1082 Section VIII: The Surgical Patient


CHAPTER 71 ANESTHESIA: PHYSIOLOGY AND POSTANESTHESIA PROBLEMS

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IMMEDIATE CONCERNS

Major Problems

Modern anesthesia is a complex art and science that involves exposing patients to various drugs and procedures in a controlled and safe environment. Even under the best of circumstances, some complications occur. The overall risk of death from anesthesia is between 1 in 112,000 and 1 in 45,000 (1). Anesthetic-related morbidity is even more common, with respiratory depression noted between 1 in 500 and 1 in 1,000 patients receiving epidural narcotics, and 1 in 100 patients given parenteral opioids (1). Studies reviewing adverse incidents and claims due to anesthetic mishaps have shown that the most common reasons for adverse events are due to respiratory problems, followed by neural injury and damage due to regional anesthesia (2). The characteristics of anesthetic injuries have changed over the past years, with an increase in problems related to cardiovascular issues and a decrease in those related to the respiratory system (3). Patients who sustain an anesthetic complication may require treatment in the intensive care unit (ICU).

Airway problems are still extremely common causes for critical perioperative anesthetic mishaps, as maintaining an adequate airway is the first priority in all anesthetic management. An algorithm for airway management during anesthesia has been formulated by the American Society of Anesthesiologists (4) (Fig. 71.1).

In the immediate postoperative period, effects from residual anesthetic and muscle relaxants may result in airway obstruction, which should be quickly diagnosed and treated.
Chapter 71: Anesthesia: Physiology and Postanesthesia Problems

**DIFFICULT AIRWAY ALGORITHM**

1. Assess the likelihood and clinical impact of basic management problems:
   A. Difficult Ventilation
   B. Difficult Intubation
   C. Difficulty with Patient Cooperation or Consent
   D. Difficult Oropharynx

2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.

3. Consider the relative merits and feasibility of basic management choices:
   A. Awake Intubation
   B. Non-invasive Technique for Initial Approach to Intubation
   C. Preservation of Spontaneous Ventilation

4. Develop primary and alternative strategies:

   **A. AWAKE INTUBATION**
   - Airway Approached by Invasive or Non-invasive Intubation
   - Succeed
     - Intubation
     - Cancel Case
     - Consider Feasibility of Other Options
   - Fail
     - Consider Feasibility of Other Options
     - Intravenous Access

   **B. INTUBATION ATTEMPTS AFTER INDUCTION OF GENERAL ANESTHESIA**
   - Initial Intubation Attempts Successful
     - Initial Intubation
     - Emergency Intubation
     - Calling for Help
     - Return to Spontaneous Ventilation
     - Awakening the Patient
   - Initial Intubation Attempts UNSUCCESSFUL
     - FROM THIS POINT ONWARDS CONSIDER:
       1. Calling for Help
       2. Returning to Spontaneous Ventilation
       3. Awakening the Patient

   **C. FACE MASK VENTILATION ADEQUATE**
   - Ventilation Adequate, Intubation Unsuccessful
     - Alternative Approaches to Intubation
     - Succeed
       - Intubation
       - Consider Feasibility of Other Options
     - Fail
       - Multiple Attempts
       - Consider Feasibility of Other Options
     - Invasive Airway Access

   **D. FACE MASK VENTILATION NOT ADEQUATE**
   - Ventilation Not Adequate, Intubation Successful
     - Consider / Attempt LMA
     - LMA Adequate
       - Ventilation Adequate
       - Emergency Pathway
     - LMA Not Adequate or Not Feasible
       - Alternative Intubation\n         - Succeed
           - Intubation
         - Fail
           - Multiple Attempts
           - Consider Feasibility of Other Options
           - Invasive Airway Access

   *Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO₂*

   a. Other options include (but are not limited to): surgical intervention utilizing laryngoscopy or bougie, fiberoptic intubation, or cervical spine block. Pursuit of these options usually implies that mask ventilation will not be practical. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.
   b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyotomy.
   c. Alternative non-invasive approaches to difficult intubation include (but are not limited to): use of different laryngoscopes; LMA as an intubation conduit (with or without fiberoptic guidance); fiberoptic intubation, including oral or nasal routes; and defibrillation.
   d. Consider re-preparation of the patient for awake intubation or canceling surgery.
   e. Options for emergency non-invasive airway ventilation include (but are not limited to): spontaneous ventilation, use of a percutaneous cricothyroid incision, or tracheostomy as a salvage technique.

**FIGURE 71.1.** American Society of Anesthesiologists difficult airway algorithm.
Hypoventilation is also a common problem. Patients should be aggressively monitored with pulse oximetry and capnography, and oxygen should be given to postoperative patients until they are shown to have adequate ventilatory drive and pulmonary function.

**STRESS POINTS**

1. Postoperative acute respiratory failure is an uncommon but dramatic complication. Several clinical diagnoses should be explored in these situations.
2. Pulmonary edema can occur in the early postoperative period. It is more common in patients with hypertension who develop an acute elevation in blood secondary to the stress response, lack of significant analgesia, or cardiac ischemia.
3. Pulmonary edema has other causes, including “negative pressure” in a patient with partial or complete airway obstruction, aspiration of gastric contents during induction or emergence, and, in special situations, a neurogenic origin in head trauma or after evacuation of a large pleural effusion.
4. Treatment in any case of hypoxemia entails delivering a high fraction of inspired oxygen (FiO₂) to ensure a pulse oximetric saturation of at least 90%—that is, a PaO₂ of about 60 mm Hg—and in more extreme cases, continuous positive airway pressure applied by mask or tracheal intubation, with or without mechanical ventilation. Although some of these complications may resolve rapidly, patients who develop significant hypoxemia after anesthesia and surgery should be closely monitored in the ICU after the event.
5. Cardiac complications also are a frequent cause of perioperative morbidity and mortality. Arrhythmias may occur anytime. Although it was previously thought that ischemia, dysrhythmias, heart failure, and myocardial infarction occurred most commonly 3 to 5 days after surgery, they can occur much earlier—on the day of surgery or the first postoperative day (5).
6. In the patient at risk for a cardiac complication, monitoring directed toward the diagnosis of silent ischemia or infarction may be useful. When a complication occurs, aggressive diagnostic and therapeutic cardiac interventions may be life saving.
7. Hypertension in the immediate postoperative period commonly results from lack of adequate analgesia. This problem should be treated without delay, because heart failure and cardiac ischemia may result from an acute hypertensive crisis.
8. Goal-directed therapy is still controversial. The benefits of aggressive monitoring and achieving normal or supranormal hemodynamic values in patients undergoing major surgery, who have suffered trauma, or who are septic are unclear. At the same time, it makes sense to monitor patients at least to a degree that allows the rapid identification and prompt therapy of disturbed respiratory and hemodynamic function.
9. Patients with malignant hyperthermia (MH) may develop the syndrome at any time after exposure to a triggering agent (e.g., potent inhalational agents or succinylcholine). When MH is suspected, all triggering agents must be stopped. If possible, surgery should be canceled, and dantrolene administered (6). An MH hotline is available in many countries and can be contacted for assistance in caring for these patients.

**UPTAKE AND DISTRIBUTION OF INHALATIONAL AGENTS**

The goal of inhalational anesthesia is to develop a critical partial pressure of the agent within the brain. Brain levels are determined by several discrete steps (7) (Table 71.1). The anesthesia system is designed to present a suitable mixture of the anesthetic agent with air, oxygen, nitrous oxide, or a combination of these agents. It must deliver a predictable concentration of agents, eliminate carbon dioxide, closely control and maintain a predictable FiO₂, and allow monitoring and control of ventilation.

**Delivery**

The brain tissue partial pressure is responsible for the depth, and some of the side effects, of anesthesia, and correlates closely with the end-tidal partial pressure.

**Concentration Effect**

The inspired concentration is important to the rate of rise of anesthetic agent concentration in the lungs; this relationship is termed the concentration effect and has two important elements. Consider an ideal alveolus filled with 1 mL of nitrous oxide and 9 mL of oxygen. Assume that 50% of the nitrous oxide is rapidly taken up by the circulation and oxygen is not taken up at all. On completion, 0.5 mL of nitrous oxide and 9 mL of oxygen remain. Thus, the nitrous oxide concentration is decreased to 5%, whereas the oxygen concentration is increased to 95%.

Clearly, this situation is ideal and is used only for explanatory purposes. If, however, 8 mL of gas is nitrous oxide, 2 mL is oxygen, and some of the side effects, of anesthesia, and correlates closely with the end-tidal partial pressure.

### Table 71.1

<table>
<thead>
<tr>
<th>FACTORS GOVERNING UPTAKE AND DISTRIBUTION OF INHALED AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DELIVERY</strong></td>
</tr>
<tr>
<td><strong>UPTAKE FROM LUNGS</strong></td>
</tr>
<tr>
<td><strong>DISTRIBUTION TO TISSUES</strong></td>
</tr>
</tbody>
</table>
agent results in a higher alveolar level in spite of uptake from the lung.

**Second Gas Effect**

When large amounts of an anesthetic agent such as nitrous oxide are rapidly taken up, the lungs do not collapse. Instead, a subatmospheric alveolar pressure is generated as a result of the rapid removal of this gas by the pulmonary blood flow, and a passive inflow of additional gas from the anesthesia circuit replaces that which is taken up. This second gas effect may have important consequences and can be used to clinical advantage. When another anesthetic agent is administered, its partial pressure increase is also more rapid than when it is administered alone because it is drawn into the lungs with the first agent.

**Alveolar Ventilation**

Another primary factor influencing the delivery of the anesthetic agent is alveolar ventilation (Vₐ). In other words, a greater Vₐ increases the rate at which the alveolar partial pressure approaches the inspired partial pressure. This factor is limited only by lung volume; that is, a larger functional residual capacity decreases the “wash-in” rate of the agent.

**Uptake from the Lungs**

**Solubility**

Solubility describes the extent to which the anesthetic agent dissolves in blood and tissues (Tables 71.1 and 71.2); the more soluble the agent is in blood, the more is dissolved in the pulmonary blood and the longer it takes to reach a necessary partial pressure of agent in the lungs and brain. This fact represents the key difference between inhaled agents and other commonly used drugs. For example, 2 g of ampicillin given intravenously is dissolved in blood, carried to the site of infection, and produces the desired pharmacologic effect. The partial pressure of the anesthetic agent reaching the brain is the determinant of its desired effect, but is controlled by the partial pressure achieved in the alveoli. Thus, the greater the amount of anesthetic dissolved in the blood—taken away from the alveoli—the longer it takes to develop the necessary alveolar and brain partial pressures to produce anesthesia.

**Table 71.2**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Blood/gas</th>
<th>Tissue/blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>0.47</td>
<td>Brain: 1.06</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.41</td>
<td>Brain: 2.6</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.78</td>
<td>Brain: 1.45</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.36</td>
<td>Fat: 36.2</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
<td>Brain: 1.7</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>Brain: 1.3</td>
</tr>
</tbody>
</table>

An agent such as nitrous oxide, with a blood/gas partition coefficient of 0.47, is relatively insoluble, and its alveolar partial pressure increases rapidly compared with that of halothane, which has a blood/gas partition coefficient of 2.36. The speed of induction of a more soluble agent can be increased by increasing the inspired fraction to a level well in excess of that required for maintenance of anesthesia (7).

**Cardiac Output**

A high cardiac output increases uptake, thereby decreasing the alveolar partial pressure of the agent. This effect is greater with more soluble inhalational anesthetics. Thus, a longer induction time is required for a patient with a high cardiac output in thyrotoxicosis. Conversely, a patient with a low cardiac output, as with compensated congestive cardiomyopathy, has a rapid increase of alveolar partial pressure, resulting in a rapid induction and possible overdose if care is not taken.

**Alveolar-Mixed Venous Anesthetic Partial Pressure Gradient**

The last major factor of importance is the influence of the alveolar-to-central mixed venous anesthetic partial pressure gradient. This factor relates the size of the anesthetic “sink” to the increase or decrease in uptake from the lungs. At the beginning of induction when the tissue anesthetic level is zero, most of the anesthetic in the arterial blood is removed. Thus, the venous anesthetic partial pressure is much lower than that in the arterial blood, and a large uptake of anesthetic occurs as the venous blood passes through the lungs. The alveolar partial pressure of the anesthetic agent, accordingly, is reduced. However, as the tissue sinks become filled, the alveolar to venous anesthetic partial pressure difference decreases, and this effect is minimized.

**Distribution**

**Tissue Solubility and Blood Flow**

The tissue distribution (delivery) of the anesthetic is dependent on two major factors (Table 71.1). The greater the solubility of an anesthetic in a tissue, the larger the capacity of that tissue for the agent. If the tissue has a large capacity but low blood flow, equilibration takes a long time; if the tissue has a small capacity and large blood flow, equilibration is rapid. Tissues can be categorized according to the blood flow they receive. The vessel-rich group is composed of the brain, liver, heart, and kidneys. An intermediate group includes muscle and skin. The vessel-poor group incorporates skeletal elements, ligaments, and cartilage, all of which have minimal blood supply. Finally, fat has a poor blood supply but a great capacity.

Based on this division, one can easily determine when the different groups equilibrate with the inspired fraction of anesthetic agent, that is, when they cease removing appreciable amounts of the anesthetic. Nitrous oxide equilibration with the vessel-rich group occurs within 5 to 15 minutes from the beginning of induction. The muscle group equilibrates within approximately 1 hour, and the vessel-poor group and fat group equilibrate within 2 to 3 hours. When a highly fat-soluble agent such as halothane is used for a long case in an obese patient, significant amounts of agent are stored in fat and are released slowly after the agent is discontinued; emergence from
anesthesia is thereby prolonged. At the end of surgery, the factors that affect elimination of the agent from the body are the same as those that govern the uptake and distribution at the beginning. Hypoventilation lengthens the period of emergence, as do increased cardiac output, use of a highly soluble anesthetic agent, and an increased alveolar-to-venous anesthetic concentration gradient.

**Diffusion Hypoxia**

Diffusion hypoxia may be apparent at the conclusion of an anesthetic if the patient is allowed to breathe room air while large quantities of nitrous oxide diffuse into the alveoli and dilute the oxygen that is present. This problem is significant only for approximately 10 minutes and can be alleviated by having the patient breathe 100% oxygen after discontinuation of the nitrous oxide.

### Effects of Illness

#### Changes in Ventilation

Organ system dysfunction can affect the uptake and distribution of inhaled anesthetic agents. For example, to control intracranial pressure (ICP) in brain-injured patients, tracheal intubation and mechanical hyperventilation may be used. For each 1 mm Hg decrease in the PaCO$_2$, caused by an increase in $V_a$, an approximate 3% to 4% decrease in cerebral blood flow (CBF) occurs. If the patient is taken to the operating room, and if hyperventilation is continued, a change in the length of time of anesthetic induction results from three factors: increased $V_a$, decreased CBF, and solubility of the inhaled agents used for induction. The induction time for a moderately soluble agent like halothane is decreased because the increased $V_a$ produces a more rapid rise in end-tidal halothane partial pressure that offsets the decrease in CBF. For a relatively nonsoluble agent such as nitrous oxide, induction time is increased because the modest increase in end-tidal nitrous oxide partial pressure obtained by hyperventilation is more than offset by the decrease in CBF.

#### Changes in Cardiac Output

This particular example can become complicated by a decrease in cardiac output, secondary to hyperventilation-induced alkalosis, and a decrease in venous return, resulting from fluid restriction and the effects of mechanical ventilation. The decrease in cardiac output yields an increase in the agent’s end-tidal partial pressure, whereas a decrease in CBF decreases transfer of the agent from the lungs to the brain. With halothane, the increase in the end-tidal partial pressure is sufficient to balance the decrease in CBF; thus, the initial rise in brain partial pressure may be normal. Eventually, no matter what agent is used, the increased end-tidal partial pressure resulting from the decrease in cardiac output and increase in $V_a$ is enough to overcome the decrease in CBF.

### INHALATION AGENTS AND ORGAN SYSTEM FUNCTION

The differential effects of various inhalation agents on organ system function must be compared at equipotent doses. The

<table>
<thead>
<tr>
<th>Table 71.3</th>
<th>MINIMUM ALVEOLAR CONCENTRATION IN PATIENTS AGED 31–53 YRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>0.75%</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.13%</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.68%</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>110%</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6%</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2.05%</td>
</tr>
</tbody>
</table>

*Obtainable only under hyperbaric conditions.

The minimum alveolar concentration (MAC) is the amount of an inhalational agent that prevents movement in 50% of patients in response to surgical incision (Table 71.3). In neonates, the MAC is less than in children, adolescents, and young adults. After approximately 31 years of age, the MAC value begins to decrease; theoretically, the value for a patient 100 years of age is only 25% to 50% that of a young adult.

### Circulatory Effects

Blood pressure is decreased with the use of all inhalational agents. This may be due to decreased contractility as with halothane, or due to decreased systemic vascular resistance as with isoflurane or desflurane (7). There is some concern regarding the effect of inhalational anesthetics on the coronary circulation. Isoflurane and desflurane lead to coronary vasodilation and may cause ischemia, although desflurane probably has a significantly lesser effect on coronary blood flow than the other inhalational agents (8). The effect of both isoflurane and desflurane on contractility is less than halothane and enfurane (8).

#### Cardiac Rhythm

Of the several methods for evaluation of the effects of inhalational agents on cardiac rhythm, a common procedure is to determine the dose of epinephrine required to produce three or more premature ventricular contractions in 50% of normal patients breathing oxygen and anesthetized at 1.25 MAC (Table 71.4). With halothane, 2.1 μg of epinephrine/kg body weight is required to produce rhythm abnormalities if the epinephrine is given with 0.5% lidocaine, the required dose increases to 3.7 μg/kg. With isoflurane, 6.7 μg/kg of epinephrine is needed, and with enfurane, approximately 10.9 μg/kg is required. Desflurane and sevoflurane have properties similar to those of enfurane. Thus, halothane is the most and enfurane, desflurane, and sevoflurane are the least arrhythmogenic of the potent inhalation anesthetics. Inhalational agents may lead to prolongation of the QT segment; desflurane at a concentration of 6% led to a significant increase in QTc in children, whereas 2% sevoflurane did not (9).

#### Hypoxic Pulmonary Vasosconstriction

Hypoxic pulmonary vasoconstriction (HPV) may be impaired when potent agents are used. If inhaled concentrations of halothane or enfurane are increased in vitro from 1 to 2 MAC and PaCO$_2$ is held constant, the local response to hypoxia is
Table 71.4: Respiratory and Circulatory Effects of the Inhalation Agents

<table>
<thead>
<tr>
<th></th>
<th>N₂O</th>
<th>Halothane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% awake response to CO₂</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓↓</td>
</tr>
<tr>
<td>% awake response to hypoxia</td>
<td>—</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Circulatory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% awake ballistocardiogram</td>
<td>—</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>% awake cardiac output</td>
<td>θ</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>% awake stroke volume</td>
<td>θ</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>μg/kg epinephrine for three or more PVCs</td>
<td>—</td>
<td>2.1–3.7</td>
<td>10.9</td>
<td>6.7</td>
</tr>
</tbody>
</table>

—, no data; θ, no change; ↓↓, decrease of ≥33%; ↓↓, decrease of 16–33%; ↓↓↓, decrease of ≤66%; PVCs, premature ventricular contractions; N₂O, nitrous oxide; Vₑ, expired volume per min; CO₂, carbon dioxide.

unchanged. Under these same conditions using isoflurane, HPV seems to be significantly impaired, with desflurane, HPV is inhibited in a concentration-dependent fashion (10). However, the clinical significance of the difference between the anesthetic agents in this regard is not clear. When looking at a porcine model of one-lung anesthesia, neither isoflurane nor desflurane were found to have a deleterious effect on oxygenation (11).

**Respiratory Effects**

All inhalational agents are respiratory depressants. Decreases in minute ventilation at 1 MAC are 20% with nitrous oxide, 28% with halothane, 34% with isoflurane, and 71% with enflurane. The ventilatory response to an elevation in PaCO₂ at 1 MAC is decreased by 50% with nitrous oxide, 60% with halothane, 35% with isoflurane, and 45% with enflurane (Table 71.4). The response to hypoxia is depressed by 30% with halothane, 40% with isoflurane, and 45% with enflurane. There is probably some genetic predisposition in the sensitivity to the different anesthetic agents. It has been shown in animal models that subjects may respond differently to the different anesthetics, but at a dose of 0.5 MAC, all anesthetics blunt the response to hypercarbia (12).

**Hepatic Effects**

Up to 20% of patients may demonstrate mild disturbances in liver function following anesthesia with halothane; these effects present as mild abnormalities of liver function tests (7). They may also be due to other physiologic disturbances such as hemodynamic abnormalities during surgery or blood transfusion. The incidence is lower when other inhalational agents are used, and to some degree this has been one of the reasons for the marked reduction in the use of halothane as a common anesthetic agent, which is the concern regarding halothane hepatitis.

Patients who underwent surgery and anesthesia with isoflurane and halothane manifested a slight increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase. The changes seen with halothane may be greater than those observed with isoflurane. A comparison of low-dose sevoflurane, high-dose sevoflurane, and isoflurane showed comparable mild increases in liver enzymes following a prolonged (greater than 10 hours) exposure in patients undergoing orthopedic surgery (13). A statistically significant increase in bromsulphthalein retention on the second postoperative day also was seen with halothane and isoflurane. The increase was greater with halothane. Neither desflurane nor sevoflurane seems to have hepatotoxic properties (14).

**Renal Effects**

All potent inhalation agents result in a dose-dependent decrease in renal blood flow from 25% to 50%, glomerular filtration rate from 23% to 40%, and urine flow from 35% to 67%. No change in creatinine clearance or ability to concentrate urine in response to subcutaneous injection of vasopressin occurs after the use of isoflurane, halothane, or enflurane. However, when comparing high- and low-dose sevoflurane to isoflurane, no significant changes in renal functions were observed in any of the groups (13). In patients with preoperative renal impairment, anesthesia with either desflurane or isoflurane did not lead to worsened renal function (15).

**Immune Function**

Anesthesia and surgery may impair immune system function, at least in vitro (Table 71.5) (16). Serious questions as to cause and effect and the relevance to clinical outcome have been raised. There are many effects on nonspecific immune system components (17).

An element of immune dysfunction may be caused by stress, with elevations in norepinephrine, epinephrine, steroids, inflammatory mediators, and other mediators of the stress response. If this supposition is true, perhaps different anesthetic techniques (18,19), or even the use of sympathetic blockade, might ameliorate these responses perioperatively and thus decrease some of the reported abnormalities.
Phagocytosis

Phagocytosis reportedly is depressed perioperatively, perhaps because of surgical stress and the direct effects of inhalation anesthetic agents (17). Everson et al. (20) showed increased mononuclear phagocyte function in the first 24 hours postoperatively in patients who had undergone an operative procedure for nonmalignant disease. Patients who underwent surgery for carcinoma had no change in mononuclear function. Shen et al. (21) believed that some members of the mononuclear phagocytic system are affected by the stress of nutritional depletion and may take up to 3 weeks to recover. How standard measures of immunocompetence correlate with the functioning of the alveolar macrophage, abnormalities of which may put the patient at risk for pulmonary infection, is unclear.

Killer Cells

Natural Killer Cells. Natural killer (NK) cells are cytotoxic to target cells and do not require the presence of complement or specific antibody to perform their killing function. The effect of surgery—laparotomy versus laparoscopy in patients undergoing surgery for benign disease—was shown to have an effect on cell-mediated immunity, but not on NK cell function (22) (Table 71.5). Tonneseen et al. (23) showed that NK cell activity increased in the perioperative period, returning toward normal by the second postoperative day after intravenous anesthesia. The reasons for and significance of these changes are unclear. The same group showed that the use of epidural anesthesia abolished the suppressive effect of surgery and anesthesia on NK cells (24). On the other hand, Katrap et al. (25) showed that mice exposed to ketamine or halothane, but not to nitrous oxide or sodium thiopental, had significantly decreased NK cell function 5 days after exposure. This decrement in NK cell function was significantly improved by treatment of exposed mice with polynosinic-polycytidylic acid (100 µg intraperitoneally). This agent is an NK cell modulator that augments activity through interferon induction. Page et al. (26) also found that surgical stimulation depleted NK cell number and decreased NK activity; the use of morphine for pain control mitigated the measured immunologic effects of surgical stress.

Neutrophils

Data on neutrophil function during and after surgery and anesthesia are more abundant but also conflicting (Table 71.5). Nakagawara et al. (27) reported that halothane, enflurane, and isoflurane depress superoxide production—the reactive oxygen species produced by neutrophils during phagocytosis—in part because of a decrease in the mobilization of intracellular calcium. In an accompanying editorial, Welch (28) suggested that calcium-blocking properties of potent inhalational agents may cause neutrophil dysfunction. He noted that the volatile anesthetics, whose potency is correlated with lipid solubility, may prevent the release of membrane-bound intracellular calcium, as well as calcium influx, by occupying hydrophobic sites in the cellular membranes. In patients undergoing various types of surgery, Ciernich and Küberl found a decrease in chemotactic, phagocytic, and bactericidal activity after both regional and general anesthesia (29). In contrast, using intravenous anesthetic agents, van Dijk et al. (30) found no changes in neutrophil phagocytosis, chemotaxis, or chemoluminescence. Pertulla et al. (31), using “balanced” anesthesia, consisting of both intravenous and relatively small doses of inhalation anesthetic agents, found minimally depressed neutrophil function that returned to preinduction values by the third postoperative day.

Lymphocytes

Lymphocyte function is believed to be impaired in the critically ill. Surgical procedures, including corneal transplantation, dilation and curettage, transurethral resection of the prostate, arthroplasty, open heart procedures, cholecystectomy, nephrectomy, hemiorthoraphy, and others, show a decrease in lymphocyte response to mitogens, such as phytohemagglutinin and concanavalin A, which stimulate most T cells, and pokeweed mitogen, which stimulates proliferation of T cells and B cells. The suppressive effect of surgery on lymphocyte function is dependent to a degree on the anesthetic technique chosen. Volk et al. showed that postoperative epidural analgesia can reduce the effect of surgery on lymphocytes but not on monocytes (32).

Hemorrhagic Stress-induced Serum Factor

Abraham and Chang (33) reported a hemorrhagic stress-induced serum factor that depresses lymphocyte proliferation, is heat stable and dialyzable, and has a molecular weight between 13,000 and 23,000 daltons. This factor, or group of factors, seems to suppress lymphocyte proliferation in a rapid and irreversible manner, and may have some significance in the suppression of cell-mediated immunity in response to the stress

### Table 71.5

<table>
<thead>
<tr>
<th>Functions</th>
<th>Halothane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil function</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Natural killer cell activity</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ADCC K-cell activity</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lymphocyte function</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

* ↑, no change; ↓, activity/function decreased; ?, needs study; ADCC, antibody-dependent cellular cytotoxicity; N₂O, nitrous oxide; *Used with intravenous anesthesia.
of anesthesia and surgery. Recently, extension of this work showed that after an approximate 30% loss of calculated blood volume, mice exposed to bacterial antigen produce significantly less antigen-specific antibody than did exposed but nonhemorrhaged animals (34). Potent inhalation agents also may cause lymphocyte dysfunction. However, this area is poorly studied and controversial.

**INTRAVENOUS AGENTS**

**Narcotics**

**General Properties**

Although opiates have been used for thousands of years, morphine sulfate was first isolated from opium in 1803. Near the end of the 19th century, morphine and scopolamine, in doses of 1 to 3 mg/kg, were used intramuscularly or intravenously to provide “complete” anesthesia. Because of the increasing operative morbidity and mortality seen with this technique, it rapidly fell into disfavor. However, the use of high-dose narcotics for anesthesia again was popularized in the 1970s. In 1973 Pert and Snyder demonstrated the specific binding sites for opiates in the central nervous system (35). Since then, the opiate receptor complex has been delineated and three major receptor groups have been described: μ, δ, and σ. The main drugs available for pain relief are relatively selective for the μ-receptor. These drugs also affect the respiratory, cardiovascular, gastrointestinal, and neuroendocrine systems (36).

Modern anesthesia practice has a diverse group of narcotic drugs at its disposal, including morphine, meperidine, methadone, fentanyl, alfentanil, sufentanil, and more recently remifentanil. Problems with morphine include recall, histamine release, prolonged postoperative respiratory depression, hypertension, and increased blood and fluid requirements because of vasoconstriction. Synthetic drugs related to the phenylpiperidines, such as fentanyl, sufentanil, alfentanil, and remifentanil, do not induce histamine release, nor do they increase blood and fluid requirements. Their use in anesthetic practice is common—less so for alfentanil and increasingly so for remifentanil—because of a rapid time to onset; a short duration of effect, which allows titration to effect; and relative hemodynamic stability (36). Remifentanil, in particular, has a time to effect that is very rapid, and since it is metabolized by plasma esterases, it has a half-life of 8 to 20 minutes independent of liver or renal function. This makes the drug ideal for situations in which rapid discontinuation of a drug is required to enable assessment of consciousness, such as in patients following neurosurgical procedures or head injury. Generally speaking, healthier patients require larger doses of drugs than sicker, older patients. If 30 μg/kg of fentanyl is given to patients ages 18 to 31 years, 57% lose consciousness; if, however, the same dose is given to patients over 60 years, 100% lose consciousness. Narcotic drugs, though, cannot be depended upon to provide complete anesthesia, which requires amnesia, hypnosis, and muscle relaxation to enable safe surgery without awareness or patient discomfort. To this end, the addition of intravenous hypnotics and muscle relaxants, or inhaled agents, is required.

**Pharmacokinetics/Pharmacodynamics**

Selected pharmacokinetic data for four commonly used opioids are summarized in Table 71.6. Similarities between the redistribution and elimination half-lives and the clearance and steady-state volume of distribution are noteworthy. The major difference is in lipid solubility, which correlates with potency. Interestingly, the peak respiratory depressant effect of morphine is 15 to 30 minutes after injection, but with fentanyl, it occurs at 5 to 10 minutes. The depressant effect from morphine usually lasts longer, although that of fentanyl can be seen even after the analgesic effect of that drug has dissipated. Remifentanil is unique in that it has a rapid onset and offset of effect, even when delivered for a prolonged infusion. Because of these traits, it is very useful as an adjuvant in different types of anesthesia (37,38).

**Hemodynamic Effects**

Hypotension can be a significant problem with morphine in a dose of 1 to 4 mg/kg. During induction of anesthesia with morphine, systolic blood pressure may decrease to less than 70 mm Hg in 10% of patients. Possible causes include vagal-induced bradycardia, vasoconstriction, and splanchic blood sequestration. The rate of infusion seems to be important, because hypotension seldom occurs at rates of 3 mg/minute or

| TABLE 71.6 | SELECTED PHARMACOKINETIC DATA FOR FOUR OPIOIDS |
|---|---|---|---|
| | Morphine | Fentanyl | Sufentanil | Remifentanil |
| Lipid solubility* | 1 | 0.80 | 1778 | 10 |
| t1/2 α (min) | 0.9–2.4 | 1–3 | 0.5–2 | 1 |
| t1/2 β (min) | 10–20 | 5–20 | 5–15 | 6 |
| CL (L/0.6m2) | 2–4 | 2–4 | 2–3 | 0.06 |
| Clearance (mL/kg/min) | 10–20 | 10–20 | 10–12 | 40–70 |
| Vdss (L/Kg) | 3.5 | 3–5 | 2.5 | 0.2–4.3 |

*Proportional to ease with which agent crosses blood–brain barrier and, hence, potency.

**Hemodynamic Effects**

Hypotension can be a significant problem with morphine in a dose of 1 to 4 mg/kg. During induction of anesthesia with morphine, systolic blood pressure may decrease to less than 70 mm Hg in 10% of patients. Possible causes include vagal-induced bradycardia, vasoconstriction, and splanchic blood sequestration. The rate of infusion seems to be important, because hypotension seldom occurs at rates of 3 mg/minute or
less, but is frequently seen at rates of 10 mg/min. Morphine as an induction agent in anesthesia is not common today because of the availability of other narcotic drugs with more stable hemodynamic profiles.

Some of the effects of morphine seem to result from histamine release. After a 1 mg/kg intravenous dose of morphine, histamine increases four to nine times above the control values. Treatment with H1 (diphenhydramine) and H2 (cimetidine) blockers attenuates the cardiovascular response to histamine. Fentanyl, 30 to 100 μg/kg, rarely causes hypotension, even in patients with poor left ventricular function, perhaps because it does not cause histamine release. No significant changes in contractility, heart rate, cardiac output, or systemic or pulmonary artery occlusion pressure occur. When blood pressure decreases with fentanyl, it is often secondary to a decrease in heart rate and is attenuated with a vagolytic agent. Remifentanil has a beneficial hemodynamic profile, similar to fentanyl. When induction of anesthesia using fentanyl was compared with remifentanil, the incidence of bradycardia, hypotension, and ischemia was the same between the two drugs (39).

Respiratory Effects

Significant dose-dependent respiratory depression can occur with opioids. Both the end-tidal partial pressure of carbon dioxide and the apneic threshold—defined as the PaCO2 below which spontaneous ventilation is not initiated unless hypoxia is present—are increased. Hypoxic ventilatory drive is decreased and the increase in ventilatory drive seen with increased airways resistance is blunted. The pontine and medullary centers for respiratory rhythmicity also are impaired, resulting in increased respiratory pauses and delayed exhalation, producing irregular and periodic breathing. A possible concern with the use of morphine is the possible triggering or worsening of bronchospasm due to histamine release. This does not occur with fentanyl, sufentanil, or remifentanil. Another issue to consider is the possible effect of fentanyl and its derivatives to cause chest wall rigidity. This is probably a condition of hyperoncity of the chest, which can occur during induction of anesthesia using fentanyl or similar drugs. While the mechanism is not well understood, it apparently does not result from a direct effect of the opioid on muscle fibers or on the neural components of muscle. Rather, it may result from stimulation of y-aminobutyric acid (GABA) receptors located on interneurons. When it occurs, it can lead to difficulties in ventilating the patient; treatment is commonly with a muscle relaxant.

Neurologic Effects

Alterations in neurophysiology are common with opioids. Morphine, at a dose of 1 to 3 mg/kg with 70% nitrous oxide, has no effect on CBF, cerebral metabolic rate for oxygen (CMRO2), or cerebral metabolic rate for glucose (CMRGl). In a rat model of subarachnoid hemorrhage, morphine 1 mg/Kg led to a decrease in cerebral blood flow, but autoregulation was better maintained than in the control group (40). Fentanyl, in a model of traumatic brain injury, did not lead to a reduction in CBF despite a decrease in arterial blood pressure (41).

Gastrointestinal Effects

The effects of analgesic doses of opioids on the gastrointestinal system are well known and include emesis secondary to stimulation of the chemoreceptor trigger zone in the area postrema of the medulla; increased gastrointestinal secretions; decreased motility that also may affect emetic action; and increased smooth muscle tone of the gastrointestinal tract and the sphincter of Oddi. Reports suggesting that the agonist-antagonist narcotics, nalbuphine or butorphanol, cause a lesser increase in gastrointestinal tract tone are controversial.

Stress

The effect to which a given drug ameliorates the surgical stress response may be important to immune system function and nutritional balance; however, the associated clinical relevance, as with the potent inhalational agents, remains controversial. High-dose, as compared to low-dose, fentanyl for abdominal surgery can suppress the stress response with regard to catecholamines and corticosteroids (42). When comparing high-dose alfentanil to balanced anesthesia with fentanyl and droperidol, Möller et al. found that the increase in cortisol and hyperglycemia associated with surgery were decreased for the duration of surgery and the 1 to 3 hours following surgery (43). The effects of morphine and fentanyl on metabolic responses are shown in Table 71.7; these data are drawn from several series, including those with patients undergoing cardiac surgery.

Immune Function

As is the case with inhalational agents, controversy exists concerning the narcotic effects on cellular immune system function. In a rat model inoculated with lung tumor cells, high-dose fentanyl suppressed NK function and led to an increase in the number of metastases (44). This type of immune suppression is not due to the impairment of ventilation. Fentanyl led to suppressed NK cells in rats that were ventilated to the same degree as rats breathing spontaneously (45). McDonough et al. (46) and Brown et al. (47) suggest that a transient impairment of the in vitro cellular immunity is demonstrable in opiate addicts. After treatment of lymphocytes with naloxone, or after cessation of intravenous opiate administration, the response to mitogen stimulation returns toward normal. Whether this apparent impairment of cellular immune function is caused by contaminants in the intravenous opioid obtained by drug abusers or whether it is a more specific effect of opioids in general is unclear. Balanced anesthesia, including fentanyl, has no depressive effects on the mitogen responses of lymphocytes. But large-dose fentanyl impairs NK cell activity following abdominal surgery (48). When atropine and

<p>| TABLE 71.7 |</p>
<table>
<thead>
<tr>
<th>OPIOID EFFECT ON STRESS RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (1–4 mg/kg)</td>
</tr>
<tr>
<td>Catecholamines ↑</td>
</tr>
<tr>
<td>Cortisol ↑</td>
</tr>
<tr>
<td>GH ↑</td>
</tr>
<tr>
<td>ADH ↑</td>
</tr>
</tbody>
</table>

Note: ↑, activity/function increased; ↓, activity/function decreased; GH, human growth hormone; ADH, antidiuretic hormone.
neomycin are used as premedication, a small number of patients show a decrease in lymphocyte response to mitogens.

**Barbiturates**

Thiobarbiturates (e.g., sodium thiopental and methohexital) are frequently used. In contradistinction to other barbiturates, the thiopental ring structure has a sulfur atom in place of the oxygen atom at carbon-2. Methohexital, while retaining its carbon-2 oxygen atom, has a methyl group that replaces the hydrogen at the nitrogen-1 position of the ring. These chemical changes confer ultrashort onset and offset action compared with other barbiturates. Sodium thiopental usually comes in a 1.5% solution with a pH greater than 10, causing the drug to be irritating if accidentally extravasated. Methohexital is two to three times more potent than thiopental.

**Pharmacokinetics/Pharmacodynamics**

The pharmacokinetics of thiopental, as well as other commonly used nonnarcotic, intravenous anesthetic agents, are summarized in Table 71.8. Thiopental is a highly lipophilic agent with a pKa of 7.6 and is 60% ionized at pH 7.4. With a standard clinical dose of 3 to 5 mg/kg, loss of consciousness occurs within one arm–brain circulation time, that is, 10 to 15 seconds. The short duration of action of this drug—5 to 10 minutes—is secondary to its redistribution from the brain to muscle, skin, and, to a lesser extent, fat. The elimination half-life of the drug is long, making thiopental into a long-acting sedative–hypnotic agent, similar to the thiobarbiturates and other benzodiazepines that may be used for induction and maintenance of anesthesia. The agent is not antianalgesic—as are the benzodiazepines—but is reported to have minimal amnestic effects (51). An alkylphenol, propofol is virtually insoluble in aqueous media and thus is provided in a 1% weight/volume (intralipid) emulsion. The emulsion is composed of 1% di-isopropylphenol (propofol), 10% soybean oil, 2.25% glycerol, and 0.25% lecithin.

### Table 71.8

<table>
<thead>
<tr>
<th>Thiopental</th>
<th>Propofol</th>
<th>Diazepam</th>
<th>Lorazepam</th>
<th>Midazolam</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2}^a ) (min)( ^a )</td>
<td>2-4</td>
<td>2-4</td>
<td>10-15</td>
<td>3-10</td>
<td>7-15</td>
</tr>
<tr>
<td>( t_{1/2}^b ) (h)( ^b )</td>
<td>10</td>
<td>1-3</td>
<td>20-40</td>
<td>10-20</td>
<td>2-4</td>
</tr>
<tr>
<td>Clearance (mL/kg/min)( ^c )</td>
<td>2.6-2.8</td>
<td>20-40</td>
<td>0.2-0.5</td>
<td>0.7-1</td>
<td>4-8</td>
</tr>
<tr>
<td>( V_d^{ss} )(L/kg)( ^d )</td>
<td>1.4-2.8</td>
<td>2.8-7.1</td>
<td>0.85-1.4</td>
<td>0.7-1.3</td>
<td>1-1.8</td>
</tr>
</tbody>
</table>

*\( t_{1/2}^a \), slow redistribution half-life.  
\( t_{1/2}^b \), elimination half-life.  
\( V_d^{ss} \), steady-state volume of distribution.  
Assumes a 70-kg person.  

**Neurologic Effects**

The mechanisms of action of the barbiturates are multiple and dose related. At clinically relevant doses, two effects are seen: facilitation of action of inhibitory—GABA—neural transmitters and inhibition of excitatory neural transmitter action. A barbiturate-induced increase in GABA neuronal hyperpolarization is believed to be related to an increase in the time that chloride (Cl\( ^- \) ions) channels remain open. Specifically, barbiturates seem to decrease the frequency of channel opening while increasing the duration of opening. Within the central nervous system (CNS), sodium thiopental results in a decrease in CMRO, CBF, and ICP. It is thus used sometimes as a drug to reduce intracranial pressure and improve cerebral hemodynamics while providing a degree of brain protection.

**Cardiorespiratory Effects**

Cardiovascular effects of thiopental are of some significance. Increases in coronary blood flow, heart rate, and myocardial oxygen consumption occur, together with a decrease in the inotropic state of the myocardium. The result is a 10% to 25% decrease in cardiac output, blood pressure, and stroke volume at clinically relevant doses. Venous tone may also decrease, resulting in decreased preload. At doses of 3 to 5 mg/kg, the responses to carbon dioxide elevation and hypoxia are impaired. After injection of thiopental, patients usually take two to three deep breaths—and often yawn—and then become apneic.

In an *in vitro* model of peripheral blood monocytes, barbiturates were found to decrease the ability to proliferate and produce cytokines (49). In patients who are given continuous barbiturate infusion, there may be an effect on immune function and they may be more prone to develop infections (50).

**Propofol**

Propofol is an intriguing intravenous anesthetic agent. It is a sedative-hypnotic agent, similar to the thiobarbiturates and benzodiazepines that may be used for induction and maintenance of anesthesia. The agent is not antialgesic—as are the thiobarbiturates—but is reported to have minimal amnestic effects (51). An alkylphenol, propofol is virtually insoluble in aqueous media and thus is provided in a 1% weight/volume (intralipid) emulsion. The emulsion is composed of 1% di-isopropylphenol (propofol), 10% soybean oil, 2.25% glycerol,
and 1.2% purified egg phosphatidyl. Histamine release is not a problem with this formulation. Propofol is 95% to 99% plasma protein bound; whereas the pH of the emulsion is 7 to 8.5, the drug itself is slightly acidic. A newer formulation of 2% propofol is used for prolonged sedation in critically ill patients.

**Pharmacokinetics/Pharmacodynamics**

The basic pharmacokinetic data of propofol are shown in Table 71.8. Like the thiobarbiturates, propofol is extensively distributed into vessel-rich tissues, and ultimately redistributed to lean muscle and fat. The pharmacokinetic data suggest that accumulation occurs with repeated bolus injections or continuous infusion. Propofol is metabolized to water-soluble, highly polar glucuronide and sulfate conjugates; the metabolites are not thought to be active and are excreted in the urine. Almost none of the parent drug is found in urine (less than 0.3%) or stool (less than 2%); extrathoracic metabolism or extrarenal elimination might occur.

In comparing propofol with the other agents in Table 71.8, one observes the high clearance and the short elimination half-life. This profile, one of the reasons that the agent is so appealing, may be increased by age (decreased clearance and dose requirement), obesity (increased clearance and volume of distribution), and type of procedure; with major intra-abdominal surgery, volume of distribution increases and the elimination half-life is prolonged, as well as with the use of narcotics and potent inhaled anesthetic agents (decreased hepatic blood flow with a prolonged elimination half-life).

With intravenous injection in a non–premedicated patient, a propofol dose of 2 to 2.5 mg/kg results in loss of consciousness in less than 60 seconds; rapid intravenous injection of 1 to 1.5 mg/kg in the elderly or a patient who has been given narcotic or benzodiazepine premedication is often sufficient for induction.

Anesthetic depth is assessed by changes in the respiratory rate in spontaneously breathing patients or by increases in heart rate, blood pressure, and autonomic activity in those receiving a balanced anesthetic technique. A need to increase the anesthetic depth may be met by increasing the infusion rate or augmenting with 20 to 40 mg boluses intravenously. A relatively linear relationship exists between maintenance infusion rate of propofol and the resultant blood levels of the agent. Nonetheless, as with other intravenous agents, interpatient variability is such that a given dosage rate can result in levels that vary by three- to sixfold.

A fairly predictable relationship also exists between the adequacy of anesthetic depth and the blood levels of propofol. For example, to achieve an adequate level of anesthesia, blood levels of the drug must be higher (3-6 μg/mL) for major as opposed to superficial (2-4 μg/mL) surgical procedures. The former blood level is frequently obtained, notwithstanding interpatient variability, with infusion rates between 100 and 150 μg/kg/minute.

Finally, the probability of awakening is reasonably predicted by observing blood levels. More than 50% of persons are awake with a level of 1 μg/mL, over 95% are awake and oriented with a level of 0.5 μg/mL, and most will have recovered baseline psychomotor function when the propofol level is 0.2 μg/mL. For propofol, the effective dose in 50% of patients studied (ED50), which is analogous to MAC for potent inhalation agents, is 53.5 μg/kg/minute (95% confidence limits; 39.9-63 μg/kg/minute) (53).

**Neurologic Effects**

The mechanisms of action of propofol are unclear. Propofol can cause desynchronization of the awake electroencephalographic (EEG) pattern when a loading dose of 2.5 mg/kg followed by an infusion of 100 to 200 μg/kg/minute are used; this effect is seen within 60 seconds of intravenous administration. Propofol in a dosage of more than 130 μg/kg/minute results in EEG burst suppression lasting 15 seconds or longer; the EEG returns to the awake state within about 11 minutes after the drug infusion is discontinued.

Some evoked potentials are altered by the drug. The latency of the primary complex may be increased and its amplitude decreased in median nerve and posterior tibial nerve somatosensory-evoked potentials. Propofol leads to a dose-related decrease in CBF and CMRO2, and leads to progressive EEG suppression with increasing dose of propofol (54). For this reason, propofol is used in patients with intracranial disease and is frequently employed in the ICU for long-term sedation.

**Cardiovascular Effects**

Like thiopental, propofol produces a dosage-dependent decrease in systolic, diastolic, and mean arterial blood pressure; this effect is enhanced by narcotic premedication. Profound cardiovascular depression may be seen when propofol is used in elderly or hypovolemic patients and those with impaired ventricular function. Despite the decrease in blood pressure, heart rate remains relatively stable; this response is thought to be caused by a central sympatholytic or vagotonic effect rather than by impaired baroreceptor sensitivity.

The agent is a negative inotrope and, when used in patients with ischemic heart disease, has been associated with an increase in myocardial lactate production. Yet, a recent study described the hemodynamic effects of propofol infusion on critically ill adults and reported no significant reductions in cardiac output, oxygen delivery, oxygen consumption, or arterial blood lactate concentrations (55).

**Respiratory Effects**

Apnea is seen on induction with propofol in 30% to 60% of unpremedicated patients, and in virtually 100% of those premedicated with narcotics. Whereas the incidence of apnea is about the same as that seen with the thiobarbiturates, the duration tends to be somewhat longer. When breathing resumes, the tidal volume is decreased and the slope of the carbon dioxide response curve is decreased by 40% to 60%. The response to hypocapnia is also significantly blunted by propofol (56). Adjuvant use of narcotics further depresses respiratory drive.

**Other Effects**

Propofol does not seem to have any clinically relevant adverse effect on the production of cortisol, although intravenous anesthesia with propofol and remifentanil does lead to a decreased stress response including cortisol production compared to balanced anesthesia with inhalational agents (57). It does not affect the coagulation profile as measured by the thrombin time, prothrombin time, partial thromboplastin time, fibrinogen level, titers of fibrin degradation products, and platelet number and function.

Up to 58% of patients with an intravenous catheter in the dorsum of the hand reported pain on injection of propofol;
This number decreased to about 10% if the drug was injected through a vein in the antecubital fossa. Administration of lidocaine through the cannula just before injection of propofol may decrease the pain. Younger patients require a higher dose of lidocaine to suppress the injection pain of propofol (58).

Midazolam. Midazolam also can be administered by intramuscular, intravenous, or oral routes. The drug undergoes extensive metabolism to active and inactive metabolites. We have extensive experience using this drug as an induction agent in thermally injured patients. Loss of consciousness is rapid after an intravenous loading dose of 300 μg/kg followed by either ketamine or, more often, a narcotic such as fentanyl in a dose of 2 to 5 μg/kg/hour after a loading dose of 5 to 10 μg/kg.

Neurologic Effects

Like barbiturates, the benzodiazepines have multiple, dose-dependent effects on the CNS and potentiate inhibitory GABA neurotransmission. They increase the frequency but not the duration of chloride channel opening. In addition, at least two specific benzodiazepine receptors have been identified: type 1, which is a postsynaptic receptor found in the cerebellum, and type 2, which is a presynaptic receptor found in the cerebellum and descending GABA pathways from the caudate nucleus to the substantia nigra. The clinical significance of these receptors is under investigation.

Loss of consciousness occurs 2 to 3 minutes after an intravenous induction dose of diazepam, lorazepam, or midazolam. Antegrade amnesia is seen with all of the benzodiazepines, but more so with lorazepam.

Cardiorespiratory Effects

When the benzodiazepines are used alone, cardiovascular effects are reported to be insignificant; however, cardiovascular depression has been observed when they are used in conjunction with other anesthetic agents. Respiratory effects are also minimal. Some decrease in the ventilatory response to carbon dioxide may occur after the use of these agents, but data are conflicting in this regard. No difference in recovery time or duration of action of either depolarizing or nondepolarizing muscle relaxants occurs when the benzodiazepines are used.

Ketamine

Pharmacokinetics/Pharmacodynamics

Ketamine is the only arylcyclclohexylamine used in anesthesia. It is structurally related to phencyclidine, known in street vernacular as “angel dust.” The pKa of ketamine is 7.5, and it is about ten times more water soluble than thiopental. Its pharmacokinetics are summarized in Table 71.8. Ketamine is approximately ten times more lipid soluble than thiopental; however, its onset of action is somewhat slower. After an intravenous dose of 2 mg/kg, consciousness is lost in little more than one arm-brain circulation time and returns 10 to 15 minutes later. Ketamine is 45% to 50% protein bound.

Recovery of consciousness probably results from rapid drug redistribution into muscle and other tissues. However, 95% of the injected drug ultimately is metabolized by the liver, and less than 5% is recovered unchanged in the urine. At least eight different metabolites of the parent compound have been identified, the most important of which is norketamine, which has approximately one-third the potency of ketamine.

Neurologic Effects

The exact mechanism of action of ketamine is not well understood. Apparently it does not facilitate GABA inhibitory
neurotransmitters, as do the benzodiazepines and barbiturates. Like barbiturates, however, ketamine blocks ion channels in the open position. Specific arylcyclohexylamine receptors in the brain may be related to the α subclass of opioid receptors. Ketamine increases CBF and so must be used with caution in individuals with elevated ICP.

**Cardiovascular Effects**

Ketamine causes an increase in systemic blood pressure and cerebrovasodilation, resulting in increased ICP. It also causes central stimulation of the sympathetic arm of the autonomic nervous system. The cardiovascular effects are primarily related to CNS stimulation. Ketamine inhibits the uptake of catecholamines by the postganglionic adrenergic neurons and the uptake of extraneuronal norepinephrine.

Because of the dose-related increase in arterial blood pressure, heart rate, and coronary vasodilation, and overall unchanged peripheral vascular resistance associated with ketamine administration, the drug often is thought not to be a myocardial depressant. Nonetheless, with sympathetic blockade or in patients in prolonged shock with a significantly stressed autonomic nervous system, cardiac depression can be seen with ketamine. Pulmonary vascular resistance and right ventricular stroke work also are frequently increased.

**Respiratory Effects**

Although ketamine is not commonly thought of as a respiratory depressant when used in anesthetic doses of 1 to 2 mg/kg, a moderate decrease in the PaO₂ may occur. The ventilatory response to carbon dioxide is maintained, and ketamine potentiates the bronchodilatory effects of catecholamines. It also increases oral secretions so that an anticholinergic agent may be necessary.

**Other Effects**

Ketamine enhances the effect of depolarizing and nondepolarizing neuromuscular blocking drugs. The drug has been used safely in patients with MH. Postanesthetic emergence reactions—nightmares and hallucinations—may occur in 5% to 30% of patients. A benzodiazepine and 2 mg/kg (or less) maximal doses of ketamine seem to decrease the incidence of this problem.

**Immune System Function**

As with the potent inhalation and opioid anesthetics, controversy exists regarding the effects of barbiturates, benzodiazepines, and ketamine on immune function. Sodium thiopental, at clinically relevant doses in vitro, decreases the mitogenic response of lymphocytes to phytohemagglutinin and inhibits cytotoxicity. Ketamine attenuates the proinflammatory response following abdominal surgery (65). In experimental animals, both thiopental in tumor-bearing mice and pentobarbital in dogs decrease lymphocyte function. The in vivo response of lymphocytes in patients exposed to thiopental, nitrous oxide, oxygen, droperidol, fentanyl, and muscle relaxants shows no adverse effect. However, balanced anesthesia, including inhaled and intravenous agents, leads to greater reduction of lymphocyte function than a purely intravenous technique (18).

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**Etomidate**

An induction agent that maintains hemodynamic stability, etomidate is commonly used in the induction of anesthesia or for intubation of critically ill patients suspected of cardiac dysfunction or hemodynamic instability from other causes. Etomidate causes a dose-dependent reduction in contractility in both normal and failing hearts, but this decrease is minimal and most likely does not have any clinical significance (66).

The major problem with etomidate is the adrenal suppression it induces when used in a prolonged infusion. It has also been demonstrated following a single dose for induction of anesthesia (67). Concern about the effect of adrenal suppression in patients as the ICU leads some clinicians to avoid the use of etomidate in patients at risk for adrenal insufficiency (68,69). On the other hand, it has been suggested that the benefits of hemodynamic stability may overweigh any concerns about adrenal dysfunction and its consequences (70).

**Dexmedetomidine**

Dexmedetomidine is a novel, new, highly selective, short-acting α₂-agonist. It is used in the ICU for providing sedation and some degree of analgesia. It is used primarily for sedation in the ICU. It provides a dose-dependent degree of sedation, analgesia, axonolysis, and sympatholysis. When used in postoperative patients in the ICU, dexmedetomidine can provide better sedation with fewer narcotics than propofol (71). Siobal et al. used dexmedetomidine to facilitate a weaning trial and extubation in patients who were ventilated and did not tolerate a weaning trial prior to the drug (72). The place of this agent in intensive care medicine practice is still being evaluated.

**PREFERRED ANESTHETIC TECHNIQUES FOR SPECIFIC CLINICAL SCENARIOS**

Should any agent or technique be used or, conversely, avoided in critically ill patients? Almost no data conclusively support one technique over another. Yet, although we prefer not to muddy the waters, we believe it makes sense in a hemodynamically unstable patient to shy away from the potent inhalation agents and to use in their place an intravenous technique of either ketamine or one of the phenylpiperidine narcotics. Furthermore, in patients with traumatic brain injury, we use intravenous benzodiazepines, barbiturates, and narcotics with isoflurane; ketamine and the other potent inhaled anesthetic agents are avoided.

The options for total intravenous anesthesia available today with the short-acting narcotics and propofol allow for an easily titratable anesthesia without the disadvantages of inhalational anesthesia. It is now possible to administer anesthesia without any significant hemodynamic embarrassment, which is easily controlled and rapidly reversed. An issue to be considered is that of respiratory function of the critically ill or injured patient undergoing surgery. If the patient has a component of respiratory failure, the need of delivering high oxygen concentration may require avoiding inhaled agents. Closed gas space such as pneumothorax, pneumoperitoneum, or bowel obstruction demands that nitrous oxide be withheld.

The less than adequate data suggest avoidance of potent inhalation anesthetic agents in patients with questionable
peroperative immune function. In such cases, intravenous narcotics or ketamine may be useful. However, no outcome studies show that parenteral sedatives increase morbidity or mortality more than agents with no demonstrated adverse effects on in vivo immune function. Emerging data indicate the significance of regional anesthesia on immune function and behavior of tumors. For example, when patients undergoing breast surgery for cancer were anesthetized with general anesthesia or a regional technique, the disease-free survival was significantly greater in the patients with regional technique (73).

**The Patient with Acute Respiratory Distress Syndrome**

Patients with acute respiratory distress syndrome (ARDS) present with difficulties in mechanical ventilation, particularly with regard to hypoxemia. Current approach to mechanical ventilation dictates the use of low tidal volumes of 6 to 8 ml/kg ideal body weight (74,75). This can be coupled with a higher respiratory rate to maintain adequate ventilation and tolerance of a higher than normal PaCO₂, so called “permissive hypercapnia.” The approach of lung protective strategy has been shown to improve outcome in patients with ARDS and should probably be maintained in patients undergoing surgery. The effect of sepsis on the development of acute lung injury can be affected by anesthesia, and in an animal model it has been shown that use of barbiturates (76) and ketamine (77) can attenuate the development of acute lung injury due to sepsis. Some intraoperative parameters such as hemodynamic instability, the need for vasoressors, fluid and blood requirements, and hypoxemia are related to the development of acute lung injury (78).

Providing adequate mechanical ventilation can now be done with most modern anesthetic ventilators. Older ventilators, on the other hand, could not provide the flows and pressures required by patients with severe lung injury. These patients may need to be ventilated with an ICU ventilator, and anesthetists maintained with intravenous anesthetic agents (79). Fluid management of patients with ARDS should be directed at the maintenance of adequate hemodynamics without fluid overload (80,81).

**The Patient with a Head Injury**

Patients with head injury present with multiple neurologic, respiratory, and hemodynamic problems. The anesthesiologist should be vigilant about maintaining optimal cerebral perfusion pressure—generally considered to be “optimized” at 60 to 65 mm Hg—by providing anesthesia directed at reducing intracerebral pressure, barbiturates, maintenance of normo- or mild hypothermia, increasing serum osmolarity, and judicious use of diuretics, while vasoressors and inotropes can improve cardiac output and blood pressure; at times, hyperventilation will be necessary. On occasion, the therapeutic dilemma of giving priority to the ICP versus a lung protective strategy may arise. Another clinical dilemma is the fluid status of the patient: Is optimizing preload going to increase cerebral edema? Our approach is to direct therapy to optimize cerebral blood flow by improving central perfusion pressure. To prevent hypovolemia, these patients should be monitored aggressively. There are many options for measuring cardiac output: invasively, as with a pulmonary artery catheter, or semi-invasively with pulse contour cardiac output, such as is done with the PiCCO, FloTrak, or LiDCO systems. Indeed, these systems can provide additional information that can be beneficial in the hemodynamic management of the patient as indicators of fluid responsiveness such as pulse pressure variation, systolic pressure variation, or stroke volume variation and, in the case of the PiCCO system, measurement of extravascular lung water.

**The Patient with Shock**

Patients in shock require therapy directed at the cause of the shock state, as well as avoidance of therapies that may be specifically problematic in this patient population. All anesthesiologists are aware of the deleterious effects of mechanical ventilation on patients with hypovolemia and shock. In these patients, it is important to keep intrathoracic pressures as low as possible while fluid resuscitation is being administered. Drugs that depress heart function and lead to vasodilatation should be avoided and, in extreme cases, even drugs that are considered to maintain hemodynamic stability, such as ketamine, can lead to hemodynamic collapse.

In patients with a cardiac source of shock, intrathoracic pressure will usually not have a detrimental, and may even have a beneficial, effect on cardiac output. Still, most anesthetics are cardiac depressants and, thus, should be used with extreme caution in patients in shock. All patients in shock should be monitored invasively to assess the degree of both hypovolemia and responsiveness to therapy (82,83).

**The Patient Requiring Tight Glucose Control**

The significance of tight glucose control in critically ill patients has become clear in recent years. The adherence to glucose levels between 80 and 110 mg/dl has been shown to improve outcome in surgical critically ill patients. This effect of controlling glucose has also been shown to be significant during surgery. In patients undergoing cardiac surgery, poor intraoperative glucose control was associated with worse outcome (84). While less clear in medical ICU patients, it appears that those in the unit for longer than 3 to 5 days are benefited by tight control of glucose.

**POSTANESTHESIA PROBLEMS**

Difficulties in the early postoperative period are common. Postanesthetic complications have been found to occur in 5% to 30% of patients; the wide range results from lack of uniform criteria defining complications, different practices in individual institutions, differences in the strictness of observational practice, and possible significant differences in populations studied.

**Hypoxemia**

Postoperative hypoxemia may result from diverse etiologies. Hypoventilation caused by residual anesthetic or muscle...
relaxant and atelectasis, which may have resulted from a one-
lung intubation during surgery, are diagnoses to be considered
and treated aggressively in the immediate postoperative period.
Upper airway obstruction due to a decreased level of conscious-
ness is a common reason for hypoxemia and hypercarbia. Con-
sideration should be given to pulmonary edema resulting from
heart failure in susceptible patients, noncardiogenic pulmonary
edema from aspiration, acute respiratory distress syndrome,
infarction, trauma, a transfusion reaction, or a head injury re-
sulting in neurogenic pulmonary edema.

Postoperative hypoxemia can lead to acute complications
such as cardiac ischemia, and may also have an effect on the
patient's immunity. Supplemental oxygen decreased the rate of
wound infections in patients following colonic resection (83) as
well as the incidence of nausea and vomiting following surgery
(86).

**Negative-pressure Pulmonary Edema**

Pulmonary edema may develop after a strenuous inspiratory
effort against an obstructed airway. This type of pulmonary
edema may appear immediately or up to 10 hours after the
episodes of airway obstruction. It most commonly is associated
with laryngospasm during anesthetic induction or emergence
from anesthesia; therefore, it frequently is diagnosed in the
postanesthesia care unit or ICU.

The pathophysiologic mechanism of negative-pressure pul-
monary edema is not completely understood, although a com-
mon explanation is that the massive negative intrathoracic pres-
sure generated during airway obstruction shifts the balance in
the Starling forces toward a large fluid transudation from the
intrasaccular to the interstitial space. The increase in extravas-
cular lung water causes a reduction in lung compliance and an
increase in shunt.

The diagnosis of negative-pressure pulmonary edema is based on the history and clinical picture of pulmonary edema in
patients without heart failure or predisposition for acute res-
piratory distress syndrome from other causes. Typically, the
patient is a young, vigorous adult who sustains an episode of
laryngospasm either before intubation or after tracheal de-
cannulation (87). The radiologic picture in negative-pressure
pulmonary edema has been described as alveolar and intersti-
tial edema, which rarely occur unilaterally. The heart size is
normal, but the vascular pedicle is enlarged.

Treatment of negative-pressure pulmonary edema is mainly
supportive. Patients should be given oxygen to maintain an
arterial saturation of at least 90%. Some patients require rein-
tubation and mechanical ventilation with positive pressure to
ensure oxygenation and to reduce work of breathing; diuretics
may be used judiciously in these cases. In most cases, the edema
resolves within 24 hours.

**Pain and Perioperative Stress**

Early postoperative pain remains a serious concern. Up to 75%
of patients receiving parenteral narcotics for moderate to severe
pain have significant residual pain after the drug is adminis-
tered. Uncontrolled pain can lead to serious physiologic conse-
quencies. For example, sympathetic nervous system stimulation
that accompanies uncontrolled pain leads to elevated plasma
catecholamine levels, tachycardia, hypertension, increased sys-
temic vascular resistance, and an increase in myocardial oxygen
requirements. In the patient with underlying coronary artery
disease, this increased oxygen demand may not be met, result-
ing in ischemia or infarction.

Surgical procedures on the upper abdomen and thorax may
have profound effects on the respiratory system. Because of the
pain and surgery-induced muscular alterations, vital capacity
and functional residual capacity may be decreased by as much
as 60% and 20%, respectively. Although these changes may
not be evident with resting tidal respiration, the ability to deep
breathe (sigh) and cough is impaired, resulting in atelectasis and
retained secretions. Decreased oxygenation and the potential
for pulmonary parenchymal infection may follow.

**Stress Response**

An area less clearly understood and described, but likely no
less important with regard to postoperative pain, is the stress
response to surgery. Weissman (88) reviews the intriguing and
manifold physiologic changes observed with an operative in-
tervention. Surgery, as any trauma, was classically described as
being composed of two stages: an initial "ebb phase" character-
ized by a shock state with low metabolic activity and cardiac
output, and a second period termed the "flow phase" which is charac-
terized by a hyperdynamic state from the endocrine, metabolic,
and cardiovascular standpoints.

The endocrine parameters of the latter stage are evidenced
by an increase in catecholamine levels, an increased secretion of
corticotropin and steroids, and resultant hyperglycemia. An
increase in antidiuretic hormone (ADH) secretion enables con-
servation of water by the kidneys. Other aspects of the response
to surgery and anesthesia are an increase in growth hormone
and, in ischemia or infarction.

The systemic response to trauma also includes an important
component of immune depression, which can appear early af-
after the stressful event (89,90) and is mediated through several
different pathways (91,92). Traditionally, the stress response
was thought to be beneficial for homeostatic stability and, in-
deed, there was perhaps an evolutionary advantage accrued to
the organism that could mount this response to major trauma,
blood loss, and organ dysfunction. Currently, however, data
show that the metabolic response to trauma may often be ex-
aggerated and thus disadvantageous.

In the otherwise well-controlled diabetic patient, for ex-
ample, one may see hyperglycemia that is extremely difficult
to regulate. An increase in catecholamine secretion that in-
creases myocardial work and oxygen consumption may result
in ischemia in patients with coronary artery disease. Increased
ADH secretion may result in a picture similar to the syndrome
of inappropriate ADH (SIADH) secretion with significant hy-
ponatremia, particularly in patients treated with hypotonic so-
lutions after surgery (93). The significant hyponatremia seen in
this syndrome can present with convulsions, respiratory arrest,
and permanent brain damage. The hypotonic syndrome has
been described in children after spinal surgery (94,95) as
well as in adults (96) and in thermally injured patients (97).

These data suggest—although we note that significant con-
troversy exists—that the stress response to surgery should at
least be attenuated if the detrimental effects are to be avoided.
Different anesthetic techniques may affect this response in
Various ways; thus, the choice of an anesthetic may affect the patient's course in the postoperative period and in the surgical ICU.

**General Anesthesia.** Patients studied under a variety of general anesthetics show an increase in corticotropin, corticosteroids, β-endorphins, and catecholamines in response to intubation, skin incision, and intra-abdominal manipulation, and on emergence (98). Nevertheless, some researchers believe that a well-maintained general anesthetic can blunt the stress response; or, at least, some of its components. Rosazza et al. (99) have used the acronym MAC-BAR, indicating the minimal alveolar concentration at which the adrenergic response is blocked; it is usually observed at approximately 2 MAC for most inhalational agents. Furthermore, others have shown that graded surgical stress causes minimal endocrine response (100). Thus, patients who undergo relatively less stressful surgery under adequate anesthesia do not mount a deleterious stress response.

High-dose narcotic techniques, commonly used in cardiac anesthesia or for patients with ischemic heart disease, have been shown to blunt the endocrine response to stress inasmuch as plasma levels of various stress hormones are not increased (101). The difference between the different types of narcotics is probably insignificant. With any general anesthetic technique, the metabolic response is triggered on emergence, even if attenuated during the surgical procedure itself. In the surgical ICU, patients may begin to mount the metabolic–endocrine response in the postoperative period (102).

**Regional Anesthesia.** The stress response to surgery is triggered by several mechanisms. Among these, an important one is that of direct neural activation by transmission of noxious stimuli from the traumatized area. This event occurs even when patients receive a general anesthetic and, therefore, are not consciously aware of the noxious stimulus. Blunting the response can be achieved by blocking this neural pathway.

Analgesia and anesthesia achieved with a regional technique do attenuate the stress response when compared with general techniques. Kehlet et al. (103,104) have studied this relationship extensively and found major differences in levels of cortisol, catecholamines, aldosterone, renin, growth hormone, prolactin, and ADH in patients undergoing surgery with epidural anesthesia compared with those given general anesthesia. Some aspects of the immune depression after surgery also may be put to use in surgery on the extremities and lower abdomen. A purely regional technique is seldom used for upper abdominal surgery; some anesthesiologists do not use regional techniques in a prolonged surgical procedure if it involves uncomfortable positioning or if immobility is important. In the latter procedures, a common approach is to use regional anesthesia, with control of the airway by intubation, inhalational agents, and positive-pressure ventilation; this approach is called combined anesthesia. The term was coined by Crile in 1921 and involves the block of surgical stimulus by a regional technique, combined with loss of consciousness achieved by light general anesthesia (105).

**Applications.** Whereas combined anesthesia usually refers to a general anesthetic combined with a spinal or epidural technique, the regional anesthetic might also be a brachial plexus or any other nerve block. Proving that combined anesthesia is successful in blunting the stress response to trauma is more difficult than in studies comparing regional anesthesia with general anesthetic techniques. This observation probably results from several factors: (a) obtaining control of the airway (the intubation) may itself elicit a strong stress response, (b) the surgical field may include areas that are not well anesthetized, and (c) part of the stress response may be mediated by the release of humoral factors from the locally injured area.

**Potential advantages.** The possible advantages of combined anesthesia over a purely general technique are controversial. Yeager et al. (106) compared major abdominal and vascular procedures done under a general anesthetic technique with those done under combined general and epidural techniques. They found significant differences in the ICU course and in outcome between the two patient groups. The combined group required less time to tracheal-decannulation and a shorter ICU stay; they had fewer infectious complications and a lower mortality. Expense per patient was considerably lower. Thus, the anesthetic choice becomes an important ICU issue. Some studies did not find an advantage to this approach (107), whereas others found specific benefits of epidural anesthesia, such as a reduced propensity for thrombosis of vascular grafts (108).

An extreme case of stress-induced hypermetabolism is burn injury. In these patients, it has been shown that decreasing the sympathetic response with β-blockers can improve the metabolic response and reverse catabolism (109). Decreasing the sympathetic response with β-blockers following high-risk surgery has been shown in a number of studies to reduce cardiac ischemia and the incidence of perioperative myocardial infarction; this has been particularly noted in patients undergoing vascular surgery (110). Despite this fact, a meta-analysis of studies looking at β-blockade in the perioperative period did not find a significant consistent effect on outcome, although ischemia and arrhythmias decreased in frequency (111).

**Cardiac output and oxygen delivery.** An important body of data regarding the significance of the stress response in terms of outcome has been generated by Shoemaker (112). He demonstrated that patients surviving high-risk surgery, sepsis, and shock states are those in whom measured parameters of cardiac function and oxygen delivery are highest. Moreover, patients with low oxygen delivery developed an oxygen deficit during surgery that was more pronounced in those who developed complications and died. Thus, hemodynamic values may be of use in predicting outcome.

Other investigators have shown that the early use of invasive monitoring may be helpful in the management of elderly (113) and young (114) trauma patients using goal-directed therapy. In a prospective study (115), three groups of general surgical patients were followed. The first group was managed with central venous pressure monitoring; the second group had a pulmonary artery catheter inserted, but therapy was directed by the surgical service according to conventional clinical criteria; and the third group was managed with a pulmonary artery catheter using a rigid protocol to maintain oxygen delivery at supranormal values; the results reported are of interest. The mortality rate decreased from about 30% in both control
The Surgical Patient

ETIOLOGY OF POSTOPERATIVE MENTAL STATUS ALTERATION

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>In the patient emergently anesthetized from the ED, street drugs such as alcohol, narcotics, and cocaine may have been present on induction; residual neuromuscular blockade must also be considered.</td>
</tr>
<tr>
<td>Postseizure</td>
<td>A seizure under anesthesia may be easily missed. One must consider the delayed emergence as a possible postictal event.</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hyperglycemia or hypoglycemia can result in altered mental status.</td>
</tr>
<tr>
<td>Metabolic causes</td>
<td>Hypoxia, hypercarbia, hypernatremia or hyponatremia, hypercalcemia, and hypothermia (usually at or below 31°C) are several examples.</td>
</tr>
<tr>
<td>Trauma</td>
<td>Again, in the patient emergently anesthetized from the ED, head trauma must be considered.</td>
</tr>
<tr>
<td>Infection</td>
<td>Agitation in an infected patient is sometimes seen; this is no less so in the postoperative period.</td>
</tr>
<tr>
<td>Psychogenic causes</td>
<td>Rarely, a patient will feign unconsciousness for some secondary gain. This may only be diagnosed after other life-threatening and treatable causes have been ruled out.</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>Hypotension, and sometimes severe hypertension, may cause mental status changes. The former may result from hypovolemia, anaphylaxis, sepsis, or ischemia.</td>
</tr>
<tr>
<td>Pain</td>
<td>Pain at the operative site, a full bladder, or gastric distention can result in agitation.</td>
</tr>
</tbody>
</table>

ED, emergency department.

Delirium

Delirium and acute confusional states (Table 71.9) can be very disturbing for patients and family members as well as impose a significant risk to patients with regard to line disconnections, dressing management, and risk of falling from the gurney or bed. The patients require additional nursing care and may require an unplanned ICU admission. The reasons for postoperative delirium are many. Dyer et al. reviewed 80 articles that studied the issue of postoperative delirium. They found that some studies described a diverse incidence from 0% to 73%, and found that age, preoperative cognitive impairment, and use of anticholinergic agents were associated with an increase in the occurrence of delirium (120). Lepouse et al. studied a group of patients following general anesthesia and found that 4.7% of them developed postoperative delirium in the postanesthesia care unit (121). The risk factors for developing delirium were benzodiazepines as premedication, breast surgery, abdominal surgery, and particularly long surgical procedures. Marcantonio et al. found that postoperative delirium was not related to the type of anesthetic used. They did find that intra- and postoperative bleeding and increasing transfusion requirements led to an increase in postoperative delirium (122). In children, some increase in the incidence has been related to the introduction of
newer inhalational agents (123). The treatment of delirium is multifactorial. It is probably accepted that the best approach is prevention, and should include exclusion of treatable physical disorders such as pain, electrolyte abnormalities, and urinary retention—a kink in the urinary drainage catheter can be an easily resolved reason for agitation.

**Treatment**

When treatment is considered, several previously discussed therapeutic modalities are available. Propofol is an attractive drug for continuous sedation, and its cost has decreased markedly in the last years. A comparison of propofol with midazolam for continuous sedation of postoperative, mechanically ventilated patients found similar results for both drugs, although some advantages were claimed for propofol in terms of tolerance of the ICU environment and duration to complete wakefulness after discontinuation of sedation (124).

For continuous propofol sedation, a loading dose of 1 to 2 mg/kg is administered over 1 to 2 minutes, followed by an infusion of 50 to 100 μg/kg/minute; the dose is titrated up or down so that, with gentle stimulation, the patient awakens. Midazolam is dosed at 0.25 to 3 mg/hour in a 70-kg adult. The use of neuromuscular blocking agents without sedation to abort nonpurposeful movement is wrong, and will lead to pain with awareness.

**Residual Neuromuscular Blockade**

Residual neuromuscular blockade usually presents in one of three ways: (a) delayed return to consciousness, which should have been noted in the operating room by both the surgeon and anesthesiologist; (b) respiratory difficulty with hypercapnia (Table 71.10); and (c) muscle weakness (Table 71.11). The major point in the diagnosis of this entity is to consider it; the major point in treatment is to protect the airway—if necessary, by replacing the endotracheal tube—while the differential diagnosis is worked through.

**Diagnosis**

Most anesthesiologists monitor the depth of neuromuscular blockade with a twitch-stimulating device or a group of clinical signs. Nevertheless, some persons arrive in the surgical ICU with residual neuromuscular blockade. This condition may take the form of an apparent alteration in mental status (Table 71.9), hypoventilation with hypercapnia, or a seemingly awake and alert status with adequate breathing but a weak or "floppy" appearance. The effect of muscle relaxants can be monitored by applying a supramaximal electrical stimulus to a motor nerve; in the operating room, the ulnar nerve is stimulated to contract the adductor pollicis brevis. If the equipment is properly set up, a single supramaximal stimulus at 50 Hz for 5 seconds that produces contraction without fade correlates with signs of clinical recovery from neuromuscular blockade.

Other more quantitative estimations of neuromuscular blockade use the train-of-four stimulus (four supramaximal stimuli in 2 seconds with each stimulus lasting 0.2 seconds), or double-burst stimulation. With the train-of-four stimulus, when the ratio of the fourth contraction to the first is more than 60%, patients are able to sustain a head lift for over 3 seconds; when the ratio is more than 75%, adequate clinical recovery is present (Table 71.12).

**Table 71.10**

<table>
<thead>
<tr>
<th>Etiology of Postoperative Hypercapnia</th>
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<tbody>
<tr>
<td>I. Central respiratory depression</td>
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<tr>
<td>II. Respiratory muscle dysfunction</td>
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<td></td>
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<tr>
<td>III. Physical factors</td>
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<tr>
<td>IV. Increased production of carbon dioxide</td>
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<td></td>
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<tr>
<td>V. Underlying hyperthermia</td>
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**Treatment**

If residual neuromuscular blockade is present, an attempt to reverse it may be in order. If blockade results from succinylcholine, which can occur in patients with pseudocholinesterase deficiency, reversal agents will not be of any benefit. The diagnosis is made by measuring pseudocholinesterase activity in plasma, and the options are either to keep the patient mechanically ventilated and sedated until neuromuscular function returns or to administer fresh frozen plasma that has the missing enzyme. If a nondepolarizing blocking agent was used, reversal may be attempted with anticholinesterases and anticholinergic drugs (Table 71.13).

An important issue with regard to neuromuscular blocking agents is that of prolonged paralysis in patients who have received neuromuscular blockers for a long period in the ICU. Although controlled studies addressing this problem have not been published, several risk factors for the development of prolonged paralysis have been delineated. Among these are renal failure, concomitant drug use, length of administration, monitoring technique used, and the use of steroids in patients receiving steroid-based drugs such as pancuronium or vecuronium. The best way to prevent this distressing complication is to avoid neuromuscular blockers as much as possible, and to monitor all patients receiving these drugs with a peripheral nerve stimulator. It should also be noted that patients may develop critical illness neuropathy, which can be difficult to differentiate from the residual effects of prolonged administration and in fact...
Anesthesia. contracture tests for MH appear within minutes of exposure to stimulating agents. Hypothermia and acidosis may be in the surgical ICU. The hallmark of the syndrome is death. After exposure to a triggering agent, a dramatic increase in aerobic metabolism occurs in the skeletal muscle of susceptible persons. Oxygen consumption can increase threefold, possibly in early, late, and postcrisis (Table 71.14). The differential diagnosis of MH includes sepsis, light anesthesia, thyrotoxicosis, and rhabdomyolysis and may be delayed for several hours; thus, the initial presentation could be pathophysiologically related (125). The use of neuromuscular blocking agents and the effect they may have on development of critical illness neuropathy has also been linked to an increased cost of illness (126).

Malignant Hyperthermia

Manifestations of malignant hyperthermia may be divided into early, late, and postcrisis (Table 71.14). The differential diagnosis of MH includes sepsis, light anesthesia, thyrotoxicosis, myotonias, neuroleptic malignant syndrome, and pheochromocytoma.

Background

Malignant hyperthermia is a pharmacogenetic clinical syndrome that usually occurs during general anesthesia. Its onset may be delayed for several hours; thus, the initial presentation may be in the surgical ICU. The hallmark of the syndrome is rapidly increasing temperature caused by uncontrolled skeletal muscle metabolism that can result in rhabdomyolysis and death. After exposure to a triggering agent, a dramatic increase in aerobic metabolism occurs in the skeletal muscle of susceptible persons. Oxygen consumption can increase threefold, whereas blood lactate may increase 15- to 20-fold. The mechanism for this entity involves myoplasmic calcium accumulation and a failure of calcium uptake by the sarcoplasmic reticulum.

The incidence of MH varies; fulminant cases are seen from 1 in 250,000 to 1 in 62,000 anesthetics, the latter incidence when triggering agents are used; suspected MH occurs in 1 in 6,000 anesthetics overall and 1 in 4,200 anesthetics with triggering agents. A 24-hour per day emergency phone number for consultations has been set up by the Malignant Hyperthermia Association of the United States (1-209-634-4917). Evaluation of susceptibility includes the family history and measurement of baseline creatine kinase level; it is elevated in 70% of those affected. The definitive test is a muscle biopsy to have no adverse anesthetic outcome when subsequently exposed to triggering anesthetic agents. However, this test is invasive and not available in all medical facilities. A new approach is that of genetic testing—the mutation conferring the susceptibility for MH is recognized and can be mapped. The future of diagnosis of MH susceptibility probably lies in genetic diagnosis (127).

**TABLE 71.11**

<table>
<thead>
<tr>
<th>I Nondepolarizing neuromuscular blocking agents</th>
<th>II Depolarizing neuromuscular blocking agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of neuromuscular blockade</td>
<td>Decreased effective pseudocholinesterase</td>
</tr>
<tr>
<td>Renal failure (decreased pancuronium excretion)</td>
<td>Phase II block</td>
</tr>
<tr>
<td>Hepatic failure (decreased pancuronium and</td>
<td>Hyperkalemia, hypermagnesemia</td>
</tr>
<tr>
<td>vecuronium excretion)</td>
<td>Drug</td>
</tr>
<tr>
<td>Residual potent inhaled anesthetic agent</td>
<td>Antibiotics (gentamicin, clindamycin, and</td>
</tr>
<tr>
<td>An inadequate dose of reversal agents</td>
<td>multiple other drugs with several mechanisms)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Local anesthetics</td>
</tr>
<tr>
<td>Acid-base state</td>
<td>Antiarhythmics (quinidine)</td>
</tr>
<tr>
<td>Hypokalemia, hypermagnesemia</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Drugs</td>
<td>Dantrolene</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Trimethaphan (possibly)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Underlying diseases (myasthenia gravis,</td>
</tr>
<tr>
<td></td>
<td>myasthenic syndrome, familial periodic</td>
</tr>
<tr>
<td></td>
<td>paralysis)</td>
</tr>
</tbody>
</table>


**TABLE 71.12**

<table>
<thead>
<tr>
<th>I Awake patient</th>
<th>II Patient who is asleep or unable to follow commands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opens eyes widely</td>
<td>Tidal volume of 5–10 mL/kg</td>
</tr>
<tr>
<td>Coughs effectively</td>
<td>PNP of greater than or equal to 25 cm H$_2$O</td>
</tr>
<tr>
<td>Sustains tongue protrusion</td>
<td>Sustained 50-Hz tetanic stimulation for 5 sec</td>
</tr>
<tr>
<td>Sustains hand grip</td>
<td>Vital capacity of greater than or equal to 35 mL/kg</td>
</tr>
<tr>
<td>Sustains head lift for more than 5 sec</td>
<td>PNP of greater than or equal to 25 cm H$_2$O</td>
</tr>
</tbody>
</table>


**TABLE 71.13**

<table>
<thead>
<tr>
<th>Anticholinesterase</th>
<th>Anticholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine 35–70 µg/kg</td>
<td>Atropine 20 µg/kg</td>
</tr>
<tr>
<td>(maximum, 5 mg)</td>
<td>or</td>
</tr>
<tr>
<td>Edrophonium 500–1,000 µg/kg</td>
<td>Glycopyrrolate 10 µg/kg</td>
</tr>
</tbody>
</table>
Diagnosis

Treating MH is easier than making the clinical diagnosis because the presenting signs may be mistaken for benign conditions, and MH is relatively uncommon. When triggering anesthetic drugs—potent inhaled anesthetic agents, succinylcholine—are used, MH must be considered in the presence of unexplained tachycardia, tachypnea, arrhythmias, mottling, cyanosis, hyperthermia, muscle rigidity, diaphoresis, or hemodynamic instability. The presence of more than one sign must initiate arterial and central venous blood gas analysis for metabolic and respiratory acidosis and hyperkalemia. Central venous oxygen and carbon dioxide partial pressures change more dramatically than do those of arterial blood.

Treatment

The mortality rate of MH has decreased from 70% to less than 5% when recognized and treated appropriately because of improved therapy (Table 71.15) (6). After brief administration of a triggering agent, discontinuation may abort the attack. With fulminant MH—PaCO₂ above 60 mm Hg and increasing; base excess more than –5 mEq/L; and a body temperature that is increasing by approximately 1°C every 15 minutes—specific therapy with dantrolene is required. The mechanism of action of dantrolene is not completely clear, but it is known to affect the ryanodine receptor, which is a major calcium release channel of the skeletal muscle sarcoplasmic reticulum, thus decreasing the intracellular calcium. Dantrolene is the key to successful MH treatment. Because of its poor water solubility, the preparation of dantrolene for intravenous use requires the full attention of at least one person. Thus, help must be requested as soon as the diagnosis is tentatively made (128).

TABLE 71.14

<table>
<thead>
<tr>
<th>Signs of Malignant Hyperthermia</th>
<th>Early signs</th>
<th>Late signs</th>
<th>Postcrisis signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle rigidity</td>
<td>Hyperpyrexia—may exceed 43°C (109.4°F)</td>
<td></td>
<td>Muscle pain, edema</td>
</tr>
<tr>
<td>Tachycardia and hypertension</td>
<td>Cyanosis</td>
<td></td>
<td>Central nervous system damage</td>
</tr>
<tr>
<td>Elevated PetCO₂</td>
<td>Serum electrolyte abnormalities</td>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Elevated serum creatinine phosphokinase</td>
<td></td>
<td>Continued electrolyte imbalance</td>
</tr>
<tr>
<td>Dyserythmias</td>
<td>Myoglobinuria</td>
<td></td>
<td>Cardiac failure and pulmonary edema</td>
</tr>
</tbody>
</table>

PetCO₂, end tidal partial pressure of carbon dioxide.

I. Discontinue all anesthetic agents.

II. Dantrolene

Intravenously 2 mg/kg every 5 min to a total of 10 mg/kg.

Effective dosage should be repeated every 10–15 h for at least 48 h.

III. Sodium bicarbonate

Initial dose (mEq) = (base excess × [body weight in kg])/4

Give half the calculated dose; repeat as determined by arterial blood gas studies.

IV. Control fever

A. Iced fluids

B. Surface cooling

C. Cooling of body cavities with sterile iced saline

D. Heat exchanger with a pump oxygenator

E. Dantrolene

V. Monitor urinary output

A. At least 0.5 mL/kg/h

B. If myoglobinuria is present, at least 1 mL/kg/h

VI. Further therapy

A. Guided by blood studies, temperature, and urine output

B. Blood studies include blood gases, electrolytes, liver profile, coagulation studies [including DIC studies], serum hemoglobin and myoglobin, and urine hemoglobin and myoglobin.

DIC, disseminated intravascular coagulation; PaCO₂, fraction of inspired oxygen.


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