Chapter 26

Inhaled Anesthetic Pharmacokinetics: Uptake, Distribution, Metabolism, and Toxicity

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Key Points

- The alveolar inhaled anesthetic concentration ($F_A$) or partial pressure ($P_{alv}$) is important, because it is the driving force determining anesthetic uptake into blood and target tissues in the central nervous system and it can be monitored as a readout of anesthetic dosage. $P_{alv}$ is influenced by both delivery and uptake of anesthetic gas.
- Inhaled anesthetic delivery to patients can be augmented by increased fresh gas flows, vaporizer output settings, and minute ventilation.
- Initial anesthetic uptake into blood increases with increased pulmonary blood flow (cardiac output) and high blood solubility of anesthetic gas. Increased uptake (as with a highly blood-soluble drug or high cardiac output) slows the rate by which anesthesia is induced by slowing the rate of rise of $P_{alv}$. Conversely, low anesthetic solubility in blood is associated with rapid onset and offset of anesthesia.
- Uptake of anesthetic into blood slows as blood and tissue partial pressures increase, resulting in higher anesthetic partial pressure in mixed venous blood.
- The higher the inspired anesthetic concentration, the less it then diminishes because of uptake (the concentration effect). At 100% inspired concentration, uptake does not cause $P_{alv}$ to change. Changes in alveolar volume result in a rapid initial uptake of N₂O, which sustains or increases concentrations of other alveolar gases (the second gas effect).
- Factors that affect anesthetic uptake similarly affect pulmonary clearance of anesthetics. The rate of clearance is also context sensitive; that is, equivalent decreases in alveolar and brain anesthetic concentrations are slower after a long exposure to inhaled anesthetics compared with a short period of exposure of equal depth.
- Toxicities of inhaled anesthetics are primarily related to their biotransformation (metabolism). Significant toxic effects are usually produced in the tissues, such as liver and kidney, in which metabolism occurs. Modern inhaled anesthetics undergo less metabolism than older drugs do, resulting in fewer toxicities.
- Halothane hepatitis is a potentially fatal syndrome of fulminant liver damage after exposure to reactive metabolites produced by oxidation of volatile anesthetics. These metabolites covalently modify liver proteins, creating neohaptens that elicit an immune response against hepatocytes. The incidence of the syndrome varies with different anesthetics, paralleling the extent of drug metabolism: halothane >> enfurane > isoflurane > desflurane.
- Defluorination of inhaled anesthetics occurs in both the liver and kidney. Free fluoride in blood can damage kidneys, resulting in high-output renal failure. Renal toxicity is almost exclusively associated with prolonged exposure to methoxyflurane. Sevoflurane metabolism also results in high fluoride levels in blood, but it does not damage kidneys. Factors that enhance the toxicity of methoxyflurane relative to sevoflurane include its high tissue solubility, slow clearance, and high degree of renal metabolism, resulting in high intrarenal fluoride levels for an extended time.
Chapter 26: Inhaled Anesthetic Pharmacokinetics: Uptake, Distribution, Metabolism, and Toxicity

INTRODUCTION

Modern inhaled anesthetics are important pharmacologic tools for reversibly altering central nervous system functions in patients. Because inhaled anesthetics are both taken up and eliminated through alveolar blood–gas exchange, drug dosage can be monitored in expired alveolar gases, and tissue-dependent metabolism is unnecessary for drug clearance. Optimal delivery of systemic drugs via inhalation requires a full understanding of the factors influencing how gas-phase compounds move into and out of various body tissues and how they are metabolized (pharmacokinetics) together with where and how these drugs and their metabolism affect tissue functions. Reversible anesthetic effects on the nervous, respiratory, and cardiovascular systems (pharmacodynamics) are covered elsewhere in this textbook (see Chapters 25, 27, and 28).

UPTAKE AND DISTRIBUTION OF INHALED ANESTHETICS

In the first part of this chapter, some of the basic concepts of chemical equilibria are reviewed and are applied to illuminate major factors influencing inhaled anesthetic uptake and distribution in patients. For this review, a physiologic model is used that closely simulates clinical observations. The model, an elaboration of that introduced in 1973 by Mapleson,1 is described both qualitatively and quantitatively (using mathematical expressions) to convey important concepts to readers with different learning styles.

BIOPHYSICAL PROPERTIES OF INHALED ANESTHETICS: PARTIAL PRESSURE, HYDROPHOBICITY AND PARTITION COEFFICIENTS

Inhaled anesthetics are administered as a component of a gas mixture. The biophysical properties of inhaled anesthetics are summarized in Table 26-1. Partial pressure is the portion of total pressure contributed by one component of a gas mixture, where each component contributes pressure in direct proportion to its molar fraction. For example, 1.5% isoflurane in air (21% O2 and 79% N2) at 1 atm (760 mm Hg) is a mixture of O2 at 157.2 mm Hg, N2 at 591.4 mm Hg, and isoflurane at 11.4 mm Hg. The partial pressure of an anesthetic gas is a measure of thermodynamic activity of the gas and determines its pharmacologic effect. The partial pressure of an anesthetic is usually reported as the percentage (or fraction)
### TABLE 26-1  CHEMICAL STRUCTURES AND PROPERTIES OF INHALED ANESTHETICS

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Nitrous Oxide</th>
<th>Halothane</th>
<th>Methoxyflurane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>$\begin{array}{c} \text{N} = \text{N} - \text{O} \ \uparrow \end{array}$</td>
<td>$\begin{array}{c} \text{F} \ \text{Br} \end{array}$</td>
<td>$\begin{array}{c} \text{Cl} \ \text{F} \ \text{H} \end{array}$</td>
<td>$\begin{array}{c} \text{F} \ \text{F} \ \text{F} \end{array}$</td>
<td>$\begin{array}{c} \text{F} \ \text{H} \ \text{F} \end{array}$</td>
<td>$\begin{array}{c} \text{F} \ \text{F} \ \text{F} \end{array}$</td>
<td>$\begin{array}{c} \text{CF}_{3} \ \text{H} \end{array}$</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>44.0</td>
<td>197.4</td>
<td>165.0</td>
<td>184.5</td>
<td>184.5</td>
<td>168</td>
<td>200.1</td>
</tr>
<tr>
<td>Boiling point (° C)</td>
<td>-88.5</td>
<td>50.2</td>
<td>104.8</td>
<td>56.5</td>
<td>48.5</td>
<td>22.8</td>
<td>58.6</td>
</tr>
<tr>
<td>Density (g/mL)</td>
<td>$1.84 \times 10^{-1}$</td>
<td>1.86</td>
<td>1.42</td>
<td>1.52</td>
<td>1.5</td>
<td>1.45</td>
<td>1.50</td>
</tr>
<tr>
<td>Vapor pressure (mm Hg)</td>
<td>43.880</td>
<td>243</td>
<td>22.5</td>
<td>175</td>
<td>238</td>
<td>664</td>
<td>157</td>
</tr>
<tr>
<td>Oil/gas partition coefficient at 37° C</td>
<td>1.3</td>
<td>197</td>
<td>950</td>
<td>98.5</td>
<td>90.8</td>
<td>19</td>
<td>47-54</td>
</tr>
<tr>
<td>Blood/gas partition coefficient at 37° C</td>
<td>0.47</td>
<td>2.5</td>
<td>12</td>
<td>1.9</td>
<td>1.4</td>
<td>0.45</td>
<td>0.65</td>
</tr>
<tr>
<td>MAC-immobility (% atm/mm Hg)$^\dagger$</td>
<td>104/800</td>
<td>0.75/5.7</td>
<td>0.2/1.52</td>
<td>1.58/12.0</td>
<td>1.28/9.7</td>
<td>6.0/45.6</td>
<td>2.05/15.6</td>
</tr>
<tr>
<td>MAC-awake†</td>
<td>71/540</td>
<td>0.41/3.21</td>
<td>0.081/0.62</td>
<td>0.51/3.88</td>
<td>0.43/3.27</td>
<td>2.4/19</td>
<td>0.63/4.79</td>
</tr>
</tbody>
</table>

Partition coefficients are from References 2-6.
MAC-immobility and MAC-awake values are from References 2, 8-11, 38.
*Properties are measured at standard temperature (20° C) and pressure (1 atm) unless otherwise specified.
†MAC is minimum alveolar concentration for subjects approximately age 40 years.
of the delivered gas mixture, where atmospheric pressure is near 1 atm (760 mm Hg). Correcting these values to absolute partial pressure is important under conditions when local atmospheric pressure differs significantly from standard, such as at high altitude, underwater, or in a hyperbaric chamber. The same inhaled concentration of an anesthetic gas results in a reduced pharmacologic effect at higher altitudes because the partial pressure of the anesthetic is lower. Because partial pressure is the thermodynamic force for gas movement in a system, anesthetics move from regions of high partial pressure to low partial pressure, unaffected by the other components of the gas mixture, and equilibrium is achieved when the partial pressure of an anesthetic is equal in the different compartments.

The maximal partial pressure of a volatile compound is its vapor pressure; this is the partial pressure of volatile anesthetic within the drug reservoir of a vaporizer. Vapor pressure is unique to each anesthetic and increases with increasing temperature. Volatile anesthetics are defined by a vapor pressure less than 1 atm at 20° C and a boiling point above 20° C (see Table 26-1). Gaseous anesthetics are defined by a vapor pressure greater than 1 atm at 20° C and a boiling point below 20° C (see Table 26-1). Volatile anesthetics typically account for a small fraction of the gas mixture delivered to patients. In contrast, gaseous anesthetics such as nitrous oxide (N₂O) and xenon, because of their relative lack of potency, typically compose a large fraction of an inhaled gas mixture and thus produce additional effects (e.g., concentration effect, second gas effect, and airspace expansion) that are negligible with potent volatile anesthetics.

Hydrophobicity is a molecular property of certain chemicals, including most general anesthetics that do not readily form hydrogen bonds and therefore display low water solubility. Hydrophobic compounds are also usually lipophilic, demonstrating high solubility in low polarity solvents such as oils. Common measures of hydrophobicity are partition coefficients between water and olive oil (which is mostly oleic acid, an 18-carbon fatty acid) or between water and n-octanol. Usually represented by the Greek letter lambda (λ), a partition coefficient is the ratio of two solute concentrations at equilibrium (i.e., at equal partial pressure) in two separate but adjacent solvents or compartments such that the solute moves freely between the compartments (Fig. 26-1). Another useful way to conceptualize a partition coefficient is that it represents the relative volume of two compartments that contain equal concentrations of the solute at equilibrium (see Fig. 26-1).

Anesthetic partition coefficients between blood and gas (λ_{b/g}) and between tissue and blood (λ_{t/b}) are important factors in uptake and distribution of inhaled anesthetics as they move from pulmonary airspace to pulmonary blood, then from blood to various tissues (Table 26-2). Blood solubility of anesthetic gases (and other gases such as O₂, N₂, and CO₂) increases as temperature decreases. Because most anesthetics are hydrophobic, they tend to display high solubility in tissues with high lipid content (e.g., fat), and they bind to many proteins that form hydrophobic or amphipathic pockets. Anesthetic partitioning into blood (blood solubility) increases after ingestion of fatty foods and may decrease in anemic or malnourished patients. Methoxyflurane (no longer in clinical use) and halothane are notable for high blood solubility. N₂O, sevoflurane, and desflurane are characterized by low blood solubility.

ANESTHETIC DELIVERY, UPTAKE, AND DISTRIBUTION: A MULTICOMPARTMENTAL MODEL

Delivering an inhaled anesthetic drug to patients is analogous to an intravenous drug infusion with two obvious
# Table 26-2: Uptake and Distribution Model Parameters for Inhaled Anesthetics

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Blood</th>
<th>Heart</th>
<th>Kidney</th>
<th>Liver</th>
<th>CNS</th>
<th>Muscle</th>
<th>Fat</th>
<th>VRG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood Flow (L/min)</td>
<td>Volume (L)</td>
<td>Blood Flow (L/min)</td>
<td>Volume (L)</td>
<td>Blood Flow (L/min)</td>
<td>Volume (L)</td>
<td>Blood Flow (L/min)</td>
<td>Volume (L)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.2</td>
<td>0.28</td>
<td>1.07</td>
<td>0.32</td>
<td>1.2</td>
<td>3.9</td>
<td>0.62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anesthetic Agent</th>
<th>( V_{eff} (L) )</th>
<th>( \lambda_{\text{Tissue/blood}} )</th>
<th>( V_{eff} (L) )</th>
<th>( \tau ) (min)</th>
<th>( \lambda_{\text{Tissue/blood}} )</th>
<th>( V_{eff} (L) )</th>
<th>( \tau ) (min)</th>
<th>( \lambda_{\text{Tissue/blood}} )</th>
<th>( V_{eff} (L) )</th>
<th>( \tau ) (min)</th>
<th>( \lambda_{\text{Tissue/blood}} )</th>
<th>( V_{eff} (L) )</th>
<th>( \tau ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>2.35</td>
<td>0.87</td>
<td>0.24</td>
<td>1.2</td>
<td>0.93</td>
<td>0.3</td>
<td>0.3</td>
<td>1.1</td>
<td>4.1</td>
<td>3.4</td>
<td>1.1</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Halothane</td>
<td>12.5</td>
<td>2.9</td>
<td>0.8</td>
<td>4.0</td>
<td>1.5</td>
<td>0.5</td>
<td>0.4</td>
<td>2.5</td>
<td>9.8</td>
<td>8.0</td>
<td>2.7</td>
<td>3.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>60</td>
<td>1.2</td>
<td>0.34</td>
<td>1.7</td>
<td>2.3</td>
<td>0.74</td>
<td>0.69</td>
<td>2.5</td>
<td>9.8</td>
<td>8.0</td>
<td>2.7</td>
<td>3.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Enflurane</td>
<td>9</td>
<td>1.3</td>
<td>0.36</td>
<td>1.8</td>
<td>2.0</td>
<td>0.64</td>
<td>0.6</td>
<td>2.1</td>
<td>8.2</td>
<td>6.7</td>
<td>1.4</td>
<td>2.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>7</td>
<td>1.3</td>
<td>0.36</td>
<td>1.8</td>
<td>2.3</td>
<td>0.74</td>
<td>0.69</td>
<td>2.4</td>
<td>9.4</td>
<td>7.6</td>
<td>1.5</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Desflurane</td>
<td>2.25</td>
<td>1.3</td>
<td>0.36</td>
<td>1.8</td>
<td>1.0</td>
<td>0.32</td>
<td>0.3</td>
<td>1.4</td>
<td>5.5</td>
<td>4.5</td>
<td>1.3</td>
<td>1.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>3.25</td>
<td>1.3</td>
<td>0.36</td>
<td>1.8</td>
<td>2.3</td>
<td>0.74</td>
<td>0.69</td>
<td>2.4</td>
<td>9.4</td>
<td>7.7</td>
<td>1.7</td>
<td>2.4</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*Based on a 70-kg patient at rest. Blood and tissue partition coefficients are from References 6, 12-14. Tissue volumes and blood flow values are approximate (Levitt, Kennedy and colleagues). Effective volumes are calculated as Tissue volume × \( \lambda_{\text{Tissue/blood}} \), and exchange time constant (\( \tau \)) for each compartment is \( V_{eff} / \text{Blood flow} \). CNS, Central nervous system; VRG, vessel-rich group.
major differences: (1) entry of drug into the body is via transalveolar exchange from gas to blood and (2) clearance is mostly via the same route. Thus, inhaled anesthetic delivery is dependent on pulmonary ventilation, whereas uptake and clearance of inhaled anesthetics are dependent on pulmonary perfusion.

Upstream and Downstream Compartments and Anesthetic Transfer: Bulk Flow and Pressure Gradients

Uptake and distribution of inhaled anesthetic can be readily understood as a series of transfer steps from upstream compartments with high partial pressure to downstream compartments with low partial pressure as depicted in Figure 26-2. First, the drug is transferred from an anesthesia delivery device, typically an anesthesia machine with a vaporizer designed to deliver specified concentrations (in percent atm) of volatile anesthetic, into a fresh gas mixture flowing in a breathing circuit. Second, ventilation transfers gases from the circuit to the alveolar airspace in the lung. Third, the anesthetic moves by transcapillary diffusion into pulmonary venous blood. Fourth, arterial blood distributes the anesthetic to various tissues including the primary target tissue, the central nervous system (CNS). Fifth, venous outflow from tissues converges in the pulmonary artery, and sixth, the mixed venous blood passes through alveolar capillaries where it again equilibrates with alveolar gases.

![Figure 26-2](image.png) Flow diagram for uptake and distribution of inhaled anesthetics. Major compartments for anesthetic flow are depicted, including the breathing circuit, alveolar gas space, and three major tissue compartments: vessel-rich group (VRG), muscle, and fat. The physiologic volumes of the tissue compartments are approximately in proportion to the labeled face of the compartment, while the blood-tissue partition coefficients are depicted as the depth of the compartment. Thus, the effective volume of the VRG is much smaller than that of muscle, which in turn is much smaller than that of fat. Carrier flows and exchange in different parts of the model are depicted by arrows. Fresh gas flow (FGF) moves anesthetic from the vaporizer to the circuit; ventilation drives exchange of anesthetic between the circuit and alveoli; pulmonary blood flow transfers anesthetic from alveoli into the circulation, which then distributes drug to different compartments depending on blood flow to various tissues. Relative blood flow is approximately proportional to the width of the arrows into and out of tissue compartments, as well as for shunts. The diagram depicts an early phase of anesthetic uptake when organs of the VRG, including the brain, are approaching equilibrium with alveolar and arterial anesthetic partial pressure, while anesthetic partial pressures in muscle and fat remain relatively low. Quantitative modeling of anesthetic gas movement in this system was performed using numerical integration of equations describing anesthetic flow into and out of each compartment (Equations 5, 8, 9, 10, and 11). Figures 26-4, 26-5, 26-6, 26-7, 26-9, 26-10, and 26-12 were all generated using this model. Standardized parameters used in the model are summarized in Table 26-2. $P_{del}$ Partial pressure in the circuit; $P_{del}$ delivered anesthetic partial pressure.
Gas flow from the machine into the breathing circuit is unidirectional. Blood circulation is also largely unidirectional. In transfers from machine (the fresh gas outlet) to breathing circuit and then to alveolar airspace, anesthetic flow can simply be understood as an exchange from upstream compartments into downstream gas phase compartments. In later steps, such as exchange between alveolar gases and pulmonary capillary blood, the flow of anesthetic molecules occurs via diffusion across adjacent compartments separated by a permeable membrane. For simplicity, we have not treated blood as a separate compartment in our model. Distribution of anesthetic to and from various tissues involves both bulk transfer via blood flow and diffusive equilibration across capillary membranes. Note that when anesthetic transfer occurs between gas and blood or between blood and tissue, the effective volume of the downstream compartment must be adjusted with the appropriate partition coefficient (see Table 26-2).

**Rate of Wash-in of the Circuit: Equilibration between Vaporizer and Circuit**

Equipment for controlled delivery of inhaled anesthetic drugs is described in Chapter 29. Wash-in of the ventilator breathing circuit represents an example of bulk transfer exchange, wherein the gas in the circuit components is replaced by fresh gases emerging from the gas outlet of the anesthesia machine.

**Anesthetic Delivery from the Vaporizer.** Volatile anesthetic delivery from a vaporizer is simply the product of the delivered anesthetic concentration (Fraction = \( F_{del} \) or Partial pressure = \( P_{del} \)) of the anesthetic gas and fresh gas flow (FGF).

\[
dV_{del}/dt = P_{del} \times FGF
\]

Thus, we can readily calculate the volume of delivered gas-phase anesthetic by simply integrating this function over time. In the simplest case where \( P_{del} \) and FGF remain constant:

\[
V_{del}(t) = P_{del} \times FGF \times t
\]

**Fresh Gas Wash-in to the Breathing Circuit.** The factors that affect the speed at which the gas mixture delivered from the anesthesia machine replaces gases in the breathing circuit (wash-in) are FGF and the breathing circuit volume (\( V_{circ} \)). Consider a typical situation in which FGF at the beginning of an anesthetic is 6 L/min and the gas volume inside the components of a breathing circuit is 6 L. If FGF is doubled to 12 L/min, then wash-in will proceed at twice the rate (halving the time). Conversely, if the \( V_{circ} \) doubles to 12 L, then wash-in will proceed at half the rate (doubling the time).

The gas exchange process is independent of the concentration of anesthetic in the circuit, because the exchange is simply through bulk flow and mixing. However, the difference between the delivered concentration and that in the circuit determines the magnitude and direction of net anesthetic gas flow. When the delivered anesthetic partial pressure (\( P_{del} \)) is greater than that in the circuit (\( P_{circ} \)), net anesthetic flow is into the circuit (and subsequently into the patient). To remove anesthetic from the circuit, \( P_{del} \) must be less than \( P_{circ} \). When there is no concentration gradient (i.e., equal partial pressures), bulk flow exchange may replace all the old gas molecules with new ones, but there is no net flow and anesthetic concentrations in the circuit remain unchanged.

Mathematically, we can describe the breathing circuit exchange process as a differential equation that incorporates all of the above factors:

\[
\frac{dP_{circ}}{dt} = \frac{FGF}{V_{circ}} \times (P_{del} - P_{circ})
\]

If \( P_{del} \) is constant, integrating this equation results in a single exponential function that defines \( P_{circ} \) at any given time following a change in \( P_{del} \) at \( t = 0 \):

\[
P_{circ}(t) = P_{circ}(0) + (P_{del} - P_{circ}(0)) \times \left(1 - e^{-t/[V_{circ}/FGF]}\right)
\]

\( P_{circ} \) approaches \( P_{del} \) following an exponential time course with a time constant of \( \tau = V_{circ}/FGF \). Thus, if \( V_{circ} = 6 \) L and FGF = 6 L/min, the exponential time constant will be 1 minute (Fig. 26-3). Each minute results in the fraction of old gas in the breathing circuit dropping by 63.1%, and after 4 minutes, less than 2% old gas remains. The half-life for the process (time for halving the vaporizer-circuit concentration difference) is 0.693 \times \tau.

Breathing circuit components, such as \( CO_2 \) adsorbents and the plastic or rubber of the circuit tubing and connectors, influence the rate of equilibration between vaporizer and circuit, because such materials can absorb volatile anesthetics, increasing the effective circuit volume. The more hydrophobic volatile anesthetics absorb more into

![Figure 26-3.](https://example.com/figure26-3.png)

**Figure 26-3.** Wash-in of the breathing circuit depends on fresh gas flow (FGF). The curves depict the rate of rise of anesthetic concentration (partial pressure) in a breathing circuit with 6 L of gas volume, depending on FGF. Higher FGF results in more rapid exchange of circuit gases with fresh gas. The exponential time constant for the wash-in process is the circuit volume in liters divided by fresh gas flow in liters per minute (see Equation 4). Cross marks overlaying the curves indicate time constants under different gas flow rates. Each time constant correlates with a 63.1% exchange.
circuit components, whereas absorption negligibly affects wash-in and wash-out of low-solubility anesthetics.

The clinical relevance of the wash-in process is readily appreciated. An example of the importance of FGF is “priming” the anesthetic circuit for a single-breath induction technique. The FGF setting and the circuit volume influence the required duration of priming. More generally, whenever the vaporizer settings are altered, the speed at which the new settings influence the wash-in or wash-out of the circuit (and subsequently the patient) depend on FGF. Open (nonrebreathing) anesthetic breathing circuits are designed to have low exchange volumes and to be used with high fresh-gas flows. These features allow rapid changes in the delivered anesthetic concentration, while minimizing rebreathing of exhaled gases. The choice of an open versus rebreathing system influences the effects of various other factors that can affect uptake and distribution of inhaled anesthetics downstream from the breathing circuit. Some of the subsequent figures show models for both conditions.

**Equilibration between Circuit and Pulmonary Airspace**

Transfer of anesthetic gases from the breathing circuit to the pulmonary airspace is another bulk exchange process similar to that from vaporizer to breathing circuit. In this case, gas flow via ventilation is cyclical and bidirectional, and the factors that determine the rate of anesthetic exchange are minute ventilation (MV) and total pulmonary airspace volume ($V_{pulm}$). Because transfer from the circuit to the lungs represents anesthetic flow out of the circuit, we alter Equation 3 to include both inflow to the circuit and outflow from the circuit:

$$\frac{dP_{circ}}{dt} = \frac{FGF}{V_{circ}} \times (P_{del} - P_{circ}) - \frac{MV}{V_{pulm}} \times (P_{circ} - P_{pulm})$$  \hspace{2cm} (5)

where $P_{pulm}$ is a weighted average of the anesthetic partial pressure in deadspace and alveolar space.

Equation 5 describes how rebreathing affects the inhaled (breathing circuit) anesthetic concentration. Most inhaled anesthetics are delivered using a rebreathing circuit, which includes one-way flow valves and adsorbent material to remove exhaled CO$_2$ chemically. Rebreathing depends primarily on the balance between fresh gas flow and minute ventilation. The anesthetic gas in the breathing circuit represents a mixture of fresh gas and exhaled gases. Increased FGF reduces rebreathing, whereas increased MV increases rebreathing.

**Alveolar Anesthetic Concentration**

The alveolar anesthetic concentration ($P_{alv}$ or $F_a$) is a critically important factor in anesthetic uptake and distribution because (1) it is in rapid equilibrium with circulating blood and highly perfused tissues, including target tissues in the CNS, and (2) $P_{alv}$ can be measured in exhaled end-tidal gases. Thus, except during periods of rapid change, $P_{alv}$ in exhaled breath represents a useful estimate of the anesthetic concentration in the patient’s CNS and other highly perfused organs.

Because only alveolar gas is relevant to transpulmonary anesthetic exchange of anesthetic into and out of the body, alveolar ventilation ($\dot{V}_{alv}$) is the proper gas flow to calculate anesthetic exchange into this part of the pulmonary airspace.

$$\frac{dP_{alv}}{dt} = \frac{\dot{V}_{alv}}{V_{alv}} \times (P_{circ} - P_{alv})$$  \hspace{2cm} (6)

where $\dot{V}_{alv}$ is MV corrected for deadspace ventilation.

**Alveolar Uptake of Anesthetic into Pulmonary Blood**

During inhaled anesthetic induction, anesthetic flows from alveolar gas to pulmonary blood across the alveolocapillary interface separating these compartments and is driven by the partial pressure gradient between alveolar gas ($P_{alv}$) and mixed venous blood ($P_{MV}$) entering the pulmonary arteries. The net flow of anesthetic reverses during anesthetic wash-out when $P_{alv}$ drops below $P_{MV}$. Anesthetic uptake into blood also depends on the pulmonary blood flow (which is typically close to cardiac output, $Q$) and the blood’s capacity to solvate anesthetic from the gas state (the blood/gas partition coefficient, $\lambda_{b/g}$):

$$\text{Uptake} = Q \times \lambda_{b/g} \times (P_{alv} - P_{MV})$$  \hspace{2cm} (7)

We therefore correct Equation 6 to reflect both anesthetic inflow into alveolar airspace and its uptake into blood:

$$\frac{dP_{alv}}{dt} = \frac{\dot{V}_{alv}}{V_{alv}} \times (P_{circ} - P_{alv}) - \frac{Q \times \lambda_{b/g}}{V_{alv}} \times (P_{alv} - P_{MV})$$  \hspace{2cm} (8)

Thus, during an inhaled induction of anesthesia, the rate of increase of $P_{alv}$ relative to $P_{circ}$ is governed by (1) alveolar ventilation, (2) cardiac output, and (3) anesthetic solubility in blood. Increased ventilation delivers more anesthetic from circuit to alveoli and increases $P_{alv}/P_{circ}$ (Fig. 26-4). Yet increased pulmonary blood flow removes more anesthetic from alveoli, thereby decreasing the rate of increase in alveolar concentration of anesthetic ($P_{alv}/P_{circ}$; Fig. 26-5). Indeed, significant decreases in cardiac output are likely when end-tidal CO$_2$ (ETCO$_2$) decreases and end-tidal concentrations of volatile anesthetic increase. The more soluble an anesthetic is in blood (i.e., the higher its $\lambda_{b/g}$), the more each volume of blood can take up anesthetic from alveolar gases (i.e., the larger the effective blood flow). Thus, as $\lambda_{b/g}$ increases, $P_{alv}/P_{circ}$ increases more slowly (Fig. 26-6).

**Other Factors That Affect the Rate of Rise of $P_{alv}$**

Other factors affecting alveolar uptake of anesthetic include ventilation–perfusion matching and the absolute concentration of anesthetic in alveolar gases.

**Deadspace.** Deadspace (i.e., ventilated but not perfused pulmonary regions) reduces effective alveolar ventilation (see Equations 7 and 8), and thus slows anesthetic uptake. This effect is strongest under open-circuit (high FGF) conditions and with low blood-solubility inhaled anesthetics. Under conditions of limited anesthetic delivery and
**PART III: Anesthetic Pharmacology**

**Figure 26-4.** Effect of ventilation on the rise of alveolar anesthetic partial pressure ($P_{alv}$). Left, A traditional open-circuit model with very high fresh gas flow (FGF) and therefore constant $P_{del} = P_{circ}$. Right, A more common clinical situation with constant vaporizer output ($P_{del}$) and partial rebreathing at a 6 L/min fresh gas flow rate. Raising minute ventilation accelerates the rise of $P_{alv}$ by delivering more anesthetic to the lungs. The effect is seen whether anesthetic is highly soluble in blood (e.g., halothane) or relatively insoluble (e.g., sevoflurane). However, the relative size of the ventilation effect is greater for soluble agents. Increased ventilation also accelerates clearance of anesthetic agents after delivery ceases. $P_{circ}$, Partial pressure in the circuit; $P_{del}$, delivered anesthetic partial pressure.

**Figure 26-5.** Effect of cardiac output on the rise of alveolar anesthetic partial pressure ($P_{alv}$). Left, A traditional open-circuit model with very high fresh gas flow (FGF) and therefore constant $P_{del} = P_{circ}$. Right, A common clinical situation with constant vaporizer output ($P_{del}$) and partial rebreathing at a 6 L/min FGF rate. Raising cardiac output slows the rise of $P_{alv}$ by increasing anesthetic uptake into blood (removing anesthetic from alveolar gases). This effect is observed for both highly soluble and relatively insoluble (e.g., isoflurane) anesthetics, but the relative effect is greater for soluble agents. Cardiac output also affects clearance of anesthetics from the lungs in the same way it affects uptake (i.e., increased cardiac output slows anesthetic clearance rate). $P_{circ}$, Partial pressure in the circuit; $P_{del}$, delivered anesthetic partial pressure.
**Chapter 26: Inhaled Anesthetic Pharmacokinetics: Uptake, Distribution, Metabolism, and Toxicity**

**Open circuit**  
FGF = 50 L/min

**Agent Delivery**
- Desflurane
- Sevoflurane
- Isoflurane
- Halothane
- Methoxyflurane

**Rebreathing circuit**  
FGF = 6 L/min

**Agent Delivery**
- Desflurane
- Sevoflurane
- Isoflurane
- Halothane
- Methoxyflurane

**Figure 26-6.** Effect of blood solubility on the rise of alveolar anesthetic partial pressure ($P_{alv}$). Left: A traditional open-circuit model with very high fresh gas flow (FGF) and therefore constant $P_{del} = P_{circ}$. Right: A more common clinical situation with constant vaporizer output ($P_{del}$) and partial rebreathing at a 6 L/min FGF rate. As blood solubility ($\lambda_{bg}$) increases, the rate of rise in $P_{alv}$ slows, because uptake into blood is greater for high solubility agents. The major effect of blood solubility is the magnitude of the rapid initial rise in $P_{alv}$, which represents a balance between anesthetic delivery and uptake into pulmonary blood. Blood solubility similarly affects clearance from alveoli after anesthetic delivery ceases (i.e., increased blood solubility results in slower clearance from alveolar gas). $P_{circ}$ Partial pressure in the circuit; $P_{del}$, delivered anesthetic partial pressure.

**Figure 26-7.** Effect of right-to-left pulmonary shunt on the anesthetic partial pressure in alveolar gas and arterial blood. The curves represent anesthetic partial pressures in alveolar gases (dashed lines) and arterial blood (dash-dot lines) under conditions of 40% right-to-left shunt and no shunt (solid lines). Pulmonary right-to-left shunting bypasses alveolar uptake, so that less anesthetic is removed from pulmonary gases; this accelerates the rise in $P_{alv}$. In addition, the anesthetic partial pressure in arterial blood ($P_{art}$) is a mixture of pulmonary venous blood at $P_{av}$ and shunted mixed venous blood at $P_{alv}$. Thus $P_{art}$, which determines the rate of anesthetic uptake into tissues, rises more slowly than $P_{alv}$ when R-to-L shunting is present. The shunt effect on $P_{art}$ versus $P_{alv}$ is larger for insoluble anesthetics (e.g., $N_2O$) than for soluble anesthetics (e.g., halothane). Other model parameters were set for open circuit delivery (constant $P_{cerv}$) with $MV = 6$ L/min and C.O. = 5 L/min. $P_{av}$ Alveolar anesthetic partial pressure. CO, Cardiac output; $MV$, minute ventilation; $P_{av}$, anesthetic partial pressure in mixed venous blood.

**Pulmonary (Right to Left) Shunting.** Pulmonary (right to left) shunting can be physiologic, pathologic, or iatrogenic, such as during one-lung ventilation. Right-to-left shunting results in a difference between $P_{alv}$ and the partial pressure of anesthetic in arterial blood ($P_{art}$). This is because arterial blood represents a mixture of shunted mixed venous blood with blood that equilibrates with alveolar gases (Equation 9). Because such shunts also reduce transcapillary gas exchange in the lung and slow anesthetic uptake (Equations 7 and 8, after correcting for deadspace on alveolar ventilation, reducing its overall effect on $P_{alv}$.

**Concentration and Second Gas Effects.** The absolute concentration of an inhaled anesthetic influences its uptake. In the previous discussion and illustrations, an inhaled anesthetic has been assumed to represent a small fraction of the inhaled gas mixture, and that transalveolar uptake of the anesthetic results in a decrease in $P_{alv}$.
and negligible changes in alveolar gas volume. However, when the inhaled anesthetic represents a large fraction of the inspired gas mixture, its rapid uptake results in a smaller relative alveolar anesthetic concentration drop, because the volume of alveolar gas also decreases. This is known as the concentration effect\(^{24}\). In an imaginary situation in which a patient is breathing 100% anesthetic, uptake into pulmonary blood reduces the volume of anesthetic in the alveoli without altering its concentration or partial pressure (oxygen-induced atelectasis occurs through a similar mechanism). A typical situation, illustrated in Figure 26-8, is delivery of 66% N\(_2\)O with 33% O\(_2\), and 1% isoflurane. Assuming cardiac output equals 5 L/min, the initial rates of N\(_2\)O uptake is given by Equation 7 as 5000 mL/min \(\times 0.47 \times 0.66\) atm = 1550 mL/min N\(_2\)O, indicating that a large fraction of N\(_2\)O is initially taken up during the first few breaths. If we assume that half the N\(_2\)O and half the isoflurane are rapidly taken up following the first breath of this gas mixture, then alveolar volume drops by 33.5% and the remaining alveolar gas contains 33 parts N\(_2\)O, 33 parts O\(_2\), and 0.5 parts isoflurane (49.6% N\(_2\)O, 49.6% O\(_2\), and 0.8% isoflurane). Despite 50% uptake of N\(_2\)O, the significant reduction in alveolar gas volume results in a concentration of remaining alveolar N\(_2\)O that is only 24% less than its initial value.

The second gas effect is also evident in this example: the rapid uptake of N\(_2\)O and reduced alveolar gas volume sustains P\(_{iso}\) near its original inspired value and increases alveolar P\(_{O2}\) thereby augmenting uptake of these gases.\(^{25}\) Note also that the rapid uptake of N\(_2\)O into blood results in an effective increase in minute ventilation, because more circuit gas is passively drawn into alveoli as alveolar gas is absorbed rapidly. These effects have been demonstrated in humans\(^{26}\) and animals,\(^{25}\) and theoretically are short-lived and pertain only to the period of initial rapid transfer of N\(_2\)O from alveoli to blood. The second gas effect may persist beyond the initial rapid phase of N\(_2\)O uptake.\(^{27}\)

**Distribution of Anesthetic into Tissues**

Blood exiting the pulmonary capillaries enters the pulmonary vein and the left heart. Inhaled anesthetics are then distributed via arterial blood to various body tissues. The rate of increase of anesthetic partial pressure within each tissue is determined by tissue-specific arterial blood flow (Q), effective volume (the product of anatomic volume and tissue/blood partition coefficient, \(\lambda_{t/b}\)), and the anesthetic partial pressure gradient between arterial blood and the tissue:

\[
\frac{dP_i}{dt} = \frac{\dot{q}_i}{V_i \times \lambda_{t/b}} \times (P_{art} - P_i)
\]

where \(i\) designates a particular organ or type of tissue. Values used in model calculations are summarized in Table 26-2. The time required for anesthetic partial pressure equilibration between arterial blood (\(P_{art} = P_{ab}\)) and a specified tissue is shorter if its blood flow is high, and longer if that tissue has a large effective volume (Figs. 26-2, 26-9).

Traditionally, anesthetic distribution has been described for four distinct tissue groups. The vessel-rich group (VRG) includes the heart, brain, spinal cord, liver, and kidney. Together, these organs compose approximately 10% of the adult human body mass; however, they receive approximately 70% of cardiac output under normal resting conditions. As a result, time constants for anesthetic equilibration between blood and these organs are typically only a few minutes (see Table 26-2). Of particular interest is the equilibration time for the CNS, where anesthetic effects are mediated. After the highly perfused VRG tissues, skeletal muscle is the next compartment to equilibrate with inhaled anesthetics. Muscle composes approximately 40% of body mass in a healthy adult, making muscle the largest single compartment based on weight. Moreover, most inhaled anesthetics partition into muscle more than into brain, resulting in an increased effective volume for anesthetic uptake into this compartment. At rest, muscle receives 10% to 15% of cardiac output (20 mL/kg/min), but this value can increase dramatically during exercise, stress, fever, or other states associated with high cardiac output.\(^{28}\) Taken together, these factors generally result in slow equilibration between anesthetic in blood and muscle, with typical time constants of hours (see Table 26-2). The third tissue

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**Figure 26-8.** Concentration and second gas effects. The figure depicts alveolar gases at the beginning of an anesthetic. After an initial inspiratory breath, alveoli are filled with the gas mixture in the circuit (66% N\(_2\)O, 33% O\(_2\), 1% isoflurane) at their normal end-inspiratory volume (left panel). After half of the N\(_2\)O and isoflurane are absorbed into pulmonary blood, the alveolar gas volume is reduced by 33.5%. At this point, the volume of N\(_2\)O equals the volume of O\(_2\), and the gas mixture is 49.6% N\(_2\)O, 49.6% O\(_2\), and 0.8% isoflurane. Inflow of additional inspired gas mixture returns alveolar volume to its original value, resulting in a gas mixture of 55.1% N\(_2\)O, 44.1% O\(_2\), and 0.8% isoflurane. The alveolar partial pressure of N\(_2\)O falls much less than the fractional uptake (the concentration effect). In addition, the partial pressure of O\(_2\) increases relative to the inspired gas O\(_2\) content, and the partial pressure of isoflurane is sustained close to the inspired value, increasing its rate of uptake (the second gas effect). Iso, Isoflurane.
compartment. Increased cardiac output slows the rate of increase of $P_{alv}$ and thus also slows the rate of increase of the anesthetic partial pressure in blood ($P_{art}$), the CNS ($P_{CNS}$), and other highly perfused tissues. The extra anesthetic uptake is primarily into muscle, which is a large tissue compartment with a high capacity for anesthetic and is where much of the excess cardiac output flows. For example, a 50% increase in cardiac output can more than double muscle blood flow, diverting the majority of anesthetic to muscle, lowering $P_{alv}$, and thus slowing anesthetic uptake into target tissues in the CNS. If one could manipulate inhaled anesthetic delivery to maintain constant $P_{alv}$, which may be achievable with automated feedback control of vaporizer output and FGF, and then increasing cardiac output might have a different effect. Model simulations where $P_{alv}$ is maintained at a constant level show that uptake into VRG tissues, including brain tissue, increases more rapidly as cardiac output increases.

In pediatric patients (see Chapter 93), the balance of cardiac output to various tissue beds differs from that in adults. Thus, although cardiac output per kilogram body weight is larger in children than in adults, induction of anesthesia is more rapid in young children than in adults, because a disproportionate amount of perfusion goes to the vessel rich organs, such as the brain.

The equilibrium distribution volumes for most inhaled anesthetics are extremely large, with the largest compartment by far being fat. However, equilibration with fat is so slow that this compartment usually plays a relatively minor role in the pharmacokinetics of inhaled anesthetics. During a typical general anesthetic lasting from 30 minutes to several hours, the blood, VRG organs, and muscle are the compartments into which inhaled anesthetics mostly distribute.

Although the model in Figure 26-2 illustrates anesthetic distribution only via arterial blood flow, intertissue diffusion takes place between abutting tissues that have large interfacial surface areas. In particular, direct diffusion from organs with high anesthetic partial pressures to abutting tissues with low partial pressure and high capacity for anesthetic uptake may also contribute to drug distribution. Examples of this process include anesthetic diffusion from the heart, liver, and kidneys to surrounding fat in the pericardium and abdomen.

**Mixed Venous Anesthetic Partial Pressure**

The anesthetic partial pressure in mixed venous blood entering the pulmonary circulation is a weighted average of the venous outflows from all tissues and organs, which converge in the right ventricle:

$$P_{MV} = \sum_{i=1}^{n} \frac{Q_i}{Q} \times P_i$$  \hspace{1cm} (11)

As $P_{MV}$ rises, the gradient driving uptake of inhaled anesthetics from alveoli weakens. The difference between the delivered (inspired) and the alveolar (end-expiratory) anesthetic concentrations also shrinks, causing transpulmonary uptake to slow (Equation 7). Systemic (left to right) shunting causes $P_{MV}$ to increase more rapidly than it would in the absence of such shunts. When blood flow to other tissues remains normal and the left-to-right shunt...
simply represents excess cardiac output, the resulting increase in anesthetic uptake (Equation 7) is offset by the increase in $P_{an}$, resulting in a slight increase in the rate of anesthetic delivery or uptake into the brain, muscle, and other tissues. In cases where large left-to-right shunts result in reduced blood flow to other tissues, anesthetic equilibration in those tissues will be relatively slow.

### SYNTHESIS OF THE MODEL AND INHALED ANESTHETIC INDUCTION: PK/PD

The rate of equilibration (pharmacokinetics) of inhaled anesthetics among the various compartments involved in delivery to a patient, vaporizer, circuit, lung, blood, and various tissues, has been discussed. However, in a clinical setting, the goal of the anesthesia provider is the reversible production of certain desired effects (amnesia, unconsciousness, and immobility) in the patient in a reasonable amount of time. To achieve these goals, pharmacokinetics must be combined with knowledge of the effects produced at different anesthetic partial pressures in target tissues (i.e., dose-response or pharmacodynamics). The most relevant pharmacodynamic guidelines are minimum alveolar concentration (MAC)–immobility, the alveolar anesthetic concentration preventing movement response to surgical stimulus in 50% of subjects, and MAC-awake, the alveolar anesthetic concentration preventing perceptive awareness in 50% of subjects, both measured under conditions where $P_{alv}$ is in equilibrium with anesthetic partial pressure in the central nervous system ($P_{CNS}$). MAC-awake for potent volatile anesthetics is typically $0.34 \times$ MAC-immobility, whereas MAC-awake for $N_2O$ is approximately $0.7 \times$ MAC immobility (see Table 26-1). During induction of anesthesia, the goal may be achieving a high probability of immobility following incision ($P_{CNS} = 1.2 \times$ MAC-immobility) within 15 minutes, while avoiding the deleterious effects of overly deep anesthesia. At the end of an anesthetic, return of level (Fig. 26-10, left). The need to maintain overpressure and slightly overshoot $P_{alv}$ derives from the fact that distribution of drug to muscle maintains a high delivery requirement after the initial rapid phase of uptake. If $P_{del}$ is decreased too quickly, then $P_{alv}$ can decrease below the target. $P_{del}$ or FGF is slowly adjusted downward as the anesthetic inspired-to-expired difference in anesthetic partial pressures ($P_{del} - P_{alv}$) decreases.

### CLOSED-CIRCUIT OR LOW-FLOW DELIVERY OF ANESTHESIA

The use of high or moderate fresh gas flows, while enabling use of less overpressure, results in far more anesthetic drug being delivered than being taken up into tissues. Note in the left panel of Figure 26-10, the amount of isoflurane delivered is 4.5-fold more than that taken up, whereas delivered sevoflurane is 7.2-fold greater than absorbed drug. Thus, over 80% of delivered volatile anesthetic is waste using the moderately high FGF approach illustrated in this example. Rebreathing circuits allow the use of fresh gas flows well below minute ventilation, which results in reduced anesthetic discharge into the waste-scavenging system. Less waste discharge translates into both reduced costs and reduced global environmental impact of anesthetic gases within the atmosphere, where these anesthetics contribute to climate change (reviewed later). Additional benefits of low FGF and rebreathing include retention of expired heat and water vapor in rebreathed gas, improving airway epithelial health, and reducing accumulation of dried airway secretions.

Closed-circuit anesthesia represents the ultimate limit of low gas flows, where fresh gases are delivered only in quantities sufficient to replace those taken up into tissues, metabolized (especially $O_2$), or otherwise lost to the environment, and the vast majority of gas in the breathing circuit undergoes rebreathing. Achieving this goal requires a leak-free breathing circuit, complete removal of $CO_2$, and careful attention to the inspired-to-expired values of oxygen and anesthetic gases, and even to the buildup of expired nitrogen that can slowly accumulate in the breathing circuit. Under these conditions, oxygen consumption in an anesthetized patient can be lower than 3 mL/kg/min, translating to $O_2$ replacement of around 200 mL/min in a patient weighing 70 kg. There are several significant limitations to this technique. Because all exhaled $CO_2$ must be removed by adsorbents, closed circuit anesthesia increases the risk of rebreathing $CO_2$ as adsorbent capacity diminishes. Anesthetic breakdown products, carbon monoxide (CO), and slowly degassing nitrogen from blood can accumulate in the breathing circuit. Clinicians must be aware that patient metabolism may deplete oxygen from the breathing circuit and can result in delivery of a hypoxic gas mixture during use of closed circuit anesthesia. When using very low FGF values, changes in the vaporizer output ($P_{del}$) result in extremely slow changes in $P_{circ}$ and the subsequent depth of anesthesia. Closed circuit anesthetic administration can be guided by the “square root of time” rule, proposed by Severinghaus and detailed in now classic descriptions. This rule states that the rate of anesthetic uptake decreases approximately at the square root of delivery time. We can estimate the uptake of 1.2 MAC isoflurane during the first minute of anesthesia using Equation 7. Thus, Cardiac output $\times \lambda_{bg} \times 1.2$ MAC = Initial uptake of isoflurane.
Figure 26-10. Effect of induction technique on uptake and delivery of inhaled anesthetics. A, Anesthetic partial pressures in both the circuit and alveoli during inhalation induction with moderate (6 L/min) fresh gas flows and modest (twofold to threefold) overpressure for sevoflurane (blue) and isoflurane (purple). $P_{alv}$ reaches 1.2 × MAC in approximately 12 minutes, and approximately 10% downward adjustment of vaporizer settings results in maintenance of $P_{alv}$ near this target level. Additional downward adjustments in vaporizer setting or fresh gas flows, or both, would be needed to maintain this $P_{alv}$ level. B, Anesthetic partial pressures in both the circuit and alveoli during inhalation induction with low (less than 2 L/min) fresh gas flows and maximal (fourfold) overpressure for sevoflurane (blue) and isoflurane (purple). $P_{alv}$ reaches 1.2 × MAC in approximately 12 minutes, and a downward adjustment of fresh gas flow results in maintenance of $P_{alv}$ near this target level. C, The total anesthetic vapor delivered and taken up into the model patient from panel A. Note that delivery far exceeds uptake, more so for the low solubility anesthetic (sevoflurane). D, The total amount of anesthetic vapor delivered and taken up into the model patient from panel B. Note that uptake is similar, whereas delivery is much lower than that using a high-FGF technique. The low-FGF technique reduces waste more so for anesthetics with low blood solubility (e.g., sevoflurane) than for highly soluble drugs (e.g., isoflurane). $P_{alv}$ Alveolar anesthetic partial pressure; MAC, minimum alveolar concentration.

Vapor (5000 mL/min × 1.4 × 0.0128 atm = 90 mL/min). Using the square root of time rule, uptake at 4 minutes would be half of the initial rate (45 mL/min), and uptake at 9 minutes would be one third of the initial rate (30 mL/min). To deliver 90 mL/min of isoflurane vapor (0.54 mL of liquid isoflurane at 20° C) at a maximal vaporizer setting of 5% requires 1800 mL/min of fresh gas flow, far greater than the target flow for closed circuit. Anesthetists can overcome this limitation by directly injecting small volumes of liquid anesthetic into the expiratory limb of the breathing circuit; however, this approach requires vigilant attention to the clock along with many other factors. In inexperienced hands, miscalculation or mistiming of anesthetic injection runs the risk of overdose.

Because of the challenges of closed-circuit administration, a more common practice is to use moderate to high fresh gas-flows to achieve rapid changes during induction of anesthesia, reserving closed-circuit anesthesia to periods where the $P_{circ}$ to $P_{alv}$ difference is small. Even so, changes in a patient’s metabolism because of temperature variation, degree of muscle relaxation, or surgical stimulation can result in the need for frequent adjustments.
to oxygen flow and anesthetic depth, making anesthesia delivery in a closed-circuit system relatively unstable and difficult.

**Low-flow anesthetic delivery**, typically with fresh gas flows of 0.5 to 1.0 L/min during maintenance, is a compromise between closed-circuit delivery of anesthesia and the use of high fresh gas flows. Much of the waste and other problems associated with high fresh gas flows are avoided, whereas the instability associated with a strict closed-circuit technique is also moderated. As noted earlier (see [Equilibration between Circuit and Pulmonary Airspace](#)), the inspired anesthetic concentration \( (P_{\text{in}}) \) depends on both \( P_{\text{del}} \) and \( P_{\text{pulm}} \) when rebreathing occurs. Thus, as FGF diminishes, \( P_{\text{del}} \) must be adjusted upward to compensate for diminished delivery. Given that the maximal output setting on most vaporizers is approximately 4 MAC for isoflurane, anesthetic delivery at 1 L/min and \( P_{\text{del}} \) is still far less than the previous example with 6 L/min and \( P_{\text{del}} = 2 \times \text{MAC} \). Higher FGF or a less soluble anesthetic drug, or both, are needed to achieve target PCNS in less than 15 minutes, but as uptake diminishes, FGF can be gradually reduced (see Fig. 26-10, right). With soluble anesthetics such as isoflurane, maximal vaporizer settings and FGF near 2 L/min is required for reasonably rapid induction. FGF can be decreased incrementally as \( P_{\text{del}} \) reaches the target level, and eventually vaporizer output is decreased as well. With low solubility anesthetics such as desflurane or sevoflurane, initial FGF values near 1.0 L/min can be used in combination with maximal vaporizer settings and a similar strategy of reducing FGF. As a result, vaporizer output results in reasonably rapid induction while minimizing waste of volatile anesthetics. Low FGF can be maintained until high FGF is again needed to achieve emergence at the end of the anesthetic administration.

When using high vaporizer output settings, diligence must be maintained to avoid overdosing the patient by reducing FGF and the vaporizer setting in a timely and deliberate manner. Thus, low-FGF techniques combined with significant overpressure should not be applied in situations when other clinical issues require the attention of the anesthesia provider.

### PHARMACODYNAMIC EFFECTS OF ANESTHETICS ON UPTAKE AND DISTRIBUTION

The pharmacodynamic effects of most inhaled anesthetics also include changes in ventilatory and cardiac function that thereby introduce dynamic changes in the drug pharmacokinetics. Spontaneous ventilation is reduced by inhalation of potent volatile anesthetics in a dose-dependent manner. As a result, spontaneously breathing patients will autoregulate to some degree by reducing their uptake of anesthetic as depth of anesthesia increases. This autoregulation provides a degree of safety that is absent in manually or mechanically ventilated patients, who may be subjected to excessive delivery of these anesthetics if a vaporizer is inadvertently set to deliver overpressure. Inhaled anesthetics also reduce cardiac output, a pharmacodynamic effect that leads to a more rapid increase in \( P_{\text{del}}/P_{\text{circ}} \) and consequently a more rapid increase in the anesthetic partial pressure in heart, brain, and other highly perfused tissues. Halothane is the anesthetic associated with the greatest decrease in cardiac output. If anesthetic delivery continues with a decreasing cardiac output, a positive feedback loop of worsening cardiac depression and a rapid descent toward hemodynamic collapse can occur. For more details on the effects of inhaled anesthetics on the respiratory and circulatory systems, see Chapters 27 and 28.

### EFFECT OF NITROUS OXIDE ON GAS-FILLED SPACES

Because \( N_2O \) is often used at high partial pressure, it diffuses into, and accumulates in, spaces containing air or other immobile gases, with potentially deleterious physiologic consequences. Clinically relevant examples include intravascular air emboli, pneumothorax, air in the inner chamber of the ear, intraventricular air bubbles (see [Chapter 84]), intrathecal air, pneumoencephalus, and air in the gastrointestinal tract. Air-filled spaces contain mostly nitrogen, a gas that composes 78% of air, but is thirtyfold less soluble in blood than \( N_2O \) (\( \lambda_{\text{kg}} \) for \( N_2 \) is 0.015). Thus, \( N_2O \) diffuses down its pressure gradient from blood and surrounding tissues into air-filled spaces, whereas \( N_2 \) removal from these spaces is far slower, even with inspired \( P_{N_2} = 0 \). As \( N_2O \) enters and the total number of gas molecules in an air space increases, it will expand in volume, increase in pressure, or both, depending on the composition of the space.

In highly compliant air-filled spaces, such as intravascular air bubbles or small pneumothoraces, \( N_2O \) accumulation increases the total volume of gas (Fig. 26-11, A) with minimal changes in pressure. Air spaces expand as \( N_2O \) enters until the \( P_{N_2O} \) within the air space matches that in surrounding blood, establishing equilibrium. The maximum potential gas volume expansion in a highly compliant space is:

\[
\frac{V}{V_{\text{init}}} = \frac{1}{1 - P_{N_2O}} \tag{12}
\]

Thus, administration of 50% \( N_2O \) can double air-space volume, whereas 67% can potentially triple air-space volume. \( N_2O \) can significantly worsen the cardiovascular or tissue consequences of intravascular air emboli, potentially making a nonlethal volume of venous air embolus lethal. Expansion of intracranial air or gastrointestinal gas volume by \( N_2O \) can result in life-threatening intracranial expansion of this gas volume or impede surgical exposure or abdominal wound closure. Gas-space compartment compliance eventually decreases as volume expands, resulting in increased pressure. For example, \( N_2O \) can expand a small pneumothorax to a point where intrathoracic pressure increases, compressing lung, displacing the mediastinum, and reducing venous return (tension pneumothorax). The endotracheal tube cuff filled with air is also susceptible to expansion by \( N_2O \). Increased tracheal cuff pressure can impair perfusion of surrounding mucosa. Air-filled laryngeal mask airway...
cuffs and the air-filled balloon of a Swan-Ganz catheter can similarly expand during N2O administration.

In noncompliant gas-filled spaces, gas pressure rises as N2O enters, until P_{N2O} within the air space matches that in blood. The maximal potential pressure in such a space, relative to surrounding ambient pressure, is therefore PN_{N2O}. Thus, in a patient inhaling 50% N2O, pressure in such a gas-filled compartment could approach 380 mm Hg, far greater than typical arterial perfusion pressures. A clinically important example is that of intravitreal sulfur hexafluoride (SF6) or perfluoropropane (C3F8) bubbles, which are injected as the sclera is closed at the end of intraocular or retinal surgery (see Fig. 26-11, B). These gases persist even longer than N2 does because of their low blood solubility. If N2O is administered to these patients at the time of intravitreal bubble injection, its diffusion into the bubble can rapidly increase intraocular pressure above that in retinal veins, producing retinal congestion. If the pressure in the eye further increases above systolic arterial pressure, retinal ischemia resulting in blindness might ensue (see Chapter 84).

The rate of N2O diffusion into gas-filled spaces in the body depends on local blood flow and the surface-to-volume ratio of the space. Thus, small air emboli expand within seconds, because they have high surface/volume ratios and are surrounded by a relatively infinite supply of blood containing dissolved N2O. Larger air emboli expand more slowly, because their surface/volume ratio is smaller (spherical surface/volume is inversely proportional to radius). Small pneumothoraces typically have large surface/volume ratios and high local blood flow. Animal experiments show that inhalation of 75% N2O approximately doubles pneumothorax volume in 10 minutes and triples it in 30 minutes (Fig. 26-12). Compared with pneumothorax air pockets, gastrointestinal air pockets have lower surface/volume ratios and lower blood flow. Thus, expansion of gas in the gastrointestinal tract is much slower than that in a pneumothorax. In animal studies (see Fig. 26-12), inhalation of 70% to 80% N2O doubled intestinal gas volume after approximately 2 hours.

N2O is contraindicated in patients with pneumothorax, pneumocephalus, and closed dura or in those at high risk for vascular air embolus. Air-space expansion can impede surgery when substantial gastrointestinal air is present and N2O exposure is prolonged, or it can be of

\[ P_{N2O} = 0 \]
\[ P_{N2} = 1.0 \]
\[ V = V_{init} \]

\[ P_{N2O} = 0.5 \text{ atm} \]
\[ P_{N2} = 0.5 \text{ atm} \]
\[ V = 2 \times V_{init} \]

\[ P_{N2O} = 0.67 \text{ atm} \]
\[ P_{N2} = 0.33 \text{ atm} \]
\[ V = 3 \times V_{init} \]

\[ P_{N2O} = 0.75 \text{ atm} \]
\[ P_{N2} = 0.25 \text{ atm} \]
\[ V = 4 \times V_{init} \]
Increasing ventilation will accelerate clearance (see Fig. 26-6). Return to consciousness, because more gas-exchange volumes are required to remove anesthetic from the larger blood flow (see Fig. 26-5). Highly blood-soluble anesthetics, which increase the effective blood flow, clear more slowly than insoluble anesthetics (see Fig. 26-6). Return to consciousness, which usually occurs after \( P_{\text{CNS}} \) drops below MAC-awake, is faster following desflurane or sevoflurane anesthesia than after isoflurane anesthesia. \( \text{N}_2\text{O} \), which is characterized by blood solubility similar to that of desflurane, provides an even faster return to consciousness, because of two additional advantages. First, the concentration effect works in reverse during clearance for \( \text{N}_2\text{O} \), increasing effective alveolar ventilation and maintaining the gradient for flow from pulmonary blood to alveoli. Second, MAC-awake for \( \text{N}_2\text{O} \) (0.71 atm at 40 years old) is near typical inhaled concentrations during general anesthesia; therefore, elimination of only a small fraction of this drug is associated with return to consciousness. This is also why \( \text{N}_2\text{O} \) as the sole hypnotic drug is associated with a high risk of intraoperative awareness, which can be prevented by using a balanced gas mixture of \( \text{N}_2\text{O} \) together with end-tidal concentrations of approximately 1 × MAC-awake of a second potent inhaled anesthetic.

Body composition has an increasing effect as the length of anesthetic exposure increases, especially for highly soluble anesthetics. Compared with standard models, patients with increased muscle or fat have larger volumes of anesthetic drug distribution over time, resulting in slower clearance rates.\(^{35}\) One important difference between anesthetic uptake and clearance is that although overpressure can be used to hasten uptake and induction of anesthesia, the vaporizer setting cannot be set to less than zero. Thus, the most readily modifiable factors to affect the rate of anesthetic clearance are fresh gas flow and minute ventilation.

**Context Sensitive Recovery from Anesthesia**

Although the concept of context-sensitive half-time is typically applied to continuously infused intravenous drugs that distribute among multiple pharmacokinetic compartments, the concept also applies to inhaled anesthetics.\(^{36}\) After a short period of inhalation and uptake, anesthetic clearance from blood is rapid through both exhalation and distribution to muscle and other tissues. As a result, \( P_{\text{alv}} \) decreases rapidly to a low value after discontinuing anesthetic delivery. After prolonged periods of inhalation and uptake, the anesthetic partial pressures in muscle and other compartments increase closer to that in blood, reducing the contribution of distributive clearance. Instead, clearance from the central blood compartment is slowed by the reverse flow of anesthetic from the high-capacity tissues. Thus, in comparison with a short period of inhalation, prolonged inhaled anesthesia is followed by a smaller initial decrease in \( P_{\text{alv}} \) and a more pronounced slow clearance phase, resulting in slower recovery from anesthesia (Fig. 26-13). As with other factors, context sensitivity is exaggerated in highly soluble anesthetics, and it has less impact with anesthetics that display low blood and tissue solubilities.\(^{37}\) The relative advantage of low blood solubility anesthetics increases with the duration of anesthesia. There is only a small difference (2.5 minutes) between predicted times to awakening after a short anesthetic with isoflurane versus desflurane, but significantly faster awakening can be achieved using the low-solubility drug for long cases.

**Percutaneous and Visceral Anesthetic Loss**

Aside from pulmonary exchange, some portion of inhaled anesthetics is lost by diffusion through other large area interfaces between the body and surrounding air. The skin surface area of an average human is approximately 2 m\(^2\), and blood flow through skin during general anesthesia may be substantial because of inhibition of normal thermoregulatory vasoconstriction.\(^{30}\) Nonetheless, transcutaneous losses of general anesthetics probably contribute negligibly to their clearance.\(^{38,39}\) During open abdominal or thoracic surgery, visceral surfaces are also

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**Figure 26-12.** The rate of air-space expansion during nitrous oxide administration. The rate and extent of expansion of air pockets injected into either the pleural space (red circles) or the gastrointestinal tract (blue squares) of dogs during the inhalation of a 25% \( \text{O}_2/75\% \text{N}_2\text{O} \) gas mixture is shown. Air pockets in stomach, small intestine, and colon expand more slowly than those in a pneumothorax do. **GI,** Gastrointestinal. (Data are approximations from Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax, Anesthesiology 26:61-66, 1965.)
Inhaled anesthetic washout and time to awakening depends on duration of anesthesia. The panels depict model calculations of $P_{\text{alv}}$ and $P_{\text{CNS}}$ normalized to MAC during washout at 10 L/min FGF following anesthesia at approximately 1.2 x MAC-immobility for 30 minutes (solid lines) or 4 hours (dashed lines). The MAC-awake (approximately 0.34 x MAC-immobility) is shown to indicate the threshold below which typical patients regain perceptive awareness after general anesthesia. Although $P_{\text{alv}}$ drops earlier than $P_{\text{CNS}}$, the clinically relevant endpoint (return of consciousness) is predicted when $P_{\text{CNS}}$ falls below MAC-awake. A, Washout using a pharmacokinetic model for isoflurane (orange is $P_{\text{alv}}$, purple is $P_{\text{CNS}}$). The 30-minute isoflurane uptake was 990 mL of vapor, and the 4-hour isoflurane uptake was 3420 mL of vapor. Prolonged anesthesia with isoflurane dramatically increases the time required to wash out sufficient drug to achieve awakening. After a 30-minute anesthetic, $P_{\text{CNS}}$ drops to MAC-awake in 9 minutes, whereas it takes more than 20 minutes of wash-out to reach the same $P_{\text{CNS}}$ following a 4-hour anesthetic.

B, Washout using a desflurane model (blue is $P_{\text{alv}}$, green is $P_{\text{CNS}}$). The 30-minute desflurane uptake was 1530 mL of vapor, and the 4-hour desflurane uptake was 4600 mL of vapor. The predicted times to awakening (5.2 versus 6.3 minutes) are much closer following different durations of desflurane anesthesia, because of its low blood solubility. Clinical studies demonstrate that emergence and recovery (time to extubation) following isoflurane anesthesia nearly doubles when exposure increases from 20 minutes to 75 minutes, while extubation is achieved in less than 10 minutes following desflurane anesthesia from 20 to 100 minutes’ duration. $P_{\text{alv}}$, Alveolar anesthetic partial pressure; $P_{\text{CNS}}$, partial pressure in the central nervous system; CO, Cardiac output; FGF, fresh gas flow; MAC, minimum alveolar concentration; MV, minute ventilation; $P_{\text{alv}}$, alveolar anesthetic partial pressure; $P_{\text{CNS}}$, partial pressure in the central nervous system; $P_{\text{MV}}$, anesthetic partial pressure in mixed venous blood.

Effect of the Anesthetic Circuit
As mentioned earlier, circuit components, including tubing, connectors, manual ventilation bag, and CO$_2$-absorbent material, absorb inhaled anesthetics, effectively creating another compartment that fills while anesthetic is flowing and needs to be emptied during washout. Low-level release of anesthetic gases from these components can continue for a considerable time.

Clearance via Metabolism of Anesthetics
Metabolism of inhaled anesthetics in tissues, particularly liver, contributes to a variable degree to drug clearance. Metabolism of inhaled anesthetics is reviewed in detail in the second part of this chapter (see Metabolism and Toxicity). Methoxyflurane, a drug that is no longer in clinical use, and halothane, an older drug that is rarely used in the United States, are highly metabolized inhaled anesthetics. Methoxyflurane undergoes extensive metabolism in humans, with only 19% of an inhaled dose recovered in exhaled gases. Approximately 20% to 25% of inhaled halothane is metabolized through biotransformation in the liver. A high rate of metabolism will reduce the anesthetic partial pressure in tissues, resulting in reduced pulmonary elimination and increased rates of overall anesthetic clearance. Tissue-dependent breakdown contributes less to clearance of newer inhaled anesthetics.

Additional Considerations and Possibilities
Modern inhaled anesthetics such as sevoflurane and desflurane have low blood solubility, and therefore provide a distinct advantage for both anesthetic induction and recovery from anesthesia. However, they present no advantage over older drugs such as isoflurane for maintenance of anesthesia during long cases. What if anesthesia is induced with one drug, followed by a switch to isoflurane during the maintenance period and then back to the more soluble drug, such as desflurane, for a period preceding emergence? This might allow for rapid induction and wake-up. Although a fast wake-up can be achieved by allowing sufficient time for near total washout of isoflurane and its replacement with desflurane, this type of crossover requires significant lead-time and high fresh gas flows. As an illustration, Neumann and colleagues compared 2-hour anesthetics at 1.25 x MAC (2 L/min FGF) with isoflurane alone, desflurane alone, or isoflurane with a crossover to desflurane during the last half hour. Although subjects awoke faster with desflurane alone, the crossover strategy did not result in acceleration of wake-up compared with isoflurane alone.
METABOLISM AND TOXICITY OF INHALED ANESTHETICS

This portion of the chapter focuses on adverse effects that are attributable to inhaled anesthetics, excluding most of the acutely reversible pharmacodynamic effects of inhaled anesthetics on various physiologic systems (see Chapters 27, 28, and 29).

The inhaled anesthetics are a unique group of drugs that can enter and leave the body unchanged through the lungs. Thus, chemical transformation of inhaled anesthetics is unrelated to their therapeutic activities, such as amnesia, hypnosis, and immobilization. Nonetheless, the carbon-halogen and other bonds of volatile alkanes and ethers can break down under certain conditions: biotransformation by enzymes in various tissues, reactions with strong bases in CO2 adsorbents, and exposure to ultraviolet radiation in the environment. Anesthetic breakdown resulting from decomposition in tissues or the breathing circuit can produce toxic reactive intermediates, which in sufficient amounts can harm patients directly or indirectly. N2O gas is not biotransformed but selectively reacts with and inactivates vitamin B12 and perturbs B12-dependent biochemical pathways. The breakdown of waste anesthetics in the atmosphere also has potential environmental and health consequences. There are potential long-term neurotoxic effects of anesthetic exposure that are not associated with chemical breakdown.

BIOTRANSFORMATION OF INHALED ANESTHETICS

The extent and location of inhaled anesthetic metabolism depends on multiple chemical factors. Inhaled anesthetics undergo varying degrees of biotransformation (Table 26-3) in various tissues. Methoxyflurane undergoes by far the greatest metabolism, estimated at 70%, and experiments indicate that only a small fraction of drug taken up into body tissues is exhaled.61 Given the remarkable lipophilicity of methoxyflurane, respiratory clearance of this drug from muscle and fat extends over a period of days (see Tables 26-1 and 26-2). Halothane is the next most lipophilic drug and ranks second in metabolic clearance (see Table 26-3). Thus, prolonged residence in body tissues is an important factor in biotransformation of inhaled anesthetics. Chemical stability is another important factor. Isoflurane is an isomer of enflurane, and the two drugs display comparable respiratory uptake, distribution, and respiratory clearance. Nonetheless, isoflurane is metabolized only one tenth as much as enflurane. Although sevoflurane and desflurane represent another pair of anesthetics, both characterized by rapid uptake, distribution, and respiratory clearance, 5% of sevoflurane is biotransformed versus 0.02% of desflurane.

Of the major organs involved in anesthetic biotransformation, the liver and kidneys are exposed to the highest metabolite concentrations and thus are most susceptible to damage from toxic metabolites. Clinically significant hepatotoxicity is primarily associated with exposure to halothane, and nephrotoxicity is associated with methoxyflurane.90 Investigations into the mechanisms of these toxicities have influenced drug development and provided important insights into human toxicology.91

Biotransformation in Liver

The liver is the major site of metabolism for most drugs, particularly lipophilic drugs, which typically are transformed into hydrophilic metabolites that are more readily excreted. The liver is large and contains high concentrations of many drug-metabolizing enzymes. Other organs that contribute to drug metabolism and clearance include the gastrointestinal tract, kidneys, and the lungs. Drug biotransformation reactions include oxidation, hydrolysis, and conjugation. A single drug can be transformed into several metabolites, depending on the relative rates of various enzyme reactions, the drug concentration in different tissues expressing relevant enzymes, competition at enzyme sites with other drugs or endogenous substances, and other factors. Oxidation and hydrolysis are also known as phase 1 reactions, and they result in introduction or exposure of a polar group on the drug. The phase 1 enzymes that metabolize inhaled anesthetics in the liver are various cytochrome P450 (CYP) isoforms in the endoplasmic reticulum of hepatocytes. These enzymes catalyze oxidation reactions, such as dehalogenation, N- and O-dealkylation, N- and S-oxidation, and deamination. These reactions require oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cytochrome P450 reductase as cofactors. Under hypoxic conditions, some P450 enzymes can also catalyze reductive reactions. More than 50 CYP isoforms are active in humans, and CYP3A4 and CYP3A5 are the most abundant. Conjugations are also known as phase 2 reactions, and they often append highly polar groups such as glucuronic acid, sulfate, or glycine to polar groups on phase 1 metabolites. The resulting hydrophilic products are readily excreted in urine via the kidneys or in bile via the gastrointestinal tract. N-Acetylation reactions are an exception that result in metabolites that are less water soluble than the parent drug.

Many factors affect hepatic drug metabolism, including concomitant drugs, disease, age, and genetics.57 Induction and inhibition of enzymes are associated with exposure to certain drugs or other exogenous substances. Induction of specific CYP isoforms is a gene-mediated response to chronic exposure to substrates of the enzyme, resulting in accelerated enzyme production or slowed turnover. For example, phenobarbital use results in increased production of CYP3A4 and NADPH-cytochrome P450 reductase, leading to dramatically increased metabolism of all CYP3A4...
TABLE 26-3 METABOLISM OF HALOGENATED VOLATILE ANESTHETICS

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Halothane</th>
<th>Methoxyflurane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of tissue metabolism (%)</td>
<td>25</td>
<td>70</td>
<td>2.5</td>
<td>0.2</td>
<td>0.02</td>
<td>5</td>
</tr>
<tr>
<td>Oxidizing enzymes</td>
<td>CYP2E1, CYP2A6</td>
<td>CYP2E1, CYP1A2, 2C9, 10, 2D6</td>
<td>CYP2E1</td>
<td>CYP2E1</td>
<td>CYP2E1</td>
<td>CYP2E1</td>
</tr>
<tr>
<td>Oxidative metabolites</td>
<td>F_3C-COOH, HBr, HCl</td>
<td>H_2C-O-CF_3-COOH, HCl, HOOC-COOH, HOCl, HF, HF</td>
<td>HF_2C-O-CF_2-COOH, HCl, HF</td>
<td>HF_2C-O-CO-CF_2-CF_3, F_3C-COOH, CF_3-HOH, HCl</td>
<td>HF_2C-O-CO-CF_2-CF_3, F_3C-COOH, CF_3-HOH, HCl</td>
<td>HF_2C-O-(CF_2)_2, HO-CH(CF_3)_2, HF</td>
</tr>
<tr>
<td>Trifluoroacetylated hepatocellular proteins</td>
<td>++++</td>
<td>n/a</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>none</td>
</tr>
<tr>
<td>Reducing enzymes</td>
<td>CYP2A6, CYP3A4</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Reductive metabolites</td>
<td>F_3 Br, F_2 C = CHCl</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Tissue toxicities</td>
<td>Hepatic</td>
<td>Renal, hepatic</td>
<td>Renal, hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Fulminant hepatitis incidence</td>
<td>1:20,000</td>
<td>Reported, incidence unknown</td>
<td>Renal, hepatic</td>
<td>1:300,000</td>
<td>70-73</td>
<td>74-78</td>
</tr>
<tr>
<td>References</td>
<td>65-69</td>
<td>70-73</td>
<td>74-78</td>
<td>75, 79-81</td>
<td>82-85</td>
<td>71, 86-89</td>
</tr>
</tbody>
</table>

The plus signs indicate relative degree of protein modification.
n/a, The specific enzymes are not identified in these cases.

halothane and bromide ions, resulting in trifluoroacetylated chloride, which reacts with water to form trifluoroacetic acid (Fig. 26-14). Reductive metabolism of halothane results initially in loss of bromide, and the intermediate either reacts with a hydrogen donor to form 2-chloro-1,1,1-trifluoroethane or captures an electron, further reducing the carbon-carbon bond to form 2-chloro-1,1-difluoroethylene (see Fig. 26-14). Halothane reduces hepatic blood flow and can cause hepatocellular hypoxia in some regions in the liver, potentially leading to an increase in its reductive metabolism. All the ether anesthetics undergo similar oxidative metabolism catalyzed by CYP2E1 (see Table 26-3, Fig. 26-15). Oxidative metabolism of these drugs results in the release of fluoride (F\(^{-}\)) and chloride (Cl\(^{-}\)) ions and the formation of reactive intermediates that react with water to form carboxylic acids. Isoflurane and desflurane both produce trifluoroacetic acid, whereas enflurane forms 2-difluoromethoxy-2,2-difluoroacetic acid. Oxidative metabolism of methoxyflurane can follow several paths, releasing Cl\(^{-}\) or F\(^{-}\) in sequential steps and producing methoxy-difluoroacetic acid, dichloroacetic acid, and acetic acid (see Table 26-3).

**Halothane Hepatotoxicity**

The first modern halogenated volatile anesthetic, halothane, was introduced in 1955. Clinical exposure to halothane is associated with two distinct types of hepatic injury. Subclinical hepatotoxicity occurs in 20% of adults who receive halothane. It is characterized by mild postoperative elevations in alanine aminotransferase and aspartate aminotransferase, but is reversible and innocuous. Anaerobic halothane reduction by CYP2A6 to a 2-chloro-1,1,1-trifluoroethyl radical (see Fig. 26-14) is thought to mediate this mild hepatic injury. The fulminant form of hepatotoxicity, commonly known as halothane hepatitis, is characterized by elevated alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase levels, and massive hepatic...
Halothane hepatitis is rare (1 in 5000 to 35,000 administrations in adults), but is fatal in 50% to 75% of these cases. Because of the potential for fatal hepatitis, halothane is no longer used in adult patients in many countries.

Halothane hepatitis is caused by a hypersensitivity reaction associated with oxidative metabolism of halothane. The highly reactive trifluoroacetyl chloride metabolite of halothane oxidation can react with nearby liver proteins (see Table 26-3). In most patients who developed hepatic necrosis after halothane anesthesia, antibodies against TFA-modified proteins were detected, suggesting that the hepatic damage is linked to an immune response against the modified protein, which acts as a neoantigen (see Figure 26-16). Accordingly, patients who develop halothane hepatitis often have a history of prior exposures to halothane or other volatile anesthetics, together with symptoms suggestive of immune reactivity, such as fever, rash, arthralgia, and eosinophilia. A current hypothesis is that TFA-protein adducts induce a cytotoxic T cell reaction in sensitized individuals, which leads to liver damage. However, the immune responses observed in halothane hepatitis might not mediate liver injury.

Hepatotoxicity and massive hepatic necrosis has occurred after halothane anesthesia in pediatrics (see Chapter 93). However, two large retrospective studies have demonstrated that the clinical syndrome of halothane hepatitis is even more rare in the pediatric population (1 in 80,000 to 200,000) than in adults. Halothane is metabolized to a similar degree in adults and children. The children are immune competent from birth. Pediatric cases of halothane hepatitis are also associated with multiple anesthetic exposures, suggesting a mechanism similar to that in adults. Why the incidence of halothane hepatitis is more frequent in the adult population is not known.

Other volatile anesthetics including enfurane, isoflurane, and desflurane have also been associated with fulminant hepatic necrosis, but compared with halothane, the incidence of this potentially fatal toxicity is rare after administration of these newer volatile anesthetics. The mechanism of severe hepatitis following enfurane, isoflurane, and desflurane may be the same as for halothane, because all these drugs are oxidatively metabolized to highly reactive intermediates that can covalently modify hepatic proteins (Fig. 26-16). As with halothane, case investigations usually reveal that patients have had prior exposure to volatile anesthetics, and antibodies to modified hepatic proteins can be detected. The extremely infrequent incidence of severe hepatitis for modern volatile anesthetics is likely due to their lower degree of oxidative metabolism and subsequent immune sensitization. In fact, hepatitis was also commonly reported soon after introduction of methoxyfluorane, another highly metabolized anesthetic that is oxidized at the fluoromethoxy C-H bond and forms hexafluoroisopropanol and inorganic $\text{F}^-$ (see Table 26-3; Fig. 26-17). Unlike all other volatile anesthetics, sevoflurane is oxidized at the fluoromethoxy C-H bond and forms hexafluoroisopropanol, is relatively stable, and modified liver proteins are not formed after sevoflurane anesthesia. Cases of hepatitis and rapid death after sevoflurane anesthesia have been reported, but there was no evidence of an immune-mediated mechanism.

### Biotransformation in Kidneys

The kidneys are large organs that receive high blood flow. Renal physiologic activities include glomerular filtration of water-soluble metabolites, reabsorption of water and essential metabolites, urinary excretion of waste, and regulation of hormones involved in vascular tone (renin) and water balance (aldosterone). The kidneys clear most of the water-soluble metabolites resulting from biotransformation of inhaled anesthetics. Kidneys also contain CYP enzymes, including CYP2E1, that catalyze both phase 1 and phase 2 reactions and are therefore additional sites where inhaled anesthetic metabolism occurs. As in the liver, various CYPs in renal parenchyma can undergo induction or inhibition by exogenous substances.

### Fluoride-Associated Nephrotoxicity

The first modern halogenated ether anesthetic, methoxyfluorane, was introduced in 1959. Methoxyfluorane causes polycyric renal insufficiency, and it is no longer used in clinical practice. The nephrotoxic effect of methoxyfluorane is attributed to inorganic fluoride ($\text{F}^-$) released during its metabolism. Investigations have provided significant insights into potential nephrotoxic mechanisms by fluorinated volatile anesthetics and have influenced the development of subsequent halogenated anesthetic agents.
Chapter 26: Inhaled Anesthetic Pharmacokinetics: Uptake, Distribution, Metabolism, and Toxicity

Absorbed methoxyflurane undergoes extensive biotransformation, including cytochrome-catalyzed oxidation that releases inorganic fluoride ions ($F^-$) into blood. Animal studies provide clear evidence of the nephrotoxicity of methoxyflurane, which includes a strong relationship between methoxyflurane dose and renal injury, increased nephrotoxicity with induction of CYP enzymes, and decreased nephrotoxicity with inhibition of methoxyflurane metabolism. Clinical data further indicate that severity of nephrotoxicity and mortality are associated with high plasma fluoride concentrations after methoxyflurane anesthesia. Patients with serum inorganic fluoride levels below 50 μM had no evidence of renal injury, whereas patients with post-methoxyflurane serum $F^-$ greater than 50 μM suffered high rates of renal dysfunction and increased mortality. Moreover, serum $F^-$ concentrations were significantly higher after the administration of methoxyflurane than with other halogenated volatile anesthetics, which are not associated with nephrotoxicity.

**Figure 26-15.** Proposed pathways for inhaled anesthetic metabolism to reactive intermediates. CYP2E1 catalyzes oxidative metabolism of halothane, enflurane, isoflurane, and desflurane to a variety of reactive intermediates that can form adducts with hepatocellular proteins. Trifluoroacetylated proteins are identical after halothane, isoflurane, and desflurane, whereas adducts following enflurane are immunologically similar.

**Figure 26-16.** Pathways generating the immune response after exposure to inhaled anesthetics. Halothane is metabolized to a reactive trifluoroacetyl intermediate that forms an amide bond with hepatocellular proteins. The altered protein triggers an immune response, which on subsequent exposure to anesthetic results in hepatocellular damage and necrosis. A similar process may ensue after exposure to other fluorinated drugs metabolized to similar halo-acyl intermediates. (Modified from Njoku D, Laster MJ, Gong DH, et al: Biotransformation of halothane, endflurane, isoflurane and desflurane to trifluoroacetylated liver proteins: association between protein acylation and liver injury, Anesth Analg 84:173-178, 1997.)
renal injury after methoxyflurane exposure was observed. Genetic heterogeneity, drug interactions, and preexisting renal disease probably account for these differences.

Since the introduction of methoxyflurane, all prospective halogenated anesthetic drugs have been extensively tested experimentally and clinically for their degree of defluorination and the resulting serum F\(^{-}\) concentrations. However, experience with newer drugs, particularly with sevoflurane, has caused investigators to reexamine the classical fluoride-induced nephrotoxicity hypothesis. Sevoflurane was initially synthesized in the 1970s, but because of its relatively large defluorination rate (2% to 5%), its introduction into clinical practice was delayed. It was first used widely in Japan in 1990. Subsequent clinical studies demonstrated no clinically significant nephrotoxicity after the administration of sevoflurane, even when high peak F\(^{-}\) concentrations greater than 50 \(\mu\)M were confirmed.\(^{111}\) Typical peak fluoride concentrations after 2 to 3 MAC-hours of sevoflurane anesthesia are 20 to 30 \(\mu\)M, and less than 5 \(\mu\)M after isoflurane and desflurane (see Fig. 26-18). Enflurane metabolism also often results in peak F\(^{-}\) concentrations greater than 20 \(\mu\)M. Isoflurane and desflurane are metabolized minimally, and they produce lower plasma fluoride concentrations. However, none of these anesthetics is associated with clinically significant renal toxicity, suggesting that methoxyflurane is unique in its ability to harm kidneys. One difference between methoxyflurane and the current volatile anesthetics is its extreme lipophilicity and extremely long residence time in tissues. This results in prolonged elevated F\(^{-}\) concentrations in blood (see Fig. 26-18), suggesting that the length of F\(^{-}\) exposure is a key risk factor. However, prolonged, moderate increases of plasma fluoride (25 to 38 \(\mu\)M) during several days of isoflurane anesthesia have occurred without adverse renal effects.\(^{125,126}\) Thus, neither the peak level nor the duration of high plasma fluoride concentration entirely explains the nephrotoxic effects by the halogenated anesthetics. It is also not clear whether the integrated concentration multiplied by time exposure to inorganic F\(^{-}\) represents the key risk factor; however, methoxyflurane is metabolized significantly within kidney parenchyma, producing high intrarenal inorganic fluoride concentrations (likely much higher than those measured in blood), which are proposed to cause renal injury.\(^{71,73}\) Thus, compared with methoxyflurane, the absence of renal toxicity with current volatile anesthetics likely derives from a combination of factors: (1) their lower tissue solubilities, particularly in kidney (see Table 26-2), resulting in lower intrarenal fluoride production; (2) lower rates of biotransformation; and (3) more rapid respiratory clearance from the body.

ANESTHETIC DEGRADATION IN CARBON DIOXIDE ABSORBENTS

Sevoflurane, Compound A, and Renal Toxicity

Halogenated anesthetics can undergo chemical breakdown while interacting with CO\(_2\) absorbents that contain strong bases such as sodium hydroxide (NaOH) and potassium hydroxide (KOH), which are present in soda lime and Baralyme.\(^{127}\) Strong bases extract a proton from

Figure 26-17. Metabolic oxidation of sevoflurane. CYP2E1 catalyzes phase 1 defluorination of sevoflurane, forming hexafluoroisopropanol. Phase 2 glucuronidation is catalyzed by uridine 5′-diphosphate glucuronosyltransferase.

Figure 26-18. Serum inorganic fluoride (F\(^{-}\)) exposure before and after methoxyflurane anesthesia is much greater than with other anesthetics. Points represent serum F\(^{-}\) measurements (mean ± SD) from multiple subjects. After 2 to 3 MAC-hours of methoxyflurane anesthesia, F\(^{-}\) rises during and after drug administration ends, peaks above 60 \(\mu\)mol/L on postanesthesia days 2 and 3, then declines slowly, remaining elevated for more than 1 week. Sevoflurane anesthesia (3.7 MAC-hours) produces an early peak F\(^{-}\) concentration averaging 31 \(\mu\)mol/L, which declines over 3 to 4 days. Enflurane anesthesia (2.7 MAC-hours) results in an early average peak of 22 \(\mu\)mol/L which declines in 3 to 4 days. Isoflurane and desflurane result in small and negligible rises in serum F\(^{-}\) concentrations. Only methoxyflurane is associated with fluoride-associated renal toxicity. MAC, minimum alveolar concentration.
the isopropyl group of sevoflurane, primarily forming a haloalkene (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether), known as compound A (Fig. 26-19). Compound A is volatile and can be absorbed via alveolar gas exchange. Compound A exposure is nephrotoxic in laboratory animals, causing proximal tubular necrosis and, with sufficient exposure, death. In rats, renal injury is observed with cumulative exposure to compound A above 150 parts per million (ppm)-hours (e.g., 50 ppm inhalation for 3 hours). Moderately severe but reversible histopathologic damage was found in rats after 200 ppm-hour exposure, associated with increased blood urea nitrogen (BUN), creatinine, and other measures of renal damage. Compound A exposure greater than 1000 ppm-hours is lethal in half of exposed rats.

Patients given sevoflurane anesthesia are routinely exposed to compound A in rebreathing circuits, and the inhaled concentration is dependent on the fresh gas flow rate and the type of CO₂ absorbent present. Fresh gas flows of 1 L/min result in maximal compound A concentrations of approximately 20 ppm with soda lime and 30 ppm with Baralyme. Higher FGF rates result in a smaller accumulation of compound A in the breathing circuit. However, compound A exposure is not associated with clinically significant nephrotoxicity in humans. There is no threshold exposure level known to cause more than subclinical renal damage. Numerous studies in which human subjects or patients were exposed to greater than 200 ppm-hours of compound A have reported that clinical measures of renal function (BUN, creatinine, urinary protein or glucose, and urine concentrating ability) and laboratory tests for subtle renal damage (N-acetyl-β-glucosaminidase, alanine aminopeptidase, γ-GTP, and β₂-microglobulin) remain unchanged. Kharasch and colleagues compared the effects of low-flow sevoflurane and isoflurane anesthesia in patients with stable renal insufficiency and found no significant difference in postoperative renal function tests. Other studies have reported normal BUN and creatinine, but transient reversible abnormalities in other renal function test values following prolonged sevoflurane anesthesia at low FGF (>330 ppm/hr compound A exposure in one study).

The evidence of nephrotoxicity in rats compared with the remarkably benign results in humans suggests that mechanisms of sevoflurane metabolism and toxicity differ between these species. The difference in the nephrotoxic effects of compound A between humans and rats may be attributed to the doses of compound A, interspecies differences in metabolic toxification, and sensitivity of the proximal tubular cells to compound A cytotoxicity. Detailed studies show that in rats, compound A undergoes S-conjugation to cysteine, and that the resulting cysteine conjugate is metabolized by renal β-lyase to a reactive thionoacyl fluoride that is proposed to damage proteins essential for kidney function. Humans have very low β-lyase activity, which is hypothetically the basis for the lack of reported nephrotoxicity in patients. Glutathione (GSH), hydrofluoric acid. (Adapted from Martin JL, Kandel L, Laster MJ, et al: Studies of the mechanism of nephrotoxicity of compound A in rats, J Anesth 11:32-37, 1997.)
PART III: Anesthetic Pharmacology

**Table 26-4: Composition of Base Chemicals and Water Content of Carbon Dioxide Absorbents**

<table>
<thead>
<tr>
<th>CO₂ Absorbent</th>
<th>Ca(OH)₂ (%)</th>
<th>Ba(OH)₂ (%)</th>
<th>KOH (%)</th>
<th>NaOH (%)</th>
<th>LiOH (%)</th>
<th>H₂O (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baralyme</td>
<td>70</td>
<td>10</td>
<td>4.6</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>—</td>
<td>2.6</td>
<td>1.3</td>
<td>—</td>
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<td>3.8</td>
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<td>16</td>
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<td>—</td>
<td>0.003</td>
<td>2.0</td>
<td>—</td>
<td>16</td>
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<tr>
<td>Sodalime II, Medisorb</td>
<td>81</td>
<td>—</td>
<td>0.003</td>
<td>2.6</td>
<td>—</td>
<td>16</td>
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<tr>
<td>Spherasorb</td>
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<td>—</td>
<td>0.003</td>
<td>1.5</td>
<td>—</td>
<td>14</td>
</tr>
<tr>
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<td>—</td>
<td>—</td>
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<tr>
<td>LofloSorb</td>
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<td>—</td>
<td>—</td>
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</tr>
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<td>Superia</td>
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<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>99</td>
</tr>
</tbody>
</table>


* Various absorbents also contain other components, such as polyvinylpyrrolidone, calcium chloride, calcium sulfate, magnesium chloride, and aluminosilicate.

†Baralyme was withdrawn from the market in 2004.

Acid (AOAA) protects rats from compound A nephrotoxicity, whereas others have found no protective effect of AOAA or other inhibitors in the proposed pathway. Alternative mechanisms underlying compound A toxicity have been proposed, including formation of reactive sulfides catalyzed by CYP3A isozymes, which are also more active in rat than in human kidneys.

Although the mechanism underlying compound A toxicity in experimental animals remains uncertain, the clinical data are reassuring concerning the lack of significant sevoflurane nephrotoxicity in humans. Compound A exposure can be limited by careful selection of fresh gas flows, vaporizer output, and CO₂ absorbent materials. The use of 2 L/min fresh gas flows ensures that for the vast majority of patients, exposure to compound A will be below the most conservative threshold for nephrotoxicity. Although clinical studies indicate that sevoflurane is most likely safe even in patients with preexisting renal dysfunction, the drug should be administered in accordance with the approved package labeling guidelines.

Like sevoflurane, halothane degrades in the presence of CO₂ absorbents to form a reactive intermediate, bromochlorodifluoroethylene (BCDFE), which has also been investigated as a possible nephrotoxin. Eger and colleagues found that in comparison with compound A, BCDFE accumulates twentyfold to fortyfold less in breathing circuits and is fourfold less reactive. Thus, the risk of BCDFE nephrotoxicity is negligible.

### Carbon Monoxide and Heat

In the presence of strong bases in dry CO₂ absorbents (water content < 5%), some halogenated volatile anesthetics undergo degradation, resulting in the formation of CO, trifluoromethane (CF₃H), and hydrogen fluoride (HF). The factors that determine the amount of CO produced include the chemical makeup of CO₂ absorbent (KOH > NaOH > Ca(OH)₂), dryness of the absorbent material, the concentration of volatile agent, and its chemical structure. Baralyme contains 4.6% KOH, whereas soda lime contains 2.5% KOH and 1.5% NaOH and reacts less vigorously with halogenated anesthetics. The relatively weak bases Ba(OH)₂ and Ca(OH)₂ are also major constituents in CO₂ absorbents, and do not catalyze CO formation (Table 26-4). The anesthetics that contain a difluoromethyl group (difluoromethyl-ethyl ethers) are most susceptible to this degradation and for this group CO production correlates with anesthetic concentration in the breathing circuit (desflurane > enflurane > isoflurane). Sevoflurane, methoxyflurane, and halothane also degrade in the presence of strong bases, but do not produce CO. Production of CO appears to require nearly complete desiccation (i.e., removal of absorbent moisture) of the CO₂ absorbent, and typically occurs after high flow flushing of the breathing circuit for 1 to 2 days. Soda lime contains 15% water by weight, and Baralyme contains 13% water by weight (see Table 26-4). CO production is observed when water content of soda lime or Baralyme falls below 1.4% and 5%, respectively. High ambient temperatures also accelerate desiccation of CO₂ absorbent materials and may increase the rate of CO producing reactions. As noted with compound A, CO accumulation in the breathing circuit is inversely related to the fresh gas flow.

Anesthetic degradation in the breathing circuit has resulted in CO poisoning during clinical anesthesia. CO has 250-fold greater affinity for hemoglobin than O₂ does; therefore, the formation of carboxyhemoglobin reduces blood oxygen carrying capacity and tissue oxygen delivery, and is difficult to reverse. The detrimental effects and signs of CO toxicity are well known; however, with general anesthesia, signs of patient exposure to CO are masked, and hypoxia may be difficult to detect, because some pulse oximetry equipment cannot distinguish between carboxyhemoglobin and oxyhemoglobin.

The degradation of volatile anesthetics by bases in CO₂ absorbents is an exothermic reaction that results in the production of heat. Sevoflurane produces the most heat production when it is used with desiccated CO₂ absorbent. The absorbent canister and anesthetic circuit can reach extremely high temperatures, which can lead to explosion or fire, or both (see Chapter 109).

Current recommendations to minimize anesthetic degradation to CO and heat include machine maintenance measures to avoid desiccation of CO₂ absorbent and the use of absorbents that contain less KOH and NaOH. Newer CO₂ absorbents (see Table 26-4) contain...
Chapter 26: Inhaled Anesthetic Pharmacokinetics: Uptake, Distribution, Metabolism, and Toxicity


Kharasch ED: Mechanistic aspects of carbon monoxide formation from
 Minimum alveolar concentration.

Figure 26-20. Inhaled anesthetic degradation and carbon monoxide production. Points represent mean ± SD of three measurements with equivalent anesthetic doses (1.5 × MAC) in the presence of dry CO2 absorbents at identical fresh gas flows. A, Degradation and CO production with Baralyme. B, Degradation and CO production with soda lime. Degradation and CO production was observed with anesthetics containing difluoromethoxy groups (desflurane, enfurane, and isoflurane), but not halothane (hal) or those with monofluoromethoxy groups such as sevoflurane (sevo) and methoxyflurane (mtyfo).

N2O is unique among anesthetics in irreversibly inhibiting cobalamin (vitamin B12) by oxidizing the Co (I) ligand. Cobalamin is ingested or produced by bacteria in the gut, and they are critical cofactors together with S-methyltetrahydrofolate in the activity of methionine synthase (Fig. 26-21). Methionine synthase catalyzes methylation of homocysteine to methionine, while also demethylating 5-methyltetrahydrofolate to produce tetrahydrofolate. Methionine, converted to S-adenosylmethionine, is the major substrate for methylation in biochemical pathways involved in the synthesis of DNA, RNA, myelin, and catecholamines. Chronic vitamin B12 deficiency (as in pernicious anemia) results in hematologic and neurologic dysfunction. Long-term N2O exposure, typically among individuals who frequently inhale it as a recreational drug, can also cause megaloblastic anemia, myelopathy, neuropathy, and encephalopathy, sometimes presenting as psychosis. Risk factors that increase susceptibility to N2O toxicity include pernicious anemia or other gastrointestinal malabsorption syndromes, extremes of age, alcoholism, malnutrition, a strict vegetarian diet, and inborn deficiencies in cobalamin or tetrahydrofolate metabolism. Inhibitors of folate metabolism, such as methotrexate, can also enhance sensitivity to N2O toxicity.

In healthy surgical patients, megaloblastic changes in the bone marrow are rare, and reported only after a prolonged period of exposure (>12 hours) to N2O. However, in seriously ill patients or those with risk factors noted earlier, shorter (or repetitive) periods of N2O exposure can lead to significant subacute pathology. Megaloblastic bone marrow changes can be induced after a short period (2 to 6 hours) of N2O exposure. Vitamin B12 deficiency or reduced methionine synthase activity can also lead to subacute myelinopathy and neuropathy. A case highlighting the potential importance of inborn metabolism was reported by Selzer and associates. In this case, a 4-month-old child developed an irreversibly and ultimately fatal seizure disorder several weeks after receiving N2O during anesthesia. Autopsy revealed widespread brain atrophy and demyelination, and biochemical investigations revealed reduced methyltetrahydrofolate reductase (MTHFR) activity, which eventually were linked to several mutations in the gene encoding MTHFR.

Another consequence of reduced methionine synthase activity is accumulation of its substrate, homocysteine (see Fig. 26-21). Homocystinuria caused by severe inborn deficiency of methionine synthase activity is associated with extremely increased blood homocysteine levels, early atherosclerosis of coronary and cerebral arteries, and premature death. These observations led to the “homocysteine hypothesis,” which postulates that homocysteine stimulates inflammation and atherosclerosis, and is a key modifiable factor in vascular morbidity and mortality. Increased homocysteine levels are an independent risk factor for cardiac and cerebrovascular morbidity, but the association between homocysteine levels and atherothrombotic disease is weak. Moreover, studies in which diet and vitamin supplementation were used to reduce homocysteine levels demonstrate improvement in some markers of vascular risk, but do not reduce the rate of myocardial infarction and atherosclerotic stroke. Thus, the importance of chronic, moderate increases in homocysteine to cardiovascular outcomes is tenuous, or perhaps only pertinent to limited patient populations.

Do the rapid increase of homocysteine levels during N2O anesthesia influence the risk of cardiovascular...
and neurovascular morbidity following surgery and anesthesia? Badner and colleagues\textsuperscript{172} reported that N\textsubscript{2}O administration significantly increased homocysteine levels and increased myocardial risk in carotid endarterectomy patients. The Evaluation of Nitrous Oxide in a Gas Mixture for Anaesthesia (ENIGMA) trial in over 2000 patients reported that avoidance of N\textsubscript{2}O combined with increased inspired oxygen concentration during anesthesia decreased the incidence of a variety of complications after major surgery but found no reduction in death, myocardial infarction, stroke, or hospital length of stay.\textsuperscript{173} A follow-up study of the ENIGMA trial patients reported that those exposed to N\textsubscript{2}O for more than 2 hours were at increased risk (odds ratio, 1.6; 95\% confidence interval, 1.01 to 2.5) of myocardial infarction up to 5.7 years after enrollment (ENIGMA-II).\textsuperscript{174} No difference in rates of death or stroke were found. Unfortunately, diagnosis of myocardial infarction in ENIGMA-II was often based on data obtained in telephone interviews, rather than established diagnostic criteria. A recent post hoc study of 5133 enrollees in the Perioperative Ischemic Evaluation (POISE) trial\textsuperscript{175} found no increase in rates of death, myocardial infarction, or stroke in approximately 1500 patients who received N\textsubscript{2}O.

Homocysteine elevation following N\textsubscript{2}O inhalation is a useful marker for assessing the sensitivity of methionine synthase and related biochemical pathways to N\textsubscript{2}O inhibition. Nagele and colleagues\textsuperscript{176} studied a small group of surgical patients with common mutations in the gene encoding MTHFR, and found that those with 667C\rightarrow T and 1298A\rightarrow C mutations were at risk of developing abnormally high homocysteine levels after N\textsubscript{2}O exposures of at least 2 hours. However, a common gene variant (66A\rightarrow G) associated with reduced methionine synthase reductase activity did not result in abnormally high homocysteine levels after anesthesia with N\textsubscript{2}O.\textsuperscript{177} Preoperative infusions of vitamin B\textsubscript{12} and folate do not prevent the normal increases in homocysteine observed following anesthesia with N\textsubscript{2}O.\textsuperscript{178}

The continued value of N\textsubscript{2}O, first used as an anesthetic in the early nineteenth century, has been questioned by some.\textsuperscript{179,180} Given the ambivalence of currently available data, we recommend that anesthesia providers carefully screen patients to identify the few most likely to suffer N\textsubscript{2}O side effects, and to avoid the drug in these cases.

**INHALED ANESTHETICS AND NEUROTOXICITY**

The ability of general anesthetics to ablate consciousness reversibly has benefitted millions of patients and enabled dramatic advances in health care. Although inhaled anesthetics were the first class of anesthetics and continue to be used in the vast majority of cases, the potential of long-lasting neurotoxic effects of inhaled and other general anesthetics does exist in patients of extreme ages\textsuperscript{181-183} (see Chapters 80 and 93). The greatest concern surrounds the effects of general anesthetics in the youngest patients during periods of rapid brain development.\textsuperscript{184} In a seminal study, Jevtovic-Tetrodovic and coworkers\textsuperscript{185} demonstrated widespread neuronal apoptosis in the brains of 7\textsuperscript{th}-day-old rats after exposure to midazolam, isoflurane, and N\textsubscript{2}O. Additional findings in these animals included long-lasting (up to 4.5 months) deficits in hippocampal long-term potentiation (a neurophysiologic correlate of learning and memory), and performance deficits in spatial learning tests. Subsequent animal studies in various species, including nonhuman primates, demonstrate that during sensitive periods of early brain development, exposure to most general anesthetics is associated with accelerated neuronal cell death (apoptosis) and degeneration.\textsuperscript{186-190} Prolonged exposure to anesthetics can lead to neuroapoptosis and neurocognitive problems.\textsuperscript{187,189}

However, other studies suggest that even low nonapoptotic concentrations of general anesthetics may inhibit normal synapse formation and damage developing neuronal networks.\textsuperscript{191} Mechanisms underlying neurodevelopmental toxicity are potentially linked to the same ion channels hypothesized to mediate general anesthesia. General anesthetic actions are attributed in part to both antagonism of N-methyl-D-aspartate receptor and potentiation of GABAA receptor signal transduction, and drugs with either or both of these activities damage developing brains.\textsuperscript{183,192,193}
Early preclinical studies of neurodevelopmental toxicity of anesthesia demanded investigation of potential neurobehavioral correlates in humans. Current epidemiologic data (2013) are inconclusive. Clinical studies within the United States point to a possible association between anesthetic exposure in early childhood and the impairment of neurocognitive development, particularly with cumulative anesthetic exposure. In contrast, studies from Europe on the effects of a single exposure to anesthesia in early life that used combined data from national health data bases and educational registries within Denmark found that early inguinal hernia repair was not associated with poor cognitive outcome; rather it is suggested that the poor academic performance of a subgroup of these children may be due to their being developmentally disadvantaged compared with the background population. In another study in sibling pairs in which one sibling received anesthesia before age 3 years, comparable test scores were reported for verbal, performance, and global intelligence between exposed and unexposed siblings. Although some of the findings from the United States are concerning, potentially significant confounding factors were not controlled in these retrospective studies and firm conclusions cannot yet be drawn regarding the neurocognitive risks of general anesthesia in young children. Ongoing prospective clinical trials are expected to provide more definite information regarding this important issue (see Chapter 93).

INHALED ANESTHETICS AND ENVIRONMENTAL EFFECTS

Anesthetic gases in the workplace and in the outdoor environment have the potential to cause harm. Three potential sequelae have been investigated: global warming, ozone depletion, and health effects from workplace exposure (Table 26-5).

Global Warming Effects

Atmospheric trapping of thermal radiation from the earth’s surface is known as the greenhouse effect, which the Intergovernmental Panel on Climate Change deems a major contributor to global warming. Inhaled anesthetics are recognized greenhouse gases, Isoflurane, sevoflurane, and desflurane, the most widely used current inhaled anesthetics, are minimally metabolized in the body, and are substantially eliminated through exhalation. Most anesthesia waste scavenging systems transfer these gases directly and unchanged into the atmosphere. Recently, attention to the ecotoxicologic properties of inhaled anesthetics has grown. The global warming potential takes into account the heat-trapping efficiency and lifespan of atmospheric gases (time for removal by chemical reaction with radicals, photolysis, and deposition). The global warming potential of volatile anesthetics ranges from 1230-fold (isoflurane) to 3714-fold (desflurane) that of an equal mass of CO₂. Recently Ryan and Nielsen suggested that the most common volatile anesthetics can significantly influence global warming, with the greatest impact produced by atmospheric desflurane.

The global warming potential of N₂O is approximately 300-fold greater than that of an equal mass of CO₂. N₂O is used in large quantities relative to volatile anesthetic gases and is remarkably stable, with an atmospheric lifespan of approximately 120 years. Atmospheric N₂O is produced by natural sources in soil and water as well as human sources including agriculture (nitrogen-based fertilizers) and combustion of fossil fuels. Sherman and Cullen first reported that N₂O could contribute to global warming and estimated that approximately 1% of man-made N₂O production was for anesthesia. More recently, the anesthetic use of N₂O may contribute 3.0% of total N₂O emissions in the United States. Although the use of N₂O is declining in many countries, data on the worldwide medical use of N₂O are not available.

Ozone Depletion

The ozone layer of the earth’s atmosphere, which has been declining 4% per decade since the 1970s, absorbs damaging ultraviolet B light (wavelengths 280 to 315 nm). The biologic consequences of increasing ultraviolet B radiation include increases in skin cancer, cataracts, damage to plants, and reduction of oceanic plankton populations. Halogenated volatile anesthetics are similar to chlorofluorocarbons (CFCs), which are major ozone depleting pollutants. Ozone depletion by halocarbons depends on molecular weight, number, and type of halogen atoms, and atmospheric lifespan. The atmospheric lifespan of halogenated anesthetics is much shorter (4.0 to 21.4 years) than that of many CFCs (up to 100 years). Fluorination is associated with longer atmospheric lifespan because of the stability of carbon-fluorine (C-F) bonds. Chemicals with a lifetime of more than 2 years are believed to reach the stratosphere in significant quantities. There they are exposed to intense ultraviolet radiation that can break carbon-halogen bonds, creating halogen radicals that catalytically destroy ozone. Chlorine-containing anesthetics such as halothane, isoflurane, and enfurane may be more destructive to the ozone layer than newer anesthetics, such as sevoflurane and desflurane, which contain only C-F bonds. Carbon-hydrogen bonds are susceptible to attack by hydroxyl radicals (OH⁻) in the troposphere, making them less likely to reach the stratosphere. However, even compounds with a lifetime of a few months may potentially contribute to ozone destruction. Contributions to total stratospheric ozone depletion were estimated as 1% for halothane and 0.02% for enfurane and isoflurane.

N₂O is the primary source of stratospheric nitrogen oxides, NO and NO₂, and both destroy ozone. Because only 10% of N₂O is converted to NOₓ, its ozone depleting potential is lower than that of an equal mass of CFCs. However, N₂O emission is the single largest ozone depleting human emission, and is expected to remain so for the rest of this century. The use of N₂O could actually contribute additional environmental harm when used with halogenated anesthetics.
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The environmental impact of all inhaled anesthetics could be reduced by up to 80% to 90% if closed-circuit anesthesia were widely employed, and to a lesser degree if low carrier gas flow rates were used routinely (see Fig. 26-13). Technologies that trap anesthetics in waste gas flows have the potential to reduce emissions into the environment, and can reduce drug costs by reusing (after redistillation) the trapped drugs.† Physician education warning that the medical use of N₂O can significantly contribute to both the greenhouse effect and ozone depletion should be maintained. Avoiding N₂O when it provides no clinical advantage is suggested as a more environmentally sound anesthetic practice.

Exposure to Waste Anesthetic Gases
Health care personnel can be exposed to waste anesthetic gases both in and out of the operating room environment. Possible adverse health effects by chronic exposure to trace concentrations of inhaled anesthetics have caused concern among health care professionals for many years. Laboratory studies suggest reproductive abnormalities in animals exposed to high concentrations of N₂O (1000 ppm or greater). However, neither animal nor epidemiologic studies have shown any evidence for adverse effects attributable to the low levels of anesthetic gases in operating room air. A long-term prospective study found no causal relationship between adverse health effects and exposure to waste anesthetic gases with or without a scavenging system. All inhaled anesthetics cross the placental-fetal exchange barrier. Teratogenicity, which has been demonstrated in animal fetuses chronically exposed to N₂O, is of particular concern in pregnant health care workers, but there is no evidence of harm in humans. Furthermore, there is no evidence of harm to fetuses of women anesthetized while pregnant although general anesthesia is associated with neuroapoptosis during critical phases of brain development (see earlier, Inhaled Anesthetics and Neurotoxicity) warrant further clinical study of outcomes after anesthetic exposure during late-term pregnancy. Current, the U.S. Occupational Safety and Health Administration (OSHA) recommends that no worker should be exposed to concentrations of halogenated anesthetic greater than 2 ppm for a period not to exceed 1 hour during anesthesia administration (http://www.osha.gov/dts/osta/anestheticgases/index.html). OSHA also recommends that no worker should be exposed to 8-hour time-weighted average concentrations greater than 25 ppm. The recommended exposure level for N₂O is 25 ppm during anesthetic administration.

Potential postoperative exposure of health care workers to exhaled anesthetic gases in postanesthesia care units, intensive care units, and other patient care areas should also be recognized. Studies have documented excessive levels of waste anesthetic gases in poorly ventilated postanesthesia care units; however, no studies have documented significant adverse health.

Xenon and Other Noble Gases
Current inhaled anesthetics represent vast improvements over earlier inhaled anesthetics, with N₂O representing the longest surviving widely used anesthetic. The noble gas xenon was first shown to produce general anesthesia in 1951, and subsequent studies have revealed that it approaches the ideal closer than any other inhaled anesthetic. It is most comparable to N₂O, but superior in a number of ways. Xenon is present as a minor constituent of air (50 parts per billion), and it is isolated by distillation of liquefied air, liquefied nitrogen, and oxygen. Xenon is entirely unreactive in the biosphere; therefore, it is the only inhaled anesthetic that is not an environmental pollutant, although its distillation from air uses considerable energy and thus creates CO₂ and other pollutants as byproducts. It is odorless, tasteless, and nonflammable, and it has a limitless shelf-life. Its solubility in blood (b₁/kg = 0.14) and body tissues is lower than that of any other inhaled anesthetic, including N₂O. As a result, it has extraordinarily rapid onset and respiratory clearance, with emergence times twofold to threefold faster when it replaces N₂O in clinical settings. It undergoes no biotransformation or reactions with CO₂ absorbers or ultraviolet light. Moreover, xenon has favorable pharmacodynamic effects in comparison with most inhaled anesthetics. It produces minimal cardiovascular depression, and it is not arrhythmogenic. As with N₂O, xenon has analgesic activity, and it reduces intraoperative opioid requirements. It does not trigger malignant hyperthermia or produce any known toxicity. In fact, xenon has cardioprotective and neuroprotective activities in preclinical models, although clinical trials have

### TABLE 26-5 ATMOSPHERIC LIFETIMES AND ENVIRONMENTAL EFFECTS OF INHALED ANESTHETICS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lifetime (yr)</th>
<th>Ozone-Depleting Potential</th>
<th>Global Warming Potential (20 yr)</th>
<th>Global Warming Potential (100 yr)</th>
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<td>298</td>
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<td>—</td>
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<td>575</td>
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<td>Desflurane</td>
<td>10†</td>
<td>0</td>
<td>3714</td>
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</tr>
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Ozone-depleting potential is the ratio of integrated perturbations to total ozone relative to an equal emission of CFC-12. Global warming potential is defined as the cumulative radiative retention integrated over a period of time from the emission of gas relative to reference gas (CFC-12). The data are based on the Intergovernmental Panel on Climate Change Fourth Assessment Report unless otherwise indicated. *CO₂ unlikely reacts and depletes ozone; however, CO₂ producing the greenhouse effect in the troposphere is predicted to reduce stratospheric temperatures and cause further ozone depletion. †Computed value for halothane relative to global warming potential for CFC-12.
not demonstrated a reduction in postoperative delirium in high-risk patients receiving xenon.238,239

Given all these advantages, why is xenon not a commonly used inhaled anesthetic? The main reason is its cost.240 At more than $15 per liter in the gas form, xenon is greater than 100-fold more expensive than N₂O and is far more expensive per patient than either desflurane or sevoflurane, which are currently the most expensive volatile anesthetics. Xenon has a MAC-immobility of 0.61 atm, and even with a strict closed-circuit technique, greater than 10 L is needed to anesthetize a typical patient. To perform closed-circuit anesthesia with xenon-oxygen also requires lengthy preanesthetic denitrogenation to prevent N₂ from accumulating in the rebreathing circuit.241 Transitioning from 100% oxygen during denitrogenation to closed-circuit xenon-oxygen anesthesia is another slow process because xenon is added to the circuit as oxygen is metabolized in the patient at 200 to 250 mL/min. High-flow xenon is otherwise necessary to make this transition short. To make xenon a more affordable anesthetic, specialized anesthesia machines have been designed to enable its efficient delivery, and new waste-scavenging systems are being introduced with cryogenic traps that can condense xenon in a liquid form from waste gases.243 This process allows relatively inexpensive recycling of xenon after it has been redistilled to a pure form.

In addition to cost, xenon presents a few other downsides. Xenon gas has a much higher density (5.9 g/L) than either N₂O (1.5 g/L) or air (1.0 g/L), resulting in increased flow resistance and work of breathing.244 Thus, it may be a poor choice for patients with compromised respiratory function. As with N₂O, high xenon partial pressures be a poor choice for patients with compromised ventilation to prevent N₂ from accumulating in the rebreathing circuit.241 Transitioning from 100% oxygen during denitrogenation to closed-circuit xenon-oxygen anesthesia is another slow process because xenon is added to the circuit as oxygen is metabolized in the patient at 200 to 250 mL/min. High-flow xenon is otherwise necessary to make this transition short. To make xenon a more affordable anesthetic, specialized anesthesia machines have been designed to enable its efficient delivery, and new waste-scavenging systems are being introduced with cryogenic traps that can condense xenon in a liquid form from waste gases.243 This process allows relatively inexpensive recycling of xenon after it has been redistilled to a pure form.

Currently, xenon remains an experimental anesthetic, with current research focusing on its potential as a clinical neuroprotectant and development of technologies to reduce its cost. Shifting the cost-benefit balance toward more xenon use in patients will depend on whether clinical studies ultimately support xenon’s potential organ protection efficacy. Other noble gases also share some of xenon’s neuroprotective actions in experimental model systems, and they are under investigation as potential clinical drugs.247

Complete references available online at expertconsult.com.

REFERENCES

REFERENCES


61. Al: Table of contents.


88. Summary of the national Halothane Study: Possible association between halothane anesthesia and postoperative hepatic necrosis, JAMA 197:775-788, 1966.


References


References


