I. LEARNING OBJECTIVES:

- Definitions: partial pressure, MAC, blood/gas partition coefficient, oil/gas partition coefficient
- What determines anesthetic potency?
- What are the 4 potential targets for the action of general anesthetics?
- How do blood/gas solubility, ventilation rate and cardiac output affect equilibration of anesthetics (rate of induction of anesthesia)?
- What is the mechanism of the “concentration effect” and the related “second gas effect”?
- What factors determine the rate of anesthetic equilibration into different tissues?
- What is the route of elimination of general anesthetics and how is recovery from anesthesia affected by the blood/gas partition coefficient, ventilation rate and cardiac output?
- What are the common pharmacological effects of inhalational anesthetics?
- Know the major differences between the inhalational anesthetics (e.g., which is most/least potent, induction/recovery rate; don’t need to memorize numbers).
- What are the major uses of the various intravenous anesthetic agents discussed and their major advantages and disadvantages?
II. STRUCTURES OF INHALED ANESTHETICS

Structures of Inhaled Anesthetics

**Agents Once in Clinical Use:**

- Cyclopropane
- Methoxyflurane
- Diethyl Ether
- Chloroform
- Fluroxene
- Trichloroethylene

**Agents in Clinical Use Today**

- Halothane
- Enflurane
- Sevoflurane
- Isoflurane
- Desflurane
- Nitrous Oxide

**Experimental:**

- Xenon
III. DEFINITIONS

**Definition Of Anesthesia or “Anesthetic State”:**
1) Immobile to Noxious Stimuli
2) Unconscious
3) Lack of autonomic response to noxious stimulus
4) State of Analgesia
5) Amnesia

**Partial Pressure (or Gas Tension):** For gas A, the partial pressure in a mixture of 3 gases (A, B and C) is:

\[
P_A = \frac{\text{# of Molecules of gas A}}{\text{Total # of molecules of gases A+B+C}} \times 760 \text{ mm Hg}
\]

**Blood/Gas Partition Coefficient (λ):** (Also called Ostwald Coefficient):

After an anesthetic is allowed to equilibrate between an equal volume of gas and blood, \( \lambda \) = the amount of anesthetic in the blood phase divided by the amount of anesthetic in the gas phase:

\[
\lambda = \frac{[\text{Anesthetic}]_{\text{blood}}}{[\text{Anesthetic}]_{\text{gas}}}
\]

This number, an indication of blood solubility, is inversely correlated with equilibration rate but has no relation to potency.

**Minimum Alveolar Concentration (MAC):** The alveolar concentration of an anesthetic at 1 atmosphere that prevents movement in 50% of patients in response to a noxious stimulus (e.g., surgical incision).

- The MAC is a measure of the potency of an anesthetic. A low MAC means high potency.
- An anesthetic's potency is correlated with its lipophilicity (i.e., low MAC = very lipophilic).
- Dose response curve is steep – 99% patients immobile by 1.3 MAC. MACs of two different agents are additive (i.e., 0.5 MAC anesthetic A + 0.5 MAC anesthetic B = effectiveness of 1.0 MAC of A or B).
- MAC is age-dependent: Highest in infants; drops to about half by age 80.
- Analgesia begins at about 0.3 MAC; Amnesia at about 0.5 MAC.

**Oil/Gas Partition Coefficient:** Concentration of anesthetic in olive oil divided by its concentration in gas at equilibrium. This number correlates directly with potency or inversely with MAC (see below).
V. MECHANISM OF ACTION

A. MEYER-OVERTON RULE (1899-1901)

Figure 13-4. The correlation of anesthetic potency with olive oil:gas partition coefficient.

The correlation is shown for a number of general anesthetic agents and other inert gases not usually used for anesthesia. Note the log scales and the excellent correlation over a very wide range of fat solubilities and potencies (see Paton, 1974). (Modified from Eger et al., 1969:

B. POTENTIAL TARGET SITES FOR GENERAL ANESTHETICS

Fig. 3-11. Four possible target sites for inhaled anesthetic molecules (●) in a neuronal membrane include (a) the lipid bilayer as a whole, (b) lipids at a protein/lipid interface, (c) a protein site bounded by lipid, and (d) a protein site exposed to an aqueous environment. (From Franks and Lieb,133 with permission.)
C. THEORIES OF ANESTHETIC ACTION

1. Change in Membrane Dimension (Critical Volume Hypothesis): Anesthetics expand the volume of membranes beyond a critical amount and thereby obstruct ion channels or alter electrical properties.

2. Change in Membrane Physical State:
   a) Fluidization Theory: Anesthetics increase the general fluidity of plasma membranes
   b) Lateral Phase Separation Theory: Anesthetics inhibit the formation of an ordered, low volume gel phase around ion channels, normally required for channel opening.

3. Protein Interaction Theory: Anesthetics bind to specific proteins that affect ion flux during membrane excitation, resulting in either potentiation of inhibitory neurotransmitters (e.g., GABA, glycine) or inhibition of excitatory neurotransmitters (e.g. glutamate NMDA receptors)

Currently Known Targets of General Anesthetics

<table>
<thead>
<tr>
<th>Anaesthetics</th>
<th>GABA&lt;sub&gt;A&lt;/sub&gt;</th>
<th>K&lt;sub&gt;2P&lt;/sub&gt; channel</th>
<th>Glycine</th>
<th>NMDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous anaesthetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Propofol</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Etomidate</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Volatile anaesthetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ether</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Ether derivatives</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Halogenated hydrocarbons</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Xenon</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

-, inhibitory effect; +, potentiating effect; 0, no effect; GABA, gamma-aminobutyric acid; K<sub>2P</sub> channel, two-pore potassium channel; NMDA, N-methyl-D-aspartate.
GOALS OF GENERAL ANESTHESIA:

1) Rapid Induction
2) Use the minimal level of anesthetic that will give:
   analgesia, unconsciousness, amnesia
3) Minimal depression of cardiovascular system
4) Rapid recovery

COMMON PRACTICE TODAY:

Anesthesiologists use a combination of drugs:
- Premedication (e.g., sedatives, opioid analgesics)
- IV anesthetic for induction,
- Muscle relaxants so a lighter level of general anesthesia can be used
- A mixture of volatile anesthetic gases to maintain anesthesia
- Initiate Inhaled anesthetic at concentration > than MAC, reduce for maintenance.

Modern methods:
- **Clinical Signs** (e.g., blood pressure, heart rate, movement, sweat, tears)
  Instrumental monitoring:
  - Skin conductance
  - Surface electromyogram
  - Heart rate variability
  - **Brain EEG monitors** ("Bispectral index" most popular)
PHARMACOKINETICS OF INHALATIONAL ANESTHETICS

Equilibration of Alveolar Gas with Inspired Gas:

For equilibration in the lung alone:
Assumptions: 1) No uptake of gas into bloodstream; 2) Total Lung Volume ($V_T$) = 5 L; 3) Inspired Volume ($V_I$) = 0.8 L
Definitions: $F_A$ = Alveolar Gas Concentration; $F_I$ = Inspired Gas Concentration;

Plotting $F_A/F_I$ vs. time gives this idealized curve:

Actual Equilibration curves for some Inhalational Anesthetics:

- **Nitrous oxide** ($\lambda = 0.47$)
- **Isoflurane** ($\lambda = 1.4$)
- **Halothane** ($\lambda = 2.4$)
- **Methoxyflurane** ($\lambda = 12.0$)
Inhalational anesthetics diffuse freely across cell membranes in the gas phase down their concentration gradient. Thus, they equilibrate according to their relative partial pressures (e.g., $P_A$ = alveolar partial pressure).

Because of uptake of anesthetic gas by the blood, the inhaled partial pressure (also called inspired fractional concentration or $F_I$) will be higher than end tidal alveolar concentration ($F_A$). $F_A$ will also be higher than the concentration of anesthetic returning to the lung because of uptake of anesthetic from the blood into the tissues. Thus, complete equilibration (where $F_I = F_A = F_{Tissue}$) will not be achieved until all tissues and blood are saturated with anesthetic. In practical terms, this will not happen in the time frame of most surgeries.

A relatively soluble anesthetic like halothane will take longer to approach equilibrium because it is much more soluble in blood and tissues than the relatively insoluble nitrous oxide. As a result, the blood and tissues represent a larger "reservoir" for halothane than for nitrous oxide as schematically illustrated here.
Equilibration of Anesthetic Gases into Tissues

**FAT**
- 6% C.O.
- 20% Mass x 50-fold more soluble
  (Nitrous oxide ~2x more soluble)

**MG**
- 10% C.O.
- 50% Mass
  (MG = muscle group; skin and muscle)

**VRG**
- 75% C.O.
- 10% Mass
  (VRG = vessel rich group; brain, heart, liver, kidney)

![Graph showing gas tension in various tissues](image)
Driving force for equilibration is **partial pressure gradient**, (NOT blood concentration per se).

**Henry's Law**: Partial pressure of a gas in a liquid is equal to its Partial pressure in the gas phase in equilibrium with that liquid. (Does **not** mean an equal number of molecules in each phase – see below)

\[
\begin{align*}
P_A & (\text{Gas}) \\
\| & \\
P_A & (\text{Liquid})
\end{align*}
\]

\[\lambda = \frac{10}{5} = 2\]

**Example**: Assume 2 anesthetic gases have equal potencies (MAC)
For Gas A, \(\lambda \text{ (blood/gas)} = 1\)
For Gas B, \(\lambda \text{ (blood/gas)} = 10\)

\[
\begin{align*}
\text{Gas} & \quad \text{vol}=1 \\
110 \text{ ml A} & \quad 110 \text{ ml B} & \quad 605 \text{ ml B} \\
55 \text{ ml A} & \quad 10 \text{ ml B} & \quad 55 \text{ ml B} \\
55 \text{ ml A} & \quad 100 \text{ ml B} & \quad 550 \text{ ml}
\end{align*}
\]

\[
\begin{align*}
P_A &= \frac{55}{1000} \times 76 \\
&= 41.8 \text{ mm Hg} \\
P_B &= \frac{10}{1000} \times 76 \\
&= 7.6 \text{ mm Hg} \\
P_B &= \frac{55}{1000} \times 76 \\
&= 41.8 \text{ mm Hg}
\end{align*}
\]
Effect of the Blood:Gas Partition Coefficient on Equilibration

EXAMPLE: II. Assume two anesthetic gases have MACs = 5%, but; For gas A, $\lambda = 1$ and for gas B, $\lambda = 10$.

I. Uptake from the Lung:

Assumptions: no flow, equal volume in Blood and Gas Phase, 1 L of both gases administered at 20% concentration.

- For gas A: $100\text{ ml A}$
- For gas B: $18\text{ ml B}$

II. Equilibration into Brain: Assume equal vol. for blood and gas phase

- For gas A: $50\text{ ml A}$
- For gas B: $16\text{ ml B}$
Pulmonary Ventilation

Pulmonary Blood Flow (Cardiac Output)
Diffusion Hypoxia

Elimination of Inhalational Anesthetics

Driving force for equilibration is partial pressure gradient, (NOT blood concentration per se).
PHARMACOLOGY OF INHALATIONAL ANESTHETICS

A. EFFECTS COMMON TO ALL INHALATIONAL ANESTHETICS
1. ↓ Blood Pressure (except Nitrous Oxide)
2. ↑ Respiratory Rate and ↓ Tidal Volume (unassisted)
3. ↑ Cerebral Blood Flow
4. ↓ Renal Blood Flow, ↓ GFR, ↓ Urinary Output
5. ↓ Hepatic Blood flow
6. Malignant Hyperthermia (not Nitrous Oxide)
   - Symptoms: muscular rigidity, rapid rise in temperature to 109°F
   - Cause: continual release of Ca++ from SR in muscle, ATP hydrolysis
   - Mechanism: autosomal dominant genetic defect (mutation) in ryanodine receptor (Ca++ release channel)
   - Treatment: dantrolene (blocks SR Ca++ release)

B. PROPERTIES OF SPECIFIC ANESTHETIC AGENTS
1. Nitrous Oxide - not used alone (except where full anesthesia not necessary; e.g. dental procedures); causes more nausea/vomiting; Contraindicated in patients with air filled cavities (e.g. air embolus, pneumothorax, etc) or vitamin B12 deficiency.
2. Sevoflurane - expensive; common uses: outpatient surgery; induction in children
3. Isoflurane - the most widely used inhalational anesthetic, especially in-patient surgeries; pungent odor, not used for induction.
4. Halothane – used for induction in children (sweet pleasant odor); toxicity – cardiac arrhythmias, "halothane hepatitis" (rare).
5. Desflurane – very rapid induction/recovery; widely used for outpatient surgery; bronchial irritant

### Comparison of Properties of Inhalational Anesthetics

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
<th>Desflurane</th>
<th>Nitrous Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>0.74</td>
<td>1.15</td>
<td>1.71</td>
<td>6.0</td>
<td>105</td>
</tr>
<tr>
<td>Oil:Gas Partition coeff.</td>
<td>224</td>
<td>99</td>
<td>55</td>
<td>19</td>
<td>1.4</td>
</tr>
<tr>
<td>Blood:Gas Partition coeff.</td>
<td>2.4</td>
<td>1.4</td>
<td>0.59</td>
<td>0.42</td>
<td>0.47</td>
</tr>
<tr>
<td>Induction/Recovery Rate (1=slow; 5=fast)</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Poor</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Good</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>----</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>↓</td>
<td>----</td>
<td>↓</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Systemic Vascular Resistance</td>
<td>----</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>----</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>+</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Metabolism</td>
<td>15-20%</td>
<td>0.2%</td>
<td>2 - 5%</td>
<td>0.02%</td>
<td>0.004%</td>
</tr>
</tbody>
</table>
INTRAVENOUS ANESTHETIC AGENTS

Benzodiazepines

Primary uses:
- Anti-anxiety agent pre-op.
- Sedation

Advantages:
- Relatively rapid onset
- Cause amnesia
- Relatively little cardiovascular effect
- Anti-convulsant

Disadvantages:
- Not analgesic
- Cause respiratory depression
- Long-acting (diazepam or repeated inj. of midazolam)

Opioids

Primary uses:
- Analgesia

Advantages:
- Profound analgesia
- Relative cardiovascular stability
- High potency, short duration (15-30 min.; Remifentanil; 5 min) except morphine
- Reduces emergence phenomena
- Reversible by opioid receptor antagonists

Disadvantages:
- Nausea
- Slow gastric emptying
- Respiratory depression at high doses (assisted ventilation required).
Primary Use: Induction of anesthesia

Advantages:
- Rapid onset (10 - 30 sec)
- Short duration (5 – 8 min) initial dose; redistributed from brain to muscle; prolonged on repeated injection

Disadvantages:
- Not analgesic
- Decrease blood pressure
- Decrease respiratory rate and tidal volume
**Propofol**

Primary uses:
- Induction
- Anesthesia for short procedures (boluses every ~5 min)
- Sedation

Advantages:
- Rapid onset/recovery, even after repeated injections
- Anti-emetic properties

Disadvantages:
- Pain on injection
- Involuntary muscular movement
- Respiratory depression
- Decreases blood pressure

**Etomidate**

Primary use: Induction in patients w/ cardiovascular problems

Advantages:
- Rapid induction
- Ultra-short acting (5 min)
- No cardiovascular depression
- Minimal respiratory depression

Disadvantages:
- Pain on injection
- Involuntary muscular movement
- Nausea and vomiting
- Hiccups
- Not analgesic
Ketamine

A complete i.v. anesthetic
-causes “dissociative anesthesia”

Primary uses:
Induction or anesthesia in at risk patients w/ cardiovascular problems
Sedation or general anesthesia in children

Advantages:
Cardiovascular stimulant
Bronchodilator
Profound analgesia and amnesia

Disadvantages:
Emergence reactions (not in children <15; adults >65)
Increases intracranial pressure
Suppresses respiration (less severe than other anesthetics)

Summary - Intravenous Anesthetic Agents

- **Pre-op Medications:**
  - Midazolam: Anti-anxiety agent
  - Opioids (Fentanyl and Sufenatnil): Analgesia

- **Induction of Anesthesia:**
  - Thiopental: in hospitalized patients
  - Propofol: in outpatient surgery
  - Etomidate: in patients with cardiovascular problems

- **Special Use Anesthetic:**
  - Ketamine: induction or anesthesia in patients w/cardiovascular problems; sedation or general anesthesia in children