History of inhalational anesthetics

- Ether (diethyl ether)
  - Originally prepared by Valerius Cordus in 1540
  - Used as an anesthetic agent in humans in 1842, but was not publicized until 1846

- Chloroform
  - First used in 1847 in clinical practice by a Scottish obstetrician

- Nitrous oxide
  - First produced in 1772
  - Used as an anesthetic in humans in 1844
  - Still commonly used in practice today
Initially, nitrous oxide was the least popular of the early three anesthetics, due to its low potency and its tendency to cause asphyxiation when used alone.

Chloroform-related cardiac arrhythmias, respiratory depression, and hepatotoxicity made it later fall out of favor.

Ether was commonly used until the 1960s.
Ether has since been replaced by potent nonflammable fluorinated hydrocarbons

- Halothane (released in 1956)
- Methoxyflurane (released in 1960) - dose related nephrotoxicity
- Enflurane (released in 1973) - could cause evidence of seizure activity on EEG
- Isoflurane (released in 1981)
- Desflurane (released in 1992)
- Sevoflurane (released in 1994)
How do inhalational agents cause anesthesia?

- Older theories include membrane expansion theories and the critical volume hypothesis- alterations in the physical properties of the membrane and ion channels

- Newer theories propose distinct molecular targets and anatomic sites of action
  - Thought to enhance inhibitory receptors including GABA-A and glycine receptors, which leads to an effect on ion channels
  - May induce an inhibitory effect on excitatory channels like neuronal nicotinic and glutamate receptors
  - Produce immobility mostly by their actions on the spinal cord
  - Likely targets for the amnestic effects are supraspinal structures, including the amygdala, hippocampus, and cortex
What are some of the characteristics of an ideal anesthetic agent?
Properties of an ideal anesthetic agent

- Ease of use
- Nonflammable
- No organ toxicity or undesirable side effects (nausea and vomiting, MH trigger)
- Quick onset and emergence
- Easy titrateability
- Availability
- Cost
- Pungency
- Delirium and “hangover” effects
- Easy estimation of concentration at the site of action
- Provide muscle relaxation
- Cardiostability and bronchodilation
Physical properties

- **Molecular structure**: halogenated hydrocarbons, except for nitrous oxide.

- **Vapor pressure**: all the inhaled anesthetics are liquids at ambient temperature, except nitrous oxide, which is a gas.
  - Nitrous oxide becomes a liquid at higher pressures.
    - N2O cylinder pressure doesn’t decrease until all liquid is gone (400/1590L).
  - Sevoflurane and isoflurane are delivered by variable-bypass vaporizers.
  - Desflurane requires a special, heated vaporizer because the vapor pressure at sea level is 700 mm Hg at 20°C and delivery by the standard vaporizer can produce unpredictable concentrations.
  - Desflurane gas is heated to 2 atm of pressure to accurately deliver vapor.

Vapor pressure and boiling point have an inverse relationship.
Variable Bypass vaporizer
Desflurane Tec 6 vaporizer
Physical properties

- **Metabolism** - can produce potentially toxic compounds
  - Sevoflurane - Compound A (trifluoroethyl vinyl ether).
  - Nephrotoxic in animals after prolonged exposure
  - In humans, low fresh gas flows for a prolonged duration causes Compound A exposure, but no increase in Cr or long-term effects

- **Interaction with carbon dioxide absorbents**
  - Desiccated CO2 absorbent and volatile anesthetics produce an exothermic reaction that can cause high temperatures inside the absorbent canister and carbon monoxide formation
  - This is only seen with older absorbants with strong bases KOH & NaOH
  - Newer absorbants will not do this despite hydration status
Pharmacokinetics of inhaled anesthetics

- Describes the uptake (absorption) from alveoli into the systemic circulation, distribution in the body, and elimination by the lungs or metabolism by the liver.

- The goal is to obtain an optimal brain partial pressure (Pbr) of anesthetic.

- The PA of the inhaled anesthetic mirrors the Pbr, and thus the PA is used as an index of anesthetic depth.
Factors that determine alveolar partial pressure

- Transfer of anesthetic from anesthesia machine to alveoli
  - Inspired partial pressure
  - Alveolar ventilation
  - Characteristics of anesthetic breathing system

- Transfer of anesthetic from alveoli to arterial blood
  - Blood-gas partition coefficient
  - Cardiac output
  - Alveolar-to-venous partial pressure difference

- Transfer of anesthetic from arterial blood to brain
  - Brain-blood partition coefficient
  - Cerebral blood flow
  - Arterial-to-venous partial pressure difference
Transfer of inhaled anesthetic from machine to alveoli

- **Inspired partial pressure (P_I)**
  - Concentration effect- a high P_I accelerates the induction of anesthesia

- **Alveolar ventilation**
  - Increased ventilation increases the rate of alveolar uptake of anesthetic

- **Characteristics of anesthetic breathing system**
  - Volume of the system
  - Solubility of the anesthetic in components of the system
  - Gas inflow from the anesthetic machine
Transfer of anesthetic from alveoli to arterial blood

- Blood-gas partition coefficient
  - A measure of solubility of the anesthetic
  - Most important single factor in determining the speed of induction and recovery
Partition coefficients

- Definition: describes the distribution of a given agent at equilibrium between two substances at the same temperature, pressure, and volume.

- Blood-gas coefficient: describes the distribution of an anesthetic between blood and gas at the same partial pressure.
  - A higher blood-gas coefficient correlates with higher solubility of anesthetic in blood and thus slowing the rate of induction.
  - The blood can be considered a pharmacologically inactive reservoir.

- Another important partition coefficient is the fat to blood.
Based on what you know about partition coefficients, does obesity affect which agent you choose to use?

Does agent choice become more important in a short case or a longer case?

Figure 8-7 An increase in the duration of anesthesia during a constant dose of anesthetic (1.6 MAC) is associated with increases in the time to recovery (i.e., motor coordination in an animal model), with the greatest increases occurring with the most blood-soluble anesthetics. MAC, minimum alveolar concentration. (From Eger EI II: Desflurane (Suprane): A Compendium and Reference. Nutley, NJ, Anaquest, 1993, pp 1-11, used with permission.)
# Partition coefficients

<table>
<thead>
<tr>
<th>Inhalational anesthetic</th>
<th>Blood-gas partition coefficient</th>
<th>Fat-blood partition coefficient</th>
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</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>45</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>27</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
<td>48</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.3</td>
<td>60</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0.47</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Transfer of inhaled anesthetic from alveoli to arterial blood

- Blood-gas partition coefficient

- Cardiac output
  - A high CO results in more rapid uptake such that the rate of rise in the PA and the speed of induction are slowed

- Alveolar-to-venous partial pressure difference
  - A large gradient will slow the rise in the PA
Second gas effect

- Definition: the ability of the large volume uptake of one gas (1st gas) to accelerate the rate of rise of the PA of a concurrently administered companion gas (2nd gas)
  - Alveolar hyperoxygenation
    - Transient increase (about 10%) in PaO$_2$ that accompanies the early phase of nitrous administration reflects the 2nd gas effect of nitrous on oxygen
  - Probably not a clinically significant phenomenon
FIGURE 61-2  A lung is filled with 80% N₂O and 1% of a second gas. Uptake of 50% of the N₂O increases the concentration of the second gas to 1.5%. Restoration of the lung gas volume by addition of more of the original 80% to 1% mixture changes the second-gas concentration to 1.4%. (Reprinted, with permission, from Eger EI II. Effect of inspired anesthetic concentration on the rate of rise of alveolar concentration. Anesthesiology. 1963;24:153-157.)
Recovery from anesthesia

- Recovery is the inverse of induction of anesthesia in many respects, with a few differences
  - Variable tissue concentrations of anesthetic at the start of recovery
    - The impact of tissue storage depends on the duration of anesthesia and the solubility of the anesthetic in various tissue compartments
  - Potential contribution of metabolism
    - Most of the inhaled agents are excreted unchanged by the lungs
    - Amount metabolized (%): isoflurane (0-0.2), halothane (15-40), desflurane (0-0.2), sevoflurane (5-8)
Diffusion hypoxia

- Results from the dilution of alveolar oxygen concentration by the large amount of nitrous oxide leaving the pulmonary capillary blood at the conclusion of nitrous oxide elimination

- Can be prevented by filling the patient’s lungs with oxygen at the conclusion of nitrous administration
Pharmacodynamics of inhalational anesthetics

- **Minimum Alveolar Concentration (MAC)-**
  - Comparison of relative potency
  - The alveolar concentration of an anesthetic at one atm that prevents movement in response to a surgical stimulus in 50% of patients
  - 1.3 MAC- abolishes the response to a surgical incision in 99% of patients
  - MAC-BAR: concentration required to block autonomic reflexes to nociceptive stimuli, 1.7-2.0 MAC
  - MAC-aware: concentration required to block appropriate voluntary reflexes and measures perceptive awareness, 0.3-0.5 MAC
  - MAC values are additive
Factors that may decrease MAC

- Age (MAC is greatest at 6-12 months of age)
- Decreased temperature
- Hyponatremia
- Opioids
- Barbiturates
- Alpha 2-blockers (clonidine, dexmetetomidine)
- Calcium channel blockers
- Acute alcohol intoxication
- Pregnancy

MAC is NOT affected by gender
MAC (%) of various agents (at 1 atm)

- Isoflurane - 1.15
- Desflurane - 6
- Sevoflurane - 1.7
- Halothane - 0.77
- Nitrous oxide - 104
Clinical pharmacology of inhalational anesthetics

- Cardiovascular
- Respiratory
- Neuro
- Neuromuscular
- Renal
- Hepatic
- Malignant hyperthermia susceptibility
MAP decreases in a dose-dependent manner
- Primarily reflects a decrease in SVR
- With nitrous oxide, in contrast, MAP is unchanged or mildly increased

Increased delivered concentrations of isoflurane, desflurane, and sevoflurane increase HR; although at different concentrations
- With sevoflurane, HR does not increase until 1.5 MAC
- When desflurane concentration is increased rapidly or at levels > 1 MAC, there is a related SNS stimulation

CI is minimally affected

Halothane: sensitizes the myocardium to catechols; potential for dysrhythmias

Volatile anesthetics exert a protective effect on the heart against myocardial ischemia by enhancing ischemic preconditioning
Figure 8-8  The effects of increasing concentrations (MAC) of halothane, isoflurane, desflurane, and sevoflurane on mean arterial pressure (mm Hg) when administered to healthy volunteers. MAC, minimum alveolar concentration. (From Cahalan MK: Hemodynamic Effects of Inhaled Anesthetics. Review Courses. Cleveland, International Anesthesia Research Society, 1996, pp 14-18, used with permission.)
**SVR**

**Cardiac Index**

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**Figure 8-9** The effects of increasing concentrations (MAC) of halothane, isoflurane, desflurane, and sevoflurane on systemic vascular resistance (dynes/sec/cm$^5$) when administered to healthy volunteers. (From Cahalan MK: Hemodynamic Effects of Inhaled Anesthetics. Review Courses. Cleveland, International Anesthesia Research Society, 1996, pp 14-18, used with permission.)

**Figure 8-10** The effects of increasing concentrations (MAC) of halothane, isoflurane, desflurane, and sevoflurane on cardiac index (L/min) when administered to healthy volunteers. MAC, minimum alveolar concentration. (From Cahalan MK: Hemodynamic Effects of Inhaled Anesthetics. Review Courses. Cleveland, International Anesthesia Research Society, 1996, pp 14-18, used with permission.)
Respiratory

- Increase RR and decrease TV

- PaCO₂ increases proportionally with anesthetic concentration in a spontaneously breathing patient

- Dose-related blunting of CO₂ responsiveness and response to arterial hypoxemia

- Inhibition of hypoxic pulmonary vasoconstriction is minimal

- Airway irritation (pungency)
  - Non-pungent- sevoflurane, halothane, nitrous

- Airway resistance
  - In the absence of bronchoconstriction, there is no significant change. In the presence of bronchoconstriction or in smokers, sevoflurane causes decreased airway resistance
Figure 8-14 Inhaled anesthetics produce drug-specific and dose-dependent increases in \( \text{Paco}_2 \). (From Eger EI II: Desflurane (Suprane): A Compendium and Reference. Nutley, NJ, Anaquest, 1993, pp 1-119, used with permission.)
**Figure 6-14** The hypercapnic ventilatory response (HCVR) is measured as the slope of the plot of $P_{CO_2}$ versus minute ventilation ($\dot{V}_E$). End-tidal $P_{CO_2}$ is usually substituted for $P_{aCO_2}$ for clinical studies. The apneic threshold is the $P_{CO_2}$ at which ventilation is zero. It can be extrapolated from the curve, but it is difficult to measure in awake volunteers, although it is easy to observe in patients under general anesthesia. A depressed carbon dioxide response results from opioids, which lower the slope and raise the apneic threshold.

**Figure 8-15** All inhaled anesthetics produce similar dose-dependent decreases in the ventilatory responses to carbon dioxide. (From Eger EI II: Desflurane (Suprane): A Compendium and Reference. Nutley, NJ, Anaquest, 1993, pp 1-119, used with permission.)
Central nervous system

- Cerebral blood flow
  - Hal/iso/sevo/desflurane
    - decrease CMRO$_2$
    - in normocapnea, there is cerebral vasodilation above 0.6 MAC
  - Cerebral autoregulation is diminished
    - Why 1/2MAC + 1/2 MACTIVA for craniotomy can be beneficial
  - Nitrous oxide causes cerebral vasodilation, increased CBF, and increased CMRO$_2$.

- Cerebral vascular responsiveness to changes in PaCO$_2$ are maintained

- All agents affect SSEPs in a dose-dependent manner
FIGURE 42-1  The relationship between cerebral blood flow (CBF) and mean arterial pressure (MAP) shows autoregulation of CBF across the range of MAP from 65 to 150 mm Hg. The relationship between PaCO₂ and CBF is linear. The PaO₂ also influences CBF at extrema values.

FIGURE 42-3  A representation of the effect of increasing the concentration of an inhalation anesthetic agent on autoregulation of cerebral blood flow. Dose-dependent cerebral vasodilation leads to attenuation of autoregulation, and both upper and lower thresholds are shifted to the left. MAP, Mean arterial pressure.  (From Patel PV, Drummond J. Cerebral physiology and the effects of anesthetic drugs. In: Miller RD, ed. Miller's Anesthesia. 7th ed. Vol. 2. Philadelphia: Elsevier; 2019:201.)
Immune-mediated liver injury

Metabolism of volatile anesthetics to trifluoroacetate with subsequent formation of trifluoroacetyl-hapatocyte moieties may trigger an immunologic response.

This may lead to severe hepatic necrosis.

Most commonly happened with halothane.
Malignant hyperthermia susceptibility

- All of the potent inhaled anesthetics have the potential to trigger MH
- Nitrous oxide is not a trigger
Neuromuscular

- All of the agents cause skeletal muscle relaxation, except nitrous oxide, which increases skeletal muscle tone
- Potentiate the effects of nondepolarizing neuromuscular blocking drugs
Nitrous oxide

- Nitrous oxide is 20 times more soluble than nitrogen (which makes up 79% of atmospheric gases).
- Nitrous oxide can diffuse 20 times faster into closed spaces than it can be removed, resulting in an expansion of that space or increased pressure in the space.
- Ex.: pneumothorax, bowel gas, air embolism, middle ear, cranium
- Inhalation of 70% nitrous oxide doubles the volume of a pneumothorax in 10 minutes
Questions
Do volatile anesthetics provide analgesia?
No, except nitrous oxide has analgesic properties
TRUE statements regarding inhaled anesthetics include:

1. The partial pressure is the pressure a gas exerts proportional to its fractional mass

2. A low-solubility agent results in a fast rise in FA/FI

3. Depth of anesthesia can be adjusted quickly

4. Fat has a slow time for equilibration with blood
Answer: all are true
Which of the following statements regarding MAC is FALSE?

- A. Pregnancy decreases MAC
- B. MAC of inhaled drugs is additive
- C. MAC is lowered in preterm neonates compared with term neonates
- D. Acute ethanol administration increases MAC
- E. MAC in an 80-year-old patient is only $\frac{3}{4}$ that in a young adult
Answer: D

- Acute ethanol administration decreases MAC
- Chronic alcohol use increases MAC and the requirements for benzodiazepines
The reason desflurane is not used for inhalational induction is because:

- A. Its low blood/gas partition coefficient
- B. Its propensity to produce hypertension in high concentrations
- C. Its propensity to produce airway irritability
- D. Its propensity to produce tachyarrhythmias
- E. Its propensity to produce nodal arrhythmias
Desflurane smells bad and the airway irritation often leads to coughing, increased salivation, breath holding, and sometimes laryngospasm.
References

- **Clinical Anesthesiology.** Morgan, Mikhail, and Murray. 4th ed. 2006.

- **Basics of Anesthesia.** Stoelting and Miller. 5th ed. 2007


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