INHALATIONAL ANESTHETICS

Dr. Mustafa Alrabayah
• **Anesthesia** defined as the abolition of all sensation
• **Analgesia** defined as the abolition of pain sensation

• “Triad of General Anesthesia”
  – need for unconsciousness
  – need for analgesia
  – Need for amnesia
  – (±) need for muscle relaxation
Signs and Stages of Anesthesia

**Sedation.** *Mild CNS depression.* Suitable for surgical procedures not requiring muscle relaxation. Most anesthetics do not produce analgesia.

**Delirium:** An excited state resulting from *cortical motor depression.* This can be avoided with rapidly acting, potent anesthetics. This stage extends from the loss of consciousness in stage 1 to surgical anesthesia in stage 3.

**Surgical Anesthesia:** Further subdivided into stages representative of increasing *muscle relaxation,* the final stage is disappearance of muscle tone.

**Deep anesthesia and Respiratory paralysis:** Generally not desirable.
Inhalational anesthesia refers to the delivery of gases or vapors from the respiratory system to produce or maintain anesthesia.

Exposure to the pulmonary circulation allows a more rapid appearance in arterial blood than intravenous administration.
Advantages of inhalational anesthesia

- Completely painless induction
- No IV (intravenous) access needed
- Rapid appearance of drug in arterial blood
- Safe: as long as patient is breathing satisfactorily, elimination of agent and emergence from anesthesia is essentially guaranteed.
1840, William Morton publically administered *ether*
1847, James Simpson introduced *chloroform*
   It was more potent but could have severe side effects such as sudden death and late onset severe liver damage
1877, introduction of *local anesthesia*
1920's *intravenous* induction agents were introduced
1940's *Muscle relaxants* were introduced
The depth of general anesthesia depends on the partial pressure (or gas fraction) exerted by the inhalational agent in the patient brain (b).

This brain partial pressure depends on arterial (a) blood partial pressure which depends on alveolar (A) partial pressure which depends on partial pressure of agent in the inspired gas (I):

\[ p_I \rightarrow p_A \rightarrow p_a \rightarrow p_b \]

**Uptake and Distribution**

FGF (fresh gas flow) is determined by the vaporizer and flowmeter settings.

\[ F_I \text{ (inspired gas concentration)} = \text{determined by (1) FGF rate; (2) breathing-circuit volume; and (3) circuit absorption.} \]

\[ F_A \text{ (alveolar gas concentration)} = \text{determined by (1) uptake (uptake = λ \text{b/g x C(A-V) x Q); (2) ventilation; and (3) the concentration effect and second gas effect:} \]

a) concentrating effect
b) augmented inflow effect

\[ F_a \text{ (arterial gas concentration)} \text{ is affected by ventilation/perfusion mismatching.} \]


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• Minimal alveolar concentration of inhalational agent that prevent movement in 50% of the patients in response to surgical stimulation (skin incision)

• Equivalent to $ED_{50}$

• MAC is important to compare the potencies of various inhalational anesthetic agents
Minimum Alveolar Concentration

• The rationale for this measure of anesthetic potency is,
  a. alveolar concentration can be *easily measured*
  b. near *equilibrium*, alveolar and brain tensions are virtually equal
  c. the high cerebral blood flow produces *rapid equilibration*

• Factors which support the use of this measure are,
  a. MAC is invariant with a variety of noxious stimuli
  b. individual variability is small
  c. sex, height, weight & anaesthetic duration do not alter MAC
  d. doses of anaesthetics in MAC's are additive
Factors affecting MAC

**PHYSIOLOGIC & PHARMACOLOGIC FACTORS AFFECTING MAC**

**Increase in MAC:**
- Hyperthermia
- Hypernatraemia
- Drug induced elevation of CNS catecholamine stores
- Chronic alcohol abuse & chronic opioid abuse
- Increases in ambient pressure (experimental)
- Cyclosporine
- Excess pheomelanin production (red hair)

**Decrease in MAC:**
- Hypothermia & Hyperthermia (if >42°C)
- Hyponatraemia
- Drug induced decrease in CNS catecholamine level
- Increasing age (6% decrease/decade)
- Preoperative medication
- Hypoaxemia (PaO2 < 38 mmHg)
- Hypotension (<40 mm Hg MAP)
- Anaemia (Hematocrit < 10%)
- Pregnancy (progesterone)
- Postpartum (returns to normal in 24-72 hrs)
- CNS depressant drugs - Opioids, Benzodiazepines, TCA’s etc.
- Other drugs - Lithium, Lidocaine, Magnesium
- Acute alcohol abuse
- Cardiopulmonary bypass
Halothane

- Halogen substituted ethane
- Volatile liquid easily vaporized, stable, and nonflammable
- Most potent inhalational anesthetic
- MAC of 0.75%
- Efficacious in depressing consciousness
- Very soluble in blood and adipose
- Prolonged emergence
Halothane

Halothane Systemic Effects

**Cardiovascular**

- **Direct myocardial depression** $\rightarrow$ dose-dependent reduction of arterial BP
- Systemic vascular resistance: unchanged
- Coronary artery vasodilator, but coronary blood flow $\downarrow$ due to systemic BP $\downarrow$
- **Blunt the reflex:** hypotension inhibits baroreceptors in aortic arch and carotid bifurcation $\rightarrow$ vagal stimulation $\downarrow$ $\rightarrow$ compensatory rise in HR
- Sensitizes the heart to the **arrhythmogenic** effects of epinephrine
Halothane Systemic Effects

Respiratory

- Rapid, shallow breathing
- Alveolar ventilation: ↓
- Resting PaCO2: ↑
- Hypoxic drive: severely depressed
- A potent bronchodilator, reverses asthma-induced bronchospasm
Halothane Systemic Effects

**Cerebral**
- Dilating cerebral vessels $\rightarrow$ cerebral vascular resistance $\downarrow$ $\rightarrow$ CBF $\uparrow$
- Blunt autoregulation (the maintenance of constant CBF during changes in arterial BP)
  - ICP: $\uparrow$
- Metabolic oxygen requirement: $\downarrow$

**Neuromuscular**
- Relaxes skeletal muscle
- A triggering agent of malignant hyperthermia
Halothane Systemic Effects

Renal

– Renal blood flow, GFR, U/O: ↓
– Part of this can be explained by a fall in arterial BP and CO, preoperative hydration limits these changes

Hepatic

– Hepatic blood flow: ↓

Biotransformation & toxicity

– Oxidized in liver by cytochrome P-450
Halothane Side Effects

**Halothane Hepatitis** – 1/35,000 cases

- oxidized in liver by cytochrome P-450 2E1 to trifluoroacetic acid
- fever, jaundice, hepatic necrosis, death
- immunologically mediated assault
- exposure dependent
Halothane

Halothane Side Effects

Malignant Hyperthermia-- 1/60,000

- **Classic** -- rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, hyperkalemia, DIC
- **physiology**--hypermetabolic state by inhibition of calcium reuptake in sarcoplasmic reticulum
- **Diagnosis** -- previous symptoms, increase CO2, rise in CPK levels, myoglobinuria
- **autosomal dominant** inheritance
- **Treatment** -- early detection, d/c agents, hyperventilate, bicarb, IV dantrolene (2.5 mg/kg), ice packs/cooling blankets, lasix/mannitol/fluids.
- **ICU monitoring**
Halothane

**Contraindications**
- Unexplained liver dysfunction following previous exposure
- Intracranial mass lesion, hypovolemic, severe cardiac disease...
- Malignant hyperthermia

**Drug interactions**
- Myocardial depression is exacerbation by β-blockers and CCB
- With aminophylline → serious ventricular arrhythmia
• Developed in 1963 by Terrell, released for use in 1972
• Stable, nonflammable liquid
• **MAC** 1.68%
• Haloginated methyl ethyl ether.
Enflurane Systemic Effects

**Cardiovascular:**
- Inhibits sympathetic baroreflex response
- Sensitizes myocardium to effects of exogenous catecholamines – arrhythmias
- Potent *inotropic and chronotropic depressant* and decreases systemic *vascular resistance* -- lowers blood pressure and conduction dramatically
Enflurane Systemic Effects

**Respiratory**
- drive is greatly depressed -- central and peripheral responses
- increases dead space
- widens A-a gradient
- produces hypercarbia in spontaneously breathing patient
- bronchodilator
Enflurane Side Effects

- Metabolism one-tenth that of halothane-- does not release quantity of hepatotoxic metabolites
- Metabolism releases fluoride ion-- renal toxicity
- Epileptiform EEG patterns
• Nonflammable, pungent
• MAC of 1.20 %
• Haloginated methyl ethyl ether
• A chemical isomer of enflurane
Isoflurane Systemic Effects

**Cardiovascular**

- Minimal cardiac depression
- Systemic vascular resistance: \( \downarrow \) (Produces most significant reduction in systemic vascular resistance) \( \Rightarrow \) BP: \( \downarrow \)
- Sensitizes myocardium to catecholamines -- less than halothane or enflurane
Isoflurane Systemic Effects

**Respiratory**
- Respiratory depression, minute ventilation: ↓
- Blunt the normal ventilatory response to hypoxia and hypercapnia
- Irritate upper airway reflex
- A good bronchodilator

**Cerebral**
- CBF, ICP: ↑, reversed by hyperventilation
- Cerebral metabolic oxygen requirement: ↓

**Neuromuscular**
- Relaxes skeletal muscle
- A triggering agent of malignant hyperthermia
Isoflurane Systemic Effects

**Renal**
- Renal blood flow, GFR, U/O: ↓

**Hepatic**
- Total hepatic blood flow: ↓
Desflurane

- Structure is similar to isoflurane
- **High vapor pressure**
- requires special vaporizer
- Low solubility → *ultrashort duration of action*
- Moderate potency
- **MAC 6%**
Desflurane systemic effects

Cardiovascular

- Systemic vascular resistance: ↓ → BP: ↓
- CO: unchanged or slightly depressed
- Rapid increases in concentration lead to transient elevation in HR, BP, catecholamine levels
Desflurane systemic effects

Respiratory
- Tidal volume: ↓, respiratory rate: ↑
- Alveolar ventilation: ↓, resting PaCO2: ↑
- Depress the ventilatory response to ↑PaCO2
- Pungency and airway irritation

Cerebral
- Vasodilate cerebral vasculature → CBF, ICP: ↑, lowered by hyperventilation
- Cerebral metabolic rate of oxygen: ↓
Desflurane systemic effects

**Neuromuscular**

- A triggering agent of malignant hyperthermia

**Renal**

- ↓ uO
Desflurane side effects

Degraded by desiccated CO2 absorbent into carbon monoxide
Contraindications

- Severe hypovolemia, malignant hyperthermia, intracranial hypertension
• Non pungency
• Rapid increase in alveolar anesthetic concentration
• Smooth and rapid inhalation inductions in pediatric and adult patients
• MAC 2%
Sevoflurane systemic effects

**Cardiovascular**
- Mildly depress myocardial contractility
- Systemic vascular resistance, arterial BP: ↓
- CO: not maintained well due to little rise in HR

**Respiratory**
- Rapid shallow breathing
- Depress respiration
- Reverse bronchospasm
Sevoflurane systemic effects

**Cerebral**
- CBF, ICP: slight ↑
- Cerebral metabolic oxygen requirement: ↓

**Neuromuscular**
- Adequate muscle relaxation for intubation of children

**Renal**
- Renal blood flow: slightly ↓
- Associated with impaired renal tubule function

**Hepatic**
- Portal vein blood flow: ↓
Sevoflurane side effects

Biotransformation & toxicity

− Degraded by alkali (barium hydroxide lime, soda lime), producing nephrotoxic end products (compound A)
Sevoflurane

Contraindications

- Severe hypovolemia, susceptibility to malignant hyperthermia, intracranial hypertension
• The only inorganic anesthetic gas in clinical use
• Characterized by inert nature with minimal metabolism
• Colorless, odorless, tasteless, and does not burn
• Week Anesthetic good analgesic agent
• Major difference is low potency
• MAC value is 104%
• Needs other agents for surgical anesthesia
• Low blood solubility
Nitrous Oxide

Nitrous Oxide Systemic Effects

**Cardiovascular**

- Depress myocardial contractility
- Arterial BP, CO, HR: unchanged or slightly ↑ due to stimulation of catecholamines
- Constriction of pulmonary vascular smooth muscle → increase pulmonary vascular resistance
- Peripheral vascular resistance: not altered
Nitrous Oxide

Nitrous Oxide Systemic Effects

**Respiratory**
- Respiratory rate: ↑
- Tidal volume: ↓
- Minute ventilation, resting arterial CO2: minimal change
- Hypoxic drive (ventilatory response to arterial hypoxia): ↓

**Cerebral**
- CBF, cerebral blood volume, ICP: ↑
- Cerebral oxygen consumption (CMRO2): ↑
Nitrous Oxide Systemic Effects

**Neuromuscular**
- Not provide significant muscle relaxation
- Not a triggering agent of malignant hyperthermia

**Renal**
- Increase renal vascular resistance
- Renal blood flow, glomerular filtration rate, U/O: ↓

**Hepatic**
- Hepatic blood flow: ↓

**Gastrointestinal**
- Postoperative nausea and vomiting
Nitrous Oxide Side Effects

- Beginning of case: second gas effect
- Inhibits vitamin B-12 metabolism
- Diffusion into closed spaces
Contraindications

- N2O diffuse into the cavity more rapidly than air (principally N2) diffuse out
  
  *Pneumothorax, air embolism, acute intestinal obstruction, intracranial air, pulmonary air cysts, intraocular air bubbles, tympanic membrane grafting*

- Avoided in pulmonary hypertension
Xenon

- Nonexplosive, nonpungent, odorless and chemically inert
- No metabolism and low toxicity
- High cost
- **MAC 71%**
- It has some *analgesic effect*.
- Reduces anesthesia-emergent nausea and vomiting
- Very close to the ‘ideal agent’
- Minimal haemodynamic effects.
- Seems not to trigger malignant hyperthermia.
<table>
<thead>
<tr>
<th>Gas</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>0.75%</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.2%</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.68%</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2%</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6%</td>
</tr>
<tr>
<td>Xenon</td>
<td>71%</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>104%</td>
</tr>
</tbody>
</table>
Cardiovascular Effects

- All cause decrease in BP
- Isoflurane and desflurane cause increased heart rate which may mask depression

Systemic vascular resistance
- Isoflurane causes most decrease
- Halothane and nitrous oxide do not change
Cardiovascular Effects

MAP

- N2O cause no or modest increase
- Halothane cause decrease by cardiac depression
- Others causes decrease by causing decrease SVR

- N2O cause PHTN
Respiratory Effects

- All cause respiratory depression
- Increased respiratory rate
- Decreased tidal volume
- CO$_2$ retention
- Decreased alveolar minute ventilation
- Abolish the hypoxic response at less than half MAC concentrations
- Fantastic bronchodilators by direct action on smooth muscle
CBF:
  – Dose dependent increase in CBF.

O2 requirements:
  – All decrease except N2O

ICP
  – All increase
Renal Effects

- All decrease arterial pressure
- They cause a dose related *decrease in renal blood flow, glomerular filtration rate and urine output.*
- Enflurane .......... nephrotoxic
Hepatic effects

Circulation
– Hepatic blood flow is maintained or decreased

Hepatic function
– Transient increase in liver enzymes
– Halothane induced hepatitis
Skeletal muscle effects

NMJ
- They cause dose dependent potentiation of NMBD (except for N2O)

Malignant hyperthermia
- Except for N2O and Xenon
Obstetric effects

- Produce dose dependent *decrease in uterine contractility* and blood flow
- may cause *uterine atony and PPH*
- They rapidly cross the placenta and *reach the fetus*
<table>
<thead>
<tr>
<th></th>
<th>Nitrous Oxide</th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
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</tr>
<tr>
<td>Blood pressure</td>
<td>N/C</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>N/C</td>
<td>↓</td>
<td>↑</td>
<td>N/C or ↑</td>
<td>↓</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>N/C</td>
<td>N/C</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output²</td>
<td>N/C</td>
<td>↓</td>
<td>N/C</td>
<td>N/C or ↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
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<tr>
<td>Tidal volume</td>
<td>↓</td>
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<td>Respiratory rate</td>
<td>↑</td>
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<td>↑</td>
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<td>↑</td>
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<tr>
<td><strong>Paco₂</strong></td>
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<tr>
<td>Resting</td>
<td>N/C/C</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Challenge</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td><strong>Cerebral</strong></td>
<td></td>
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<tr>
<td>Blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Intracranial pressure</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cerebral metabolic rate</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td>↓</td>
<td>↓</td>
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<tr>
<td><strong>Neuromuscular</strong></td>
<td></td>
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<tr>
<td>Nondepolarizing blockade³</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
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<tr>
<td>Renal blood flow</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Glomerular filtration rate</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Urinary output</td>
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<tr>
<td><strong>Hepatic</strong></td>
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<tr>
<td>Blood flow</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Metabolism⁴</strong></td>
<td>0.004%</td>
<td>15% to 20%</td>
<td>0.2%</td>
<td>&lt;0.1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

¹N/C, no change.
²Controlled ventilation.
³Depolarizing blockade is probably also prolonged by these agents, but this is usually not clinically significant.
⁴Metabolism in the liver.
Figure 29.5  Ranking of clinical properties of volatile agents. D = desflurane, H = halothane, I = isoflurane, S = sevoflurane

<table>
<thead>
<tr>
<th>Property</th>
<th>Worst</th>
<th>Worse</th>
<th>Better</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>D</td>
<td>I</td>
<td>H</td>
<td>S</td>
</tr>
<tr>
<td>Cardiovascular stability</td>
<td>H</td>
<td>I</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>Respiratory irritation</td>
<td>D</td>
<td>I</td>
<td>H</td>
<td>S &amp; D</td>
</tr>
<tr>
<td>Ease of titration</td>
<td>H</td>
<td>I</td>
<td>S</td>
<td>D</td>
</tr>
<tr>
<td>Emergence</td>
<td>H</td>
<td>I</td>
<td>S</td>
<td>D</td>
</tr>
<tr>
<td>Metabolism/toxicity</td>
<td>H</td>
<td>S</td>
<td>I</td>
<td>D</td>
</tr>
</tbody>
</table>

Figure 29.6  Grading of clinical properties of volatile agents. ○○○○ = least effect, ●●●● = maximum effect

<table>
<thead>
<tr>
<th>Property</th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pungency</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>○○○○○</td>
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<tr>
<td>Respiratory irritation</td>
<td>○○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>○○○○○</td>
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<tr>
<td>Respiratory depression</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>○○○○○</td>
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<tr>
<td>Cardiovascular depression</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>○○○○○</td>
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<tr>
<td>Coronary vasodilatation</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>○○○○○</td>
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<tr>
<td>Muscle relaxation</td>
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<td>●○○○○</td>
<td>●○○○○</td>
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<tr>
<td>Intracranial pressure elevation</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>○○○○○</td>
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