, and the potential for an immune response to the compound. Significant reductions in both loading dose and maintenance infusion rate are necessary in patients who have decreased creatinine clearance, and it may be prudent to avoid lepirudin altogether in patients receiving dialysis. Approximately 40% of patients who have HIT and who are treated with lepirudin develop IgG antihirudin antibodies that decrease renal elimination of the drug rather than exerting any in vivo neutralizing effect. This development results in an increased intensity of anticoagulation that necessitates a reduction in the rate of infusion. Recommended lepirudin dosing regimens and target aPTT values for various indications and functional renal status are available [134].

**Bivalirudin**

Bivalirudin (Angiomax, The Medicines Company, Parsippany, NY, USA) is a small, 20–amino acid molecule, with a plasma half-life of 24 minutes. It is a synthetic derivative of hirudin and thus acts as a DTI. Bivalirudin binds to both the catalytic binding site and the anion-binding exosite on fluid-phase and clot-bound thrombin [135]. The part of the molecule that binds to thrombin actually is cleaved by thrombin itself, so the elimination of bivalirudin activity is independent of specific organ metabolism. Bivalirudin has been used successfully as an anticoagulant in interventional cardiology procedures as a replacement for heparin therapy [136,137]. In this setting, bivalirudin has been associated with less bleeding and equivalent ischemic outcomes than seen with heparin plus a platelet inhibitor [138]. This reduced bleeding may result from bivalirudin’s being both an antithrombin anticoagulant and an antithrombin at the level of the platelet. Merry and colleagues [139] showed equivalence with regard to bleeding outcomes and an improvement in graft flow after off-pump cardiac surgery when bivalirudin was used (0.75 mg/kg bolus; 1.75 mg/kg/h infusion) [139]. Case reports confirm the
safety of bivalirudin use during coronary bypass surgery, and clinical trials are underway.

The rise and fall of ximelagatran

Oral drug administration is clearly preferable for patients who require long-term outpatient anticoagulation (eg, in the setting of atrial fibrillation, a prosthetic heart valve, or indwelling coronary artery stent). Since its introduction into clinical use in the early 1950s, warfarin has been the standard oral anticoagulant. As discussed previously, however, significant limitations and potentially serious risks are associated with its use.

Ximelagatran (Exanta, AstaZeneca, Wilmington, DE) is the first new oral anticoagulant developed in more than half a century. Once absorbed (peak levels are reached in 15–30 minutes), ximelagatran is converted to the DTI, melagatran (peak levels are reached in 1 to 2 hours), which exhibits a plasma half-life of approximately 2.5 to 3.5 hours in healthy volunteers [140,141]. Melagatran binds to the active site of thrombin resulting in inhibition of thrombin-mediated activation of coagulation factors and platelets. Like the other DTIs, melagatran inhibits both free and clot-bound thrombin but theoretically has a superior benefit:risk ratio because its small size and univalent binding to only the active site give it better access to fibrin-bound thrombin [142]. In contrast to warfarin, it has no major reported food or drug interactions and does not require therapeutic monitoring. There is, in fact, no routinely performed test of coagulation that could be used reliably; melagatran prolongs the PT, the aPTT, the ecarin clotting time, and the thrombin time, but the prolongations seen are highly variable, making these assays unsuitable for melagatran monitoring [143,144]. In contrast to warfarin, ximelagatran has a wide therapeutic index (risk of bleeding is not significantly increased with increased dose in the usual range) as well as predictable and stable pharmacokinetics regardless of body weight, age, sex, or ethnicity [141,145,146]. Although melagatran does not undergo metabolism in vivo, it does require 80% renal elimination, and caution is needed when treating patients who have even mild renal insufficiency. It is contraindicated in patients who have creatinine clearance less than 30 mL/min [147]. Although there is no specific antidote, the effects of melagatran can be attenuated by recombinant factor VIIa [148], dialysis, and hemofiltration [149].

As a potential replacement for oral anticoagulation with warfarin, proposed indications for this promising new oral anticoagulant include prevention of DVT and other vascular thromboses in high-risk settings (eg, after orthopedic surgery) as well as secondary prevention and treatment of acute venous thromboses and chronic management of atrial fibrillation. Another possible indication is as an alternative anticoagulant for patients who have HIT.

The safety and efficacy of ximelagatran for the secondary prevention and acute treatment of venous thromboembolism was assessed in the Thrombin Inhibitor in Venous Thromboembolism (THRIVE) trials conducted in primarily European centers. Overall, the THRIVE trials demonstrated that twice-daily ximelagatran is “as effective as standard therapy” for the acute treatment...
and secondary prevention of venous thromboembolic events, with fixed dosing and no requirement for anticoagulation monitoring [150–152]. A statistically significant cumulative risk of transient elevation in liver function tests (alanine aminotransferase levels more than three times the upper limit of normal) was demonstrated in the ximelagatran group (compared with the placebo group in THRIVE III), however [153]. In patients in whom the elevated enzyme levels normalized, normalization followed a similar time-course regardless of whether the administration of the drug was stopped, and there was no pattern of symptoms or signs in patients who had elevated levels.

For prevention of DVT associated with lower extremity orthopedic surgery, the Melagatran Thromboprophylaxis in Orthopedic Surgery (METHRO) and Expanded Prophylaxis Evaluation Surgery Study (EXPRESS) trials investigated various doses of melagatran/ximelagatran and timing of initiation of perioperative prophylactic anticoagulation in comparison with standard European LMWH prophylaxis (eg, with dalteparin or enoxaparin) [154,155]. Taken together, these trials demonstrated the efficacy of ximelagatran for prevention of perioperative DVT and also established that both the timing and dosing of melagatran/ximelagatran are important determinants of safety. The favorable results of these large trials allowed the approval of melagatran/ximelagatran in the European Union in 2004 for DVT prevention in patients undergoing elective knee or hip replacement.

Trials conducted mostly in North American centers compared ximelagatran with warfarin prophylaxis in orthopedic surgical patients. Both agents were shown to decrease the incidence of venous thromboses and pulmonary embolism with similar efficacy in 680 patients undergoing knee surgery [156]. It was concluded that ximelagatran is at least as effective as warfarin but without the need for monitoring. The subsequent large Exanta Used to Lessen Thrombosis (EXULT) trials compared ximelagatran with warfarin in more than 4600 patients undergoing knee replacement surgery [157,158]. These trials had extremely complicated designs (eg, double-blinded, double-dummy, parallel-group comparison) and assessed the optimal dosing of ximelagatran. Although the large number of subjects ostensibly provided sufficient power to demonstrate superiority of ximelagatran over warfarin, it was also sufficient to reveal a potentially adverse effect of the medication, because there was a trend toward a higher incidence of posttreatment cardiovascular events (eg, myocardial infarction) in the groups that had received ximelagatran. Another interesting finding was that although ximelagatran (in the higher-dose group) reportedly demonstrated superiority over warfarin in “reducing the incidence of a composite primary end point of all venous thromboembolic events and death,” no significant differences were detected among the groups in the secondary end points: proximal DVT, symptomatic DVT, pulmonary embolism, and death. Examination of the published data shows that the apparent superiority of the higher-dose ximelagatran over warfarin was driven by a highly significant reduction in the incidence of asymptomatic distal DVT; the clinical significance of this finding has been questioned.
Ximelagatran also was demonstrated to be “not inferior” to warfarin in the setting of chronic nonvalvular atrial fibrillation by the Stroke Prevention using Oral Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trials [159,160] that enrolled more than 7500 patients in 24 countries. As seen in the THRIVE trials, however, transient elevations in hepatic alanine transferase were detected in significantly larger percentages in the ximelagatran groups of the SPORTIF trials. The incidence of major bleeding episodes was not different between agents in the two trials, although a significant decrease in minor bleeding allowed reporting of a significantly decreased overall incidence of bleeding in the ximelagatran groups.

Despite the efficacy of ximelagatran for a variety of indications demonstrated in these clinical trials, the Food and Drug Administration failed to approve ximelagatran for use in the United States, primarily because of concerns about the safety of the agent [161]. The main safety concerns expressed by the agency in their decision to deny the drug application included

- The increased incidence of bleeding with ximelagatran in some of the trials
- The increased hepatic alanine transferase levels, with a sevenfold higher event rate in the ximelagatran group than in the warfarin group during follow-up periods, and the unknown effect on liver toxicity beyond 4 to 6 weeks
- A higher proportion of adverse coronary events that occurred after stopping treatment with ximelagatran compared with warfarin or placebo

The advisory committee ultimately concluded that the benefits of ximelagatran therapy for any of the three indications under consideration did not outweigh the risks, particularly of liver failure.

**ANTIPLATELET AGENTS**

Once the initiation of coagulation has occurred, there is a rapid movement to the acceleration phase, in which platelets play a key role. Platelets are activated by exposure to collagen, tissue factor, and other agents released from damaged tissue and injured endothelium. The unstimulated platelet, which is discoid in shape, undergoes a conformational change when activated. The activated platelet is spherical, extrudes pseudopodia, and expresses an increased number of activated surface receptors that can be measured to quantitate the degree of platelet reactivity. The intensity of this platelet activation occurs in proportion to the quantity and nature of the platelet stimulus and increases in a graded fashion with increasing concentrations of agonists.

Once activated, platelets avidly adhere to basement membrane cells, leukocytes, other platelets, and nonbiologic surfaces. The platelet receptor that mediates this adhesion is the glycoprotein Ib (GPIb) receptor. GPIb receptor activation allows for binding of von Willebrand’s factor, collagen, and other circulating and endothelial ligands [162,163]. Once activated, platelets undergo a phase change that allows them to spread over the surface of injury, become more spiculated and less spherical, and release the contents of their granules. This ATP-dependent process requires the internal release of calcium
and subsequent actin and myosin contraction. As granule contents are released, other platelets are attracted, and the formation of a platelet plug occurs. The platelet plug is of critical importance to stop the oozing of surgical wound edges.

The platelet initiation phase and coagulation cascades may seem like separate processes, but they are completely interdependent. The glycoproteins platelet surfaces are the sites upon which the coagulation cascade proteases mediate their reactions. The GPIb receptor is the site for von Willebrand’s factor binding. It is also the site for factor XIa to bind and then trigger factor IXa, leading to the macromolecular complex of factors X, VIII, calcium, and platelet factor 3 (the tenase complex). Immediately adjacent to the GPIb binding site is the glycoprotein IIb/IIIa (GPIIb/IIIa) binding site. GPIIb/IIIa is the binding site for fibrinogen/fibrin [164]. Each fibrinogen molecule can bind up to six GPIIb/IIIa binding sites. Therefore, the possibilities for molecular interaction and cross-linking seem nearly infinite, given that fibrin-to-fibrin interactions are possible between multiple molecules. This interaction and cross-linking has important clinical implications. The GPIIb/IIIa receptors are the critical mediators of the final common pathway for platelet aggregation and are why antagonists of this receptor are such potent inhibitors of platelet activity.

Aspirin
Aspirin is a nonspecific inhibitor of cyclooxygenase. In platelets, aspirin irreversibly acetylates serine-529 of cyclooxygenase-1, inhibiting the production of various prostaglandins and thromboxane from arachidonic acid. The inhibition of thromboxane A2 synthesis mildly reduces platelet activation for 7 to 10 days (the approximate lifespan of a platelet). The effective half-life of orally ingested aspirin is only about 15 minutes [11], but this time is sufficient to acetylate cyclooxygenase in circulating platelets as they pass through the portal system. Because of aspirin’s short half-life and lack of circulating plasma levels, transfusion of fresh platelets can restore hemostatic competence. This measure is rarely necessary, however, because, despite the potent and irreversible inhibition of platelet cyclooxygenase, aspirin ultimately exerts only a mild antiplatelet effect because of the multiplicity of alternative pathways of platelet activation in vivo (Fig. 3). This mild antiplatelet effect has been characterized as a minimal prolongation of the bleeding time, a modest inhibition of in vitro aggregation, and a slight overall decline in normal hemostatic function at the clinical level [165,166].

The dose of aspirin required to inhibit platelets is much lower than that used for analgesia or antipyresis. Whereas a dosage of 325 to 650 mg every 4 hours is generally required to treat a headache or fever, daily oral doses as low as 30 mg have been demonstrated to prevent clinical thromboses using aspirin alone [167] or in combination with another antiplatelet agent [168]. Larger doses of aspirin are associated with gastrointestinal distress and gastric mucosal ulceration. Cyclooxygenase inhibition also causes a reduction in the tone of the
efferent renal arteriole and can contribute to renal insufficiency in susceptible patients. Thus, aspirin has a relatively high therapeutic index, because low doses are generally given for the antithrombotic effect, with a time-honored low risk of adverse side effects.

Aspirin is prescribed for prevention of arterial occlusive disease throughout the body. Most patients who have coronary artery disease are maintained on aspirin therapy to prevent coronary artery occlusions, and those at the highest risk are prescribed aspirin beginning at a relatively young age. Patients who

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**Fig. 3.** Currently accepted mechanisms of action of antiplatelet agents. Three ADP receptors are believed to be present on the platelet surface. Concurrent signaling from two of these (the P2Y1 and the P2Y12 receptors) is believed to be necessary for platelet activation and ultimate aggregation through expression of the gpIIb/IIIa receptor (fibrinogen receptor). Thienopyridine binding, as indicated, prevents ADP from affecting a decrease in intraplatelet cAMP levels through the inhibitory G-protein–linked receptor, resulting in overall increased cAMP levels in the platelet. This process ostensibly removes one of the signals necessary for platelet activation, but occupation of other surface receptors can compensate for this signal. The gpIIb/IIIa antagonists (abciximab, tirofiban, and eptifibatide) antagonize the fibrinogen receptor directly, preventing platelet aggregation. Although aspirin does not bind directly to a platelet surface receptor, it prevents conversion of arachidonic acid to thromboxane A2, which would then bind to a platelet surface receptor (not shown) and contribute signaling needed for platelet activation. AA, arachidonic acid; AC, adenylate cyclase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; Ca²⁺, calcium; cAMP, cyclic adenosine monophosphate; COX1, cyclooxygenase 1; Gi, inhibitory G-protein; Gq, a subclass of G-protein; IP3, inositol triphosphate; PGs, prostaglandins; PLC, phospholipase C; TXA2, thromboxane A2. (Data from: Daniel JL, Dangelmeier C, Jin J, et al. Molecular basis for ADP-induced platelet activation. Evidence for three distinct ADP receptors on human platelets. J Biol Chem 1998;273(4):2042–9; and Jin J, Kunapuli SP. Coactivation of two different G-protein-coupled receptors is essential for ADP-induced platelet aggregation. Proc Natl Acad Sci USA 1998;95(14):8070–4.)
require a percutaneous coronary intervention are generally maintained on aspi- 
rin therapy (81 mg by mouth daily) for life. Demonstrated long-term benefits 
of aspirin therapy in this population include the prevention of future major car-
diovascular events (eg, myocardial infarction, stroke, and death) and may con-
tribute to the prevention of late coronary stent thromboses [169,170].

Not all patients are compliant with a prescribed, life-long antithrombotic reg-
umen, however, and the efficacy of aspirin therapy is not consistent across pop-
ulations [171]. There are subsets of patients whose genetic makeup makes them 
insensitive to the antithrombotic effects of aspirin. Patients who express poly-
morphism of the PI(A) portion of GPIIb/IIIa represent a subset of the population 
resistant to the effects of aspirin [172]. Using a point-of-care assay to measure 
aspirin sensitivity, Chen and colleagues [173] studied a cohort of coronary inter-
vention patients who were appropriately pretreated with clopidogrel. The au-
thors found aspirin resistance to be a risk factor for myonecrosis after 
coronary intervention with an odds ratio of 2.9 (95% confidence interval, 
1.2–6.9).

In preparation for elective surgery, cessation of aspirin therapy is usually rec-
ommended for 7 to 10 days to allow new, hemostatically competent platelets to 
be produced. It often has been anecdotally observed, however, that aspirin use 
one alone does not contribute a significant risk of intraoperative bleeding, even 
when maintained up to the time of surgery. Although large clinical trials are 
lacking in the peer-reviewed, indexed literature, a few recent publications 
have reported that continued perioperative aspirin use did not confer a major 
risk of bleeding in patients undergoing cardiac, ophthalmologic, and oral sur-
geries [174–176]. This is not the situation, however, when dual antiplatelet 
therapy with aspirin and another agent is used (eg, after implantation of an in-
tracoronary stent), because a synergy results from the dual assault on the plate-
let [177]. Patients receiving dual antiplatelet therapy should be considered 
significantly hemostatically impaired. The following paragraphs describe alter-
native antiplatelet agents and their perioperative implications.

Thienopyridines—ticlopidine and clopidogrel
There are three described adenosine diphosphate (ADP) receptors on the plate-
let surface (see Fig. 3). Normal activation of one of the ADP receptors (the in-
hibitory G-protein [Gi]-linked ADP receptor P2Y12) is critical for platelet 
activation through inhibition of adenylyl cyclase. In conjunction with other sec-
ondary messengers generated from the activation of the other platelet surface 
receptrons, the subsequent reduction in cyclic adenosine monophosphate 
(cAMP) in the platelet leads to platelet activation and allows expression of 
the gpIIb/IIIa receptor (fibrinogen receptor) that mediates platelet aggregation. 
The thienopyridines, ticlopidine and clopidogrel, partially block this process 
(and thus platelet activation and aggregation) by irreversibly antagonizing 
the Gi-linked ADP receptor (P2Y12), for the lifespan of the affected platelet.

Ticlopidine hydrochloride (Ticlid, Roche Pharmaceuticals, Nutley, NJ, 
USA) was approved for use in the United States in 1991. Ticlopidine is
a pro-drug, an active metabolite of which inhibits platelet activation through irreversibly binding to the P2Y12 ADP receptor on the platelet surface. The efficacy of this drug was demonstrated with the prevention of ischemic cerebrovascular events in the Ticlopidine Aspirin Stroke Study Group (TASS) trial [178], and it was widely prescribed by cardiologists and vascular surgeons in the 1980s and early 1990s as an anticoagulant for patients who ad peripheral atherosclerotic vascular disease and after intracoronary stenting. It is rarely used anymore because of its undesirable side effects (eg, aplastic anemia, neutropenia, and thrombotic thrombocytopenic purpura) and the requirement for thrice-daily dosing. Its efficacy has been compared recently with equipotent doses of a newer thienopyridine derivative, clopidogrel. Ticlopidine was shown to be inferior to clopidogrel when measuring antiplatelet effects and protection from adverse myocardial outcomes [179].

Clopidogrel bisulfate (Plavix, Sanofi-Aventis, Paris, France) is a thienopyridine pro-drug metabolized by hepatic cytochrome P-450 to an active compound that (like ticlopidine) irreversibly binds the G$\text{i}$-linked ADP receptor on the platelet’s surface, partially blocking platelet activation by ADP. Clopidogrel has largely replaced ticlopidine in clinical practice because of a much lower incidence of the adverse hematologic side effects, although recent reports have raised awareness that the incidence of these side effects is probably higher than previously recognized [180,181]. The effective half-life of the active metabolite of clopidogrel is short, and daily dosing is required to maintain the overall antiplatelet effects of the agent as new platelets are produced [182]. It is believed that the activity of clopidogrel lasts approximately 7 days (the accepted lifespan of a platelet). As with aspirin, transfusion of fresh platelets can effectively reverse the antiplatelet effects of clopidogrel, although circulating platelets already bound with clopidogrel remain inhibited. Like aspirin, clopidogrel is believed to affect forming platelets in the megakaryocytes, although it has not yet been demonstrated how long this effect may be clinically relevant after cessation of clopidogrel therapy.

The efficacy of clopidogrel was demonstrated in the Clopidogrel versus Aspirin in Patients at Risk of Ischemia (CAPRIE) trial [183], and it since has been widely prescribed as an antiplatelet agent for patients at risk of ischemic complications of both central and peripheral atherosclerotic vascular disease (eg, stroke, myocardial infarction, and limb ischemia). Clopidogrel also is commonly prescribed for patients with indwelling vascular stents. After implantation of a bare metal intracoronary stent, the incidence of death, emergent coronary artery bypass grafting, myocardial infarction, and angiographic stent thrombosis are decreased significantly by administration of dual antiplatelet therapy with a thienopyridine and aspirin, when compared with aspirin alone or aspirin plus warfarin [169,184]. Although many of the early studies to determine the optimal poststenting antiplatelet regimen were conducted with ticlopidine, it has been shown that clopidogrel has the same benefits as ticlopidine in the prevention of stent thrombosis, with a lower incidence of serious side effects [179]. It has also been demonstrated that administration of
clopidogrel and aspirin before stent deployment decreases the overall incidence of myocardial infarction, death, and the need for target vessel revascularization [170].

Although manufacturer’s recommendations indicate that clopidogrel should be maintained for at least 3 months after deployment of a sirolimus-eluting stent and for at least 6 months after placement of a paclitaxel-eluting stent, different centers have their own maintenance regimens. Some interventionalists recommend that clopidogrel be continued indefinitely, because clopidogrel therapy alone has been shown to decrease the incidence of ischemic stroke, myocardial infarction, and death in patients who have atherosclerotic disease. There may be another reason to continue clopidogrel therapy in patients who have paclitaxel-eluting stents, because case reports of in-stent thromboses have been documented more than 1 year after drug-eluting stent implantation when antiplatelet therapy was discontinued [185].

As discussed previously, the effects of clopidogrel plus aspirin are synergistic, and this synergism may explain why cardiac surgical patients having received this combination of drugs seem to have excessive postoperative bleeding [186]. Patients receiving these medications who present for cardiac or noncardiac surgery are at increased risk for bleeding complications. ASRA guidelines regarding cessation of clopidogrel therapy in anticipation of a surgical procedure when regional anesthesia will be employed specify that this agent should be discontinued at least 7 days before the procedure [37], but this precaution may not always be feasible and may not always occur. In these situations specific platelet function monitoring could guide potential platelet transfusion therapy. Alternatively, patients taking these medications who do not present for surgery could simply be monitored by specific platelet function testing to guide therapy for optimal safety and efficacy.

Glycoprotein IIb/IIIa receptor inhibitors
The gpIIb/IIIa receptor on the platelet surface is the base for the fibrin cross-linking responsible for platelet aggregation. Unlike the thienopyridines, which decrease effective aggregation by 40% to 50%, gpIIb/IIIa inhibitors directly block the fibrinogen receptor, preventing aggregation altogether. Currently available gpIIb/IIIa antagonists include abciximab (Reopro, Eli Lilly and Co., Indianapolis, IN, USA), eptifibatide (Integrelin, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA), and tirofiban (Aggrastat, Merck & Co., Inc., Whitehouse Station, NJ, USA). The administration of gpIIb/IIIa receptor inhibitors is confined largely to the cardiac catheterization laboratory at this time.

Abciximab is a human-murine chimeric monoclonal Fab antibody fragment that binds nonspecifically to the gpIIb/IIIa receptor, preventing platelet aggregation. The effective half-life is approximately 12 hours, with approximately 50% inhibition of platelet function remaining 24 hours after stopping the infusion [187]. Once the infusion is stopped, the anticoagulant effects of abciximab can be reversed by transfusion of fresh platelets [188], although the already bound platelets remain inhibited.
Eptifibatide is a cyclic heptapeptide based on the KGD amino acid sequence that binds selectively to the gpIIb/IIIa receptor. The effective half-life is approximately 2 hours, with platelet function returning to more than 50% of normal within 4 hours after discontinuation [189]. Despite the short half-life, the effects of eptifibatide are not reversed by transfusion of fresh platelets until several hours after discontinuation of the infusion [190]. Eptifibatide is cleared renally.

Tirofiban is a nonpeptide tyrosine derivative that binds selectively to the gpIIb/IIIa receptor. Like eptifibatide, the effective half-life is approximately 2 hours, and platelet function returns to more than 50% of normal within 4 hours after discontinuation [191]. As with eptifibatide, the effects of tirofiban are not reversible by transfusion of fresh platelets [192]. Tirofiban clearance depends on both renal and biliary elimination.

The differential ability of platelet transfusion to reverse the effects of these agents stems from the stoichiometric ratios of drug to receptor in vivo. With abciximab, the ratio of drug to receptor is nearly 1:1 because unbound drug is degraded by plasma proteases. Because less than 4% of the administered dose remains unbound after 2 hours, the overall effects of this long-acting and “irreversible” agent can be “reversed” once the infusion is discontinued [190]. In contrast, the short-acting competitive agents eptifibatide and tirofiban continually bind to and dissociate from the GPIIbIIIa receptor, and the free drug:receptor ratio is greater than 1:1. For this reason, transfused platelets are antagonized by these agents for a few hours after discontinuation of their infusion. Fortunately, the short half-life of these two agents makes emergency platelet transfusion a rare necessity.

Although some centers reserve the gpIIb/IIIa antagonists for cases considered to be high risk (eg, acute coronary syndrome, diabetic patients, bifurcation lesions, restentings), some routinely employ these potent platelet antagonists because the use of the gpIIb/IIIa inhibitors during coronary stenting has been associated with significant reductions in myocardial infarction and mortality at 30 days and 6 months after intervention [191,192]. Large-scale multicenter studies have shown that rethrombosis and infarction rates after percutaneous angioplasty and after stenting procedures have been reduced with the use of these drugs. Additionally, a reduction in the mortality rate for diabetics during interventional procedures was demonstrated for abciximab (2.5%) versus placebo (4.5%) [193].

**POINT-OF-CARE PLATELET FUNCTION TESTING**

The ideal platelet function test is one that is measurable at the point of care and that specifically measures the platelet defect in question. Such a test may be available soon for clopidogrel therapy. Implementation of platelet function testing into blood transfusion algorithms in cardiac surgery has been demonstrated to reduce overall transfusion requirements [194–197]. Much of this reduction derives from the elimination of empiric transfusions of platelet concentrates.
in patients who have received antiplatelet agents. In the absence of a measurable platelet defect, most cardiac surgical patients will stop bleeding, if given a modest period of time.

Preoperative determination of platelet function may also be of benefit to the general surgical patient who has been receiving antiplatelet therapy. The absence of a defect or demonstration of only a minimal residual defect may allow the use of a regional anesthetic technique when appropriate. Additionally, the temptation to transfuse the patient with platelet concentrates at the first sign of bleeding might be avoided.

Most clinicians are familiar with monitoring the drugs typically used for anticoagulation. Heparin and its monitoring by the ACT (at high doses) and by the aPTT (at lower doses) have been in clinical practice for decades. Even the newer thrombin inhibitors can be monitored using well-studied coagulation tests such as the ACT, aPTT, and thrombin time [198–203]. The measurement of platelet function by bedside testing is a more complex and dynamic challenge. Tests such as bleeding time or the viscoelastic measures of clot formation reflect the contribution of platelet function to overall clot formation because they take into account the time-dependent nature of platelet-mediated hemostasis. They are nonspecific in nature because of the absence of a platelet-specific agonist, but the tests generally can be modified to overcome this limitation.

Thromboelastography (TEG), is one such test that has been used in many different clinical scenarios to diagnose coagulation abnormalities [204–210]. TEG can be performed on site and provides a rapid whole-blood analysis that yields information about clot formation and dissolution. Within minutes, information is obtained regarding the integrity of the coagulation cascade, platelet function, platelet-fibrin interactions, and fibrinolysis. A small volume of whole blood is instilled into an oscillating cuvette, into which a piston is lowered. As the blood begins to thicken and clot, the oscillation of the cuvette exerts a force on the piston. This force is translated into a graphic depiction of the formation and strengthening of the clot. The R time is the time to the initiation of clot formation. It is highly dependent on clotting factors and inhibitors. The K time is a measure of the speed of clot formation and fibrinogen turnover. The alpha angle is a graphic depiction of the kinetics of clot formation. Maximal amplitude (MA) reflects the maximal force that the clot exerts on the piston and indicates platelet-fibrin interactions. Fig. 4 illustrates the TEG technology, an example of a normal TEG tracing, and a current machine.

One common modification of the TEG involves the addition of recombinant human tissue factor as an activator to accelerate the rate of thrombin formation and, thus, the formation of fibrin. This acceleration shortens the time required for development of MA. Because MA primarily reflects clot strength and platelet function, this information can be obtained more quickly with tissue factor enhancement. The recombinant tissue factor is a thromboplastin agent and is available from a number of manufacturers.

A clinically useful application of TEG technology is the monitoring of GPIIb/IIIa receptor blockade [211]. As described previously, TEG with tissue
factor acceleration speeds the appearance of MA and is accurate for monitoring the platelet inhibition by Reopro. Reduction of MA is used as an index of platelet inhibition by this GPIIb/IIIa receptor blocker. Comparison with the baseline MA yields a relative measure of the degree of platelet inhibition. A further modification of the TEG is included in the commercially available Platelet Mapping Assay (Haemoscope, Skokie, IL). This assay removes thrombin from the available agonists for clot formation and allows more specific platelet agonists to be studied. By using the Platelet Mapping Assay with arachidonic acid or ADP, specific inhibition of platelet function by aspirin and clopidogrel can be measured respectively [205].

Ultega (Accumetrics, San Diego, CA) is a point-of-care monitor originally designed specifically to measure the platelet response to a thrombin receptor agonist peptide (TRAP). It was approved in 1999 by the Food and Drug Administration for use as a platelet function assay. In whole blood, it measures TRAP activation–induced platelet agglutination of fibrinogen-coated beads using an optical detection system [214]. Because of the importance of the GPIIb/IIIa receptor in mediating fibrinogen–platelet interactions, the Ultega has been especially useful in accurately measuring receptor inhibition in invasive cardiology patients receiving GPIIb/IIIa-inhibiting drugs [212,213]. Since its approval, additional cartridges that measure platelet inhibition by aspirin and by clopidogrel have been introduced. The clopidogrel assessment cartridge was approved for use in 2005 and to date has not been extensively studied or validated clinically.
PlateletWorks (Helena Laboratories, Beaumont, TX) is a point-of-care monitor of platelet function that utilizes a modified form of aggregometry to estimate platelet function [214]. A platelet count is performed before and after addition of an agonist, and the degree to which the platelet count is diminished by the agonist is proportional to platelet function. A commercially available test is in clinical use and has been shown to be useful for measuring the platelet defect after cardiac surgery. This test has also been studied in assessing clopidogrel inhibition [215], but a closer correlation with standard aggregometry has been demonstrated using a research tube with an altered concentration of ADP [216].

The Platelet Function Analyzer (PFA-100) (Dade Behring, Miami, FL) is a monitor of platelet adhesive capacity that is currently approved by the Food and Drug Administration and is able to identify drug-induced platelet abnormalities, von Willebrand’s disease platelet dysfunction, and other acquired and congenital platelet defects [217]. The test is conducted as a modified in vitro bleeding time. Whole blood is drawn through a chamber by vacuum and is perfused across an aperture in a collagen membrane coated with an agonist (epinephrine or ADP). Platelet adhesion and formation of aggregates will seal the aperture, thus indicating the closure time measured by the PFA-100. In cardiac surgical patients, the PFA-100 closure time was incorporated into a transfusion algorithm for clopidogrel-treated and control patients after cardiopulmonary bypass. The algorithm reduced transfusion rates in both groups of patients in comparison with a recent historical control group at the same institution [194].

SUMMARY
It is important to understand the prevalent need for anticoagulant and antithrombotic medications in the current era of cardiovascular medicine. Many new anticoagulants are currently undergoing human clinical trials to assess their efficacy and safety profile compared with the time-honored, standard agents. It is critical that anesthesiologists be familiar with the mechanisms of action, durations of effect, and potential side effects of currently used and new anticoagulant agents so they can participate in decision-making processes that involve the timing of surgery and the appropriateness of regional anesthesia for patients in whom these agents have been employed. It also is important to be familiar with the various mechanisms by which antiplatelet agents act to inhibit platelet function, because this understanding allows a rational approach to restoration of hemostatic competence where necessary. The ability to monitor the hemostatic defect induced by antiplatelet agents and the incorporation of such tests into therapy-directed algorithms ultimately will reduce bleeding complications and the occurrence of empiric transfusions.

References


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PRESENT AND FUTURE ANTICOAGULANTS


Organization to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial


PRESEN T AND FUTURE ANTICOAGULANTS


Over the last 10 years, off-pump coronary artery bypass surgery (OPCAB) has gained acceptance as an operative treatment of coronary artery disease. However, controversy remains over whether OPCAB is superior to traditional coronary artery bypass grafting utilizing cardiopulmonary bypass and cardioplegia (CABG). The American Heart Association Council on Cardiovascular Surgery and Anesthesia Scientific Statement on this topic from May 2005 summarized that, although definitive conclusions about the relative benefits of each technique are difficult to reach from the currently available studies, some trends can be observed. According to the American Heart Association, findings favoring OPCAB indicate that the procedure has been associated consistently with lower transfusion incidence and a smaller release of enzymatic biomarkers associated with myocardial injury. Several reports favoring OPCAB also suggest a lower incidence of early neurocognitive dysfunction (especially in patients with a calcified aorta) and of postoperative renal insufficiency whereas length of hospital stay, mortality, long-term neurologic function, and cardiac function appear to be similar with both techniques [1]. For the anesthesiologist, the two procedures are substantially different in many aspects. Intraoperative care for the patient undergoing OPCAB procedures involves some fundamentally different approaches and challenges. Of primary importance is the maintenance of hemodynamic stability and coronary perfusion pressure during surgical phases of direct manipulation of the heart and occlusion of coronary arteries.

**HISTORY**

OPCAB has played an important part in the evolution of coronary artery bypass surgery. The first successful experimental studies on coronary artery
bypass grafting were reported in the 1950s [2]. The first reported operative coronary artery revascularization procedure was performed without extracorporeal circulation in 1964 in the former Soviet Union. Kolessov [3] performed an anastomosis of the internal mammary artery to branches of the left coronary artery through a left thoracotomy incision on a beating heart. The first successful coronary artery bypass graft surgery utilizing a venous graft, performed in the same year (1964) by Drs. Garret, Dennis, and DeBakey, was also on the beating heart [4,5]. In the following decades, with evolution of surgical techniques and the invention and refinement of cardiopulmonary bypass with cardioplegia, most cardiac surgeons preferred operating in a motionless and relatively bloodless surgical field. Conventional CABG utilizing cardiopulmonary bypass has been the standard of care for about 25 years. However, studies of surgical outcome began to underscore the risks of extracorporeal circulation, and several series of successful OPCAB surgeries have been reported, for example, from Favaloro and Ankeney in the USA, and Bisarya in Canada [6–8]. In the 1980s Benetti and coworkers [9] and Buffolo and coworkers [10] reported a large series of OPCAB in South America. Their published mortality rates were in the range of conventional CABG surgery but were not risk adjusted.

The introduction and steady improvement of cardiac stabilizers for off-pump surgery in the early 1990s lead to increased popularity of the technique, primarily because OPCAB avoids the nonphysiologic conditions of extracorporeal circulation. Furthermore, aortic cannulation and full-thickness aortic cross clamping are unnecessary.

Coronary surgery without cardiopulmonary bypass can be performed via two different techniques. The first is minimally invasive direct-access coronary artery bypass grafting (MIDCAB) [11], a technique providing revascularization to the left anterior descending coronary artery via a left internal mammary artery graft performed through a lateral thoracotomy. The second, more commonly performed technique of OPCAB allows for revascularization of multiple coronary vessels with venous or arterial grafts facilitated by the use of cardiac stabilizers. The MIDCAB technique is surgically more demanding, and only the left anterior descending coronary artery can be grafted; moreover, patients may experience more postoperative pain compared with that in OPCAB [12]. For these reasons, the utilization of the MIDCAB technique is decreasing while OPCAB procedures are steady or slightly rising. In the United States, 18.6% of coronary bypass procedures in the 2001 registry of The Society of Thoracic Surgeons’ database were performed off pump, and that figure is estimated to be about 25% for the year 2004 [13].

**PHYSIOLOGY AND OUTCOMES IN OFF-PUMP CORONARY ARTERY BYPASS SURGERY VERSUS CORONARY ARTERY BYPASS GRAFTING**

Inflammation and immune mechanisms

Inflammation is a physiologic response to injury or contact to foreign surfaces and manifests in various degrees after any surgical procedure. Systemic
inflammatory response syndrome (SIRS) is an intense degree of inflammation that can contribute to significant postoperative morbidity [14]. In CABG patients, inflammation involves both chemical and cellular elements and is triggered by conversion to nonpulsatile flow, myocardial ischemia, hypothermia, and the contact of the patient’s blood with the artificial surfaces of the extracorporeal circuit [15]. Higher release of cytokines and greater complement activation have been seen in CABG compared with OPCAB patients [16–20]. However, there is evidence that a substantial degree of inflammation is also seen during and after OPCAB. Although a characteristic pattern in cellular response has been observed in OPCAB compared with CABG patients [21], a relationship between the degree of inflammation and clinical outcome has not been shown. Elderly patients and subsets of patients with severe coexisting morbidities, particularly renal failure and possibly advanced left ventricular dysfunction, may benefit from avoiding extracorporeal circulation, because an elevated inflammatory response can be expected in these patients [20,22,23].

Hematologic changes
Intraoperative hemodilution owing to the volume of cardiopulmonary bypass circuit priming solution is avoided during OPCAB. Therefore, the low hemoglobin values reported in studies of CABG surgery patients are seen less frequently in OPCAB procedures. For CABG patients, these low hemoglobin values during cardiopulmonary bypass have been shown to be associated with negative outcome [24,25]. However, as with inflammation intensity, the impact of the degree of anemia on outcome remains undescribed in CABG or OPCAB.

Consistently, lower intra- and postoperative blood loss and lower transfusion requirements have been observed in OPCAB patients versus CABG patients [26–30]. Not surprisingly, lower rates of surgical re-exploration for control of bleeding have also been reported [27,30]. The diminished blood loss in these studies suggests a preservation of the coagulation system in OPCAB surgery, primarily owing to less dilution of coagulation factors and better preservation of platelet function. The physical avoidance of pumps, cardiotomy suction, and the foreign surfaces of the extracorporeal circulation circuit are thought to preserve the integrity of clot formation. Other coagulation-sparing features of OPCAB are the avoidance of hypothermia and (in some centers) lower heparin doses. Although a common standard for initiation of cardiopulmonary bypass is an activated clotting time (ACT) of greater than 400 seconds, protocols for heparin administration during OPCAB vary [31,32]. Many OPCAB centers administer heparin with a target ACT of 250 to 300 seconds, and initial heparin doses of 100 to 150 U/kg are routine. Heparin reversal with protamine administration after OPCAB also varies greatly from center to center. Anticoagulation practice patterns are an important future area of investigation in light of recently published reports suggesting that a hypercoagulable state, similar to that found after noncardiac surgery [32], or at least a preserved hemostasis [33], occur after OPCAB. This has prompted many centers to administer platelet receptor antagonists (eg, clopidogrel) in addition to aspirin after OPCAB revascularization.
Neurologic injury

In cardiac surgery, severe neurologic sequelae have become rare events; however, the incidence of more subtle neuropsychological deficits postoperatively has been described to be as high as 60% [34,35]. The majority of deficits are described to be transient [36]. Central nervous system abnormalities after CABG are classified as type I or type II injuries. Type I injury is defined as death owing to stroke or hypoxic encephalopathy, nonfatal stroke, stupor, or coma at the time of hospital discharge. Type II injury is defined as a new deterioration in intellectual function, confusion, agitation, or memory deficits without evidence of focal injury. Risk factors for type I injury include proximal aortic atherosclerosis, a history of neurologic abnormality suggesting pre-existing impairment of cerebral blood flow and autoregulation, and diabetes mellitus [37]. Small microemboli or inadequate perfusion most likely play dominant roles in the evolution of type II injury [38,39]. Neurologic and neuropsychological deficits can be attributed mainly to the following mechanisms: embolization, hypoperfusion owing to hemodynamic instability, and inflammation. There is increasing evidence that hyperthermia is also a significant factor contributing to neurologic injury.

These four etiologies of cerebral injury after coronary revascularization (embolization, hypoperfusion, hemodynamic instability, and hyperthermia) may occur during either OPCAB or CABG. However, cerebral embolization with atheromatous plaque material or air is theoretically more likely to occur during CABG owing to aortic instrumentation and cross-clamping. Furthermore, the embolization of fat as a mechanism of organ injury should be restricted solely to CABG. Likewise, hyperthermia should be restricted to cardiac surgery with extracorporeal circulation. Cellular markers are consistently lower with OPCAB suggesting that overall inflammation is more pronounced in CABG. Hypoperfusion owing to hemodynamic instability, however, can occur with both techniques, but is more frequently associated with OPCAB procedures.

The belief that there are fewer mechanisms of injury leads some to postulate that the patient undergoing CABG is at higher risk for postoperative neurologic morbidity compared with the patient undergoing OPCAB. Several studies support this hypothesis and show a higher incidence of postoperative neurologic morbidity, including higher stroke rates, in CABG patients compared with OPCAB patients [26,27,39–43]. However, there are also reports on limited numbers of low and moderate risk patients that show no difference in neurologic outcome between the two procedures [44,45]. Studies on neurologic and quality-of-life outcomes 1 year after surgery failed to show differences between the two procedures [46–49].

Myocardial function

Temporary occlusion of coronary arteries to facilitate suturing of the anastomoses is a component of OPCAB surgery, and thus intraoperative myocardial ischemia accompanies this procedure. As assessed by enzymatic biomarker release, the degree of myocardial injury is lower in OPCAB compared with
A retrospective study of 17,000 patients reported a lower rate of myocardial infarction in OPCAB versus CABG patients after propensity matching [26]. In a study of low-risk patients with one- or two-vessel coronary occlusive disease, the postoperative need for inotropic support was lower in the OPCAB patients [54]. For patients with impaired left ventricular function, based on the available data, there seems to be a tendency toward better survival rates and lower rates of myocardial infarction with OPCAB procedures [55–57]. For patients with acute myocardial infarction, there is evidence that both procedures are safe, with a trend toward lower early mortality rates in OPCAB [58]. At least one study suggests a lower rate of postoperative dysrhythmias (mainly atrial fibrillation) in OPCAB patients compared with CABG [26].

Pulmonary function
In CABG procedures, postoperative pulmonary dysfunction and impaired gas exchange may result from atelectasis, increased shunting, inflammation, surgical trauma, crystalloid and colloid infusions, high doses of opioids, and postoperative pain. In OPCAB procedures, positive pressure ventilation is not discontinued, and intraoperative infusions and transfusion requirements are often lower. The intensity of the inflammatory response is less with OPCAB. These theoretical considerations have led some to suggest that postoperative pulmonary function should be better preserved in OPCAB surgery. The available data in the literature, however, do not support this theory. In several reports, no significant differences in pulmonary outcomes were observed between the two techniques [58–61].

Renal function
Preserved renal function after surgical procedures depends on the maintenance of stable hemodynamics, adequate intravascular volume, and avoidance of nephrotoxic drugs. Inflammatory processes are also implicated in renal dysfunction and renal failure. Nonrandomized studies suggest that renal function is better preserved after OPCAB. OPCAB seems to offer an advantage to patients with nondialysis-dependent renal failure in reducing the rates of postoperative acute renal failure [62]. The rate of renal failure is lower in OPCAB patients in some observational studies with large patient numbers [26–28]. Some postulate that patients with preoperative renal dysfunction or diabetes may profit from the avoidance of cardiopulmonary bypass [63]. In CABG patients, postoperative creatinine clearance has been reported to be lower compared with that in OPCAB [64]. However, some reports indicate no differences between CABG and OPCAB in postoperative renal function 1 month after surgery [65].

Gastrointestinal complications
Gastrointestinal complications are rare but critical events after cardiac surgery. Postoperative mesenteric ischemia is a life-threatening condition, usually reflecting a severe systemic state of hypoperfusion. One retrospective study of
more than 68,000 patients found a higher rate of gastrointestinal complications after CABG [27]. In other large series of patients, no differences in gastrointestinal complications have been noted.

**Wound infections**

Impaired microcirculation, inflammation, and transfusion-related immunosuppression are suspected mediators of postoperative wound infections. In two series of patients, the incidence of wound infections was lower in the OPCAB group compared with the CABG group [26,28]. However, the significance of these results is undetermined, because differences in the rate of wound infections have not been observed in all studies comparing both procedures.

**Graft patency, graft function, survival**

Graft patency depends to a large extent on the skill of the surgeon and, probably, to a lesser extent on other factors such as flow (output/resistance) and platelet adhesion. Several randomized trials have examined the issue of graft patency. Although similar short-term graft patency rates in OPCAB and CABG patients have been reported by Puskas and colleagues [66] and Nathoe and coauthors [67], some reports suggest lower graft patency rates in OPCAB patients. In a randomized trial of 103 patients by Khan and coauthors [30], the graft patency rate was 88% in OPCAB compared with 98% in the CABG group. Although the patients were assigned randomly in the latter study, OPCAB patients more often had arterial free grafts performed when compared with the CABG group. Studies consistently find a lower incidence of graft patency in OBCAB patients in the right coronary artery distribution (Fig. 1), suggesting a vulnerability of that anatomic area to low perfusion pressure and stasis. In contrast to CABG, the early postoperative period after OPCAB is associated with more normal coagulation and platelet function that could potentially impair early graft patency rates [32,68].

**Death**

Data on survival is difficult to interpret, because most of the comparisons reported in the literature are not randomized, controlled trials. The published survival rates may not be valid for all patients (Figs. 2 and 3). For example, in the retrospective study by Racz and coworkers [27] of more than 68,000 patients, the patients in the CABG group showed a significantly higher survival rate than OPCAB patients (89.6% versus 88.8%, \( P = .002 \)), but some reports in large numbers of patients show no difference in survival rates between the procedures [26]. Conversion of a planned OPCAB to CABG, however, has been consistently shown to convey a much higher mortality and morbidity risk than a planned CABG procedure [69,70].

**Economics**

Several studies report a shorter overall length of hospital stay with OPCAB [29,71]. Also, some reports show a decrease in length of intensive care unit stay, a shorter duration of ventilatory support, and reduced overall costs for OPCAB procedures [20,66,72–75]. However, the results again are not
consistent and cannot be generalized. General statements on the economic impact of either procedure need to be based on prospective, randomized, controlled trials. Reports of fast-track or “ultra-fast-track” procedures utilizing standard perioperative anesthesia and analgesia or thoracic epidural anesthesia are very promising for single centers but need confirmation on a larger scale [75,76].

Summary

According to the American Heart Association Council on Cardiovascular Surgery and Anesthesia Scientific Statement from May 2005, it can be summarized that both procedures, CABG and OPCAB, may provide an excellent outcome for patients [1]. Factors like the skill of the surgeon, quality of the institution, and application of a systems approach seem to be more important in determining the outcome after coronary revascularization than the choice of OPCAB or CABG [1]. Nevertheless, each technique has its own characteristics and risk profile. There are numerous reports of comparisons between the two procedures, but there is need for randomized, controlled trials to answer many unresolved questions. OPCAB has advanced to be a safe and established therapeutic measure for the treatment of coronary artery disease. Those who may benefit most from OPCAB are elderly patients, patients with severe extracardiac morbidities (particularly renal failure), patients with advanced left ventricular dysfunction, and patients with severe atheromatous disease of the aorta. These patients are simultaneously at greatest risk for reduced graft

Fig. 1. Graft patency in left anterior descending circumflex and right coronary artery in a comparison of CABG and OPCAB. (From Khan NE, De Souza A, Mister R, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med 2004;350:21–8; with permission.)
patency and hemodynamic instability during OPCAB revascularization and represent a substantial challenge to the cardiac surgical team. Table 1 summarizes the putative mechanistic physiologic perturbations associated with each technique.

HEMODYNAMIC MANAGEMENT DURING OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Monitoring

For the anesthesiologist, prevention and treatment of hypotension, low cardiac output, and dysrhythmias are major focuses of the intraoperative management in cardiac surgery. This is especially true in OPCAB in which the heart is displaced and coronary arteries are being temporarily occluded. Hemodynamic monitoring of patients undergoing OPCAB may include an arterial catheter, a Swan-Ganz pulmonary artery catheter, a five-lead ECG with ST-segment analysis, and transthoracic echocardiography (TEE). The pulse contour cardiac output (PiCCO) system may also serve as a means for assessing the volume status intraoperatively. A Swan-Ganz catheter equipped with fiberoptic oximetry can be used to monitor continuous mixed venous oxygen saturation.
In our experience, the most useful monitor (beyond arterial pressure and ECG) during OPCAB is TEE. TEE allows continual assessment of cardiac preload, global contractile performance, and regional wall motion abnormalities. Intra-cardiac and valve pathologies can also be detected.

To avoid inappropriate intervention, the limitations of hemodynamic monitors in OPCAB need to be recognized. During operative displacement of the heart, the signal obtained from the ECG will change significantly. This is especially important for ST-segment analysis. Accordingly, automated ST-segment analysis should be recalibrated for isoelectricity after changes in position of the heart to obtain valid results. TEE monitoring may also be affected by cardiac displacement. Standard views may not be obtainable at all times, and image
quality may be suboptimal. Also, new regional wall motion abnormalities have to be interpreted recognizing the presence and influence of cardiac stabilizers.

**Hemodynamic management**

Maintenance of a normal intravascular volume status is important to promote adequate cardiac preload that can be compromised when the heart is maneuvered surgically. Preload augmentation by intravascular volume loading and the Trendelenburg position can help to maintain cardiac output and perfusion pressure during cardiac displacement.

Cardiac displacement and compression of ventricular walls by stabilizers alter ventricular geometry. Mitral insufficiency may occur owing to disruption of normal annular geometry (Fig. 4). A challenging surgical period is the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pathophysiological mechanisms in coronary artery bypass grafting with cardioplegia and off-pump coronary artery bypass grafting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technique</td>
<td>CABG</td>
</tr>
<tr>
<td>Embolization type</td>
<td></td>
</tr>
<tr>
<td>Plaque</td>
<td>+++</td>
</tr>
<tr>
<td>Air</td>
<td>++</td>
</tr>
<tr>
<td>Fat</td>
<td>+++</td>
</tr>
<tr>
<td>Hemodynamic fluctuation</td>
<td></td>
</tr>
<tr>
<td>Nonpulsatile flow</td>
<td>++</td>
</tr>
<tr>
<td>Low perfusion pressure</td>
<td>+++</td>
</tr>
<tr>
<td>Low cardiac output</td>
<td>+++</td>
</tr>
<tr>
<td>Venous hypertension</td>
<td>+++</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>+++</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+++</td>
</tr>
<tr>
<td>Hypercoaguable state</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 4. Ischemic MR with native LAD occlusion in OPCAB. (From Eltzschig HK, Shernan SK, Rosenberger PN. Ischemic mitral regurgitation during temporary coronary-artery ligation. N Engl J Med 2004;350:2424–5; with permission.)
revascularization of the circumflex vascular bed, because optimal visualization
and surgical conditions require a maximum of cardiac displacement combined
with compression of the ventricular wall by the stabilizer. Occlusion of the
proximal right coronary artery for grafting may lead to severe bradyarrhyth-
mias. The pulmonary artery catheter helps assess the volume status and mea-
sure cardiac output intraoperatively. However, each myocardial displacement
alters pulmonary and central venous pressures. Therefore, the effect of repositioning needs to be factored into the interpretation of those pressures.

Stable intraoperative hemodynamics, with the mean arterial pressure above
70 mm Hg, mixed venous oxygen saturation (SvO₂) greater than 60%, and no
left ventricular dilatation monitored via TEE are the anesthesiologist’s goals [77].
Good communication between anesthesiologist and surgeon are of paramount
importance in OPCAB. The surgeon and anesthesiologist should discuss the sur-
gical plan before each cardiac manipulation. During revascularization, the anes-
thesiologist acts as the surgical facilitator, identifying hemodynamically
unsustainable myocardial positions and maintaining stability until the comple-
tion of each anastomosis.

Hemodynamic instability may occur at any time, most often secondary to
myocardial displacement or deterioration in systolic or diastolic function owing
to iatrogenic vessel occlusion. We have adopted a stabilize-wait, occlude-wait
sequence for each distal anastomosis. This sequence facilitates correct diagnosis
of hemodynamic aberrations and allows for timely intervention. Hemody-
namic stability in the revascularization position should be achieved before pro-
gression to the next step. Using cardiac filling pressure and TEE guidance,
careful fluid administration or placing the patient in Trendelenburg position
as well as small doses of a vasopressor will lead to hemodynamic stability in
most cases. However, if hemodynamic stability cannot be achieved, the dis-
placement of the heart should be corrected by the surgeon before vessel occlu-
sion. Occlusion of the coronary artery should begin only after ascertaining that
the myocardial displacement is being well tolerated. Ideally, one should be con-
fident that the patient will tolerate the duration of the occlusion (time to com-
pletion of the distal anastomosis) before the coronary arteriotomy.

Arteriotomy may be associated with ischemia and pharmacologic augmenta-
tion of diastolic pressure or insertion of a coronary shunt may be necessary. If
severe decompensation occurs, acute conversion to cardiopulmonary bypass
may be required. The stabilize-wait, occlude-wait sequence minimizes the chances
of the patient requiring resuscitation measures during completion of the distal
anastomosis because it identifies the patients most likely to not tolerate coro-
nary occlusion. In addition, a brief coronary occlusion before arteriotomy
may contribute to myocardial preconditioning.

Left anterior descending (LAD) artery grafting usually is well tolerated be-
cause little or no repositioning of the heart is required. LAD grafting should
be done first, because this will provide improved perfusion for the balance of
the procedure to the large amount of the left ventricle that is supplied by this
vessel. It is helpful to understand factors that determine tolerance to long or
short periods of hemodynamic instability (Table 2). After distal anastomoses are completed, the proximal anastomoses for the vein grafts are accomplished with partial occlusion clamping of the aorta. Blood pressure should be lowered during the application of the clamp to limit the risk of aortic dissection.

**Management of myocardial ischemia**

Vigilance must be maintained for detection of ischemia, observing for possible decreases in cardiac output, increases in pulmonary artery pressure, electrocardiographic changes, or the appearance of new regional wall motion abnormalities, mitral, or tricuspid insufficiency on TEE. Treatment of ischemia is guided by the patient’s overall hemodynamic status. Therapies to consider include placement of a temporary intracoronary shunt across the arteriotomy site, augmentation of blood pressure to improve collateral flow, decrease in Trendelenburg position to decrease left ventricular filling pressure and wall stress, commencement of inotropic support, and insertion of an intra-aortic balloon pump. It is our opinion that immediate availability of cardiopulmonary bypass (CPB) is necessary for all OPCAB cases. Indications for conversion to CPB include persistence of a cardiac index less than 1.5 L min$^{-1}$ m$^{-2}$, $\text{SvO}_2$ less than 60%, mean arterial pressure less than 50 mm Hg, malignant arrhythmias, ST changes greater than 2 mm, or complete cardiovascular collapse [77,78]. To prevent intraoperative dysrhythmias during manipulation of the heart and coronary occlusion, a prophylactic dose of magnesium sulfate (2–4 g) has been suggested before the first distal anastomosis. In patients with a serum potassium level less than 4.0 mmol/L, a slow infusion of potassium given to keep the level above 4.0 mmol/L is justified. A cardiac pacing device and a defibrillator must be readily available in case pacing of the heart is required, especially to treat bradycardias associated with right coronary artery anastomoses. A short-acting $\beta$ adrenergic blocker like esmolol can be used to control the heart rate intraoperatively but should be used with caution, especially in the setting of reduced ventricular contractile

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**Table 2**

**Tolerance to hemodynamic instability**

<table>
<thead>
<tr>
<th>Longer</th>
<th>Shorter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LV function</td>
<td>Poor ventricular function/CHF</td>
</tr>
<tr>
<td>Normal end organ function</td>
<td>Valve disease</td>
</tr>
<tr>
<td>Stable blood pressure (MAP &gt; 70)</td>
<td>Decreased renal function</td>
</tr>
<tr>
<td>No new RWMA or MR or TR on TEE</td>
<td>Significant global or RWMA or presence of increasing amounts of MR or TR on TEE</td>
</tr>
<tr>
<td>Stable PA pressure</td>
<td>Ischemic ECG changes</td>
</tr>
<tr>
<td>Age &lt; 70</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Need for large amount of vasopressors and inotropes</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; MR, mitral regurgitation; RWMA, regional wall motion abnormality; TR, tricuspid regurgitation.
function. Calcium antagonists like diltiazem may also be used as continuous infusion to control the heart rate and to contribute to vasodilatation in arterial grafts. Nitroglycerine used to treat spasm of native coronaries or arterial conduits must be infused with caution in OPCAB procedures, because it leads to a reduction in preload, and adequate preload is essential for maintaining stable hemodynamics when the heart is displaced surgically.

SPECIAL TECHNIQUES TO REDUCE ISCHEMIC COMPLICATIONS

Preconditioning
Ischemic preconditioning is the phenomenon of an increased tolerance to ischemia after prior short periods of ischemia and reperfusion. Ischemic preconditioning was first described in an animal model in 1986. It could be shown that four episodes of coronary occlusion and reperfusion before a longer coronary occlusion could reduce myocardial infarct size by 75% [79]. A short period of clamping of the coronary artery followed by reperfusion before the definitive clamping for suturing the coronary anastomosis may be beneficial. The optimal period for each occlusion and recovery period have not been defined. There is increasing evidence that preconditioning can also be achieved pharmacologically, and volatile anesthetics have been shown to mediate this effect [80,81]. This protective effect has been shown in experimental studies for Sevoflurane and isoflurane. The promising results from experimental studies have been confirmed by a clinical trial in OPCAB surgery, in which a lesser myocardial injury was observed in patients anesthetized with sevoflurane compared with those anesthetized with propofol [82].

Intra-aortic balloon pump
For high-risk patients including those who have left main coronary artery disease, intractable resting angina, postinfarction angina, left ventricular dysfunction (ejection fraction <35%), or unstable angina, the intraoperative use of intra-aortic balloon counterpulsation has been reported to help to maintain stable hemodynamics for posterior-vessel OPCAB [83].

Axial blood flow pump
The Hemopump cardiac assist system (Johnson & Johnson Interventional Systems, Rancho Cordova, California), a transvalvular, intra-aortic axial-flow pump, has been tested for its feasibility in providing stable hemodynamics during OPCAB. Hemopump-supported coronary artery bypass graft operation has been shown to be a safe and feasible procedure in a small case series [84].

Perfusion assistance machine
A perfusion device, myocardial protection device (MPS), developed by Quest Medical Allen, Texas, can be used to selectively perfuse the coronary artery via the graft after the distal anastomosis and before the proximal anastomosis has been completed. This device permits supraphysiologic flow and provides the
potential for additives (such as vasodilators or inotropic drugs). The device has reportedly facilitated off-pump surgery by promoting rapid recovery, enhancing hemodynamic stability, and providing increased flexibility in the sequence of grafting [85].

Other techniques
Besides the use of intracoronary shunting devices, other operative techniques that reduce the period of ischemia include performance of the proximal anastomosis first, which allows immediate flow after completion of distal anastomosis. The disadvantage of this technique is the difficulty for the surgeon to estimate the length and the final position of the graft.

SUMMARY
OPCAB has evolved into a safe and established technique in cardiac surgery. Elderly patients, those with severe extracardiac comorbidities (in particular renal failure), patients with advanced left ventricular dysfunction, and patients with severe calcification of the aorta are among those for whom OPCAB is most strongly indicated. Questions remain regarding the value of thoracic epidural anesthesia and analgesia, and the economic impact of fast-track recovery protocols in OPCAB. There is increasing evidence that pharmacologic preconditioning with volatile anesthetics may help improve tolerance to myocardial ischemia. For the anesthesiologist, the technique requires great vigilance, a profound knowledge of the pathophysiology associated with the surgical procedure, and excellent cooperation with the cardiac surgeon. The anesthesiologist’s contribution to hemodynamic stability and tolerance of surgically induced myocardial ischemia are vital to successful outcome and provides great professional satisfaction to participation in these demanding surgeries.

References


Fatigue in Anesthesia—the Impact on Patient and Provider Safety: Update on Work-Hour Limitations

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The invention of the light bulb by Thomas Edison in 1879 heralded a new era of productivity for society, providing the means for continuous operation. Today, approximately 15\% of America’s full-time workforce has a rotating work-shift schedule, with close to 8\% engaged in evening and night-shift work\textsuperscript{[1]}. Maintaining the health, safety, and economy of modern society requires 24/7 availability of services, such as health care, law enforcement, and transportation. This situation is analogous to the one that anesthesia providers face when delivering quality care to patients at all hours. The uninterrupted nature of that work presents unusual physiologic demands to individuals called on to provide such services in a safe manner. Humans have a genetically determined need for sleep and programmed circadian patterns that dictate levels of alertness and performance. This delicate system of sleep-wake physiology evolved over millions of years; thus, it is no wonder that since Edison’s time, modern society faces challenges when attempting to oppose it.

The issue of fatigue in health care has gained attention on a national level. It was first highlighted 20 years ago in New York State after a high-profile investigation regarding the death of Libby Zion, to which long hours without sleep was identified as a contributing factor\textsuperscript{[2]}. Most recently, the Accreditation Council for Graduate Medical Education (ACGME) implemented mandatory work-hour restrictions in 2003 for all resident physicians to address concerns regarding patient and health care provider safety. Many factors contributed to the changes mandated by the ACGME, including (1) a well-established body of research on the deleterious effects of fatigue on performance\textsuperscript{[3–7]}, (2) concern for the safety of patients\textsuperscript{[8]}, (3) the consequences of long hours on residents’ lives, and (4) pending congressional legislation. The repercussions of these hours of service changes still are being evaluated and the results thus far are variable and controversial\textsuperscript{[9,10]}.
The impact of sleep deprivation on performance has special significance to the field of anesthesiology. Anesthetic management requires unique cognitive demands of practitioners in order to deliver patient care safely. Continuous monitoring and evaluation of data, quick recall of prior drug delivery, and complex decision making all are examples of difficult tasks that are especially vulnerable to the effects of fatigue. The objective of this review is to present the physiology of fatigue in light of historical and recent scientific findings, to relate this information to the practice of anesthesiology, and to recommend strategies that can minimize the inevitable effects of fatigue that arise from continuous operations. In addition, it addresses how work hours reform is a necessary but not sufficient part of a comprehensive fatigue management plan for health care practitioners.

THE RISKS TO SAFETY, PERFORMANCE, AND HEALTH

Strenuous work schedules commonly result in sleep loss and the disruption of natural circadian rhythms. This disturbance can lead to increased risks in safety, health, and performance. Personal awareness of the consequences of sleep loss and fatigue occasionally are known but, even if known, commonly ignored. The effect of chronic sleep loss often is subtle and likely internalized to become an individual’s new norm, because optimally rested states are uncommon. This is likely the reason why drowsy driving is so dangerous—most of the time people arrive at their destinations unharmed. The timeworn lesson, “it only takes one time,” applies well to these risks, and there are many examples that illustrate the danger of continually testing probability. Repeated exposure to these underappreciated risks reveals significant human and economic costs when that “one time” inevitably strikes.

Impacts on safety

There are many well-known catastrophes where the effects of sleep loss and disruption of circadian rhythms have been identified in the chain of accident evolution. One example is the infamous Exxon Valdez marine grounding that resulted in billions of dollars of environmental clean-up and legal costs. Although alcohol consumption commonly is cited as the key factor in this incident, the National Transportation Safety Board (NTSB) investigation revealed that fatigue and increased workload of the third mate was the probable cause of this accident [11]. Likewise, the world’s worst nuclear power accident at Chernobyl and America’s own nuclear disaster at Three Mile Island both occurred in the early morning hours, when circadian programming is primed for sleep rather than alertness [12,13]. It is suggested that the Chernobyl accident resulted in more than 2500 deaths and more than $12.8 billion of monetary loss to the Soviet economy [14]. Fatigue, secondary to the abnormal work-rest patterns of managers prior to the space shuttle Challenger launch, played a significant role in the flawed decision making that led to that national tragedy [15].

Fatigue-related accidents in the transportation industry have been well known for many years. The NTSB, whose mission includes the investigation
of all significant transportation accidents in the United States, states that fatigue is found as a causal or contributing factor in crashes in every mode of transportation—including aircraft crashes, train wrecks, pipeline explosions, highway crashes, and ship incidents [16]. This issue is of such great concern that the NTSB has included operator fatigue on its annual Most Wanted list of recommendations to the federal government since the list’s inception in 1990 [17]. Fatigue is such an important national issue in transportation that the recently opened NTSB Academy offers a course on investigating human fatigue in transportation accidents [18].

An alarming body of research shows that the risks of sleep loss are especially pertinent in drowsy driving. The National Sleep Foundation’s 2005 *Sleep in America* poll indicates that 60% of Americans have driven a car or motor vehicle while feeling drowsy within the past year. In addition, 37% of respondents reported that they have nodded off or fallen asleep while driving, and 13% of this group reported having done so at least once a month [19]. Therefore, it should come as no surprise that drowsy driving causes more than 56,000 motor vehicle crashes on United States highways every year [20]. Recent research in health care has brought this issue closer to home for physicians. Safety researchers find that the odds that interns will have a documented motor vehicle crash on their commute after an extended work shift (24 hours or more) were more than double after a nonextended shift. This report goes on to state that near-miss incidents were more than five times as likely to occur in those working an extended shift than in non–sleep-deprived drivers [21]. These findings are consistent with the data showing unintentional injuries (including motor vehicle crashes) as the leading cause of death in this age group (25–34 years old) [22]. Landmark legislation in New Jersey has given the nation its first law (Maggie’s Law) that specifically states that a sleep-deprived driver (without sleep for 24 consecutive hours) can be deemed reckless and convicted of vehicular homicide [23]. Because the current system of physician training sets up individuals to meet and exceed this criterion, the legal risks that hospitals and training programs face in the near future may be increased.

**Performance risks**

The fatigue that results from loss of sleep and circadian disruption is shown to degrade various levels of performance and human ability. These well-known effects include decreases in attention-vigilance, impaired memory, degraded decision making, longer reaction times, and disrupted communication [3–7]. Subjectively, sleep loss also is shown to affect mood and the outlook on one’s work environment negatively [7,24–27]. The combination of these factors is powerful, resulting in motivational decline and decay in critical functions, such as problem solving and the learning new information. Performance also becomes more variable and inconsistent as alertness waxes and wanes—one moment performance is maintained and the next moment performance can be “zero,” as sleepy individuals become perceptually disengaged from the environment (falling asleep).
As a result, a fatigued individual’s performance changes in predictable ways. For example, work often slows down in order to maintain the accuracy of tasks being performed, which is described as a speed-accuracy tradeoff [28]. Evidence of this appears in a study of anesthesiology residents performing real operating room cases while fatigued. Residents required significantly more time to glean data from primary physiologic monitors during the night as opposed to during a regular workday [29]. Hence, the sleep-deprived anesthesiologists needed to allocate greater cognitive resources to complete routine clinical tasks.

Attentional failures
Fatigue-related accidents sometimes occur simply by falling asleep for a brief period of time (e.g., drowsy driving accidents). These lapses in attention, termed attentional failures or microsleeps, are characterized by momentary, spontaneous, and uncontrolled episodes of physiologic sleep [30]. These lapses of attention can affect performance severely before and after their occurrence [31,32]. Microsleep events are expressed electrophysiologically as slow eye movements and slowing of the electroencephalogram (EEG), which is similar to natural sleep onset. During these periods, slowed cognitive throughput, impaired memory, slowed reaction time, and lowered optimal reasoning can create an increased opportunity for errors to occur [33]. For example, in an operating room, an anesthesia provider might feel “awake” during a case, but the intrusion of these short lapses in attention can affect the vigilant monitoring of clinical data and the ability to continually evaluate its significance adversely. Diagnosing a problem too late or failure to notice important trends during intraoperative care can lead to serious consequences in patient outcome. Research is beginning to reveal how prevalent these attentional failures are in clinical settings.

A recent study objectively assessed attentional failures in resident physicians working in critical care units [34]. During this study, interns who worked a traditional schedule (24-hour shifts; mean 84.9 hours work per week) experienced more than double the rate of attentional failures during on-call nights than when on an intervention schedule (less than 17-hour shifts; mean 65.4 hours work per week; 5.8 hours more sleep per week). These data show promise that decreasing extended work shifts can increase sleep times and decrease sleepiness significantly in patient care settings.

Behavioral manifestations of these microsleeps were well documented in an experiment of sleep-deprived and well-rested anesthesiologists. Sleepy behaviors (e.g., head nodding and eyes slowly opening and closing) were prevalent in subjects performing anesthesia on a simulated patient after being awake for 24 hours. These behaviors essentially were absent when the subjects were well rested (averaging > 9 hours of sleep per night) [35].

Alcohol correlations
Some of the most alarming and compelling data on impairment from sleep loss appear when correlated with alcohol ingestion. Most of society can relate to the detrimental effects that alcohol consumption has on decision making and
performance either from personal experience or from witnessing others. Because some of these effects mimic those of sleep loss, the serious nature of attempting critical tasks while sleep deprived becomes clear. For example, after 17 hours of wakefulness, it is found that performance on a hand-eye tracking task declines to a level of impairment equivalent to a blood alcohol concentration (BAC) of 0.05%. After 24 hours of sustained wakefulness (not unlike many on-call periods), the decline in psychomotor ability is found equivalent to a 0.1% BAC, a level that warrants arrest for driving illegally under the influence [36,37].

A recent study used alcohol ingestion as a reference for functional impairment and compared this to training-related performance impairment resulting from prolonged work hours [38]. It was found that during a heavy call rotation (every fourth or fifth night; 34–36 consecutive hours per overnight call; average 80 hours of work per week), performance decrements in attention, vigilance, and simulated driving were equivalent to or worse than the impairments associated with a BAC of 0.04% to 0.05%. These data reveal that by using alcohol as a reference, the serious nature of fatigue-related effects can be understood better by policymakers and the general public.

**Long-term performance effects**

Little is known regarding the long-term consequences of chronic sleep deprivation, but a recent study suggests a connection with degradation of cognitive abilities [39]. Rouch and colleagues demonstrate that cognitive functioning (ie, verbal memory and speed performance) tend to be impaired by long-term (10–20 years) exposure to night-shift work and that performance tends to degrade with increasing duration of night-shift work exposure. Furthermore, current male night-shift workers show lower cognitive scores than workers who have never worked on shift and there is some evidence that the effect can be reversed after cessation of shift work. More research is necessary to determine if a career in health care marked by frequent periods of sleep deprivation and circadian disruption may lead to similar impairment, but the possibility of such a correlation should not be dismissed.

**Health correlations**

In addition to safety risks and performance impairment, the effects of sleep deprivation also are associated with specific health disorders. Strong evidence exists for associations with gastrointestinal and heart disease. A robust study from Japan examined 11,657 employees from various work settings (factories, banks, and schools) and found that the relative risk of duodenal ulcers was doubled in night-shift workers compared to day workers [40]. Regarding cardiovascular disease (CVD), a meta-analysis of 17 studies on shift work concludes that shift workers have a 40% excess risk for CVD compared with day workers [41]. Research shows that shift work affects the onset of hypertension independently and reveals shift work as a major risk factor for this disease [42]. A graphic representation of how night or rotating shift work may be associated with disease is shown in Fig. 1.
Work schedules associated with sleep loss also are shown to affect pregnancy outcomes adversely. An increased incidence of preterm birth is associated with shift work [43], and fixed night work alone during pregnancy is shown to increase the risk of late fetal loss [44]. Beyond work schedules, changes in sleep physiology and sleep deprivation are proposed as contributing factors in perinatal maternal psychiatric disorders [45].

Sleep deprivation has detrimental effects on the immune system, supporting the common perception that susceptibility to infection increases in those who are sleep deprived. Questionnaire data from more than 12,000 workers in the Netherlands reveals that shift work is associated with a higher risk for common infections and differences in health compared with day work [46]. The effect of sleep deprivation on cellular immune function yields inconsistent results, but there is evidence of a reciprocal relationship between sleep and immunity. Irwin and associates find that even a modest disturbance of sleep (sleep deprivation between 10 PM and 3 AM) reduces T-cell cytokine production and natural immune responses in 42 healthy male subjects [47]. Dinges and coworkers find that 64 hours of induced sleep deprivation increases the levels of total white blood cells and natural killer cell (NK) activity [48]. The increases in NK activity and physiologic leukocytosis were eliminated by a night of sleep recovery. Minimal research exists on the clinical significance of these observed immune changes, but new findings are emerging. A recent study reveals enhanced formation of antibodies to hepatitis A antigens in humans who had regular sleep on the night after vaccination compared to a night of sleep deprivation [49].
Positron emission tomography shows altered brain activity and function with sleep loss and circadian disruption. A study in which subjects were scanned for brain activity during 85 hours of sleep deprivation reveals that even short-term sleep deprivation produces global decreases in brain activity [50]. Larger reductions in activity were observed in the thalamus and prefrontal and posterior parietal cortices, which are the structures involved in alertness, attention, and higher-order cognitive processing. Decreases in brain activity in these regions correlate with reductions in alertness and cognitive performance in this study.

Evidence exists that sleep deprivation may affect mortality and cancer risk. A study of elderly patients using EEG measures of sleep architecture shows that poor quality sleep, including difficulty in falling asleep, is linked significantly with mortality [51]. Studies also indicate that increased mortality is associated with either shorter (less than 4 hours daily) or longer (greater than 10 hours daily) regular sleep durations [52,53]. The incidence of certain cancer types is increased in those exposed to night-shift work. A recent meta-analysis concludes that studies collectively show an increased breast cancer risk among women who work night shifts [54]. One study involving 78,562 nurses during 10 years of follow-up through the Nurses’ Health Study [55] finds the risk of breast cancer significantly elevated in postmenopausal women who had worked 30 or more years on rotating night shifts versus those who never worked rotating night shifts. It also was observed that premenopausal women increased their breast cancer risk by 23% after 1 to 14 years of shift work.

SLEEP PHYSIOLOGY
Sleep—a basic need
According to Carskadon and Dement, sleep is a complex, active state of reversible behavioral disengagement from and unresponsiveness to the environment and is vital to human survival [56]. As with other basic needs (eg, hunger or thirst), the central nervous system signals that physiologic needs are not met if deprived of sleep—the individual response is sleepiness. If deprivation is severe (acute or chronic), the brain can shift uncontrollably from wakefulness to sleep with minimal awareness from an individual, which is the physiologic basis for attentional failures. The safety risks in these situations are marked when envisioning these microsleep episodes occurring in an operating room or perhaps on the drive home after call.

Sleepiness is pervasive in society. Large national surveys by the National Sleep Foundation consistently reveal that Americans, on average, sleep 1 hour less than what they require every night. Not surprisingly, there is evidence that anesthesiologists also suffer from the effects of sleep loss and disrupted circadian rhythms. A laboratory experiment designed to evaluate daytime sleepiness in anesthesiologists reveals that individuals in their baseline condition (not on call and averaging 7 hours sleep per night) demonstrate (1) levels of pathologic sleepiness similar to patients who have narcolepsy and sleep
apnea, (2) levels of sleepiness indistinguishable from postcall conditions, and (3) difficulty distinguishing the likelihood of falling asleep or whether or not they actually had fallen asleep [57].

An average adult requires more than 8 hours of sleep per 24-hour period to maintain optimal alertness and function at peak levels. On a population basis, sleep need is distributed normally so that for every individual who needs “only” 6 hours of sleep, there is another individual who requires 10! During the course of the workweek, it is not uncommon for individuals to generate a significant sleep debt [58]. If personal sleep need is 8 hours per day, but only 7 hours of sleep are obtained, a 5-hour sleep debt accumulates prior to the weekend—hence, the common phenomenon of sleeping late on the weekends to catch up on lost sleep. Luckily, lost sleep does not have to be replaced hour for hour. One to two nights of optimal sleep typically recuperate sleep debt, allowing return to normal function. This occurs only if recuperative sleep is obtained when given the opportunity. Sleep need is determined genetically and does not change with age. In fact, it tends to be more difficult to obtain restorative sleep with age because of several factors (eg, benign prostatic hyper trophy, menopause, or increased prevalence of sleep disorders) [59].

Circadian clock
Humans have a cluster of special cells located in the suprachiasmatic nucleus in the hypothalamus that controls the timing of many physiologic and behavioral functions. The circadian clock regulates hormone secretion and temperature regulation, but for this discussion, the 24-hour pattern of sleep-wake functions and performance capability is of particular interest [60]. This clock programs humans to be awake during the day and sleep at night, and performance potential also follows this pattern. There are two vulnerable periods of decreased alertness/performance that occur every 24 hours—from 3:00 AM to 7:00 AM and 1:00 PM to 4:00 PM. The time of greatest safety risk, which corresponds to the circadian nadir, is during the early morning hours of 3:00 AM to 7:00 AM, when sleepiness is greatest and performance is lowest.

The circadian clock is resistant to change. The consequence of this can be seen when trying to alter the typical sleep-wake cycle (eg, crossing times zones during travel or trying to work during the night). Jet lag and difficulty converting to night shift work occur when the clock’s strong forces are opposed [61].

Night-shift work creates a difficult situation for human operators because it reverses the day-awake and night-sleep cycle. The alerting mechanism of the clock dissipates during the night (making it difficult to stay awake) and conversely is programmed for wakefulness the following day when an individual attempts to obtain sleep. Sleep during the day often is compromised because most of society is day oriented. Routine activities in the home, such as errands and family responsibilities, have to be performed during the day and sleep often is the activity that is forfeited. Most night-shift workers revert to the usual daytime activity during days off so the clock never has a chance to adjust fully [62].
IN THE WAKE OF WORK HOURS REFORM

As of July 1, 2003, the ACGME instituted common duty-hour requirements for all accredited residency training programs. They are:

- 80 hours per week, averaged over a 4-week period and inclusive of all in-house call activities
- 1 day (continuous 24-hour period) in 7 free from all educational and clinical duties, averaged over 4 weeks
- In-house call must occur no more frequently than every third night, averaged over a 4-week period
- In-house call must not exceed 24 hours; residents may remain on duty for up to 6 additional hours to participate in didactic activities or transfer of care, conduct outpatient clinics, and maintain continuity of care
- No new patients may be accepted after 24 hours of continuous duty
- A 10-hour time period must be provided between all daily duty periods and after in-house call to give adequate time for rest and personal activities
- Moonlighting hours must be considered part of the 80-hour weekly limit
- Duty hour exceptions: a residency review committee may grant exceptions for up to 10% increase in the 80-hour limit to individual programs on a case-by-case basis


There are no work-hour restrictions for experienced practitioners or anyone other than residents in training. Many physician educators are concerned about their ability to train competent physicians in this new health care environment with stricter work-hour limits. Training programs are given no clear method as to how to alter the educational system to match the goals of residency education under the new rules.

Critics note that enforcement of such time restrictions has adverse effects on continuity of patient care and potentially has the unintended consequence of making the system less safe. This dispute is imperfect given that patient care is noncontinuous between caregivers. Transfer of care always has occurred, even before the advent of any work-hour limits. If transfer of patient care is identified as a potential source of error, then efforts should be made to make this critical time more error resistant [63]. Supporters of the limitations argue that excessive work hours increases medical errors, increases fatigue, impairs mood, and has a negative impact on learning. In addition, supporters cite that job satisfaction and quality of life are important factors that affect residents’ clinical performance and recruitment into specialty-training programs.

Subjective findings

In order to assess the transition that occurred in July 2003 as a result of ACGME regulations, many survey-based studies have been conducted on the perceptions of residents and physician educators. Surveys tend to focus
on the specialties that have the most impact, specifically the surgical subspecialties. In a national survey of 93 program directors and 617 residents in neurosurgery, the majority believed that the ACGME duty-hour guidelines have had an adverse effect on continuity of patient care and resident training [64]. In a recent study of the perceptions of general surgery residents, 39% of those surveyed believed that the requirements had worsened their quality of surgical training, but 75% believed that, overall, the requirements were a good thing [65]. This survey found that most surgical residents do not believe that the duty-hour requirements achieved their intention of improving quality of care and that they are ambivalent about the effects on the quality of their training and their lives in general.

Distinctions in residents’ attitudes by specialty also are observed. One study reports a consistent pattern of positive responses toward the standards among internal medicine residents, which contrasts with less favorable responses from residents in general surgery programs [66]. Job satisfaction surveys were performed before and 1 year after duty-hour changes in a group of residents in obstetrics/gynecology, with varied results [67]. The average satisfaction rating for all residents surveyed in 2003 and again in 2004 was not different, but positive attitudes were seen regarding the increased ability to participate in educational components of residency education (e.g., reading and research). One negative impact noted was a decreased interest in spending time teaching colleagues (fellow residents and medical students) because of the need to complete their many clinical responsibilities within the limited duty-hour requirements.

Additional findings
The long-term impacts of the implementation of the ACGME’s work-hour restrictions are unknown, but a recent meta-analysis has been published [10]. The analysis suggests a general improvement in residents’ quality of life, with effects on resident education (surgical experience, test scores, and satisfaction) that vary between studies. Understanding of the long-term effects of this reform will unfold and refine over the next several years.

Maintaining safe patient care is a major concern regarding the implementation of work-hour restrictions, but a definitive answer to this issue has yet to be obtained. A systematic review on the effects of the restrictions on patient safety concludes that the intervention has had unclear effects and that the evidence thus far regarding patient safety is inconclusive [9]. Nevertheless, recent studies show that the number of hospital-wide adverse drug events remained constant after the limitations [68] and that postoperative outcomes are not affected [69] in the programs studied. Another recent study finds that decreasing work hours to levels stricter than those imposed by the ACGME reduces serious medical errors made by interns by 35.9% [70]. Errors in this study were assessed while interns worked in an intensive care unit on a traditional schedule (an every-third-night call schedule), with extended (24 hours or more) work shifts, compared to an intervention schedule with reduced work shifts (less than 17 hours) and reduced work hours per week.
Objective findings are beginning to emerge on the impact on residency education. In surgery programs, one convenient measure of residents’ clinical exposure is caseload. A recent communication by the Residency Review Committee-Surgery, which is one of 10 surgical specialties of the ACGME, reports results from their evaluation of residents’ surgical volume of general surgical services before and after duty limits [71]. Their evaluation includes all resident surgical procedures completed from 1997 to 2004, and particular interest was paid to the procedures-per-resident measure. They found no significant change in overall surgical experience for major procedures per resident. In an additional study that compiled retrospective data on cases performed by general surgery residents in each graduate year, the number of cases per year was found statistically similar before and after work-hour restrictions [72]. Similar results were found in an evaluation of the impact of work-hours compliance in trauma and emergency surgery residency training [73]. The investigators report a 50% reduction in senior residents’ call responsibility and a 19% decrease in work hours but no significant change in trauma/emergency patient care exposure or caseload. Based on this preliminary work, the concern of work-hours reform limiting clinical experience is unfounded.

The 80-hour workweek also has had secondary effects on staff physicians, but data is limited also in this area. At a level 1 trauma center, faculty work hours increased slightly despite a decrease in faculty call as a result of the restrictions [73]. In a survey of surgery faculty at the Washington University School of Medicine, it was found that their work hours had not increased in the 6 months after the duty hours implementation, but the majority of the faculty believed that patient care and resident education had deteriorated [74].

Meeting the challenges of implementation

The implementation of work-hour reductions is new in the United States, but far stricter trainee work-hour regulations already are established in Europe. In August 2004, the new European Working Time Directive was enacted across the European Union (EU) restricting junior doctors’ hours to an average 48-hour workweek over the course of a few years [75]. The results of these restrictions on patient and provider safety still are being evaluated [76], and their findings may have an impact any future restrictions that may occur within the United States system. Empiric studies of these changes in the EU are lacking, although there are several argumentative pieces for and against the directive [76].

The challenge of maintaining optimal patient care and resident education while complying with the ACGME guidelines has led many programs to implement innovative adaptations. The surgery department of the University of Vermont College of Medicine addressed this challenge in their level I trauma service through a policy of direct admission of patients who have neurosurgical and orthopedic injuries to the subspecialty service after evaluation in an emergency department [77]. This policy was studied by comparing complications, missed injuries, delayed diagnoses, and admission rates before and after the work-hour restrictions. No significant difference was found in these measures.
in the pre- and postperiods, and the policy resulted in a 15% reduction in admissions to the trauma service and a 9.7% reduction in resident work hours, allowing many residents to meet the 80-hour workweek requirement. Likewise, a recent study examined the effect of work-hour reforms on the case volume for surgery residents [78]. This program hired physician extenders and decreased trainee call schedules to every fourth night in order to meet the workweek mandate. Overall, no change was observed in the average operative volume per year for surgical residents in this program. Other creative adaptations, such as the development of computerized sign-out systems, are reported to decrease the time needed by residents to complete rounds by up to 3 hours per week [79]. At one continuity clinic site for pediatric residents, an evening continuity clinic was added to the regular clinic day, when they were neither post call nor on call, in substitution for a postcall clinic day [80]. This change prevented residents from working beyond the 24-hour limit and they rated their overall satisfaction with this change as good/outstanding (89%). The ACGME has established a dedicated area on its Web site, entitled “Innovative Approaches to Address Its New Duty Hour Standards,” that presents systems and detailed modifications for residency programs to meet the new policies while maximizing their educational mission [81].

The ACGME has tracked the compliance rate of residency programs through site visits and a confidential internet survey of more than 50,000 residents [82]. The survey data for the 2004–2005 academic year indicates that 3% of residents reported working more than 80 hours per week, down from 3.3% the previous year, and of the 2002 programs reviewed, 7.3% received citations related to duty-hour noncompliance. Many surgical programs have requested and have been given a 10% work-hour extension, allowing 88 hours of work per week. It is not known how many requests for extension residency review committees deny.

The data regarding the effects of work-hour restrictions are mixed but are not as negative as some educators had feared. A significant change to such a complicated system that attempts to balance physician training and patient care is bound to have varied repercussions, as observed thus far. These effects deserve further exploration to evaluate safety, clinical, and educational outcomes.

**FURTHER RISKS IN THE HEALTH CARE SETTING**

The detrimental effects of fatigue on performance are caused by physiologic factors, and no amount of pride or professionalism can overcome them. In addition to the findings regarding patient and provider safety (discussed previously), a growing body of evidence on the effects of sleep loss in health care personnel exists. Subjective data reveal that the prevalence of fatigue in health care settings is significant. A New Zealand survey documenting anesthesiologists’ perceptions on safety limits reports that 58% believed they exceeded their self-defined safety limits for continuous anesthesia, and 86% reported having committed a fatigue-related error [83]. Surveys of internal medicine residents find alarming percentages reporting the possibility of dozing while performing
tasks, such as writing notes in charts (69%), reviewing medication lists (61%), interpreting laboratory results (51%), and writing orders (46%) [84].

Performance and safety risks in health care personnel also have been studied. Attention and working memory show deterioration in anesthesia residents after periods of night duty [85,86], and fatigue is associated with increased technical errors in laparoscopic simulators by surgery residents [87–89].

Quality patient care is compromised by fatigue, and consequences of these effects are documented. Data from 5600 reports of critical incidents in the Australian Incident Monitoring Study from 1987 to 1997 find fatigue a contributing factor in 152 reports (3%) [90]. Another study asked residents about the most serious mistake they committed within the past year and 41% attributed the mistake to fatigue [91]. Moreover, house officers who reported being fatigued were found less likely to seek information about their mistakes.

BARRIERS TO CHANGE
The two main barriers to change in the health care work environment stem from historical tradition and economics. At the beginning of the previous century, young physicians in training vied for unpaid hospital appointments, agreeing to literally live in the hospital, hence the term, resident [92]. Archaic views that residency training is a necessary rite of passage prevent change in and proactive reflection on the current state of clinical education. With technology continually revising health care delivery and critically ill patients living longer, patient care has become more complex, demanding, and stressful. Extensive experience is required to master any specialty area, but the question remains as to how well a trainee can learn when exhausted. Hard work and long hours are hallmarks of medical training that do not end in residency. Fatigue clearly has an impact on all providers—a fact that should not be lost in the discussion of work-hour reform.

Economics also plays an important role in the maintenance of the status quo for medical trainees. Residents provide a relatively cheap source of labor for the hospitals that employ them, but this may not be in the best interest of patients because of lack of experience [92]. For trained physicians in certain practices (eg, fee-for-service), there are real economic incentives to work. Working the day after call under conditions of fatigue likely is more palatable when paid for the work.

MANAGING ALERTNESS IN HEALTH CARE: A PROPOSED SOLUTION
Given the complexity of these challenges, a comprehensive approach to managing alertness provides the greatest potential for change. Such an approach involves at least the following four elements: education, alertness strategies, healthy sleep, and scheduling policies [93]. Many of these ideas can be implemented reasonably into existing practices.

Education
Disseminating the basic knowledge of sleep medicine and the physiologic factors that underlie fatigue is a foundation for change in any comprehensive
fatigue management plan. For many physicians, the time spent in medical school and residency provides little or no information regarding sleep, sleep disorders, and related topics [94]. Armed with knowledge about the risks of performing suboptimally because of fatigue, physicians should be more open to change. Successful educational modules to address fatigue have been developed for other high-risk industries that health care can model [95]. The American Society of Anesthesiologists sponsored an educational videotape addressing the implications of fatigue in their field [96].

Alertness strategies
A variety of strategies have been tested in the laboratory and in field studies and are found to improve alertness and performance. Three effective strategies are planned naps, the strategic use of caffeine, and good sleep habits.

Planned naps
The use of planned naps is one of the most basic interventions for sleep deprivation, as it requires no training and addresses the physiologic need for sleep directly. Napping can be used (1) to maintain alertness by maximizing sleep before night work, (2) during duty periods when feasible, and (3) before driving home post shift. The beneficial effects of naps are proved in field studies and laboratories. Planned naps were evaluated in a National Aeronautics and Space Administration field study [97], where pilots were allowed a 40-minute nap in the cockpit. Pilots who napped increased their performance by 34% and physiologic alertness by 54% compared with pilots who did not nap. Laboratory investigations show the benefit of planned naps on alertness and performance [98,99], and one study reveals that even a short nap containing only 3 minutes of stage 2 sleep has recuperative effects [100]. Some guidelines for good napping are:

- For a short nap, do not exceed 45 minutes
- A longer nap of approximately 2 hours allows for a full nonrapid eye movement (NREM)-REM cycle
- Allow for a 15-minute wake-up period after napping
- Refrain from long naps close to planned sleep periods


Caffeine
The most widely used drug in the world to maintain alertness is caffeine. Unfortunately, it is also the most abused drug, and the majority of individuals do not use it strategically to benefit from its alerting effects. Using caffeine

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*This reduces the likelihood of awakening in deep NREM sleep and experiencing sleep inertia.
strategically involves aligning ingestion with the vulnerable dips in circadian rhythm (ie, 1:00 PM – 4:00 PM and 3:00 AM – 7:00 AM). Constantly consuming caffeine throughout the day serves to minimize its effects secondary to the development of tolerance and, therefore, should be avoided in order to take full advantage of its alerting effect. In general, the onset time for caffeine is 15 to 30 minutes, with its effects lasting approximately 3 to 4 hours. A significant performance and alertness boost can be achieved with 200 mg of caffeine, with positive effects corresponding to doses ranging from 100 to 600 mg (7 oz of drip coffee contains 110–175 mg). Caffeine’s side effects include dose-related tremors and heart palpitations, which may limit its usefulness at higher dosages.

**Good sleep habits**

Good sleep habits can help promote sleep quality and quantity at home or in a hospital setting. These provide simple methods to improve alertness in the workplace that can be implemented by anyone at no cost. Guidelines for good sleep habits are:

- Utilize a presleep routine that gives cues for relaxation and sleep
- Avoid negative sleep signals in the bedroom setting (ie, don’t engage in work or anxiety-related activities in the sleep setting)
- If hungry or thirsty prior to sleep, have a light snack or drink
- Avoid caffeine intake at least 3 h before sleep
- Avoid exercise within 2–3 h of sleep
- Follow a 30-min toss-and-turn rule, such that if you are unable to fall asleep in 30 min, get out of bed, engage in some sleep-promoting activity, and return to bed when ready
- Use relaxation techniques to promote sleep, or return to sleep after awakening
- Aim for 8 h of sleep every 24 h (consider a supplement nap if necessary)
- Limit intake of ethanol or nicotine-containing products close to bedtime


**Modafinil: another alertness-enhancing drug**

Modafinil (Provigil) is a schedule IV, nonamphetamine, psychostimulant drug with low addictive potential. In January 2004, modafinil was approved in the United States for the treatment of excessive sleepiness (ES) associated with obstructive sleep apnea and shift-work sleep disorder, expanding its previous designation for treatment of ES resulting from narcolepsy. The precise mechanism of action of modafinil is unknown, but relative to placebo, it is found to improve fatigue levels, motivation, reaction time, and vigilance [101]. Recently, Czeisler and colleagues administered modafinil to patients who had shift-work sleep disorder and found that ES was reduced and a small but significant improvement in performance was observed compared with placebo [102]. Residual sleepiness still was observed, however, in treated patients. Controversy has arisen in the medical field regarding the ethical use of such a stimulant
while performing duties related to patient care [103]. This debate prompted an executive at Cephalon (Provigil’s manufacturer) to state that the drug is “not intended for use in helping residents work longer hours” [103]. Research on the use of modafinil for symptoms of sleepiness in health care personnel is limited [104]. Further scientific studies regarding the safety and effectiveness of this compound are ongoing and likely there will be debate as to how (or if) the drug should be used to enhance the alertness and performance of health care providers.

Healthy sleep—diagnosis and treatment of sleep disorders
According to the International Classification of Sleep Disorders, there are more than 80 different sleep disorders [105]. Alertness and performance can be altered dramatically by most of these disorders. Activities and information related to healthy sleep should be a part of any comprehensive fatigue management program. The components could include the following: (1) providing information on sleep disorders and resources for diagnosis and treatment; (2) having resources available that allow individuals to seek evaluation where appropriate; and (3) identifying individuals at risk though formal screening processes (eg, sleep apnea screening). Family outreach also should be included when addressing healthy sleep, as it is a vital resource for identification and treatment of individuals at risk [106].

Scheduling issues
For many reasons, scheduling is one of the most difficult areas to address in any alertness management program. Beyond fatigue, optimal scheduling must take into account resources (economic and individual) and the lifestyles of personnel involved in the patient care setting. Health care is just beginning to integrate physiologic principles into scheduling practice. Some of the physiologic factors that need to be taken into account are:

- Shift length
- Off-duty and minimum rest opportunities
- Effects of cumulative fatigue resulting from consecutive duty periods or reduced rest opportunities
- Recovery periods
- Direction of shift rotation
- Start and end times of shifts
- One day off in seven


Examples of complex scheduling policies in other high-hazard industries are listed in Box 1. Relying on work limitations alone does not manage the scheduling issues regarding fatigue effectively. Intervention studies allowing for increased sleep opportunities find that there is no guarantee that individuals will use this strategy and actually increase their sleep [107,108]. Instead,
Box 1: Work-hour regulations in the transportation industry

Aviation
- Pilots flying domestic air carriers, including major airlines and cargo haulers, may fly up to 30 h/wk, 100 h/mo, and 1000 h/y.
- If scheduled flight time is < 8 h, the minimum rest period in the 24 hours prior to the completion of the flight segment is 9 hours. This time may be reduced to 8 hours if the following rest period, beginning no later than 24 hours after the completion of the reduced rest period, is increased to 10 hours.
- If scheduled flight time is 8–9 hours, the minimum rest period in the 24 hours prior to the completion of the flight segment is 10 hours. This time may be reduced to 8 hours if the following rest period, beginning no later than 24 hours after the completion of the reduced rest period, is increased to 11 hours.
- If scheduled flight time is ≥ 9 hours, the minimum rest period in the 24 hours prior to the completion of the flight segment is 11 hours. This time may be reduced to 9 hours if the following rest period, beginning no later than 24 hours after the completion of the reduced rest period, is increased to 12 hours.

Motor carrier
- Drivers may drive for 10 hours or be on duty for 15 hours.
- Drivers must have 8 consecutive hours off after a 10/15 on-duty period.
- If drivers use a sleeper berth, they may split the 8-hour period into two periods as long as neither period is less than 2 hours.
- Drivers may not exceed 70 hours in 8 days, if the carrier is in operation 7 days a week.
- Drivers may not exceed 60 hours in 7 days if the carrier does not operate every day of the week.

Marine
- Hours-of-service or watch requirements vary depending on type of vessel.
- An officer must be off duty for at least 6 hours within the 12 hours immediately prior to leaving port.
- On an oceangoing or coastwise vessel of not more than 100 gross tons, a licensed individual may not work more than 9 of 24 hours when in port or more than 12 of 24 hours at sea, except in an emergency.
- On a tanker, a licensed individual or seaman may not work more than 15 hours in any 24-hour period or more than 36 hours in any 72-hour period, except in an emergency or a drill.
- Officers in charge of a navigational or engineering watch on board any vessel that operates beyond the boundary line shall receive a minimum of 10 hours rest in any 24-hour period. The hours of rest do not need to be maintained in an emergency. The hours of rest may be reduced to 6 hours if no reduction extends beyond 2 days and not less than 70 hours of rest are provided in each 7-day period.
some individuals choose to use the time to catch up on paperwork and other tasks. In such cases, educational programs can be used to teach a provider the importance of prioritization of sleep and, perhaps, increase compliance with the designed change. A recent house staff survey notes that administrative tasks related to scheduling are some of the most frequent barriers to participation in educational activities [109]. These studies point to the need for innovative approaches to scheduling that take into account what residents are doing with their time and how this affects their quality of education and amount of sleep.

SUMMARY
The volume of data concerning sleep deprivation and fatigue makes clear the intimate relationship between fatigue and safety risks. The human body communicates its priority for sleep through degradation of cognitive and psychomotor functions with each passing hour of deprivation. With this in mind, it is important to focus current attention on ways to improve the system of care so that patients and providers have a safe journey through their time in the health care environment.

Many aspects of the modern lifestyle (24-hour internet access, video games, and so forth) pave the way for society’s chronic sleep deprivation. The competing interests in a 24/7 world serve to make sleep a low priority for many individuals, including those in health care. If sleep is not given a reasonable priority, fatigue will continue to be an issue for all human performers. Neither individual patients nor society as a whole would tolerate providers coming to work impaired because of alcohol or drugs. Similar levels of impairment are found in individuals deprived of sleep, yet this is tolerated. Professional behavior should include arriving at work prepared—not impaired for any reason.

Furthermore, if feeling impaired from fatigue, admitting this fact should not be associated with guilt and should not be a barrier to acknowledging this genetically programmed part of physiology. In a profession dedicated to saving life, more effort must be put forward to safeguarding patients from the dangers of fatigue.
of human error. The aspects of the health care system that foster conditions of suboptimal performance and safety risks to its own providers must be addressed.

References


Update on Unintended Intraoperative Awareness

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In October 2004 the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) published a sentinel event alert, “Preventing and managing the impact of anesthesia awareness” [1]. JCAHO has been issuing sentinel event alerts with varying degrees of impact on anesthesia care providers since 1998, but none of the previous issues had generated the water cooler buzz in anesthesiology departments like that of the 2004 alert, coming as it did with a wave of increasing media and public attention to the problem of unintended intraoperative awareness during general anesthesia. At the same time the American Society of Anesthesiologists (ASA) had commissioned a task force to review the problem of intraoperative awareness, with specific attention to the role of brain function monitoring for its prevention. Their “Practice Advisory for Intraoperative Awareness and Brain Function Monitoring” was approved for publication in October 2005. There is controversy within the anesthesia community as to whether this level of attention is disproportionate to the frequency of the occurrence of this anesthetic complication or whether it focuses needed attention and research on an under-recognized problem with significant sequelae.

This article reviews the literature on the definition, incidence, and causation of unintended intraoperative awareness. Strategies for preventing awareness with specific emphasis on the role of brain function monitoring are reviewed. The importance of recognizing episodes of awareness and treating patients after an episode, with the goal of preventing long-term complications, is delineated. The implications for individual clinicians and departments of the ASA practice advisory and JCAHO sentinel event alert are discussed.

DEFINITION AND INCIDENCE

Consciousness during general anesthesia can be conceptualized using an iceberg metaphor, with explicit recall of intraoperative events spontaneously reported to the anesthesiologist being the visible part of the iceberg and other phenomena, such as unreported explicit recall, implicit recall, and
intraoperative dreaming, forming the submerged portion (Fig. 1). This analogy should not suggest a simple continuum, because the relationships between these areas of consciousness during general anesthesia are not delineated precisely.

Intraoperative awareness is the explicit recall of intraoperative events confirmed by a structured postanesthetic interview, most commonly the modified Brice questionnaire (Box 1) [2]. Episodes of awareness are classified into possible and confirmed awareness, primarily based on expert review of the detail and content of the reported memory. This distinction can be difficult to make with certainty. Patients who have experienced awareness during anesthesia commonly describe auditory perceptions, the sensation of paralysis, sensations associated with laryngoscopy, anxiety, helplessness, and, less frequently, pain [3].

Implicit recall involves changes in performance or behavior that are produced by previous experiences without any conscious recollection of those experiences. Implicit recall has been studied by using a variety of techniques such as auditory cues simulating an intraoperative crisis, word completion tests, and monitoring postoperative patient responses to commands given under anesthesia. Studies of implicit recall have demonstrated inconsistent results: some have suggested dramatic postanesthetic responses under hypnosis, whereas others found no conclusive evidence for implicit recall [4,5].

Intraoperative dreaming is less amenable to study, and its significance is unknown. The incidence of intraoperative dreaming and implicit recall seems to be higher than explicit awareness and may be associated with some adverse outcomes such as postoperative sleep disturbance and anxiety.

Fig. 1. The iceberg of consciousness during general anesthesia.
In 2004 Sebel and colleagues [6] completed the first large-scale prospective study of awareness in anesthesia practice in the United States, reporting an incidence of awareness of 0.18% in 19,575 patients. In a study from Sweden, Sandin and colleagues [7] reported an incidence of 0.16% in 11,785 patients. In a study of patient satisfaction with anesthetic care conducted by Myles and colleagues [8] in Australia, 12 of 10,811 patients (0.11%) reported awareness. Thus, all of the incidence data published since 2000 from three different continents have been remarkably consistent. These studies were optimized for the capture of incidents of intraoperative awareness by their prospective design utilizing multiple postoperative interviews. Ranta and colleagues [9] from Finland reported an incidence of 0.4% in a prospective study published in 1996, and in 1991 Liu and colleagues [10] detected awareness with a single postoperative interview in 0.2% of patients. Some surgical procedures seem to be associated with a higher incidence of awareness: major trauma (11%–43%) [11], cardiac surgery (1%–9%) [12,13], and general anesthesia for cesarean section (0.4%) [14].

ETIOLOGY
Awareness of intraoperative events during general anesthesia is the result of an imbalance between the requirement for and the delivery of anesthesia. It has been associated with patient and operative factors and with problems with anesthetic delivery systems.

The infrequency of awareness events makes the review of awareness cases the most effective tool for the analysis of etiologic factors. The database from the Closed Claims Project [15] contained 79 cases for analysis as of 1999. Bergman and colleagues [16] contributed reports of 50 definite and 31 highly probable cases of awareness in the Anesthetic Incident Monitoring Study (AIMS), a voluntary anonymous reporting system based in Australia.

Both databases distinguish between episodes of awareness under anesthesia and cases of awake paralysis, with 18 of 79 (23%) of the Closed Claims and 32 of the 81 (40%) AIMS cases being caused by a medication error resulting in inadvertent paralysis of an awake patient. These errors usually involve syringe swaps, medication labeling problems, or technical problems with the intravenous line on induction. Of the awareness cases that were not caused by awake paralysis, vaporizer and circuit problems were considered causal in 13% to 20%.

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**Box 1: The modified Brice questionnaire**

What was the last thing you remember before you went to sleep for your operation?
What was the first thing you remember after your operation?
Can you remember anything in between these two periods?
Did you dream during your operation?
What was the worst thing about your operation?
In patients who have hemodynamic instability because of limited anesthetic tolerance, anesthesiologists often use hemodynamically stable anesthetic techniques (eg, nitrous/narcotic/relaxant) and decrease the concentration of potent inhalational agent. These strategies were related to awareness in 36% of the Closed Claims (11 cases of nitrous/narcotic/relaxant use and 11 cases in which potent inhalational agents were decreased or discontinued) but in only 5% of the cases in the AIMS analysis (four cases).

The Closed Claims Analysis reviewed eight cases in which the cause of awareness was considered to be failure to adjust the dose of induction hypnotic medications for the altered pharmacokinetics of a morbidly obese patient. The increasing prevalence of morbid obesity in patients presenting for anesthetic care makes this an area requiring careful attention.

In both of these series, 6% of the cases of awareness were considered to be caused by problems posed by the management of difficult airways, including difficult ventilation leading to compromised delivery of inhaled anesthetic and/or failure to redose induction hypnotic medications.

Patients have described vividly the trauma of being paralyzed and aware, putting the use of neuromuscular blockade with inadequate anesthesia at the heart of any analysis of the etiology of awareness. In the prospective case study of 11,785 patients by Sandin [7], the incidence of awareness was 0.18% in cases in which neuromuscular blocking drugs were used and 0.10% in their absence. The important qualitative difference in the accounts of patients who were paralyzed and aware versus those who were not should be considered when assessing the incidence and also the severity of the impact of awareness with paralysis [3,17–19].

Total intravenous anesthesia (TIVA) may be more likely to result in cases of awareness because of the wider variability in patient response to intravenous anesthetic agents versus potent inhaled agents and the absence of a clinically available measurement or proxy of agent concentration at the target site. The studies on this topic are inconclusive. Two large case series examining TIVA and awareness generated incidences up to 0.2% [7,20], whereas a smaller TIVA trial using a fixed dose of propofol of 100 µg/kg/min reported an incidence of awareness of 7% [21]. The causes of awareness with TIVA seemed to be equally divided between technical problems in anesthetic delivery and greater-than-expected anesthetic requirement.

In all studies of awareness under general anesthesia there seem to be cases in which there is no identifiable cause for the episode. In both the Closed Claims and AIMS studies, 16% of the cases fit this description. Subtler cases of suboptimal anesthetic performance are difficult to detect in any type of study design and probably account for a proportion of awareness. The wide variability in anesthetic requirement and hemodynamic tolerance of anesthesia among patients almost ensures that there will be cases in which the most experienced and vigilant anesthesiologists may not be able to avert awareness while pursuing the primary goal of supporting the patient’s life (Box 2).
STRATEGIES FOR PREVENTION OF AWARENESS

The goal of preventing awareness is inseparable from the provision of good general anesthesia; therefore, many of the individual factors useful for the prevention of awareness are not amenable to randomized prospective study. With the notable exception of Bispectral Index (BIS) monitoring [22], the strategies for prevention are based on data from the case-report literature and pharmacologic studies. The ASA Task Force on Intraoperative Awareness recognized the limitations of the evidence supporting various individual strategies for the prevention of awareness and consequently recommended a multimodal approach to awareness prevention [23]. A summary from the “Practice Advisory for Intraoperative Awareness and Brain Function Monitoring” is provided in Appendix 1.

Anesthesia machine maintenance and testing along with efforts to avoid syringe swaps and medication errors are fundamental to anesthetic safety and are the essential first steps in an awareness-prevention strategy. Particular attention should be directed to the conspicuous identification of neuromuscular blocking agents and to the timing and technique of administration of these medications.

During the preoperative interview and chart review, the anesthesiologist should identify higher-risk patients and situations for awareness. These situations include anesthesia for patients who have limited cardiovascular reserve (eg, high-risk cardiac surgery, acute trauma with hypovolemia), emergency cesarean section, a history of opioid, benzodiazepine, alcohol, or protease inhibitor use, a history of awareness under anesthesia, and anatomy consistent with a difficult airway [22]. Identification of patients at risk optimizes the opportunity for prevention planning and discussion with the patient regarding awareness.

Vigilant observation and timely response to the patient’s vital signs and reflex responses (lacrimation, sweating, flushing) are also central to anesthetic

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**Box 2: Etiologic factors for awareness**

- Medication errors involving neuromuscular blockade
- Vaporizer and circuit problems
- Increased anesthesia requirement caused by concomitant medications and conditions
- Light anesthesia
- Limited cardiac reserve and hemodynamic instability
- Intravenous line or syringe pump problems with total intravenous anesthesia
- Nitrous oxide/narcotic/relaxant techniques
- Routine use of complete neuromuscular blockade
- Management of the difficult airway
- Failure to adjust induction doses for morbidly obese patients
care. Moerman and colleagues [19] undertook a blinded assessment of the anesthetic records of patients who had experienced awareness. Their study admittedly is subject to the limitations of the written anesthesia record [24,25], but their analysis of 12 cases revealed blood pressure and heart rate in the normal range in 4 patients (33%). The Closed Claims Analysis [15] and a study of TIVA [20] also documented the limited predictive value of vital signs in the identification of awareness. The problem of a lack of correlation between the expected appearance of hypertension and tachycardia with awareness is compounded further by the use of agents such as beta-adrenergic blockers and calcium-entry blockers to achieve intraoperative hemodynamic goals.

Patient movement in response to a surgical stimulus is, of course, the defining variable for the minimal alveolar concentration (MAC) of inhalational agents and is an important factor in the clinical assessment of anesthetic depth in unparalyzed patients. When neuromuscular blockade is used, an objective measure of the degree of muscle weakness should be monitored, and an attempt should be made to titrate the paralysis to a level that is acceptable but less than total. Patient movement as an early sign of light anesthesia has the advantage of having the eyes and hands of the entire surgical team aiding the anesthesiologist’s vigilance, because surgeons usually comment on patient movement immediately and request prompt treatment.

Most patient movement under anesthesia is mediated by spinal cord level reflexes, providing the anesthesiologist with an opportunity to address it before it becomes a manifestation of awareness with explicit recall. Frequently, even purposeful movement in response to command is not remembered by patients under anesthesia [26]. In patients with restrained extremities and protected eyes, it may be impossible to differentiate a reflex movement from an attempt by the patient to alert the anesthesiologist to awareness. For that reason, the anesthesiologist’s response to patient movement should never be the administration of neuromuscular blockade alone. Patient accounts of awareness have described the distressing scenario of being reparalyzed rather than reanesthetized when moving in an attempt to indicate their predicament.

As an individual factor contributing to the clinical composite of the depth of anesthesia, lack of movement in an unparalyzed patient is extremely useful but is not a guarantee of adequate anesthetic depth. Case reports provide evidence that even in the absence of neuromuscular blockade, not all patients will move during an episode of awareness [7,20].

Pharmacologic evidence supports the use of benzodiazepines to induce anterograde amnesia and decrease awareness, but the evidence from clinical studies is less conclusive. A single randomized clinical trial evaluating the preventive administration of midazolam for procedures under a fixed-dose TIVA technique reported a lower frequency of intraoperative awareness in the midazolam-treated group [21]. This study reported an exceptionally high incidence of awareness (7% overall; 19% in the placebo group, and 3% in the midazolam group) in an outpatient orthopedic surgery population. This awareness incidence is at odds with most of the studies in this area and may limit the
generalizability of its findings. In their large case series, Sandin and colleagues [7] reported no difference in the incidence of awareness between patients who had received benzodiazepines before anesthesia and those who had not.

For patients whose preoperative assessment or evolving intraoperative hemodynamic status indicates that they probably will be intolerant of an anesthetic dose of volatile anesthetic agents, the administration of intravenous amnestics should be considered. Although there is a paucity of solid evidence to guide the practitioner in this area, all anesthesiologists should consider a plan for the provision of amnesia when a substantial decrease of anesthetic depth seems to be necessary during times of extreme hemodynamic instability. These strategies may involve the use of benzodiazepines, ketamine, or scopolamine. In cases of hemodynamic instability and minimal anesthesia with the possibility of patient awareness, it may be helpful to reassure patients verbally regarding their care at the time of the crisis.

With regard to retrograde amnesia, reports from the Closed Claims database are notable for their descriptions of cases of awake paralysis caused by medication error. In these cases the anesthesiologists often had attempted to avert awareness with the administration of a rescue dose of amnestic medication immediately upon realization of the error but, in the context of having been reported as a Closed Claim, obviously without success [15].

Volatile anesthetics are central to strategies to prevent awareness. In spite of their long history of use, conclusions remain tentative concerning the exact MAC level that will ensure lack of recall. Authors in the field have proposed a range from 0.45 to 1.2 MAC [27–29], taking coadministered medications into consideration. Ghoneim [30] suggested the awareness-suppressing MAC of potent inhalational agent is 0.6 when supplemented by nitrous oxide and opioid and 0.8 to 1 when used alone. An examination of the references supporting these assertions reveals that they are based on clinical experience and relatively small studies of response to stimuli and learning under anesthesia. These studies frequently were not performed while administering a surgical stimulus, nor were they all performed using a balanced anesthetic technique. Therefore their precise relationship to the level of potent inhalation agent that reliably suppresses awareness in a clinical setting is unknown. There have been no randomized trials or prospective dose-finding studies in a large number of patients to establish an end-tidal concentration of an inhalational agent that reliably suppresses awareness. The questionable ethics of any prospective dose-finding study means the state of knowledge regarding potent inhalation agents and awareness is unlikely to advance beyond the present level of evidence, which is based on expert opinion and case reports.

The data for the case series of Sandin and colleagues [7] were gathered at a transitional time during the incorporation of end-tidal anesthetic concentration monitoring into clinical practice. In this series, the use of this technology did not seem to have a demonstrable impact on the incidence of unintended intraoperative awareness, because end-tidal agent monitoring was used in 83% of the reported cases of awareness. If the anesthesiologist titrates the agent
to a specific end-tidal concentration, then the monitoring modality is only as good as the underlying conclusions regarding the MAC required to suppress awareness. At the very least, end-tidal agent monitoring can alert the anesthesiologist to a vaporizer or circuit problem by indicating a discrepancy between the intended and the delivered anesthetic level, one hopes before this discrepancy becomes a problem leading to awareness.

The importance of maintaining professionalism in communication about the patient under anesthesia is obvious from the perspective of courtesy and respect, but this practice also may have a role in the prevention of awareness. There is evidence suggesting that patients under anesthesia more readily recall information that is emotionally charged for them [3,5,17,19]. Patients have been able to provide verbatim postoperative accounts of derogatory remarks made about them while under anesthesia, suggesting that the particular content of an auditory stimulus may move it from the status of unremarkable background sound to explicitly recalled conversation.

**BRAIN FUNCTION MONITORING IN THE ASSESSMENT OF DEPTH OF ANESTHESIA**

In spite of the historic limitations in measuring depth of anesthesia, anesthesiologists have managed to provide anesthesia without awareness in about 499 out of every 500 patients without brain function monitoring. Brain function monitoring of the depth of anesthesia must therefore have a very high degree of sensitivity and specificity for it to add safety to standard monitoring and practice.

The first broad division in depth of anesthesia monitors can be made between those that process the spontaneous electroencephalographic and/or electromyographic activity and those that process auditory evoked potentials (AEP). The processing algorithms involved in the conversion of the electroencephalographic signal to digital data and artifact recognition may be either published and in the public domain or proprietary. The systems have been designed to generate dimensionless indices with scales representing the differentiation between the awake state and various depths of anesthesia.

AEPs are the electrical responses of the brainstem, the auditory radiation, and the auditory cortex to sound stimuli delivered through headphones. The early cortical responses and the middle-latency AEP change with increasing depth of anesthesia with either inhaled or intravenous agents, whereas the brainstem responses are relatively insensitive to anesthetic effects. The high-frequency components of AEPs are detected in responsive but not in unconscious patients [31]. These signals are extremely small and require signal filtering and averaging for their accurate detection and analysis. There is currently no widely available AEP monitoring technology for clinical anesthetic care.

The proprietary Bispectral Index algorithm of Aspect Medical Systems has the most extensive research support and clinical use of all the depth-of-anesthesia monitoring systems. The original algorithm was based on data prospectively gathered from 1500 different anesthetics and has gone through
a number of iterations since its first derivation. These updates were intended to address problems reported to the manufacturer and in the literature. The most common remaining problem is interference with signal quality by the use of electrocautery. A less commonly recognized problem, but one of concern, a problem with the monitor, was raised by a study of paralysis in awake volunteers [32]. The investigators reported that during succinylcholine-induced neuromuscular blockade preceded by a defasciculating dose with no hypnotic medications, the BIS declined in all subjects and in one subject declined to a low of 10. This study was performed with the older A-1000 BIS monitor. More recent product information provided by Aspect acknowledges that the administration of neuromuscular blocking agents will alleviate electromyographic artifact and may result in a spurious decrease in the BIS number. Volunteer participants in awake paralysis studies describe a “sleepy” sensation associated with the deafferentation of muscle paralysis that may contribute to this effect of neuromuscular blockade on the BIS number. A number of other factors have been reported to interfere with the degree of correlation between the BIS number and the patient’s state of consciousness. Although these factors have the potential to undermine the anesthesiologist’s confidence in the accuracy of the monitor, it is less likely that these factors will contribute to an increase in awareness, because the majority manifest as higher-than-expected BIS numbers or numbers displayed with a low signal quality index alerting the provider to the potential problem. A summary of a number of these factors is presented in Table 1 [33].

In 2004 Myles and colleagues [22] published a trial in which patients suspected of being at higher risk for awareness were assigned randomly to either standard anesthetic care or to care in which the anesthesiologists were advised to maintain the BIS number between 40 and 60 from induction until emergence. The blinded assessment by repeated, structured postanesthetic interviews revealed explicit conscious recall of intraoperative events in 2 of 1225 patients (0.16%) in the BIS-monitored group and in 11 of 1238 (0.89%) in the routine care group. This finding was sufficient to demonstrate a statistically significant reduction in awareness in the monitored group by a narrow margin, one case. If the cases of possible awareness were included in the analysis, the difference was not significant. The classification of the cases was blinded, however, eliminating observer bias from contributing to this difference.

Ekman and colleagues [34] published the results of a cohort study using historical controls with similar results. Two patients in the BIS-monitored series of 4945 patients experienced explicit awareness (0.04%), whereas 14 of 7826 patients (0.18%) in the historical controls experienced awareness, again a statistically significant 80% reduction in awareness. The impact of the study is diminished by the use of historical controls, leaving open the possibility that factors other than BIS monitoring (eg, increased use of end-tidal anesthetic monitoring) may account for the decreased incidence of awareness in the later cohort.

The study by Sebel and colleagues [6] in 2004 generated an incidence in the BIS-monitored group of 0.18% and an incidence of 0.10% in the group in which
BIS monitoring was not used. This difference did not reach statistical significance and was part of a retrospective data analysis, limiting the validity of any conclusions that can be drawn from these data.

The studies by Ekman and colleagues[34] and Myles and colleagues[22] each reported two cases in which BIS monitoring was employed but the patients experienced awareness. Three of the four cases were similar in their timing and in the BIS numbers recorded, that is, memories of laryngoscopy and the immediate postinduction period, with BIS numbers higher than 60. This finding indicates not so much a failure of the monitoring technology as a failure to administer a sufficient anesthetic dose with a BIS monitor in use.

### Table 1
Effect of anesthetic agents, electric devices, different clinical conditions, abnormal electroencephalographic patterns, electromyographic activity and neuromuscular blockade on Bispectral Index monitoring

<table>
<thead>
<tr>
<th>Effect</th>
<th>Bispectral Index Model</th>
<th>Bispectral Index Change</th>
<th>Explanation</th>
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<td>N₂O termination</td>
<td>A-1000</td>
<td>Paradoxical BIS ↓</td>
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<td>Ketamine</td>
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<td>A-1000</td>
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<td>High BIS</td>
<td>Different cortical effect</td>
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<td>Artifact</td>
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</table>

Abbreviations: BIS, Bispectral Index; EEG, electroencephalographic; EMG, electromyographic; NMBD, neuromuscular blocking drugs.

Modified from Dahaba AA. Different conditions that could result in the Bispectral Index indicating an incorrect hypnotic state. Anesth Analg 2005;101:767.
The other BIS-monitored awareness case in the Myles study and a number of other reported cases in the literature indicate that the use of a BIS monitor to titrate the anesthetic level between 40 and 60 might not guarantee prevention of awareness [35–37]. The details of one case report published in May 2005 are notable [35]. In the setting of a presumed functioning thoracic epidural and hypotension treated with vasopressor and fluids, the sevoflurane component of the general anesthesia for an open gastric bypass was titrated to an average BIS number of 44, with no number greater than 51, and a resulting end-tidal concentration as low as 0.45%. Despite an “appropriate” BIS target, the patient emerged from anesthesia with a vivid account of awareness.

The emotional impact of the accounts of patient awareness occurring during BIS monitoring is powerful, but the evidence provided by these case reports does not supercede that of a randomized clinical trial that has demonstrated the utility of the BIS monitor in patients at high risk for awareness. These case reports emphasize the importance of using a multimodal approach to prevent awareness and of not overly relying on any one monitor, even processed electroencephalographic monitors.

The ASA task force report [23] provides a synthesis of the literature in this area and a survey of consultants and ASA members for their expert opinion on the use of brain function monitoring. Notably, the majority of those surveyed agreed or strongly agreed with the statement that brain function monitoring is valuable and should be used for: patients who have conditions that may place them at risk for intraoperative awareness, patients requiring smaller dosages of general anesthetics, patients undergoing cesarean section under general anesthesia, and patients undergoing trauma surgery under general anesthesia. In its summary, the task force concluded (1) brain function monitoring is not routinely indicated for general anesthesia patients, and (2) the decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients (eg, light anesthesia).

**COMPLICATIONS ASSOCIATED WITH AWARENESS AND EXPLICIT RECALL**

Awareness during anesthesia is important because of the distress that the patient may experience during the episode itself and because of the long-term complications that the episode may cause. In the early 1960s reports began to appear of traumatic neuroses in patients who awakened with paralysis during surgery. The common symptoms were repetitive nightmares, generalized anxiety, irritability, and a preoccupation with death [38]. The diagnosis of post-traumatic stress disorder (PTSD) was introduced to psychiatric practice after these reports, but these initial descriptions of traumatic neuroses after anesthesia awareness fit the PTSD criteria.

Lennmarken and colleagues [39] reported on the psychologic sequelae in patients identified in the prospective study by Sandin and colleagues [7] as having experienced awareness during anesthesia. Approximately 2 years after the intraoperative event, only 9 of the 18 patients who had been identified by the
study could be contacted and would agree to be interviewed. Of the nine patients who were interviewed, four were experiencing symptoms that met the diagnostic criteria for PTSD. The study is significant as an attempt to gather data on a consecutive series of patients who had experienced awareness. Detailed information is available for only half the cases of identified awareness, and there is no matched group of case controls who underwent similar surgical procedures without awareness. This lack of data limits the scope of the conclusions that can be drawn from this study regarding the incidence of PTSD after awareness. If all nine of the patients lost to follow-up were free of symptoms, the incidence of PTSD after awareness would be 4 of 18 (22%); obviously, the incidence could be higher if this assumption is false. The Closed Claims database [15] reported an incidence of PTSD of 10% among claimants in cases of awareness.

The idea that paralysis with awareness leads to a more traumatic experience is supported by Lennmarken and colleague’s [39] follow-up on two of the nine patients who did not receive neuromuscular blockade during their episode of intraoperative awareness. Neither of these patients had symptoms meeting PTSD criteria. In this small group of patients, the memory of pain with awareness was less common (one of nine) than anxiety (five of nine), and all four patients who had PTSD came from the group who reported experiencing anxiety during their awareness episode.

An important finding in this study is that only half the patients who met the PTSD diagnostic criteria had sought help with their symptoms before their interview. This finding is consistent with another study indicating that there may be reluctance to report an episode of awareness and to seek help for the problems that are associated with it [19]. Patients also have reported their belief that their account of awareness was not received empathetically by health care providers, including anesthesiologists, or even by their family members.

The symptoms that patients experience after awareness may be severe enough to disrupt all aspects of daily life. Patients have reported that even the simple act of lying flat on their backs can trigger the intrusive memories and anxiety associated with the episode, making sleeping in a bed impossible for them. Other reports indicate symptoms that are more limited in their impact but nonetheless significant, such as a loss of confidence in anesthesia and severe anxiety at the thought of having to undergo surgery and anesthesia in the future.

The JCAHO sentinel event alert [1] provided the following postoperative guidelines for anesthesia providers of a patient who has experienced an episode of awareness:

- Interview the patient after the procedure, taking a detailed account of his or her experience, and include it in the patient’s chart.
- Apologize to the patient if anesthesia awareness has occurred.
- Assure the patient of the credibility of his or her account and sympathize with the patient’s suffering.
- Explain what happened and its reasons (eg, the necessity to administer light anesthesia in the presence of significant cardiovascular instability).
• Offer the patient psychologic or psychiatric support, including referral of the patient to a psychiatrist or psychologist.
• Notify the patient’s surgeon, nurse, and other key personnel about the incident and the subsequent interview with the patient.

**MEDICOLEGAL IMPLICATIONS OF AWARENESS**

Awareness claims accounted for 1.8% of all claims within the Closed Claims Project database [15]. In the United Kingdom awareness claims formed a larger proportion, approximately 12% [39] of all claims against anesthesiologists, whereas a Finnish study [41] revealed a proportion of claims similar to that in the United States (1%) [40]. This frequency is similar to claims for conditions such as aspiration pneumonia and myocardial infarction.

The Closed Claims Project made the distinction in their analysis between claims for awake paralysis and for awareness under anesthesia. The anesthesia care was judged to be substandard in 96% in the awake paralysis claims and in 44% of other claims for awareness. Payments for claims were made in 76% of cases of awake paralysis, with a median payment of $10,250 (range, $1000–$215,000). In other claims for awareness, payment was made in 56% of cases, with a median payment of $20,000 (range, $1700–$750,000).

The payments for malpractice claims generally are higher for conditions for which there is a recognized monitor for prevention. The emergence of the BIS monitor, coupled with the increased attention in the media to awareness under anesthesia and brain function monitoring, theoretically may lead to both increased claims for awareness and increased payments for claims.

**IMPLICATIONS FOR DEPARTMENTS**

After the JCAHO sentinel event alert, the issue of unintended awareness under general anesthesia is likely to be a focus for future JCAHO inspections of anesthesia departments. Every department should demonstrate documentation and implementation of an anesthesia awareness policy that addresses the recommendations from the sentinel event alert:

1. Identify patients at proportionately higher risk for an awareness experience and discuss with such patients, before surgery, the potential for anesthesia awareness.
2. Effectively apply available anesthesia-monitoring techniques.
3. Apply timely maintenance of anesthesia equipment.
4. Actively follow up all patients who have undergone general anesthesia, including children, using an interview structure such as the modified Brice questionnaire.
5. Identify, manage, and, if appropriate, refer patients who have experienced awareness.
6. Assure access to necessary counseling or other support for patients who are experiencing posttraumatic stress syndrome or other mental distress.

Neither the JCAHO sentinel event alert [1] nor the ASA task force report [23] indicated that brain function monitoring for the assessment of the depth...
of anesthesia is required or standard monitoring. Any decision about the use of brain function monitoring technology for patients remains with the department and the individual clinician.

The economic implications for anesthesia departments of utilizing brain function monitoring go beyond its role in the prevention of awareness. There are direct and indirect financial costs associated with the occurrence of awareness that may be offset by the use of brain function monitoring for prevention. Myles and colleagues [22] estimated that with a cost of routine BIS monitoring at $16 US per use in Australia and a number needed to treat of 138, the cost of preventing one case of awareness in high-risk patients is about $2200 US.

There is some evidence suggesting decreased use of anesthetic agents and improved operating room efficiency when brain function monitoring is used. A meta-analysis analyzing the cost-benefit of the use of BIS monitoring in ambulatory surgery estimated that BIS-monitored anesthesia costs $5.55 more per case [42]. This model used assumptions of anesthetic agent cost of $26 per case, cost savings of $40.49 for each case of postoperative nausea and vomiting prevented, postanesthesia care unit costs of $0.65/min, and a BIS strip cost of $15.48. The cost of the BIS monitor was not included in this calculation because various manufacturers offer different types of BIS monitors with various financial arrangements.

If the conclusion that BIS costs are $5.55 more per case is applied to the results of Myles and colleagues [22] for higher-risk patients using the formula: cost = price/(efficiency * incidence) [43], the cost per case of awareness prevented is $780. This conclusion is very sensitive to the underlying assumptions. If the purchase costs of the monitor are considered, if the cost savings in postanesthesia care unit time and anesthetic agents are not realized, and if the monitor is used in lower-risk patient groups, the cost per awareness case prevented will be substantially higher.

**SUMMARY**

Explicit recall under anesthesia occurs with a frequency in general anesthesia between 0.1% and 0.2%. A multimodal strategy that includes the use of brain function monitoring in high-risk cases is optimal for prevention of awareness. Awareness may be unavoidable under certain challenging anesthetic conditions. When awareness does occur, it can cause significant long-term disturbance to the patient’s health, including PTSD. The follow-up and treatment of patients who have experienced awareness should be proactive and probably will be a focus of JCAHO inspections of anesthesia departments.

**APPENDIX 1: SUMMARY OF AMERICAN SOCIETY OF ANESTHESIOLOGISTS PRACTICE ADVISORY**

Preoperative evaluation

- Review patient medical records for potential risk factors.
  - Substance use or abuse
Previous episode of intraoperative awareness
History of difficult intubation or anticipated difficult intubation
Chronic pain treated with high doses of opioids
American Society of Anesthesiologists status 4 or 5
Limited hemodynamic reserve

- Interview patient.
  - Level of anxiety
- Information regarding previous experiences with anesthesia
- Determine other potential risk factors.
  - Cardiac surgery
  - Cesarean section
  - Trauma surgery
  - Emergency surgery

- Reduced anesthetic doses in the presence of paralysis
- Planned use of muscle relaxants during the maintenance phase of general anesthesia
- Planned use of nitrous oxide-opioid anesthesia
- Patients whom the individual clinician considers to be at substantially increased risk of intraoperative awareness should be informed of the possibility of intraoperative awareness when circumstances permit.

Preinduction phase of anesthesia

- Adhere to a checklist protocol for anesthesia machines and equipment to assure that the desired anesthetic drugs and doses will be delivered.
- Verify the proper functioning of intravenous access, infusion pumps, and their connections, including the presence of appropriate back-flow check valves.
- The decision to administer a benzodiazepine prophylactically should be made on a case-by-case basis for selected patients (eg, patients requiring smaller dosages of anesthetics).

Intraoperative monitoring

- Use multiple modalities to monitor depth of anesthesia.
  - Clinical techniques (ie, checking for purposeful or reflex movement)
    - Neuromuscular blocking drugs may mask purposeful or reflex movement
  - Conventional monitoring systems (eg, ECG, blood pressure, heart rate, end-tidal anesthetic analyzer, capnography)
  - Brain function monitoring
    - Not routinely indicated for general anesthesia patients
    - The decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients (eg, light anesthesia)

Intraoperative and postoperative management

- The decision to administer a benzodiazepine intraoperatively after a patient unexpectedly becomes conscious should be made on a case-by-case basis.
- Speak with patients who report recall of intraoperative events to obtain details of the event and to discuss possible reasons for its occurrence.
- A questionnaire or structured interview may be used to obtain a detailed account of the patient’s experience.
• Once an episode of intraoperative awareness has been reported, an occurrence report concerning the event should be completed for the purpose of quality management.
• Offer counseling or psychologic support to patients who report an episode of intraoperative awareness.

A copy of the full text [23] can be obtained from the American Society of Anesthesiologists, 520 North Northwest Highway, Park Ridge, IL 60068.

References


[28] Chortkoff BS, Bennett HL, Eger EI II. Subanesthetic concentrations of isoflurane suppress learning as defined by the category-example task. Anesthesiology 1993;79:16–22.


An increasing numbers of awake intracranial procedures are being performed for various reasons. The author reviews anesthetic care for patients undergoing these complicated procedures. The goal of neuroanesthesiologists during these procedures is to facilitate safe, effective, pain-free surgery while maximizing patient comfort. The patient outcome goal is to control the neurologic problem and have minimal or no new postoperative deficit. The indications, contraindications, and preoperative planning and preparation of the patient and medical team for awake craniotomy are reviewed. The perioperative events for which patients must be deeply sedated and when they must be wide awake, yet comfortable, for the testing and resection of a lesion or placement of a stimulator are described. The major intraoperative difficulties that arise during many of these procedures and possible remedies are described. Pharmacologic options for sedation and analgesia are reviewed, as are medications that are contraindicated. Throughout the article there is a plea for continuous vigilance, building rapport with and communicating with patients, surgeons, and persons who are performing the intraoperative testing and monitoring— from preoperative evaluation through the procedure and postoperative course. Finally, the author stresses that anesthesiologists must carefully review and re-evaluate the surgeon’s expectations, patient selection, monitoring requirements, and alternative plans well in advance of the operation.

BACKGROUND OF AWARE INTRACRANIAL PROCEDURES

Awake neurosurgical procedures are being performed more frequently for a wider variety of indications and with better results. For example, one common indication for awake craniotomy is seizure focus excision. The earliest report of operative treatment of seizures was performed by Horsley in 1886 [1]. The first procedures were performed as measures of last resort and often left patients with major neurologic deficits. In the ensuing 120 years, these procedures have been refined greatly and often include intraoperative testing of...
awake patients. Even the lay literature has graphic depictions of the whole
testing and operative process [2].

Most awake intracranial procedures are performed in specialized centers by
experienced teams of surgeons and neuroanesthesiologists. For general consid-
erations, see Box 1 [3,4]. These specialists report a high success rate and low
rate of new postoperative neurologic deficit. They use careful intraoperative
monitoring either with electrocorticography (ECoG) or awake neurologic test-
ing. Each area that could be involved in the pathologic process is assessed care-
fully for vital brain function before proceeding with neurosurgical intervention.
A patient’s perioperative experience also has been improved dramatically with
advances in sedative and analgesic techniques [5,6]. The awake state allows the
inoperable lesion to become operable, because surgical intervention would
leave the patient with devastating neurologic deficits. Neurosurgical interven-
tions for lesions previously considered inoperable are increasingly being per-
formed awake. This technique allows for safe surgery, good neurologic
outcomes, no major anesthetic complications, and no permanent psychological
sequelae. The indications for awake craniotomy are being expanded as the in-
cidence of major complications decreases and success rate increases. Neurosur-
geons are performing more and more invasive procedures that require
intraoperative patient cooperation.

**INDICATIONS**
The first major indication for awake craniotomy is the need for intraoperative
assessment verifying preservation of neurologic function when the surgical
intervention involves an eloquent area of the brain. Examples include temporal
lobe surgery for seizure focus, tumor, or arteriovenous malformation (AVM)
excision [3,4,7]. The second major indication is the need to verify that the
neurosurgical intervention has controlled the patient’s neurologic problem,
such as the movement disorder of Parkinson’s disease [8,9]. Less involved procedures that are sometimes performed awake include drainage of chronic subdural hematomas and stereotactic biopsies of deep-seated brain lesions.

It should be noted that performing the operation under local anesthesia minimizes the impact of sedatives and anesthetic agents on intraoperative testing, such as ECoG and psychological and motor evaluation during the resection [7,10,11]. This approach allows for maximal control of the neurologic disorders with minimal risk of new neurologic deficit postoperatively (Box 2).

**CONTRAINDICATIONS**

The inability to communicate or cooperate, as with very young children and patients with mental impairment or behavioral problems, is a contraindication to awake intracranial procedures. For patients with complicating premorbid conditions, such as a difficult airway, the risks and benefits must be weighed carefully before proceeding with an awake neurosurgical intervention. Patients

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**Box 2: Indications and contraindications for awake neurosurgical procedures**

**Indications**
- Surgical intervention in or near an eloquent part of the brain
  - Seizure focus excision
  - Tumor resection
  - AVM resection
- Deep brain stimulator placement for movement disorders of Parkinsonism, multiple sclerosis, and generalized dystonia
- Chronic subdural hematoma
- Stereotactic biopsy
- Motor cortex stimulation
  - For refractory neuropathic pain

**Contraindications**
- Inability to cooperate or communicate
  - Small children
  - Mental impairment
  - Behavioral problems
- Complicating premorbid conditions
  - Difficult airway
- Inexperienced neurosurgical, anesthesia, testing, or nursing team
who are undergoing a brief, minimally invasive procedure, such as drainage of a subdural hematoma without pinning the head, are at much lower risk than patients who are undergoing a long and involved intervention with the head in pins. Surgery that involves a big AVM with large anticipated blood loss and minimal pulmonary reserve is possibly too risky to undertake with an awake procedure. An involved procedure should not be attempted by an inexperienced team or in a facility without extensive neurointensive postoperative care support (see Box 2).

PATIENT SELECTION
Craniotomy under local anesthesia is difficult for patients, surgeons, and anesthesiologists. Patients must be selected based on their level of maturity and the ability to understand the process from preoperative preparation to postoperative recovery [3,12]. In general, patients and their families have an excellent understanding of the chronic debilitating neurologic disorder for which the awake intervention is being considered. It is imperative, however, that patients and their support groups understand that they are voluntarily undergoing these procedures and that although a trusted, experienced team will perform the sedation, the testing, and the surgery, there is no guarantee that all of their neurologic problems will be eliminated.

The determination of whether it is worth undergoing an awake neurosurgical procedure is ultimately a patient’s decision. This technique maximizes surgical treatment success and minimizes postoperative neurologic deficits. Patients should be aware that other approaches are available. Perioperatively, there is a different set of potential benefits and complications for awake procedures compared with a craniotomy under general anesthesia for treatment of the same disorder. Physicians and patients should understand the benefits of awake intracranial procedures. They can be expected to be highly motivated to undergo life-prolonging tumor resections awake, if there is a reasonable hope of being neurologically intact afterward. Patients who undergo seizure focus excision are highly motivated and cooperative because this is a way to be liberated of most or sometimes all of their seizures, medications, and lifestyle limitations. The movement disorder patients, such as persons who have Parkinson’s disease, who undergo deep brain stimulator placement are highly motivated to be free of the disabling movement disorder and side effects of the medical therapy. Although there are some commonalities among these cases, each situation is unique because the comorbidities, pathologic brain abnormalities, and treatment goals vary. Each case has unique anesthetic, monitoring, and surgical requirements to be considered in patient selection and the risk/benefit assessment.

SURGICAL PLANNING AND LESION LOCALIZATION
Seizure focus, tumor, and AVM excision are relatively common conditions for which awake intracranial procedures are performed. The process of deciding who is a candidate for awake resection depends greatly on the location of
the lesion to be treated and the proximity of it to areas of the brain involved in language control (eloquent areas of the brain). When the lesion is in or near an eloquent area of the brain, speech and motor function must be tested during awake craniotomies.

Seizure focus excision is the most common indication for awake neurosurgical intervention at the author’s institution. Currently, 300,000 to 400,000 people in the United States suffer from seizure disorders. Approximately 10,000 new cases are diagnosed each year. Surgery at an early age is thought to improve later psychosocial status and adaptive function, which is related to fewer adverse effects of medications used to control epilepsy. Avoiding the cumulative effects of the negative psychosocial aspects of the disease is critical to most patients.

Several types of procedures currently are performed for seizure focus excision. They range from radical procedures (eg, temporal lobectomy, amygdalo-hippocampectomy, hemispherectomy, and corpus collosotomy under general anesthesia) to stereotactic excisions or multiple subpial transactions during awake craniotomy with intraoperative testing. There is no consensus as to the optimal combination of tests and conditions that go into the planning for an awake craniotomy to excise a seizure focus.

In the 1800s, the French anatomist Paul Broca first identified an area in the dominant frontal lobe that caused an expressive aphasia when lesioned (ie, it controlled motor mechanisms of speech)[2,13]. Shortly thereafter, a German neurologist, Carl Wernicke, identified a zone in the dominant, usually left, temporal lobe innermost internal capsule that controlled the ability to comprehend language and speak intelligibly[2,13]. Depending on the proximity or degree of overlap of the eloquent area of the brain and the pathology to be treated, patients are referred for specific interventions. Some patients undergo intracarotid amytal to lateralize speech and memory functions. Over time, functional mapping with MRI or intraoperative optical imaging of intrinsic signaling has allowed for clear delineation of specific eloquent areas of the brain relative to the lesion to be resected[14,15]. Via intraoperative testing, the final determination is made to intervene surgically or limit or abort the treatment. Asleep craniotomy is appropriate for lesions that are not located in or deep to eloquent areas of the brain. Radiosurgery is recommended for most patients in whom there is complete overlap of the eloquent area and the pathology. Awake neurosurgical procedures are most important for patients who require interventions close to or partially overlapping eloquent brain[14]. Concomitant intraoperative optical imaging of intrinsic signaling and awake testing allows for more reliable identification of multiple areas involved in speech, particularly in multilingual patients[11]. Less invasive and more localized procedures leave patients with fewer deficits.

Several methods are used to identify specific eloquent brain areas. Techniques are being developed to use some of these imaging techniques intraoperatively in anesthetized patients. They are performed in highly specialized centers with often expensive, somewhat cumbersome, and time-consuming
intraoperative functional imaging efforts [15,16]. Intraoperative imaging systems in and of themselves also present specialized new challenges for surgical and anesthetic teams but are well described and manageable [17].

**PREOPERATIVE EVALUATION**

Once a decision is made to perform a surgical intervention possibly awake, a neuroanesthesiologist should be involved in the preoperative decision-making process. The anesthesiologist, surgeon, and testing team must build rapport and gain a patient’s confidence preoperatively and reassure the patient during the procedure [3]. These goals are critical to the success of the whole process. If the anesthesiologist cannot communicate effectively with a patient or there is some underlying condition, such as a difficult airway, that would create a situation deemed too risky for a patient, the discussion of an awake procedure should not be continued. Meeting with a patient on several occasions also allows one to build rapport with him or her and facilitate intraoperative communication and cooperation during testing.

Ideally, a meeting takes place with the neurosurgeon, neurologist, patient, and his or her family or support group to review the requirements for the patient, monitoring, and surgical conditions. The team should present a timeline of the events that will occur on the day of the operation. Patients should be instructed about the testing process and made aware that they may experience transient deficits during the testing. Patients should be warned about the noise in the operating room and vibrations during parts of the procedure. They should be reassured that the anesthesiologist will be with them the entire time. Patients must know that it is important to verbalize concerns rather than move during the procedure. This meeting gives everyone involved a chance to get information, ask questions, and mentally prepare for the procedure to avoid surprises during the perioperative period. The neurosurgeons, family, and neurologists must be realistic about what can be accomplished.

**Stereotactic frame application and scanning**

Stereotactic frames are used for many of these awake neurosurgical procedures. Many surgeons apply them in the preoperative holding area and then send patients for a scan to allow for the final surgical planning. The application of the frame is painful, and patients must have at least local anesthesia administered before pin placement. The author administers the initial cutaneous local anesthesia with carbonated lidocaine via jet injection for the scalp block, pin placement, and any other painful procedures [18]. Alternatively, you can recommend that the surgeon warm and carbonate (0.1 mEq Na\(^+\) bicarbonate/mL of local anesthesia) the local anesthetic solution [19] and inject it slowly via a small needle to decrease the pain of infiltration [20]. The author sedates patients with small, titrated doses of remifentanil (6.25 \(\mu\)g intravenously slowly until respiratory rate is six to eight breaths per minute). Remifentanil works well for this part of the sedation because it is a potent analgesic and has such a short half-life that patients are not at risk for resedation in the scanner.
Anesthesiology personnel do not need to accompany patients to the imaging suite. The scanning, computerized planning, and integration of the scan with the stereotactic frame in place takes time. If you must give longer acting drugs for the frame placement, you must monitor patients and accompany them to the scanner. Alternatively you can recover patients until the effects of the sedation have worn off and then let them go to the scanner. Monitoring is becoming less of a challenge as more procedures are being performed using frameless stereotactic craniotomies [21].

Patients usually return to the preoperative holding area after the scan. You should wait until the neurosurgeon, monitoring team, all equipment, and personnel are ready before taking the patient into the operating room, which minimizes patient time on the table and potentially anxiety-producing time listening to preparations in the operating room. As sedation is titrated, also administer antibiotics and antiemetics, such as decadron and a 5 HT₃ (serotonin) blocker. Monitors, an arterial catheter, a central venous catheter, and a urinary catheter must be placed, the head must be shaved, and the scalp block must be performed.

THE SCALP BLOCK
The scalp block should be performed at least 20 minutes but not longer than 2 hours before the procedure. Performing the block well in advance of the procedure allows the local anesthesia to take full effect before surgical manipulation [3]. It also decreases the likelihood of local anesthetic toxicity. The greater and lesser occipital nerves, the auriculotemporalis nerve, zygomatico temporal nerve, and supraorbital nerves, each should be infiltrated with 3 to 5 mL 0.5% bupivacaine with 5 µg/mL epinephrine (Fig. 1) [22]. Deep infiltration of the temporalis muscle and fascia (from the supraorbital ridge to the posterior margin of the zygoma) and hemostatic field block should be performed around the time of skin incision with 50 to 60 mL of 0.25% to 0.33% bupivacaine with 5 µg/mL epinephrine. (This totals approximately 300 mg of bupivacaine in divided doses [3].) The epinephrine prevents rapid diffusion from the site of infiltration, which decreases potential toxicity of this large dose, prolongs the effect, and affords surgical hemostasis [3]. The analgesia lasts for 6 to 10 hours. The dura is also sensitive and should be infiltrated with plain 1% lidocaine during the surgical opening [3]. Sedation cannot overcome inadequate local anesthesia and continue to allow for safe and adequate conditions for surgery and testing. The surgeon may need to supplement the block to continue safely. Of note, brain tumors sometimes grow rapidly under the influence of pregnancy-associated hormones. These cases are occasionally encountered. If a patient is pregnant, consider using less bupivacaine or a combination of local anesthetic agents to avoid the cardiotoxicity of bupivacaine for the scalp block.

PREPARATION IN THE SURGICAL SUITE
The room should be quiet and the temperature as comfortable for the patient as possible. Everyone in the room must be aware that the patient is awake and
keep their conversations to a minimum, which facilitates communication among the neurosurgeon, monitoring team, patient, anesthesiologist, and nursing personnel. The patient should position himself or herself comfortably on the operating room table. Standard monitors and O₂ via nasal prongs with capnography capability should be applied. Special monitors, such as a precordial Doppler, should be considered. If the Doppler is used, the volume must be kept low so it does not interfere with communication. The stereotactic frame is secured to the operating room table and the patient may be put into a slightly head-up position. It is good to decrease the sedation temporarily to ascertain that the patient is comfortable with the head position and make slight adjustments if necessary. Make sure to pad pressure points and secure extremities that are not being tested.

The scalp is prepared and drapes applied, taking care to keep the face as free and accessible as possible to facilitate communication with the patient and help prevent claustrophobia. Airway interventions are also easier if they become necessary. Next, the local field block in the line of incision and deep temporalis infiltration is performed. At that time the patient can be sedated deeply with short-acting agents.

Fig. 1. Cutaneous nerves that provide sensory innervation to the scalp. Open circles show the points at which each nerve can be blocked most easily with local anesthetic injections. Bupivacaine 0.5%, approximately 3 to 5 mL, injected at each of the points shown delivered 20 to 60 minutes before the start of surgery provides stable anesthesia for the procedure. (From Grivin JP. Neurosurgical considerations and general methods for craniotomy under local anesthesia. Int Anesthesiol Clin 1986;24(3):92; with permission.)
SURGICAL INCISION AND BONE FLAP REMOVAL

Skin incision should be uneventful if the local anesthesia has had enough time to take effect. Takedown of the temporalis can be stimulating secondary to heat buildup from the cautery, however. Local irrigation can reduce this buildup. The noise and vibration of the power drilling of the skull and bone flap elevation are stimulating. The patient should be warned before this takes place. Additional sedation is also appropriate in anticipation of these events. Alternately, the surgeon can open with a hand perforator and Gigli saw, which takes a little longer but is much quieter and better tolerated by patients. During these procedures, temporarily deepen the sedation carefully and treat any nausea with antiemetics. One can rely on the rapport developed with the patient.

Immediately after the bone flap is removed and the dura is reflected, the level of sedation should be reduced in anticipation of the testing and treatment phase of the operation. The patient should be aroused gently, and the team that is performing neuropsychiatric testing, ECoG, or the microstimulations should reiterate the process to the patient.

INTRAOPERATIVE TESTING

Testing is a stressful time for all personnel involved in the procedure. It is the time when the rapport you have built with the patient preoperatively is most important. The patient’s head is wide open, and the surgeon and testing team are making decisions as to what areas to resect or lesion based on the patient’s response to testing. During testing, transient changes in neurologic function often are experienced. In some cases, stimulus-induced speech arrest or inability to move a particular digit occurs. In other cases an abnormal movement may increase and decrease, or a seizure may occur. Patients must be reassured that these things are exactly what is anticipated during testing and help to ensure that normal function will be preserved. The surgeon should be as aggressive as possible with interventions yet avoid inciting a new neurologic deficit. The surgeon should work as quickly as possible to keep the procedure tolerable for the patient.

TESTING FOR SELECTED NEUROSURGICAL PROCEDURES

Seizure focus excision

Cortical mapping is required for this procedure. It is a meticulous, time-consuming process. Sometimes subdural grids are placed during asleep craniotomy approximately 1 week before the resection. Extraoperative monitoring for seizure activity and testing of eloquent areas is performed (Fig. 2). Origins of the seizures and areas that the seizure spreads to are identified. For cases in which the area causing the seizure is in close proximity to or overlaps with eloquent brain, the areas are repeatedly tested intraoperatively to determine that eloquent brain is preserved during the surgical treatment. Based on the mapping, multiple subpial transections are performed or areas are resected. Where the superficial tissue was removed, the tissue deep to it is tested for seizure activity. Incremental resection of small areas is performed. It can be a prolonged process that tries everyone’s patience.
Arteriovenous malformation or tumor resection
During awake AVM or tumor resection, the team tests neurologic function as the resection proceeds. The anesthesiologist must keep in constant communication with the surgeon and administer appropriate fluids, blood products, and medications without alarming the patient.

Deep brain stimulators
Deep brain stimulator placement is performed to treat Parkinsonism and other movement disorders, including generalized dystonia, tremors of multiple sclerosis, and refractory epilepsy [8,9]. The lasting effects of these procedures are sustained improved motor function and decreased dosage requirement for chronic medications [9]. Patients are not sedated or only lightly sedated throughout. The procedures are performed through small bilateral incisions and bur holes with the patient in the supine, slightly head-up position. Patients are off their chronic medication and are often highly active with uncontrollable abnormal movements. Patients must refrain from taking their medications before surgery for movement disorders because surgeons must be certain the abnormal movements are controlled during the intraoperative trial of the stimulator leads. As the stimulator is positioned and activated carefully, the abnormal movements abate and the normal functions are preserved. Early stimulator placement leads to fewer side effects of the chronic illness and medical therapies.

In many centers, neurosurgeons perform deep brain stimulator placement without any sedation or anesthesia personnel present. In the United States, anesthesiologists are usually present to monitor the patient and tend to any emergencies that might arise. When performing sedation for deep brain stimulators, one is much less limited in the choice of medications. Benzodiazepines

![Fig. 2. Example of the lateral aspect of left hemisphere with two mapping grids. Using extraoperative mapping, each electrode is depicted as an open circle and is numbered. Eloquent brain is marked as a circle with a dot in it. Seizure focus is depicted as a circle with lines radiating from it. The decision as to whether to perform the resection in the awake patient depends on the amount of overlap between the areas of seizure focus and eloquent brain. Any areas of overlap are carefully tested intraoperatively before intervention.](image)
and other medications with anticonvulsant properties are not a problem. Metoclopropamide, phenothiazines, and butyrophenones, all medications that may block dopamine receptors centrally, should be avoided. Caution must be used to keep patients in a completely cooperative state. Many interesting issues, usually related to the underlying disorder, can arise during these minimally invasive procedures.

In one case, a patient who had Parkinson’s disease was experiencing such vigorous movements accompanied by profuse sweating that it was difficult to carry out the procedure and the monitoring. She also was being treated for mild nausea, which she related to having her head in a fixed position when her body was moving so much. Eventually, hypoglycemia from all the energy expenditure was diagnosed. A little intravenous glucose was given and she was able to go on with the testing. These procedures are truly amazing. Patients who could not hold a cup, let alone take a drink, usually can drink water from a cup without spilling after the placement and activation of the deep brain stimulator [9].

**COMPLICATIONS**

Airway obstruction/hypoventilation

Many varied complications may arise during awake craniotomy [3,23–25]. Some of the most severe and most common complications are addressed in Table 1. At any time during the procedure patients may experience less stimulation relative to the degree of sedation and either become apneic or suffer airway obstruction. The anesthesiologist must open the airway immediately with a gentle jaw thrust or chin lift. Use caution so as to not startle the patient or move the surgical field. Warn the surgeon before touching the patient’s head. If repositioning does not help resolve the situation, try inserting an oral or nasal airway. This process is usually too stimulating for the patient to tolerate and he or she breathes well enough after the attempted placement not to require it any more. If the airway is properly placed and ventilation is still inadequate, however, bag mask ventilation should be performed. Sometimes the stereotactic frame is low over the patient’s nose so that the mask must be turned sideways. In this position, the side of the mask can be placed to occlude the nose while ventilating through the mouth. The patient also may move and strain during the process, which usually means that he or she will resume breathing once the obstruction is relieved.

In a situation that requires continued airway support, if at all possible place a laryngeal mask airway or other minimally stimulating oropharyngeal airway without removing drapes or frame. It is good to have practiced placing these devices from in front of the patient, using your thumb to guide them, before having to do it emergently in the awake craniotomy scenario [7]. Usually the positioning allows for enough oral opening such that the airway device can be slipped into place. Several cuffed pharyngeal airway devices can be used. For example, the King LT (King Systems Corp, Noblesville, Indiana) is less bulky than the LMA (The Laryngeal Mask Company Limited, Henley-on-Thames, United Kingdom) [26]. An endotracheal tube can be placed through either of these devices if it is deemed necessary. The anesthesiologist should use
techniques and devices with which he or she is familiar and comfortable. If this approach is not successful, the anesthesiologist can proceed with mask ventilation until the sedation wears off enough that a patient can maintain his or her own respirations. In the event of severe desaturation or airway emergency, the field must be covered and all or part of the frame removed to secure the airway. It is not necessarily a failure of skill to change to an anesthetized technique. It is in the patient’s best interest to convert to general anesthesia if he or she cannot tolerate the process or has a persistent or recurrent seizure, swollen brain, or other issue that requires more control of the airway. If, as the anesthesiologist in charge of the case, you convert to general anesthesia, remember to use a technique that allows for continued monitoring of the electrical activity of the brain, which allows the surgeon to complete the guided resection.

Shortness of breath
Patients must be reassessed for adequacy of ventilation and oxygenation. If either is inadequate, determine why and eliminate the cause, if possible. Conversion to general anesthesia with controlled ventilations should be considered.
Blowing air or oxygen by a patient’s face to prevent rebreathing of exhaled CO₂ might be helpful. It can enhance patient general sense of well-being because they are confined under drapes.

Tight brain
Tight brain is an infrequent occurrence but must be dealt with quickly to facilitate surgery and prevent herniation of the brain out of the calvarium. Mannitol and furosemide can be given, but the patient becomes uncomfortable with sensations of thirst and urinary urgency. Self-hyperventilation or doxapram can be used, but if these maneuvers do not prove satisfactory, patients quickly become uncomfortable. Slightly elevating the head of the bed and assuring that the neck veins are not compromised by clothing and monitors or extreme rotation often quickly relieve the problem. If none of these maneuvers works, a patient may have to undergo general anesthesia and controlled ventilation. Again, constant communication with the surgeon is important. If the procedure or the patient is being compromised, change to general anesthesia.

Intraoperative seizure
Approximately 16% of patients experience a seizure during awake craniotomy for seizure focus excision [24,25]. Most often it occurs as the neurosurgeon stimulates the area of interest. It may be typical of a patient’s seizures before surgery or different, depending on the relationship of the surgical stimulation to the patient’s intrinsic seizure focus. It is important to communicate quickly to the surgeon that you are observing a physical seizure. Often the seizure is localized to the face or an extremity initially but rapidly becomes generalized if not immediately interrupted. The neurosurgeon can irrigate the area with iced Ringer’s lactate to interrupt the seizure rapidly and reliably [27]. It also interrupts the ECoG briefly but is completely reversible. Administration of intravenous barbiturates or benzodiazepines as anticonvulsants interrupts the ability to stimulate and monitor for seizures for a longer time. Medications also take longer to control the seizure and may cause significant delays until effective monitoring can resume. If a patient goes into a persistent seizure, you must protect the airway and administer medications such as thiopental, propofol, or benzodiazepines to stop it.

Large blood loss
AVM resection can incite large blood losses. If this occurs, an assistant should be enlisted to deal with transfusion-related issues, so the person who developed the best rapport with the patient—hopefully the anesthesiologist—is able to focus on keeping the patient calm. With large volume transfusions, arterial oxygen desaturation can occur. If this happens, the patient must be intubated and ventilated.

Thirst
The patient should be warned that thirst might occur during the procedure, especially if mannitol or furosemide is administered. The anesthesiologist must depend on the rapport previously developed with the patient. Sometimes a little
ice or a damp cloth on the lips is helpful. Reassure the patient that the team is working as fast as possible and that adequate fluid is being given intravenously.

**Uncomfortable position**
The best way to avoid discomfort is to expedite the procedure after positioning. One also should rouse the patient after the head is positioned before surgical drape placement to be certain that the position is as comfortable as possible. Once the drapes are on and the skull is open, repositioning is daunting and ill-advised. Padding all pressure points as guided by the patient during initial positioning is crucial.

**Nausea and vomiting**
Preventing nausea and vomiting is key. Many factors can cause nausea—anxiety, pain, narcotics, and surgical manipulations, to mention a few. Patients should be premedicated with a 5-HT₃ blocker, metoclopropamide, and steroids. Narcotics should be minimized and some propofol should be used as an adjunct to the antiemetic regimen. The problem of nausea and vomiting intraoperatively is so dangerous and difficult to deal with that all these efforts to prevent it are warranted. Postoperative nausea and vomiting are actually less common after awake craniotomy than after asleep craniotomy [28].

**Urinary urgency**
Again, prevention is key. Using lidocaine jelly to lubricate the urinary catheter at the time of insertion is helpful. Minimizing intravenous fluids and avoiding diuretics are helpful. In some situations, catheterization is avoided completely during reliably short procedures.

**Claustrophobia**
Drape as openly as possible so the patient can see into an open, preferably well-lit area. Make sure the patient can see you, the anesthesiology provider, and can speak easily to you or motion to you with a free hand without disturbing the surgical field. In general, patients with fewer restraints are more comfortable. You must make the decision to allow a free extremity based on the patient’s ability to cooperate. If you sense that the patient will reach up and interfere with the procedure, gently restrain the hand or arm.

**Intolerance of the process**
If a patient squirms, the anesthesiologist must gain control. Do not force the surgeon to operate with a patient in a noncooperative state, which is far too dangerous and stressful for all involved. Either deepen the sedation slightly to gain control quickly (the author’s preference) or wait for the sedation to wear off enough to have a communicative, cooperative patient again.

**ANESTHETIC TECHNIQUES**
There are three general approaches and many variations to anesthetic care for patients undergoing awake intracranial procedures (Box 3) [3,6,7,29]. Each institution varies based on the types of cases being performed awake, the needs of
the surgeons, and the needs of the patients (see Table 1). The techniques range from asleep-awake-asleep with a secure airway during the asleep parts of the cases to monitored and comfort care only with interventions reserved for cases that become complicated. Each case is unique and anesthesia must be tailored to a patient’s specific needs.

Asleep-awake-asleep
Many practitioners put a patient to sleep with a formal airway for the initial part of the procedure. They awaken the patient and extubate the trachea for the testing and then reanesthetize the patient, and replace the endotracheal tube or laryngeal mask airway for the closure. What is done with airway

<table>
<thead>
<tr>
<th>Box 3: Anesthetic techniques</th>
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<tr>
<td><strong>Asleep-Awake-Asleep</strong></td>
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<tr>
<td>With airway</td>
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<tr>
<td>Laryngeal mask airway</td>
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<tr>
<td>King laryngeal tube</td>
</tr>
<tr>
<td>Endotracheal tube</td>
</tr>
<tr>
<td>Without airway</td>
</tr>
<tr>
<td>Supplemental O₂</td>
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<tr>
<td>Nasal prongs with CO₂ monitoring capabilities</td>
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<tr>
<td><strong>Monitored anesthetic care</strong></td>
</tr>
<tr>
<td>Supplemental O₂ and intervention only as needed</td>
</tr>
<tr>
<td><strong>Conscious sedation</strong></td>
</tr>
<tr>
<td>Supplemental O₂</td>
</tr>
<tr>
<td>CO₂ monitoring</td>
</tr>
<tr>
<td><strong>Sedative</strong></td>
</tr>
<tr>
<td>Propofol</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
</tr>
<tr>
<td><strong>Narcotic</strong></td>
</tr>
<tr>
<td>Remifentanil</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Sufentanil</td>
</tr>
<tr>
<td><strong>Benzodiazepine</strong></td>
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<td>As permitted, if no ECoG</td>
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management depends on the comfort level of the neurosurgeon, the anesthesiologist, and the patient.

Conscious sedation-awake-conscious sedation
Selected patients are candidates for this type of anesthetic management. The patient must be cooperative, be able to communicate effectively, and preferably have a good airway. The patient is heavily sedated at the start of the procedure for the scalp blocks, invasive monitoring, and craniotomy. Sedation is stopped 10 to 20 minutes before the anticipated testing begins. The patient must be completely rousable or wide awake and cooperative for testing and neurosurgical intervention. Depending on the type of procedure, certain medications are avoided. If ECoG is used, benzodiazepines should be avoided. If the intervention is for a movement disorder, metoclopropamide, phenothiazines and butyrophenones, which block central dopamine receptors, should be avoided throughout the procedure and recovery. Once the intervention is completed, the patient is again heavily sedated for the closure (Table 2).

Monitored care
This technique is often chosen for deep brain stimulator placement using bur holes for treatment of Parkinson’s disease, in which maximal control of the abnormal movements depends critically on patient input. Patients receive minimal or no sedation. The case is conducted completely under local

<table>
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<th>Table 2</th>
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<tr>
<td><strong>Times during the procedure at which anesthesiologists need to increase the level of sedation and/or analgesia</strong></td>
</tr>
<tr>
<td>Event</td>
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<tr>
<td>Head frame/halo application</td>
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<tr>
<td>Scalp block</td>
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<tr>
<td>Positioning on the operating room table</td>
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<tr>
<td>Arterial and central venous cannula and urinary catheter placement (if required)</td>
</tr>
<tr>
<td>Field block</td>
</tr>
<tr>
<td>Takedown of temporalis muscle</td>
</tr>
<tr>
<td>Dural opening</td>
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<tr>
<td>Testing and surgical intervention</td>
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<tr>
<td>Closure of the craniotomy</td>
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</tbody>
</table>
anesthesia, with anesthesia personnel continuously monitoring and immediately available to intervene should a patient experience a complication.

**ANESTHETIC MEDICATIONS**

The goal is to maximize patient comfort and surgical conditions while taking advantage of drug interactions to minimize toxicity and side effects and optimize resource use. As always, prevention of complications is key. Commonly used medications are listed in Table 3. For completeness, prophylactic antibiotics are listed, because they are easily forgotten during preoccupation with sedation technique. Intraoperative nausea and vomiting are difficult to manage, so prophylactic antiemetic agents, such as dexamethasone and a 5HT₃ antagonist, are given at the beginning of the sedation. Often propofol, with its antiemetic effects, is used for part of the sedative technique. Some anesthesiologists choose to add metoclopropamide.

**Sedatives**

*Dexmedetomidine*

One good choice of sedative for these procedures is dexmedetomidine (either as an infusion or as a carefully titrated bolus 10-μg doses) because it does not interfere with the respiratory drive or increase secretions. Most patients are uncannily calm and yet able to awaken themselves and cooperate when coached. The neuromonitoring capabilities seem to be preserved as long as a patient is aroused (Konstanatin Slavin, MD, personal communication, 2003). Patients feel as if they have had a pleasant experience. Dexmedetomidine is a short-acting, highly selective centrally acting alpha 2 agonist. It is a methylol derivative like medetomidine (Fig. 3). It has a 1620:1, alpha 2:alpha 1 receptor interaction ratio.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Medications</th>
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<tr>
<td><strong>Action of drugs</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>5HT₃ blockers of your choice</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide (except for deep brain stimulators)</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
</tr>
<tr>
<td>Sedatives</td>
<td>Dexmedetomidine</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines (if not performing electrocorticography)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Sufentanil</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
</tr>
<tr>
<td>Amnesia inducers</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Patient’s chronic medications</td>
<td>Anticonvulsants</td>
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<tr>
<td></td>
<td>Anti-Parkinson’s medication</td>
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selectivity, which eliminates many of the undesirable effects (e.g., dry mouth, depression, and prolonged effects) of clonidine, which has a 200:1 alpha 1:alpha 2 selectivity. The sedative and anxiolytic effect of dexmedetomidine occurs by means of interaction at the locus ceruleus in the brain stem. It decreases central sympathetic output by increasing the firing of inhibitory neurons. Its known mechanisms of action include inhibition of pertussis toxin sensitive protein and increased conductance through potassium channels [30]. It is capable of producing significant sedation without appreciable ventilatory effects.

At low plasma concentrations (0.7 and 1.2 ng/mL), the human subject is sedated and has mild analgesia. Cardiovascular and respiratory function is preserved [31,32]. At higher plasma concentrations (>1.9 ng/mL), cardiac output and heart rate progressively decrease and blood pressure, systemic vascular resistance, pulmonary vascular resistance, and pulmonary capillary wedge pressure increase transiently [32]. Even at low doses (0.25 μg/kg) catecholamine levels are significantly decreased for up to 5 hours [33]. The clinically desired levels of sedation for awake neurosurgical procedures are generally in the lower range. One should be cautious to avoid levels that preclude arousal when increasing the infusion. Although dexmedetomidine is 94% protein bound, it does not displace nor is it displaced by phenytoin. It undergoes direct glucuronidation at CYP2A6 then urinary excretion (95%). The T1/2 Alpha is 6 minutes and the T1/2 Beta is 2 hours. Clearance is progressively decreased in patients with liver impairment.

Dexmedetomidine is the author’s choice of major sedative for the invasive craniotomies. It produces sedation, anxiolysis, and analgesia without causing respiratory depression. It does not contribute to the most feared complications—airway obstruction or respiratory depression—even at profound levels of sedation. It provides effective anxiolysis yet allows the patient to wake up fully for intraoperative testing. The dexmedetomidine can be continued during testing because of the ability of the patient to wake up repeatedly without startling or becoming anxious [34]. It causes a state that approaches normal sleep. It inhibits fear-cued memory formation in mice [35]. Human studies are not yet available; however, individuals who have received the medication describe sedation with dexmedetomidine as the sweetest sleep they ever have experienced (Verna L Baughman, MD, personal communication, 2002).

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**Fig. 3.** The chemical structure of dexmedetomidine. Dexmedetomidine is a short-acting, highly selective centrally acting alpha 2 agonist. It is a methylol derivative similar to medetomidine.

![Chemical Structure of Dexmedetomidine](image.png)
Dexmedetomidine is neither an analgesic nor an amnesic, but it greatly potentiates all of the sedative and anxiolytic drugs. As a result, some narcotic and amnesic agents must be administered if these effects are needed to conduct the case [32]. There are many approaches for its effective use and many combinations with other medications to afford analgesia and amnesia for an awake neurosurgical procedure. One approach is to use dexmedetomidine, 10-µg boluses with or without an infusion, to keep a patient comfortably awake without respiratory depression supplemented with small amounts of narcotics and propofol during the most stimulating portions of the procedure. Some prefer to initiate the sedation with 1 µg/kg infused over 10 minutes and then provide an infusion of 0.2 to 0.7 µg/kg/h titrated to effect [29]. In the author’s experience, 1 µg/kg loading dose is more than is needed for the initiation of sedation for some patients. On occasion, patients become bradycardic with this dose delivered over a few minutes. Other patients require more than 1 µg/kg to achieve adequate sedation and demonstrate little or no change in heart rate, even when dexmedetomidine is combined with small amounts of benzodiazepines and narcotics. Profound levels of sedation do render a patient unarousable. This level of sedation is not necessary for patients to tolerate an awake craniotomy. It is the author’s preference to titrate in 10-µg boluses to the desired level of sedation and heart rate.

Caution also must be exercised, because dexmedetomidine causes transient hypertension and reflex bradycardia during rapid administration [32]. Some patients, particularly individuals who are concomitantly treated with beta-blockers, may experience bradycardia related to additive sympatholytic effects of the two classes of medications. If severe bradycardia occurs during dexmedetomidine administration, the infusion or bolus should be stopped and small doses (10- to 20-µg increments) of epinephrine given until the heart rate comes up. Atropine and glycopyrrolate, as vagolytics, do not counter the actual effect of the alpha 2 agonist.

**Propofol**

Many centers exclusively use propofol sedation for awake neurosurgical procedures [4,6,10]. It is a medication that is readily available and familiar to every anesthesia practitioner. Propofol is a potent anesthetic and antiepileptic medication. It must be discontinued 5 to 15 minutes in advance of the ECoG or intraoperative testing [10]. The most commonly described protocols involve an initial titration with bolus doses of 10 to 20 mg at a time, then infusions of 75 to 100 µg/kg/min to maintain the level of sedation. Propofol has no analgesic effects, so a narcotic must be administered concomitantly. Bolus doses of fentanyl (0.5–1 µg/kg) must be given at stimulating times during the procedure. Alternatively, remifentanil (0.03–0.05 µg/kg/min) can be titrated to effect [6]. This combination of the propofol and narcotic must be adjusted carefully during the procedure to avoid respiratory embarrassment.

When the neurosurgical intervention is completed, you should resume the patient’s anticonvulsant medications based on blood concentration, if possible.
Antiepileptic drugs should be resumed during closure and guided by concentrations, because they may change dramatically perioperatively. If large blood losses occur, concentrations may be subtherapeutic postoperatively. Alternatively, the concentrations may be surprisingly elevated because the antiepileptic drugs are highly protein bound and may be displaced by other perioperative drugs. Toxic levels can occur and mimic intracranial complications.

Benzodiazepines are used as a part of almost every anesthetic regimen to promote amnesia and anxiolysis. During sedation for procedures that require ECoG, benzodiazepines must be avoided until all mapping and testing procedures have been completed. For this reason, many anesthesiologists wait until the dura is closed to initiate the benzodiazepine therapy, which is done to avoid problems if the surgeon returns to resect more tissue. Although this is unlikely in the hands of an experienced team, it does occasionally occur. If a surgeon returns to resect more or optimize the intervention after sedation has been increased, a discussion should take place regarding the patient’s ability to cooperate. Flumazenil and naloxone awaken the patient, but these agents are somewhat unpredictable and you may end up with a dangerously awake and frustrated patient who may have a seizure. There is no right answer. If possible, allow a bit of time to pass; when the patient is able to be aroused, retest and complete the resection.

**POSTANESTHESIA CARE UNIT**

Neurologic status and antiepileptic drug concentrations should be reassessed on admission. Monitoring for general complications should be done as with any other craniotomy. Visit with patients postoperatively. Often they appreciate your efforts. They sometimes need reassurance that the whole process went well.

Occasionally, despite appropriate intraoperative management, a new deficit develops or a patient still has the neurologic symptoms the procedure was meant to treat. Recapitulate the preoperative discussions of all possible outcomes and complications, if necessary. Open discussion between the anesthesiologist, the neurosurgeon, the patient, and the family regarding the intraoperative events and the possible reasons for the outcome helps to ward off bad feelings.

**SUMMARY**

Awake intracranial procedures, which are really challenging cases for anesthesiologists, are becoming more common. Review of the procedure and expectations with everyone involved in advance of operating room entry cannot be overemphasized. Likewise, building rapport with patients is key. Use medications and airway management techniques with which you are familiar and comfortable. Keep in constant communication with the patient and surgeon and the cases will go well and everyone will be satisfied in the end. This is not a procedure that should be undertaken without a large amount of preparation of the patient, family, and the whole perioperative management team. Prevention of perioperative problems is key to this process as it is to all
anesthetic procedures. Many management strategies are available at various institutions. The techniques described in this article should be considered as starting points from which to tailor optimal management for individual cases.

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References


Diversity and Disparities in Health and Health Care: Why it Matters to Anesthesiology

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The American Society of Anesthesiologists is an educational, research and scientific association of physicians organized to raise and maintain the standards of the medical practice of anesthesiology and improve the care of the patient.

Since its founding in 1905, the society’s achievements have made it an important voice in American medicine and the foremost advocate for all patients who require anesthesia or relief from pain.

As physicians, anesthesiologists are responsible for administering anesthesia to relieve pain and for managing vital life functions, including breathing, heart rhythm and blood pressure, during surgery. After surgery, they maintain the patient in a comfortable state during the recovery, and are involved in the provision of critical care medicine in the intensive care unit.

ASA mission statement

The United States is rapidly becoming an increasingly diverse nation with more minorities and women than ever seen in the world [1–3]. Throughout United States history, sociodemographic factors (eg, race, ethnicity, and gender) played a significant role in determining overall health status and quality of life and quality of care [4–6]. More specifically, the literature provides ample evidence for differences in health and health care based on these sociodemographic factors [7–12]. These factors influenced the ability to access many careers in the health professions, including becoming a medical doctor [13,14]. Most anesthesiologists do not consciously consider the importance of sociodemographic factors when evaluating their patients, however. For instance, women make up more than 50% of the population, but little consideration is given to the unique implications that gender has on assessment, management, and outcomes. By 2030, non-white racial and ethnic groups...
(eg, African Americans, Hispanics, and Native Americans) and women will constitute a majority of the American population, yet there are no guidelines specifically designed to improve the quality of care that women and racial and ethnic minorities receive during the perioperative period. The literature continues to report problems with assessing and treating the pain complaints of racial and ethnic minorities and those of women [15].

The importance of disparities and diversity as they relate to health and health care has attracted Congressional attention [16]. For the past 5 years, several agencies have addressed the inequality of health and health care across a full spectrum of disease and treatments [17]. The United States Congress charged the Institute of Medicine (IOM) of the National Academy of Sciences to assess health care inequities and disparities in the delivery of health care services and diversity in the health care workforce. The IOM specifically addressed these topics in a scholarly fashion in “Unequal treatment: racial and ethnic disparities in health care” [18] and “In the nation’s compelling interest: ensuring diversity in the health-care workforce” [19]. These books provide evidence that disparities and diversity in health care are critical underpinnings that are intrinsically linked to the quality of health care that all Americans receive throughout the health care delivery system [20]. Although much is written about disparities based on gender, the IOM provided little information on gender-related disparities in health or health care or gender-related diversity as it relates to the health professions. The minimal attention devoted to these matters may be caused by the breadth of its charge or that greater differences and disparities are seen based on a patient’s race and ethnicity.

Although the IOM viewed pain management as one of the clinical areas in which disparities in health care exist, of particular interest to anesthesiologists is the minimal attention they paid to pain (arguably the most visible part of our practice to patients and their families) [18]. Unfortunately, the discussions regarding pain were limited to acute and cancer pain only. There is a significant and emerging literature documenting disparities in pain care based on race, ethnicity, and gender across a large variety of painful conditions (ie, acute, cancer, and chronic pain) and treatment settings (eg, ambulatory, inpatient) [15,21–24]. In general, minority patients (ie, African Americans, Native Americans, and Hispanics) and women (regardless of age) receive lesser treatment for pain and lesser quality of pain care when compared to white men [15,25–27]. Overall, the IOM provided support for diversity in general and provides evidence that a diverse workforce plays a significant role in reducing and eliminating disparities in health and health care in particular. Their work supporting the importance of diversity primarily focused on the importance of diversifying the pipeline of students into the health professions but did not address the challenges facing faculty and academic medicine in a substantive manner. Both IOM reports intrinsically supported the importance of cultural awareness, sensitivity, and competence.

This article explores pertinent literature regarding diversity and disparities for minorities and women and why they are important for anesthesiologists
(particularly academic anesthesiologists). Background information and a platform for discussing the role of race, ethnicity, and gender in our increasingly aging and diversifying society are provided for anesthesiologists. Potential research priorities to move the research and treatment community closer to reducing and eliminating disparities in treatment and increasing the diversity of the anesthesiology workforce are presented. Finally, potential recommendations for anesthesiology as it relates to health care policy, patients, and the general public while reaffirming the need for mentorship for women and racial and ethnic minority physicians are presented.

**HISTORY**

In the recent United States Supreme Court case *Grutter v Bollinger*, the court narrowly ruled (5 to 4) that the University of Michigan may consider sociodemographic factors, specifically race and ethnicity, as factors in admission to the University of Michigan’s law school [14]. The Supreme Court further ruled that the University of Michigan’s law school did not violate the constitutional rights of nonminority applicants by doing so. The amicus briefs provided by the corporate sector (eg, Ford Motor Company) and the military provide evidence that creating a “critical mass” of racial and ethnic diversity was in the best interest of the students, school, university, and the nation. Beyond ensuring that race and ethnicity can be used as one of many factors in selecting students for admission to the law school, the ruling impacts women and socioeconomically disadvantaged individuals. Most importantly, it has far-reaching implications for medical schools into the new century as the patients they care for become increasingly diverse. The potential impact of this decision on health care and health care disparities is tremendous.

According to the Bureau of Labor Statistics, the overall labor force participation rates will continue to rise for women and minorities between 1998 and 2008 [28]. In 2008, women will make up approximately 48% of the total labor force and underrepresented minorities (ie, racial and ethnic minority groups that are underrepresented in the medical profession relative to their numbers in the general population) make up approximately 30% of the total labor force [29]. With an increasingly diverse medical profession, the practice of medicine clearly will change to reflect this population [30–36].

The Association of American Medical Colleges reported that women represented 50% of applicants to medical schools, 49% of first-year students, 49% of medical students, 47% of medical school graduates, and 42% of residents and fellows in 2004. Overall, women represent 32% of medical school faculty members, but they represent 21% of instructors or other ranks (versus 10% men), 48% of assistant professors (versus 37% men), 19% of associate professors (versus 23% men), and 12% of full professors (versus 30% men) in 2004–2005. Although surgery and orthopedics continue to have lower percentages of women faculty, obstetrics and gynecology, pediatrics, public health, and preventive medicine have higher percentages (>40%) of women in faculty positions [30,37]. Women currently represent 30% of academic anesthesiologists overall,
but they represent 33% of assistant professors, 26% of associate professors, and 13% of full professors in anesthesiology [29].

Many health profession educational groups have worked tirelessly to increase the preparation, participation, and status of underrepresented minorities and women in medical careers. Overall, the representation of racial and ethnic minorities within medicine (especially academic medicine) and all health professions is significantly less than their representation in the general population [38]. The cost of a medical education is often a significant barrier to increasing the number of underrepresented minorities in medicine. Underrepresented minorities often have lower economic resources and require more federal and state grants and loans to finance their medical education. Data continue to support the idea that underrepresented minority and low-income medical students have increased educational debt after medical school. It follows that recent state and federal policies reducing governmental financial aid for education when combined with the recent economic down turn results in increased financial barriers to a career in medicine. These policies also influence residency choice and the ability to choose a career in academic medicine.

Less detailed information on underrepresented minority faculty in academic medicine is available [38]. What remains clear is that promotions for underrepresented minority faculty lag beyond their white counterparts, despite their growth in the ranks of academic medicine. Although there are gains in the promotion of women in academic medicine and increasing numbers in the ranks, many consider underrepresented minority faculty an endangered species. In a study that examined the promotion rates among minority faculty over 17 years (1980–1997) there were no increases [39]. Overall, underrepresented minorities and all other minorities are promoted at much lesser rates than white faculty. Table 1 provides more information about the current status of faculty in academic medicine based on race and gender by academic rank.

When examining the demographics of leadership for academic medicine, women represented 18% of division/section chiefs, 11% of department chairs, 45% of assistant deans, 29% of associate and senior associate/vice deans, and

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10% of medical school deans in academic medical centers in 2005 [29]. Currently, approximately 10% of academic anesthesiology department chairs are women. Little is known about the numbers of minority faculty who are division/section chief, department chairs, assistant deans, associate and senior associate/vice deans, and medical school deans, however, because their numbers are exceedingly small [29]. Although the US Department of Education strongly encourages accreditation boards to be more aggressive in formulating and enforcing standards that yield an increase in a critical mass of underrepresented minorities in academic medicine, the author was unable to obtain accurate information based on race and ethnicity for academic anesthesiology.

Many medical schools have designed faculty development and leadership programs and mentoring programs without regard to race and gender. It is well established, however, that underrepresented minorities and women are less likely to have mentors and are less able to benefit from these relationships. Toward this end, several organizations devoted to increasing the diversity of academic medicine have developed highly acclaimed programs aimed at advancing the status of women and underrepresented minorities and increasing their numbers in academic medicine (eg, Association of American Medical Colleges Minority Faculty Professional Development Seminar, Association of American Medical Colleges Junior and Senior Women Faculty Professional Development Seminars). The von Amerigen Hedwig Executive Leadership in Academic Medicine has been in existence for 10 years and remains the only program specifically designed to provide women with the leadership skills to become executives in academic medicine. It is important to note that four of the ten women (one is an African-American woman) who are currently deans of an academic medical school are Executive Leadership in Academic Medicine graduates. The data provided on the status of women in academic medicine is done so without regard to racial or ethnic backgrounds, whereas the status of underrepresented racial and ethnic minorities in academic medicine is done without regard to gender. Many complexities distinguish the problems that underrepresented racial and ethnic minority women confront. The leadership and academic issues that beset underrepresented minorities (especially women) are often difficult to disentangle and are beyond the scope of this article; however, it is clear that we must begin to collect the data.

WHY SHOULD HEALTH CARE DISPARITIES MATTER TO ANESTHESIOLOGISTS?

Several federal agencies have defined health care disparities as a difference in incidence, prevalence, mortality, and burden of disease and other adverse health conditions [40]. Others have defined health care disparities as racial and ethnic differences in the quality of health care that are not caused by access-related factors, clinical needs, preferences, or appropriateness of interventions [37,41,42]. An operational definition of a health care disparity is differences in health, disease burden, or clinical decisions or outcomes associated with disadvantage. Overall, the US Department of Health and Human
Services has sponsored many research initiatives and spent millions of dollars attempting to reduce and eliminate health care disparities. The importance of reducing and eliminating disparities has received bipartisan support based on the fact that disparities increase health care expenditures.

“Racial and ethnic disparities in health care are unacceptable in a country that values equality and equal opportunity for all. And that is why we must act now with a comprehensive initiative that focuses on health care and prevention for racial and ethnic minorities” (President Bill Clinton).

“These gaps are simply unacceptable in America. Turning our back on these health disparity problems would be a national failure” (Senate Majority Leader, Senator Bill Frist, MD).

**THE ROLE OF GENDER AND RACE ON HEALTH STATUS AND MEDICAL CARE**

Several studies have identified that race and gender are determinants for overall health status and health care treatment options [43]. The landmark paper by Schulman clearly demonstrated that women and African Americans who present with chest pain were less likely to receive recommendations for cardiac catheterizations than men or their white counterparts. Schulman also showed that black women were significantly less likely to be referred for catheterizations than other groups [44]. Overall, several studies confirmed that disparities in health care exist within and across all racial and ethnic groups [45].

Health insurance allows access to health care, yet racial and ethnic minorities, low-income individuals, and women are more likely to be uninsured or underinsured, thereby limiting their access to health care and contributing to diminished health [9]. For instance, racial and ethnic minorities with insurance are more likely to rate their health as poor and are more likely to report financial difficulties in obtaining care than similar whites [46–49]. Health insurance is not the great equalizer. Even at higher incomes, whites generally fare better than blacks, Hispanics, and Native Americans who have increased access to specialty care (including pain care) and specialized treatments, including access to opioid analgesics in their local community pharmacies [50–52].

**THE ROLE OF PHYSICIAN VARIABILITY IN DECISION MAKING**

Physician and patient gender also plays a significant role in determining health care [53,54]. For instance, male physicians were more likely to offer rectal examinations to their male patients than they were to offer pap smears and mammograms to their female patients. Gender and race also affect decisions about pain management. Male primary care physicians prescribed more pain medicine to their male patients than to their female patients [53,54]. Women primary care physicians also were shown to have similar prescribing methods, except they prescribed more pain medicine to their female patients than their male patients [29]. Regardless of the type of pain, however, the literature continues to suggest that women and minorities receive lesser quality pain care [44,55,56].
Although training in cultural competency is incorporated in the curriculum of most US medical schools, residents who completed their final year of residency training believed that they were unprepared to deal with patients from diverse cultures [57–61]. A large proportion of residents reported that they received little or no cross-cultural training. They also felt unprepared to treat patients with religious beliefs that were not Western beliefs, patients who do not trust in the US health system, patients who have religious beliefs that may affect treatment, patients who use complementary or alternative medicines, or patients who are new immigrants [57]. These findings imply that although cultural competency is part of the medical school curriculum, translating the principles of cultural competence into clinical practice is much more problematic. It is not surprising that disparities in health and health care persist.

Physician-patient communication can contribute to disparities in health care [62–65]. During the perioperative period, anesthesiologist-patient communication usually entails a short amount of time during the preoperative period and an even shorter amount of time during the postoperative period. Anesthesiologists generally have a few minutes to gather information and develop rapport with their patients, but this time is crucial [66]. There is considerable opportunity for miscommunication (especially for non-English speaking patients). Differences in the way that women and minorities convey their complaints (especially their pain complaints) and patient attitudes and perceptions contribute to problematic physician-patient communication [67–69]. Identifying and addressing potential communication barriers based on race, ethnicity, gender, and culture between patients and their anesthesiologists can improve patient satisfaction with care [70]. It follows that the quality of care received is improved through active listening by anesthesiologists and yields more effective communication, especially with an increasingly diverse patient population. The extra time taken is worth it for all parties involved.

DISPARITIES IN PAIN CARE

Overall, disparities in analgesic administration have been documented for all types of pain (ie, acute, chronic, and cancer pain) and in all settings [15]. Todd and colleagues [71] showed that Hispanics with isolated long bone fractures were twice as likely as whites to receive no pain medication during their emergency department visit regardless of the patient’s gender or primary language. Pain assessment (the cornerstone of quality pain care) seems to be the most likely mediator for the physician decision-making process and severity of illness because in a follow-up study in 1994, Todd and colleagues [72] found no differences in pain assessment when patients had less severe bone trauma. In the acute postoperative pain setting, Ng and colleagues [73,74] found that ethnic minorities were prescribed less opioid analgesics for their pain via patient-controlled analgesia after similar orthopedic procedures than whites. The amount that patients self-administered did not differ based on race, however [75]. Several studies revealed that minorities with cancer pain received significantly less potent analgesics than those recommended by World Health Organization
standards [15]. In settings with predominant minority patients, 60% of those patients were undertreated by World Health Organization standards. The chronic pain literature also revealed disparities in health based on race, regardless of age and gender. More specifically, African Americans had diminished health, with increased depression, posttraumatic stress disorder, and increased pain when compared to whites [15,76]. They also were more likely to report that chronic pain was a significant financial burden for them and that they should have been referred to the pain clinic sooner for treatment [52]. Chronic pain seems to impact racial and ethnic minorities disproportionately.

WHY IS RACIAL, ETHNIC, AND GENDER DIVERSITY IMPORTANT TO ANESTHESIOLOGY?

Overall, the literature supports that increasing diversity yields improved educational experiences for all students and physicians in training (regardless of race and gender) and for their patients [64,77–80]. African Americans, Hispanics, and Native Americans are significantly underrepresented in the field of medicine (and anesthesiology), however. Underrepresented minority physicians are more likely to serve medically underserved, racial, and ethnic minority populations [81]. Given a choice, racial and ethnic minority patients are also more likely to choose a physician with the same racial or ethnic background [82]. The result may be improved physician-patient communication, improved access to health care, greater patient satisfaction, and better quality of care.

Gender congruence is also important in understanding disparities. Female physicians spend more time with their patients than their male counterparts, leading to more positive discussions, explanations, rapport, and emotional support [83]. The National Ambulatory Medical Care Survey reported that female physicians spent 23.5 minutes with their patients when compared to men, who spent on average 18.7 minutes, yielding increased patient satisfaction [84]. In a study of pediatricians, doctor visits with female physicians were 29% longer than those of men. Female physicians are engaged in more social exchange, more encouragement and reassurance, more communication during the physical examination, and more information gathering with children when compared to male physicians. Of particular importance to pediatric anesthesiologists is that parents were more satisfied with female physicians and children communicated more with female physicians than with male physicians. Some of these unique communication skills may need to be incorporated by men as well to improve physician-patient communication.

Transforming the professional and institutional climate to support diversity and eliminate disparities

Many benefits from diversity go beyond the ability to recruit and retain excellent talent [82,85]. Increased diversity among anesthesiologists and other health care professionals increases the creativity of the team and leads to new options for complex system problems. Minority health professionals provide benefits to the larger community by their community service. In academic medicine and
professional societies, underrepresented minorities and women are disproportionately asked to provide scientific service (e.g., serving on committees, mentoring) while enhancing diversity. Unfortunately, their service is often unrecognized, although it is important to the institutions that they serve. The American Society of Anesthesiologists committee on professional diversity primarily focuses on the status of women anesthesiologists. In light of a diversifying United States, the committee’s work should be broadened to specifically examine pipeline issues and special challenges in academic medicine for both women and minorities. Organizations such as the Association of University Anesthesiologists should take a role in ensuring the advancement of minorities and women in science and academic anesthesiology by establishing a task force to assess and address issues related to these underrepresented groups [86].

Admission to residency programs should go beyond quantitative measures, such as GPA, honors, and USMLE scores, and include many other factors (e.g., service to the community) to reflect our commitment to diversity and respect for the patients we will care for in the new century. For instance, the American Society of Anesthesiologists mission statement does not address the fundamental importance of diversity to the organization. More specifically, a clear statement about the value of diversity in anesthesiology education and in providing anesthetic care should be incorporated to reflect our diversifying profession and patient population.

RECOMMENDATIONS FOR THE FUTURE
Additional research on women and minorities in anesthesiology is necessary because many questions remain regarding their professional lives, advancement in the specialty, and work/life balance. Research designed to evaluate the effectiveness of pipeline programs is also necessary to collect comprehensive demographic data to monitor the movement and career trajectories of underrepresented minorities and women in anesthesiology. Systematic data on recruitment, retention, promotion, and earnings are also needed. New research is imperative to specifically examine, encourage, and support underrepresented minorities and women who move into organizational leadership roles in anesthesiology (especially academic anesthesiology). Finally, anesthesiologists should be vigilant about monitoring their outcomes from the care they provide until health care disparities no longer exist and diversity is ensured [87].

References


The development of new health care technologies continues at a rapid pace in the United States [1]. These new technologies have resulted in more and more diagnostic and therapeutic procedures outside of the operating room. For example, between 1998 and 2001, use of MRI by Medicare enrollees increased 16% per year [2]. To accomplish these procedures in an expeditious and safe manner, patients must be immobile. This requirement for immobility to get clear images and the need for analgesia for painful interventional procedures has led to the increased need for sedation, analgesia, and general anesthesia outside of the operating room. Cooperative adults can tolerate many of these procedures without any sedation, but babies and infants and older children and adults with behavior or movement disorders cannot be immobile for these procedures.

GUIDELINE DEVELOPMENT

Because of sedation-related adverse events in children, the American Academy of Pediatrics in conjunction with the Section on Anesthesiology issued guidelines in 1985 for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric patients [3]. Subsequent updates and revisions by the American Academy of Pediatrics have delineated more thoroughly the responsibilities of practitioners when sedating children [4,5].

The American Society of Anesthesiology (ASA) has issued a formal statement to describe the continuum of depths of sedation and define general anesthesia and the levels of sedation/analgesia.

- Minimal sedation is a state during which patients have a normal response to verbal stimulation. The airway, spontaneous ventilation, and cardiovascular function are not affected.
- Moderate sedation/analgesia results in a depression of consciousness with purposeful responses to verbal or tactile stimulation. The airway and spontaneous ventilation are adequate, and cardiovascular function is usually maintained.
Deep sedation/analgesia depresses consciousness so that patients are not easily aroused but respond purposefully to repeated or painful stimulation. Intervention may be required to maintain the airway. Spontaneous ventilation may be inadequate, but cardiovascular function is usually maintained.

General anesthesia causes patients to be unarousable, even with a painful stimulus. Intervention is often required to maintain the airway. Spontaneous ventilation is frequently inadequate, and cardiovascular function may be impaired [6].

In conjunction with the ASA, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has mandated that all practitioners who provide moderate or deep sedation and analgesia must have competency-based education and training in the administration of the pharmacologic agents, the appropriate monitoring techniques, evaluation of patients for sedation, and the ability to rescue patients who slip into a deeper than desired level of sedation/analgesia. The oversight of this education and credentialing process falls to each institution’s department of anesthesiology [7].

In response to the JCAHO requirement, the ASA has developed credentialing guidelines for practitioners who are not anesthesia professionals but must be able to administer anesthetic drugs to establish a level of light to moderate sedation [8].

As a result of these guidelines, the incidence of hospital-wide adverse events during procedural sedation and analgesia seems to be declining [9]. By following these guidelines, health care providers are able to improve patient safety and facilitate the delivery of health care in a timely manner. There are not enough anesthesia providers to be present for all of these procedures outside of the operating room; however, many procedures still require deep sedation or general anesthesia and must involve the participation of an anesthesiologist in the care of the patient.

INDICATIONS FOR ANESTHESIA

Screening criteria for patients who will undergo a procedure outside the operating room that may indicate the need for care by an anesthesiologist include the following:

- Age (baby or small child)
- Behavioral disorder (ie, autism, attention deficit and hyperactivity disorder, or schizophrenia)
- Movement disorder (ie, Parkinsonism, chronic tremor, or severe muscle spasm)
- Claustrophobia
- History of failed sedation
- Critical illness (ie, respiratory failure or new-onset neurologic changes)
- Known or potential airway compromise
- Complexity and duration of the interventional procedure (ie, coil embolization of an intracranial aneurysm in the neuroradiology unit)
GENERAL REQUIREMENTS FOR ANESTHETICS OUTSIDE THE OPERATING ROOM

Areas of the hospital in which anesthesiology may be needed most frequently for elective procedures outside of the operating room fall into these categories: the radiology imaging suite, the MRI unit, the cardiac catheterization laboratory, the radiation therapy unit, the gastrointestinal endoscopy unit, and the psychiatric unit. When asked to provide anesthesia in one of these areas, an anesthesiologist must provide the same standard of care as in the operating room. Basic monitoring must include qualified anesthesia personnel who are continuously present unless there is a direct known hazard (eg, radiation). A patient’s oxygenation during general anesthesia must be ensured by monitoring the inspired gas with an oxygen analyzer and assessing blood oxygenation with pulse oximetry. Ventilation is ensured by continual monitoring for the presence of expired carbon dioxide. If a mechanical ventilator controls ventilation, there must be a disconnect monitoring device with an audible signal. Circulation must be monitored with a continuous electrocardiogram and a noninvasive blood pressure measurement device or an intra-arterial pressure line. Body temperature must be maintained at an appropriate level and monitored if significant changes are anticipated [10].

These “away” locations have many obstacles that make management of anesthesia more difficult. The rooms are frequently filled with bulky immovable equipment that prevents easy access to a patient or anesthesia equipment. The lighting may be dim. The room temperature is usually frigid to protect the function of the computerized imaging equipment. There may not be any way to scavenge anesthetic waste gases. Piped-in gases and suction may not be located in a convenient spot, and the supporting personnel in these areas do not understand the problems that can develop during induction, intubation, positioning, extubation, and emergence from general anesthesia.

The ASA has issued guidelines for non–operating room anesthetizing locations that reinforce the mandate by JCAHO that the same standards for general anesthesia apply outside the operating room as in the operating room [11,12]. These guidelines by the ASA insist on a reliable primary and backup oxygen source, an adequate and reliable source of suction, and a system for scavenging waste anesthetic gases. There must be a readily available self-inflating hand resuscitation bag, adequate anesthesia drugs, supplies and equipment, adequate monitoring equipment, and sufficient electrical outlets, including an emergency power supply. The room must have adequate illumination and sufficient space to accommodate equipment and personnel and allow quick access to patients and the anesthesia equipment. Every area must have an emergency drug cart with a defibrillator, adequate staff trained to support the anesthesia provider, two-way communication, building and safety code compliance, and appropriate postanesthesia management [13].

To streamline the preparation and scheduling of patients for these procedures with anesthesiology, the anesthesiologist must have a system in place
for evaluating patients and obtaining consent before administering anesthesia. The patient or the patient’s caregivers need NPO instructions. Standardized orders provide discharge criteria and instructions for contacting the anesthesiologist for problems. A physician also must be designated who is responsible for admitting patients if there are complications that require monitoring, evaluation, and therapy. To ensure that a designated anesthesia team is available at the time of the scheduled procedure, it is best to have these “out of the OR” procedures placed on the main operating schedule. Scheduling these procedures with the main operating room requires extensive education of the entire hospital staff for it to happen in a consistent manner. Certain days of the week can be designated for different “away sites.” The usage of these times can be monitored and changed as the workload changes.

UNIQUE CONSIDERATIONS FOR EACH AREA

Radiology suite
This area consists of interventional angiography for aortic endovascular procedures, neurovascular procedures, and uroradiologic procedures; CT alone or combined with radiofrequency ablation of lesions or combined with positron emission tomography (PET); myelography alone or combined with CT. In addition to the previously described problems for these remote sites, all of these procedures have the risk of excessive radiation exposure to patients and health care workers and the risk of radiocontrast media reactions for patients.

To minimize radiation exposure, it is important to minimize total radiation time, maintain a distance of more than 36 inches from the source of ionizing radiation, and use radiation shielding (lead aprons, thyroid collars, and lead-lined shielding screens). To monitor cumulative exposure, radiation dosimeter badges must be worn at chest level outside any shielding aprons [14].

Contrast media reactions are a well-known problem. Mild reactions consist mostly of transient vasodilatation; however, acute anaphylactic and idiosyncratic anaphylactoid reactions can be fatal. Radiocontrast media consist of two groups: first-generation ionic, hyperosmolar agents and second-generation nonionic hypo- and iso-osmolar agents. The first-generation older agents are more toxic and more immunogenic. Iohexol (Omnipaque) is a second-generation media that is currently most frequently used for arteriography, cardiac angiography, urography, and gastrointestinal and CT examinations. It is in a tri-iodinated, isotonic solution that is excreted unchanged through the kidneys. Although this agent is less immunogenic than the older first-generation agents, there is a report of an anaphylactic reaction with shock within 5 minutes of administration during an endoluminal repair of an abdominal aortic aneurysm.

This reaction was confirmed by sampling for serum mast cell tryptase concentration. Tryptase is a marker for mast cell degranulation and release of histamine [15]. Anesthesia providers must anticipate these life-threatening anaphylactic or anaphylactoid reactions and be prepared to treat with crystalloids and vasoactive agents, such as epinephrine and norepinephrine.
Aortic endovascular procedures
Stent-graft procedures offer the advantages of decreased stress response, improved perioperative hemodynamic stability, fewer embolic complications, earlier discharge, and reduced cost; however, there can be major morbidity and mortality caused by aneurysm rupture and cerebral, abdominal, pelvic, or lower extremity ischemia caused by malposition or migration of stents or distal embolization of plaques or thrombi. Embolic events are associated with guidewire advancement, device deployment, balloon inflation, and vigorous flushing of catheters. Strategies to minimize problems during the device deployment and balloon inflation include vena cava occlusion with a balloon, electrically induced ventricular fibrillation, adenosine-induced temporary asystole, and intravenous nitroglycerine to produce temporary hypotension[16]. Some surgeons have reported success with the induction of moderate bradycardia using esmolol combined with sodium nitroprusside to induce hypotension plus a valsalva maneuver during balloon inflation[17]. Either local anesthesia with sedation and general endotracheal anesthesia have been used for these procedures. Local anesthesia with sedation offers the advantage of more quickly identifying sudden embolic events that affect the brain, but anesthesiologists also must be prepared to manage sudden acute blood loss and be ready for conversion to an open procedure with general anesthesia[18].

Neurovascular procedures
Interventional neuroendovascular radiologic procedures are part of the increasing minimalism in the field of neurosurgery. One example is the recent introduction of detachable coils to occlude aneurysms endovascularly as an alternative to the craniotomy and clipping of aneurysms. Surveys of the published literature indicate that coiling is associated with a better outcome than clipping[19,20]. With this evidence, more neuroendovascular procedures will move from the operating room to the neuroradiology suite. Because these coiling procedures can take several hours, they are usually conducted under general anesthesia, with systemic blood pressure monitoring provided from the catheter introduced into the femoral artery by the neuroradiologist. These procedures are not painful but do require periods of immobility to achieve correct placement of the catheters and coils. Because a rapid wakeup is desirable at the end of this high-risk procedure to assess neurologic function, the anesthetic plan should include short-acting agents that do not significantly alter cerebral circulation and allow for rapid emergence[21].

Interventional uroradiology
The most common urologic procedure that requires general anesthesia in the angiography suite is the placement of percutaneous nephrostomy tubes in infants and children who have either bilateral severe hydronephrosis with post-obstructive renal failure or a severely obstructed single kidney. This procedure provides relief of the renal collecting system until a more definitive surgical procedure can be completed. The radiologist uses combined sonographic-fluoroscopic guidance to place the tube with the child in a lateral or prone
position [22]. This procedure can be technically difficult in small babies, and the procedure can sometimes take 2 to 3 hours to complete. It is easy to dislodge the catheter after it is placed, so it is important to protect the catheter when repositioning the baby at the end of the procedure. Because of the duration of the procedure and the cold environment in the angiography suite, a forced air warming blanket can help prevent hypothermia. General endotracheal anesthesia is best for this therapeutic procedure, which is painful and usually requires a prone position.

CT
CT consists of multiple radiographic measurements that are made around the body. Programmed mathematic computations produce the image. As the power and speed of computers increase, the scanning speed of CT scanners increases.

New developments in CT technology are rapidly decreasing the need for anesthesia because these radiographic imaging devices are able to obtain diagnostic images for a head in less than 5 minutes and for an abdomen in less than 10 minutes. There is still the occasional need for anesthesia involvement in procedures such as CT-guided liver or lung biopsies and the CT-guided percutaneous radiofrequency ablation of osteoid osteomas. The ablation of osteoid osteomas can take 1 to 2 hours and has been performed under either regional or general anesthesia. After location of the nidus of the osteoma by CT, a 14-gauge bone biopsy needle is introduced. The radiofrequency needle is inserted through the biopsy needle and connected to a radiofrequency generator for as long as 8 minutes [23]. This procedure is painful and requires an immobile patient to ensure correct placement of the radiofrequency needle. At the conclusion of the procedure after emergence from anesthesia and recovery in the postanesthetic care unit, patients are able to return home on the same day.

CT-guided percutaneous radiofrequency ablation of renal tumors using general anesthesia also was described recently in the literature. Adult patients required overnight observation after the procedure and returned for repeat ablations in a series of sessions [24].

PET
PET is an imaging technology that measures the metabolism and functional activity of living tissue by electronic detection of positron-emitting radiopharmaceuticals [25]. Radiopharmaceuticals most commonly used for this procedure are fluoro-deoxyglucose and oxygen-15 labeled water. The physical half-life of these isotopes is 110 minutes for fluoro-deoxyglucose and 2 minutes for oxygen-15 labeled water. This technology is most useful in oncology and neurology. PET scanning is a painless procedure but does require a calm patient to assess metabolic activity in the brain. Studies in the pediatric population [26], especially for older babies and toddlers, may require deep sedation to ensure immobility. Small babies usually rest quietly in the cushioned seat without the need for sedation if the study is timed for their sleep cycle. Preparing for these studies is complicated because the tracer must be injected 30 minutes before a brain scan and 10 to 15 minutes before a whole-body scan, while the
blindfolded patient rests in a quiet environment. To establish optimal target/background ratio for assessment of metabolic activity, patients must fast 4 to 6 hours before the scan. Because many sedatives and anesthetic agents affect the cerebral blood flow and metabolism [27,28], the administration of these drugs must be timed carefully to minimize interference with studies of cerebral function. Dosing of sedatives must be postponed until 30 minutes after the tracer injection, when most of the uptake has occurred [26]. With PET scanning alone, the primary radiation hazard is from the patient who emits some radiation for the life of the tracer, so this must be considered when planning for recovery after the procedure.

During the past 5 years, PET and CT have combined to improve specificity and sensitivity of tumor imaging. PET/CT combined scans are also faster than PET alone, with the combined scan lasting 30 minutes or less. This technology is useful for staging and therapy monitoring of many tumors [29]. Anesthesia is unlikely to be needed in the adult population but might be required for children.

**Myelography**

Myelograms require a prone position for the placement of the spinal needle under fluoroscopy by the radiologist. After the correct needle placement is confirmed, the radiologist injects contrast media into the subarachnoid space. To obtain good images of the spinal canal, it is necessary to change the patient’s position from supine to reverse Trendelenberg. Because the contrast dye can irritate the meninges [30], it is important to avoid the Trendelenberg position if possible. General anesthesia may be required for babies and small children or for uncooperative adults. Because of the prone positioning, endotracheal intubation is best to control the airway; however, it is important to remember that with the changes in patient position, the endotracheal tube position can shift.

Often it is necessary to combine this study with a CT scan to improve the sensitivity and specificity of the examination. This combination requires transportation of anesthetized patients to a different area of the radiology suite. To keep patients asleep during the move, an intravenous infusion of a hypnotic agent (eg, propofol) is necessary. This move also requires a transport monitor, self-inflating hand resuscitation bag, and oxygen tank. Extra personnel are needed to set up the anesthesia equipment in the CT scanner. The CT scan may only take 10 minutes and usually can be accomplished with an intravenous technique that allows for rapid awakening at the end of the procedure.

**MRI**

Although the MRI unit is part of the whole-body imaging suite in the radiology department, this imaging modality has special considerations, the primary one being the hazard of the constant powerful static magnetic field, which is critical for high-quality imaging. The MRI image is based on the response of hydrogen protons in a strong magnetic field to the effect of a brief radiofrequency pulse. Many different pulse sequences are used based on the indication for the examination. Some of the more common sequences that are referenced in reports
include T1, T2, T2 FLAIR, proton density, diffusion, and STIR [31]. Three different energy fields are required to generate an image: the static magnetic field, time-varying gradient magnetic field, and radiofrequency pulses. Over the past 20 years as the technology has evolved, each of these energy fields has become stronger and more powerful and, as a result, more hazardous [32].

Most MR systems currently operate with static magnetic fields that range from 0.2 to 3.0 T. To understand the relative strength of these powerful magnets, the earth’s magnetic field is 0.3 to 0.7 G. A refrigerator door magnet has a field of 150 to 250 G. One Tesla is equal to 10,000 G. An MRI magnet operating at 3.0 T is operating at 30,000 G. The primary risk of this powerful static field is that ferromagnetic objects quickly become projectiles when brought into this field. There have been case reports of standard oxygen tanks, vacuum cleaners, and transport carts being pulled into the magnet bore and causing serious injury or death to patients and costly damage to the MRI unit [33,34]. Patients who have metallic implants and medical devices, such as pacemakers and defibrillators, are also at risk for device dislocation, malfunction, and burns. For this reason, every MRI unit must have a standard screening system in place before patients or health care workers are allowed into the unit. Because thousands of different medical implants and devices are in use, manuals and websites are available for technicians to reference for screening purposes. Each MRI unit must be designed with a holding area that allows MRI technicians the opportunity to inspect every new person and piece of equipment that comes into the unit. The unit is locked from the outside so that all visitors must obtain permission before entering.

The gradient magnetic field that is activated during the MR scanning procedure is the primary source of acoustic noise. Rapid alterations of current within gradient coils produce large forces in the presence of the static magnetic field. These forces cause motion or vibration of the coils against the mountings. This motion results in loud tapping or knocking sounds [32], which can interfere with communication and be frightening to anxious patients and children. Every patient must receive disposable ear plugs or noise-abatement headphones before beginning the scan.

Most of the radiofrequency power is transformed into heat as a result of resistive losses within a patient’s tissues. Many factors can affect this heating process, and if normal thermoregulatory mechanisms (eg, convection, conduction, radiation, and evaporation) do not succeed in dissipating the heat load, the patient develops an elevation in tissue temperature [32]. The low ambient temperature and the tendency by general anesthesia to trigger hypothermia can counteract this heating process. MRI scanners have built-in safety features to avoid excessive heating, but small children actually can overheat in this environment [35]. The authors of this report suggest that the manufacturers may need to revise calculations used to prevent excessive heating of infants and young children.

In the presence of radiofrequency waves, cables and cords can act as antennae for the radiofrequency power, which can lead to image degradation. If the
cables and cords are coiled, they generate excessive heat that can cause burns. To prevent burns, the Institute for Magnetic Resonance Safety, Education and Research has developed guidelines for patient screening, positioning and padding in the scanner, placement of ECG electrodes and leads, use of electrical equipment, and placement of cables [32]. All monitoring equipment must be tested and determined to be safe and compatible for the MRI unit.

Because of the special problems in the MRI unit, manufacturers have responded to the challenge and have developed monitoring systems, infusion pumps, and anesthetic machines that can be used safely in the magnet room without degrading the image or causing harm to patients if appropriate guidelines are followed. When working in this environment, it is imperative to institute and follow guidelines that prevent hazardous events from occurring.

MRI does offer two advantages when compared to the other whole-body imaging modalities. Patients do not have any exposure to radiation, and the contrast agent—gadolinium—is much safer than the iodinated contrast agents used for CT and angiography.

Future developments include more MRI-guided surgery and more use of MRI imaging to evaluate cardiovascular function.

**CARDIAC CATHETERIZATION LABORATORY**

Interventional cardiac procedures have exploded over the past 20 years and supplanted invasive cardiac surgical procedures. Most of these procedures in adults are managed with local anesthesia and sedation. Even in children, most diagnostic studies are performed while they are sedated rather than anesthetized because a sedated patient’s hemodynamic values are closer to awake values than those while anesthetized.

Cardiac interventional procedures include vascular stent placement, umbrella occlusion device insertion, coil embolization, balloon dilatation, transcatheter ablation of accessory conduction pathways, and cardioversion. Although many of these procedures are accomplished with intravenous sedation and local anesthesia, some do require general anesthesia. For example, transcatheter ventricular septal defect device closures require a long time and are associated with significant hemodynamic instability. Mitral valve dilatation with balloon inflation can result in severe hemodynamic disturbance, so it is best managed with general anesthesia. Transcatheter ablation procedures are conducted with intravenous sedation for adults, but because the procedure can take several hours, general anesthesia is best for small children [36].

The effect of anesthetic agents on the cardiac conduction system is an important consideration when planning anesthesia for one of these procedures. Intravenous agents that have been studied that have no effect on the conduction system include fentanyl [37], sufentanil [38], alfentanil [39], midazolam [39], and lorazepam [38]. Droperidol increases the refractory period [37]. Volatile agents do increase the refractoriness within accessory and normal pathways and may be contraindicated during ablation procedures [38]. Another important consideration is the option of air as a carrier gas on the anesthesia machine.
Cardiologists prefer patients to breathe air spontaneously to have the least disturbance of hemodynamic values. Finally, positioning can be tricky when a patient is asleep. Cardiologists like to have the arms above the head, but this position in an asleep patient can increase the risk of a brachial plexus injury [36].

**RADIATION THERAPY**

External beam radiotherapy with the cobalt isotope presents a special challenge if deep sedation or general anesthesia is required. Because of the huge doses of radiation involved in this therapy, the anesthesia team cannot stay in the room with a patient. Movement during radiotherapy may result in inadequate tumor irradiation, so it is necessary for a patient to be still during the therapy. Adults usually can cooperate, but small children may not be able to, so deep sedation or general anesthesia with laryngeal mask airway or endotracheal intubation is necessary. When anesthesia is required, it is important that the same monitoring standards be followed as in the operating room. The therapy area should have a video camera that is trained on the patient and on the monitor, which can be placed near the patient’s head. The anesthesia provider can monitor the patient with this camera during the therapy process. Usually these patients require multiple sessions with repeated anesthetics [40].

**GASTROINTESTINAL ENDOSCOPY SUITE**

Most procedures for adults in the gastrointestinal endoscopy suite can be performed with intravenous sedation without the involvement of an anesthesia provider; however, endoscopic retrograde cholangiopancreatography may require general anesthesia. This the most complex endoscopic procedure and the preferred treatment for most pancreatic-obiliary diseases [41]. Patients who need this procedure are frequently ill and may be at significant risk for hypoxia during the procedure if their airway is not controlled. Because of the nature of their disease, these patients are also at risk for vomiting and aspiration. Usually this procedure is performed with patients in a lateral or even prone position so a controlled airway with an endotracheal tube is preferable.

Pediatric patients may require deep sedation or general anesthesia with a laryngeal mask airway for colonoscopic procedures. Upper gastrointestinal endoscopy procedures are best performed with general endotracheal intubation to have better control of the airway.

**PSYCHIATRIC UNIT**

Electroconvulsive therapy procedures under general anesthesia are an important therapy in the treatment of severe depression and mania and in the therapy of schizophrenia. During the acute phase of therapy, electroconvulsive therapy may be performed as often as three times per week for 6 to 12 sessions. According to institutional preference and staffing, these procedures may be performed in the psychiatric unit or may be scheduled for the operating room.

The physiologic response to the electrical stimulus can be significant. An initial parasympathetic-induced bradycardia occurs for 10 to 15 seconds followed
by a sympathetic response with tachycardia and hypertension. The seizure activity is accompanied by a generalized convulsion that can result in fractures and muscle pain.

To attenuate the cardiovascular response, anticholinergic drugs, such as glycopyrrolate, can block the parasympathetic response. Beta blockers, such as esmolol, can blunt the sympathetic response. The most widely used anesthetic agent for electroconvulsive therapy is methohexital, but thiopental, thiamylal, propofol, and etomidate have been used successfully. To reduce the intense muscle contractions, succinylcholine is usually given before the electrical stimulus, and ventilation is assisted with a bag and circle system or a bag-valve-mask system [42].

SUMMARY
An increasing number and variety of diagnostic and therapeutic procedures outside of the operating room require the involvement of an anesthesiologist either directly or indirectly. Although many patients are sedated for these procedures by practitioners who are not anesthesiologists, the standards for sedation are set by the anesthesiology department and the credentialing process for the use of sedative drugs is under the charge of the anesthesiology department. If general anesthesia is required, the same standards for the operating room apply to any other sites in the hospital. The American Society of Anesthesiology and the Joint Commission for Accreditation of Healthcare Organizations have worked together to develop guidelines for the safe management of sedation and anesthesia for these procedures. To ensure safe, efficient, and effective patient care, all practitioners who use sedative and anesthetic agents must be familiar with these guidelines.

References


Dexmedetomidine (Precedex) is a highly selective, potent alpha-2 adrenergic receptor agonist. It has sedative, analgesic, and anxiolytic properties with, amazingly, no effect on the respiratory rate. Dexmedetomidine binds alpha-2 receptors eight times more avidly than does clonidine and is shorter acting. Its mechanism of action includes stimulation of receptors in the locus ceruleus to provide sedation and in the spinal cord to enhance analgesia.

Among the drugs used for anesthesia, alpha-2 agonists are unique in that they provide hemodynamic and sympathoadrenal stability and possess sedative, hypnotic, and analgesic properties [1]. Of the alpha-2 agonists, clonidine has been studied most extensively. Aside from its common use as an antihypertensive, it is widely known that clonidine, with its ability to cause a decrease in circulating catecholamines, is also highly effective in minimizing the perioperative stress response. Its use as such is limited by a common side effect, however: sedation. Anesthesia for surgical procedures may exploit these benefits and the side effects. Dexmedetomidine, a newer alpha-2 agonist, shares the advantages of clonidine but with greater selectivity for the alpha-2 receptor [2]. With this increased selectivity, dexmedetomidine is capable of reducing circulating catecholamines by 90%, is much more effective than clonidine in blunting the sympathetic response during laryngoscopy and intubation, and is a much more potent analgesic [3–7].

The use of dexmedetomidine as an anesthesia adjunct in balanced anesthesia and total intravenous (IV) anesthesia for surgical procedures has been increasing. Aside from the benefits of alpha-2 agonism discussed previously, dexmedetomidine is advantageous in the balanced anesthesia setting because it reduces the minimum alveolar concentration requirements for volatile anesthetics and has an additive effect when combined with benzodiazepines and narcotics [8–10]. With dexmedetomidine, satisfactory balanced anesthesia, hemodynamic stability, and rapid emergence can be achieved with lower doses of coadministered drugs.
Analgesia is defined as insensibility to pain without loss of consciousness. This state can be achieved various methods, including pharmacologic interventions, acupuncture, psychotherapy, and invasive methods. Dexmedetomidine is one the pharmacologic methods to achieve analgesia.

Sedation is described as reduction of anxiety, stress, irritability, or excitement usually caused by administration of drugs. Dexmedetomidine is a safe sedative agent because of the properties described in the following sections.

**PHARMACOLOGY**

Dexmedetomidine exhibits an affinity for alpha-2 adrenoceptors over alpha-1 adrenoceptors 1620:1, as demonstrated in vitro [11]. Dexmedetomidine has a half-life of approximately 6 minutes. Dexmedetomidine infusion also shows linear kinetics in the dose range of 0.2 to 0.7 $\mu$g/kg/h for up to 24 hours. In healthy volunteers, dexmedetomidine is 94% protein bound. It is not significantly displaced by some commonly used drugs, nor does it displace drugs such as phenytoin, warfarin, theophylline, and digoxin [11].

**Metabolism**

Dexmedetomidine undergoes glucuronidation and cytochrome P450–mediated metabolism in the liver. It is excreted mainly via the urine (95%). Dose reduction should be considered in patients with significant hepatic impairment (Child-Pugh class A, B, or C) [11].

**Elimination**

The elimination half-life for dexmedetomidine is 2 hours. There is no change in the pharmacokinetics with respect to gender or renal impairment [11].

**MECHANISM OF ACTION**

Alpha-2 receptors are mainly located in the presynaptic nerve terminals. Activation of alpha-2 receptors presynaptically decreases the release of norepinephrine. Stimulation of the postsynaptic alpha-2 receptor causes hyperpolarization of the membrane, which produces a negative feedback loop and decreases release of norepinephrine even more. In the central nervous system, stimulation of the alpha-2 receptor reduces sympathetic outflow, which causes vasodilatation, sedation, reduction in brain noradrenergic activity, decreased heart rate, and analgesia. The adrenoreceptors in the locus ceruleus control wakefulness; stimulation of alpha-2 receptors causes sedation. The reduction in sympathetic tone also leads to decreased myocardial oxygen consumption [12].

**CLINICAL EFFECTS**

**Sedation**

As demonstrated by Martin and colleagues [13] in a double-blinded, randomized, multicenter trial, 60% of patients on dexmedetomidine for postoperative intensive care unit (ICU) sedation needed no additional sedative (Fig. 1). Dexmedetomidine has significant analgesic properties, which were also demonstrated...
in the study by Martin and colleagues [13]. In that study, dexmedetomidine was found to have marked morphine-sparing effects (Fig. 2).

Respiratory stability
Dexmedetomidine is a unique sedative that does not cause respiratory depression. Venn and colleagues [14] showed in a retrospective study that there was no difference in oxygen saturation and arterial pH in patients who received a placebo versus infusion of dexmedetomidine. They also showed an improvement in the ratio of partial arterial oxygen tension and fraction of inspired oxygen with dexmedetomidine treatment. In a study of healthy volunteers, they found no change in respiratory rate and oxygen saturation between infusions of placebo versus dexmedetomidine.

Hemodynamic profile
Dexmedetomidine demonstrates hemodynamic predictability [11], and moderate blood pressure and heart rate reductions should be anticipated [15]. Caution should be exercised when administering dexmedetomidine to patients with advanced heart blockage or severe ventricular dysfunction [16].

Dosing
Currently, dexmedetomidine is approved by the US Food and Drug Administration (FDA) for sedation in intubated patients in intensive care not to exceed
24 hours. It must be administered via infusion, and the usual loading dose is 1 \( \mu g/kg \) over 10 minutes, followed by a maintenance dose of between 0.2 and 0.7 \( \mu g/kg/h \) to achieve the desired effect. The use of dexmedetomidine has not been studied in the pediatric and obstetric populations.

**OFF-LABEL USE OF DEXMEDETOMIDINE**

The uses of a drug other than those listed on the prescription label are considered off-label uses. Off-label uses include those that differ from the approved labeling in dosage or dose regimen, patient population, and indication for use [17]. Two populations of patients are more likely to be given medications that are unlicensed or prescribed for off-label use: pediatric and obstetric populations. Many studies have discussed the incidence of prescriptions for off-label uses and unlicensed drugs in the pediatric population and their possible detrimental effects [18–20]. A European survey showed that more than half of pediatric patients received off-label or unlicensed prescriptions. In the obstetric population, almost 22% of the prescriptions include off-label or unlicensed use of medication [21,22]. In both groups, clinical trials are not always possible or practical because of ethical and technical reasons.

The off-label use of medication often is rational and evidence based; it is not the result of incorrect use of the medication by the physician but an inadequate process of evaluation by industry. Unfortunately, off-label use of drugs can be described as uncontrolled experiments that result in unreliable data. This phenomenon is rampant around the world. The US FDA is establishing new rules
to allow the spread of information about off-label uses of certain medications if these uses have been documented in reputable, peer-reviewed scientific publications [22]. The reporting of experiences with off-label uses of medications helps physicians decide what role the off-label use of the medication will play. This process does not, however, substitute for controlled trials that evaluate the safety, effectiveness, and dosing for a particular off-label scenario.

The off-label use of a medication is acceptable if there is no suitable alternative and if a physician feels confident that he or she is using the medication in accordance with current medical opinion [23]. Physicians who prescribe the off-label use of a medication should document the rationale for that use and any discussions they may have with the patient regarding that use [24].

The US FDA recognizes that although off-label uses may represent a deviation from their specific recommendations, these uses play an important role in the progression and evolution of modern medicine [17]. The US FDA states, “once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations” [17].

Off-label use of dexmedetomidine in the operating room
The US FDA approved dexmedetomidine in 1999 for short-term use (defined as less than 24 hours) in adult intensive care patients who are initially intubated and mechanically ventilated [17,25]. In our practice, which is based in a university-affiliated tertiary care cancer hospital with a patient population that encompasses all cancer diagnoses and stages, the authors have used dexmedetomidine advantageously off-label in various anesthetic scenarios in the operating room, including (1) regional anesthesia, (2) awake fiberoptic intubation/airway surgery, including monitored anesthesia care sedation cases with field (airway) avoidance, (3) cardiothoracic surgery, and (4) neurosurgery (spinal surgery/awake craniotomies).

Regional anesthesia
Dexmedetomidine is a useful anesthetic adjunct for sedation during either the placement of regional anesthetic blocks or the conduction of regional anesthesia. At MD Anderson, the use of dexmedetomidine in patients undergoing regional anesthesia allows us to maintain a relatively deep level of anesthesia with reduced administration of narcotics and benzodiazepines, while at the same time allowing spontaneous respirations and easy arousal, which are important for communicating with patients to gauge the effectiveness of the block. In the sedation regimen, the benzodiazepine midazolam is limited to 0.5 to 2 mg IV, remifentanil is titrated starting at 0.02 µg/kg/min, and dexmedetomidine is titrated (no bolus) at a rate of 0.2 µg/kg/h. Propofol also may be introduced at a low infusion rate (5–10 µg/kg/min) and titrated to effect. Once the desired level of sedation is achieved (ie, the patient is relaxed, spontaneously breathing, and easily arousable), infiltration of local anesthesia in the desired field and
regional anesthesia are performed. This technique provides a good level of anes-
thesia with preserved respiration, stable hemodynamics, and decreased benz-
diazepine/narcotic administration. For patients continuing on with surgery
under regional anesthesia and monitored anesthesia care sedation, dexmedeto-
midine and remifentanil are continued, and the infusions are adjusted to
achieve an adequate level of comfort. For patients continuing on with surgery
under general anesthesia, the dexmedetomidine and remifentanil infusions may
be continued into the general anesthesia phase, which reduces the amount of
coadministered anesthetic drugs needed to maintain an adequate level of gen-
eral anesthesia. Dexmedetomidine also has been reported to possibly improve
the quality of analgesia and decrease the analgesic requirement in IV regional
anesthetic techniques when administered as part of the local anesthetic solution
[26].

Awake fiberoptic intubation/airway surgery
A patient who presents with a challenging airway that requires fiberoptic endo-
tracheal intubation also may benefit from dexmedetomidine as a sedative agent
[27]. The maintenance of spontaneous ventilation and cooperation during fiber-
optic-guided intubation is of prime importance. Dexmedetomidine results in
less respiratory depression than other comparable anesthetic agents and has
been shown to blunt the sympathoadrenal response to endotracheal intubation
[7,10]. Another benefit of the alpha-2 agonist characteristics of dexmedetomi-
dine is decreased salivation and secretions, although glycopyrrolate still may
be coadministered for a further reduction in oral secretions.

A sedation regimen using low-dose dexmedetomidine combined with care-
fully titrated reduced doses of benzodiazepines and ultra–short-acting narcotics
is used for awake airway manipulation. The level of anesthesia desired can
be obtained easily during the administration of local airway anesthesia. The
main advantages of dexmedetomidine over a comparable anesthetic agent,
such as propofol, are the maintenance of spontaneous ventilation, arousability/
cooperation, and hemodynamic stability during this critical and stressful period
time for the patient and anesthetist. Once the intubation is completed, end-tidal
CO$_2$ can be confirmed and fiberoptic bronchoscopy may be performed for tube
positioning before induction of general anesthesia.

For airway surgery, IV anesthesia (either total or as a supplement to inhala-
tion anesthesia) may be the only means of providing adequate anesthesia to the
patient, because there is frequently a breech in the continuity of the trachea or
in one of the conducting portions of the airway. In the setting of total IV anes-
thesia, other sedative hypnotic agents, such as propofol, may be included in the
infusion regimen (at reduced doses) to supplement the sedative action of dex-
medetomidine. Using dexmedetomidine as a main total IV anesthesia agent al-
lows the maintenance of spontaneous ventilation in some types of airway
surgery in which it is essential to maintain spontaneous ventilation while pro-
viding adequate anesthesia. A main advantage of dexmedetomidine in patients
with difficult/challenging airways (especially in the total IV anesthesia setting) is
rapid emergence from anesthesia, with a return of spontaneous ventilation and airway reflexes, at the end of the operation.

Finally, dexmedetomidine in combination with low-dose benzodiazepines and narcotics also has been used with success in monitored anesthesia care sedation cases in which rapid access to a patient’s airway may not be possible (ie, cases in which field avoidance is necessary). Because it does not cause respiratory depression and spares the use of opiates, dexmedetomidine is an ideal choice in this anesthetic scenario, in which airway maintenance maneuvers and assisted ventilation may not be performed readily.

**Cardiothoracic surgery**

Because of its stable hemodynamic profile, dexmedetomidine may be the sedative hypnotic of choice for patients undergoing cardiac, vascular, or thoracic surgery. The ability of dexmedetomidine to decrease circulating catecholamines and decrease hemodynamic instability in the perioperative setting may decrease the likelihood of ischemic events in this high-risk population. It has been shown to reduce the occurrence of ischemic events in vascular surgery [28,29]. In thoracic surgery, volume restriction with preserved hemodynamics is essential but may be difficult to achieve. One-lung ventilation, lateral thoracotomy position, open pneumothorax, surgical manipulation of the heart and lungs, and patient comorbidities all contribute to intraoperative instability in patients undergoing thoracic surgery.

At the MD Anderson Cancer Center, a combination of IV volatile and regional anesthetic agents (with dexmedetomidine being the main sedative-hypnotic) are used to provide anesthesia to this potentially hemodynamically unstable population of patients. The regimen includes premedication with 0.5 to 2 mg IV midazolam, dexmedetomidine infusion with an initial dose of 0.2 μg/kg/h (started before the placement of the thoracic epidural) with no bolus loading, and remifentanil infusion at reduced doses (0.025–0.05 μg/kg/min started before thoracic epidural placement). The incidence of adverse effects associated with dexmedetomidine, namely hypotension, hypertension, bradycardia, and atrial fibrillation, may be reduced by avoiding bolus loading doses. Infusions are continued through induction, and reduced doses of propofol (10–30 mg prn) are administered (guided by hemodynamics, bispectral index monitoring, and subjective assessment of patient anesthetic depth) to achieve an adequate plane of anesthesia for intubation. Once the airway is secured, invasive monitors are in place, the patient is hemodynamically stable, and the bispectral index value is appropriate, a short-acting volatile anesthetic agent (eg, desflurane) is titrated to a monitored anesthesia care “amnesia” level (0.4–0.5 end-tidal concentration) and maintained. Epidural narcotics are administered before skin incision, and dexmedetomidine and remifentanil/narcotic infusions are adjusted to reflect changes in bispectral index or hemodynamics. If necessary, low-dose propofol IV infusion or low-concentration local anesthesia via an epidural may be used to ensure adequate anesthesia. Intraoperative bispectral index monitoring is used with other standard parameters to assist in
assessing a patient’s anesthetic depth. In preparation for emergence, the volatile anesthesia is discontinued upon muscle closure, the remifentanil is discontinued upon skin closure, and a bolus of local anesthesia is administered via the thoracic epidural. The patient is maintained on dexmedetomidine until extubation.

This method of carefully titrated and mainly IV anesthesia offers the cardio-protective effects of alpha-2 agonism: stable hemodynamics and rapid awakening/extubation. Dexmedetomidine has been shown to be a potentially effective analgesic alternative to thoracic epidural anesthesia and may be useful in patients in whom an epidural is contraindicated [30].

**Neurosurgery**

Dexmedetomidine has been used successfully in awake craniotomies, in which alternating light and deep levels of sedation are required intraoperatively [31]. The advantages of using dexmedetomidine in these procedures include rapid awakening, hemodynamic stability, and decreased dosage of coadministered anesthetics. Because of its ability to cause a decrease in cerebral blood flow, some authors caution against the use of dexmedetomidine in patients with intracranial pathology [32]. Dexmedetomidine is also suitable for neurosurgical operations that involve the spinal cord and using somatosensory evoked potentials to monitor for possible spinal cord compromise. At MD Anderson Cancer Center, dexmedetomidine is used as an anesthesia adjunct to volatile anesthetics, which can interfere with somatosensory evoked potentials waveforms [33].

**Non-intensive care unit out-of-operating-room use of dexmedetomidine**

Use of dexmedetomidine in the pediatric population and for adults outside the ICU and operating room is still novel. A review of the literature suggests that it has been used for sedation in various ICU scenarios and as an adjuvant during general anesthesia but was found to be inadequate for sedation during outpatient procedures when used alone [24,34]. Dexmedetomidine is an excellent agent for sedation in patients with respiratory compromise caused by a mediastinal mass or obesity, however.

**Mediastinal mass**

Sometimes, mediastinal tumors can cause life-threatening complications, such as upper airway obstruction, superior vena cava obstruction, cardiac or pulmonary artery compression, and acute pulmonary edema. These complications can be exacerbated when the sedation given to patients decreases muscle tone or patients become apneic and cannot breathe spontaneously to maintain patency of the airway (all the way from the oropharynx to the carina). These cases are challenging for anesthesiologists, and they become even more complex when the anesthesia/sedation must be administered outside of the operating room. The key to sedation of a patient with a large mediastinal mass is keeping the patient breathing spontaneously. In a review by Ferrari and
Bedford [35], 20% of pediatric patients with an anterior mediastinal mass had respiratory complications during general anesthesia.

**Obesity**

Patients with morbid obesity or obstructive sleep apnea are tricky to sedate for out-of-operating-room procedures, mainly because increasing the propofol dose can result in dose-dependant collapse of the airway [36].

Several different methods can be used to provide sedation/anesthesia in these patients: (1) Using ketamine as an analgesic and sedating agent. It does have a risk of unpleasant neuropsychiatric side effects, however, which may not be acceptable in an outpatient setting. (2) Using propofol for procedural sedation. There is a risk of apnea and collapse of the airway, however, which could be fatal in this subset of patients. (3) Using dexmedetomidine alone or in combination with ketamine. At a tertiary cancer referral center, procedural sedation for large mediastinal mass biopsies, radiation therapy is often performed. The usual loading dose of dexmedetomidine that we use is $1 \mu g/kg/h$ for 10 minutes and then 0.2 to 0.7 $\mu g/kg/h$ maintenance infusions. This regimen has been used on patients from 11 months to 85 years of age without any complications. There are some suggestions that dexmedetomidine might attenuate the neuropsychiatric symptoms of ketamine [37].

Although dexmedetomidine has not been studied formally in the pediatric population, there are increasing reports regarding its safety and efficacy. It has not proved to be a great solo agent for sedation, but in combination with ketamine or propofol it has been useful [38,39].

The quality of sedation is similar to propofol, but patients may be aroused with stimuli. There also may be a more profound drop in blood pressure and heart rate with dexmedetomidine compared to propofol. Compared with propofol, dexmedetomidine takes longer to achieve peak effect (up to 20 minutes) and wear off after infusion is stopped (up to 20 minutes) after short-term use for sedation.

**Off-label uses of dexmedetomidine in the intensive care unit**

Among the current off-label uses of dexmedetomidine in the ICU are (1) prolonged administration of a continuous infusion (ie, more than 24 hours), (2) continuous infusion without a prior loading dose, (3) higher-than-recommended dosage levels, (4) use in pediatric ICU patients, and (5) use in sedative-hypnotic withdrawal.

**Prolonged duration of administration**

According to the current recommendations, more than 24 hours of continuous dexmedetomidine infusion is considered long-term infusion. Since its initial approval of dexmedetomidine, the US FDA has requested phase IV studies of long-term continuous infusion of dexmedetomidine to evaluate further its pharmacokinetics, safety, and effectiveness in ICU patients and patients with renal failure [17]. In the initial new drug application submitted for dexmedetomidine, only 78 patients (of 3038 subjects, with 1473 ICU patients) received
Dexmedetomidine for more than 24 hours, with none receiving the medication for longer than 40 hours [17]. Dexmedetomidine is increasingly being used in the ICU for durations exceeding 24 hours, however. In 2004, Dasta and colleagues [40] retrospectively reviewed data from ten institutions regarding the administration of dexmedetomidine as part of routine adult patient care. They found that the average duration of treatment was 54 hours, there were no rebound effects regardless of the duration, and no statistically significant adverse drug reactions were noted.

No loading dose
Increasing evidence in the literature seems to suggest a trend toward foregoing the administration of a bolus or a loading dose when the dexmedetomidine infusion is initiated. Studies have shown that there is an initial fall in cardiac output shortly after the loading dose, although dexmedetomidine exerts no direct effects on the heart [41,42]. It is presumed that this effect is caused by an initial transient increase in afterload [43]. A retrospective review of 136 patients by Dasta and colleagues [40] showed that only 33% of the patients who received dexmedetomidine received a loading dose. Others have suggested that the reasons for limited use of the loading dose included omission of the loading dose in the institution’s protocol and never having used the loading dose at that institution.

Greater-than-recommended dosage
The US FDA-approved and recommended dexmedetomidine infusion dosing is 0.2 to 0.7 μg/kg/h. Although the recommended dose is generally followed and reviews reveal that only 27% of patients receive dexmedetomidine above the maximum dose, doses ranging from 0.7 to 1.4 μg/kg/h have been reported in the literature [40]. One study reported the use of rates as high as 2.5 μg/kg/h, with only modest decreases in blood pressure, heart rate, and cardiac output [43]. From their experience, Venn and colleagues [43] noted that an infusion rate more than 1.5 μg/kg/h did not seem to improve or augment the sedation effects. There is, however, literature in the form of case reports, in which dexmedetomidine was administered at dosages as high as 5 and 10 μg/kg/h, as a component of total IV anesthesia [44]. These authors maintained that dexmedetomidine’s properties of sedation, analgesia, and no respiratory depression persisted even at the anesthetic doses. No significant bradycardia or hypotension was noted in these case reports. The dosage ceiling for sedation with dexmedetomidine infusion is still unclear, and additional studies are necessary to clarify this.

Pediatric intensive care unit patients
In the initial new drug application for dexmedetomidine, no data were submitted regarding safety in pediatric patients [17]. Since the approval of dexmedetomidine in 1999, there have been multiple articles regarding the use of this medication in the pediatric population, ranging from anecdotal to prospective, randomized trials and including intubated and nonintubated ICU and
non-ICU patients. Tobias and Berkenbosch [45] prospectively compared dexmedetomidine (0.25 or 0.5 µg/kg/h) and midazolam (starting at 0.1 mg/kg/h) for sedation of infants and children during mechanical ventilation. The lower dose of dexmedetomidine (0.25 µg/kg/h) provided sedation equivalent to 0.22 mg/kg/h of midazolam; however, the higher dose (0.5 µg/kg/h) provided sedation and analgesia superior to midazolam, as evidenced by the more appropriate Ramsay sedation scores and the lower requirement for supplemental morphine doses over a 24-hour period in the dexmedetomidine group [45]. Systolic or diastolic blood pressures did not differ significantly between the three groups; however, heart rates were significantly lower in the two dexmedetomidine groups as compared to the midazolam group [45].

Sedative-hypnotic withdrawal
Dexmedetomidine also has been used for sedative-hypnotic withdrawal in the ICU. A case report from 2003 presented the use of dexmedetomidine in a multiple-substance abuser with acute respiratory distress syndrome and ventilator-associated pneumonia who was successfully weaned from the ventilator, lorazepam, and IV fentanyl after 7 days of continuous dexmedetomidine infusion [46]. This patient had no adverse cardiovascular sequelae from the prolonged dexmedetomidine use.

Use of dexmedetomidine in noninvasive procedures
Dexmedetomidine has been evaluated anecdotally and prospectively for sedation during noninvasive procedures in children. In one study, dexmedetomidine was used successfully to sedate 48 children undergoing electroencephalography, MRI (head or other), and nuclear medicine imaging without significant changes in heart rate, blood pressure, or respiratory rate [47]. Dexmedetomidine use also was reported in a retrospective case series that described its use as a rescue sedation agent (loading and maintenance infusions) in five children undergoing MRI who had failed conventional sedation with chloral hydrate or midazolam [48]. The mean loading doses were 0.78 ± 0.42 µg/kg/h, the mean maintenance infusion rates were 0.57 ± 0.06 µg/kg/h, and no clinically significant cardiorespiratory changes were reported [38].

USE OF DEXMEDETOMIDINE BY NONANESTHESIOLOGISTS
Nonanesthesiologists (eg, adult and pediatric intensivists, surgeons, and pharmacists) are using dexmedetomidine more and more frequently [25,40]. Dasta and colleagues [40] reported that anesthesiologists were the most common prescribers of dexmedetomidine (38%). Other specialists who prescribed dexmedetomidine included surgical specialists (13%), critical care specialists (11%), pulmonologists (9%), and pharmacists (8%).

SAFETY CONSIDERATIONS
The major safety concerns regarding dexmedetomidine include the following: (1) A 24-hour limitation on the use of dexmedetomidine as a continuous infusion was instituted secondary to concerns regarding possible tolerance,
rebound withdrawal, and accumulation of active metabolites. (2) Dexmedetomidine has not been approved in the pediatric population. (3) Patients older than 65 years are prone to conduction defects, and this drug should be used with caution in this subset of patients. (4) Dose reduction should be considered in patients with renal impairment. (5) No data are available on the safety of dexmedetomidine in the obstetric population.

The sedative and sympatholytic effects of dexmedetomidine are dose dependently antagonized by IV atipamezole. Both drugs have similar half-lives [48].

Adverse reactions
According to Dasta and colleagues [40], the most common adverse reaction to dexmedetomidine was hypotension, which occurred in 23% of patients, followed by bradycardia, which occurred in 4.4% of patients. Table 1 shows the incidence of bradycardia and hypotension from various studies dating from 1997 to 2004 [25]. Of significance is the finding that most of the bradycardia and hypotension occurred shortly after administration of the loading dose. In the studies in which no loading dose was given, the incidences of bradycardia and hypotension were 0% to 5% and 0%, respectively (Table 1).

Other adverse reactions include nausea (11%), atrial fibrillation (7%), anemia (3%), pain (3%), pleural effusion (3%), leukocytosis (2%), oliguria (2%), pulmonary edema (2%), infection (2%), and thirst (2%).

Drug interactions
Dexmedetomidine administration may be affected by various drug interactions. CYP2A6 inhibitors, such as isoniazid, methoxsalen, and miconazole, may increase the level and effects of dexmedetomidine. Conversely, dexmedetomidine may increase the levels and effects of CYP2D6 substrates, which include amphetamines, selected beta blockers, and lidocaine. Dexmedetomidine may decrease the levels and effects of CYP2D6 prodrug substrates, such as codeine, oxycodone, and tramadol. Adverse reactions associated with dexmedetomidine, such as hypotension and bradycardia, may be augmented or potentiated by vasodilators and heart rate–lowering medications, such as digoxin and esmolol [49].

Tolerance and withdrawal
Although tolerance with the potential for rebound or withdrawal effects is a common complication of sedation, it has not been reported to date with dexmedetomidine [40]. Even long-term administration of dexmedetomidine infusion (averaging 33 hours) did not result in clinically significant rebound after drug discontinuation [43].

Pregnancy
Experience and safety data regarding dexmedetomidine in the obstetric population are lacking. Currently, dexmedetomidine is considered a category C by the US FDA for use in pregnancy, which indicates that “risk cannot be ruled out” (Table 2).
<table>
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<th>Year</th>
<th>No. of patients</th>
<th>No. (%) of patients</th>
<th>Comments</th>
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</tr>
<tr>
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<td>22</td>
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<tr>
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<td>NA (7)</td>
<td>NA (28)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

References


Table 2
FDA Use-in-Pregnancy Ratings for Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
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<tr>
<td>A</td>
<td>Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in humans: Either animal findings show risk (but human findings do not) or, if no adequate human studies have been done, animal findings are negative</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out: Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. Potential benefits may justify the potential risk, however</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk: Investigational or postmarketing data show risk to the fetus. Potential benefits may outweigh the risk</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated in pregnancy: Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient</td>
</tr>
</tbody>
</table>


Anesthesia for Robotic Heart Surgery

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The face of cardiac surgery is changing and, with it, the face of cardiac anesthesia. A glance at almost any operating room schedule confirms that cardiac surgical volume is down. Patients rarely present for coronary surgery without a prior percutaneous intervention, if not the “full metal jacket” of stents down the entire left anterior descending artery. Lipid-lowering therapy, statins, lifestyle modification, and better control of hypertension and diabetes all have contributed to the decline in the number of patients presenting for coronary artery bypass grafting (CABG). In general, outcomes of percutaneous interventions are comparable with surgery \cite{1}. One response to this trend is a decline in interest in cardiac surgery among American graduates \cite{2,3}. Another is the incorporation of percutaneous techniques into the curriculum of surgical training programs. Finally, the move to less invasive operative techniques, which cause less pain and allow faster return to normal functioning, has been well underway for some time. Valvular disease, congenital defects, and arrhythmias all currently are addressed with percutaneous and minimally invasive techniques.

Since the merger of Computer Motion (Goleta, California) and Intuitive Surgical (Mountain View, California), Intuitive’s daVinci System is the only robot currently in production. The surgical instruments provide 7 degrees of freedom and 90 degrees of articulation. Dual cameras provide stereoscopic vision, and the controlling software provides tremor reduction. A typical setup for coronary artery surgery is shown in Fig. 1. This technique is labor and technology intensive, contributing to increased case duration.

ANESTHETIC TECHNIQUE

Patient selection is key to successful robotic heart surgery. Evidence of pulmonary hypertension (PH) should be sought and evaluated carefully. Preexisting PH resulting from either cardiac or intrinsic lung disease is exacerbated by

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one-lung ventilation, surgical compression, and the iatrogenic pneumothorax, which may be needed for surgical exposure. Right ventricular (RV) failure can occur if a marginal RV is stressed further by intraoperative increases in pulmonary artery (PA) pressure. Chest wall deformities, such as extreme pectus excavatum or kyphoscoliosis, not only elevate PA pressures and compress lung tissue, making ventilation difficult, but may make access to the heart difficult using the usual thoracoscopic ports. Obesity can lead to increased PA pressures and make management of one-lung ventilation and positioning more difficult. Patients who have poor left ventricular function may be managed better through sternotomy, because bypass can be initiated rapidly should hemodynamic deterioration occur. Patients who have prior coronary revascularization needing isolated mitral valve (MV) surgery can be managed with minimally invasive approaches with decreased blood loss and less chance of graft injury.

Positioning

Care and ample padding should be used when positioning the arms to avoid nerve damage and compression of intravenous or arterial catheters. For MV surgery, the right arm is positioned below the right hemithorax with a small bolster under the right scapula (Fig. 2). The left arm is positioned similarly for internal mammary artery (IMA) takedown and coronary grafting. Brachial plexus and ulnar nerve injuries are possible during robotic surgery. This arm position places intravenous and arterial catheters at risk. For coronary artery surgery, the right radial artery is catheterized. The left radial is used for mitral, tricuspid, or atrial septal defect (ASD) procedures unless an endoarteric occlusion catheter is used, in which case both radial arteries are cannulated to monitor for innominate artery occlusion (discussed later). Patients are positioned at the edge of the operating table in order to provide clearance for the robot. Therefore, care should be used when tilting the table from side to side. The hips remain flat for access to the femoral vessels.
Temperature management
Robotic techniques frequently require longer set-up and preparation time than their open counterparts, making avoidance of hypothermia important and difficult. Avoidance of hypothermia is especially true for procedures done off pump. All applicable temperature preservation techniques should be used, including heated fluids, forced air warming, heat and moisture exchangers in the anesthesia circuit, and minimizing exposure to ambient temperatures. The positioning requirements for robotic surgery make some of these difficult; however, several manufacturers have developed forced air blankets designed to avoid the thoracic surgical field. Sterile forced air blankets are available, making it possible to cover areas not being operated on without breaking the sterile field. Because topical cooling rarely is used in robotic surgery, the PA temperature can be used as a measure of core temperature.

Lung separation
A quiet operative field and room to work within the hemithorax are key to a successful outcome. The particular lung separation technique depends on the skill and experience of individual anesthesiologists. Use of a single-lumen tube with high-frequency jet ventilation of the lung in the nonoperative hemithorax is reported, but most anesthesiologists use some form of lung separation and conventional ventilation. Bronchial blockers incorporated either within the endotracheal tube (Univent, Fuji Systems, Tokyo, Japan) or as separate devices (Arndt or Cohen blockers, Cook, Bloomington, Indiana) are used with success. The convenience of not having to change the endotracheal tube at the end of the case is mitigated somewhat by their greater tendency to dislodge during intrathoracic manipulation. In the end, most anesthesiologists find it more convenient simply to place a standard endobronchial tube.

The details of managing one-lung ventilation are well reviewed in several standard texts, most recently by Campos [4]. Two points are worth repeating,
however. First, position changes and obstruction of superior vena cava (SVC) flow can lead to edema of the head and upper airway. Care should be taken when changing the endobronchial tube to a single-lumen tube at the end of the case. An easy intubation prior to bypass may not predict an easy tube change at the end of the case. There should be a low threshold for using a tube exchanger and, rarely, the endobronchial tube must be left in place until the swelling resolves. Secondly, within the confines of a closed hemithorax, application of continuous positive airway pressure frequently obstructs the surgeon’s vision. Positive end-expiratory pressure (PEEP) on the nonoperative side may be tolerated better from an exposure standpoint. During MV surgery, PEEP applied to the nonoperative lung is helpful sometimes in moving the mediastinum closer to the operative ports, thereby improving surgical exposure. When inserting ports into the left hemithorax, however, patients should be taken off the ventilator briefly to allow the heart to fall away from the left chest wall, thus avoiding injury to the left ventricle.

Most patients can be weaned from bypass while maintaining single-lung ventilation. When two-lung ventilation is resumed, it is important to remember to cut the pericardial stitches prior to inflating the lung on the operative side. These sutures run from the edges of the pericardium to the chest wall and form a sling supporting the heart. The stitches (usually silk) are taut enough to lacerate lung tissue if inflation is begun while they are in place. Persistent air leaks and increased length of stays not infrequently result.

Fluid management
Fluids are given to optimize filling pressures and cardiac output using the same hemodynamic and echocardiographic criteria as during open cases.

Monitors
Standard American Society of Anesthesiologists (ASA) monitors are applied prior to induction, and most anesthesiologists add an arterial catheter placed under local anesthesia for all but the most healthy patients. External defibrillator pads are placed as closely as possible to the manufacturer’s recommendations while still avoiding the operative field. Electrocardiography (ECG) leads must be placed similarly to avoid the operative field, particularly during left-sided port access for IMA takedown and CABG. Using V1 or V2, which are good leads for arrhythmia detection, may be helpful, but shifting of the heart within the thorax and the decreased amplitude caused by the pneumothorax may make any ECG interpretation difficult. Reciprocal changes in the ST segments of V1 or V2 may help with ischemia detection but may be unreliable for the reasons discussed previously.

Hemodynamic monitoring with PA or central venous pressure (CVP) catheters generally follows the same guidelines as for open procedures. The CVP should be monitored using a port that is above the level of the right atrium (RA). This arrangement is important especially if the SVC is snared off as is done when the RA is opened. CVP can be monitored from the sidearm of the PA introducer sheath or from the RA port of the PA catheter after ensuring
it is in the mid to high SVC. Increased CVP is cause to search for venous obstruction. If a PA catheter is placed, the authors have a lower threshold for using one with pacing capabilities in the presence of preexisting conduction abnormalities, because access to the heart is limited should emergency pacing become necessary. If a PA venting catheter is used (discussed later), it can be used to monitor the PA pressure intraoperatively; however, it should be changed to a heparin-coated PA catheter if one is needed in the postoperative period.

**ECHOCARDIOGRAPHY**

As the operative field decreases, the importance of accurate transesophageal echocardiography (TEE) increases exponentially. Cannula placement, ventricular function, ventricular filling, and quality of surgical repair must be assessed with TEE, because little of the heart is available for direct inspection. A complete TEE examination is performed on every patient prior to bypass, with special attention to the operative pathology. Multiple views are required and experience with the technique is a prerequisite to successful robotic surgery [5,6].

Cannula placement is guided primarily by ultrasound. Fluoroscopy use varies with institutional and operator preference, finding its main use in placement of percutaneous coronary sinus (CS) catheters (Fig. 3). A complete discussion of the echocardiographic views and techniques is well described in Coddens and colleagues [5] and Clements and colleagues [6]. Four-chamber and bicaval views are used to direct the CS cannula. During SVC and IVC cannulation, the right heart is imaged using a bicaval view. Drainage of the SVC is accomplished either with a cannula inserted into the femoral vein and positioned with the distal tip in the SVC or using a separate cannula inserted through the right internal jugular vein (RIJ) and positioned with the tip at the junction of the SVC and the RA. PA vent catheters are flow directed,

![Fig. 3. Transesophageal echocardiogram (A) and line drawing (B) (bicaval views) showing pulmonary venting catheter and CS catheter in place. CSC, coronary sinus catheter; LA, left atrium; PVC, pulmonary venting catheter. (From Coddens J, Deloof T, Hendricks J, et al. Transesophageal echocardiography for port-access surgery. J Cardiothor Vasc Anesth 1999;13:618; with permission.)](image)
similar to conventional PA catheters. As seen in Fig. 4, there are multiple can-
nulas in the right heart and it is not uncommon for one (usually the CS can-
nula) to be dislodged when inserting subsequent catheters (in particular the
SVC or IVC cannula). In spite of this, the CS cannula usually is inserted first,
because having other cannulas in the RA makes maneuvering the CS cannula
more difficult.

Echocardiographic evaluation for mitral repair (pre and post repair) is well
described [7] and the same criteria are used during robotic and conventional
surgery. Postrepair evaluation includes an estimation of the MV orifice size,
the amount of any residual regurgitation, and examination of the left ventricu-
lar outflow tract for systolic anterior motion of the anterior leaflet.

Evaluation of the aortic valve for regurgitation prior to going on cardiopul-
monary bypass (CPB) is important just as it is prior to conventional bypass.
Significant regurgitation allows ventricular distention when CPB is initiated.
In the presence of aortic regurgitation, antegrade cardioplegia is less effective
(if it works at all), so retrograde administration of cardioplegia becomes critical
because direct access with handheld cannulas is difficult.

CARDIOPULMONARY BYPASS
The move to robotic surgery has necessitated changes in cannulation technique
and other aspects of CPB.

Venous cannulation and drainage
For surgeries not requiring complete diversion of venous return, a venous can-
nula inserted through the femoral vein provides adequate drainage when combi-

![Fig. 4. Drawing showing several catheters used for robotic heart surgery. (Courtesy of Ethicon-Cardiovations, New Brunswick, NJ; with permission.)](image-url)
bicaval TEE image is used to ensure that the cannula crosses to the SVC to provide adequate venous of the head. Using this configuration, air can be entrained through a patent foramen ovale or ASD once the left atrium is opened to perform a MV repair or replacement, so the atrial septum should be examined carefully to exclude these conditions.

Some favor separate SVC and IVC cannulas for ASD or tricuspid valve procedures, because there is a potential for a cannula crossing the atrium to distort it, making the repair more difficult [8]. If complete diversion is believed necessary, a 17- or 19-Fr cannula can be inserted through the RIJ using a Seldinger technique to provide drainage of the head and is positioned with the tip above the junction of the RA and SVC so that some room remains for application of the snare or caval clamps. After the internal jugular (IJ) is accessed with the wire, heparin is administered to prevent clot formation in the cannula. Progressively larger dilators are advanced over the wire until the final cannula-dilator unit can be passed. The SVC and IVC cannulas are joined via a Y connector prior to connection to the main venous draining line to the reservoir (Fig. 5). The potential for complications during IJ venous drainage cannula insertion is significant. To minimize this, the bicaval view may be imaged after wire insertion to make sure that the wire is indeed progressing down the SVC to the RA and again to monitor and finalize catheter advancement and tip position [9]. At the start of CPB, the SVC clamp is removed, allowing drainage of the head. The clamp is reapplied at the termination of bypass.

Assisted venous drainage allows the use of smaller cannulas and eliminates the need for SVC cannulation in many cases. Kinetic assist is performed using a standard rotary pump head on the venous line. Vacuum assist (using −40 mm Hg) is a simpler technique if a hardshell cardiotomy reservoir is used [10]. If assisted venous drainage is used, there is increased risk of bubble
formation because of gas entrainment on the venous side. These small bubbles may pass through to the arterial side, so increased vigilance is advised [11]. This problem is mitigated somewhat by flooding the operative field with CO₂. Some groups use slightly smaller venous drainage tubing on a circuit with assisted venous drainage, believing that this improves efficiency.

If a separate IJ venous drainage cannula is used, it should be removed after heparin reversal. Removal is done most conveniently after removing the drapes, and no problems with thrombus formation during the time from heparin reversal to wound closure have occurred. Digital pressure is applied for approximately 20 minutes and the head of the bed elevated to approximately 30°. If necessary, the double-lumen–tracheal tube is changed to a single-lumen tube prior to removing the cannula so that any hematoma that may develop does not impinge on the airway. Similarly, care is taken to avoid bucking or straining, which increases venous pressure and could lead to a hematoma and possible airway compromise.

Some surgeons wish to maintain complete control of the venous draining. In such situations, the IJ can be accessed with a 14- or 16-ga catheter, which then is prepped into the surgical field. When it is time to cannulate the SVC, a surgeon can pass a wire through the catheter and perform the IJ cannulation using a Seldinger technique. A final alternative is to cannulate the SVC directly from the surgical field. Although not an ideal solution, the increased clutter is manageable. Surgical approaches are needed when anatomic conditions prevent IJ cannulation.

Arterial cannulation and aortic occlusion

Inflow access to the arterial tree can be established in one of several ways. Retrograde perfusion using one of the femoral arteries has the longest history. A 17-21–Fr cannula inserted via cutdown provides adequate flow and is easy to establish for most adult patients. Although the potential exists for increased embolic burden because of “sandblasting” the descending aorta with the arterial inflow, the technique generally is well tolerated. If simple femoral cannulation is used, aortic occlusion may be accomplished using one of several specialized clamps for transthoracic application [12].

Femoral cannulation can be combined with endoaortic clamping. Femoral cannulas are available with a second opening to allow an endoaortic occlusion cannula to be advanced up the aorta to the sinotubular junction. The endoaortic clamp has an end orifice for administration of cardioplegia. Alternatively, cannulas are available that combine endoaortic occlusion with antegrade aortic flow (Fig. 6). Antegrade flow may provide less embolic burden than retrograde flow. Whenever endoaortic clamping is used, the potential exists for the balloon to dislodge. Migration away from the aortic valve (as may occur with cardioplegia administration) has the potential for the balloon to obstruct the innominate artery, causing cerebral ischemia. Several techniques are available to monitor for this occurrence. Placing of bilateral radial artery catheters is widely practiced and simple. Significant disagreement between the
readings is cause for investigation of balloon position. Repeated Doppler evaluation of the carotids using a handheld probe and cerebral oximetry also has its supporters. At the time of aortic occlusion, surgeons inflate the balloon with dilute radiographic contrast, so fluoroscopy is possible, although cumbersome. The asanguinous solution does give an outline of the balloon’s position on TEE as it displaces blood within the aortic root. The distal wall of the balloon is placed at the sinotubular junction (Fig. 7). To avoid balloon migration resulting from systolic ejection of blood into the aortic root, Casselman [13] recommends injecting adenosine midway through inflation to induce asystole and allow easier final placement of the balloon. Migration toward the aortic valve is possible because of pressure from retrograde arterial flow. Aortic regurgitation caused by migration of the catheter across the valve leads to ventricular distension.

**Fig. 6.** Catheter combining endoaortic occlusion with antegrade aortic flow. (Courtesy of Es-tec Corporation, Danville, CA; with permission.)

**Fig. 7.** Properly placed endoaortic occlusion clamp. (Courtesy of Ethicon-Cardiovations, New Brunswick, NJ; with permission.)
Endoaortic occlusion is associated with several complications: balloon migration leading to cerebral ischemia or aortic insufficiency [5], aortic dissection, embolization, balloon rupture, and difficulty in placement [14]. Some surgeons believe that endoaortic clamping is best avoided in patients who have severe aortic disease [15], whereas others advocate its use in patients who have severely calcified (“porcelain”) aortas, even during open procedures.

In an effort to avoid the rare but devastating complication of retrograde aortic dissection that may accompany femoral perfusion, methods for cannulating the ascending aorta directly either transthoracically or through the minithoracotomy incision have been developed. The ascending arch can be cannulated directly and an endoaortic clamp passed through the aortic cannula, allowing simultaneous antegrade perfusion and endoaortic clamp placement (Fig. 8). Monitoring for balloon migration still is necessary. Finally, a standard aortic cannula inserted through the thoracotomy or a separate stab incision combined with conventional cross clamping and antegrade cardioplegia is possible using modified instruments and is familiar to all surgeons.

**Left ventricular venting**

Venting can be accomplished through the PA. A balloon flotation catheter is advanced using pressure waveform guidance into the PA. Because of the large size of the catheter relative to the balloon, positioning sometimes can be difficult. Echocardiographic guidance sometimes is helpful.

**Retrograde cardioplegia**

If a minimal incision is used (eg, MV repair) the retrograde cannula can be placed by a surgeon from the field. Usually some TEE guidance is necessary, because surgeons are unable to palpate the back of the heart to guide the catheter into the CS. Alternatively, the retrograde cardioplegia cannula can be placed percutaneously. Bicaval and four-chamber TEE views are used to guide the catheter (see Fig. 3A, B). Although some centers find TEE guidance sufficient, others use fluoroscopy. Although this may seem cumbersome at first, given the amount of equipment already in the operating room, the proponents

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**Fig. 8.** In this system, the aortic root is cannulated directly and an endoaortic occlusion catheter passed through it into the aortic root. (From Glower DD, Komtebedde J, Clements FM, et al. Direct aortic cannulation for port-access mitral or coronary artery bypass grafting. Ann Thorac Surg 1999;68(5):1879; with permission.)
of fluoroscopy believe that it is key to successful placement. After CS catheter placement, the CS pressure is transduced. In a beating heart, the CS pressure should be phasic. A flat tracing indicates displacement of the catheter.

CS catheters come in steerable and nonsteerable varieties. Lumens are available for administration of cardioplegia and measurement of the CS pressure. A third lumen leads to the balloon, which is filled with dilute radiocontrast. The balloon should be deflated between cardioplegia administrations. To avoid overfilling of the balloon, the authors start cardioplegia administration with the balloon deflated. Cardioplegia is “trickled in” through the cannula while the balloon is inflated slowly. A prompt rise in the CS perfusion pressure indicates occlusion of the CS by the balloon, and inflation is stopped. The full dose of cardioplegia then is administered. Blood accumulating behind the heart on TEE or welling up through the pericardiotomy should raise the suspicion of damage to the CS (perforation or dissection). Radiocontrast injection through the CS catheter under fluoroscopy can be helpful in diagnosing CS perforation. CS damage sometimes can be repaired through a minithoracotomy, but often a sternotomy is required.

Several large catheters of various types are required during robotic surgery. The CS catheter and pulmonary vent use 11-Fr and 9-Fr introducer sheaths, respectively. Both are inserted through the RIJ using a Seldinger technique. It is easiest to insert both wires into the IJ before passing either sheath to avoid potential needle injury to the first sheath during the second needle stick. In cases where the RIJ is used for venous drainage, the PA catheter is inserted from the left subclavian vein and only the CS catheter and SVC drainage cannula are placed in the RIJ.

**Anticoagulation**

Previously, anticoagulation with less than the full CPB dose of heparin had been advocated for off-pump surgery. Most groups currently use full-dose heparin for on- and off-pump procedures, using the same parameters to assess adequacy of anticoagulation. Because the coagulopathy associated with CPB is not present after off-pump cases, some groups do not fully antagonize the heparin anticoagulation at the termination of the surgery to help prevent early graft closure, but this practice varies widely among institutions.

**Deairing procedures**

Deairing is more difficult owing to the inability of surgeons to manipulate the heart. Oftentimes, radical changes in table position are required. This problem is mitigated somewhat by the insufflation of CO₂ into the operative hemithorax.

**SPECIFIC SURGERIES**

**Coronary artery bypass**

CABG can be performed either on or off bypass. Takedown of the IMA and coronary grafting is done through ports on the left hemithorax. In addition to lung separation, CO₂ is insufflated into the hemithorax to increase the working space. This iatrogenic pneumothorax can cause hypotension and bradycardia if
the intrapleural pressure is excessive [16]. Generally, less than 10 mm Hg is sufficient. Alpha agonists or inotropes are helpful in mitigating this hemodynamic response to CO₂ insufflation. Positioning and stabilization are performed with devices similar to those used for conventional CABG surgeries that are modified for closed chest procedures. As in open-chest procedures, the degree of hemodynamic compromise depends on intravascular volume, the underlying inotropic state of the heart, and the degree of displacement of the heart itself. These newer stabilization devices contribute to a decrease in operative times [17] but increase the cost of the procedures.

The same caveats apply whether or not the off-pump CABG is performed open or robotically. Because the anastomoses take longer with the robot, coronary shunts frequently are used; however, these do not eliminate ischemia and reperfusion issues completely. Control of heart rate and contractility to decrease movement is less critical with the new stabilizers, but the lowest possible amount of beta agonist should be used. Prophylactic lidocaine and magnesium sulfate have their supporters to prevent reperfusion arrhythmias.

Valve repair and replacement
Aortic, mitral, and tricuspid lesions all have been managed robotically, using ports on the right hemithorax. These can be accomplished totally endoscopically or by combining robotics and a minithoracotomy [10]. Resection and cordal implant and transfer techniques are performed with results similar to open techniques.

Miscellaneous conditions
Atrial myxomas [18], radiofrequency ablation for supraventricular arrhythmias [19], and ASDs are addressed robotically [8]. Epicardial lead placement for bi-ventricular pacing therapy also is performed robotically when the anatomy precludes transvenous placement.

POSTOPERATIVE MANAGEMENT
Robotic surgery, with its limited incisions, lends itself well to fast-track anesthetic techniques (the definition of which varies widely). In the authors’ experience, the major limitation to extubation in operating rooms is patients’ comorbid conditions. PH frequently increases during emergence, making early extubation difficult if the right heart is compromised. Dexmedetomidine is helpful in blunting the stress response on emergence, and it is helpful in preventing increases not only in heart rate and systemic blood pressure but also pulmonary pressures.

American anesthesiologists have been slower to embrace neuraxial opioids and local anesthetics in cardiac surgery, probably because of fear of spinal hematoma. Anterior spinal artery syndrome [20] is reported after minimally invasive surgery, complicating the diagnosis further should neurologic problems develop in a patient after robotic cardiac surgery. Murkin and Ganapathy [16] believe paravertebral block to be safe and effective.
Using a combination of intercostal blocks and continuous infiltration of the surgical site (on-Q, I-Flow Technologies, Lake Forrest, California) along with dexmedetomidine, ketorolac, and judicious use of narcotic patient-controlled analgesia, most patients can be extubated in an operating room with good respiratory mechanics and in relative comfort. Other groups report similar results; discharging patients the day after surgery [21], or within 48 to 72 hours, is common.

SUMMARY
Robotic technology allows most types of cardiac procedures to be done either completely via port access or through a minimal incision. This technique provides more rapid return to normal function, less pain and immobility, and a superior cosmetic result. The use of robotics will expand as experience with the technology grows and gains acceptance.

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