INTRODUCTION

Modern anesthesia is a complex art and science that involves use of various drugs and procedures in a controlled but safe environment. The overall risk of death from anesthesia is between 1 in 112,000 and 1 in 450,000 (1). Studies show that the most common adverse events are due to respiratory problems, followed by neural injury and damage due to regional anesthesia (2). Over the past years, there is an increase in problems related to cardiovascular issues with a decrease in respiratory events (3). Patients with anesthetic complications may require treatment in the intensive care unit (ICU).

UPTAKE AND DISTRIBUTION OF INHALATIONAL AGENTS

The goal of inhalational anesthesia is to develop a critical partial pressure of the agent within the brain through discrete mechanisms (6) (Table 54.1). The anesthesia system is designed to deliver the anesthetic agent with air, oxygen, nitrous oxide, or a combination achieving a predictable concentration, eliminate carbon dioxide, maintain a predictable FiO₂, while allow monitoring and control of ventilation.

Delivery

Brain tissue partial pressure correlates closely with the end-tidal partial pressure.

Concentration Effect

The inspired concentration directly increases the anesthetic agent concentration in the lung (concentration effect). As a rule, a higher initial inspired concentration of the agent results in a higher alveolar level in spite of uptake from the lung.

Second Gas Effect

When a second anesthetic agent is administered, its partial pressure increases more rapidly than when it is administered alone, because it is drawn into the lungs with the first agent.

Alveolar Ventilation

A greater alveolar ventilation (Vₐ) increases the rate at which the alveolar partial pressure approaches the inspired partial pressure. It is limited only by lung volume, thus, a larger functional residual capacity (FRC) decreases the “wash-in” rate of the agent.

Uptake from the Lungs

Solubility

The more soluble an inhaled agent is in blood, the more it 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 is how inhaled agents differ from other commonly used drugs. For example, ampicillin given intravenously is dissolved in blood, carried to the site of infection, and produces the desired pharmacologic effect as its concentration in the blood increases. However the greater the amount of an inhaled agent dissolved in the blood and hence taken away from the alveoli—the longer it takes to develop the necessary alveolar concentration which in turn reflects brain concentration and longer it takes for anesthesia to take effect.

Agents such as nitrous oxide (blood/gas partition coefficient of 0.47), are relatively insoluble, and achieve alveolar partial pressure rapidly compared with that of halothane (blood/gas partition coefficient of 2.36). The speed of induction of a soluble agent can be increased by increasing the inspired fraction to a level well in excess of that required for maintenance of anesthesia (6).

Cardiac Output

High cardiac output increases uptake, decreasing the alveolar partial pressure. It is greater with more soluble inhalational anesthetics resulting in a longer induction time as in thyrotoxicosis. Low cardiac output states result in a rapid induction and possible overdose.

Alveolar–Mixed Venous Anesthetic Partial Pressure Gradient

The alveolar-to-central mixed venous anesthetic partial pressure gradient relates the size of the anesthetic “sink” to the increase or decrease in uptake from the lungs. At the beginning of induction the venous anesthetic partial pressure is much lower than that in the arterial blood, leading to a large uptake of the anesthetic as the venous blood passes through the lungs. However, as the tissue sinks become filled, the alveolar-to-venous anesthetic partial pressure difference decreases, and this effect is minimized. Thus once anesthesia is achieved it is easier to maintain it.

Distribution

Tissue Solubility and Blood Flow

The tissue distribution (delivery) of the anesthetic is dependent on solubility in the tissue and the blood flow to that tissue (Table 54.1). The greater the solubility, 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; for example, fat and a highly fat-soluble agent such as halothane in an
TABLE 54.1 Factors Governing Uptake and Distribution of Inhaled Agents

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<th>Delivery</th>
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<tr>
<td>Inspired concentration</td>
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<td>Concentration effect</td>
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<td>Second gas effect</td>
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<td>Ventilation</td>
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<th>Uptake from lungs</th>
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<td>Solubility</td>
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<td>Cardiac output</td>
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<td>Alveolar-mixed venous partial pressure gradient</td>
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<th>Distribution to tissues</th>
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<td>Solubility of agent in tissue</td>
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<td>Blood flow to tissue</td>
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obese patient, can accumulate but is released after discontinuation of the agent thereby prolonging emergence. If the tissue has a small capacity and large blood flow, equilibration and hence anesthetic induction is rapid (e.g., brain). An intermediate group includes muscle and skin.

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.

Factors that govern the elimination of the agent from the body are the same as those that govern the uptake and distribution at the beginning. Hypoventilation, increased cardiac output, highly soluble agents, increased alveolar-to-venous anesthetic concentration gradient, all lengthens the period of emergence.

Diffusion Hypoxia

At the end of an anesthetic, large quantities of nitrous oxide diffuse into the alveoli and dilute the oxygen that is present. This lasts for approximately 10 minutes and, if during this time the patient is allowed to breathe room air, hypoxia may ensue.

Changes in Ventilation

For each 1 mmHg decrease in the PaCO₂ caused by an increase in VA, an approximate 3% to 4% decrease in cerebral blood flow (CBF) occurs. A change in the length of time of anesthetic induction results from three factors: increased VA, decreased CBF, and solubility of the inhaled agents. For a moderately soluble agent like halothane the increased VA produces a more rapid rise in end-tidal halothane partial pressure that offsets the decrease in CBF. For a relatively insoluble agent such as nitrous oxide, induction time is increased as the modest increase in end-tidal nitrous oxide partial pressure obtained by hyperventilation is more than offset by the decrease in CBF.

Eventually, no matter what agent is used, the increased end-tidal partial pressure resulting from the decrease in cardiac output and increase in VA is enough to overcome the decrease in CBF.

INHALATION AGENTS AND ORGAN SYSTEM FUNCTION

The minimum alveolar concentration (MAC) is the amount of an inhalational agent that prevents movement in 50% of patients in response to surgical incision. 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 all inhalational agents and can be due to decreased contractility (e.g., halothane) or decreased systemic vascular resistance (e.g., isoflurane or desflurane) (6). Isoflurane and desflurane lead to coronary vasodilation and may cause ischemia. The effect of both isoflurane and desflurane on contractility is less than halothane and enflurane (7).

Cardiac Rhythm

Halothane is the most arrhythmogenic agent while enflurane, desflurane, and sevoflurane are the least. Desflurane at a concentration of 6% led to a significant increase in QTc in children, whereas 2% sevoflurane did not (8).

Hypoxic Pulmonary Vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) is inhibited in a concentration-dependent fashion (9). 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 was found to have a deleterious effect on oxygenation (10).

Respiratory Effects

All inhalational agents are respiratory depressants. Compensatory responses to both hypoxia and hypercarbia are blunted (11).

Hepatic Effects

Up to 20% of patients may demonstrate mild disturbances in liver function following anesthesia with halothane (6). Neither desflurane nor sevoflurane seems to have hepatotoxic properties (12).

Renal Effects

All potent inhalation agents result in a dose-dependent decrease in renal blood flow. In patients with preoperative renal impairment, anesthesia with either desflurane or isoflurane did not lead to worsened renal function (13).

INTRAVENOUS AGENTS

Narcotics

General Properties

Morphine sulfate was first isolated from opium in 1803. The use of high-dose narcotics for anesthesia was popularized in the 1970s.

The opiate receptor complex has three major receptor groups: μ, δ, and κ. Pain relief is mediated by the μ-receptor and also affect the respiratory, cardiovascular, gastrointestinal, and neuroendocrine systems (14).

Modern anesthesia practice includes morphine, meperidine, methadone, fentanyl, alfentanil, sufentanil, and, more
recently, remifentanil. Morphine is associated with recall, histamine release, respiratory depression, hypertension, and vasodilation. Synthetic drugs related to the phenylpiperidines, such as fentanyl, sufentanil, alfentanil, and remifentanil, do not induce histamine release or vasodilation and thus hemodynamically stable (14). Remifentanil, has a rapid onset, metabolized by plasma esterases, and has a half-life of 8 to 20 minutes independent of liver or renal function thus making it ideal in patients following neurosurgical procedures or head injury who need frequent neurologic assessments. However, narcotic drugs cannot be depended upon to provide complete anesthesia alone.

**Pharmacokinetics/Pharmacodynamics**

Selected pharmacokinetic data for four commonly used opioids are summarized in Table 54.2. 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. The depressant effect from morphine and fentanyl can be seen even after the analgesic effect of that drug has dissipated.

**Hemodynamic Effects**

Hypotension is seen with morphine dose of 1 to 4 mg/kg secondary to vagal-induced bradycardia, vasodilation, histamine release, and splanchnic blood sequestration. Hypotension seldom occurs at a rate of 5 mg/min or less.

Treatment with H1 (diphenhydramine) and H2 (cimetidine) blockers attenuates the cardiovascular response to histamine. Fentanyl, 30 to 100 μg/kg, rarely causes hypotension, changes in contractility, heart rate, cardiac output, or systemic or pulmonary artery occlusion pressure even in patients with poor left ventricular function, perhaps because it does not cause histamine release. Remifentanil has a beneficial hemodynamic profile, similar to fentanyl (15).

**Respiratory Effects**

Dose-dependent respiratory depression is seen. Hypoxic and hypercarbic ventilatory drives are decreased. The pontine and medullary centers for respiratory rhythmicity are impaired, resulting in increased irregular and periodic breathing.

With morphine triggering or worsening of bronchospasm due to histamine release is possible but not seen with fentanyl, sufentanil, or remifentanil. Fentanyl and its derivatives can cause chest wall rigidity. The mechanism is not well understood, but may be a result of γ-aminobutyric acid (GABA) receptor stimulation located on interneurons. Treatment is commonly with a muscle relaxant.

**Neurologic Effects**

Morphine has no effect on CBF, cerebral metabolic rate for oxygen (CMRO2), or cerebral metabolic rate for glucose (CMRglu) in CBF, but autoregulation was better maintained than in the control group (16). Fentanyl, in a model of traumatic brain injury, did not lead to a reduction in CBF despite a decrease in arterial blood pressure (17).

**Gastrointestinal Effects**

Opioids can cause emesis by 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. The effects of opiates on the GIT can be ameliorated by methylaltrexone which does not cross the blood–brain barrier.

**Immune Function**

Effects on the immune system are variable but opiates may be associated with suppression of natural killer cells and the immune response in animal studies (18–21).

**Barbiturates**

Thiobarbiturates (e.g., sodium thiopental and methohexital) are frequently used due to their ultrashort onset and offset action compared with other barbiturates. Methohexital is two to three times more potent than thiopental.

**Pharmacokinetics/Pharmacodynamics**

Thiopental is highly lipophilic. A dose of 3 to 5 mg/kg induces loss of consciousness within one arm–brain circulation time (10 to 15 seconds). The short duration of action of this drug (5 to 10 minutes) is due 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 drug with larger doses.

Methohexital is only slightly less lipid-soluble and the onset and duration of loss of consciousness are approximately the same as with thiopental because of its rapid redistribution, but it is more dependent on hepatic blood flow for clearance.

**Neurologic Effects**

Barbiturates facilitate inhibitory—GABA—neural transmitters and inhibition of excitatory neural transmitter action and lead to an increase in the duration that chloride (Cl–) ion channels remain open. There is a decrease in CMRO2, CBF, and ICP and hence used for brain protection.

**Cardiorespiratory Effects**

Contractility is decreased with a 10% to 25% decrease in cardiac output, blood pressure, and stroke volume at clinically relevant doses. A decrease in venous tone decreases preload. The responses to carbon dioxide elevation and hypoxia are impaired.

A continuous barbiturate infusion, affects immune function increasing chances of developing infections (22).
Propofol

Propofol is a sedative–hypnotic agent. The agent is not antianalgesic—as are the thiobarbiturates but has minimal amnestic effects (23). It is insoluble in aqueous media and hence available in a 1% weight/volume (Intralipid) emulsion composed of soybean oil, glycerol, and purified egg phosphatide. No histamine release is seen.

Pharmacokinetics/Pharmacodynamics

Propofol is extensively distributed into vessel-rich tissues, and ultimately redistributed to lean muscle and fat. It has high clearance and the short elimination half-life but affected by age (decreased clearance and dose requirement), obesity (increased clearance and volume of distribution), and type of procedure.

A 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. The effective dose in 50% of patients studied (ED50), which is analogous to MAC for potent inhalation agents, is 53.5 μg/kg/min (95% confidence limits; 39.9 to 63 μg/kg/min) (24).

Neurologic Effects

The mechanisms of action of propofol are unclear. At a dosage of more than 150 μg/kg/min results in EEG burst suppression lasting 15 seconds or longer returning to the awake state within 11 minutes of drug discontinuation.

Propofol leads to a dose-related decrease in CBF and CMRO2, and leads to progressive EEG suppression with increasing dose of propofol (25) thus beneficial in patients with intracranial disease and for long-term sedation in the ICU.

Cardiovascular Effects

Propofol is a negative inotrope and produces a dose-dependent decrease in systolic, diastolic, and mean arterial blood pressure; an effect 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.

Respiratory Effects

Apnea is seen on induction with propofol and the response to hypoxia is also significantly blunted (26). Adjuvant use of narcotics further depresses respiratory drive.

Propofol Related Infusion Syndrome

First described by Parke et al. (27) propofol related infusion syndrome (PRIS) has been described in adults also (28,29). It is associated usually with high dose (>4 mg/kg/hr) and prolonged infusions (>48 hours) but has also been described after short-term infusions (30). A syndrome characterized by unexplained metabolic acidosis, bradycardia, hypotension, arrhythmias, EKG changes consistent with a brugada-like picture, rhabdomyolysis and renal failure (31). Fatty infiltration of the liver is very common early in the syndrome (Table 54.3).

Propofol increases the activity of malonyl CoA, inhibiting the entry of long chain fatty acids into the mitochondria and uncoupling beta oxidation. This leads to accumulation of fatty acids in muscle and other organ systems. This is more pronounced in a high catecholamine, low carbohydrate state as seen in critically ill malnourished populations such as the extremes of age who are at higher risk of the syndrome (32,33).

Treatment is largely supportive. Triglycerides levels should be monitored when patients are on propofol.

Benzodiazepines

The benzodiazepines most commonly employed are diazepam, lorazepam, and midazolam. Diazepam and lorazepam are insoluble in water. Lorazepam is less lipid-soluble than diazepam, and its slow entry into the CNS may be significant to its slower onset of action.

Pharmacokinetics/Pharmacodynamics

Diazepam. Intramuscular injection is painful, and absorption is erratic. Clearance involves oxidation to active metabolites. With hepatic disease, the volume of distribution increases and metabolism decreases, resulting in an increase in the half-life from 40 to 80 hours.

Lorazepam. Lorazepam is unaltered by age or renal disease, but hepatic disease increases the half-life.

Midazolam. Midazolam also can be administered by intramuscular, intravenous, or oral routes. The drug undergoes extensive metabolism to active and inactive metabolites.

Neurologic Effects

Benzodiazepines have dose-dependent effects on the CNS and potentiate inhibitory GABA neurotransmission. They increase the frequency but not the duration of chloride channel opening.

Antegrade amnesia is seen with all of the benzodiazepines, but more so with lorazepam.

Ketamine

Pharmacokinetics/Pharmacodynamics

Ketamine is structurally related to phencyclidine, known in street vernacular as “angel dust.” 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 secondary to rapid drug redistribution into muscle and other tissues. The most important metabolite is norketamine, and has approximately one-third the potency of ketamine.

Neurologic Effects

The exact mechanism of action of ketamine is not well understood but most likely is NMDA receptor antagonism. It can have hallucinogenic effects including “out of body experiences.”
It is a potent analgesic and a dissociative anesthetic, a feeling of indifference to the outside surroundings but preserved muscle tone. Ketamine increases CBF and so must be used with caution in individuals with elevated ICP.

**Cardiovascular Effects**

Ketamine causes central stimulation of the sympathetic arm of the autonomic nervous system and the cardiovascular effects are primarily related to CNS stimulation with an increase in systemic blood pressure and cerebrovasodilation, resulting in increased ICP. Pulmonary vascular resistance and right ventricular stroke work also are frequently increased.

**Respiratory Effects**

Ketamine is not a respiratory depressant; the ventilatory response to carbon dioxide is maintained while potentiating the bronchodilatory effects of catecholamines. Ketamine increases oral secretions, necessitating the use of an anticholinergic agent.

**Other Effects**

The drug has been used safely in patients with malignant hyperthermia (MH). Postanesthetic emergence reactions—nightmares and hallucinations—occur in 5% to 30% of patients and can be attenuated by using a benzodiazepine.

**Etomidate**

An induction agent that maintains hemodynamic stability, and hence employed for intubation of critically ill patients with hemodynamic instability. It can cause adrenal suppression when used in a prolonged infusion but has also been demonstrated following a single dose (34). However, the benefits of hemodynamic stability may overcome any concerns about adrenal dysfunction and its consequences (35).

**Dexmedetomidine**

Dexmedetomidine is a highly selective, short-acting central 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, anxiolysis, and sympatholysis (alpha 2a receptor mediated), inhibits shivering (alpha 2b receptors) and associated with decreased delirium (alpha 2c receptor). When used in postoperative patients in the ICU, dexmedetomidine can provide better sedation with fewer narcotics than propofol (36). It does not cause respiratory depression and hence can be used through an extubation protocol.

It is chemically related to clonidine but has eight times the affinity for alpha 2 receptors.

A biphasic response is seen with initial hypertension and bradycardia followed by a decrease in BP. It can be used perioperatively in cardiac surgery (37) and has some protective effect in brain trauma (38) the MENDS study showed a lower incidence of delirium (39).

**Acute Respiratory Distress Syndrome**

The development of acute respiratory distress syndrome (ARDS) is hypothesized by a two-hit mechanism. A patient at risk for cytokine release due to various mechanisms (e.g., trauma, sepsis, critical illness, pancreatitis, extensive surgery), if exposed to a second hit such as blood transfusions, high tidal volumes, inappropriate antibiotics can develop lung injury.

ARDS presents with hypoxemia secondary to atelectasis and shunt, thus presenting challenges to mechanical ventilation. Use of low tidal volumes of 6 to 8 mL/kg ideal body weight is preferred (18,40). A higher than normal PaCO2, “permissive hypercapnia” is tolerated. 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 (18,41,42). The use of PEEP to prevent derecruitment is important, but the exact amount is still under debate (43–45).

Identifying patients who are at risk for developing lung injury (lung injury predictive score) and avoiding a second trigger such as blood transfusion, high tidal volumes could prevent progression to ARDS (46).

Management of patients with ARDS should be directed at the maintenance of adequate hemodynamics without fluid overload (47,48).

The use of dynamic markers such as pulse pressure variation (PPV) and systolic pressure variation (SPV) may be challenging in a setting of low compliance and low tidal volumes such as ARDS (49). Other techniques such as a response of stroke volume index, cardiac index or increase in end-tidal CO2 (ETCO2) with passive leg raise (PLR) or an end expiratory occlusion could be employed safely in this setting (50–54).

**The Patient with a Head Injury**

Optimal cerebral perfusion pressure—generally considered to be “optimized” at 60 to 65 mmHg is the goal. Anesthesia directed at reducing intracerebral pressure, barbiturates, maintenance of normothermia or mild hypothermia, increasing serum osmolality, and judicious use of diuretics, use of vasopressors and inotropes to improve cardiac output and blood pressure and at times, hyperventilation. The approach is to direct therapy to optimize CBF by improving central perfusion pressure.

**The Patient with Shock**

In hypovolemic, septic shock patients, it is important to minimize intrathoracic pressures during fluid resuscitation. Drugs that depress contractility and cause vasodilation should be avoided. Sometimes in extreme cases, even drugs that are...
considered to maintain hemodynamic stability, such as ketamine, can lead to hemodynamic collapse.

In patients with cardiogenic shock, intrathoracic pressure is not detrimental, and may even be beneficial. However, most anesthetics are cardiac depressants and should be used with caution in patients with shock. All patients in shock need invasive hemodynamic monitoring to assess fluid responsiveness (55,56).

**POSTOPERATIVE CARE**

Postoperative complications have been found to occur in 5% to 30% of patients.

**Hypoxemia**

Postoperative hypoxemia can result from diverse etiologies (Table 54.4).

**Hypoventilation** caused by residual anesthetic or muscle relaxant especially in patients who are predisposed such as obesity-hyperventilation syndromes, obstructive sleep apnea (OSA), neuro muscular disorders like myasthenia gravis, amyotrophic lateral sclerosis. Atelectasis could be secondary to one-lung intubation, upper abdominal and thoracic surgery especially in patients who have pre-existing lung conditions such as COPD, kyphoscoliosis.

Note that closing capacity and FRC alter with age and the older individuals are more predisposed. Early recognition of this condition and application of noninvasive ventilation (NIPPV-CPAP/BiPAP, aggressive incentive spirometry) can prevent the complications such as hypoxia and pneumonia.

Upper airway obstruction due to a decreased level of consciousness is a common reason for hypoxemia and hypercarbia especially in patients with OSA. Pulmonary edema could be cardiogenic or noncardiogenic. Noncardiogenic may be due to aspiration, infection, ARDS, trauma, transfusion-associated lung injury (TRALI) or neurogenic pulmonary edema. Pulmonary vascular permeability index can be measured and can differentiate between cardiogenic and noncardiogenic pulmonary edema. Negative-pressure pulmonary edema can develop after a strenuous inspiratory effort against an obstructed airway and can take up to 10 hours after the episode of airway obstruction. It is most commonly secondary to laryngospasm during anesthetic induction of or emergence from anesthesia.

The pathophysiology is poorly understood. A common explanation is that the massive negative intrapleural pressure generated during airway obstruction shifts the balance in the Starling forces toward a large fluid transudation from the intravascular to the interstitial space.

The radiologic picture in negative-pressure pulmonary edema has been described as alveolar and interstitial edema. Treatment is mainly supportive and in most cases resolves in 24 hours. Pulmonary embolism (PE) can result in hypoxia and hypotension. Patients at risk include those with renal cell cancer, hip and knee joint surgery, pelvic trauma, and pelvic malignancies.

PE results in decrease in dead space resulting in a large gradient of CO2 between the arterial blood gas and ETCO2. Pneumothorax should be considered especially after thoracic surgery, laparoscopic surgery, trauma, emphysema, and central line placement. Distended neck veins with decreased breath sounds and hypotension are the clinical findings. Emergent needle decompression or placing a chest tube is the treatment. Lately, pneumothorax can be diagnosed with ultrasound techniques.

**Pain and Perioperative Stress**

Seventy-five percent of patients receiving parenteral narcotics for moderate-to-severe pain have significant residual pain. Sometimes there may be a paradoxical response to opioids known as opioid-induced hyperalgesia (OIH) and can be managed with NMDA receptor antagonist such as ketamine, dextromethorphan, and methadone (57). Uncontrolled pain causes sympathetic nervous system stimulation with elevated plasma catecholamine levels, tachycardia, hypertension, increased systemic 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, resulting in ischemia or infarction.

Surgical procedures on the upper abdomen and thorax can cause splinting and lead to pulmonary complications secondary to a decrease in FRC. These can be minimized by adequate pain relief.

**Stress Response**

Stress response to surgery has an initial ebb phase characterized by a shock state with low cardiac output, and a later flow phase characterized by a hyperdynamic state from the endocrine, metabolic, and cardiovascular standpoints.

The endocrine response is evidenced by an increase in catecholamine levels, antidiuretic hormone (ADH) secretion, corticotropin and steroids, and hyperglycemia.

The systemic response to trauma includes an immune depression, which can appear early after the stressful event (58,59) and is mediated through several different pathways (60,61).

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**TABLE 54.4 Etiology of Postoperative Hypercapnia**

| I. Central respiratory depression | Inhale anesthetic agents |
| II. Respiratory muscle dysfunction | Use of drugs that enhance neuromuscular blockade (gentamicin, cindamycin, neomycin, turosemide) |
| III. Physiological factors | Physiologic factors that prevent reversal of neuromuscular blockade (hypokalemia, respiratory acidosis) or enhance the blockade (hypothermia, hypermagnesemia) |
| IV. Increased production of carbon dioxide | Use of drugs that enhance neuromuscular blockade (gentamicin, cindamycin, neomycin, turosemide) |
| V. Underlying hyperthermia | Physiologic factors that prevent reversal of neuromuscular blockade (hypokalemia, respiratory acidosis) or enhance the blockade (hypothermia, hypermagnesemia) |

Different anesthetic techniques may affect this response in various ways.

**General Anesthesia.** Roizen et al. (62) 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 (63).

In the surgical ICU, patients may begin to mount the metabolic–endocrine response in the postoperative period (64).

**Regional Anesthesia.** Kehlet et al. (65,66) have studied this relationship extensively and found major differences in levels of corticosteroids, catecholamines, aldosterone, renin, growth hormone, prolactin, and ADH in patients undergoing surgery with epidural anesthesia compared with those given general anesthesia.

**Combined Anesthesia.** The term coined by Crile in 1921, involves the block of surgical stimulus by a regional technique, combined with loss of consciousness achieved by light general anesthesia (67) and can be used in procedures in lower abdomen and extremities. The benefits of combined over general techniques are controversial (68–70). An extended-release formulation of epidural morphine is available and shown to provide postoperative pain relief for 48 hours with a single dose (71).

**Hemodynamic Management**

**Hypertension:** Acute postoperative hypertension is one of the most common complications and can lead to cardiac complications. Causes are usually related to pain and hypoxia.

**Hypotension:** Hypotension has a varied etiology including hypovolemia secondary to blood loss or an increased SIRS (systemic inflammatory response syndrome) state. The role of fluid responsiveness using dynamic markers has been established (73). Use of dynamic markers such as PPV, SPV have been established (55).

However, these techniques have limitations in the spontaneously breathing patients. In such patients, the response to a PLR could be used (74). The response of ETCO2 and cardiac index to PLR has been validated (50–54).

In mechanically ventilated patients, increase in ETCO2 or stroke volume index (SVI) with an end expiratory occlusion of 15 seconds is considered fluid responsive (53).

Supranormal delivery of oxygen (75) although initially promising, did not show benefit with other studies (76,77).

A protocolized treatment with a pulmonary artery catheter found no advantage compared to standard care without invasive monitoring (78). In contrast, Rivers et al. found that, in the early hours of sepsis, goal-directed therapy that is delivered in the emergency room can improve outcome and decrease hospital mortality (79). However the PROCESS, ARISE, and PROMISE studies (80–82) did not show any difference in outcomes with goal-directed therapy. However, early fluid resuscitation was the standard of care in all these trials and should be targeted aggressively.

**Postoperative AKI**

Acute kidney injury (AKI) could be prerenal, renal, and postrenal. Various classifications have been proposed such as RIFLE (Risk of Acute Kidney Injury) (50–54). The index to PLR has been validated (50–54).

AKI (Acute Kidney Injury Network) and KDIGO Clinical practice guidelines (83). In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) released their clinical practice guidelines for AKI, which build off of the RIFLE criteria and the AKIN criteria (84) (Table 54.5).

Type of IV fluids for resuscitation merits some discussion. The SAFE study showed no difference between the use of 4% albumin versus normal saline as a resuscitation fluid with regard to outcome (85). In traumatic brain injury, however, use of albumin was associated with higher mortality rates (86).

The use of hydroxyl ethyl starch (HES) has been shown to have poor renal outcomes as in the 6S and CHEST studies. This is hypothesized to be due to the deposition of starch molecules in the kidney (87,88). The use of chloride-rich fluids has also been associated with AKI (89).

**Postoperative Nausea and Vomiting**

Postoperative nausea and vomiting (PONV) is seen in 30% of the general population and as high as 80% in high-risk patients. Patients at risk for PONV are younger females with a previous history of PONV or motion sickness. Exposure to volatile anesthetics, nitrous oxide, and opioids increases the risk of PONV as does procedures like cholecystectomy, laparoscopy, and gynecologic procedures.

The Apfel risk score (90) is based on four predictors and can predict PONV with a 10% risk in those patients with zero score (77) (Table 54.6).

The IMPACT study and two other meta-analyses (91–93) showed that avoiding nitrous oxide and using TIVA reduces PONV (Table 54.7).
Treatment of PONV involves use of serotonin antagonists such as ondansetron and ramosetron, NK1 receptor antagonists such as aprepitant, rolapitant, corticosteroids, haloperidol, and meclizine. Avoiding postoperative pain can also decrease PONV. Combination antiemetic therapy is preferable to single drug (91).

Delirium

Delirium can be very disturbing for patients and family members and imposes a significant risk to patients. Marcantonio et al. found that postoperative delirium was not related to the type of anesthetic used but intra- and postoperative bleeding and increasing transfusion requirements led to an increase in postoperative delirium (94). Pain, electrolyte abnormalities, and urinary retention can predispose to delirium. Postoperative delirium is not temporally related to emergence from anesthesia. It is associated with increased mortality, cognitive impairment, and dementia in the long term (95,96).

Delirium occurs as a result of inflammatory response and a breakdown of the blood–brain barrier leading to disturbances in the neurotransmitter systems (97).

Risk factors include older age, pre-existing dementia, and use of narcotics/benzodiazepines.

Precipitating factors include use of physical restraints, polypharmacy, malnutrition, presence of urinary bladder catheter, and acute pain (Table 54.8).

Various screening tools are present for diagnosing delirium. The most commonly used are the confusion assessment method for the ICU (CAM-ICU) (98) or intensive care delirium check list (ICDSC) (99) (Table 54.9).

Treatment

Use of antipsychotics is common but the evidence is difficult to interpret because of the heterogeneity of various studies. However, use of antipsychotics reserved only for short term in the agitated patient.

Minimizing sedation, using a daily sedation holiday (100) and a targeted sedation score (101) can minimize delirium.

The use of dexmedetomidine (MENDS study) also showed less delirium (39).

Residual Neuromuscular Blockade

Residual neuromuscular blockade presents in one of three ways: delayed return to consciousness, respiratory difficulty with hypercapnia, or muscle weakness (Table 54.10). It is important to consider it and protect the airway.

Diagnosis

One can monitor the depth of neuromuscular blockade with a twitch-stimulating device or a group of clinical signs. The effect of muscle relaxants can be monitored by applying a supramaximal electrical stimulus to a motor nerve such as the ulnar nerve and monitor the contraction of adductor pollicis brevis.

A single supramaximal stimulus at 50 Hz for 5 seconds that produces contraction without fade correlates with signs of clinical recovery from neuromuscular blockade.

Train-of-four stimulus (four supramaximal stimuli in 2 seconds with each stimulus lasting 0.2 seconds), or double-burst stimulation can also be used. With the train-of-four stimulus, the ratio of the fourth contraction to the first being greater

TABLE 54.8 Risk Factors for Postoperative Delirium

<table>
<thead>
<tr>
<th>Age &gt;65 yrs</th>
<th>Poor pain control</th>
<th>Cognitive impairment</th>
<th>Sleep deprivation</th>
<th>Severe illness/comorbidities</th>
<th>Hypoxia</th>
<th>Hearing or vision impairment</th>
<th>Hypercarbia</th>
<th>Hip fracture</th>
<th>Electrolyte abnormalities</th>
<th>Infection</th>
<th>Polypharmacy</th>
</tr>
</thead>
</table>

TABLE 54.9 CAM–ICU (Confusion Assessment Method)

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset/fluctuating course</td>
<td>Inattention</td>
<td>Altered level of consciousness</td>
<td>Disorganized thinking</td>
</tr>
</tbody>
</table>

TABLE 54.10 Etiology of Prolonged Neuromuscular Blockade

Nondepolarizing neuromuscular blocking agents
- Intensity of neuromuscular blockade
  - Renal failure (decreased metocurine and pancuronium excretion)
  - Hepatic failure (decreased pancuronium and vecuronium excretion)
- Residual potent–inhaled anesthetic agent
- Inadequate dose of reversal agents
- Hypothermia
- Acid–base state
- Hypokalemia, hypermagnesemia
- Drugs
  - Antibiotics (gentamicin, clindamycin, and multiple other drugs with several mechanisms)
- Local anesthetics
- Antiarrhythmics (quinidine)
- Furosemide
- Dantrolene
- Trimethaphan (possibly)
- Underlying diseases (myasthenia gravis, myasthenic syndrome, familial periodic paralysis)

Depolarizing neuromuscular blocking agents (succinylcholine)
- Decreased effective pseudocholinesterase
- Phase II block
- Hypermagnesemia
- Local anesthetics

than 60%, patients and ability to sustain a head lift for 3 seconds or when the ratio is greater than 75%, predicts clinical recovery (Table 54.11).

### Treatment

If residual neuromuscular blockade is present, an attempt is made to reverse it. If blockade results from succinylcholine, usually in patients with pseudocholinesterase deficiency, reversal agents will not be of any benefit. The diagnosis can be made by measuring pseudocholinesterase activity in plasma. One can keep the patient mechanically ventilated until neuromuscular recovery or administer fresh-frozen plasma. If a nondepolarizing blocking agent was used, reversal may be attempted with anticholinesterases and anticholinergics (Table 54.12).

### Critical Care Illness Neuropathy and Myopathy

Critical illness polyneuropathy and myopathy (CINMA) is a sensory and motor neuropathy associated with weakness, electrophysiologic abnormalities, and respiratory muscle weakness. Prolonged ICU stay, use of vasopressors, renal failure, steroids, and muscle relaxants have been implicated.

Nerve conduction studies reveal mixed axonopathy and can be seen as early as 24 to 48 hours of the critical care illness. Combining protocols for early sedation management while minimizing use of steroids and muscle relaxants can prevent this condition (102–104).

### Glucose Control

Interventions directed at reducing blood glucose showed improved outcomes in some, but not all, studies. After initial studies showing benefit, others, and a metaanalysis of 21 trials, found no benefit from intensive insulin therapy (105,106).

Current evidence suggests that levels between 140 and 180 show benefit in the critically ill populations (107). Targets less than 110 or tight control are not recommended.

The largest trial, the recent NICE-SUGAR study (107) showed an increase in mortality in the group with intensive insulin control (<108 mg/dL).

Current recommendations are not to use intensive insulin therapy in the SICU, MICU patients with or without diabetes mellitus but target a blood glucose of 140 to 180 mg/dL (108).

### MALIGNANT HYPERPYREXIA

Manifestations of MH may be divided into early, late, and postcrisis (Table 54.13). MH is a pharmacogenetic clinical syndrome that usually occurs with general anesthesia. Its onset may be delayed for several hours. 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 and oxygen consumption can increase threefold, whereas blood lactate may increase 15- to 20-fold. The mechanism involves myoplasmic calcium accumulation due to a failure of calcium uptake by the sarcoplasmic reticulum.

Susceptibility is increased in those with a family history and an elevated creatine kinase. The definitive test is a muscle biopsy for contracture studies after exposure to halothane, caffeine, halothane plus caffeine, or potassium. A new approach is that of genetic testing—the mutation conferring susceptibility for MH is recognized and can be mapped. The future of diagnosis of MH susceptibility probably lies in genetic diagnosis (109).

### Diagnosis

MH clinical signs overlap with many other conditions. When triggering agents—potent inhaled anesthetics, succinylcholine—are used, MH must be considered in the presence of unexplained

### Glucose Control

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### MALIGNANT HYPERPYREXIA

### TABLE 54.11 Clinical Signs of Recovery from Neuromuscular Blockade

<table>
<thead>
<tr>
<th>Awake patient</th>
<th>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>PNN of ≥20 cm H₂O</td>
</tr>
<tr>
<td>Sustains tongue protrusion</td>
<td>Sustained 50-Hz tetanic stimulation for 5 sec</td>
</tr>
</tbody>
</table>

PNN: peak negative pressure.


### Critical Care Illness Neuropathy and Myopathy

Critical illness polyneuropathy and myopathy (CINMA) is a sensory and motor neuropathy associated with weakness, electrophysiologic abnormalities, and respiratory muscle weakness. Prolonged ICU stay, use of vasopressors, renal failure, steroids, and muscle relaxants have been implicated.

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### Diagnosis

MH clinical signs overlap with many other conditions. When triggering agents—potent inhaled anesthetics, succinylcholine—are used, MH must be considered in the presence of unexplained

### TABLE 54.12 Reversal Agents Used with Neuromuscular Blocking Agents

<table>
<thead>
<tr>
<th>Anticholinesterase</th>
<th>Anticholinergic</th>
</tr>
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<tbody>
<tr>
<td>Neostigmine 35–70 μg/kg (maximum, 5 mg)</td>
<td>Atropine 20 μg/kg or</td>
</tr>
<tr>
<td>Edrophonium 500–1,000 μg/kg</td>
<td>Glycopyrrolate 10 μg/kg</td>
</tr>
<tr>
<td>Pyridostigmine 175–350 μg/kg (maximum, 20 mg)</td>
<td></td>
</tr>
</tbody>
</table>

tachycardia, tachypnea, arrhythmias, mottling, cyanosis, hyperthermia, muscle rigidity, diaphoresis, or hemodynamic instability. Arterial and central venous blood gas analysis show metabolic and respiratory acidosis.

**Treatment**

The mortality rate of MH has decreased from 70% to less than 5% with improved treatment (Table 54.14). Discontinuing the triggering agent and Dantrolene therapy are recommended along with other supportive measures. 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 decreasing the intracellular calcium. Dantrolene is the key to

**Key Points**

- Postoperative acute respiratory failure is uncommon but dramatic and could be secondary to multiple reasons.
- Pulmonary edema in the early postoperative period could be secondary to increased vascular permeability (TRALI, ARDS, aspiration) or increased hydrostatic pressure (left ventricular failure, HTN) or other special situations such as neurogenic stress/negative pressure pulmonary edema/postexpansion edema after large volume thoracentesis.
- Treatment of hypoxemia entails delivering a high fraction of inspired oxygen (FiO₂) via nasal cannula, face mask, high flow devices, Noninvasive positive pressure ventilation or mechanical ventilation. They may need to be closely monitored in the ICU.
- Cardiac complications include arrhythmias, ischemia, dysrhythmias, heart failure, and myocardial infarction are seen usually 3 to 5 days after surgery, but can occur much earlier even on the first postoperative day (4). Monitoring patients at risk for a cardiac complication, for silent ischemia/infarction and earlier interventions can be lifesaving.
- An acute hypertensive crisis in the immediate postoperative period is usually the result of inadequate analgesia and can result in heart failure and cardiac ischemia.
- Goal-directed therapy is more directed toward achieving euvoilemic in a timely fashion. Supranormal delivery of oxygen is not helpful and targeting central venous saturation may not be necessary.
- MH can develop at any time after exposure to a triggering agent (e.g., potent inhalational agents or succinylcholine). Treatment is supportive along with administering dantrolene. A malignant hyperthermia hotline is available in many countries.

**TABLE 54.14 Acute Therapy for Malignant Hyperthermia**

<table>
<thead>
<tr>
<th>Therapy</th>
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<tbody>
<tr>
<td><strong>Discontinue all anesthetic agents</strong></td>
</tr>
<tr>
<td>Hyperventilate with an FiO₂ of 1.0.</td>
</tr>
<tr>
<td>CO₂ is increased; so hyperventilate to achieve a normal PaCO₂.</td>
</tr>
<tr>
<td><strong>Dantrolene</strong></td>
</tr>
<tr>
<td>Intravenously 2 mg/kg every 5 min to a total of 10 mg/kg</td>
</tr>
<tr>
<td>Effective dosage should be repeated every 10–15 hrs for at least 48 hrs</td>
</tr>
<tr>
<td><strong>Sodium bicarbonate</strong></td>
</tr>
<tr>
<td>Initial dose (mEq) = (base excess x (body weight in kg))/4</td>
</tr>
<tr>
<td>Give half the calculated dose; repeat as determined by arterial blood gas studies.</td>
</tr>
<tr>
<td><strong>Control fever</strong></td>
</tr>
<tr>
<td>Iced fluids</td>
</tr>
<tr>
<td>Surface cooling</td>
</tr>
<tr>
<td>Cooling of body cavities with sterile iced saline</td>
</tr>
<tr>
<td>Heat exchanger with a pump oxidogenator</td>
</tr>
<tr>
<td><strong>Dantrolene</strong></td>
</tr>
<tr>
<td><strong>Monitor urinary output</strong></td>
</tr>
<tr>
<td>At least 0.5 mL/kg/hr</td>
</tr>
<tr>
<td>If myoglobinuria is present, at least 1 mL/kg/hr</td>
</tr>
<tr>
<td><strong>Further therapy</strong></td>
</tr>
<tr>
<td>Guided by blood studies, temperature, and urine output</td>
</tr>
<tr>
<td>(Blood studies include blood gases, electrolytes, liver profile, coagulation studies (including DIC studies); serum hemoglobin and myoglobin, and urine hemoglobin and myoglobin.)</td>
</tr>
</tbody>
</table>

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