Chapter 9

INHALATIONAL ANESTHESIA

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ANESTHESIA IN THE FIELD

SUMMARY

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INTRODUCTION

A variety of anesthetic agents may be administered by different routes to produce both unconsciousness and the absence of sensation to allow for surgical procedures. Typically, general anesthesia is accomplished by the inhalation of anesthetic gases, and although drug administration by inhalation may appear to be unusual, complicated, and awkward to most physicians, it is a familiar route of drug delivery to all anesthesiologists. The pulmonary bed provides an excellent interface for controlling the delivery or removal of inhaled anesthetic agents, oxygen, or carbon dioxide, and measuring the alveolar partial pressure of gases allows for precise control of the depth of anesthesia.

With the exception of nitrous oxide, the modern inhalational anesthetic agents are volatile liquids that are vaporized for administration. These agents are potent, stable, storable for extended periods of time, nonflammable, and useful in almost any surgical setting. Military anesthesia providers deployed with the U.S. Department of Defense’s Deployable Medical Systems (DEPMEDS)—equipped forward hospitals may find that the inhalational anesthetic technique, not regional or other methods that are commonly used in civilian hospitals, is the one most often used.

OBSERVATIONS ON MECHANISMS OF ACTION

Although general inhalational anesthetics have been employed for almost 150 years, an understanding of their interaction with organ systems and structures to produce the anesthetic state has not been well delineated. Modern research has been focusing on structural changes in biological membranes on exposure to anesthetic molecules, but any theory of anesthetic action must take into account the following observations that are related to a state of narcosis:

• An extensive array of unrelated chemical structures produce general anesthesia. They do not share any common structure–activity relationship.
• During narcosis, alterations of function occur in all body systems. Physiological, metabolic, and structural changes occur that must be rationalized and explained by an organized system.
• The lipid solubility of anesthetics seems to be important, as the wide range of effective concentrations of agents is reduced to a small range when lipid solubility is calculated and taken into account.
• The phenomenon of pressure reversal that is observed in general anesthesia must be explained by any mechanistic theory of anesthesia.

To expand on the above observations, a major point in the study of the action of general anesthetics is that all the proposed theories have been based on observations of anesthetic agents in living organisms. Based on these observations, and after careful determinations of an anesthetic’s potency, four specific pharmacological characteristics have been described for an agent to be considered to have the qualities of a true general anesthetic: (1) lack of structural specificity, (2) cutoff effect of anesthetic potency, (3) lack of stereoselectivity, and (4) demonstration of pressure reversal.

Lack of Structural Specificity

An amazing number of chemically different molecules cause general anesthesia. The implication of this observation is that there is no single specific receptor that mediates general anesthesia. Early in this century, Hans H. Meyer and Charles E. Overton each independently observed that anesthetic potency correlates well with an agent’s solubility in the simple organic solvent, olive oil. This correlation of anesthetic potency with lipid solubility has been termed the Meyer-Overton rule and is easily demonstrated (Figure 9-1). The Meyer-Overton rule can be interpreted to mean that the product of an index of anesthetic potency and the agent’s solubility in a lipid is a constant, which, in theory, should be the same for all inhalational agents. The Meyer-Overton rule is usually taken to mean that inhalational agents have their site of action in the lipid component of cells. However, it is more correct to say that the site is nonpolar.

J. Ferguson proposed in 1939 that an anesthetic’s potency can be expressed in terms of thermodynamic activity: whatever the concentration of a given anesthetic agent required to produce a given level of anesthesia, the thermodynamic activity would be
Inhalational Anesthesia

Fig. 9-1. These data, in which an inhalational anesthetic’s minimal alveolar concentration is plotted as a function of its solubility in lecithin, are shown in a modern representation of the observations that led Meyer and Overton individually to propose that anesthetic potency is related to lipid solubility. The curve has the mathematical form: \[ \text{constant} = XY. \] A straight line with a negative slope is obtained when the data are plotted using log-log coordinates. Data source: Taheri S, Halsey MJ, Liu J, Eger EI II, Koblin DD, Laster MJ. What solvent best represents the site of action of inhaled anesthetics in humans, rats, and dogs? Anesth Analg. 1991;72:Table 1, p 631; Table 4, p 632.

The thermodynamic activity of a volatile agent (which, for purposes of this chapter, can be considered its vapor pressure) is a property of the anesthetic molecule. Ferguson’s rule can be interpreted to mean that the quotient of \((a)\) the partial pressure of an anesthetic agent at which one half of the subjects are anesthetized, and \((b)\) the vapor pressure of the agent at the appropriate temperature is a constant that, in theory, should be the same for all inhalational agents. Ferguson’s rule is silent as to the anesthetic’s site of action.

The rules of Meyer-Overton and Ferguson both have notable exceptions that provide insight into the mechanisms by which inhalational anesthetics act. Both exaggerate the potency of hydrogen and certain inert gases such as helium and neon, while the Ferguson rule also underestimates the anesthetic potency of short-chained fluorocarbons. The failure to predict the anesthetic potential of low-molecular-weight gases is now recognized to be a consequence of the phenomenon of pressure reversal.\(^6\)

### Cutoff Effect

In 1939, when he was studying homologous series of primary alcohols, Ferguson noted that carbon chained compounds demonstrate an anesthetic cutoff effect.\(^5\) Beginning with methanol \((C_N=1)\), anesthetic potency increases logarithmically with the addition of carbon atoms until the effect abruptly stops, and further addition of carbon moieties not only does not enhance potency, but such molecules are devoid of anesthetic potential. In the first series studied, potency ended at \(C_N=12\). This was termed the cutoff effect. When other homologous series were studied, both the type of bonds in the compound and the addition of other radicals attached to the first carbon were found to alter the absolute number of carbon atoms required for anesthetic cutoff. Interestingly, the fully fluorinated alkanes demonstrate cutoff at a very short carbon length: at octafluoropropane \((C_3F_8)\).\(^7\) The cutoff effect may have implications regarding the molecular binding site of anesthetics.
It has generally been assumed that the cutoff effect results from the failure of anesthetic agents with large molecular dimensions to dissolve at the site of action in a concentration sufficient to cause an effect. This explanation is now known to be untenable, at least for highly lipophilic alcohols with more than 12 carbon atoms.

Stereoselectivity

In general, anesthetics do not exhibit stereoselective effects. For example, both D-halothane and L-halothane, when inhaled, inhibit synaptic transmission and cause a disordered spin-labeling of the bilipid membrane. Interestingly, the optical isomers of isoflurane have markedly different effects on the nicotinic acetylcholine receptors of isolated neurons, even though their bulk lipid solubilities are identical. Although such findings suggest that an agonist–receptor interaction could mediate the effects of certain inhalational agents, the lack of stereospecificity for inhalational agents, when assessed as general anesthetics, speaks against such a phenomenon’s importance.

Pressure Reversal

The phenomenon of an anesthetic action’s being reversed by the application of high pressure was described in 1951 in tadpoles and confirmed later in other species. One possible explanation for pressure reversal is that it is an artifact caused by the helium gas that is used to raise atmospheric pressure in these studies. Helium itself is now known to be an anesthetic agent but has such limited lipid solubility that anesthesia is seen only at the very high pressures that are associated with pressure reversal. It is now accepted that pressure reversal is caused by ambient pressure acting on specific anesthetic sites of action in the lipid bilayer that constitutes the membrane of excitable cells. The mechanism is unclear but was originally thought to be due to the direct hydrostatic compression of the dissolved anesthetic agent; this smaller volume lessens the perturbation of the lipid bilayer in proximity to ion channels. Not all ion channels show pressure reversal—the nicotinic acetylcholine receptor, for example, does not—and even more interestingly, pressure reversal is seen only in species in which the amino acid glycine functions as a neurotransmitter. The latter observations strongly suggest that pressure acts on specific receptors rather than causing a generalized effect (eg, the compression of dissolved gas to a critical volume that is unable to affect the structure of ionic channels).

HYPOTHESES OF INHALATIONAL ANESTHETIC ACTION

Determining the mechanisms of action of inhalational anesthetic agents is one of the most difficult problems facing neuropharmacology. Based on the aforementioned observations, prevailing hypotheses as to the modes of action fall into the categories of lipid, protein, and lipid–protein interaction (Figure 9-2).

Lipid Hypotheses

Both Meyer and Overton pursued their lipid hypotheses of anesthetic action without the benefit of our current understanding of the phospholipid bilayer structure of cell membranes. They used olive oil as a surrogate for a biological lipid, although, interestingly, Meyer proposed that the biologically important lipid in which inhalational anesthetics exert their effect is the phosphocholine lecithin, which we now know is an important constituent of myelin sheaths. The simple dissolving of the anesthetic agent throughout the lipid-containing portion of the cell can no longer be viewed as a tenable hypothesis: there is no obvious mechanism through which the bulk presence of the agent can alter the function of ionic channels, which mediate the excitability of cells. Although it might seem possible that the presence of dissolved inhalational agent, by swelling or expanding the membrane (Figure 9-2a), might sufficiently distort the function of ionic channels, measured changes in the thickness of cell membranes due to the presence of an inhalational agent are surprisingly small: from 0.15% to 0.36%.

Attempts have been made to refine the lipid membrane–expansion hypothesis by assuming that the action of the inhalational agents is actually localized to discrete sites within the cell membrane, where a local change in the physical properties of the phospholipid bilayer affects ionic channels responsible for anesthesia. The “lipid–phase-transition” and “membrane-disordering” hypotheses are the best-known formulations that employ this approach.

The lipid–phase-transition hypothesis proposes that the lipid moiety of the lipid bilayer that is in proximity to ionic channels exists in two phases: the first consisting of liquid, low-density crystals; the
The membrane-expansion hypothesis. The inhalational agent so distorts the membrane that the ionic channel cannot open.

The phase-separation hypothesis. The lipid within the cell membrane is assumed to exist in two physical states: as a tightly packed gel and as loosely packed liquid crystals. When the ionic channel opens, neighboring liquid crystals are converted to gel. The presence of an inhalational agent prevents this phase transition, thereby inhibiting the opening of the channel.

The membrane-disordering hypothesis. The presence of an inhalational agent breaks up the normally parallel arrangement of lipid molecules. In an unknown manner, this perturbation prevents the ionic channel from opening.

The protein hypothesis. The inhalational agent activates a receptor on a protein which is a constituent of an ionic channel causing it to open. Viewed in terms of this hypothesis, the correlation between lipid solubility and anesthetic potency is epiphenomenal.

The lipid–protein interaction hypothesis. Normal functioning of an ionic channel depends on contact with lipid molecules. The inhalational agent affects the lipid so that this relationship is broken.

Fig. 9-2. A highly schematic and speculative rendering of hypotheses that purport to show possible mechanisms by which inhalational anesthetic agents might cause anesthesia. The crucial assumption is that the agent interferes with the normal function of neuroexcitatory cells. In each of the five sets of diagrams, membrane lipid is shown in yellow; ionic channels in cell membranes are shown in blue; and inhalational agent is shown in red. Each figure shows the ionic channel’s resting state (left); the bifurcating arrows indicate the transition to the active state (right), with the ionic channel open (upper) and the state caused by the anesthetic agent (lower).
second, a solid, high-density gel. Opening of the ionic channel pushes aside the neighboring liquid crystals, which then undergo a transition to the more tightly packed gel phase (Figure 9-2b). The presence of the dissolved inhalational agent is thought to prevent this transition. This hypothesis, however, finds little experimental support.

The membrane-disordering hypothesis is derived from spectroscopic evidence that the normal parallel orientation of fatty acid chains of lipid molecules in the cell membrane is disordered by the presence of an inhalational agent (Figure 9-2c). The disordering effect of inhalational agents is seen only when the membrane contains cholesterol in an amount equal to the phospholipid component—an important observation. The membrane-disordering hypothesis assumes that the disorder introduced into the membrane in some unknown way interferes with the function of ionic channels. How and why this happens remain to be determined, but two of the phenomena that must be understood for a putative theory of inhalational agents to have face validity find explanation in the membrane-disordering hypothesis:

1. Pressure reversal is seen to result from the pressure-induced decrease in the random molecular motion of the fatty acid chains that comprise the central portion of the membrane lipids. This ordering of the membrane components reverses the disordering caused by the dissolved inhalational agent.

2. The cutoff phenomenon may be related not to the inability of high-molecular-weight agents to dissolve in the lipid membranes in a concentration that would cause anesthesia, but from their failure to disrupt or disorder the architecture of the lipid bilayer.

Protein Hypothesis

Although the affinity of inhalational anesthetic agents for lipids is commonly used as evidence that their site of action must be in lipids, the term “lipid solubility” actually refers to their solubility in nonpolar or hydrophobic media. Many proteins have nonpolar regions that could serve as sites for the dissolving of inhalational agents. However, these regions are usually centrally located within the protein and, therefore, are effectively shielded from the action of all but pharmacological concentrations of inhalational agents. Such unlikely, nonspecific interactions of proteins and inhalational agents are to be distinguished from interactions of great specificity (eg, those that occur between receptor and agonist). There is no question that inhalational anesthetic agents are capable of specific interactions with proteins (Figure 9-2d):

- Nicotinic acetylcholine receptors are inhibited by halothane, isoflurane, and methoxyflurane at minimal alveolar concentrations (MAC, which is discussed later in this chapter), the end-alveolar concentration of an inhalational anesthetic agent that prevents somatic response to a painful stimulus in 50% of individuals.
- γ-Aminobutyric acid (GABA) receptors are activated by halothane and isoflurane at MAC concentrations.
- The calcium-release channel of the sarcoplasmic reticulum in skeletal muscle is activated by halothane.
- Chemoluminescence liberated by the action of the firefly enzyme D-luciferase is inhibited by inhalational agents.

The question is not so much whether inhalational agents can affect proteins—they can—but whether these effects are necessary for the induction of general anesthesia. Much needs to be known before this question can be answered. For example, is either (a) the inhibition of the nicotinic acetylcholine receptor or (b) the activation of the GABA receptor a necessary concomitant for anesthesia? In genetically predetermined individuals, intracellular calcium release by halothane is a profoundly important clinical problem but in normal people is trivial. The inhibition of chemoluminescence by inhalational agents is well described, but there is no evidence that a mammalian equivalent exists. It is perhaps best to defer judgment as to the importance of the protein hypothesis until more data have been collected and reviewed.

Lipid–Protein Interaction Hypothesis

The evidence supporting the protein hypothesis was derived from lipid-free systems. Since biomembranes are aggregates of lipoproteins, it is appropriate to ask whether inhalational agents produce anesthesia by affecting lipoproteins or those lipids in direct contact with proteins of the ionic channel (Figure 9-2e). The lipids that are in direct association with the transmembrane-receptor proteins are known as the boundary lipids.
Current research is centered on trying to establish whether inhalational anesthetic-induced perturbation of boundary lipids can be coupled selectively to ionic channels, causing protein conformational changes. Knowledge of the mechanism of action of inhalational anesthetics has practical importance, because it furthers the process of designing new agents. Nevertheless, it is apparent that a given agent may have a multitude of effects, some of which may be unrelated to the induction of a state of general anesthesia. Even the induction of general anesthesia can be mediated by several mechanisms. For example, inhalational anesthetics fall into two broad classes: alkanes and ethers. Cyclopropane and halothane are alkanes; diethyl ether, enflurane, isoflurane, desflurane, and sevoflurane are ethers. The alkanes are purely lipophilic and therefore dissolve primarily in the lipid portion of the cell membrane, where they exert a nonspecific effect. The halogenated ethers, being more polar, both dissolve in the lipid membrane and form hydrogen bonds with protein moieties of ionic channels. Thus, the ether anesthetics are capable of both specific and nonspecific interactions. It is likely that the stereospecificity of the optical isomers of isoflurane arises from the ability of only one isomer to form hydrogen bonds with receptor proteins.

**SITE OF ACTION**

A large body of work has been directed toward locating the major areas of interaction within the central nervous system (CNS) that are influenced by the anesthetic agents. It is now obvious that anesthetics do not exert their action through one specific effect in any one particular region of the CNS. Based on this information, more recent work has been directed at the cellular rather than the regional level of the CNS. One early and consistent observation has been that general anesthetic agents block neural transmission at the synapse at much lower concentrations than the concentrations required to block conductance within the axon. Based on this information, the synapse has been the focus of most recent studies. Because synapses are either excitatory or inhibitory in nature, general anesthetic agents should have a depressant effect on excitatory postsynaptic potentials (EPSPs), an augmentation of inhibitory postsynaptic potentials (IPSPs), or both. It should be appreciated, however, that synaptic transmission can be subdivided into four areas for further study:

1. axonal conductance along the afferent axon,
2. neurotransmitter release into the synaptic cleft,
3. binding of the neurotransmitter by specific receptors in the postjunctional area, and
4. changes in conductance, leading to propagation of the action potential.

When both the CNS and the peripheral nervous system have been studied, the general anesthetic agents do have a depressant effect on EPSPs, although the magnitude of effect on EPSPs is diverse within the area of the hippocampus. These findings suggest that either (a) EPSPs do not play a major role in the action of anesthetic agents or (b) the hippocampus is not relevant to general anesthetic action.

The principal inhibitory neurotransmitter within the CNS is GABA. The data regarding general anesthetic action on IPSPs are conflicting, especially information suggesting that halothane and isoflurane cause a reduction in IPSPs. This phenomenon has been explained as an indirect action due to a depression of excitatory synapses acting on GABA-ergic inhibitory cells. More work is necessary to elucidate the role of inhibitory monosynapses in the absence of excitatory synapse transmission.

To summarize, the synapse is probably the cellular site of action of the general anesthetic agents, based on the low concentrations needed to affect transmission. What is not understood is exactly how these agents work at this level, as there is not an anesthetic effect that is common to all synapses or, indeed, to all anesthetic agents that have been studied. Based on all available information, two main theories have been promulgated to explain anesthetic action at the synaptic level. The unitary theory holds that all general anesthetic agents work by a common mechanism. A more robust, conflicting theory called the degenerate theory holds that different general anesthetic agents have different mechanisms of actions at possibly different sites of action. Two strategies attempt to elucidate information surrounding the degenerate theory: the pharmacological approach studies relative potencies of anesthetic agents in animals, while the mechanistic approach looks at well-defined molecular models in an attempt to discover a yet-unknown site of action in the CNS.
**OVERVIEW: MODERN INHALATIONAL ANESTHETIC AGENTS**

During the 1920s, the frustrations encountered in clinical practice (e.g., difficulties with the older inhalational agents in delivery, side effects, and flammability) coupled with an understanding of the expanding scientific basis for anesthesia and surgery mandated that newer anesthetic agents be developed to replace ether and chloroform. A variety of carbon-chain–based agents were studied and marketed, and cyclopropane became the most important new inhaled anesthetic introduced in the 1930s. Prior to the 1950s, all inhalational anesthetic agents possessed one or both of these two defects: they were explosive, and they were toxic to biological tissues. Fortuitously, research in other fields made possible the development and production of fluorinated carbon-based anesthetic agents, which are both biologically safe and nonexplosive.

A vast increase in our knowledge of the chemistry of elemental fluorine occurred during World War II as a byproduct of the Manhattan Project. A crucial step in the fabrication of the first atomic bombs was the separation of the naturally fissionable isotope of uranium, $^{235}$U, from the much more common $^{238}$U. The separation depended on the availability of uranium hexafluoride, and the ability to synthesize and manipulate this unusual substance safely led to a better understanding of fluorine chemistry. The mass manufacturing of fluorinated carbon-based compounds could then follow. The addition of a fluorine molecule to carbon was associated with decreased flammability. The fluorine–carbon bond was more stable than the carbon–carbon bond, tended to undergo less biological metabolism, and was therefore associated with less organ toxicity. The fluorinated anesthetic compound first marketed was fluroxene, which was introduced in 1954 and used until 1975. Although fluroxene had the desirable qualities of low solubility in blood and minimal tendency to depress cardiovascular function, it was associated with nausea and vomiting and was flammable at higher concentrations. After a large experience with fluroxene had been collected, this compound was found to be rarely associated with hepatotoxicity and possible carcinogenesis. Fluroxene was an important bridging compound in inhalational anesthetic practice until the development and clinical introduction of safer and more desirable agents.

Fluorinated compounds are today’s anesthetic agents of choice (Table 9-1). The ones most commonly used are halothane, enflurane, isoflurane, and desflurane; sevoflurane was added to the armamentarium in 1995. Nitrous oxide is neither fluorinated nor available in DEPMEDS-equipped hospitals but is included for the sake of completeness.

**Halothane**

![Halothane](image)

Halothane (1,1,1-trifluoro-2-bromo-2-chloroethane) is an aliphatic hydrocarbon of the alkane series (specifically, a halogenated ethane) that was introduced into the clinical practice of anesthesia in 1956. This important compound was a tremendous improvement over the earlier alkanes and ethers and still has a role in civilian and military anesthesia. The agent is somewhat unstable in the presence of physical factors associated with the delivery of anesthesia, and due to its spontaneous oxidation and affinity for breakdown by ultraviolet light must be stabilized with 0.01% thymol and stored in dark brown bottles. In current practice, halothane’s main drawbacks are its propensity to sensitize the myocardium to the effects of epinephrine and its association with a metabolic-related hepatotoxicity.

Halothane is well known to conventionally trained anesthesiologists and continues to be a very useful inhalational anesthetic agent—although its use in the United States is much less than that of the inhalational ethers. Halothane enjoys a greater potency and has less airway irritability than the newer halogenated ether agents and, therefore, is better tolerated when a straight inhalational induction technique is employed. Owing to its association with a metabolic-related hepatotoxicity, halothane has been used as an induction agent in adults and then discontinued and replaced by one of the halogenated ether agents. A main disadvantage of halothane is its effect on the myocardium—from both a dose-related myocardial depression, which causes hypotension, and the enhanced sensitizing effect it has with circulating and administered catecholamines. Cerebral blood flow (CBF) increases with halothane (due to its
### TABLE 9-1
GENERAL PROPERTIES OF INHALATIONAL ANESTHETICS

<table>
<thead>
<tr>
<th>Property</th>
<th>N₂O</th>
<th>ISO</th>
<th>ENF</th>
<th>HAL</th>
<th>DES</th>
<th>SEV</th>
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<tr>
<td>Molecular weight</td>
<td>44</td>
<td>184.5</td>
<td>184.5</td>
<td>197.4</td>
<td>168</td>
<td>218</td>
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<tr>
<td>Boiling point (°C)</td>
<td>−88.5</td>
<td>48.5</td>
<td>56.5</td>
<td>50.2</td>
<td>23.5</td>
<td>58.5</td>
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<td>Specific gravity (25°C)</td>
<td>1.53</td>
<td>1.5</td>
<td>1.52</td>
<td>1.86</td>
<td>1.45</td>
<td>1.50</td>
</tr>
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<td>Vapor pressure (20°C) (mm Hg)</td>
<td>38,770</td>
<td>238</td>
<td>172</td>
<td>243</td>
<td>664</td>
<td>160</td>
</tr>
<tr>
<td>MAC (in O₂) (%)</td>
<td>105</td>
<td>1.28</td>
<td>1.58</td>
<td>0.75</td>
<td>4.6–6</td>
<td>1.71</td>
</tr>
<tr>
<td>MAC (in 70% N₂O) (%)</td>
<td>—</td>
<td>0.56</td>
<td>0.57</td>
<td>0.29</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>AD₉₅</td>
<td>—</td>
<td>1.68</td>
<td>1.88</td>
<td>0.90</td>
<td>2.07</td>
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<td>MAC-aware (multiple)</td>
<td>0.6–0.8</td>
<td>0.52</td>
<td>0.53</td>
<td></td>
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<td></td>
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<tr>
<td>MAC as partial pressure (mm Hg)</td>
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<td>12.0</td>
<td>5.7</td>
<td>34.9–45.6</td>
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<td>Partition coefficients (37°C)</td>
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<td>Blood–gas</td>
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<td>1.4</td>
<td>1.8</td>
<td>2.3</td>
<td>0.42</td>
<td>0.59</td>
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<td>Brain–blood</td>
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<td>2.6</td>
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<td>2.9</td>
<td>1.3</td>
<td>1.7</td>
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<td>Muscle–blood</td>
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<td>45</td>
<td>36</td>
<td>60</td>
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<td>Rubber–gas</td>
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<td>62</td>
<td>74</td>
<td>120</td>
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<td>30</td>
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<tr>
<td>Flammability (in 70% N₂O/30%O₂) (%)</td>
<td>7</td>
<td>5.8</td>
<td>4.8</td>
<td>17</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Stability</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkali</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Some instability</td>
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<td>Very unstable</td>
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<td>Corroses</td>
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<td>Stable</td>
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<td>Preservative</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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<td>None</td>
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<tr>
<td>Recovered as metabolites (%)</td>
<td>0.0</td>
<td>0.2</td>
<td>2.4</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N₂O: Nitrous oxide; ISO: Isoflurane; ENF: Enflurane; HAL: Halothane; DES: Desflurane; SEV: Sevoflurane; MAC: minimal alveolar concentration; AD₉₅: anesthetic depth (the dose that prevents movement in 95% of subjects in response to standard surgical incision)

*Specific gravity for N₂O is for the gas relative to air, but for the other anesthetics is for the liquid relative to water

vasodilating properties), and the potential exists for an increase in intracranial pressure (ICP) that may only be partially responsive to the elimination of carbon dioxide via hyperventilation. Halothane also causes an important decrease in splanchnic circulation and decreased total hepatic circulation, with portal venous and hepatic arterial blood-flow decrements that may place the patient at risk for hepatic ischemia and hepatocellular tissue hypoxia. The major route of elimination is via the pulmonary bed, but up to 20% of halothane may be biotransformed in the liver. A combination of decreased hepatic blood flow, major hepatic biotransformation, and a possible immunologically mediated tissue injury may contribute to the hepatotoxicity seen in a small number (1:10,000) of adult patients exposed to halothane. This incidence is even lower in children. All the potent volatile agents are associated with a dose-related, muscle-relaxation effect.
Enflurane and Isoflurane

The ethers enflurane (1,1,2-trifluoro-2-chloroethyl difluoromethyl ether) and isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) are isomers. They share the same chemical formulae and molecular weight but differ in their physical and pharmacological properties owing to the position of the carbon atom to which hydrogen and chlorine are attached. These methyl-ethyl ethers are synthesized when bromine is removed from the halothane molecule and an ether link, with a difluoromethyl group attached, is created. The substitution of fluorine for chlorine and bromine increases molecular stability while reducing potency and solubility. The alkanes (e.g., halothane) appear to be associated with cardiac toxicity, due to their ability to sensitize the myocardium to catecholamines. The interposition of oxygen in an ether linkage within an anesthetic molecule reduces this myocardial irritability.

Enflurane

Enflurane was the first of the modern halogenated ether inhalational agents to be released for clinical use (in 1972). Its principal advantage over halothane is its reduced association with hepatotoxicity and catecholamine-induced myocardial irritability. Enflurane is approximately one half as potent as halothane but can still provide prompt induction of anesthesia. Like halothane, enflurane causes a dose-related decrease in blood pressure that makes this drug difficult to titrate between adequate depth of anesthesia and unacceptably hypotension. The dose-related hypotension is due to a combination of myocardial depression and peripheral vasodilation with decreased systemic vascular resistance (SVR). As does halothane, enflurane causes increased CBF and the potential exists for increased ICP and cerebral hypoxia. Although total hepatic blood flow is decreased during enflurane anesthesia, the relation between hepatic arterial and portal blood flow remains preserved. Enflurane produces a dose-dependent respiratory depression, hypercarbia, and an increased alveolar–arterial gradient that is greater than that seen with halothane. Enflurane has been associated with tonic-clonic muscle activity and confirmed electroencephalographic (EEG) evidence of seizure activity at higher doses, especially in the setting of hypocarbia, although at lower doses it does not appear to predispose patients with epilepsy to further seizure activity. The major route of elimination is via the lungs, with 2% to 3% being biotransformed in the liver. Major metabolic by-products of concern include fluoride ions and difluoromethoxydifluoroacetic acid. Because nephrotoxicity has been associated with the fluoride ion by-product during very prolonged use, many anesthesiologists prefer to avoid enflurane in patients with renal compromise. The level of fluoride ion that is required to produce nephrotoxicity (40–50 µmol/L) is rarely exceeded except during dramatically prolonged enflurane anesthesia.

Isoflurane

Isoflurane, released for clinical use in 1981, is probably the most popular potent volatile anesthetic agent currently administered in the United States. Its major advantages include its ease of administration, lack of serious hepatotoxicity, and minimal biotransformation with fluoride ion production. As with all of the volatile vapors, it is a potent respiratory depressant and, although isoflurane can be used to induce anesthesia, some patients have complained of respiratory discomfort on inhalational induction. Isoflurane preserves cardiac output throughout all levels of anesthesia better than either halothane or enflurane (Figure 9-3).

Isoflurane is associated with a dose-dependent hypotension without myocardial depression that is solely mediated by a decrease in SVR. This vasodilating effect can actually be exploited when a relatively hypotensive anesthetic technique is desirable. Tachycardia is a commonly seen event with isoflurane and appears more frequently with younger patients. There does not appear to be any appreciable myocardial irritability with circulating catecholamines during the use of isoflurane,
and although the phenomenon of coronary steal is theoretically possible, it is infrequently observed. Again, as with halothane, CBF increases. Although isoflurane may cause an increase in ICP, this effect can be totally abolished with hypocarbia.\textsuperscript{36} Previously, isoflurane had been thought to have less effect on cerebral circulation than halothane, but the effect may, in fact, be the same.\textsuperscript{30,37} Evidence from studies with animals indicates that isoflurane offers better cerebral protection from ischemia or hypoxia when compared with the other volatile agents, and anesthesiologists who provide care for neurosurgical procedures may therefore consider isoflurane to be the potent volatile agent of choice.\textsuperscript{28} There is a reduction of total hepatic blood flow seen with isoflurane; however, total flow, hepatic oxygen transport, hepatic oxygenation, and arterial compensation for reduced portal flow are all better maintained with isoflurane than with either halothane or enflurane.\textsuperscript{30,39,40} Hepatic injury has not been associated with isoflurane, and this may be related to the protective mechanisms mentioned above. Renal blood flow is decreased under isoflurane administration, but this appears to be a function of decreased total perfusion rather than changes in regional vascular resistance.\textsuperscript{31} Isoflurane is excreted via the lungs, and only 0.2% of the agent undergoes biotransformation. The biotransformation of isoflurane is only 1% of that of halothane and 10% of that of enflurane, with the fluoride and trifluoroacetic acid metabolites being insufficient to be associated with significant cellular injury or toxicity.\textsuperscript{42} The major complications associated with isoflurane are related to the spectrum of its pharmacological activity (eg, hypotension, tachycardia, hypercarbia) rather than to any specific organ toxicity per se. Indeed, the major advantage of isoflurane is its rather remarkable lack of significant complications or evidence of associated hepatic toxicity. Isoflurane is a major inhalational agent available to the military anesthesiologist in the field.

**Desflurane**

Desflurane (1-fluoro-2,2,2-trifluoroethyl difluoro-methyl ether) is a fluorinated methyl-ethyl ether in which the chlorine has been totally removed from the molecule. The lower solubility and chemical stability afforded by this fluorine substitution is at the cost of lower potency and a very high vapor pressure: 664 mm Hg at 20°C. A special vaporizer is required to deliver this agent. Although desflurane may prove to be a valuable agent in the civilian setting because it allows for rapid emergence from anesthesia, the need for a special vaporizer makes it highly unlikely that this agent will be used in the military field setting.
Introduced into clinical practice in 1992, desflurane has the lowest solubility in blood of any of the inhalational agents. Owing to its physical property of a low blood–gas partition coefficient (0.42), its main clinical advantage appears to be a rapid emergence from anesthesia. Its main disadvantages are airway irritation, which limits its use as an induction agent, and its physical property of a high vapor pressure (desflurane boils at room temperature), which requires a specially constructed vaporizer to allow for its delivery in ordinary operating room settings. The circulatory and cerebral effects of desflurane are identical to those seen with isoflurane.\(^43,44\) The route of excretion is via the lungs, and the biotransformation of desflurane is trivial. Trifluoroacetic acid production is slight (0.17 \(\mu\)mol/L), and is 10% of that seen with isoflurane.\(^27\) The desflurane molecule is extremely stable.

**Sevoflurane**

Sevoflurane (1,1,1,3,3,3-hexafluoro-2-propyl fluoroethyl ether) is another highly fluorine-substituted structural modification of the ether link. In this situation, the oxygen is located between an ethyl and a propyl group, which allows for low solubility. The addition of the propyl side chain increases the agent’s potency.

Sevoflurane is the newest halogenated ether anesthetic agent and was released for clinical use in the United States in 1995. Due to its low blood–gas partition coefficient (0.59), sevoflurane has the advantage of rapid induction and emergence from anesthesia. The cardiovascular effects of sevoflurane appear to be similar to those of isoflurane.\(^45,46\) The respiratory depression seen with sevoflurane is significant but less than that seen with halothane. Changes in tidal volume and respiratory excursion are greater with sevoflurane than with isoflurane, and this suggests a neural control response to sevoflurane different from that seen with isoflurane.\(^47\) The route of excretion is via the lungs but the biotransformation of sevoflurane is very significant: up to 10% of patients undergoing sevoflurane anesthesia have plasma fluoride levels that exceed 50 \(\mu\)mol/L, which is considered to be the threshold for renal toxicity.\(^48\) Thus, a major disadvantage of sevoflurane is that it may be limited to use for short procedures to avoid potential renal damage, although prolonged sevoflurane anesthesia (9.5 MAC-hours) has been reported not to impair renal concentrating function on days 1 and 5 after anesthesia.\(^49\) Finally, sevoflurane is very unstable in alkali and may not be suitable in situations where low fresh-gas-flow states are needed, such as the military setting, where gas supplies must be conserved and strict economy of available resources preserved.

**Nitrous Oxide**

In passing, it should be noted that the old standby inhalational agent of the past—nitrous oxide—is not fielded with DEPMEDS equipment and will only be available in fixed military medical treatment facilities. Although nitrous oxide can successfully be coadministered with other inhalational anesthetic agents, it must be stored in bulky gas cylinders, it supports combustion almost as well as oxygen, and it is subject to contamination from other oxides of nitrogen that may be toxic, owing to the production of free radicals. Because of weight and storage constraints, and especially because it expands in closed spaces, nitrous oxide will probably not be available to military anesthesia providers in the field. Although nitrous oxide can be used by itself as an analgesic agent for minor surgical procedures, it is rarely used as a sole agent in modern anesthetic practice: its lack of potency and its MAC of 105% make it impossible to use as a total anesthetic agent. Nitrous oxide is employed mainly to minimize the total dose of other potent volatile anesthetic agents by taking advantage of the additive property of MAC. Owing to its physical properties, nitrous oxide exhibits both the second-gas and the concentration effects, which are discussed later in this chapter. Nitrous oxide demonstrates a mild increase in sympathetic nervous system activity that may be matched by a mild myocardial depressant effect. By itself, nitrous oxide exerts little effect on carbon dioxide response but
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is associated with respiratory depression when combined with other potent agents.\(^{50}\) Elimination of nitrous oxide is via the pulmonary system, with minimal biotransformation. The main complications associated with the use of nitrous oxide center on its association with the diffusion anoxia experienced on anesthetic emergence; its ability to expand in closed, gas-containing spaces; and a dose-related bone marrow depression caused by the inhibition of methionine synthetase, which is a cofactor in amino acid and vitamin metabolism.

UPTAKE AND DISTRIBUTION

Biophysical Properties

The amount of inhalational anesthetic agent that is delivered to a patient can be expressed as a percentage of the total gas volume delivered (vol %) or as a partial pressure of the total gas pressure (mm Hg). The convention in the United States is to use the expression “volume percent delivered,” but an understanding of partial atmospheric pressure is essential to appreciate how anesthetic agents reach equilibrium. For example, a 2% concentration of isoflurane delivered at sea level at standard temperature with a standard barometric pressure (P\(_{\text{bar}}\)) of 760 mm Hg (ie, 1 atm) would contain a partial pressure of 15.2 mm Hg (0.02 \times 760 = 15.2) isoflurane. However, if 2% isoflurane were to be delivered at an elevation of 6,000 ft above sea level (a slightly higher elevation than that seen in Denver, Colo.), where the P\(_{\text{bar}}\) is 609 mm Hg, the calculated delivered partial pressure would be 12.2 mm Hg. To further complicate the issue, if a modern temperature-compensated variable-bypass vaporizer were used, the vaporizer constants would be (a) the gas dilution ratio of the vaporizer (21:1 diluent gas to gas flow at 2% flow) and (b) the saturated vapor pressure of isoflurane (238 mm Hg), both of which are independent of P\(_{\text{bar}}\). The actual delivery of isoflurane set at 2% on the dial at an altitude just higher than that of Denver, Colorado, would be 17.1 mm Hg (or 2.8% isoflurane) instead of the calculated 15.2 mm Hg. Therefore, it may be more prudent to consider anesthetic delivery in terms of partial pressure rather than volume percent (Figure 9-4).\(^{27}\)

Although the inhalational anesthetic agents are delivered via the pulmonary alveolar bed, and the desired inhaled and exhaled anesthetic concentrations are measured as alveolar gas concentrations, the primary intent is to deliver these agents to the brain. The main determinant of anesthetic delivery to target tissues is the biophysical property of solubility, which is also related to anesthetic potency. As the brain is an organ that is extraordinarily well perfused, the partial pressure of anesthetic agent in the blood and that of the brain approach equilibrium very quickly. The exchange of anesthetic gases across the alveolar membrane is quite efficient, and the partial pressure of agent in the pulmonary circulation is very close to that found in the alveolar gas; therefore, the brain partial pressure closely follows alveolar partial pressure. The reason that patients do not fall asleep immediately on exposure to an anesthetic gas, or wake up immediately
Anesthesia and Perioperative Care of the Combat Casualty

Anesthesia and Perioperative Care of the Combat Casualty

An anesthetic agent, on discontinuation, is mainly due to the solubility of the anesthetic agent in the blood. It may be helpful to understand that the uptake of anesthetic agent occurs in three stages of delivery:

1. Vaporization and delivery into the airways
2. Transfer across the alveolar membrane with uptake into the blood, and
3. Transfer from the blood across a tissue membrane, with uptake into target tissue.

There may be factors that influence any of these stages of anesthetic delivery.

The solubility of an anesthetic agent can be expressed as a partition coefficient, which is essentially the ratio of the solubilities for two media. Partition coefficients are independent of partial pressure and are critical in describing uptake and distribution properties of each agent. An example would be the brain–blood partition coefficient, which quantitates the ratio of solubility for blood compared with that of the brain. The solubility of anesthetic agents in the blood and tissues determines how much drug uptake is required across the alveolar membrane to increase anesthetic partial pressure in the brain, the ultimate target organ for anesthetic agents. Drug uptake ultimately influences the time of induction or emergence from anesthesia. A low blood–gas partition coefficient is desirable for a potent anesthetic agent.

Three points need to be appreciated regarding the practical use of inhalational agents. First, to reach equilibrium, the direction that gas molecules move will always be from the higher partial-pressure phase to the lower. Second, when partial pressures are expressed for media in both gaseous and nongaseous phases, the ultimate reference is to the gaseous phase. Third, the actual amount of vapor contained in a nongaseous phase (eg, within tissues) depends on the partial pressure and its solubility in that particular tissue. This is important, as different body tissues such as brain, muscle, and fat have different partition coefficients, which are expressed as the brain–blood, muscle–blood, and fat–blood coefficients. Prior to achieving equilibrium, an inhalational agent moves from alveolar gas to blood, then to brain, to muscle, and finally to fat. Well-perfused tissues such as the brain are called the vessel-rich group, whereas poorly perfused tissues such as fat are called the vessel-poor group. The brain may reach an anesthetic partial pressure concentration that is adequate for anesthesia, while the partial pressure lags behind in the vessel-poor tissues. On termination of inhalational anesthetic agents, the order is reversed, but ultimate excretion of anesthetic gas is limited to these pressure gradients (Figure 9-5).

The blood–gas coefficient of nitrous oxide at 37°C is 0.47 and is one of the lowest of the available inhalational agents. However, this coefficient is still approximately 31-fold greater than the blood–gas coefficient for gaseous nitrogen. When nitrous

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![Fig. 9-5. A representation of the distribution of partial pressures (mm Hg) and concentration (vol %) of 2% enflurane into body tissues 10 minutes after induction of anesthesia. At this time, alveolar partial pressure is approximately half of inspired pressure. The anesthetic flow is in the direction of decreasing partial pressure, and is quantitatively represented by the magnitude and direction of the arrows. Note that the vessel-rich groups are close to equilibrium with blood and that the muscle and fat groups are not. The concentration of enflurane depends on partition coefficients, and anesthetic uptake continues into vessel-rich and fat groups. If the anesthetic were terminated at this point, the fat group would continue to take up anesthetic while the vessel-rich groups would begin to release agent back into the blood for ultimate elimination through the lungs. Reprinted with permission from Longnecker DE, Miller FL. Pharmacology of inhalational anesthetics. In: Rogers MC, Tinker JH, Covino BG, Longnecker DE. Principles and Practice of Anesthesiology. St. Louis, Mo: Mosby–Year Book; 1993: 1059.](image-url)
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Nitrous oxide is administered, it will exchange for nitrogen and occupy a volume 30-fold greater than that occupied by nitrogen. At equilibrium using an inhalational gas mixture that contains 70% nitrous oxide, any gas-filled cavity—whether caused by a pathological or a therapeutic process—will expand in size up to 4-fold. Therefore, the use of nitrous oxide is contraindicated in those situations (eg, bowel obstruction, thoracic injury). Although the same exchange phenomenon occurs with the potent inhalational agents, their partial pressures are small (eg, 2% isoflurane vs 70% nitrous oxide) and they occupy less volume in gas-filled spaces.

Factors Affecting Uptake and Distribution

When an anesthetic mixture is selected for administration, three variables must be taken into account for the intended alveolar partial pressure of the desired agent to be achieved. First, the gas circuit itself must be washed out with the fresh gas mixture to achieve a circuit concentration equal to that selected on the vaporizer. This can be accomplished by elapsed time, high gas flows, and the overpressure effect (ie, selecting an initial higher inspired concentration than is ultimately intended). Second, the inhalational agent will move into rubber and plastic parts of the anesthesia circuit (as predicted by the rubber–gas partition coefficient) and the soda lime absorbent will also absorb agent to some degree. The third and most important factor is the concept of alveolar gas uptake (FAx) in relation to the inspired fractional concentration (F1x) and the ultimate uptake by the blood (x). This has been expressed as FAx/F1x (Figure 9-6). The major factors that can delay anesthetic uptake to the brain include

- highly soluble anesthetic agents,
- a state of increased cardiac output, and
- a large gradient between the partial pressures of alveolar and mixed-venous blood.

Increasing the speed of delivery of the inhaled agents to the brain can be simply accomplished by increasing the inspired partial pressure of the anesthetic or by increasing alveolar ventilation. Figure 9-7 demonstrates how partition coefficients for various tissue groups affect drug delivery to these sites.

Two other phenomena that can affect anesthetic uptake are known as the concentration effect and the second-gas effect. When high concentrations (ie, overpressures) of gas are delivered, large volumes of gas are removed by alveolar uptake and a large gradient is established. Returning expired gases are enriched and concentrated by the high inspired concentration, therefore maintaining a high inspired fraction. The second-gas effect is stated,
Minimal Alveolar Concentration

The understanding of the potency of the inhaled anesthetic agents during their clinical administration was made conceptually simpler by the introduction of the term MAC in 1965. MAC was defined as the minimal alveolar concentration (in volume percent of atmosphere) of an anesthetic that prevented movement in 50% of subjects in response to a noxious stimulus. Although it was originally defined in terms of volume percent, the relevant unit for MAC is actually partial pressure. This unit is most important when anesthetics are administered under hyperbaric or hypobaric conditions and has been introduced earlier in this chapter. The MAC for each agent is not static and may vary with the age of the patient, extremes of physiology, the environment (e.g., temperature), and the effects of drugs or alcohol. The addition of drugs such as narcotics or sedatives lowers inhalational MAC requirements to prevent patients from responding to the noxious stimulus of a surgical incision. Conceptually, MAC parallels the median effective dose (ED₅₀) that has been described for other pharmacological agents. Since most clinicians would prefer that fewer than 50% of patients respond to a surgical stimulus, the term anesthetic depth (AD₉₅) is used to describe the MAC of an anesthetic agent at which 95% of patients do not respond. A total dose of approximately 1.3 MAC prevents movement in nearly all patients during surgery. The MAC and AD₉₅ for each of the inhalational agents are found in Table 9-1. In addition, other values such as MACawake (the concentration at which awareness returns) have been described. A very useful and important concept of MAC is that MACs are additive and may also be proportionally substituted. In other words, inhalational agents may be added to one another, and their combined MACs are equal to that of a single agent. This concept is commonly used clinically when 70% nitrous oxide (0.66 MAC) is combined with another potent inhalational agent such as 0.74% isoflurane (0.64 MAC) in oxygen to administer a total dose of 1.3 MAC (0.66 MAC + 0.64 MAC = 1.3 MAC).
Although there is no one perfect anesthetic agent, an ideal one would have the characteristics listed in Exhibit 9-1. Until the perfect anesthetic agent can be produced, the potent inhalational agents—halothane, enflurane, isoflurane, desflurane, and sevoflurane—provide the major components needed in a single, complete anesthetic agent: analgesia, amnesia, hypnosis, and relaxation of skeletal muscles. Unfortunately, all the potent inhaled agents alter normal organ-system physiology. For the sake of simplicity, only the effects of the first three potent agents on major organ systems will be discussed, and those briefly.

The Respiratory System and the Carbon Dioxide–Response Curve

Control of respiration is mediated by the medulla and the pons. Inspiration and expiration are modulated within the medulla at the dorsal respiratory group and the ventral respiratory group, respectively. In the pons, the pneumotaxic center regulates the rate and pattern of respiration and the apneustic center theoretically has a feedback loop to the dorsal respiratory group to affect maximal inspiration. The physiological goal is to maintain oxygen, carbon dioxide, and hydrogen ion concentration (clinically represented as blood pH) in normal ranges, and the feedback for these parameters is accomplished by chemoreceptors within the medulla that are in close relationship with the cerebral spinal fluid. The inspiratory centers are sensitive to changes in pH and concentrations of carbon dioxide. If the alveolar ventilatory response is plotted against carbon dioxide concentration and pH, a response curve can then be constructed (Figure 9-8). A decrease in the PO2 will increase the slope of the curve, while a state of acidosis will shift the curve to the left without a change in slope.

The administration of halothane, enflurane, or isoflurane will cause a dose-dependent decrease in the ventilatory response to carbon dioxide, with enflurane tending to be the most potent in this regard. This is graphically expressed by a decreased slope of the carbon dioxide–response curve without a shift to either the left or the right. Clinically, in the patient who is spontaneously breathing a potent inhalational agent at a surgical plane, the PaCO2 should be in the range of 50 to 55 mm Hg. A reaction to surgical stimulation may lower this response by 4 to 5 mm Hg. The addition of a narcotic to a potent inhalational anesthetic technique will further depress and shift to the right the slope of the carbon dioxide–response curve.

The Central Nervous System

The clinical endpoint of the potent inhalational anesthetic agents is a dose-related, reversible depression or excitation of brain function that results in the anesthetized state. This change in CNS function is associated with alterations in cerebral metabolic rate for oxygen (CMRO2), CBF, EEG changes, and somatosensory (SSEP) and motor evoked potentials (MEP). In the normal brain, CBF and CMRO2 enjoy a proportionally coupled relation that does not usually change independently. Under inhalational anesthesia with the potent volatile agents, there appears to be an uncoupling of the normal CBF:CMRO2 ratio with increasing anesthetic doses. It is important to realize that this effect is seen only when cerebral vascular autoregulation is intact and normal intracranial blood pressure ranges (50–150 mm Hg) are maintained. An increase in cerebral vasodilation with increased CBF results in a decrease in CMRO2. This effect is diminished or abolished with decreasing blood pressure. The effect is

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**EXHIBIT 9-1**

**CHARACTERISTICS OF AN IDEAL INHALATIONAL ANESTHETIC AGENT**

- Absence of flammability
- Easily vaporized at ambient temperature
- Low blood solubility (rapid induction and recovery from anesthesia)
- Minimal metabolism
- Compatible with epinephrine
- Produces skeletal muscle relaxation
- Suppresses excessive sympathetic nervous system response
- Not irritating to airways
- Absent or minimal myocardial depression
- Absence of cerebrovascular dilation
- Absence of hepatic and renal toxicity
also blunted by an increase in the amount of hypocapnia produced. Therefore, the cerebral vasodilation caused by the volatile anesthetic agents can be attenuated by hypocapnia, although these responses may not be operative in the injured brain. Of the three inhalational agents under discussion, halothane is the most potent cerebral vasodilator, followed by enflurane and isoflurane. The main problem associated with increased CBF is that the cerebral volume is increased, with a resultant increase in ICP. Critical CBF (cCBF) has been defined as the flow at which ipsilateral EEG changes indicative of cerebral ischemia are seen. In the presence of halothane, the cCBF is 18 to 20 mL/100 g/min; for enflurane, it is 15 mL/100 g/min; and for isoflurane, 10 mL/100 g/min.

At clinically useful concentrations, halothane cannot cause an isoelectric EEG. While decreasing CMRO$_2$ may be beneficial, especially in the setting of an isoelectric EEG, halothane has been associated with dangerously low levels of CMRO$_2$ that may reflect cerebral toxicity. Enflurane has been associated with seizure activity at 1.5 to 2 MAC concentrations, with a resultant 50% increase in CMRO$_2$. On the other hand, isoflurane can cause an isoelectric EEG that is associated with a 50% reduction in CMRO$_2$. The effective recording of SSEPs is not abolished by concentrations of 0.5 to 0.75 MAC with any of the volatile agents. Data concerning the recording of MEPs during inhalational anesthesia are sparse, although MEPs appear to be hindered at clinical doses. Recent work concerning the successful recording of spinal evoked potentials (SpEP) in animals during 1.3 to 2.0 MAC halothane has entered the literature.

### The Cardiovascular System

All of the potent, volatile anesthetic agents depress the cardiovascular system, but their hemodynamic effects differ. The clinical endpoint of cardiovascular depression is hypotension. Halothane’s effect is due mainly to a decrease in myocardial contractility and rate, with minimal decrement in SVR. Enflurane causes both myocardial depression and decreased SVR, while isoflurane’s effect is due mainly to its action on SVR. The newer agents can be expected to have an effect on the cardiovascular system similar to that of isoflurane. This depressive effect is dose related, and for any potent volatile anesthetic, the arterial blood pressure can be decreased by approximately 50% of baseline by the administration of 2 MAC of agent. Although halothane is associated with negative chronotropic effects, both enflurane and isoflurane may cause an increase in heart rate. This chronotropic effect may be related to halothane’s impairing the baroreceptor function to a greater degree than enflurane or isoflurane, but studies with animals indicate that while isoflurane may depress both vagal and sympathetic function, vagal depression predominates, leading to a noticeably increased heart rate. This positive chronotropic effect with isoflurane is seen especially in younger patients but tapers off after age 40. Cardiac output is decreased—due mainly to a decreased stroke volume—by halothane and enflurane (minimally by isoflurane). All of the aliphatic hydrocarbon anesthetic agents sensitize the myocardium to circulating catecholamines; this effect is greatest for halothane and least for isoflurane. Because of

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**Fig. 9-8.** The effects of increased arterial P$_{CO_2}$ and decreased arterial pH on the rate of alveolar ventilation. Reprinted with permission from Guyton AC. *Textbook of Medical Physiology.* 8th ed. Philadelphia, Pa: WB Saunders; 1991: 447
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its vasodilating effects, isoflurane has been implicated theoretically in the phenomenon of coronary steal in dogs, but this effect has not been proven clinically in human subjects.56

The Hepatic System

Because of its high metabolic rate, the liver is a highly vascular organ; it receives 25% of the cardiac output. The blood supply consists of two parallel circulations: the hepatic artery supplies fully oxygenated blood at high pressure, and the low-pressure portal vein supplies partially desaturated blood from the splanchnic bed. Owing to this unique anatomical arrangement, the hepatic cells adjacent to the hepatic venules are very susceptible to hypoxia, and centrilobular necrosis can occur. Although autoregulation of total hepatic blood flow can be demonstrated during the metabolically active fed state in dogs, its presence in humans is controversial. Hepatic blood flow is subject to the effects of multiple hormones. The main determinants of hepatic compromise during inhalational anesthesia are related to diminished total hepatic blood flow, which is primarily due to decreases in cardiac output and mean arterial blood pressure. Halothane is more closely associated with these decrements in total hepatic blood flow, cardiac output, and blood pressure than is isoflurane, and although the data are limited, enflurane appears to be similar to halothane.57 Hepatic oxygen supply–demand ratios are better preserved by isoflurane than by halothane.58 Other factors that may compromise total hepatic blood flow include (a) an operative site near the liver and (b) the use of controlled ventilation with high peak pressures and positive end-expiratory pressures, which causes an increase in hepatic venous pressure. The metabolism of drugs with a high extraction ratio is affected by decreased total hepatic blood flow. Finally, transient elevations of liver function tests sometimes occur following anesthesia, but owing to the enormous reserve of the liver, the significance of these elevations is not known and possibly may be related to a surgical site close to the hepatic bed.

The Renal System

The potent inhalational anesthetic agents usually have an adverse impact on renal function due to the secondary effects of the altered cardiovascular, endocrine, and sympathetic nervous systems. The main determinants of an adverse renal outcome are decreased cardiac output and blood pressure. These effects on the renal system are typically transient in nature and resolve spontaneously once the anesthetic action has been terminated. The main key to preventing these altered physiological effects is the maintenance of an adequate preoperative state of hydration. All the potent inhalational agents in use today are fluorinated to some degree, and there is some concern that inorganic fluoride released during their oxidative dehalogenation during hepatic metabolism can cause a primary renal injury. Renal injury from this cause is rarely seen clinically. Owing to the way it is metabolized, enflurane can theoretically place the kidney at the most risk for fluoride toxicity, although a recent clinical study59 did not support this contention. Interestingly, the metabolism of sevoflurane, the newest halogenated agent, is associated with increased serum fluoride levels and may again open this issue to further discussion and investigation.

ANESTHESIA IN THE FIELD

It is impossible to predict the nature of deployments. The most reasonable assumption is that most military anesthesia in the future will take place in the DEPMEDS environment of ISO (International Standards Organization) shelters and TEMPER (tents, extendable, modular, personnel) tents. However, reasonable alternative possibilities range from the marked austerity of draw-over devices in shelters of opportunity to the sophistication of servo-mechanism ventilators in modern, host-nation, fixed facilities. Most anesthesiologists routinely use a balanced anesthetic technique in their peacetime practice, and it should be possible to use this same method in the vast majority of field environments.

Currently, the U.S. Army stocks two devices for delivering inhaled anesthetic agents, the Ohmeda Portable Anesthesia Circuit (PAC) and the Ohmeda Model 885A field anesthesia machine (both manufactured by Ohmeda, Inc., Madison, Wis.), in its DEPMEDS inventory. The Ohmeda PAC is a draw-over device, and the 885A is an anesthesia machine based on flow-over technology. Neither apparatus is supplied with a ventilator, although many field hospitals do carry small ventilators as separate items of operating room equip-
ment. Until recently, little or no training was provided on either apparatus. However, the teaching protocol for the draw-over device is now being implemented at selected medical centers, and a protocol for the 885A is being developed (see also Chapter 2, Combat Anesthesia Overview, and Chapter 7, Military Anesthesia Machines). Military anesthesia providers should at least read about these two devices before they deploy. The draw-over device is simple, but its unfamiliarity may cause the inexperienced anesthesiologist some concern. The 885A is an actual anesthesia machine and may appear more familiar than the PAC to the unpracticed eye, but it, too, has dangers associated with its operation. The 885A is capable of delivering hypoxic mixtures of nitrous oxide and oxygen, and the ambient temperature in the operating room can drastically affect the output of the vaporizer. These two design problems can lead to lethal hypoxic mixtures.

Both halothane and isoflurane are available through the medical logistics system. As a general rule, if the logistical support necessary for surgery is available, the support will also be sufficient to perform the usual anesthetic methods. More than anything else, the condition of the patient will dictate the anesthetic technique. For example, if routine surgery is being done on children as part of a civil action program, an inhalational technique might be selected. On the other hand, some casualties with traumatic injuries will be severely hypovolemic and will not be able to tolerate any anesthetic at all until the hemorrhage is controlled and volume and red blood cell mass restored. A common practice in these latter cases is to begin the procedure with oxygen, a muscle relaxant, and scopolamine (as an amnestic agent), and then carefully titrate small increments of inhaled agents as the casualty’s vital signs begin to improve. In other words, anesthetic practice in the field will usually closely resemble the balanced techniques prevalent in peacetime practice.

**SUMMARY**

Inhalational anesthetic agents are the most important drugs in the pharmacopeia of both military anesthesia providers and civilian practitioners. It is, therefore, not a little odd that their mechanism of action remains imperfectly understood. Although there is clear evidence that anesthetic potency correlates with lipid solubility, the physical basis for this observation is unknown. It is unlikely to be due to a generalized expansion of the lipid membrane that is caused by the presence of a large volume of the inhalational agent, which thereby prevents normal function of ionic channels. More likely explanations are that inhalational agents either (a) perturb the normal, ordered structure of the bilipid membrane or (b) reversibly alter lipids in contact with proteins in ionic channels; both changes interfere with membrane excitability. There is less doubt about the site of action of inhalational anesthetics: this is at the neural synapse rather than at the axon.

Presently used inhalational agents fall into two categories: the alkanes, such as halothane, and the ethers, such as enflurane and isoflurane. Halothane is more potent and less irritating to the airway than more recently developed inhalational agents, has the propensity to sensitize the myocardium to epinephrine, and may cause severe hepatotoxicity (in isolated instances). Enflurane, although less potent than halothane, has fewer of the potential side effects of the latter. Isoflurane is notable for its ease of administration, lack of serious hepatotoxicity, and minimal biotransformation with fluoride-ion production. Isoflurane is associated with dose-dependent hypotension that is solely mediated by a decrease in systemic vascular resistance and not by myocardial depression.

The amount of inhalational anesthetic agent that is delivered to a patient can be expressed as a percentage of the total gas volume delivered or as a partial pressure of the total gas pressure. The solubility of an anesthetic agent can be expressed as a partition coefficient, which is essentially the ratio of the solubilities for two media. The solubility of anesthetic agents in the blood and tissues determines how much drug uptake is required across the alveolar membrane to increase the partial pressure of the anesthetic agent in the brain, the ultimate target organ for anesthetic agents. Major factors can delay anesthetic uptake to the brain, including the use of an agent with a high solubility, a state of increased cardiac output, and a large gradient between the partial pressures of alveolar and mixed-venous blood. The amount of inhalational agent required is quantitated as the MAC, and is measured as the partial pressure.

Inhalational agents have the potential to cause major organ dysfunction outside the CNS. Depres-
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...sion of the respiratory and cardiovascular systems is to be expected. The liver and kidneys are at risk from decreased blood flow and, in rare instances, devastating agent-induced toxicity.

The administration of inhalational agents in deployed hospitals requires a special understanding of the characteristics of the agents because they will be administered by draw-over and flow-over technologies. Halothane and isoflurane are available in DEPMEDS-equipped hospitals.

REFERENCES


