Inhaled Anesthetics

History

The discovery of the anesthetic properties of nitrous oxide, diethyl ether, and chloroform in the 1840s was followed by a hiatus of about 80 years before other inhaled anesthetics were introduced (Fig. 4-1). In 1950, all inhaled anesthetics, with the exception of nitrous oxide, were flammable or potentially toxic to the liver. Recognition that replacing a hydrogen atom with a fluorine atom decreased flammability led to the introduction, in 1951, of the first halogenated hydrocarbon anesthetic, fluroxene. Fluroxene was used clinically for several years before its voluntary withdrawal from the market due to its potential flammability and increasing evidence that this drug could cause organ toxicity.

Halothane was synthesized in 1951 and introduced for clinical use in 1956. However, the tendency for alkane derivatives such as halothane to enhance the arrhythmogenic effects of epinephrine led to the search for new inhaled anesthetics derived from ethers. Methoxyflurane, a methyl ethyl ether, was the first such derivative. Methoxyflurane was introduced into clinical practice in 1960. Although methoxyflurane did not enhance the arrhythmogenic effects of epinephrine, its high solubility in blood and lipids resulted in a prolonged induction and slow recovery from anesthesia. More importantly, methoxyflurane caused hepatic toxicity. Extensive hepatic metabolism increased plasma concentrations of fluoride, which caused nephrotoxicity, especially with prolonged exposures to the anesthetic. Methoxyflurane has analgesic properties at concentrations far below those that induce anesthesia. Although its use was abandoned in the United States and Canada in the 1970s, it continues to be used in Australia for brief painful procedures and emergency transport. Enflurane, the next methyl ethyl ether derivative, was introduced for clinical use in 1973. This anesthetic, in contrast to halothane, does not enhance the arrhythmogenic effects of epinephrine or cause hepatotoxicity. Nevertheless, side effects were present, including metabolism to inorganic fluoride and stimulation of the central nervous system (CNS), lowering the seizure threshold. In search of a drug with fewer side effects, isoflurane, a structural isomer of enflurane, was introduced in 1981. This drug was resistant to metabolism, making organ toxicity unlikely after its administration.

Inhaled Anesthetics for the Present and Future

The search for even more pharmacologically “perfect” inhaled anesthetics did not end with the introduction and widespread use of isoflurane. The exclusion of all halogens except fluorine results in nonflammable liquids that are poorly lipid soluble and extremely resistant to metabolism. Desflurane, a totally fluorinated methyl ethyl ether, was introduced in 1992 and was followed in 1994 by the totally fluorinated methyl isopropyl ether, sevoflurane. The low solubility of these volatile anesthetics in blood facilitated rapid induction of anesthesia, precise control of end-tidal anesthetic concentrations during maintenance of anesthesia, and prompt recovery at the end of anesthesia independent of the duration of administration. The development, introduction, and rapid clinical acceptance of desflurane and sevoflurane reflects market forces (ambulatory surgery and the desire for rapid awakening possible with poorly soluble but potent anesthetics) more than an improved pharmacologic profile on various organ systems as compared with isoflurane. The challenge to the anesthesiologist is to exploit the pharmacokinetic advantages of these drugs while minimizing the risks (airway irritation, sympathetic nervous system stimulation, carbon monoxide production from interaction with carbon dioxide absorbent and complex vaporizer technology with desflurane, and compound A production from sevoflurane) and the increased expense associated with the manufacture and increased cost of administration of desflurane and sevoflurane.

Cost Considerations

Cost is an important consideration in the adoption of new drugs, including inhaled anesthetics. Factors that may
rebreathed gases. This conservation offsets the decreased potency of a drug such as desflurane compared with isoflurane. For example, desflurane is one-fifth as potent as isoflurane, yet the amount of desflurane that must be delivered to sustain minimal alveolar concentration (MAC) is only slightly more than threefold the amount of isoflurane. Similarly, although MAC of sevoflurane is 74% greater than isoflurane, the amount of sevoflurane that must be delivered to sustain MAC is only 30% greater.

**Current Clinically Useful Inhaled Anesthetics**

Commonly administered inhaled anesthetics include the inorganic gas nitrous oxide and the volatile liquids isoflurane, desflurane, and sevoflurane (Table 4-1) (Fig. 4-2).\(^4,5\) Halothane and enflurane are administered infrequently but are included in the discussion of the comparative pharmacology of volatile anesthetics since halothane in particular has been studied extensively.\(^4,5\)

Volatile liquids are administered as vapors after their vaporization in devices known as vaporizers. Diethyl ether and chloroform are still available, but mostly used only in veterinary medicine. Xenon is an inert gas with anesthetic properties, but its clinical use is hindered by its high cost.\(^7\)

**Nitrous Oxide**

Nitrous oxide is a low-molecular-weight, odorless to sweet-smelling nonflammable gas of low potency and poor blood solubility (blood:gas partition coefficient 0.46) that is most commonly administered in combination with opioids or volatile anesthetics to produce general anesthesia. Although nitrous oxide is nonflammable, it will support combustion.\(^8\) Its poor blood solubility permits rapid achievement of an alveolar and brain partial pressure of the drug (Fig. 4-3). The analgesic effects of nitrous oxide are prominent but short lived, dissipating after about

### Table 4-1

<table>
<thead>
<tr>
<th>Physical and Chemical Properties of Inhaled Anesthetics</th>
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<tbody>
<tr>
<td><strong>Nitrous Oxide</strong></td>
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<tr>
<td>Molecular weight</td>
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<tr>
<td>Boiling point (°C)</td>
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<tr>
<td>Vapor pressure (mm Hg; 20°C)</td>
</tr>
<tr>
<td>Odor</td>
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<tr>
<td>Preservative necessary</td>
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<tr>
<td>Stability in soda lime (40°C)</td>
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<tr>
<td>Blood:gas partition coefficient</td>
</tr>
<tr>
<td>MAC (37°C, 30–55 years old, (F_{\text{H}}) 760 mm Hg) (%)</td>
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</table>
The benefits of nitrous oxide must be balanced against its possible adverse effects related to the high-volume absorption of nitrous oxide in gas-containing spaces, potential increase in the risk of postoperative nausea and vomiting, and its ability to inactivate vitamin B₁₂.

**Halothane**

Halothane is a halogenated alkane derivative that exists as a clear, nonflammable liquid at room temperature. The vapor of this liquid has a sweet, nonpungent odor. An intermediate solubility in blood, combined with a high potency, permits intermediate onset and recovery from anesthesia using halothane alone or in combination with nitrous oxide or injected drugs such as opioids.

Halothane was developed on the basis of predictions that its halogenated structure would provide nonflammability, intermediate blood solubility, anesthetic potency, and molecular stability. Specifically, carbon-fluorine decreases flammability, and the trifluorocarbon contributes to molecular stability. The presence of a carbon-chlorine and carbon-bromine bond plus the retention of a hydrogen atom ensures anesthetic potency. Despite its chemical stability, halothane is susceptible to decomposition to hydrochloric acid, hydrobromic acid, chloride, bromide, and phosgene. For this reason, halothane is stored in amber-colored bottles, and thymol is added as a preservative to prevent spontaneous oxidative decomposition. Thymol that remains in vaporizers after vaporization of halothane can cause vaporizer turnstiles or temperature-compensating devices to malfunction.

**Enflurane**

Enflurane is a halogenated methyl ethyl ether that exists as a clear, nonflammable volatile liquid at room temperature and has a pungent, ethereal odor. Its intermediate solubility in blood combined with a high potency permits intermediate onset and recovery from anesthesia, using enflurane alone or in combination with nitrous oxide or injected drugs such as opioids. Enflurane decreases the threshold for seizures. Enflurane is oxidized in the liver to produce inorganic fluoride ions that can be nephrotoxic. It is primarily used for procedures in which a low threshold for seizure generation is desirable, such as electroconvulsive therapy.

**Isoflurane**

Isoflurane is a halogenated methyl ethyl ether that exists as a clear, nonflammable liquid at room temperature and has a pungent, ethereal odor. Its intermediate solubility in blood combined with a high potency permits intermediate onset and recovery from anesthesia using isoflurane alone or in combination with nitrous oxide or injected drugs such as opioids.
Although isoflurane is an isomer of enfurane, their manufacturing processes are not similar. The compounds used at the start of manufacturing are different, with 2,2,2-trifluoroethanol the starting compound for isofoflurane and chlorotrifluoroethylene for enfurane. The subsequent purification of isoflurane by distillation is complex and expensive. Isoflurane is characterized by extreme physical stability, undergoing no detectable deterioration during 5 years of storage or on exposure to carbon dioxide absorbents or sunlight. The stability of isoflurane obviates the need to add preservatives such as thymol to the commercial preparation.

**Desflurane**

Desflurane is a fluorinated methyl ethyl ether that differs from isoflurane only by substitution of a fluorine atom for the chlorine atom found on the alpha-ethyl component of isoflurane. Fluorination rather than chlorination increases vapor pressure (decreases intermolecular attraction), enhances molecular stability, and decreases potency. Indeed, the vapor pressure of desflurane exceeds that of isoflurane by a factor of three such that desflurane would boil at normal operating room temperatures. A new vaporizer technology addresses this property, producing a regulated concentration by converting desflurane to a gas (heated and pressurized vaporizer that requires electrical power), which is then blended with diluent fresh gas flow. The only evidence of metabolism of desflurane is the presence of measurable concentrations of serum and urinary trifluoroacetate that are one-fifth to one-tenth those produced by the metabolism of isoflurane. The potency of desflurane as reflected by MAC is about fivefold less than isoflurane.

Unlike halothane and sevoflurane, desflurane is pungent, making it unlikely that inhalation induction of anesthesia will be feasible or pleasant for the patient. Indeed, the pungency of desflurane produces airway irritation and an appreciable incidence of salivation, breath-holding, coughing, or laryngospasm when >6% inspired desflurane is administered to an awake patient. Carbon monoxide results from degradation of desflurane by the strong base present in desiccated carbon dioxide absorbents. Desflurane produces the highest carbon monoxide concentrations, followed by enfurane and isoflurane, whereas amounts produced from halothane and sevoflurane are trivial.

Solubility characteristics (blood:gas partition coefficient 0.45) and potency (MAC 6.6%) permit rapid achievement of an alveolar partial pressure necessary for anesthesia followed by prompt awakening when desflurane is discontinued. It is this lower blood-gas solubility and more precise control over the delivery of anesthesia and more rapid recovery from anesthesia that distinguish desflurane (and sevoflurane) from earlier volatile anesthetics.

**Sevoflurane**

Sevoflurane is a fluorinated methyl isopropyl ether. The vapor pressure of sevoflurane resembles that of halothane and isoflurane, permitting delivery of this anesthetic via a conventional unheated vaporizer. The solubility of sevoflurane (blood:gas partition coefficient 0.69) resembles that of desflurane, ensuring prompt induction of anesthesia and recovery after discontinuation of the anesthetic. Compared with isoflurane, recovery from sevoflurane anesthesia is 3 to 4 minutes faster and the difference is magnified in longer duration surgical procedures (>3 hours) (Fig. 4-4). Sevoflurane is nonpungent, has minimal odor, produces bronchodilation similar in degree to isoflurane, and causes the least degree of airway irritation among the currently available volatile anesthetics. For these reasons, sevoflurane, like halothane, is acceptable for inhalation induction of anesthesia.

**FIGURE 4-4** Analysis of variance results showing times to emergence, responses to commands, orientation, and discharge from the postanesthesia care unit (PACU) with differing durations of anesthesia. Mean ± SEM. (From Ebert TJ, Robinson BJ, Uhrich TD, et al. Recovery from sevoflurane anesthesia: a comparison to isoflurane and propofol anesthesia. *Anesthesiology.* 1998;89:1524–1531, with permission.)

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Part II • Neurologic System

Xenon

Xenon is an inert gas with many of the characteristics considered important for an ideal inhaled anesthetic.\(^7\) MAC is 63% to 71% in humans, suggesting that this gas is more potent than nitrous oxide (MAC 104%).\(^15\) MAC-awake for xenon is 33%.\(^16\) Unlike MAC for other volatile anesthetics, there is evidence that xenon MAC is gender-dependent, being less in females.\(^17\) Xenon is non-explosive, nonpungent, odorless, and chemically inert as reflected by absence of metabolism and low toxicity. Unlike other inhaled anesthetics, it is not harmful to the environment because it is prepared by fractional distillation of the atmospheric air. To date, its high cost has hindered its acceptance in anesthesia practice. This disadvantage may be offset to some degree by using low fresh gas flow rates and development of a xenon-recycling system. Nevertheless, even if cost considerations can be negated, acceptance of xenon as a replacement for current inhaled anesthetics (that also share many of the same advantages of xenon) will be based more on evidence that morbidity and mortality is less when this drug is administered during anesthesia.\(^7\)

Xenon has a blood:gas partition coefficient of 0.115, which is lower than that of other clinically useful anesthetics and even lower than that of nitrous oxide (0.46), sevoflurane (0.69), and desflurane (0.42). Like nitrous oxide, xenon anesthesia results in gas exchange conditions that favor air bubble expansion, which could worsen neurologic injury from venous air embolism.\(^18\) Diffusion of xenon into highly compliant bowel occurs but is less compared with nitrous oxide (Fig. 4-6).\(^19\) It is possible this minimal effect on bowel may be different when xenon diffuses into less compliant cavities as represented by pneumothorax, pneumoperitoneum, and pneumopericardium. Xenon does not trigger malignant hyperthermia in susceptible swine.\(^20\) Emergence from xenon anesthesia, regardless of the duration of anesthesia, is two to three times faster than that from equal-MAC nitrous oxide plus isoflurane or sevoflurane.\(^21\) Xenon is a potent hypnotic and analgesic, resulting in suppression of hemodynamic and catecholamine responses to surgical stimulation. Unlike other inhaled and injected anesthetics, xenon does not produce hemodynamic depression...

Sevoflurane may be 100-fold more vulnerable to metabolism than desflurane, with an estimated 3% to 5% of the dose undergoing biodegradation. The resulting metabolites include inorganic fluoride (plasma concentrations exceed those that occur after enflurane) and hexafluoroisopropanol. The chemical structure of sevoflurane is such that it cannot undergo metabolism to an acyl halide. Sevoflurane metabolism does not result in the formation of trifluoroacetated liver proteins and therefore cannot stimulate the formation of antitrifluoroacetated protein antibodies. In this regard, sevoflurane differs from halothane, enflurane, isoflurane, and desflurane, all of which are metabolized to reactive acyl halide intermediates with the potential to produce hepatotoxicity as well as cross-sensitivity between drugs.\(^13\) Sevoflurane is the least likely volatile anesthetic to form carbon monoxide on exposure to carbon dioxide absorbents. In contrast to other volatile anesthetics, sevoflurane breaks down in the presence of the strong bases present in carbon dioxide absorbents to form compounds that are toxic in animals (Fig. 4-5).\(^5\) The principal degradation product is fluoromethyl-2, 2-difluoro-1-(trifluoromethyl) vinyl-ether (compound A). Compound A is a dose-dependent nephrotoxin in rats, causing renal proximal tubular injury. Although this finding is a concern, the levels of these compounds (principally compound A) that occur during administration of sevoflurane to patients are far below speculated toxic levels, even when total gas flows are 1 L per minute.\(^13,14\)

![FIGURE 4-5 Degradation products of sevoflurane on exposure to soda lime. The formation of these degradation products is increased under experimental conditions in which the soda lime is heated to \(\geq 65^\circ\)C.](image)

![FIGURE 4-6 Pressures in obstructed bowel segments after 4 hours of air or anesthesia administration. After 4 hours of anesthesia, intraluminal pressures were significantly higher in the presence of nitrous oxide. (From Reinelt H, Schirmer U, Marx T, et al. Diffusion of xenon and nitrous oxide into the blood. Anesthesiology. 2001;94:475-7, with permission.)](image)
in healthy adults. Neuromuscular blocking effects of rocuronium are not different when given during propofol versus xenon anesthesia.\textsuperscript{22} A risk of recall would seem to be present but has not been observed in small numbers of patients. Like ketamine, xenon exerts antagonist effects at \textit{N}-methyl-\textit{D}-aspartate (NMDA) subtypes of glutamate receptors, which have been shown to have both neuroprotective and neurotoxic properties. Xenon is unique among known NMDA antagonists in exhibiting neuroprotection without coexisting psychotomimetic behavioral changes.\textsuperscript{23} The reason why ketamine and nitrous oxide, but not xenon, produce neurotoxicity may reflect actions on dopaminergic pathways that do not occur in the presence of xenon.

**Pharmacokinetics of Inhaled Anesthetics**

The pharmacokinetics of inhaled anesthetics describes their (a) absorption (uptake) from alveoli into pulmonary capillary blood, (b) distribution in the body, (c) metabolism, and (d) elimination, principally via the lungs. The pharmacokinetics of volatile anesthetics may be influenced by aging, reflecting decreases in lean body mass and increases in body fat.\textsuperscript{24} The volume of distribution (Vd) of the central compartment (plasma volume) is smaller, whereas the apparent Vd (steady state) for these drugs in the elderly is larger, especially for those anesthetics most soluble in fat. In addition, impaired pulmonary gas exchange may decrease anesthetic clearance with age. Furthermore, reduced cardiac output in the elderly decreases tissue perfusion, increases time constants, and may be associated with an altered regional distribution of anesthetics. Opposite effects on the pharmacokinetics of inhaled anesthetics might be expected in the very young.

A series of partial pressure gradients beginning at the anesthetic machine serve to propel the inhaled anesthetic across various barriers (alveoli, capillaries, cell membranes) to their sites of action in the CNS. The principal objective of inhalation anesthesia is to achieve a constant and optimal brain partial pressure of the inhaled anesthetic.

The brain and all other tissues equilibrate with the partial pressures of inhaled anesthetics delivered to them by arterial blood (Pa). Likewise, arterial blood equilibrates with the alveolar partial pressures (Pa) of anesthetics. This emphasizes that the Pa of inhaled anesthetics mirrors the brain partial pressure (P\textsubscript{BRAIN}) at steady state. This is the reason that Pa is used as an index of (a) depth of anesthesia, (b) recovery from anesthesia, and (c) anesthetic equal potency (MAC). It is important to recognize that equilibration between the two phases means the same partial pressure exists in both phases. Equilibration does not mean equality of concentrations in two biophases. Understanding those factors that determine the Pa and thus the P\textsubscript{BRAIN} permits control of the doses of inhaled anesthetics delivered to the brain so as to maintain a constant and optimal depth of anesthesia. This relationship is applicable because volatile anesthetics are only minimally metabolized and as such are excreted from the lung. The availability of an “online” readout of end-tidal partial pressure, which at equilibrium matches brain partial pressure, makes volatile anesthetic dosing easier than intravenous anesthetic dosing.

**Determinants of Alveolar Partial Pressure**

The Pa and ultimately the P\textsubscript{BRAIN} of inhaled anesthetics are determined by input (delivery) into alveoli minus uptake (loss) of the drug from alveoli into arterial blood (Table 4-2). Input of anesthetics into alveoli depends on the (a) inhaled partial pressure (PI), (b) alveolar ventilation, and (c) characteristics of the anesthetic breathing (delivery) system. Uptake of inhaled anesthetics from alveoli into the pulmonary capillary blood depends on (a) solubility of the anesthetic in body tissues, (b) cardiac output, and (c) alveolar-to-venous partial pressure differences (A-vD).

**Inhaled Partial Pressure**

A high PI delivered from the anesthetic machine is required during initial administration of the anesthetic. A high initial input offsets the impact of uptake, accelerating induction of anesthesia as reflected by the rate of rise in the Pa and thus the P\textsubscript{BRAIN}. With time, as uptake into the blood decreases, the PI should be decreased to match the decreased anesthetic uptake and therefore maintain a constant and optimal P\textsubscript{BRAIN}. If the PI is maintained constant

<table>
<thead>
<tr>
<th>Factors Determining Partial Pressure Gradients Necessary for Establishment of Anesthesia</th>
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<tr>
<td><strong>Transfer of inhaled anesthetic from anesthetic machine to alveoli (anesthetic input)</strong></td>
</tr>
<tr>
<td>Inspired partial pressure</td>
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<tr>
<td>Alveolar ventilation</td>
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<tr>
<td>Characteristics of anesthetic breathing system</td>
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<tr>
<td>Functional residual capacity</td>
</tr>
<tr>
<td><strong>Transfer of inhaled anesthetic from alveoli to arterial blood (anesthetic loss)</strong></td>
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<tr>
<td>Blood:gas partition coefficient</td>
</tr>
<tr>
<td>Cardiac output</td>
</tr>
<tr>
<td>Alveolar-to-venous partial pressure difference</td>
</tr>
<tr>
<td><strong>Transfer of inhaled anesthetic from arterial blood to brain (anesthetic loss)</strong></td>
</tr>
<tr>
<td>Brain:blood partition coefficient</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>Arterial-to-venous partial pressure difference</td>
</tr>
</tbody>
</table>
with time, the \( P_a \) and \( P_{\text{BRAIN}} \) will increase progressively as uptake diminishes.

**Concentration Effect**

The impact of PI on the rate of rise of the \( P_a \) of an inhaled anesthetic is known as the *concentration effect* (Fig. 4-7).\(^{25}\) The concentration effect states that the higher the PI, the more rapidly the \( P_a \) approaches the PI. The higher PI provides anesthetic molecule input to offset uptake and thus speeds the rate at which the \( P_a \) increases.

The concentration effect results from (a) a concentrating effect and (b) an augmentation of tracheal inflow.\(^{26}\) The concentrating effect reflects concentration of the inhaled anesthetic in a smaller lung volume due to uptake of all gases in the lung. At the same time, anesthetic input via tracheal inflow is increased to fill the space (void) produced by uptake of gases.

**Second-Gas Effect**

The second-gas effect reflects the ability of high-volume uptake of one gas (first gas) to accelerate the rate of increase of the \( P_a \) of a concurrently administered "companion" gas (second gas) (Fig. 4-8).\(^{27}\) For example, the initial large-volume uptake of nitrous oxide accelerates the uptake of companion (second) gases such as oxygen and volatile anesthetics. This increased uptake of the second gas reflects increased tracheal inflow of all the inhaled gases (first and second gases) and higher concentration of the second gas or gases in a smaller lung volume (concentrating effect) due to the high-volume uptake of the first gas (Fig. 4-9).\(^{26}\) Conceptually, the loss of lung volume may be compensated for by decreased expired ventilation as well as increased inspired ventilation (increased tracheal inflow). The implication that extra gas is routinely drawn into the lungs to compensate for loss of lung volume is misleading if compensatory changes include decreased expired ventilation and/or a decrease in lung volume.\(^{28}\)

**Alveolar Ventilation**

Increased alveolar ventilation, like PI, promotes input of anesthetics to offset uptake. The net effect is a more rapid
rate of increase in the Pa toward the PI and thus induction of anesthesia. In addition to the increased input, the decreased PaCO₂ produced by hyperventilation of the lungs decreases cerebral blood flow. Conceivably, the impact of increased input on the rate of rise of the Pa would be offset by decreased delivery of anesthetic to the brain. Decreased alveolar ventilation decreases input and thus slows the establishment of a Pa and P_{BRAIN} necessary for the induction of anesthesia. The greater the alveolar ventilation to functional residual capacity (FRC) ratio, the more rapid is the rate of increase in the Pa. In neonates, this ratio is approximately 5:1 compared with only 1.5:1 in adults, reflecting the greater metabolic rate in neonates compared with adults. As a result, the rate of increase of Pa toward the PI and thus the induction of anesthesia is more rapid in neonates than in adults (Fig. 4-10).

**Spontaneous versus Mechanical Ventilation**

Inhaled anesthetics influence their own uptake by virtue of dose-dependent depressant effects on alveolar ventilation. This, in effect, is a negative feedback protective mechanism that prevents establishment of an excessive depth of anesthesia (delivery of anesthesia is decreased when ventilation is decreased) when a high PI is administered during spontaneous breathing (Fig. 4-11). As anesthetic input decreases in parallel with decreased ventilation, anesthetic present in tissues is redistributed from tissues in which it is present in high concentrations (brain) to other tissues in which it is present in low concentrations (skeletal muscles). When the concentration (partial pressure) in the brain decreases to a certain threshold, ventilation increases and delivery of the anesthetic to the lungs increases. This protective mechanism against development of an excessive depth of anesthesia (anesthetic overdose) is lost when mechanical ventilation of the lungs replaces spontaneous breathing.

**Impact of Solubility**

The impact of changes in alveolar ventilation on the rate of increase in the Pa toward the PI depends on the solubility of the anesthetic in blood. For example, changes in alveolar ventilation influence the rate of increase of the
The solubility of the inhaled anesthetics in blood and tissues is denoted by the partition coefficient (Table 4-3). A partition coefficient is a distribution ratio describing how the inhaled anesthetic distributes itself between two phases at equilibrium (partial pressures equal in both phases). For example, a blood:gas partition coefficient of 0.5 means that the concentration of inhaled anesthetic in the blood is half that present in the alveolar gases when the partial pressures of the anesthetic in these two phases is identical. Similarly, a brain:blood partition coefficient of 2 indicates a concentration of anesthetic in the brain is twice that in the blood when the partial pressures of anesthetic are identical at both sites.

Partition coefficients may be thought of as reflecting the relative capacity of each phase to accept anesthetic. Partition coefficients are temperature dependent such that the solubility of a gas in a liquid is decreased when the temperature of the liquid increases.

### Blood:Gas Partition Coefficients

The rate of increase of the Pa toward the PI (maintained constant by mechanical ventilation of the lungs) is inversely related to the solubility of the anesthetic in blood (see Fig. 4-3). Based on their blood:gas partition coefficients, inhaled anesthetics are categorized traditionally as soluble, intermediately soluble, and poorly soluble (see Table 4-3). Blood can be considered a pharmacologically inactive reservoir, the size of which is determined by the solubility of the anesthetic in blood. When the blood:gas partition coefficient is high, a large amount of anesthetic must be dissolved in the blood before the Pa equilibrates.
with the Pa. For example, the high blood solubility of methoxyflurane slows the rate at which the Pa and Pa increase relative to the PI, and the induction of anesthesia is slow. The impact of high blood solubility on the rate of increase of the Pa can be offset to some extent by increasing the PI above that required for maintenance of anesthesia. This is termed the overpressure technique and may be used to speed the induction of anesthesia, recognizing that sustained delivery of a high PI will result in an anesthetic overdose.

When blood solubility is low, minimal amounts of inhaled anesthetic must be dissolved before equilibration is achieved; therefore, the rate of increase of Pa and Pa, and thus onset-of-drug effects such as the induction of anesthesia, are rapid. For example, the inhalation of a constant PI of nitrous oxide, desflurane, or sevoflurane for about 10 minutes results in a Pa that is \( \geq 80\% \) of the PI (see Fig. 4-3).\(^{32}\)\(^{33}\) Use of an overpressure technique with sevoflurane is more readily accepted by patients because this anesthetic is less pungent than desflurane. Indeed, one or more vital capacity breaths of high concentrations of sevoflurane (7% with 66% nitrous oxide) may result in loss of the eyelash reflex.\(^{34}\)

Associated with the rapid increase in the Pa of nitrous oxide is the absorption of several liters (up to 10 L during the first 10 to 15 minutes) of this gas, reflecting its common administration at inhaled concentrations of 60% to 70%. This high-volume absorption of nitrous oxide is responsible for several unique effects of nitrous oxide when it is administered in the presence of volatile anesthetics or air-containing cavities (see the sections "Concentration Effect," "Second-Gas Effect," and "Nitrous Oxide Transfer to Closed Gas Spaces").

Percutaneous loss of inhaled anesthetics occurs but is too small to influence the rate of increase in the Pa.\(^{35}\) With the possible exception of methoxyflurane, the magnitude of metabolism of inhaled anesthetics is too small to influence the rate of increase of the Pa. This lack of effect reflects the large excess of anesthetic molecules administered and the saturation, by anesthetic concentrations of inhaled drugs, of enzymes responsible for anesthetic metabolism.\(^{36}\)

Blood:gas partition coefficients are altered by individual variations in water, lipid, and protein content and by the hematocrit of whole blood.\(^{37}\)\(^{38}\) For example, blood:gas partition coefficients are about 20% less in blood with a hematocrit of 21% compared with blood with a hematocrit of 43%. Presumably, this decreased solubility reflects the decrease in lipid-dissolving sites normally provided by erythrocytes. Conceivably, decreased solubility of volatile anesthetics in anemic blood would manifest as an increased rate of increase in the Pa and a more rapid induction of anesthesia. Ingestion of a fatty meal alters the composition of blood, resulting in an approximately 20% increase in the solubility of volatile anesthetics in blood.\(^{39}\)

The solubility of inhaled anesthetics in blood varies with age (Fig. 4-12).\(^{40}\) The blood solubilities of halothane, enfurane, methoxyflurane, and isofluorane are about 18% less in neonates and the elderly compared to young adults. In contrast, the solubility of the less soluble anesthetic sevoflurane (presumably also true for desflurane) is not different in neonates and adults.\(^{41}\)

**Tissue:Blood Partition Coefficients**

Tissue:blood partition coefficients determine uptake of anesthetic into tissues and the time necessary for equilibration of tissues with the Pa. This time for equilibration can be estimated by calculating a time constant (amount of inhaled anesthetic that can be dissolved in the tissue divided by tissue blood flow) for each tissue. One time constant on an exponential curve represents 63% equilibration. Three time constants are equivalent to 95% equilibration. For volatile anesthetics, equilibration between the Pa and \( P_{\text{BRAIN}} \) depends on the anesthetic’s blood solubility and requires 5 to 15 minutes (three time constants). Fat has an enormous capacity to hold anesthetic, and this characteristic, combined with low blood flow to this tissue, prolongs the time required to narrow anesthetic partial pressure differences between arterial blood and fat. For example, equilibration of fat with isoflurane (three time constants) based on this drug's fat:blood partition coefficient and an assumed fat blood flow of 2 to 3 mL per minute per 100 g fat is estimated to be 25 to 46 hours. Fasting before elective operations results in transport of fat to the liver, which could increase anesthetic uptake by this organ and modestly slow the rate of increase in the Pa of a volatile anesthetic during induction of anesthesia.\(^{42}\)

**Oil:Gas Partition Coefficients**

Oil:gas partition coefficients parallel anesthetic requirements. For example, an estimated MAC can be calculated as 150 divided by the oil:gas partition coefficient. The constant, 150, is the average value of the product of oil:gas partition coefficients and the blood solubility.
solubility and MAC for several inhaled anesthetics with widely divergent lipid solubilities. Using this constant, the calculated MAC for a theoretical anesthetic with an oil:gas partition coefficient of 100 would be 1.5%.

**Nitrous Oxide Transfer to Closed Gas Spaces**

The blood-gas partition coefficient of nitrous oxide (0.46) is about 34 times greater than that of nitrogen (0.014). This differential solubility means that nitrous oxide can leave the blood to enter an air-filled cavity 34 times more rapidly than nitrogen can leave the cavity to enter blood. As a result of this preferential transfer of nitrous oxide, the volume or pressure of an air-filled cavity increases. Passage of nitrous oxide into an air-filled cavity surrounded by a compliant wall (intestinal gas, pneumothorax, pulmonary blebs, air bubbles) causes the gas space to expand (Fig. 4-13). Conversely, passage of nitrous oxide into an air-filled cavity surrounded by a noncompliant wall (middle ear, cerebral ventricles, supratentorial space) causes an increase in intracavitary pressure.

The magnitude of volume or pressure increase is influenced by (a) partial pressure of nitrous oxide, (b) blood flow to the air-filled cavity, and (c) duration of nitrous oxide administration. In an animal model, the inhalation of 75% nitrous oxide doubles the volume of a pneumothorax in 10 minutes (see Fig. 4-7). The finding emphasizes the high blood flow to this area. Likewise, air bubbles (emboli) expand rapidly when exposed to nitrous oxide (Fig. 4-14). Nevertheless, in neurosurgical patients operated on in the sitting position, 50% nitrous oxide has no measurable effect on the incidence or severity of venous air embolism if its administration is discontinued immediately upon Doppler detection of venous air embolism. In contrast to the rapid expansion of a pneumothorax, the increase in bowel gas volume produced by nitrous oxide is slow but can result in an increase in distention and postoperative pain after a 3-hour surgery.

The middle ear is an air-filled cavity that vents passively via the Eustachian tube when pressure reaches 20 to 30 cm H₂O. Nitrous oxide diffuses into the middle ear more rapidly than nitrogen leaves, and middle ear pressures may increase if Eustachian tube patency is compromised by inflammation or edema. Indeed, tympanic membrane rupture has been attributed to this mechanism after administration of nitrous oxide. Negative middle ear pressures may develop after discontinuation of nitrous oxide, leading to serous otitis. Nausea and vomiting that may follow general anesthesia may be due to multiple mechanisms, but the role of altered middle ear pressures as a result of nitrous oxide is a consideration.

Intraocular gas bubbles as used for internal retinal tamponade (retinal detachment, macular hole repair, complicated vitrectomy) may persist in the eye for up to 10 weeks following ocular surgery. Administration of nitrous oxide for periods as brief as 1 hour during this time period may result in rapid increases in the volume of intraocular gas within the rigid closed eye that is sufficient to compress the retinal artery with resulting visual loss.

**Cardiopulmonary Bypass**

Cardiopulmonary bypass produces changes in blood-gas solubility that depend on the constituents of the priming solution and temperature. Nevertheless, the overall effect of hypothermic cardiopulmonary bypass and a crystalloid prime on blood-gas solubility is only 2%. Volatile anesthetics initiated during cardiopulmonary bypass take longer to equilibrate, whereas the same drugs...
already present when cardiopulmonary bypass is initiated are diluted, potentially decreasing the depth of anesthesia.

**Cardiac Output**

Cardiac output (pulmonary blood flow) influences uptake and therefore Pa by carrying away either more or less anesthetic from the alveoli. An increased cardiac output results in more rapid uptake, so the rate of increase in the Pa and thus the induction of anesthesia are slowed. A decreased cardiac output speeds the rate of increase of the Pa, because there is less uptake to oppose input.

The effect of cardiac output on the rate of increase in the Pa may seem paradoxical. For example, the uptake of more drugs by an increased cardiac output should speed the rate of increase of partial pressures in tissues and thus narrow the A-vD for anesthetics. Indeed, an increase in cardiac output does hasten equilibration of tissue anesthetic partial pressures with the Pa. Nevertheless, the Pa is lower than it would be if cardiac output were normal. Conceptually, a change in cardiac output is analogous to the effect of a change in solubility. For example, doubling cardiac output increases the capacity of blood to hold anesthetic, just as solubility increases the capacity of the same volume of blood.

As with alveolar ventilation, changes in cardiac output most influence the rate of increase of the Pa of a soluble anesthetic. Conversely, the rate of increase of the Pa of a poorly soluble anesthetic, such as nitrous oxide, is rapid regardless of physiologic deviations of the cardiac output around its normal value. As a result, changes in cardiac output exert little influence on the rate of increase of the Pa of nitrous oxide. In contrast, doubling the cardiac output will greatly increase the uptake of soluble anesthetic from alveoli, slowing the rate of increase of the Pa. Conversely, a low cardiac output, as with shock, could produce an unexpectedly high Pa of a soluble anesthetic.

Volatile anesthetics that depress cardiac output can exert a positive feedback response that contrasts with the negative (protective) feedback response on spontaneous breathing exerted by these drugs. For example, decreases in cardiac output due to an excessive dose of volatile anesthetic results in an increase in the Pa, which further increases anesthetic depth and thus cardiac depression. The administration of a volatile anesthetic that depresses cardiac output, plus controlled ventilation of the lungs, results in a situation characterized by unopposed input of anesthetic via alveolar ventilation combined with decreased uptake because of decreased cardiac output. The net effect of this combination of events can be an unexpected, abrupt increase in the Pa and an excessive depth of anesthesia.

Distribution of cardiac output will influence the rate of increase of the Pa of an anesthetic. For example, increases in cardiac output are not necessarily accompanied by proportional increases in blood flow to all tissues. Preferential perfusion of vessel-rich group tissues when the cardiac output increases results in a more rapid increase in the Pa of anesthetic than would occur if the increased cardiac output was distributed equally to all tissues. Indeed, infants have a relatively greater perfusion of vessel-rich group tissues than do adults and, consequently, show a faster rate of increase of the Pa toward the PI (see Fig. 4-10).

**Impact of a Shunt**

In the absence of an intracardiac or intrapulmonary right-to-left shunt, it is valid to assume that the Pa and Pa of inhaled anesthetics are essentially identical. When a right-to-left shunt is present, the diluting effect of the shunted blood on the partial pressure of anesthetic in blood coming from ventilated alveoli results in a decrease in the Pa and a slowing in the induction of anesthesia. Monitoring the end-tidal concentration of anesthetic or carbon dioxide reveals a gradient between the Pa and Pa in which the Pa underestimates the Pa. A similar mechanism is responsible for the decrease in Pao2 and the gradient between the Pa and Pa in the presence of a right-to-left shunt.

The relative impact of a right-to-left shunt on the rate of increase in the Pa depends on the solubility of the anesthetic. For example, a right-to-left shunt slows the rate of increase of the Pa of a poorly soluble anesthetic more than that of a soluble anesthetic. This occurs because uptake of a soluble anesthetic offsets dilutional effects of shunted blood on the Pa. Uptake of a poorly soluble drug is minimal, and dilutional effects on the Pa are relatively unopposed. This impact of solubility in the presence of a right-to-left shunt is opposite to that observed with changes in cardiac output and alveolar ventilation. All factors considered, it seems unlikely that a right-to-left shunt alone will alter the speed of induction of anesthesia significantly.

Left-to-right tissue shunts (arteriovenous fistulas, volatile anesthetic–induced increases in cutaneous blood flow) result in delivery to the lungs of blood containing a higher partial pressure of anesthetic than that present in blood that has passed through tissues. As a result, left-to-right shunts offset the dilutional effects of a right-to-left shunt on the Pa. Indeed, the effect of a left-to-right shunt on the rate of increase in the Pa is detectable only if there is a concomitant presence of a right-to-left shunt. Likewise, the effect of a right-to-left shunt on the rate of increase in the Pa is maximal in the absence of a left-to-right shunt.

**Alveolar-to-venous Partial Pressure Differences**

The A-vD reflects tissue uptake of the inhaled anesthetic. Tissue uptake affects uptake at the lung by controlling the rate of increase of the mixed venous partial pressure of anesthetic. Factors that determine the fraction of anesthetic removed from blood traversing a tissue parallel those factors that determine uptake at the lungs (tissue solubility, tissue blood flow, and arterial-to-tissue partial pressure differences).
Highly perfused tissues (brain, heart, kidneys) in the adult account for <10% of body mass but receive 75% of the cardiac output (Table 4-4). As a result of the small mass and high blood flow, these tissues, known as vessel-rich group tissues, equilibrate rapidly with the Pa. Indeed, after about three time constants, approximately 75% of the returning venous blood is at the same partial pressure as the Pa. For this reason, uptake of a volatile anesthetic is decreased greatly after three time constants (5 to 15 minutes, depending on the blood solubility of the inhaled anesthetic), as reflected by a narrowing of the inspired-to-alveolar partial pressure difference. Continued uptake of anesthetic after saturation of vessel-rich group tissues reflects principally the entrance of anesthetic into skeletal muscles and fat. Skeletal muscles and fat represent about 70% of the body mass but receive only about 25% of the cardiac output (see Table 4-4). As a result of the large tissue mass, sustained tissue uptake of the inhaled anesthetic continues and the effluent venous blood is at a lower partial pressure than the Pa. For this reason, the A-vD difference for anesthetic is maintained and uptake from the lungs continues, even after several hours of continuous administration of inhaled anesthetics.

The time for equilibration of vessel-rich group tissues is more rapid for neonates and infants than for adults. This difference reflects the greater cardiac output to vessel-rich group tissues in the very young as well as decreased solubility of anesthetics in the tissues of neonates. Furthermore, skeletal muscle bulk comprises a small fraction of body weight in neonates and infants.

**Table 4-4**

<table>
<thead>
<tr>
<th>Body Tissue Composition</th>
<th>Body Mass (% of 70-kg Adult)</th>
<th>Blood Flow (% of Cardiac Output)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel-rich group</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>Muscle group</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>Fat group</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Vessel-poor group</td>
<td>20</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Recovery from Anesthesia

Recovery from anesthesia is depicted by the rate of decrease in the Pa (Fig. 4-15). The rate of washout of anesthetic from the brain should be rapid because inhaled anesthetics are not highly soluble in brain and the brain receives a large fraction of the cardiac output. Although similarities exist between the rate of induction and recovery, as reflected by changes in the Pa of the inhaled anesthetic, there are important differences between the two events. In contrast to induction of anesthesia, which may be accelerated by the concentration effect, it is not possible to speed the decrease in Pa by this mechanism (you cannot administer less than zero). Furthermore, at the conclusion of every anesthetic, the concentration of the inhaled anesthetic in tissues depends highly on the solubility of the inhaled drug and the duration of its administration. This contrasts with tissue concentrations of zero at the initiation of induction of anesthesia. The failure of certain tissues to reach equilibrium with the Pa of the inhaled anesthetic during maintenance of anesthesia means that the rate of decrease of the Pa during recovery from anesthesia will be more rapid than the rate of increase of the Pa during induction of anesthesia (see Figs. 4-3 and 4-15). Indeed, even after a prolonged anesthetic, skeletal muscles probably, and fat almost certainly, will not have equilibrated with the Pa of the inhaled anesthetic. Thus, when the PI of an anesthetic is abruptly decreased to zero at the conclusion of an anesthetic, these tissues initially cannot contribute to the transfer of drug back to blood for delivery to the liver for metabolism or to the lungs for exhalation. As long as gradients exist between the Pa and tissues, the tissues will continue to take up anesthetic. Thus, during recovery from anesthesia, the continued passage of anesthetic from blood to tissues, such as fat, acts to speed the rate of decrease in the Pa of that anesthetic. Continued tissue uptake of anesthetic will depend on the solubility of the inhaled anesthetic and the duration of anesthesia, with the impact being most

![FIGURE 4-15](https://example.com/figure415)
important with soluble anesthetics.\textsuperscript{49} For example, time to recovery is prolonged in proportion to the duration of anesthesia for soluble anesthetics (halothane and isoflurane), whereas the impact of duration of administration on time to recovery is minimal with poorly soluble anesthetics (sevoflurane and desflurane) (Fig. 4-16).\textsuperscript{1}

Anesthetic that has been absorbed into the components of the anesthetic breathing system will pass from the components back into the gases of the breathing circuit at the conclusion of anesthesia and retard the rate of decrease in the \( P_a \) of the anesthetic. Likewise, exhaled gases of the patient contain anesthetic that will be rebreathed unless fresh gas flow rates are increased (at least 5 L per minute of oxygen) at the conclusion of anesthesia.

In contrast to the rate of increase of the \( P_a \) during induction of anesthesia, the rate of decrease in the \( P_a \) during recovery from anesthesia is not entirely consistent with what might be predicted from the inhaled anesthetic’s blood:gas partition coefficient (Fig. 4-17).\textsuperscript{50,51} For example, the \( P_a \) for halothane decreases more rapidly than that for isoflurane and enfurane despite the greater blood solubility of halothane. Similarly, the \( P_a \) of methoxyflurane decreases below that of enfurane even though methoxyflurane is about six times more soluble in blood than is enfurane. The more rapid decrease in the \( P_a \) for halothane and methoxyflurane is, in large part, due to the metabolism of these drugs in the liver\textsuperscript{50,51} (see Chapter 2). This suggests that metabolism can significantly influence the rate of recovery from halothane and methoxyflurane anesthesia. In contrast, the rate of induction of anesthesia is not influenced by the magnitude of metabolism even for drugs such as halothane and methoxyflurane.

**Context-Sensitive Half-Time**

The pharmacokinetics of the elimination of inhaled anesthetics depends on the length of administration and the blood-gas solubility of the inhaled anesthetic. As with injected anesthetics, it is possible to use computer simulations to determine context-sensitive half-times for volatile anesthetics. In this regard, the time needed for a 50% decrease in anesthetic concentration of enfurane, isoflurane, desflurane, and sevoflurane is <5 minutes and does not increase significantly with increasing duration of anesthesia.\textsuperscript{52} Presumably, this is a reflection of the initial phase of elimination, which is primarily a function of alveolar ventilation. Determination of other decrement times (80% and 90%) reveals differences between various inhaled anesthetics. For example, the 80% decrement times of desflurane and sevoflurane are <8 minutes and do not increase significantly with the duration of anesthesia, whereas 80% decrement times for enfurane and isoflurane increase significantly after about 60 minutes, reaching plateaus of approximately 30 to 35 minutes. The 90% decrement time of desflurane increases slightly from 5 minutes after 30 minutes of anesthesia to 14 minutes after 6 hours of anesthesia, which is significantly less than sevoflurane (65 minutes), isoflurane (86 minutes), and enfurane (100 minutes) after 6 hours of administration. Based on the simulated context-sensitive half-times and assuming that MAC-awake is 0.5 MAC, there would be little difference in recovery time among these volatile anesthetics when a pure inhalation anesthetic technique is
used. The major differences in the rates at which desflurane, sevoflurane, isoflurane, and enflurane are eliminated occur in the final 20% of the elimination process.

### Diffusion Hypoxia

**Diffusion hypoxia** occurs when inhalation of nitrous oxide is discontinued abruptly, leading to a reversal of partial pressure gradients such that nitrous oxide leaves the blood to enter alveoli.\(^5\) This initial high-volume outpouring of nitrous oxide from the blood into the alveoli can so dilute the PaO\(_2\) that the PaO\(_2\) decreases. In addition to dilution of the PaO\(_2\) by nitrous oxide, there is also dilution of the PaCO\(_2\), which decreases the stimulus to breathe.\(^5\) This decreased stimulus to breathe exaggerates the impact on PaO\(_2\) of the outpouring of nitrous oxide into the alveoli. Outpouring of nitrous oxide into alveoli is greatest during the first 1 to 5 minutes after its discontinuation at the conclusion of anesthesia. Thus, it is common practice to fill the lungs with oxygen at the end of anesthesia to ensure that arterial hypoxemia will not occur as a result of dilution of the PaO\(_2\) by nitrous oxide.

### Pharmacodynamics of Inhaled Anesthetics

#### Minimal Alveolar Concentration

MAC of an inhaled anesthetic is defined as that concentration at 1 atmosphere that prevents skeletal muscle movement in response to a supramaximal painful stimulus (surgical skin incision) in 50% of patients.\(^5\) MAC is an anesthetic 50% effective dose (ED\(_{50}\)). Immobility produced by inhaled anesthetics as measured by MAC is mediated principally by effects of these drugs on the spinal cord and only a minor component of immobility results from cerebral effects.\(^5\) For example, in animals, MAC for isoflurane is 1.2% when delivered to the intact animal but delivery of inhaled anesthetic only to the brain results in isoflurane MAC increasing to nearly 3%.\(^5\) Further evidence that MAC reflects effects of the inhaled anesthetics at the spinal cord is the observation that decerebration does not change MAC (Fig. 4-18).\(^5\)

MAC is among the most useful concepts in anesthetic pharmacology as it establishes a common measure of potency (partial pressure at steady state) for inhaled anesthetics. This concept is used to provide uniformity in dosages of inhaled anesthetics, to establish relative amounts of inhaled anesthetics to reach specific endpoints (MAC\(_{awake}\)), and to guide the search for mechanisms responsible for mechanisms of anesthetic action.\(^5\) A unique feature of MAC is its consistency varying only 10% to 15% among individuals. This small degree of pharmacodynamic variability for inhaled anesthetics is unique in pharmacology. The use of equally potent doses (comparable MAC concentrations) of inhaled anesthetics is mandatory for comparing effects of these drugs not only at the spinal cord but also at all other organs (Table 4-5). For example, similar MAC concentrations of inhaled anesthetics produce equivalent depression of the spinal cord, whereas effects on cardiopulmonary parameters may be different for each drug (see Chapter 2). This emphasizes that MAC represents only one point on the dose-response curve of effects produced by inhaled anesthetics and that these dose-response curves are not parallel. It is remarkable though that MAC\(_{awake}\), the concentration of anesthetic that prevents consciousness in 50% of persons, is reliably about half of MAC and that MAC\(_{memory}\), the concentration of anesthetic that is associated with amnesia in 50% of patients, is significantly less than MAC\(_{awake}\). If this were not the case, an ED\(_{50}\) would not be satisfactory endpoint for clinical anesthesia! A surgeon may tolerate 50% of his or her patients moving but having 50% of patients have awareness under anesthesia would clearly not be acceptable.

### Table 4-5

<table>
<thead>
<tr>
<th>Comparative Minimum Alveolar Concentration of Inhaled Anesthetics</th>
<th>MAC (%)</th>
<th>30 to 55 Years Old at 37°C, Pn 760 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide*</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>Desflurane</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Xenon</td>
<td>63–71</td>
<td></td>
</tr>
</tbody>
</table>

* Determined in a hyperbaric chamber in males 21 to 55 years old.

MAC, minimum alveolar concentration
Factors that Alter Minimal Alveolar Concentration

Inhalation anesthetic requirements are remarkably uniform in humans, mainly being affected by age and body temperature. MAC allows a quantitative analysis of the effect, if any, of various physiologic and pharmacologic factors on anesthetic requirements (Table 4-6). For example, increasing age results in a progressive decrease in MAC of about 6% per decade that is similar for all inhaled anesthetics (Figs. 4-19 and 4-20). MAC is decreased nearly 30% in the early postpartum period, returning to normal 24–72 hours postpartum.

### Table 4-6

Impact of Physiologic and Pharmacologic Factors on Minimum Alveolar Concentration

<table>
<thead>
<tr>
<th>Increases in MAC</th>
<th>Decreases in MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Excess pheomelanin production (red hair)</td>
<td>Increasing age</td>
</tr>
<tr>
<td>Drug-induced increases in central nervous system catecholamine levels</td>
<td>Preoperative medication</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Drug-induced decreases in central nervous system catecholamine levels</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>( \alpha )-2 agonists</td>
</tr>
<tr>
<td>Drug-induced increases in central nervous system catecholamine levels</td>
<td>Acute alcohol ingestion</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Postpartum (returns to normal in 24–72 hours)</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Lithium</td>
<td>No change in MAC</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Anesthetic metabolism</td>
</tr>
<tr>
<td>Neuraxial opioids (?)</td>
<td>Chronic alcohol abuse</td>
</tr>
<tr>
<td>Ketanserin</td>
<td>Duration of anesthesia (?)</td>
</tr>
<tr>
<td>( P_{O_2} ) &lt;38 mm Hg</td>
<td>( P_{O_2} ) 15–95 mm Hg</td>
</tr>
<tr>
<td>Blood pressure &lt;40 mm Hg</td>
<td>( P_{O_2} ) &gt;38 mm Hg</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>Hyperkalemia or hypokalemia</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Thyroid gland dysfunction</td>
</tr>
</tbody>
</table>

MAC, minimum alveolar concentration.
ies showing a decrease, whereas others fail to demonstrate any change. Despite prolongation of sleeping times in animals, cyclosporine increases rather than decreases isoflurane MAC. MAC is defined by the response to a surgical incision, which is considered to be a supramaximal stimulus. MAC values may vary with the type of stimulus; tetanic stimulation and trapezius squeeze are considered noninvasive stimulation patterns that are relatively equivalent to surgical skin incision, although in contrast to skin incision, these events can be repeated (Fig. 4-24).

Tracheal intubation requires the highest MAC to prevent skeletal muscle responses and may represent a true supramaximal stimulation (see Fig. 4-24). MAC values for inhaled anesthetics are additive. For example, 0.5 MAC of nitrous oxide plus 0.5 MAC isoflurane has the same effect at the brain as does a 1 MAC concentration of either anesthetic alone. The strict additivity of the interactions among inhaled anesthetics implies either a common site of action or that anesthetic action occurs with only a small fraction of the binding sites occupied.

Opioids synergistically decrease anesthetic requirements for volatile anesthetics. For example, 25 minutes after the administration of fentanyl, 3 μg/kg or 6 μg/kg IV, MAC for desflurane is decreased 48% and 68%, respectively. Similar decreases in isoflurane MAC are also produced by these doses of fentanyl.

Dose-response curves for inhaled anesthetics, although not parallel, are all steep. This is emphasized by the fact that a 1 MAC dose prevents skeletal muscle movement in response to a painful stimulus in 50% of patients, whereas a modest increase to about 1.3 MAC prevents movement in at least 95% of patients.
Evidence supporting distortion of sodium channels by dissolved anesthetic molecules is the observation that high pressures (40 to 100 atm) partially antagonize the action of inhaled anesthetics (pressure reversal), presumably by returning (compressing) lipid membranes and their sodium channels to their "awake" contour.\textsuperscript{76}

The most compelling evidence against the Meyer-Overton theory of anesthesia is the fact that effects of inhaled anesthetics on the fluidity of lipid bilayers is implausibly small and can generally be mimicked by temperature changes of 1°C.\textsuperscript{77} Furthermore, not all lipid-soluble drugs are anesthetics, and, in fact, some are convulsants. For example, the observation that, among \textit{n}-alkanes, \textit{n}-decanol is anesthetic and decanol is not (for \textit{n}-alkanes the cutoff is after octane) suggests that anesthetic binding to protein pockets or clefts and not lipid membranes is important in the mechanism of anesthesia. Based on these negative observations, lipid theories have been refined to postulate that specialized domains in membranes (boundary membranes surrounding proteins) are not only particularly sensitive to anesthetics but also are critical to membrane function. Indeed, either binding to proteins or dissolving in lipids can account for the Meyer-Overton correlation.

\textbf{Stereoselectivity}

The effects of inhaled anesthetics on ion channels responsible for neuronal action are readily demonstrated (Fig. 4-25).\textsuperscript{77} The most definitive evidence that general anesthetics act by binding directly to proteins and not a lipid bilayer comes from observations of stereoselectivity.\textsuperscript{78} Inhalation anesthetics exist as isomers, and isoflurane has been shown to act stereoselectively on neuronal channels, with the levoisomer being more potent than the diastereoisomer.
dextroisomer in enhancing potassium conductance in neurons\textsuperscript{29} and in with respect to the loss of righting reflex in animals.\textsuperscript{80} The relevance to anesthetic mechanisms of the differing effects of enantiomers of volatile anesthetics on in vitro nerve conduction would be supported by parallel changes in MAC in the intact animal. Indeed, in rats, MAC for the levoisomer of isoflurane was 60\% more potent than the dextroisomer.\textsuperscript{81} In contrast, others have not found a significant difference in the effects of the enantiomers of desflurane or desflurane on anesthetic effects in animals.\textsuperscript{82} Receptor specificity is also suggested by conversion of an anesthetic to a nonanesthetic by increasing the molecular volume, despite corresponding increases in lipid solubility. Nevertheless, there is evidence that molecular shape (bulkiness) and size provide limited insight into the structure of the anesthetic site of action.\textsuperscript{83}

Potential Mediators of Anesthetic Action

Ionotropic and Metabotropic Receptors

Neurotransmitters signal through two families of receptors designated as ionotropic and metabotropic. Ionotropic receptors are also known as ligand-gated ion channels because the neurotransmitter binds directly to ion channel proteins and this interaction causes opening (gating) of the ion channels allowing transmission of specific ions resulting in changes in membrane potential. Ionotropic receptors are often composed of several subunits. Indeed the GABA\textsubscript{A} and nicotinic acetylcholine receptors are constructed from large families of evolutionarily related subunits that come together to make pleiomorphic receptors. In contrast, metabotropic receptors are usually monomeric receptors consisting of seven transmembrane segments. Binding of neurotransmitters (acetylcholine) to metabotropic receptors causes activation of guanosine triphosphate binding proteins (G proteins) associated with the receptors, and these G proteins act as second messengers to activate other signaling molecules such as protein kinases, or potassium or calcium channels.\textsuperscript{56}

Inhaled anesthetics do not seem to stimulate the release of endogenous opioids and do not suppress autonomic or ventilatory responses to surgical stimulation at concentrations that suppress movement. The fact that small doses of opioids decrease MAC reflects their ability to provide an effect (analgesia) that is not present with inhaled anesthetics alone.

Inhibitory Ligand-Gated and Voltage-Gated Channels (Glycine and GABA\textsubscript{A} Receptors)

Glycine receptors are major mediators of inhibitory neurotransmission in the spinal cord and may mediate part of the immobility produced by inhaled anesthetics.\textsuperscript{84} Their spinal localization and potentiation by volatile anesthetics at clinical concentrations is consistent with their being a target for mediating immobility as defined by MAC. Intravenous and intrathecal administration of strychnine, a glycine receptor antagonist increases MAC. However, glycine is a nonspecific stimulant. An argument in favor of a role for glycine receptor potentiation in mediating MAC is the fact that strychnine only reverses the effect of ketamine (which does not affect glycinergic currents) to a threshold while it affects dose dependent reversal of volatile anesthetic effect.

Although β3-subunit containing GABA\textsubscript{A} receptors mediate hypnosis and part of the immobility produced by injected anesthetics (propofol, etomidate),\textsuperscript{85} there is evidence that GABA\textsubscript{A} receptors do not mediate immobility produced by inhaled anesthetics. In this regard, although GABA\textsubscript{A} receptors are potentiated at MAC concentrations of all clinically used volatile anesthetics, their enhancement of GABA\textsubscript{A} receptor activation minimally influences MAC.\textsuperscript{86}

Glutamate (NMDA, AMPA, and Kainate Receptors)

Inhaled anesthetics decrease excitatory neurotransmission in the CNS. Glutamate is the principal excitatory neurotransmitter in the mammalian CNS. Glutamate receptors include G protein–coupled receptors and the ligand-gated receptors (NMDA, AMPA, and kainate). NMDA receptors may mediate some important behavioral effects of inhaled anesthetics. Volatile anesthetics separate into two different classes in terms of their efficacy for NMDA blockade. At 1 MAC concentration, different volatile anesthetics inhibit NMDA receptors by between 12\% and 74\% with those anesthetics having cation–π interactions having the greatest NMDA blockade.\textsuperscript{87}

Two-Pore Potassium Channels

Two-pore potassium channels are intrinsic membrane receptor/ion channels that normally act to maintain the cell's resting potential and responds to internal stimuli such as a change in pH. Several members of this family have been recently found to be sensitive to volatile anesthetics at clinically used concentrations. TREK and TASK channel activity is potentiated by volatile anesthetics in an agent-specific manner.\textsuperscript{88} TASK-3 receptors are anesthetic sensitive receptor that play a role in maintaining theta oscillations in the EKG that are associated with anestheisa and natural deep sleep.\textsuperscript{89}

Voltage-Gated Sodium Channels

Despite the historical notion that inhaled anesthetics do not block axonal conduction and thus voltage-dependent sodium channels, it is now clear that there are many subtypes of sodium channels. Although sodium channels that mediate axonal conduction are not significantly effected at MAC concentrations of volatile anesthetics, those that modulate the release of neurotransmitter may be more sensitive to anesthetics. There is evidence that by interacting with specific subtypes of sodium channel that are expressed at the presynaptic junction, these drugs can inhibit the release of neurotransmitters, particularly glutamate.\textsuperscript{90}
Indeed, intravenous administration of lidocaine, which is a nonspecific sodium channel blocker, decreases MAC.

**Hyperpolarization-Activated Cyclic Nucleotide–Gated Channels**

Hyperpolarization-activated cyclic nucleotide–gated (HCN) channels are voltage-gated ion channels that are expressed throughout the body but are particularly important in regulating rhythmogenicity in heart and brain. There is some suggestion that halothane may affect HCN channels in motor neurons to induce anesthetic immobility.91

**Mechanism of Immobility**

MAC is based on the characteristic ability of inhaled drugs to produce immobility by virtue of actions of these drugs principally on the spinal cord rather than on higher centers.56 The observation that immobility during noxious stimulation does not correlate with electroencephalographic activity reflects the fact that cortical electrical activity does not control motor responses to noxious stimulation. Effects of inhaled anesthetics on the spinal cord leading to immobility are diverse. In this regard, inhaled anesthetics depress excitatory AMPA and NMDA receptor-mediated currents by actions independent of inhibitory GABA\(_A\) and glycine receptor-mediated currents. Actions on two-pore potassium channels may also be important in producing immobility. Conversely, cholinergic receptors do not seem to exert a significant role in anesthetic-induced immobility at the spinal cord level.92 Likewise, although opioids and stimulation of \(\alpha_2\) adrenergic receptors (clonidine) decrease MAC, it is unlikely that immobility produced by inhaled anesthetics is due to activation of these receptors.93 Inhaled anesthetics do not act via opioid receptors. Overall, no inhaled anesthetic action on a single group of receptors yet described can explain immobility, and immobility as a result of concurrent actions on many receptors is unlikely.56,93

**Mechanism of Anesthesia-Induced Unconsciousness**

A comprehensive explanation of the mechanism by which volatile anesthetics cause loss of consciousness (suppression of awareness) is not known.94 Hypnosis is typically studied in animal models as loss of righting reflex. In human studies, it can be measured as loss of response to command and in the presence of neuromuscular blockers the spared arm technique uses a tourniquet to block muscle relaxant access to an arm, which is then used to indicate consciousness. Subtle differences in the clinical effects of inhaled anesthetics may be attributed to distinct actions on a number of critical molecular targets. There is evidence that loss of consciousness (hypnosis), amnesia, and the response to skin incision (immobility as defined by MAC) are not a single continuum of increasing anesthetic depth but rather separate phenomena.95,96 Combining these two observations, it has been proposed that general anesthesia is a process requiring a state of unconsciousness of the brain (produced by volatile or injected anesthetics) plus immobility in response to a noxious stimulus (surgical skin incision) that is mediated by the action of volatile anesthetics on the spinal cord administered at concentrations equivalent to MAC for that drug.

It has been proposed that clinical anesthesia is a hierarchical process in which afferent sensory impulses are diminished by some drugs (opioids, regional anesthesia, ketamine) while the central activating systems are depressed by another mechanism and sometimes other drugs (benzodiazepines, barbiturates, propofol, etomidate, ketamine and volatile anesthetics) and motor reflexes are depressed by yet another mechanism (volatile anesthetics, propofol, etomidate, barbiturates). As defined by MAC, only agents which depress motor reflexes in addition to the other actions can be properly considered general anesthetics but many agents are able to provide one or the other behavioral outcome and can be used as part of a general anesthetic regimen. Volatile anesthetics have been called **total anesthetics** because they can be used as a single agent to provide general anesthesia. It was long assumed that they decreased pain transmission, but after more thorough consideration, it appears that volatile anesthetics have a biphasic dose response for nociceptive influences such that they are increased at very low volatile anesthetic concentrations (about 10% MAC) and they diminish thereafter.97

Presynaptic inhibition of neurotransmitter release may explain how certain inhaled anesthetics can inhibit synaptic transmission. Inhibition of neurotransmitter release by inhaled anesthetics appears to be mediated by inhibition of neurosecretion rather than by inhibition of transmitter synthesis or storage. The mechanism by which anesthetics act to inhibit neurotransmitter release might reflect actions at ion channels that regulate the probability of neurotransmitter release or could act on the machinery of release itself. As mentioned earlier, halogenated volatile anesthetics inhibit some types of sodium channels in native neurons and in heterologous expression systems.98 Although sodium channels can presynaptically modulate the release of both glutamate and GABA, their effect on the release of glutamate is greater than on the release of GABA.99

**Comparative Pharmacology of Gaseous Anesthetic Drugs**

Inhaled anesthetics evoke different pharmacologic effects at comparable percentages of MAC concentrations, emphasizing that dose-response curves for these drugs are not necessarily parallel. Measurements obtained from normothermic volunteers exposed to equal potent concentrations of inhaled anesthetics during controlled
ventilation of the lungs to maintain normocapnia have provided the basis of comparison for pharmacologic effects of these drugs on various organ systems. In this regard, it is important to recognize that surgically stimulated patients who have other confounding variables may respond differently than healthy volunteers (Table 4-7).

Desflurane and sevoflurane provide one specific advantage over other currently available potent inhaled anesthetics. Their lower blood and tissue solubility permit more precise control over the induction of anesthesia and a more rapid recovery when the drug is discontinued. Most of the other properties of these new volatile anesthetics resemble their predecessors, especially at concentrations of ≤1 MAC.

### Central Nervous System Effects

Mental impairment is not detectable in volunteers breathing 1,600 ppm (0.16%) nitrous oxide or 16 ppm (0.0016%) halothane. It is therefore unlikely that impairment of mental function in the personnel who work in the operating room using modern anesthetic scavenging techniques can result from inhaling trace concentrations of anesthetics. Reaction times do not increase significantly until 10% to 20% nitrous oxide is inhaled.

Cerebral metabolic oxygen requirements are decreased in parallel with drug-induced decreases in cerebral activity. Drug-induced increases in cerebral blood flow may increase intracranial pressure (ICP) in patients with space-occupying lesions. The effects of desflurane and sevoflurane on the CNS do not differentiate these inhaled anesthetics from the older inhaled drugs.

### Electroencephalogram

Volatile anesthetics in concentrations of <0.4 MAC similarly increase the frequency and voltage on the electroencephalogram (EEG). This enhancement is representative of the "excitement stage" of anesthesia. At about 0.4 MAC, there is an abrupt shift of high-voltage activity from posterior to anterior portions of the brain. Cerebral metabolic oxygen requirements also begin to decrease abruptly at about 0.4 MAC. It is likely that these changes reflect a transition from wakefulness to unconsciousness. Furthermore, amnesia probably occurs at this dose of volatile anesthetic. As the dose of volatile anesthetic approaches 1 MAC, the frequency on the EEG decreases and maximum voltage occurs. During administration of isoflurane, burst suppression appears on the EEG at about 1.5 MAC, and at 2 MAC, electrical silence predominates. Electrical silence does not occur with enflurane, and only acceptably high concentrations of halothane (>3.5 MAC) produce this effect. The effects of nitrous oxide on the EEG are similar to those produced by volatile anesthetics. Slower frequency and higher voltage develop on the EEG as the dose of nitrous oxide is increased or when nitrous oxide is added to a volatile anesthetic to provide a greater total MAC concentration.

Desflurane and sevoflurane cause dose-related changes in the EEG similar to those that occur with isoflurane. With desflurane, the EEG progresses from an initial increase in frequency and lowering of voltage at low anesthetic concentrations to increased voltage at anesthetizing concentrations. Higher concentrations of desflurane produce decreasing voltage and increasing periods of electrical silence with an isoelectric EEG at 1.5 to 2.0 MAC. The addition of nitrous oxide to a given level of anesthesia with desflurane causes little or no change in the EEG.

### Seizure Activity

Enflurane can produce fast frequency and high voltage on the EEG that often progresses to spike wave activity that is indistinguishable from changes that accompany a seizure. This EEG activity may be accompanied by tonic-clonic twitching of skeletal muscles in the face and extremities. The likelihood of enflurane-induced seizure activity is increased when the concentration of enflurane is >2 MAC or when hyperventilation of the lungs decreases the PACO₂ to <30 mm Hg. Repetitive auditory stimuli can also initiate seizure activity during the administration of enflurane. There is no evidence of anaerobic metabolism in the brain during seizure activity produced by enflurane. Furthermore, in an animal model, enflurane does not enhance preexisting seizure foci, with the possible exception being certain types of myoclonic epilepsy and photosensitive epilepsy.

Isoflurane does not evoke seizure activity on the EEG, even in the presence of deep levels of anesthesia, hypocapnia, or repetitive auditory stimulation. Indeed, isoflurane possesses anticonvulsant properties; it is able to suppress seizure activity produced by flurothyl. An undocumented speculation is that the greater MAC value for enflurane compared with its isomer, isoflurane, reflects the need for a higher concentration to suppress the stimulating effects of enflurane in the CNS.
Desflurane and sevoflurane, like isoflurane, do not produce evidence of convulsive activity on the EEG either at deep levels of anesthesia or in the presence of hypocapnia or auditory stimulation. Nevertheless, there are reports of pediatric patients with epilepsy and otherwise healthy adults who developed EEG evidence of seizure activity during sevoflurane anesthesia. Sevoflurane can suppress convulsive activity induced with lidocaine.

The administration of nitrous oxide may increase motor activity with clonus and opisthotonus even in clinically used concentrations. When nitrous oxide is administered in high concentrations in a hyperbaric chamber, abdominal muscle rigidity, catatonic movements of extremities, and periods of skeletal muscle relaxation, clonus, and opisthotonus. Although very rare, tonic-clonic seizure activity has been described after administration of nitrous oxide to an otherwise healthy child. Animals suspended by their tails may experience seizures in the first 15 to 90 minutes after discontinuation of nitrous oxide but not of volatile anesthetics. It is possible that these withdrawal seizures reflect acute nitrous oxide dependence. In patients, delirium or excitement during recovery from anesthesia that included nitrous oxide could reflect this phenomenon.

**Evoked Potentials**

Volatile anesthetics cause dose-related decreases in the amplitude and increases in the latency of the cortical component of median nerve somatosensory evoked potentials, visual evoked potentials, and auditory evoked potentials. Decreases in amplitude are more marked than increases in latencies. In the presence of 60% nitrous oxide, waveforms adequate for monitoring cortical somatosensory evoked potentials are present during administration of 0.5 to 0.75 MAC halothane and 0.5 to 1.0 MAC enflurane and isoflurane. Peri-MAC concentrations of desflurane (0.5 to 1.5 MAC) increasingly depress somatosensory evoked potentials in patients. Even nitrous oxide alone may decrease the amplitude of cortical somatosensory evoked potentials.

**Mental Function and Awareness**

By definition, inhaled anesthetics cause loss of response to verbal command at MAC-awake concentrations. Subtle effects on mental function (learning) may occur at lower anesthetic concentrations (0.2 MAC). Gaseous anesthetics may not be equally effective in preventing awareness. For example, 0.4 MAC isoflurane prevents recall and responses to commands, whereas nitrous oxide requires greater than 0.5 to 0.6 MAC to produce similar effects. Surgical stimulation may increase the anesthetic requirement to prevent awareness.

**Cerebral Blood Flow**

Volatile anesthetics produce dose-dependent increases in cerebral blood flow (CBF). The magnitude of this increase is dependent on the balance between the drug’s intrinsic vasodilatory actions and vasoconstriction secondary to flow-metabolism coupling. Volatile anesthetics administered during normocapnia in concentrations of 0.6 MAC produce cerebral vasodilation, decreased cerebral vascular resistance, and resulting dose-dependent increases in CBF (Fig. 4-26). This drug-induced increase in CBF occurs despite concomitant decreases in cerebral metabolic requirements. Sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect but this effect is less than that of isoflurane. Desflurane and isoflurane are similar in terms of increases in CBF and the preservation of reactivity to carbon dioxide (Fig. 4-27). Nitrous oxide also increases CBF, but its restriction to concentrations of <1 MAC limits the magnitude of this change. In fact, nitrous oxide may be a more potent cerebral vasodilator than an equipotent dose of isoflurane alone in humans.
Anesthetic-induced increases in CBF occur within minutes of initiating administration of the inhaled drug and whether blood pressure is unchanged or decreased, emphasizing the cerebral vasodilating effects of these drugs. Animals exposed to halothane demonstrate a time-dependent return to baseline from the previously increased CBF beginning after about 30 minutes and reaching predrug levels after about 150 minutes.\(^\text{120}\) This normalization of CBF reflects a concomitant increase in cerebral vascular resistance that is not altered by α- or β-adrenergic blockade and is not the result of changes in the pH of the cerebrospinal fluid.\(^\text{121}\)

Unlike the decay in CBF with time observed in animals, CBF remains increased relative to cerebral metabolic oxygen requirements for as long as 4 hours during administration of halothane, isoflurane, or sevoflurane to patients during surgery (see Fig. 4-26).\(^\text{122}\) Furthermore, in these patients, isoflurane possesses greater capability to maintain global CBF relative to cerebral metabolic oxygen requirements than does halothane or sevoflurane (Fig. 4-28).\(^\text{122}\) An unchanging EEG during this period suggests that CBF is increased over time without decay rather than a parallel change in CBF and cerebral metabolic oxygen requirements.

In animals, autoregulation of CBF in response to changes in systemic blood pressure is retained during administration of 1 MAC isoflurane but not halothane (Fig. 4-29).\(^\text{100,123}\) Indeed, increases in systemic blood pressure produce smaller increases in brain protrusion during administration of isoflurane and enflurane compared with halothane.\(^\text{123}\) It is speculated that loss of autoregulation during administration of halothane is responsible for the greater brain swelling seen in animals anesthetized with this drug. Inhaled anesthetics including desflurane and sevoflurane do not alter autoregulation of CBF as reflected by the responsiveness of the cerebral circulation to changes in PaCO\(_2\).\(^\text{118,124,125}\) For example, cerebrovascular carbon dioxide reactivity is described as intact during administration of 1 MAC desflurane.\(^\text{126}\) Nevertheless, others describe impairment of autoregulation by desflurane with 1.5 MAC nearly abolishing autoregulation.\(^\text{127}\)

**Cerebral Metabolic Oxygen Requirements**

Inhaled anesthetics produce dose-dependent decreases in cerebral metabolic oxygen requirements that are greater during the administration of isoflurane than with an equivalent MAC concentration of halothane.\(^\text{128}\) When the EEG becomes isoelectric, an additional increase in the concentration of the volatile anesthetics does not produce further decreases in cerebral metabolic oxygen requirements. The greater decrease in cerebral metabolic oxygen

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**FIGURE 4-28** A: When compared at 1.5 MAC, the average increase in cerebral blood flow (CBF) in the patients receiving isoflurane is greater than in those receiving halothane or sevoflurane. B: Likewise, the average value of the internal jugular venous oxygen tension (PjVO\(_2\)) is higher in patients receiving isoflurane. The increased CBF present at 1.5 MAC was sustained over time. (From Kuroda Y, Murakami M, Tsuruta J, et al. Preservation of the ratio of cerebral blood flow/metabolic rate for oxygen during prolonged anesthesia with isoflurane, sevoflurane, and halothane in humans. *Anesthesiology*. 1996;84:555–561, with permission.)
requirements produced by isoflurane may explain why CBF is not predictably increased by this anesthetic at concentrations lower than 1 MAC. For example, decreased cerebral metabolism means less carbon dioxide is produced, which thus opposes any increase in CBF. It is conceivable that isoflurane could evoke unexpected increases in CBF if administered to a patient in whom cerebral metabolic oxygen requirements were already decreased by drugs. Desflurane and sevoflurane decrease cerebral metabolic oxygen requirements similar to isoflurane.

**Cerebral Protection**

In animals experiencing temporary focal ischemia, there is no difference in neurologic outcome when cerebral function is suppressed by isoflurane or thiopental if systemic blood pressure is maintained.\(^1\) In humans undergoing carotid endarterectomy, the CBF at which ischemic changes appear on the EEG is lower during administration of isoflurane than during enflurane or halothane (Fig. 4.30).\(^2\) Although neurologic outcome is not different based on the volatile anesthetic administered, these data suggest that relative to enflurane and halothane, isoflurane may offer a degree of cerebral protection (blunts necrotic processes resulting from cerebral ischemia) from transient incomplete regional cerebral ischemia during carotid endarterectomy.\(^3\) Unchanged CBF and decreased cerebral metabolic oxygen requirements during isoflurane-induced controlled hypotension for clipping of cerebral aneurysms indicates that global cerebral oxygen supply-demand balance is favorably altered in patients anesthetized with this anesthetic.\(^4\)

**Intracranial Pressure**

Inhaled anesthetics produce increases in ICP that parallel increases in CBF produced by these drugs. Patients with space-occupying intracranial lesions are most vulnerable to these drug-induced increases in ICP. In hypocapnic humans with intracranial masses, desflurane concentrations of <0.8 MAC do not increase ICP whereas 1.1 MAC increases ICP by 7 mm Hg.\(^5\) Hyperventilation of the lungs to decrease the Paco\(_2\) to about 30 mm Hg opposes the tendency for inhaled anesthetics to increase ICP.\(^6\) With enflurane, it must be remembered that hyperventilation of the lungs increases the risk of seizure activity, which could lead to increased cerebral metabolic oxygen requirements and carbon dioxide production. These enflurane-induced changes will tend to increase CBF, which could further increase ICP. The ability of nitrous oxide to increase ICP is probably less than that of volatile anesthetics, reflecting the restriction of the dose of this drug to <1 MAC.

**Cerebrospinal Fluid Production**

Enflurane increases both the rate of production and the resistance to reabsorption of cerebrospinal fluid (CSP), which may contribute to sustained increases in ICP associated with administration of this drug.\(^7\) Conversely, isoflurane does not alter production of CSP and, at the same time, decreases resistance to reabsorption.\(^8\) These observations are consistent with minimal increases in ICP observed during the administration of isoflurane. Increases in ICP associated with administration of nitrous oxide presumably reflect increases in CBF because enhanced production of CSP does not occur in the presence of this inhaled anesthetic.\(^9\)

**Circulatory Effects**

Inhaled anesthetics produce dose-dependent and drug-specific circulatory effects. The circulatory effects of desflurane and sevoflurane parallel many of the characteristics
of older inhaled anesthetics with desflurane most closely resembling isoflurane, whereas sevoflurane has characteristics of both isoflurane and halothane.1,138

Drug-induced circulatory effects manifest as changes in systemic blood pressure, heart rate, cardiac output, stroke volume, right atrial pressure, systemic vascular resistance, cardiac rhythm, and coronary blood flow. Circulatory effects of inhaled anesthetics may be different in the presence of (a) controlled ventilation of the lungs compared with spontaneous breathing, (b) preexisting cardiac disease, or (c) drugs that act directly or indirectly on the heart. The mechanisms of circulatory effects are diverse but often reflect the effects of inhaled anesthetics on (a) myocardial contractility, (b) peripheral vascular smooth muscle tone, and (c) autonomic nervous system activity (see the section “Mechanisms of Circulatory Effects”).

Mean Arterial Pressure

Halothane, isoflurane, desflurane, and sevoflurane produce similar and dose-dependent decreases in mean arterial pressure when administered to healthy human volunteers (Fig. 4-31).139 The magnitude of decrease in mean arterial pressure in volunteers is greater than that which occurs in the presence of surgical stimulation. Likewise, artificially increased preoperative levels of systemic blood pressure, as may accompany apprehension, may be followed by decreases in blood pressure that exceed the true pharmacologic effect of the volatile anesthetic. In contrast with volatile anesthetics, nitrous oxide produces either no change or modest increases in systemic blood pressure.100,140 Substitution of nitrous oxide for a portion of the volatile anesthetic decreases the magnitude of blood pressure decrease produced by the same MAC concentration of the volatile anesthetic alone (Fig. 4-32).100 The decrease in blood pressure produced by halothane is, in part or in whole, a consequence of decreases in myocardial contractility and cardiac output, whereas with isoflurane, desflurane, and sevoflurane, the decrease in systemic blood pressure results principally from a decrease in systemic vascular resistance (see the section "Mechanisms of Anesthesia").

Heart Rate

Isoflurane, desflurane, and sevoflurane, but not halothane, increase heart rate when administered to healthy human volunteers (Fig. 4-33).139 Sevoflurane increases heart rate only at concentrations of >1.5 MAC, whereas isoflurane and desflurane tend to increase heart rate at lower concentrations. Heart rate effects seen in patients undergoing surgery may be quite different than those documented

![FIGURE 4-31](image1)  ![FIGURE 4-32](image2)  ![FIGURE 4-33](image3)
in volunteers because so many confounding variables influence heart rate. For example, a small dose of opioid (morphine in the preoperative medication or fentanyl intravenously immediately before induction of anesthesia) can prevent the heart rate increase associated with isoflurane and presumably the other volatile anesthetics (Fig. 4-34).\textsuperscript{141} Increased sympathetic nervous system activity, as accompanies apprehension, may artificially increase heart rate and the magnitude of the true pharmacologic effect of the volatile anesthetic. Similarly, excessive parasympathetic nervous system activity may result in unexpected increases in heart rate when anesthesia is established.

The common observation of an unchanged heart rate despite a decrease in blood pressure during the administration of halothane may reflect depression of the carotid sinus (baroreceptor-reflex response) by halothane, as well as drug-induced decreases in the rate of sinus node depolarization. Junctional rhythm and associated decreases in systemic blood pressure most likely reflect suppression of sinus node activity by halothane. Halothane also decreases the speed of conduction of cardiac impulses through the atrioventricular node and His-Purkinje system. At 0.5 MAC, desflurane produces decreases in systemic blood pressure similar to those caused by isoflurane but does not evoke an increased heart rate as does isoflurane. This difference is not explained by disparate effects of these anesthetics on the baroreceptor-reflex response.\textsuperscript{142} In neonates, administration of isoflurane is associated with attenuation of the carotid sinus reflex response, as reflected by drug-induced decreases in blood pressure that are not accompanied by increases in heart rate.\textsuperscript{143} Heart rate responses during administration of isoflurane also seem to be blunted in elderly patients, whereas isoflurane-induced increases in heart rate are more likely to occur in younger patients and may be accentuated by the presence of other drugs (atropine, pancuronium) that exert vagolytic effects. Nitrous oxide also depresses the carotid sinus, but quantitating this effect is difficult because of its limited potency and its frequent simultaneous administration with other injected or inhaled drugs.

**Cardiac Output and Stroke Volume**

Halothane, but not isoflurane, desflurane, and sevoflurane, produces dose-dependent decreases in cardiac output when administered to healthy human volunteers (Fig. 4-35).\textsuperscript{139} Sevoflurane did decrease cardiac output at 1 and 1.5 MAC, but at 2 MAC cardiac output had recovered to nearly awake values. Sevoflurane causes a

![Graph showing heart rate and surgical stimulation](image_url)
smaller decrease in cardiac output than does halothane when administered to infants. Due to different effects on heart rate (halothane causes no change and heart rate increases in the presence of the other volatile anesthetics), the calculated left ventricular stroke volume was similarly decreased 15% to 30% for all the volatile anesthetics. In patients, the increase in heart rate may tend to offset drug-induced decreases in cardiac output. Cardiac output is modestly increased by nitrous oxide, possibly reflecting the mild sympathomimetic effects of this drug.

In addition to better maintenance of heart rate, isoflurane's minimal depressant effects on cardiac output could reflect activation of homeostatic mechanisms that obscure direct cardiac depressant effects. Indeed, volatile anesthetics, including isoflurane, produce similar dose-dependent depression of myocardial contractility when studied in vitro using isolated papillary muscle preparations. The vasodilating effects of the ether-derivative volatile anesthetics make the direct myocardial depression produced by these drugs less apparent than that of halothane. Indeed, excessive concentrations of these drugs administered to patients can produce cardiovascular collapse. In vitro depression of myocardial contractility produced by nitrous oxide is about one-half that produced by comparable concentrations of volatile anesthetics. Direct myocardial depressant effects in vivo are most likely offset by mild sympathomimetic effects of nitrous oxide.

Another possible explanation for the lesser impact of isoflurane on myocardial contractility may be its greater anesthetic potency relative to that of halothane. For example, the multiple of MAC times the oil:gas partition coefficient for halothane is 168 and 105 for isoflurane. The implication is that isoflurane may more readily depress the brain and thus, at a given MAC value, appear to spare the heart. Indeed, in animals, the lesser myocardial depression associated with the administration of isoflurane manifests as a greater margin of safety between the dose that produces anesthesia and that which produces cardiovascular collapse.

**Right Atrial Pressure**

Halothane, isoflurane, and desflurane, but not sevoflurane, increase right atrial pressure (central venous pressure) when administered to healthy human volunteers (Fig. 4-36). These differences are not predictable based on the many other similarities between sevoflurane, desflurane, and isoflurane. The peripheral vasodilating effects of volatile anesthetics would tend to minimize the effects of direct myocardial depression on right atrial pressure produced by these drugs. Increased right atrial pressure during administration of nitrous oxide most likely reflects increased pulmonary vascular resistance due to the sympathomimetic effects of this drug.

**Systemic Vascular Resistance**

Isoflurane, desflurane, and sevoflurane, but not halothane, decrease systemic vascular resistance when administered to healthy human volunteers (Fig. 4-37). Thus, although these four volatile anesthetics decrease systemic blood pressure comparably, only halothane does so principally by decreasing cardiac output. For example, the absence of changes in systemic vascular resistance during administration of halothane emphasizes that decreases in systemic blood pressure produced by this drug parallel decreases in myocardial contractility. The other volatile anesthetics decrease blood pressure principally by decreasing systemic vascular resistance. Nitrous oxide does not change systemic vascular resistance.

Decreases in systemic vascular resistance during administration of isoflurane principally reflect substantial (up to fourfold) increases in skeletal muscle blood flow. Cutaneous blood flow is also increased by isoflurane. The implications of these alterations in blood flow may include (a) excess (wasted) perfusion relative to oxygen needs, (b) loss of body heat due to increased cutaneous
blood flow, and (c) enhanced delivery of drugs, such as muscle relaxants, to the neuromuscular junction.

Failure of systemic vascular resistance to decrease during administration of halothane does not mean that this drug lacks vasodilating effects on some organs. Clearly, halothane is a potent cerebral vasodilator and cutaneous vasodilation is prominent. These vasodilating effects of halothane, however, are offset by decreases in systemic vascular resistance that are not present in other vascular beds such that the overall effect is unchanged calculated systemic vascular resistance.

The increase in cutaneous blood flow produced by all volatile anesthetics arterIALIZED peripheral venous blood, providing an alternative to sampling arterial blood for evaluation of pH and PaCO₂ (Fig. 4-38). These drug-induced increases in cutaneous blood flow most likely reflect a central inhibitory action of these anesthetics on temperature-regulating mechanisms. In contrast to volatile anesthetics, nitrous oxide may produce constriction of cutaneous blood vessels.

**Pulmonary Vascular Resistance**

Volatile anesthetics appear to exert little or no predictable effect on pulmonary vascular smooth muscle. Conversely, nitrous oxide may produce increases in pulmonary vascular resistance that is exaggerated in patients with pre-existing pulmonary hypertension. The neonate with or without pre-existing pulmonary hypertension may also be uniquely vulnerable to the pulmonary vascular constricting effects of nitrous oxide. In patients with congenital heart disease, these increases in pulmonary vascular resistance may increase the magnitude of right-to-left intracardiac shunting of blood and further jeopardize arterial oxygenation.

**Duration of Administration**

Administration of a volatile anesthetic for 5 hours or longer is accompanied by recovery from the cardiovascular depressant effects of these drugs. For example, compared with measurements at 1 hour, the same MAC concentration after 5 hours is associated with a return of cardiac output toward predrug levels (Figs. 4-39 and 4-40). After 5 hours, heart rate is also increased, but systemic blood pressure is unchanged, as the increase in cardiac output is offset by decreases in systemic vascular resistance.

**FIGURE 4-38** There is a linear relationship between PvCO₂ measured in “arterialized” peripheral venous blood and the PaCO₂. (From Williamson DC, Munson ES. Correlation of peripheral venous and arterial blood gas values during general anesthesia. *Anesth Analg*. 1982;61:950–952, with permission.)

**FIGURE 4-39** Comparison of circulatory effects of halothane during spontaneous breathing (SR) and controlled ventilation of the lungs (CR) after 1 and 5 hours of administration of halothane. (From Bahlman SH, Eger EI, Halsey MJ, et al. The cardiovascular effects of halothane in man during spontaneous ventilation. *Anesthesiology*. 1972;36:494–502, with permission.)
Evidence of recovery with time is most apparent during administration of halothane and is minimal during inhalation of isoflurane. Minimal evidence of recovery during administration of isoflurane (and presumably desflurane and sevoflurane) is predictable, because this drug does not substantially alter cardiac output even at 1 hour.

The return of cardiac output toward predrug levels with time, in association with increases in heart rate and peripheral vasodilation, resembles a β-adrenergic agonist response. Indeed, pretreatment with propranolol prevents evidence of recovery with time from the circulatory effects of volatile anesthetics.155

Cardiac Dysrhythmias

The ability of volatile anesthetics to decrease the dose of epinephrine necessary to evoke ventricular cardiac dysrhythmias is greatest with the alkane derivative halothane and minimal to nonexistent with the ether derivatives isoflurane, desflurane, and sevoflurane (Figs. 4-41 to 4-43).156–158 In contrast to adults, children tolerate larger doses of subcutaneous epinephrine (7.8 to 10.0 µg/kg) injected with or without lidocaine during halothane anesthesia.159,160 Mechanical stimulation associated with injection of epinephrine for repair of cleft palate has been associated with cardiac dysrhythmias.160

Inclusion of lidocaine 0.5% in the epinephrine solution that is injected submucosally nearly doubles the dose of epinephrine necessary to provoke ventricular cardiac dysrhythmias (see Fig. 4-41).156 A similar response occurs

**FIGURE 4-40** Comparison of circulatory effects of enflurane after 1 hour (solid line) and 6 hours (broken line) of administration during controlled ventilation of the lungs to maintain normocapnia. CV, cardiovascular. (From Calverley RK, Smith NT, Pryse-Roberts C, et al. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg. 1978;57:619–628, with permission.)

**FIGURE 4-41** Percentage of patients developing ventricular cardiac dysrhythmias (three or more premature ventricular contractions [PVCs]) with increasing doses of submucosal epinephrine injected during administration of 1.25 MAC of halothane, isoflurane, or enflurane. (From Johnston PR, Eger EI, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg. 1976;55:709–712, with permission.)

**FIGURE 4-42** Responses to submucosally injected epinephrine in patients receiving desflurane (DES) or isoflurane (ISO) anesthesia. PVCs, premature ventricular contractions. (From Moore MA, Weiskopf RB, Eger EI, et al. Arrhythmic doses of epinephrine are similar during desflurane or isoflurane anesthesia in humans. Anesthesiology. 1993;79:943–947, with permission.)
When lidocaine is combined with epinephrine injected submucosally during administration of enflurane. Despite the apparent protective effect of lidocaine, the systemic concentrations of the local anesthetic are <1 µg/mL after its subcutaneous injection with epinephrine.

In animals, enhancement of the arrhythmogenic potential of epinephrine is independent of the dose of halothane between alveolar concentrations of 0.5% and 2%. If true in patients, it is likely that cardiac dysrhythmias due to epinephrine will persist until the halothane concentration decreases to <0.5%. For this reason, therapeutic interventions other than decreasing the inhaled concentration of halothane may be required to treat cardiac dysrhythmias promptly due to epinephrine.

The explanation for the difference between volatile anesthetics and the arrhythmogenic potential of epinephrine may reflect the effects of these drugs on the transmission rate of cardiac impulses through the heart's conduction system. Nevertheless, halothane and isoflurane both slow the rate of sinoatrial node discharge and prolong His-Purkinje and ventricular conduction times (see Chapter 48).

**FIGURE 4-43** Responses to submucosally injected epinephrine in patients receiving sevoflurane (SEVO) or isoflurane (ISO) anesthesia. (From Navarro R, Weiskopf RB, Moore MA, et al. Humans anesthetized with sevoflurane or isoflurane have similar arrhythmic response to epinephrine. Anesthesiology. 1994;80:545–549, with permission.)

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**Coronary Blood Flow**

Volatile anesthetics induce coronary vasodilation by preferentially acting on vessels with diameters from 20 µm to 50 µm, whereas adenosine, in addition, has a pronounced impact on the small precapillary arterioles. It has been suggested that isoflurane as well as other coronary vasodilators (adenosine, dipyridamole, nitroprusside) that preferentially dilate the small coronary resistance coronary vessels would be capable of redistributing blood from ischemic to nonischemic areas, producing the phenomenon known as **coronary steal syndrome**. Nevertheless, this phenomenon is not clinically significant and volatile anesthetics, including isoflurane, are cardioprotective (see the section "Cardiac Protection [Anesthetic Preconditioning"]).

**Neurocirculatory Responses**

The solubility characteristics of desflurane make this volatile anesthetic a good choice to treat abrupt increases in systemic blood pressure and/or heart rate as may occur in response to sudden changes in the intensity of surgical stimulation. Nevertheless, abrupt increases in the alveolar concentrations of isoflurane and desflurane from 0.55 MAC (0.71% isoflurane and 4% desflurane) to 1.66 MAC (2.12% isoflurane and 12% desflurane) increase sympathetic nervous system and renin-angiotensin activity and cause transient increases in mean arterial pressure...
and heart rate (Figs. 4-44 to 4-46). Desflurane causes significantly greater increases than isoflurane. The magnitude of the response to a rapid increase from 4% to 8% desflurane was similar to that produced by a rapid increase from 4% to 12%, suggesting that the stimulus provided by 8% desflurane produced a maximum response. Small (1%) increases in the desflurane concentration also transiently increase systemic blood pressure and heart rate, but the magnitude is less than those same changes that occur with an increase from 4% to 12%. Sites mediating sympathetic nervous system activation in response to desflurane are present in the upper airway (larynx and above) and in the lungs. These sites may respond to direct irritation. The increase in basal levels of sympathetic nervous system activity that accompany increasing inhaled concentrations of desflurane does not reflect the effects of drug-induced hypotension or alterations in baroreceptor activity.

In contrast to desflurane and isoflurane, neurocirculatory responses do not accompany abrupt increases in the delivered concentration of sevoflurane (Fig. 4-47).

Fentanyl (1.5 to 4.5 μg/kg IV administered 5 minutes before the abrupt increase in desflurane concentration), esmolol (0.75 mg/kg IV 1.5 minutes before), and clonidine (4.3 μg/kg orally 90 minutes before) blunt the transient cardiovascular responses to rapid increases in desflurane concentration. Fentanyl may be the most clinically useful of these drugs because it blunts the increase in heart rate and blood pressure, has minimal cardiovascular depressant effects, and imposes little postanesthetic sedation. Alfentanil, 10 μg/kg IV, in conjunction with the induction of anesthesia, also blunts the hemodynamic responses to

![Figure 4-44](image-url)  
**Plasma norepinephrine (NE) concentrations increased from awake levels (A) and those present when the anesthetic concentrations were abruptly increased to 1.66 MAC (B). The increase was greater in the presence of desflurane than isoflurane (P < .05). Data are mean ± SE. (From Weiskopf RB, Moore MA, Eger EI, et al. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increases in isoflurane concentration in humans. Anesthesiology. 1994;80:1035–1045, with permission.)**

![Figure 4-45](image-url)  
**An abrupt and sustained increase in the concentration of desflurane from 0.55 MAC to 1.66 MAC (0) resulted in a substantial but transient increase in mean arterial pressure (MAP). A similar increase in isoflurane MAC produced an increase in MAP that was substantially less than that observed in patients receiving desflurane. Within 5 minutes after increasing the anesthetic concentration, the MAP had decreased below awake (A) and 0.55 MAC values (B) reflecting the greater depth of anesthesia present at this time. (t, P < .05 compared with the value at 0.55 MAC of the same anesthetic; *P < .05 compared with isoflurane at the same time point.) (From Weiskopf RB, Moore MA, Eger EI, et al. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increases in isoflurane concentration in humans. Anesthesiology. 1994;80:1035–1045, with permission.)**

![Figure 4-46](image-url)  
**An abrupt and sustained increase in the concentration of desflurane from 0.55 MAC to 1.66 MAC (0) resulted in a substantial but transient increase in heart rate. A similar increase in isoflurane MAC produced an increase in heart rate that was substantially less than that observed in patients receiving desflurane. Within 5 minutes after increasing the anesthetic concentration, the heart rate remained above awake (A) and baseline values at 0.55 MAC (B), reflecting the greater depth of anesthesia present at this time. (t, P < .05 compared with the value at 0.55 MAC of the same anesthetic; *P < .05 compared with isoflurane at the same time point.) (From Weiskopf RB, Moore MA, Eger EI, et al. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increases in isoflurane concentration in humans. Anesthesiology. 1994;80:1035–1045, with permission.)**
myocardial depression that does not occur in patients without heart disease. Valvular heart disease may influence the significance of anesthetic-induced circulatory effects. For example, peripheral vasodilation produced by isoflurane (presumably also desflurane and sevoflurane) is undesirable in patients with aortic stenosis but may be beneficial by providing afterload reduction in those with mitral or aortic regurgitation. Arterial hypoxemia may enhance the cardiac depressant effects of volatile anesthetics. Conversely, anemia does not alter anesthetic-induced circulatory effects compared with measurements from normal animals.

Prior drug therapy that alters sympathetic nervous system activity (antihypertensives, β-adrenergic antagonists) may influence the magnitude of circulatory effects produced by volatile anesthetics. Calcium entry blockers decrease myocardial contractility and thus render the heart more vulnerable to direct depressant effects of inhaled anesthetics. In animals, the depressant effects of verapamil on cardiac output are greater during administration of enfurane than of isoflurane (see Chapter 18).

Mechanisms of Circulatory Effects

There is no known single mechanism that explains the cardiovascular depressant effects of volatile anesthetics, just as there is none for the neurobehavioral effects. Proposed mechanisms include (a) direct myocardial depression, (b) inhibition of CNS sympathetic activity, (c) peripheral autonomic ganglion blockade, (d) attenuated carotid sinus reflex activity, (e) decreased formation of cyclic adenosine monophosphate, (f) decreased release of catecholamines, and (g) decreased influx of calcium ions through slow channels. Indeed, negative inotropic, vasodilating, and depressant effects on the sinoatrial node produced by volatile anesthetics are similar to the effects produced by calcium entry blockers. However, voltage-gated calcium channels are only inhibited to a small extent by inhalational anesthetics. Plasma catecholamine concentrations typically do not increase during administration of volatile anesthetics, which is evidence that these drugs do not activate and may even decrease activity of the central and peripheral sympathetic nervous systems.

Isoflurane may be unique among the volatile anesthetics in possessing mild β-adrenergic agonist properties. This effect is consistent with the maintenance of cardiac output, increased heart rate, and decreased systemic vascular resistance that may accompany administration of isoflurane. A β agonist effect of isoflurane, however, is not supported by animal data that fail to demonstrate a difference between volatile anesthetics with or without β-adrenergic blockade. The increase in blood pressure that is associated with rapid increases in desflurane concentration is accompanied by a significant increase in plasma epinephrine suggesting enhanced release from the adrenal gland.

Nitrous oxide administered alone or added to unchanging concentrations of volatile anesthetics produces an abrupt increase in the delivered concentration of desflurane; however, the increase in plasma norepinephrine concentrations that accompany the abrupt increase in desflurane concentration are not predictably prevented by the prior administration of opioids.
signs of mild sympathomimetic stimulation characterized by (a) increases in the plasma concentrations of catecholamines, (b) mydriasis, (c) increases in body temperature, (d) diaphoresis, (e) increases in right atrial pressure, and (f) evidence of vasoconstriction in the systemic and pulmonary circulations. Evidence of the sympathomimetic effect is more prominent when nitrous oxide is administered in the presence of halothane than of enflurane or isoflurane. It is presumed that this mild sympathomimetic effect masks any direct depressant effects of nitrous oxide on the heart. Nitrous oxide-induced increases in sympathetic nervous system activity may reflect activation of brain nuclei that regulate β-adrenergic outflow from the CNS. \(^{182}\) Sympathetic nervous system stimulation may also result because nitrous oxide can inhibit uptake of norepinephrine by the lungs, making more neurotransmitter available to receptors. \(^{183}\) Interestingly, nitrous oxide shares its sympathomimetic aspect with another NMDA blocking anesthetic, ketamine.

In contrast to sympathomimetic effects observed with the administration of nitrous oxide alone or added to volatile anesthetics, the inhalation of nitrous oxide in the presence of opioids results in evidence of profound circulatory depression, characterized by decreases in systemic blood pressure and cardiac output and increases in left ventricular end-diastolic pressure and systemic vascular resistance. \(^ {184, 185}\) It is possible that opioids inhibit the centrally mediated sympathomimetic effects of nitrous oxide, thus unmasking its direct depressant effects on the heart.

### Cardiac Protection (Anesthetic Preconditioning)

Brief episodes of myocardial ischemia occurring before a subsequent longer period of myocardial ischemia providing protection against myocardial dysfunction and necrosis is termed ischemic preconditioning (IPC). \(^ {186}\) The preconditioning protection seems to be mediated by release of adenosine, which binds to adenosine receptors and increases protein kinase C activity. The resulting phosphorylation of adenosine triphosphate (ATP) sensitive mitochondrial potassium channels (\(K_{\text{ATP}}\)) results in these channels being less sensitive to inhibition by ATP. These channels are important in regulating vascular smooth muscle tone by causing hyperpolarization and relaxation when oxygen delivery results in decreased ATP production. When \(K_{\text{ATP}}\) channel activity is increased, there is a decrease in the voltage gradient and decrease in calcium ion accumulation, the cardiac action potential shortens, accompanied by a mild negative inotropic action and remarkable protection against subsequent sustained ischemic or hypoxic insult. Opening of \(K_{\text{ATP}}\) channels is critical for the beneficial cardioprotective effects of IPC. Brief exposure to a volatile anesthetic (isoflurane, sevoflurane, desflurane) can activate \(K_{\text{ATP}}\) channels resulting in cardioprotection (anesthetic preconditioning) against subsequent prolonged ischemia and myocardial reperfusion injury that is identical to IPC. \(^ {187-191}\) Concentrations of isoflurane as low as 0.25 MAC are sufficient to precondition myocardium against ischemic injury, although higher doses may provide even greater cardiac protection. \(^ {192}\) Combined administration of isoflurane and morphine enhances protection against myocardial infarction to a greater extent than either drug alone. \(^ {193}\)

Reperfusion injury is defined as cellular injury that is caused by reperfusion itself and not the preceding ischemia. Manifestations of reversible reperfusion injury include cardiac dysrhythmias, contractile dysfunction (“stunning”), and microvascular injury. \(^ {194}\) In addition to myocardium, a similar effect induced by volatile anesthetics on vascular endothelium may result in protection from ischemia in other tissues. If anesthetic preconditioning is to be of clinical value, it will most likely be because it affords additional time before occurrence of dysfunction and/or infarction that will allow either spontaneous reperfusion or application of therapies such as angioplasty to relieve a coronary occlusion. \(^ {195}\) The preconditioning effects of volatile anesthetics may be beneficial in patients who are susceptible to myocardial infarction during and following surgery. Indeed, patients receiving sevoflurane for cardiac surgery (off-bypass or cardiopulmonary bypass) had less myocardial injury (lower release of troponin I) during the first 24 postoperative hours than patients receiving propofol (Figs. 4-48 and 4-49). \(^ {196, 197}\) In patients undergoing coronary artery surgery with cardiopulmonary bypass, the cardioprotective effects of sevoflurane were clinically more apparent when this volatile anesthetic was administered throughout the operation compared with administration during only a part of the anesthetic (see Fig. 4-49). \(^ {198}\) Cardiac output was improved in patients

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**FIGURE 4-48** Cardiac troponin I concentrations in sevoflurane-anesthetized patients during and after anesthesia. Samples were obtained before induction of anesthesia (T1), before ischemia (T2), 15 minutes after reperfusion (T3), at arrival in the postanesthesia care unit (T4), and 3 (T5), 6 (T6), 12 (T7), 18 (T8), and 24 hours (T9) after arrival. (From Conzen PF, Fischer S, Detter C, et al. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *Anesthesiology.* 2003;99:826–833, with permission.)
receiving sevoflurane but not propofol suggesting better maintenance of myocardial function.

IPC is a fundamental endogenous protective mechanism against tissue injury (best characterized in the heart but also present in other tissues) ubiquitous to all species in which it has been studied. An early phase of IPC persists for 1 to 2 hours before disappearing and then reoccurring 24 hours. This second or late window of preconditioning may last for as long as 3 days.

**Ventilation Effects**

Inhaled anesthetics produce dose-dependent and drug-specific effects on the (a) pattern of breathing, (b) ventilatory response to carbon dioxide, (c) ventilatory response to arterial hypoxemia, and (d) airway resistance. The PaO₂ predictably declines during administration of inhaled anesthetics in the absence of supplemental oxygen. Drug-induced inhibition of hypoxic pulmonary vasoconstriction as a mechanism for this decrease in oxygenation has not been confirmed during one-lung ventilation in patients breathing halothane or isoflurane. Changes in intraoperative PaO₂ and the incidence of postoperative pulmonary complications are not different in patients anesthetized with halothane, enflurane, or isoflurane.

**Pattern of Breathing**

Inhaled anesthetics, except for isoflurane, produce dose-dependent increases in the frequency of breathing. Isoflurane increases the frequency of breathing similarly to other inhaled anesthetics up to a dose of 1 MAC. At a concentration of >1 MAC, however, isoflurane does not produce a further increase in the frequency of breathing. Nitrous oxide increases the frequency of breathing more than other inhaled anesthetics at concentrations of >1 MAC. The effect of inhaled anesthetics on the frequency of breathing presumably reflects CNS stimulation. Volatile anesthetics stimulate central respiratory chemoreceptor neurons likely through activation of THIK-1 receptors, a two-pore potassium channel that is responsible for a background potassium current. Activation of pulmonary stretch receptors by inhaled anesthetics has not been demonstrated. The exception may be nitrous oxide, which, at anesthetic concentrations of >1 MAC, may also stimulate pulmonary stretch receptors.

Tidal volume is decreased in association with anesthetic-induced increases in the frequency of breathing. The net effect of these changes is a rapid and shallow pattern of breathing during general anesthesia. The increase in frequency of breathing is insufficient to offset decreases in tidal volume, leading to decreases in minute ventilation and increases in PaCO₂. There is evidence in patients that isoflurane produces a greater decrease in minute ventilation than does halothane (Fig. 4-50). The pattern of breathing during general anesthesia is also characterized as regular and rhythmic in contrast to the awake pattern of intermittent deep breaths separated by varying intervals.

**Ventilatory Response to Carbon Dioxide**

Volatile anesthetics produce dose-dependent depression of ventilation characterized by decreases in the ventilatory response to carbon dioxide and increases in the PaCO₂ (Fig. 4-51). Desflurane and sevoflurane depress ventilation, producing profound decreases in ventilation leading to apnea between 1.5 and 2.0 MAC. Both of these volatile anesthetics increase PaCO₂ and decrease the ventilatory response to carbon dioxide. Depression of ventilation produced by anesthetic concentrations up to 1.24 MAC desflurane are similar to the depression produced by isoflurane.
The presence of chronic obstructive pulmonary disease (COPD) may accentuate the magnitude of increase in PaCO₂ produced by volatile anesthetics. Nitrous oxide does not increase the PaCO₂, suggesting that substitution of this anesthetic for a portion of the volatile anesthetic would result in less depression of ventilation. Indeed, nitrous oxide combined with a volatile anesthetic produces less depression of ventilation and increase in PaCO₂ than does the same MAC concentration of the volatile drug alone. This ventilatory depressant–sparing effect of nitrous oxide is detectable with all volatile anesthetics (see Fig. 4-49).

Despite the apparent benign effect of nitrous oxide on ventilation, the slope of the carbon dioxide response curve is decreased similarly and shifted to the right by anesthetic concentrations of all inhaled anesthetics (Fig. 4-52). Subanesthetic concentrations (0.1 MAC) of inhaled anesthetics, however, do not alter the ventilatory response to carbon dioxide. In addition to nitrous oxide, painful stimulation (surgical skin incision) and duration of drug administration influence the magnitude of increase in PaCO₂ produced by volatile anesthetics.

**Surgical Stimulation**

Surgical stimulation increases minute ventilation by about 40% because of increases in tidal volume and frequency of breathing. The PaCO₂, however, decreases only about 10% (4 to 6 mm Hg) despite the larger increase in minute

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**FIGURE 4-50** Minute ventilation (VE) and end-tidal carbon dioxide concentration (PETCO₂), as measured in volunteers breathing halothane or isoflurane in oxygen spontaneously at 1.2 (low) and 2.0 (high) MAC. (*P < .05 compared with halothane; +, P < .05 compared with low MAC.) (From Canet J, Sanchis J, Zegri A, et al. Effects of halothane and isoflurane on ventilation and occlusion pressure. Anesthesiology. 1994;81: 563–571, with permission.)

**FIGURE 4-51** Inhaled anesthetics produce drug-specific and dose-dependent increases in PaCO₂. (From Eger EI. Desflurane [Suprane]: A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1–119, with permission.)

**FIGURE 4-52** All inhaled anesthetics produce similar dose-dependent decreases in the ventilatory response to carbon dioxide. (From Eger EI. Desflurane [Suprane]: A Compendium and Reference. Nutley, NJ: Anaquest; 1993: 1–119, with permission.)
ventilation (Fig. 4-53).\(^{100}\) The reason for this discrepancy is speculated to be an increased production of carbon dioxide resulting from activation of the sympathetic nervous system in response to painful surgical stimulation. Increased production of carbon dioxide is presumed to offset the impact of increased minute ventilation on Pa\(_2\).

**Duration of Administration**

After about 5 hours of administration, the increase in Pa\(_2\) produced by spontaneous breathing of a volatile anesthetic is less than that present during administration of the same concentration for 1 hour (Table 4-8).\(^{169}\) Likewise, the slope and position of the carbon dioxide response curve returns toward normal after about 5 hours of administration of the volatile anesthetics.\(^{205}\) The reason for this apparent recovery from the ventilatory depressant effects of volatile anesthetics with time is not known.

**Mechanism of Depression**

Anesthetic-induced depression of ventilation as reflected by increases in the Pa\(_2\) most likely reflects the direct depressant effects of these drugs on the medullary ventilatory center. An additional mechanism may be the ability of halothane and possibly other inhaled anesthetics to selectively interfere with intercostal muscle function, contributing to loss of chest wall stabilization during spontaneous breathing.\(^{206}\) This loss of chest wall stabilization could interfere with expansion of the chest in response to chemical stimulation of ventilation as normally produced by increases in the Pa\(_2\) or arterial hypoxemia. Furthermore, this loss of chest wall stabilization means the descent of the diaphragm tends to cause the chest to collapse inward during inspiration, contributing to decreases in lung volumes, particularly the FRC. It is thus likely that halothane-induced depression of ventilation reflects both central and peripheral effects of the drug. The ventilatory depression associated with sevoflurane may result from a combination of central depression of medullary inspiratory neurons and depression of diaphragmatic function and contractility.\(^{207}\)

**Management of Ventilatory Depression**

The predictable ventilatory depressant effects of volatile anesthetics are most often managed by institution of mechanical (controlled) ventilation of the patient’s lungs. In this regard, the inherent ventilatory depressant effects of volatile anesthetics facilitate the initiation of controlled ventilation. Assisted ventilation of the lungs is a questionably effective method for offsetting the ventilatory depressant effects of volatile anesthetics. For example, the apneic threshold (maximal Pa\(_2\) that does not initiate spontaneous breathing) is only 3 to 5 mm Hg lower than the Pa\(_2\) present during spontaneous breathing.\(^{208}\) As a result, a Pa\(_2\) increase to 50 mm Hg due to ventilatory depressant effects of a volatile anesthetic could only be lowered to 45 to 46 mm Hg by assisted ventilation of the lungs before apnea occurs.

**Ventilatory Response to Hypoxemia**

All inhaled anesthetics, including nitrous oxide, profoundly depress the ventilatory response to hypoxemia that is normally mediated by the carotid bodies. For example, 0.1 MAC produces 50% to 70% depression, and 1.1 MAC produces 100% depression of this response.\(^{209,210}\) This contrasts with the absence of significant depression of the ventilatory response to carbon dioxide during administration of 0.1 MAC of volatile anesthetics. Inhaled anesthetics also attenuate the usual synergistic effect of arterial hypoxemia and hypercapnia on stimulation of ventilation. Sevoflurane-induced decreases in hypoxic responses are not different in men and women which contrasts with morphine which produces greater depression of the ventilatory response to hypoxia in women.\(^{211}\) Sevoflurane is useful during thoracic surgery as it is a potent

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**Table 4-8**

**Evidence for Recovery from the Ventilatory Depressant Effects of Volatile Anesthetics**

<table>
<thead>
<tr>
<th>Arterial Pco(_2)</th>
<th>1 Hour of Administration</th>
<th>5 Hours of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enflurane</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td>1 MAC</td>
<td>61</td>
<td>46</td>
</tr>
<tr>
<td>2 MAC</td>
<td>Apnea</td>
<td>67</td>
</tr>
</tbody>
</table>

bronchodilator, its low blood-gas solubility permits rapid adjustment of the depth of anesthesia, and effects on hypoxic pulmonary vasoconstriction are small.\(^{212}\)

**Airway Resistance and Irritability**

Risk factors for developing bronchospasm during anesthesia include young age (<10 years), perioperative respiratory infection, endotracheal intubation, and the presence of COPD.\(^{213}\) Nevertheless, isoflurane and sevoflurane produce bronchodilation in patients with COPD (Fig. 4-54).\(^{214}\) Sevoflurane causes moderate bronchodilation that is not observed in patients receiving desflurane or thiopental (Fig. 4-55).\(^{215}\) Bronchoconstriction produced by desflurane is most likely to occur in patients who smoke (Fig. 4-56).\(^{215}\) Administration of fentanyl 1 \(\mu g/\text{kg IV}\) or morphine 100 \(\mu g/\text{kg IV}\) prior to inhalation induction with desflurane and nitrous oxide significantly decreases airway irritability associated with desflurane.\(^{216}\) After tracheal intubation in patients without asthma, sevoflurane decreases airway resistance as much or more than isoflurane (Fig. 4-57).\(^{217}\) Sevoflurane and desflurane have been administered without evidence of bronchospasm to patients with bronchial asthma.\(^{4}\)

The assessment of the cough response to tracheal stimulation by endotracheal tube cuff inflation is a reliable and clinically meaningful measure of upper airway reactivity. At 1 MAC, sevoflurane is superior to desflurane for suppressing moderate and severe responses to this stimulus (Fig. 4-58).\(^{218}\) However, the irritant effects of desflurane are thought to be as a result of stimulation of TRPA1 receptors in the airways (Pungent general anesthetics activate transient receptor potential-A1 to produce hyperalgesia and neurogenic bronchoconstriction).\(^{219}\) Administration of desflurane, 1.8% to 5.4%, does not produce secretions, coughing, or breath-holding in human volunteers.\(^{1}\)

Despite the typical lack of irritant effects of sevoflurane on the airways, there is evidence that exposure of sevoflurane to desiccated carbon dioxide absorbents, especially those containing potassium hydroxide, may result in production of toxic gases and subsequent inhalation of these products causing airway irritation and impaired gas exchange.\(^{220,221}\) This airway irritation may be caused by formaldelyde which is generated in isomolar concentrations with methanol. Compound A is not an airway irritant.

In the absence of bronchoconstriction, the bronchodilating effects of volatile anesthetics are difficult to demonstrate, because normal bronchomotor tone is low and only minimal additional relaxation is possible. Like other inhaled anesthetics, nitrous oxide decreases FRC; this may be exaggerated by nitrous oxide–induced skeletal muscle rigidity.

**Hepatic Effects**

**Hepatic Blood Flow**

In patients receiving 1.5% end-tidal isoflurane, total hepatic blood flow and hepatic artery blood flow was maintained while portal vein blood flow was increased confirming that isoflurane was a vasodilator of the hepatic circulation providing beneficial effects on hepatic oxygen delivery.\(^{222}\) In contrast, halothane acts as a vasoconstrictor on the hepatic circulation. In another report, patients receiving 1 MAC isoflurane plus nitrous oxide demonstrated increases in hepatic blood flow and increased hepatic...
Inhaled Anesthetics

Drugs such as propranolol is decreased by 54% to 68% by inhaled anesthetics. In the overall hepatic clearance of drugs, decreases in hepatic blood flow seem less important than anesthetic-induced inhibition of hepatic drug-metabolizing enzymes.

Liver Function Tests

Transient increases in the plasma alanine aminotransferase activity follow administration of enflurane and desflurane, but not isoflurane administration, to human volunteers (Fig. 4-60). Transient increases in plasma concentrations of alpha glutathione transferase (sensitive indicator of hepatocellular injury) follow administration of isoflurane or desflurane for surgical anesthesia. In the presence of surgical stimulation, bromsulphalein retention and increases in liver enzymes follow transiently the administration of even isoflurane, suggesting that changes in hepatic blood flow evoked by painful stimulation can adversely alter hepatic function independent of the volatile anesthetic.

Drug Clearance

Volatile anesthetics may interfere with clearance of drugs from the plasma as a result of decreases in hepatic blood flow or inhibition of drug-metabolizing enzymes. Intrinsic clearance by hepatic metabolism of drugs such as propranolol is decreased by 54% to 68% by inhaled anesthetics. In the overall hepatic clearance of drugs, decreases in hepatic blood flow seem less important than anesthetic-induced inhibition of hepatic drug-metabolizing enzymes.

Liver Function Tests

Transient increases in the plasma alanine aminotransferase activity follow administration of enflurane and desflurane, but not isoflurane administration, to human volunteers (Fig. 4-60). Transient increases in plasma concentrations of alpha glutathione transferase (sensitive indicator of hepatocellular injury) follow administration of isoflurane or desflurane for surgical anesthesia. In the presence of surgical stimulation, bromsulphalein retention and increases in liver enzymes follow transiently the administration of even isoflurane, suggesting that changes in hepatic blood flow evoked by painful stimulation can adversely alter hepatic function independent of the volatile anesthetic.

Hepatotoxicity

Postoperative liver dysfunction has been associated with most volatile anesthetics, with halothane receiving the most attention. Injected and inhaled anesthetics studied in the hypoxic rat model that includes enzyme induction may produce centrilobular necrosis, but the incidence is greatest with halothane. It is likely that inadequate hepatocyte oxygenation (oxygen supply relative to oxygen demand) is the principal mechanism responsible for hepatic dysfunction that follows anesthesia and surgery. Any anesthetic that decreases alveolar ventilation and/or decreases hepatic blood flow could interfere with adequate hepatocyte oxygenation. Enzyme induction increases oxygen demand and could make patients vulnerable to decreased hepatic oxygen supply due to anesthetic-induced ventilatory or circulatory events that decrease hepatic oxygen delivery. Preexisting liver disease, such as hepatic cirrhosis, may be associated with marginal hepatocyte oxygenation, which would be further
Jeopardized by the depressant effects of anesthetics on hepatic blood flow and/or arterial oxygenation. Indeed, liver transaminase enzymes are increased more in cirrhotic than noncirrhotic animals exposed to halothane (Fig. 4-62).\(^{231}\) Hypothermia, which decreases hepatic oxygen demand, may protect the liver from drug-induced events that decrease hepatic oxygen delivery.

**Halothane**

Halothane produces two types of hepatotoxicity in susceptible patients. An estimated 20% of adult patients receiving halothane develop a mild, self-limited postoperative hepatotoxicity that is characterized by nausea,
It is likely that the more common self-limited form of hepatic dysfunction following halothane is a nonspecific drug effect due to changes in hepatic blood flow that impair hepatic oxygenation. Conversely, the rarer, life-threatening form of hepatic dysfunction characterized as halothane hepatitis is most likely an immune-mediated hepatotoxicity.²²⁹

**Halothane Hepatitis**

Clinical manifestations of halothane hepatitis that suggest an immune-mediated response include eosinophilia, fever, rash, arthralgia, and prior exposure to halothane. Risk factors commonly associated with halothane hepatitis include female gender, middle age, obesity, and multiple exposures to halothane. The predominant histologic feature is acute hepatitis. The most compelling evidence for an immune-mediated mechanism is the presence of circulatory immunoglobulin G antibodies in at least 70% of those patients with the diagnosis of halothane hepatitis.²²⁹ These antibodies are directed against liver microsomal proteins on the surface of hepatocytes that have been covalently modified by the reactive oxidative trifluoroacetyl halide metabolite of halothane to form neoantigens (Fig. 4-63).²³⁶ This acetylation of liver proteins in effect changes these proteins from self to nonself (neoantigens), resulting in the formation of antibodies against this new protein. It is presumed that the subsequent antigen–antibody interaction is responsible for the liver injury characterized as halothane hepatitis. The possibility of a genetic susceptibility factor is suggested by case reports of halothane hepatitis in closely related relatives.²³⁷,²³⁸ Indeed, metabolism of halothane appears to be under genetic influence in humans.²³⁹

**FIGURE 4-61** Hepatic damage may occur in the rat model after administration of inhaled or injected drugs when the inhaled oxygen concentration is 10%. Conversely, hepatic damage occurs after administration of halothane, but not enflurane or isoflurane, when the inhaled concentration of oxygen is 12% or 14%. (From Shingu K, Eger EI, Johnson BH, et al. Effect of oxygen concentration, hyperthermia, and choice of vendor on anesthetic-induced hepatic injury in rats. *Anesth Analg.* 1983;62:146–150, with permission.)

**FIGURE 4-62** Increases (mean ± SE) in liver transaminase enzymes after administration of 1.05% halothane for 3 hours to noncirrhotic or cirrhotic rats. (From Baden JM, Serra M, Fujinaga ME, et al. Halothane metabolism in cirrhotic rats. *Anesthesiology.* 1987;67:660–664, with permission.)

**FIGURE 4-63** Halothane is metabolized to a trifluoroacetylated (TFA) adduct that binds to liver proteins. In susceptible patients, this adduct (altered protein) is seen as nonself (neoantigen), generating an immune response (production of antibodies). Subsequent exposure to halothane may result in hepatotoxicity. A similar process may occur in genetically susceptible individuals after anesthetic exposure to other fluorinated volatile anesthetics (enflurane, isoflurane, desflurane) that also generate a TFA adduct. (From Njoku D, Laster MJ, Gong DH, et al. Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. *Anesth Analg.* 1997;84:173–178, with permission.)
Several observations suggest that reductive metabolism is not the primary mechanism in the development of halothane hepatitis. For example, neither enflurane nor isoflurane undergoes reductive metabolism, yet these drugs both produce centrilobular necrosis in the hypoxic rat model. Furthermore, metabolites produced by reductive metabolism of halothane do not themselves produce hepatotoxicity. Finally, fasting does not alter metabolism but enhances hepatotoxicity by volatile anesthetics.

**Enflurane, Isoflurane, and Desflurane**

The mild, self-limited postoperative hepatic dysfunction that is associated with all the volatile anesthetics most likely reflect anesthetic-induced alterations in hepatic oxygen delivery relative to demand that results in inadequate hepatocyte oxygenation. More disturbing, however, is the realization that enflurane, isoflurane, and desflurane are oxidatively metabolized by liver cytochrome P450 enzymes to form acetylated liver protein adducts by mechanisms similar to that of halothane (Fig. 4-64). As a result, acetylated liver proteins capable of evoking an antibody response could occur after exposure to halothane, enflurane, isoflurane, or desflurane. Indeed, trifluoroacetyl-modified proteins have been described in a patient with hepatitis associated with isoflurane. This raises the possibility that enflurane, isoflurane, and desflurane could produce hepatotoxicity by a mechanism similar to that of halothane but at a lower incidence because the degree of anesthetic metabolism appears to be directly related to the potential for hepatic injury. Considering the magnitude of metabolism of these volatile anesthetics, it is predictable that the incidence of anesthetic-induced hepatitis would be greatest with halothane, intermediate with enflurane, and rare with isoflurane. Desflurane is metabolized even less than isoflurane, and from the standpoint of immune-mediated hepatotoxicity, desflurane should be very safe because it would have the lowest level of adduct formation. Nevertheless, even very small amounts of adduct may be able to produce an immune response manifesting clinically as drug-induced hepatitis. (From Martin JL, Plevak DJ, Flannery KD, et al. Hepatotoxicity after desflurane anesthesia. *Anesthesiology*. 1995;83:1125–1129, with permission.)

**FIGURE 4-64** Pathways for the oxidative metabolism of fluorinated volatile anesthetics by cytochrome P450 enzymes to form acetylated protein adducts. In genetically susceptible individuals, the resulting trifluoroacetates are thought to produce an immune response manifesting clinically as drug-induced hepatitis. (From Martin JL, Plevak DJ, Flannery KD, et al. Hepatotoxicity after desflurane anesthesia. *Anesthesiology*. 1995;83:1125–1129, with permission.)
to precipitate massive hepatotoxicity, particularly if the patient was previously sensitized against trifluoroacetyl proteins. Indeed, hepatotoxicity after desflurane anesthesia has been described in a patient who may have been previously sensitized by exposure to halothane 18 years and 12 years previously. Fulminant hepatic failure accompanied by high plasma concentrations of CYP2A6 autoantibodies has been observed in a patient 22 years following exposure to enflurane. Similarly, halothane may be able to sensitize patients against protein adducts formed by other fluorinated volatile anesthetics.

The risk of fulminant hepatic failure after exposure to enflurane, isoflurane, or desflurane after previous exposure to halothane is probably less than the overall risk associated with anesthesia.

Environmental exposure of operating room personnel to trace concentrations of volatile anesthetics could stimulate antibody production. Indeed, measurement of plasma autoantibody concentrations demonstrated increased levels in pediatric anesthesiologists (especially females) compared with general anesthesiologists and controls. It is presumed that pediatric anesthesiologists experience greater occupational exposure to trace concentrations of volatile anesthetics due to the frequent use of nonbreathing anesthesia delivery systems and use of uncuffed endotracheal tubes. Despite these higher antibody levels, pediatric anesthesiologists did not have increased liver transaminase enzymes compared with general anesthesiologists, suggesting these antibodies may be insufficient to cause appreciable damage to normal hepatic cells.

Sevoflurane

The chemical structure of sevoflurane, unlike that of other fluorinated volatile anesthetics, dictates that it cannot undergo metabolism to an acetyl halide (Fig. 4-65). Sevoflurane metabolism does not result in the formation of trifluoroacetylated liver proteins and therefore cannot stimulate the formation of antitrifluoroacetylated protein antibodies. In this regard, sevoflurane differs from halothane, enflurane, and desflurane, all of which are metabolized to reactive acetyl halide metabolites. Therefore, unlike all the other fluorinated volatile anesthetics, sevoflurane would not be expected to produce immune-mediated hepatotoxicity or to cause cross-sensitivity in patients previously exposed to halothane. Rare reported cases of sevoflurane hepatotoxicity are without explanation or proven cause and effect.

Compound A, a product of sevoflurane interaction with carbon dioxide absorbents, is hepatotoxic in animals, but the concentration present in the anesthesia breathing circuit is far below the toxic level in animals. Nevertheless, small increases in the plasma alanine aminotransferase have been observed in volunteers receiving sevoflurane for prolonged periods of time during which the compound A concentration averaged 41 ppm. Similar changes in the plasma transaminase concentrations did not occur in volunteers receiving desflurane, suggesting that mild transient hepatic injury was limited to the sevoflurane-treated individuals. Conversely, others have not observed differences in liver function enzyme changes in patients receiving sevoflurane compared with isoflurane.

Renal Effects

Volatile anesthetics produce similar dose-related decreases in renal blood flow, glomerular filtration rate, and urine output. These changes are not a result of the release of arginine vasopressin hormone but rather most likely reflect the effects of volatile anesthetics on systemic blood pressure and cardiac output. Preoperative hydration attenuates or abolishes many of the changes in renal function associated with volatile anesthetics. Renal function after kidney transplantation is not uniquely influenced by the volatile anesthetic administered. Volatile anesthetics appear to induce a protective activity on the kidney similar to that of the heart via spingosine kinase and spingosine-1-phosphate generation.

Fluoride-Induced Nephrotoxicity

Fluoride-induced nephrotoxicity (polyuria, hypernatremia, hyperosmolarity, increased plasma creatinine, inability to concentrate urine) was first recognized in patients after the administration of methoxyflurane, which undergoes extensive metabolism (70% of the absorbed dose) to inorganic fluoride, which acts as a renal toxin. In these patients, no renal effects were observed when peak plasma fluoride was <40 μmol/L, subclinical toxicity was accompanied by peak plasma fluoride concentrations of 50 to 80 μmol/L, and clinical toxicity occurred when peak plasma fluoride concentrations were >80 μmol/L. The methoxyflurane nephrotoxicity theory has been extended to other fluorinated volatile anesthetics despite the absence of data to support...
this extrapolation. Furthermore, a plasma fluoride concentration of 50 \( \mu \text{mol/L} \) has been adopted as an indicator that renal toxicity may occur from other volatile anesthetics. Nevertheless, all volatile anesthetics introduced since methoxyflurane undergo significantly less metabolism, and their decreased solubility compared with methoxyflurane means that substantial amounts of the anesthetic are exhaled and thus not available for hepatic metabolism to fluoride. The absence of renal toxicity despite peak plasma fluoride concentrations exceeding 50 \( \mu \text{mol/L} \) after administration of enflurane or sevoflurane suggests that this peak value alone cannot be accepted as an indicator for fluoride-induced nephrotoxicity after administration of these volatile anesthetics. Reversible depression of urine concentrating ability observed in healthy volunteers following prolonged enflurane administration (8 hours) may reflect alkaline degradation products of enflurane that are conjugated to thiol compounds, forming S-conjugates. Enzyme induction, obesity, and preexisting renal dysfunction appear to be risk factors for enflurane nephrotoxicity.

**Sevoflurane**

Sevoflurane is metabolized to inorganic fluoride, and peak plasma fluoride concentrations consistently exceed those peak levels that occur after a comparable dose of enflurane (Fig. 4-66).\(^{260–263}\) Despite higher peak plasma fluoride concentrations compared with enflurane, prolonged sevoflurane anesthesia does not impair renal concentrating function as evaluated with desmopressin testing 1 and 5 days postanesthesia in healthy volunteers (Fig. 4-67).\(^{260,262}\) In the same report, two patients receiving enflurane developed transient impairment of renal concentrating ability despite lower peak plasma fluoride concentrations than the patients receiving sevoflurane.\(^{262}\) In another report, there were no significant differences between urine concentrating abilities after enflurane (6 MAC hours) or sevoflurane (9 MAC hours).\(^{263}\)

Despite reports failing to show renal impairment after the administration of sevoflurane, there are observations of transient impairment of renal concentrating ability and increased urinary excretion of \( \beta \)-N-acetylglucosaminidase (NAG) in patients exposed to sevoflurane and developing peak plasma inorganic fluoride concentrations >50 \( \mu \text{mol/L} \) (Figs. 4-68 and 4-69).\(^{264}\) Urinary excretion of NAG is considered an indicator of acute proximal renal tubular injury. Despite these changes, the blood urea nitrogen and plasma creatinine did not change, and the authors concluded that clinically significant renal damage did not accompany administration of sevoflurane to patients with no preexisting renal disease. Concern that
It has been postulated that intrarenal production of inorganic fluoride may be a more important factor for nephrotoxicity than hepatic metabolism that causes increased plasma fluoride concentrations. This would explain why patients with increased plasma concentrations of fluoride after administration of sevoflurane occasionally experience less renal dysfunction than patients receiving enflurane and manifesting lower plasma fluoride concentrations (see Figs. 4-66 and 4-67). Presumably, inhaled anesthetics such as methoxyflurane and enflurane undergo greater intrarenal metabolism to fluoride than sevoflurane whereas sevoflurane undergoes greater hepatic metabolism, thus accounting for the higher plasma concentrations of fluoride.

Vinyl Halide Nephrotoxicity

Carbon dioxide absorbents containing potassium and sodium hydroxide react with sevoflurane and eliminate hydrogen fluoride from its isopropyl moiety to form breakdown products (see Fig. 4-5). The degradation product produced in greatest amounts is fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether (compound A). Compound A is a dose-dependent nephrotoxin in rats causing proximal renal tubular injury at concentrations of 50 to 100 ppm. The concentration of compound A fatal to 50% of rats after a 3-hour exposure is about 400 ppm.

In patients, the mean maximum concentration of compound A in the anesthesia breathing circuit averages 19.7, 8.1, and 2.1 ppm during fresh gas flows of 1, 3, and 6 L per minute, respectively (Fig. 4-71). During closed-circuit anesthesia with sevoflurane administered to patients undergoing operations lasting longer than 5 hours, the average concentration of compound A in the anesthesia circuit was <20 ppm and no evidence of renal dysfunction occurred based on measurements of blood urea nitrogen and plasma creatinine concentrations (Fig. 4-72). Higher concentrations of compound A...
occurred in the presence of Baralyme (no longer clinically available) probably as a result of higher absorbent temperatures compared with soda lime.\textsuperscript{5,82} Similarly, carbon dioxide production increases the absorbent temperature and thus the production of compound A. Probenecid is a selective inhibitor of organic anion transport and pre-treatment with this drug prevents compound A–induced renal injury in rats and may provide similar protection in humans.\textsuperscript{274} The rationale for utilizing at least a 2 L per minute fresh gas flow rate when administering sevoflurane is intended to minimize the concentration of compound A that may accumulate in the anesthesia breathing circuit. To assess the adequacy of this recommendation, the nephrotoxicity of 2, 4, or 8 hours of anesthesia with 1.25 MAC sevoflurane has been compared with a similar exposure to desflurane.\textsuperscript{255,275} Compound A concentrations ranged from 40 to 42 ppm during the three different durations of sevoflurane administration. In patients receiving 1.25 MAC sevoflurane for 8 hours or 4 hours, there was transient evidence of injury to the glomeruli (albuminuria), proximal renal tubules (glucosuria and increased urinary excretion of glutathione-S-transferase), and distal renal tubules (increased urinary excretion of glutathione-S-transferase) that was greater in the 8-hour group. Urine-concentrating ability and plasma creatinine were not altered despite these findings in the patients receiving sevoflurane. Desflurane administered at 1.25 MAC for 2, 4, or 8 hours or sevoflurane exposure for 2 hours did not produce any evidence of renal injury. Conversely, comparisons of the renal effects of sevoflurane and isoflurane using fresh gas flows of 1 L per minute or less demonstrated no difference between these drugs based on measurement of indices of renal function.\textsuperscript{276,277} In children, sevoflurane anesthesia lasting 4 hours using total fresh gas flows of 2 L per minute produced concentrations of compound A of <15 ppm, and there was no evidence of renal dysfunction.\textsuperscript{278}

The amount of compound A produced under clinical conditions has consistently been far below those concentrations associated with nephrotoxicity in animals.\textsuperscript{5} A proposed mechanism for nephrotoxicity is metabolism of compound A via the beta-lyase pathway to a reactive thiol. Because humans have less than one-tenth of the enzymatic activity for this pathway compared to rats, it is possible that humans should be less vulnerable to injury by this mechanism. Nevertheless, there are data indicating that humans are not less vulnerable to injury from compound A compared with rats.\textsuperscript{275} Halothane, like sevoflurane, is degraded by carbon dioxide absorbents to unsaturated volatile compounds that are nephrotoxic to rats. Based on the long history of halothane use without evidence of nephrotoxicity, it has been suggested the same may also be true for sevoflurane. There is evidence, however, that the product of halothane breakdown (CF\textsubscript{2} = CBrCl) from exposure to carbon dioxide absorbents is less nephrotoxic than compound A.\textsuperscript{279} For this reason, the clinical absence of halothane nephrotoxicity does not necessarily indicate a similar absence for sevoflurane.

**Skeletal Muscle Effects**

**Neuromuscular Junction**

Volatile anesthetics inhibit muscle type nicotinic receptors incompletely at MAC concentrations.\textsuperscript{280} Ether derivative fluorinated volatile anesthetics produce skeletal muscle relaxation that is about twofold greater than that associated with a comparable dose of halothane. Nitrous oxide does not relax skeletal muscles, and in doses of >1 MAC (delivered in a hyperbaric chamber), it may produce skeletal muscle rigidity.\textsuperscript{140} This effect of nitrous oxide is consistent with enhancement of skeletal muscle rigidity produced by opioids when low concentrations of nitrous oxide are administered. The ability of skeletal muscles to sustain contractions in response to continuous stimulation is impaired in the presence of increasing concentrations of ether derivative volatile anesthetics but not in the presence of halothane or nitrous oxide (Fig. 4-73).\textsuperscript{1}

Volatile anesthetics produce dose-dependent enhancement of the effects of neuromuscular-blocking drugs, with the effects of enflurane, isoflurane, desflurane, and sevoflurane being similar and greater than halothane (see Chapter 8). In vitro, isoflurane and halothane produce similar potentiation of the effects of neuromuscular-blocking drugs.\textsuperscript{281} Nitrous oxide does not significantly potentiate the in vivo effects of neuromuscular-blocking drugs.

**Malignant Hyperthermia**

All volatile anesthetics including desflurane and sevoflurane can trigger malignant hyperthermia in genetically susceptible patients even in the absence of concomitant administration of succinylcholine.\textsuperscript{282–284} In one report,
Conversely, uterine relaxation produced by volatile anesthetics may contribute to blood loss due to uterine atony. Indeed, blood loss during therapeutic abortion is greater in patients anesthetized with a volatile anesthetic compared with that in patients receiving nitrous oxide–barbiturate–opioid anesthesia.\(^2\)\(^9\)\(^0\),\(^2\)\(^9\)\(^1\) Propofol inhibits uterine contractility only slightly at anesthetic concentrations.\(^2\)\(^9\)\(^2\)

In animals, evidence of fetal distress does not accompany anesthetic-induced decreases in maternal uterine blood flow as long as the anesthetic concentration is \(<\) 1.5 MAC.\(^2\)\(^9\)\(^3\) Furthermore, volatile anesthetics at about 0.5 MAC concentrations combined with 50% nitrous oxide ensure amnesia during cesarean section and do not produce detectable effects in the neonate.\(^2\)\(^9\)\(^4\) Inhaled anesthetics rapidly cross the placenta to enter the fetus, but these drugs are likewise rapidly exhaled by the newborn infant. Nitrous oxide–induced analgesia for vaginal delivery develops more rapidly than with most volatile anesthetics (desflurane and sevoflurane may be exceptions), but, after about 10 minutes, all inhaled drugs provide comparable analgesia. Despite the popularity of nitrous oxide for intrapartum analgesia, in animal models, nitrous oxide–induced analgesia dissipates rapidly while only sedative properties remain.\(^2\)\(^9\)\(^5\) It is not known over what period of time the analgesic properties recover.

**Obstetric Effects**

Volatile anesthetics produce similar and dose-dependent decreases in uterine smooth muscle contractility and blood flow (Fig. 4-74).\(^1\)\(^0\)\(^0\),\(^2\)\(^8\)\(^8\),\(^2\)\(^8\)\(^9\) These changes are modest at 0.5 MAC (analgesic concentrations) and become substantial at concentrations of \(\geq 1\) MAC. Nitrous oxide does not alter uterine contractility in doses used to provide analgesia during vaginal delivery. As such, nitrous oxide is particularly useful in obstetrical anesthesia to reduce the need to volatile anesthetic that promotes uterine atony while avoiding opioids and benzodiazepines that may cause prolonged depression of the newborn.

In some settings, anesthetic-induced uterine relaxation may be desirable to facilitate removal of retained placenta but nitroglycerine can also be used for this purpose.

**Resistance to Infection**

Many normal functions of the immune system are depressed after patient exposure to the combination of anesthesia and surgery.\(^2\)\(^9\)\(^6\) It would seem that many of the immune changes seen in surgical patients are primarily the result of surgical trauma and the subsequent endocrine (increased catecholamines and corticosteroids) and inflammatory responses (cytokines and chemokines) rather than the result of the anesthetic exposure itself. However, inhaled anesthetics, particularly nitrous oxide, produce dose-dependent inhibition of polymorphonuclear leukocytes and their subsequent migration (chemotaxis) for phagocytosis, which is necessary for the inflammatory...
response to infection. Nevertheless, decreased resistance to bacterial infection due to inhaled anesthetics seems unlikely, considering the duration of administration and dose of these drugs. Furthermore, when leukocytes reach the site of infection, their ability to phagocytize bacteria appears to be normal.

Inhaled anesthetics do not have bacteriostatic effects at clinically used concentrations. Conversely, the liquid form of volatile anesthetics may be bactericidal. All volatile anesthetics (doses as low as 0.2 MAC) produce dose-dependent inhibition of measles virus replication and decrease mortality in mice receiving intranasal influenza virus. This inhibition may reflect anesthetic-induced decreases in DNA synthesis.

**Genetic Effects**

The Ames test, which identifies chemicals that act as mutagens and carcinogens, is negative for enflurane, isoflurane, desflurane, sevoflurane, and nitrous oxide, and their known metabolites. Compound A, which is formed from sevoflurane degradation by carbon dioxide absorbents, might be expected to be an alkylating agent (and thus a mutagen), but tests of this product do not reveal mutagenicity. Halothane also results in a negative Ames test, but some of its potential metabolites may be positive. In animals, nitrous oxide administered during vulnerable periods of gestation may result in adverse reproductive effects manifesting as an increased incidence of fetal resorptions (abortions). Conversely, administration of volatile anesthetics during these vulnerable periods does not increase the incidence of fetal resorptions. Learning may be impaired in newborn animals exposed in utero to inhaled anesthetics. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. The widespread neuronal degeneration that results is thought to be a natural programmed response to synaptic silencing. Prolonged anesthesia with ketamine in neonatal monkeys (more than 9 hours) results in neuronal degeneration in the frontal cortex. Whether normal exposures of young children to anesthetics for typical time periods could have neurodevelopmental effects is not known but is being actively studied.

Studies of the risk of spontaneous abortion in operating room personnel that were conducted before modern scavenging procedures have suggested an increase in risk. A more recent meta-analysis that considered the relative value of comparison groups has placed the relative risk of anesthetic exposure at 1.9. The increased incidence of spontaneous abortions in operating room personnel in older studies may reflect a teratogenic effect from chronic exposure to trace concentrations of inhaled anesthetics, especially nitrous oxide. Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin B₁₂ such that the activity of vitamin B₁₂-dependent enzymes (methionine synthetase and thymidylate synthetase) is decreased. In patients undergoing laparotomy with general anesthesia including 70% nitrous oxide, the half-time for inactivation of methionine synthetase is about 46 minutes (Fig. 4-75). Volatile anesthetics do not alter activity of vitamin B₁₂-dependent enzymes.

Methionine synthetase converts homocysteine to methionine, which is necessary for the formation of myelin. Thymidylate synthetase is important in the conversion of DNA to thymidine and the subsequent formation of DNA. Interference with myelin formation and DNA synthesis could have significant effects on the rapidly growing fetus, manifesting as spontaneous abortions or congenital anomalies. Inhibition of these enzymes could also manifest as depression of bone marrow function and neurologic disturbances. The speculated but undocumented role of trace concentrations of nitrous oxide in the production of spontaneous abortions has led to the use of scavenging systems designed to remove waste anesthetic gases, including nitrous oxide, from the ambient air of the operating room. Health care workers exposed to nitrous oxide have lower levels of vitamin B₁₂ in proportion to their exposure.

**Bone Marrow Function**

Interference with DNA synthesis is responsible for the megaloblastic changes and agranulocytosis that may follow prolonged administration of nitrous oxide. Megaloblastic changes in bone marrow are consistently found in patients who have been exposed to anesthetic concentrations of nitrous oxide for 24 hours. Exposure to nitrous oxide lasting 4 days or longer results in agranulocytosis. These bone marrow effects occur as a result of nitrous
is the ability of nitrous oxide to oxidize irreversibly the co-balt atom of vitamin B<sub>12</sub> such that activity of vitamin B<sub>12</sub>-dependent enzymes is decreased (see the section “Genetic Effects”).

**Total Body Oxygen Requirements**

Total body oxygen requirements are decreased by similar amounts by different volatile anesthetics. The oxygen requirements of the heart decrease more than those of other organs, reflecting drug-induced decreases in cardiac work associated with decreases in systemic blood pressure and myocardial contractility. Therefore, decreased oxygen requirements would protect tissues from ischemia that might result from decreased oxygen delivery due to drug-induced decreases in perfusion pressure. Decreases in total body oxygen requirements probably reflect metabolic depressant effects as well as decreased functional needs in the presence of anesthetic-produced depression of organ function.

**Metabolism**

The metabolism of inhaled anesthetics is very small but is important for two reasons. First, intermediary metabolites, end-metabolites, or breakdown products from exposure to carbon dioxide absorbents may be toxic to the kidneys, liver, or reproductive organs. Second, the degree of metabolism may influence the rate of decrease in the alveolar partial pressure at the conclusion of the anesthetic for the most highly metabolized drugs such as halothane and methoxyflurane. Conversely, the rate of increase in the alveolar partial pressure during induction of anesthesia is unlikely to be influenced by metabolism because inhaled anesthetics are administered in great excess to the amount metabolized. Metabolism of modern drugs does not significantly affect either onset or offset of drug concentration.

Assessment of the magnitude of metabolism of inhaled anesthetics is by (a) measurement of metabolites or (b) comparison of the total amount of anesthetic recovered in the exhaled gases with the amount taken up during administration (mass balance). The advantages of the mass balance technique are that knowledge of metabolite pharmacokinetics and identification and collection of metabolites are not necessary. Indeed, recovery of metabolites may be incomplete, leading to an underestimation of the magnitude of metabolism. A disadvantage of the mass balance approach is that loss of anesthetic through the surgical skin incision, across the intact skin, in urine, and in feces may prevent complete recovery, and these losses would be construed as due to metabolism. Nevertheless, the error introduced by these losses is likely to be insignificant, with the occasional exception of large and highly perfused wound surfaces.

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**Peripheral Neuropathy**

Animals exposed to 15% nitrous oxide for up to 15 days develop ataxia and exhibit evidence of spinal cord and peripheral nerve degeneration. Humans who chronically inhale nitrous oxide for nonmedical purposes may develop a neuropathy characterized by sensorimotor polyneuropathy that is often combined with signs of posterior lateral spinal cord degeneration resembling pernicious anemia. The speculated mechanism of this neuropathy is the ability of nitrous oxide to oxidize irreversibly the co-
Part II • Neurologic System

zyme activity, (c) blood concentration of the anesthetic, and (d) genetic factors.

Chemical Structure

The ether bond and carbon-halogen bond are the sites in the anesthetic molecule most susceptible to oxidative metabolism. Oxidation of the ether bond is less likely when hydrogen atoms on the carbons surrounding the oxygen atom of this bond are replaced by halogen atoms. Two halogen atoms on a terminal carbon represent the optimal arrangement for dehalogenation, whereas a terminal carbon with fluorine atoms is very resistant to oxidative metabolism. The bond energy for carbon-fluorine is twice that for carbon-bromine or carbon-chlorine. The absence of ester bonds in inhaled anesthetics negates any role of metabolism by hydrolysis.

Hepatic Enzyme Activity

The activity of hepatic cytochrome P450 enzymes responsible for metabolism of volatile anesthetics may be increased by a variety of drugs, including the anesthetics themselves. Phenobarbital, phenytoin, and isoniazid may increase defluorination of volatile anesthetics, especially enflurane. There is evidence in patients that brief (1 hour) exposures during surgical stimulation increase hepatic microsomal enzyme activity independently of the anesthetic drug (halothane or isoflurane) or technique (spinal) used. Conversely, surgery lasting &gt;4 hours can lead to depressed microsomal enzyme activity.

For unknown reasons, obesity predictably increases defluorination of halothane, enflurane, and isoflurane. Peak plasma fluoride concentrations after administration of sevoflurane are higher in obese compared with nonobese patients (Fig. 4-77). Conversely, another report describes no difference in peak plasma fluoride concentrations based on body weight.

Blood Concentration

The fraction of anesthetic that is metabolized on passing through the liver is influenced by the blood concentration of the anesthetic (Fig. 4-78). For example, a 1 MAC

<table>
<thead>
<tr>
<th>Table 4-9</th>
<th>Magnitude of Metabolism</th>
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<tbody>
<tr>
<td>Anesthetic</td>
<td>Metabolite Recovery (%)</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0.004</td>
</tr>
<tr>
<td>Halothane</td>
<td>15–20</td>
</tr>
<tr>
<td>Enflurane</td>
<td>3</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0.2</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.02</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>5</td>
</tr>
</tbody>
</table>

*aMetabolism of isoflurane assumed to be 0 for this calculation. Data adapted from Carpenter RL, Eger EI, Johnson BH, et al. The extent of metabolism of inhaled anesthetics in humans. *Anesthesiology. 1986;65: 201–205.*

Comparison of metabolite recovery and mass balance studies results in greatly different estimates of the magnitude of metabolism of volatile anesthetics (Table 4-9). For example, mass balance estimates of the magnitude of metabolism are 1.5 to 3 times greater than estimates determined by the recovery of metabolites. This is not surprising because recovery of metabolites will underestimate the magnitude of metabolism unless all metabolites are recovered. Based on mass balance studies, it is concluded that alveolar ventilation is principally responsible for the elimination of enflurane and isoflurane (presumably also desflurane and sevoflurane), metabolism plays an increasing role for elimination of halothane, and that metabolism is the most important mechanism for the elimination of methoxyflurane.

Determinants of Metabolism

The magnitude of metabolism of inhaled anesthetics is determined by the (a) chemical structure, (b) hepatic enzyme activity, (c) blood concentration of the anesthetic, and (d) genetic factors.
free radicals that could produce toxic effects on cells. The potential toxic role of these metabolites, however, remains undocumented. Oxygen concentrations of >10% in the gastrointestinal tract and antibiotics inhibit metabolism of nitrous oxide by anaerobic bacteria. There is no evidence that nitrous oxide undergoes oxidative metabolism in the liver.321

**Halothane**

An estimated 15% to 20% of absorbed halothane undergoes metabolism (see Table 4-9).239 Halothane is uniquely metabolized because it undergoes oxidation by cytochrome P450 enzymes when ample oxygen is present but reductive metabolism when hepatocyte $P_0^2$ decreases.

**Oxidative Metabolism**

The principal oxidative metabolites of halothane resulting from metabolism by cytochrome P450 enzymes are trifluoroacetic acid, chloride, and bromide. In genetically susceptible patients, a reactive trifluoroacetyl halide oxidative metabolite of halothane may interact with (acetylate) hepatic microsomal proteins on the surfaces of hepatocytes (neoantigens) to stimulate the formation of antibodies against this new foreign protein (see Fig. 4-64).241 These autoantibodies can cause severe necrotic liver failure in rare cases.

The energy bond for carbon-fluorine is strong, accounting for the absence of detectable amounts of inorganic fluoride as an oxidative metabolite of halothane. It is estimated that the plasma concentration of bromide increases 0.5 mEq/L for every MAC hour of halothane administration (Fig. 4-79).322 Because signs of bromide toxicity, such as somnolence and confusion, do not occur until plasma concentrations of bromide are >6 mEq/L, the likelihood of symptoms from metabolism of halothane to bromide seems remote. Nevertheless, prolonged halothane anesthesia may more likely be associated with concentration saturates hepatic enzymes and decreases the fraction of anesthetic that is removed (metabolized) during a single passage through the liver. Conversely, subanesthetic concentrations (≤0.1 MAC) undergo extensive metabolism on passage through the liver. Disease states such as cirrhosis of the liver or congestive heart failure could theoretically alter metabolism by decreasing hepatic blood flow and drug delivery or by decreasing the amount of viable liver and thus enzyme activity. Inhaled anesthetics that are less soluble in blood and tissues (nitrous oxide, enflurane, isoflurane, desflurane, sevoflurane) tend to be exhaled rapidly via the lungs at the conclusion of an anesthetic. As a result, less drug is available to pass through the liver continually at low blood concentrations conducive to metabolism. This is reflected in the magnitude of metabolism of these drugs (see Table 4-9).50,51 Halothane and methoxyflurane are more soluble in blood and lipids and thus likely to be stored in tissues that act as a reservoir to maintain subanesthetic concentrations conducive to metabolism for prolonged periods of time after discontinuation of their administration.

**Genetic Factors**

Overall, genetic factors appear to be the most important determinant of drug-metabolizing enzyme activity. In this regard, humans are active metabolizers of drugs compared with lower animal species such as the rat.

**Metabolism of Specific Inhaled Anesthetics**

**Nitrous Oxide**

An estimated 0.004% of an absorbed dose of nitrous oxide undergoes reductive metabolism to nitrogen in the gastrointestinal tract.319,320 Anaerobic bacteria, such as *Pseudomonas*, are responsible for this reductive metabolism. Reductive products of some nitrogen compounds include

![FIGURE 4-78](attachment:image.png) Fraction of halothane removed during passage through the liver at progressively decreasing alveolar concentrations. (From Sawyer DC, Eger EI, Bahlam SH, et al. Concentration dependence of hepatic halothane metabolism. *Anesthesiology*. 1971;34:230–235, with permission.)

![FIGURE 4-79](attachment:image.png) Serum bromide concentrations in volunteers after prolonged (about 7 hours) exposure to halothane. (From Johnstone RE, Kennell EM, Behar MG, et al. Increased serum bromide concentration after halothane anesthesia in man. *Anesthesiology*. 1975;42:598–601, with permission.)
intellectual impairment than a similar dose of an anesthetic that is not metabolized to bromide.

**Reductive Metabolism**

Reductive metabolism, which, among the volatile anesthetics, has been documented to occur only during metabolism of halothane, is most likely to occur in the presence of hepatocyte hypoxia and enzyme induction. Reductive metabolites of halothane include fluoride and volatile products, some of which result from the reaction of halothane with carbon dioxide absorbents. In the past, reductive metabolites were considered to be potentially hepatotoxic. Nevertheless, data do not support a role for reductive metabolism in the initiation of halothane hepatitis (see the section "Halothane Hepatitis"). Increased plasma fluoride concentrations reflect reductive metabolism of halothane in obese patients and children with cyanotic congenital heart disease (Fig. 4-80). The level of plasma fluoride (<10 μmol/L) is far below the level likely to produce even subclinical nephrotoxicity (50 μmol/L), and changes in liver transaminase enzymes as evidence of hepatotoxicity due to reductive metabolism are not seen in these patients.

**Enflurane**

An estimated 3% of absorbed enflurane undergoes oxidative metabolism by cytochrome P450 enzymes to form inorganic fluoride and organic fluoride compounds (see Table 4-9). Like halothane, enflurane also undergoes cytochrome P450–mediated oxidative metabolism to adducts, which may cause the formation of neoantigens in susceptible patients (see Fig. 4-64) (see the section "Hepatic Effects"). Fluoride results from dehalogenation of the terminal carbon atom. Oxidation of the ether bond and release of additional fluoride does not occur, reflecting the chemical stability imparted to this bond by the surrounding halogens. As with isoflurane, the methyl portion of the molecule seems to be resistant to oxidative metabolism and reductive metabolism does not occur. Minimal metabolism of enflurane reflects its chemical stability and low solubility in tissues such that the drug is exhaled unchanged rather than repeatedly passing through the liver at low plasma concentrations conducive to metabolism.

Enzyme induction with phenobarbital or phenytoin increases the liberation of fluoride from enflurane in vitro but not in vivo. This observation is most likely due to low tissue solubility of enflurane such that, in vivo, the availability of substrate (enflurane) becomes the rate-limiting factor, whereas in vitro, the substrate concentration is controlled and the effect of enzyme induction manifests as increased metabolism of enflurane to inorganic fluoride. For these reasons, it seems unlikely that the nephrotoxic potential of enflurane would be increased by enzyme induction. An exception may be patients who are being treated with isoniazid, because this drug can increase defluorination of enflurane in genetically determined patients who are rapid acetylators.

**Isoflurane**

An estimated 0.2% of absorbed isoflurane undergoes oxidative metabolism by cytochrome P450 enzymes (see Table 4-9). Metabolism begins with oxidation of the carbon-halogen link of the alpha carbon atom, leading to an unstable compound that subsequently decomposes to difluoromethanol and trifluoroacetic acid (Fig. 4-81). Trifluoroacetic acid is the principal organic fluoride metabolite of isoflurane. Like halothane, isoflurane also undergoes cytochrome P450–mediated oxidative metabolism to adducts, which may cause formation of neoantigens in susceptible patients (see Fig. 4-64) (see the section "Hepatic Effects"). Reductive metabolism of isoflurane does not occur.

Minimal metabolism of isoflurane reflects the drug's chemical stability and low solubility in tissues such that the drug is exhaled unchanged rather than repeatedly passing through the liver at low plasma concentrations conducive to metabolism.
likely parallel those for isoflurane although the greater strength of the carbon-fluorine bond renders desflurane less vulnerable to metabolism than its chlorinated analog, isoflurane (see Fig. 4-81).\(^1\) Metabolism begins with the insertion of an active oxygen atom between the alpha ethyl carbon of desflurane and its hydrogen. The resulting unstable molecule degrades ultimately to inorganic fluoride, trifluoroacetic acid, carbon dioxide, and water. The only evidence of metabolism of desflurane is the presence of measurable concentrations of urinary trifluoroacetic acid equal to about one-fifth to one-tenth that produced by metabolism of isoflurane.\(^{329}\) Neither plasma fluoride concentrations nor urinary organic fluoride excretion increase significantly after even prolonged administration of desflurane (7.4 MAC hours) to humans.\(^{329}\) Enzyme induction with phenobarbital or ethanol does not influence the magnitude of metabolism of desflurane in animals.\(^{330}\) Kinetic studies in humans indicate that all the desflurane absorbed during its administration can be recovered during elimination, emphasizing both the molecular stability of this compound as well as its poor blood and tissue solubility.\(^{32,33}\) Despite its minimal overall metabolism, desflurane also undergoes cytochrome P450–mediated oxidative metabolism to adducts, which may cause formation of neoantigens in susceptible patients (see Fig. 4-64)\(^{241}\) (see the section ”Hepatic Effects”).

**Carbon Monoxide Toxicity**

Carbon monoxide formation reflects the degradation of volatile anesthetics that contain a CHF\(_2\) moiety (desflurane, enflurane, and isoflurane) by the strong bases present in desiccated carbon dioxide absorbents.\(^{331}\) Indeed, increases in intraoperative carboxyhemoglobin concentrations have been attributed to this degradation. Factors that influence the magnitude of carbon monoxide production from volatile anesthetics include (a) dryness of the carbon dioxide absorbent with hydration preventing formation, (b) high temperatures of the carbon dioxide absorbent as during low fresh gas flows and/or increased metabolic production of carbon dioxide, (c) prolonged high fresh gas flows that cause desiccation (dryness) of the carbon dioxide absorbent, and (d) type of carbon dioxide absorbent.\(^{332-335}\) Desflurane produces the highest carbon monoxide concentration (package insert for desflurane describes this risk) followed by enflurane and isoflurane. A carboxyhemoglobin concentration of 36% has been described in a patient receiving desflurane.\(^{336}\) Halothane and sevoflurane do not possess a vinyl group and thus carbon monoxide production on exposure to carbon dioxide absorbents has been considered unlikely. Nevertheless, carbon monoxide formation is a risk of sevoflurane administration in the presence of desiccated carbon dioxide absorbent especially when an exothermic reaction between the volatile anesthetic and desiccated

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**FIGURE 4-81** The proposed metabolic pathways for isoflurane and desflurane are similar. (From Eger EI. Desflurane [Suprane]: A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1–119, with permission.)

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absorbed. In the presence of carbon dioxide absorbent temperatures >70°C, hexafluoroisopropanol, an intermediate of sevoflurane metabolism, degrades to carbon monoxide to a small degree. Nevertheless, completely desiccated carbon dioxide absorbent and high patient minute ventilation could result in significant carbon monoxide exposure. As such, it is not possible to completely avoid hazards of carbon monoxide by using sevoflurane. It is concluded that the potential for carbon monoxide formation is a property of all modern volatile anesthetics contacting dry carbon dioxide absorbents that contain potassium hydroxide and/or sodium hydroxide (patients with low hemoglobin quantities (anemia, pediatric patients) are at greater risk for high carboxyhemoglobin concentrations in response to exposure to carbon monoxide). Precautions to ensure carbon dioxide absorbents that contain strong bases have not become desiccated is important for preventing the formation of carbon monoxide during administration of volatile anesthetics. Current Environmental Protection Agency limits for carbon monoxide exposure are 35 ppm for 1 hour.

**Intraoperative Diagnosis**

Intraoperative detection of carbon monoxide is difficult because pulse oximetry cannot differentiate between carboxyhemoglobin and oxyhemoglobin. Moderately decreased pulse oximetry readings despite adequate arterial partial pressures of oxygen (especially during the first case of the day, “Monday morning phenomena”) should suggest the possibility of carbon monoxide exposure and the need to measure carboxyhemoglobin. Furthermore, there is no routinely available means to reliably identify the presence of carbon monoxide in the breathing circuit nor to detect when carbon dioxide absorbent has become desiccated (absorbent color change does not occur in response to desiccation or carbon monoxide formation). In addition to decreased pulse oximeter readings, an erroneous gas analyzer reading (indicates mixed gas readings or enflurane when desflurane is being administered) has been described as an early indirect warning of carbon monoxide formation. This erroneous gas analyzer reading was attributed to trifluoromethane, which is produced along with carbon monoxide by degradation of isoflurane, enflurane, and desflurane, but not sevoflurane. Trifluoromethane has an infrared absorption profile similar to enflurane resulting in the gas analyzer indicating administration of this volatile anesthetic when the vaporizer is known to contain desflurane or isoflurane. An erroneous gas analyzer reading as an early warning of carbon monoxide exposure does not occur during administration of sevoflurane. Delayed neurophysiologic sequelae due to carbon monoxide poisoning (cognitive defects, personality changes, gait disturbances) may occur as late as 3 to 21 days after anesthesia. Intraoperative hemolysis has the potential to result in carbon monoxide exposure, which can mimic carbon monoxide production from degradation of volatile anesthetics.

**Endogenous Carbon Monoxide**

Endogenous carbon monoxide production reflects heme catabolism. The rate-limiting enzyme in formation of carbon monoxide from heme is heme oxygenase-1. This enzyme is induced by its substrate (heme) and by various oxidative stresses. Heme oxygenase-1 is thought to confer protection against oxidative tissue injuries. Conversion of the heme moiety of hemeproteins (hemoglobin, myoglobin, cytochrome P450) to biliverdin (a green bile pigment) results in liberation of carbon monoxide. This endogenous carbon monoxide diffuses from cells into the circulation to form carboxyhemoglobin and is also transported to the lungs where it is exhaled. Independent of volatile anesthetics and carbon dioxide absorbents, the exhaled carbon monoxide and carboxyhemoglobin concentrations are increased on the day following surgery. This suggests that oxidative stress associated with anesthesia and surgery may induce heme oxygenase-1, which catalyzes heme to produce carbon monoxide.

**Sevoflurane**

An estimated 5% of absorbed sevoflurane undergoes oxidative metabolism by cytochrome P450 enzymes to form organic and inorganic fluoride metabolites (see Table 4-9 and Fig. 4-64). In addition, sevoflurane is degraded by desiccated carbon dioxide absorbents containing strong bases to potentially toxic compounds (see the section “Vinyl Halide Nephrotoxicity”). Unlike all the other fluorinated volatile anesthetics, sevoflurane does not undergo metabolism to acetyl halide that could result in formation of trifluorinated liver proteins. As a result, sevoflurane cannot stimulate the formation of antitrifluoroacetylated protein antibodies leading to hepatotoxicity by this mechanism (see the section “Hepatic Effects”).

Cytochrome P450–mediated sevoflurane oxidation at the fluoromethoxy carbon produces a transient intermediate that decomposes to inorganic fluoride and the organic fluoride metabolite hexafluoroisopropanol. Hexafluoroisopropanol undergoes conjugation with glucuronic acid and this conjugate is excreted in the urine. There is no evidence that hexafluoroisopropanol is toxic.

Peak plasma fluoride concentrations are higher after administration of sevoflurane than after comparable doses of enflurane. Nevertheless, the duration of exposure of renal tubules to fluoride that results from sevoflurane metabolism is limited because of the rapid pulmonary elimination of this poorly blood-soluble anesthetic. Furthermore, hepatic production of fluoride from sevoflurane may be less of a nephrotoxic risk than is intrarenal production of fluoride from enflurane.

Sevoflurane is absorbed and degraded by desiccated carbon dioxide absorbents, especially when the temperature of the absorbent is increased (see Fig. 4-5). Among
these compounds, only compound A (and to a lesser extent compound B) is produced under conditions likely to be encountered clinically. The type of carbon dioxide absorbent may influence the magnitude of compound A production.\(^5\) Compound A is nephrotoxic and hepatotoxic in animals (see the sections “Hepatic Effects” and “Renal Effects”). Nevertheless, the amount of compound A produced under clinically relevant circumstances has always been substantially lower than that which produces toxicity in animals.\(^5\)

**Carbon Dioxide Absorber Fires**

Sevoflurane reacts chemically with desiccated carbon dioxide absorbents (especially Baralyme\(^6\), which is no longer clinically available) to produce carbon monoxide and flammable organic compounds, including methanol and formaldehyde. The reaction produces heat and heat increases the reaction speed so the rate of sevoflurane breakdown can accelerate rapidly. Sevoflurane may be so extensively consumed that maintaining anesthesia is difficult. At high temperatures, flammable metabolites can spontaneously combust (formaldehyde gas). A peak absorbent canister temperature of 120° to 140°C is generally reached 10 to 50 minutes after the start of the reaction followed by a rapid decrease in the canister temperature. In nonhuman trials utilizing anesthesia machines the carbon dioxide absorbent temperatures increased rapidly to greater than 300°C and parts of the absorbent canister melted.\(^221\)

In the presence of desiccated carbon dioxide absorbent, temperature increases are greater with sevoflurane than with other volatile anesthetics, and at absorbent temperatures >70°C, there is increased likelihood of degradation of sevoflurane to flammable products and carbon monoxide (Figs. 4-82 and 4-83)\(^221,337,342\). For example, temperatures of desiccated soda lime exposed to 1.5 MAC isoflurane and desflurane peaked at about 100°C and then decreased progressively, whereas temperatures in desiccated carbon dioxide absorbents exposed to 1.5 MAC increased progressively to nearly 200°C and spontaneous combustion in the anesthesia circuit occurred in some instances (see Fig. 4-83).\(^342\) Spontaneous combustion and even explosions involving the carbon dioxide absorber and anesthesia breathing circuit have been described clinically and are most often (perhaps always) associated with Baralyme\(^6\) carbon dioxide absorbent (no longer clinically available); anesthesia machine use factors that contribute to desiccation of the absorbent (flow of dry gases through the absorber during a weekend, “Monday morning phenomena”) and administration of sevoflurane.\(^221,343–346\) Apparently, under certain conditions, exothermic chemical reactions between sevoflurane and desiccated carbon dioxide absorbent creates high temperatures with production of flammable gases (formaldehyde, methanol) and autoignition of plastics and gases in the absorber. The critical observation regarding fires and production of carbon monoxide is that desiccated carbon dioxide absorbents

![Figure 4-82](image1.png)

**FIGURE 4-82** Carbon monoxide (CO) concentrations in parts per million (ppm) are plotted against absorbent temperatures measured in the center of the canister. Most clinically relevant CO concentrations do not occur until the absorbent temperature exceeds 70°C. (From Holak E, Mei DA, Dunning MB, et al. Carbon monoxide production from sevoflurane breakdown: Modeling of exposures under clinical conditions. *Anesth Analg*. 2003;96:757–764, with permission.)

![Figure 4-83](image2.png)

**FIGURE 4-83** Temperatures recorded from the bottom of the desiccated carbon dioxide absorbent canister peaked at about 100°C when exposed to 1.5 MAC desflurane and isoflurane and then decreased. Temperatures in the desiccated carbon dioxide absorbent canister increased progressively to over 200°C when exposed to 1.5 MAC sevoflurane and spontaneous flames occurred in some of the anesthesia circuits. (From Lester M, Roth P, Eger, EI. Fires from the interaction of anesthetics with desiccated absorbent. *Anesth Analg*. 2004;99:769–774, with permission.)
containing strong bases allow these reactions to occur. Clinically, delayed increases or unexpected sudden decreases in inspired sevoflurane concentrations relative to the vaporizer setting may reflect excessive heating of the carbon dioxide absorber canister. Pulmonary injury has been observed following an exothermic reaction between sevoflurane and the carbon dioxide absorbent.\(^4\)\(^5\) Furthermore, formaldehyde alone as a byproduct of sevoflurane breakdown may cause pulmonary injury.

These dangerous chemical reactions can be avoided by utilizing carbon dioxide absorbents devoid of strong bases.\(^5\)\(^6\) Nevertheless, the ability of absorbents lacking strong bases to adequately absorb carbon dioxide in all situations is unclear.\(^3\)\(^8\) Water also inhibits these chemical reactions but may evaporate particularly with prolonged flows through the absorbent when the breathing circuit is not connected to a patient. Strong bases are included in absorbents to enhance carbon dioxide absorption.

### References


76. Lynch C, Pancrazio JJ. Snails, spiders, and stereospecificity—is there a role for calcium channels in anesthetic mechanisms? Anesthesiology. 1994;81:1–5.


146. Smith 1970?!


QUERIES

AQ1: Please verify what polarographic Po2 measurements are or supply a simpler description, if any.
AQ2: Please include in Figure 4-4 legend the significance of the following symbols seen in the figure: *, †, ¥.
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