INHALATIONAL ANESTHETICS

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What is it?

- Liquids with tendency to vaporise. Liquids at room temperature, which easily vaporise and have a low boiling point. Delivered through respiratory system (Inhaled). Usually halogenated hydrocarbons or ethers.

- Delivered to the patent via a *vaporizer.*

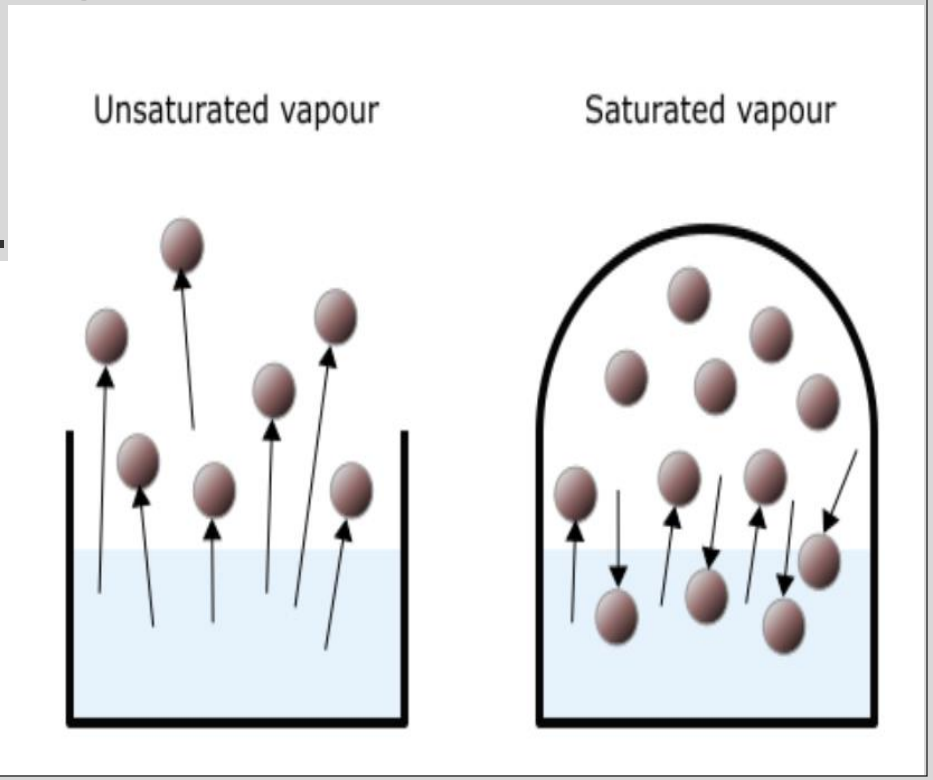
- *Critical temperature*: temperature above which a substance can not be liquified (only gas form). Below this liquids co-exist with their gas form (vapor).

- Ex. Water: 374 C.

Saturated Vapour Pressure (SVP)

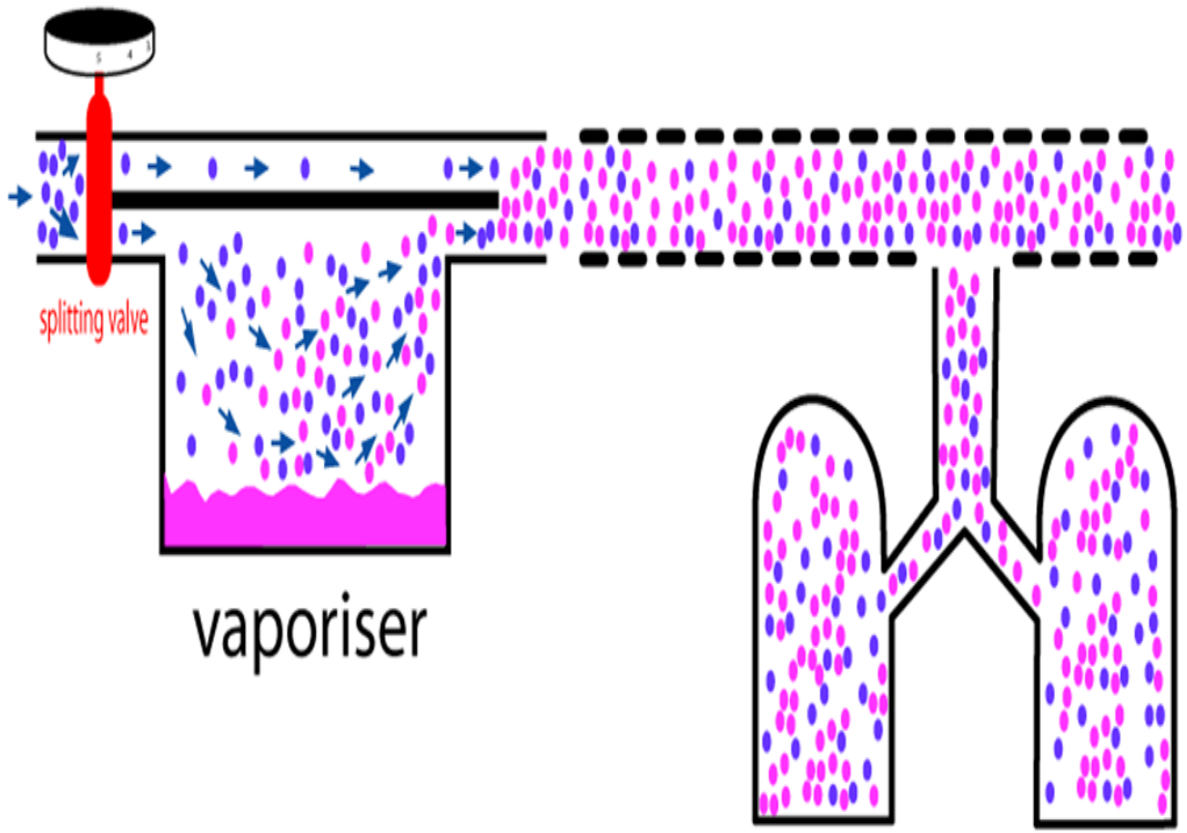
- At any given temperature, there will be a dynamic equilibrium where the number of molecules entering the liquid phase equals those leaving it and the vapour is therefore saturated.
- SVP is the pressure exerted by the vapour phase of a substance when in equilibrium with the liquid phase.

Agent	Boiling point (°C)	SVP at 20°C (kPa)
Desflurane	23	89
Sevoflurane	59	21
Isoflurane	49	32
Halothane	50	33



What is it?


Flow meter
ventilator
bellow
vaporizer
Corrugated tube
APL valve
Scavenging system
Soda lime


splitting valve
vaporiser

Inhalational Anesthetic Agents

Inhalational anesthesia refers to the delivery of *gases or vapors* from the respiratory system to produce or maintain anesthesia

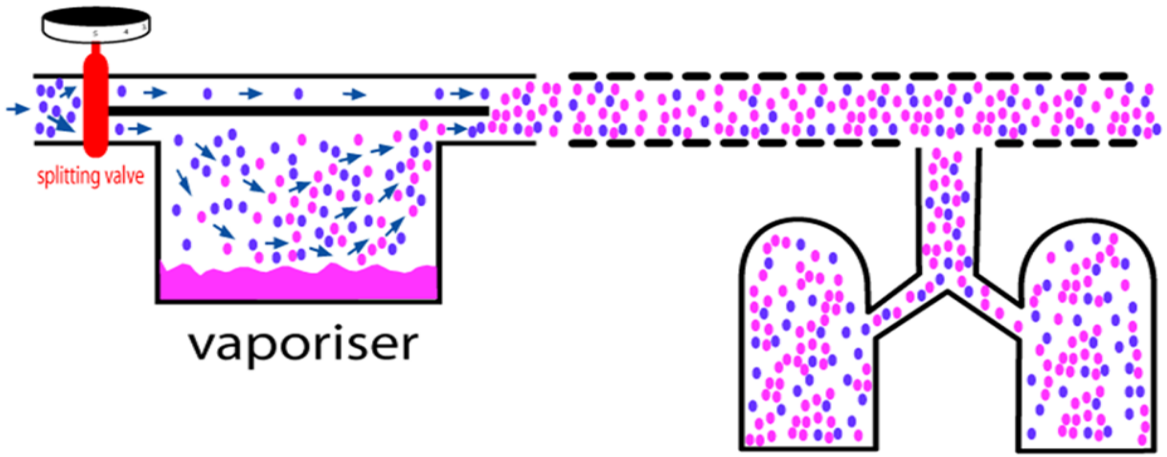
Exposure to the pulmonary circulation allows build up of concentration in arterial blood. It is slower than IV induction.

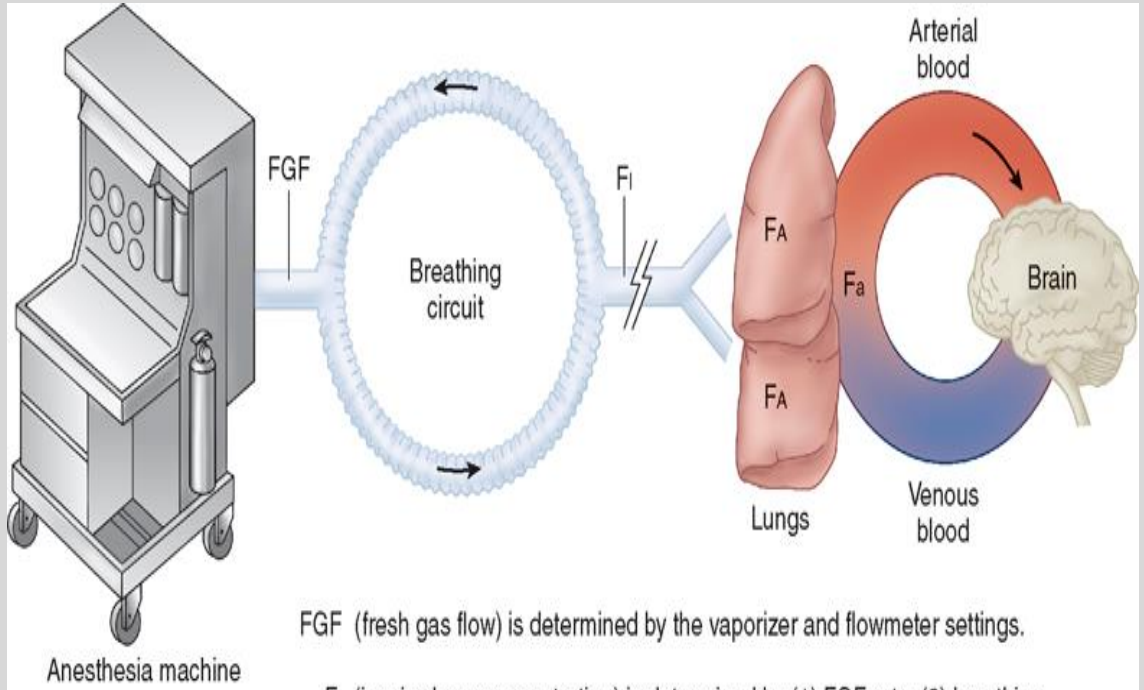
PHARMACOKINETICS OF INHALATION ANESTHETICS

Uptake and Distribution

The depth of general anesthesia depends on the partial pressure (or gas fraction) exerted by the inhalational agent in the patient brain (b).

p_I -> p_A -> p_a -> p_b





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

F_I (inspired gas concentration) is determined by (1) FGF rate; (2) breathing-circuit volume; and (3) circuit absorption.

F_A (aveolar gas concentration) is determined by (1) uptake (uptake = λb/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

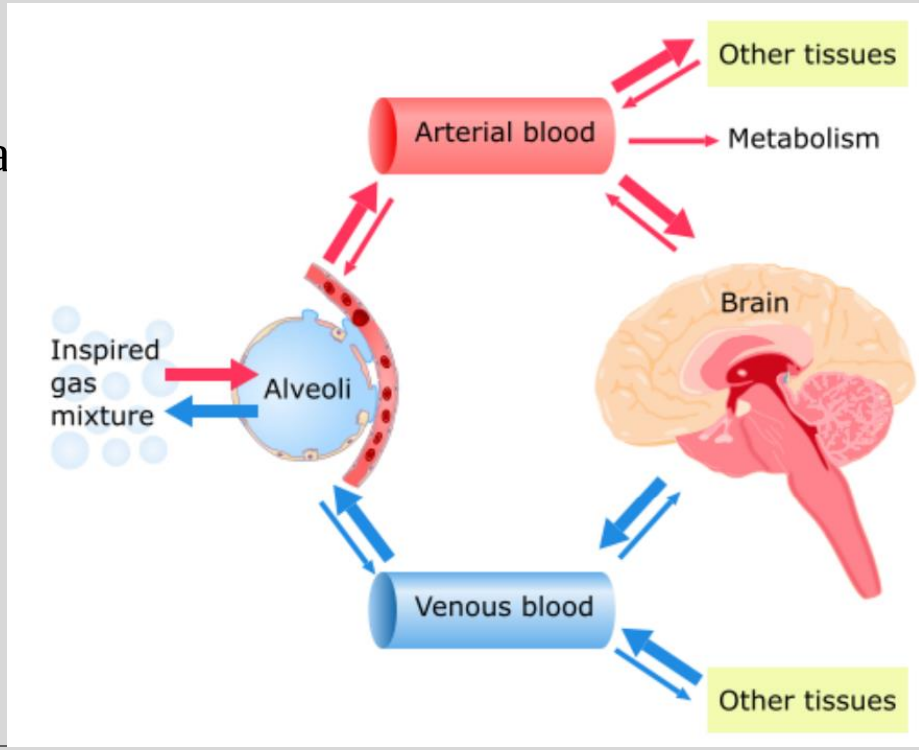
F_a (arterial gas concentration) is affected by ventilation/perfusion mismatching.

Source: Butterworth JF, Mackey DC, Wasnick JD: *Morgan & Mikhail's Clinical Anesthesiology*, 5th Edition: www.accessmedicine.com

Partition Coefficients

- Relative solubilities of an anesthetic in air, blood, and tissues are expressed as partition coefficients.

- Each coefficient is the ratio of the concentrations of the anesthetic vapour in each of two phases at steady state. Steady state is defined a equal partial pressures in the two phases.

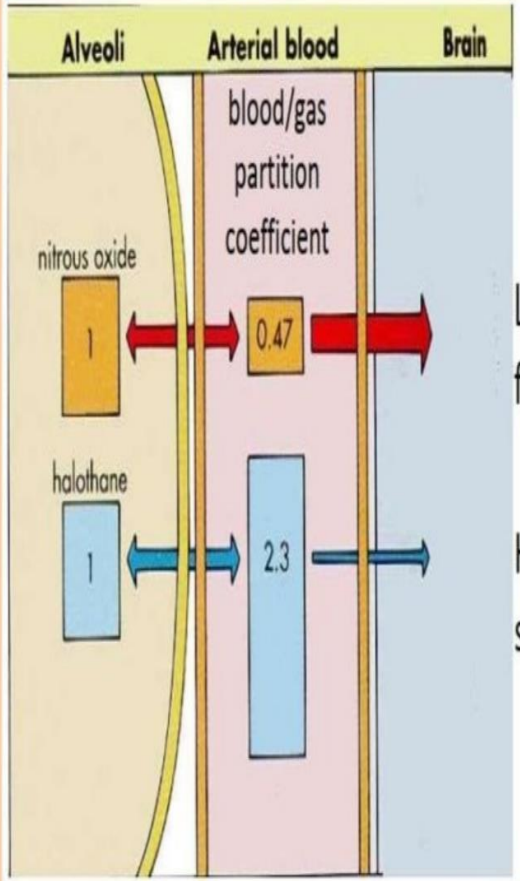


Blood:Gas partition coefficient (λb/g)

- Blood compared to alveoli.

High solubility in blood	Low solubility in blood
High blood/gas partition coefficient	Low blood/gas partition coefficient
- Slow induction and recovery	- Rapid induction and recovery
- Slow adjustment of depth of anaesthesia	- Rapid adjustment of depth of anaesthesia
(Blood acts as a reservoir (store) for the drug so it doesn't enter or leave the brain readily until the blood reservoir is filled)	(Because the blood reservoir is small the anaesthetic is available to pass into/out of the brain quicker)

Agent	Blood:gas coefficient at 37°C
Desflurane	0.45
Sevoflurane	0.65
Isoflurane	1.4
Halothane	2.3
N_2O	0.47



MORE POTENT?

LOW solubility in blood= fast induction and recovery

HIGH solubility in blood= slower induction and recovery

Oil:Gas partition coefficient

- Brain compared to blood.
- related to lipid solubility and potency.
- Potency is measured by MAC.

Agent	MAC (%)
Desflurane	6.6
Sevoflurane	2.0
Isoflurane	1.1
Halothane	0.75
N_2O	104

Minimum Alveolar Concentration

- Partial pressure of gas in the alveolus which will equilibrate with concentration in the brain is the most important factor

- **Minimal alveolar concentration (MAC) of inhalational agent that prevent movement in 50% of the patients in response to surgical stimulation (skin incision)**
- Equivalent to ED_{50}

- It provides a standard way of estimating anesthetic depth and comparing one agent to another.

Minimum Alveolar Concentration

- MAC values are additive between different inhalational agents

- It is inversely proportional to potency (lipid solubility).
  - MAC 0.3 – 0.4 = MAC-awake = awakening form anesthesia in absence of other agents
  - MAC 1.3 = ED95 = blunting of response in 95% of patients
  - MAC 1.5 = MACBAR Blocking of adrenergic response to surgical stimulus

Minimum Alveolar Concentration

The rationale for this measure of anesthetic potency is,

- alveolar concentration can be *easily measured*
- near *equilibrium*, alveolar and brain tensions are virtually equal

Factors which support the use of this measure are,

- MAC is invariant with a variety of noxious stimuli
- individual variability is small
- sex, height, weight & anaesthetic duration do not alter MAC
- doses of anaesthetics in MAC's are additive

Factors affecting MAC

PHYSIOLOGIC & PHARMACOLOGIC FACTORS AFFECTING MAC

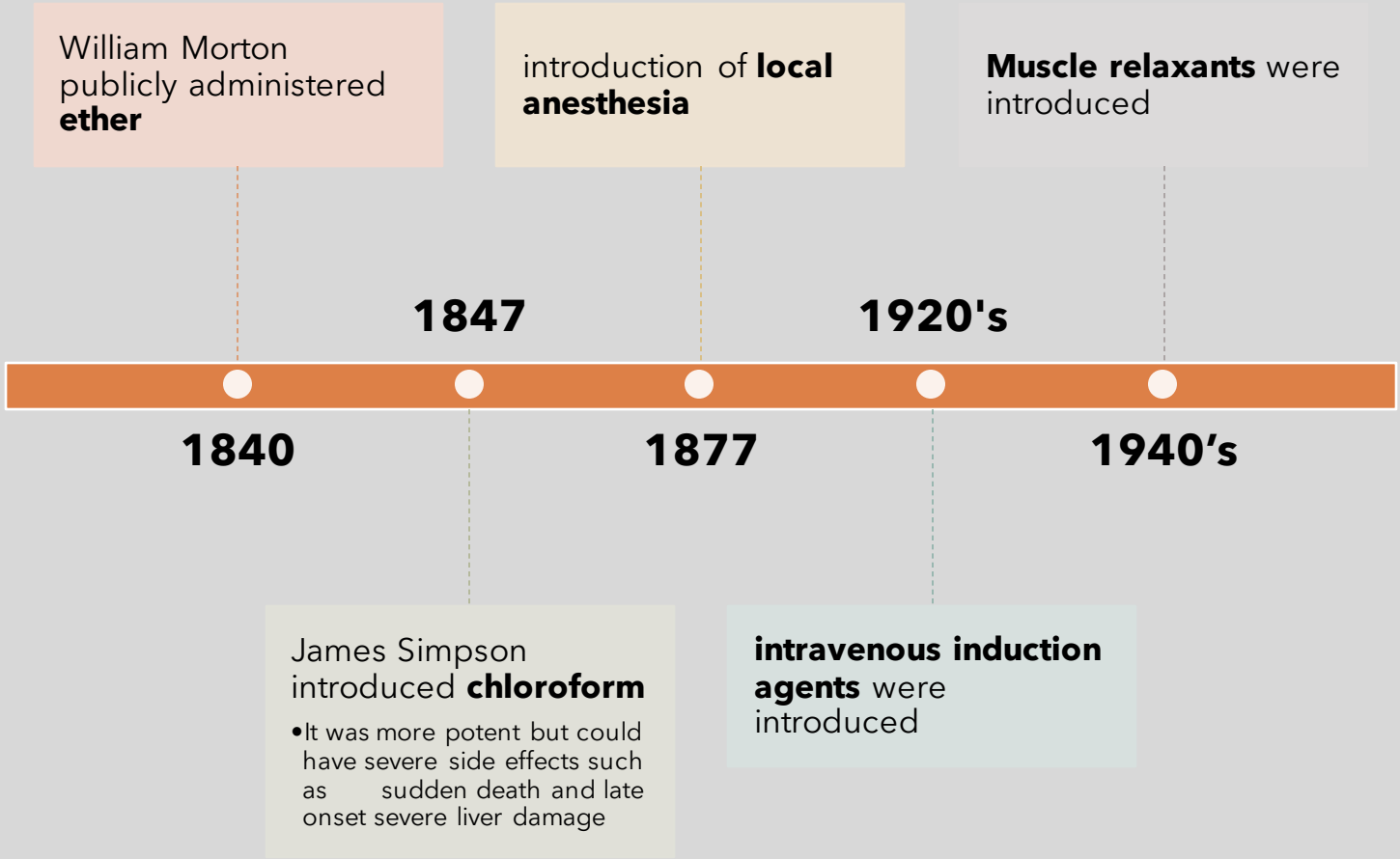
Increase in MAC:-

- 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
- Hypoxaemia (PaO_2< 38mmHg)
- Hypotension(<40 mm hg- MAP)
- Anaemia (Haematocrit< 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

History of anesthesia drugs



Advantages of inhalational anesthesia

- Less traumatic (children, needle phobic adults, adults with learning disability).
- Difficult IV access.
- Spontaneous ventilation and airway tone.
- Titration of dept of anaesthesia.
- Bronchodilatation.
- Brief anaesthesia.

Disadvantages of inhalational anesthesia

- Smell.
- Airway irritation.
- Excitation phase of anaesthesia.
- Cardiac and respiratory depression.
- Theatre pollution.
- Malignant hyperthermia.

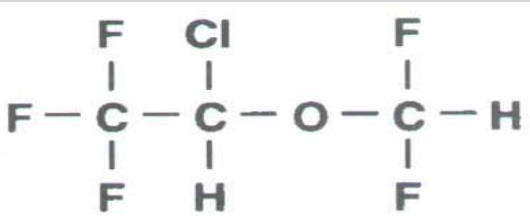
MOA (Current Working Model)

- Mechanism of action is complex, and agents act at multiple specific target sites; likely a combination of membrane proteins, receptors and channels. (Multisite Hypothesis).
- Impair neuronal activity in different parts of the brain, namely the fronto-parietal cortices and the thalamus.
- Shown to affect receptors of GABA-A (+), NMDA (+), glycine (+), nACh (-), 5-HT3 (-), Glutamate (-).

Ideal inhalational agents

- Low blood:gas partition coefficient allowing rapid induction
- Non-flammable
- Non-pungent (or odourless)
- Non-irritant to the airway
- Non-cardiac depressant
- Non-respiratory depressant
- Non-toxic to liver and kidneys

Isoflurane



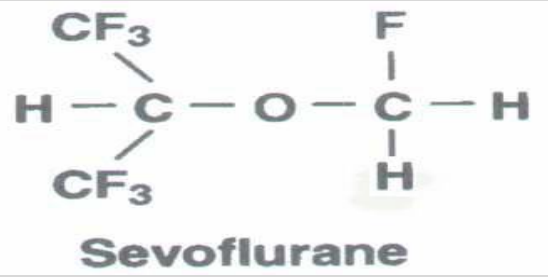
Isoflurane

- Haloginated methyl ethyl ether.
- Nonflammable, pungent (not used for induction).

Physical properties	
MAC	1.2 %
Vaporiser concentration range	0-5%

Physiological effects	
CNS	↑ CBF, ICP at >> 1 MAC : reversed by hyperventilation ↓ Cerebral metabolic oxygen requirement
CVS	Most significant reduction in SVR → ↓ BP
Respiratory	↓ Minute ventilation, Blunt the normal ventilatory response to hypoxia and hypercapnia, Irritate upper airway reflex, a good bronchodilator
Neuromuscular	Relaxes skeletal muscle
Renal	↓ Renal blood flow: ↓ GFR and U/O
Hepatic	↓ Total hepatic blood flow

Sevoflurane



- Fluorinated methyl-isopropyl ether.
- Non pungency and relatively low MAC → most common for inhalational induction.

Physical properties	
MAC	2.0%
Vaporiser concentration range	0-8 %

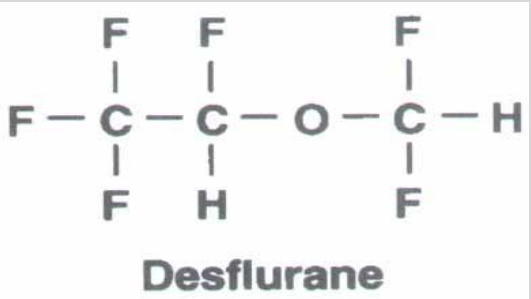
Physiological effects	
CVS	Mildly depress myocardial contractility ↓ Systemic vascular resistance: ↓ arterial BP small rise in HR: CO not maintained well
Respiratory	Rapid shallow breathing, Depress respiration, Reverses bronchospasm
Cerebral	↑ CBF and ICP, ↓ Cerebral metabolic oxygen requirements
Neuromuscular	Adequate muscle relaxation for intubation of children
Renal	Slight ↓ Renal blood flow Associated with impaired renal tubule function
Hepatic	↓ Portal vein blood flow

Sevoflurane

Biotransformation & toxicity

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

Desflurane



- Halogenated Ether.
- High SVP which requires special vaporizer.
- Low solubility → *rapid onset and offset.*

Physical properties	
MAC	6 %
Vaporiser concentration range	0-18%

Physiological effects	
CNS	↑ CBF, ICP:, lowered by hyperventilation ↓ Cerebral metabolic rate of oxygen
CVS	↓ Systemic vascular resistance: ↓ BP, CO: unchanged or slightly depressed (inc. in HR). Rapid increases in concentration lead to transient elevation in HR, BP, catecholamine levels
Respiratory	↓ Tidal volume:, ↑ respiratory rate: ↓ Alveolar ventilation: ↑ resting PaCO2, Depress the ventilatory response to ↑PaCO2 Pungency and airway irritation

Desflurane

- Degraded by desiccated CO2 absorbent into **carbon monoxide**

Halothane

- Halogen substituted ethane.
- Nonflammable. Sensitive to light (dark bottles).
- Most potent inhalational anesthetic
- Very soluble in blood and adipose → Prolonged emergence

Physical properties	
MAC	0.75 %
Vaporiser concentration range	0-5 %

Physiological effects	
CVS	Direct myocardial depression → dose-dependent reduction of arterial BP, SVR: unchanged, Coronary artery vasodilator, but coronary blood flow↓ due to systemic BP↓ Blunt the reflex: hypotension inhibits baroreceptors in aortic arch and carotid bifurcation → vagal stimulation↓→ compensatory rise in HR Sensitizes the heart to the arrhythmogenic effects of epinephrine
CNS	↑ CBF, Blunt autoregulation, ↑ ICP, ↓ Metabolic oxygen requirement

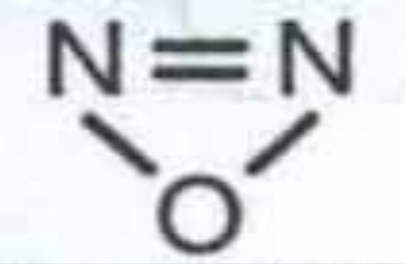
Respiratory	Rapid, shallow breathing: ↓ Alveolar ventilation and ↑ resting $PaCO_2$, Hypoxic drive: severely depressed A potent bronchodilator, reverses asthma-induced bronchospasm
Neuromuscular	Relaxes skeletal muscle
Renal	↓ Renal blood flow: ↓ GFR, U/O
Hepatic	Hepatic blood flow: ↓

Halothane

Halothane Hepatitis" -- 1/35,000 cases

- Oxidized in liver by cytochrome P-450 2EI to trifluroacetic acid
- Increased serum alanine and aspartate transferase (ALT and AST) , elevated bilirubin (leading to jaundice), and encephalopathy.
- Immunologically mediated reaction, anti-hepatocytes antibodies.
- Hypoxic model.
- Exposure dependent

Nitrous Oxide



Physical properties	
MAC	105 %

- The only inorganic anesthetic gas in clinical use.
- Inert nature with minimal metabolism.
- Colorless, odorless, tasteless. Week Anesthetic good analgesic agent.

Physiological effects	
CNS	↑ CBF, cerebral blood volume, ICP, ↑ Cerebral oxygen consumption
CVS	Depress myocardial contractility but 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
Respiratory	↑ Respiratory rate and↓Tidal volume: minimal change in minute ventilation and resting arterial CO2, ↓ Hypoxic drive

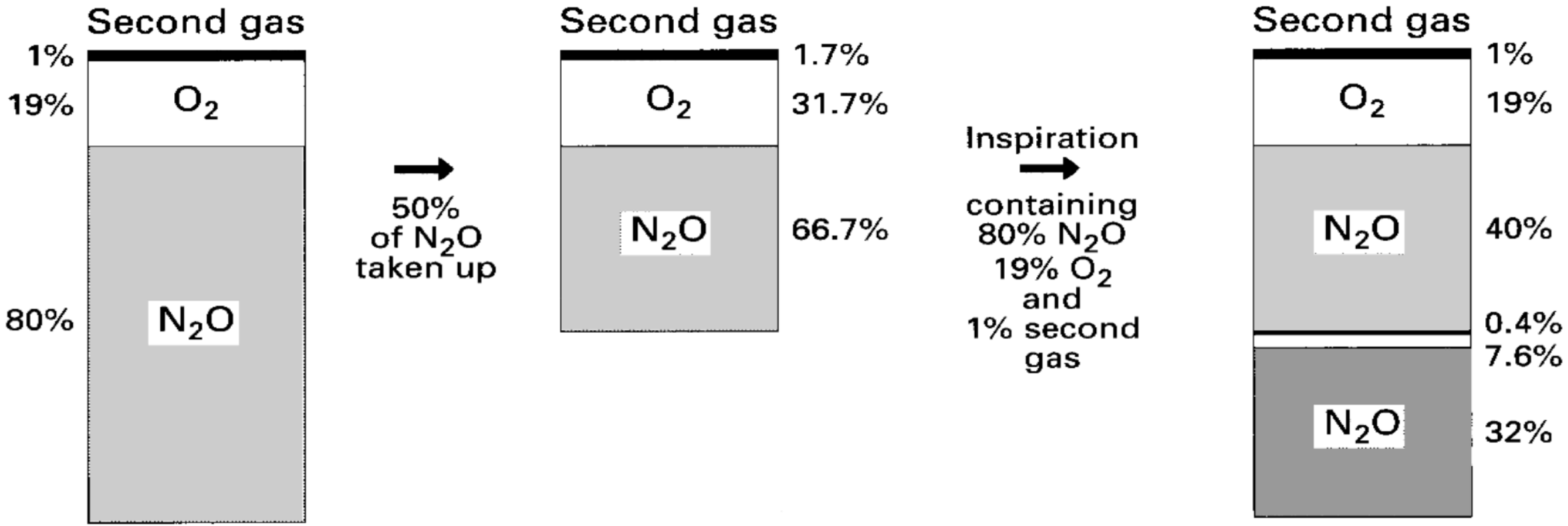
Neuromuscular	Not provide significant muscle relaxation
Renal	↓ Renal blood flow: ↓ GFR and U/O
Hepatic	↓ Total hepatic blood flow
GIT	Increase nausea and vomiting

Nitrous Oxide

- Does not trigger malignant hyperthermia
- Inhibits vitamin B-12 metabolism
- Diffusion into closed spaces

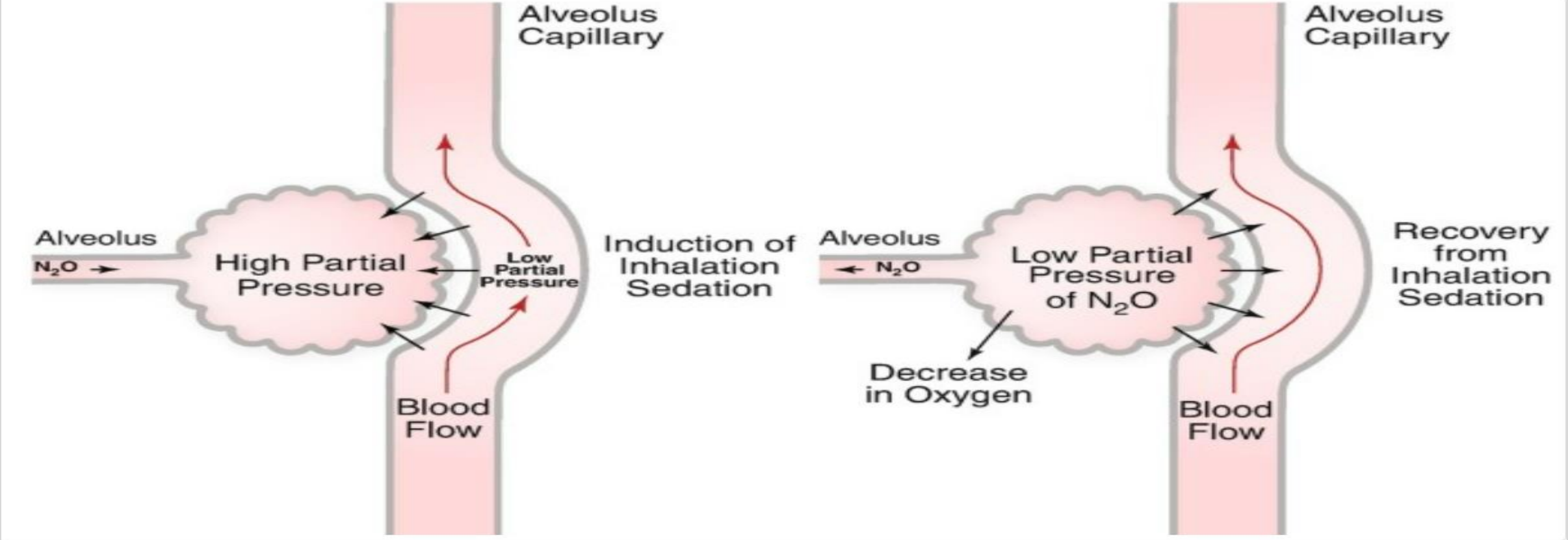
Nitrous Oxide second gas effect (concentration effect)

- Beginning of case: second gas effect



Nitrous Oxide Diffusion hypoxia

- At the end of the case: diffusion hypoxia



Nitrous Oxide

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

Obstetric effects (all previous inhalational)

- Dose dependent decrease in uterine contractility and blood flow
- May cause uterine atony and PPH
- They rapidly cross the placenta and reach the fetus

Xenon

- Nonexplosive, non-pungent, 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 hemodynamic effects.
- Seems not to trigger malignant hyperthermia.

Malignant Hyperthermia

- **Genetic hypermetabolic disease (AD),** commonly appear with exposure to inhaled general anesthetics (except for N2O) or succinylcholine (triggering agents).
  - Gene for the ryanodine (Ryr1) receptor located on chromosome 19.
  - 1:15000 paediatrics to 1:40000 in adults
  - Induction, intraoperatively, or postoperatively
  - 50% occur on second exposure
  - Adult: Young males

- **Pathophysiology**: Uncontrolled sudden release of calcium from the sarcoplasmic reticulum skeletal muscles → increase in intracellular calcium → removes the inhibition of troponin → sustained muscle contraction.
- Markedly increase ATP activity → uncontrolled hypermetabolic state → increased oxygen consumption (hypoxia) and CO2 production (hypercapnia), severe lactic acidosis and hyperthermia.

Malignant Hyperthermia

Markedly increased metabolism
- Increased carbon dioxide production
- Increased oxygen consumption
- Reduced mixed venous oxygen tension
- Metabolic acidosis
- Cyanosis
- Mottling

Increased sympathetic activity
- Tachycardia
- Hypertension
- Arrhythmias

Muscle damage
- Masseter spasm
- Generalized rigidity
- Increased serum creatine kinase
- Hyperkalemia
- Hypernatremia

Hyperphosphatemia

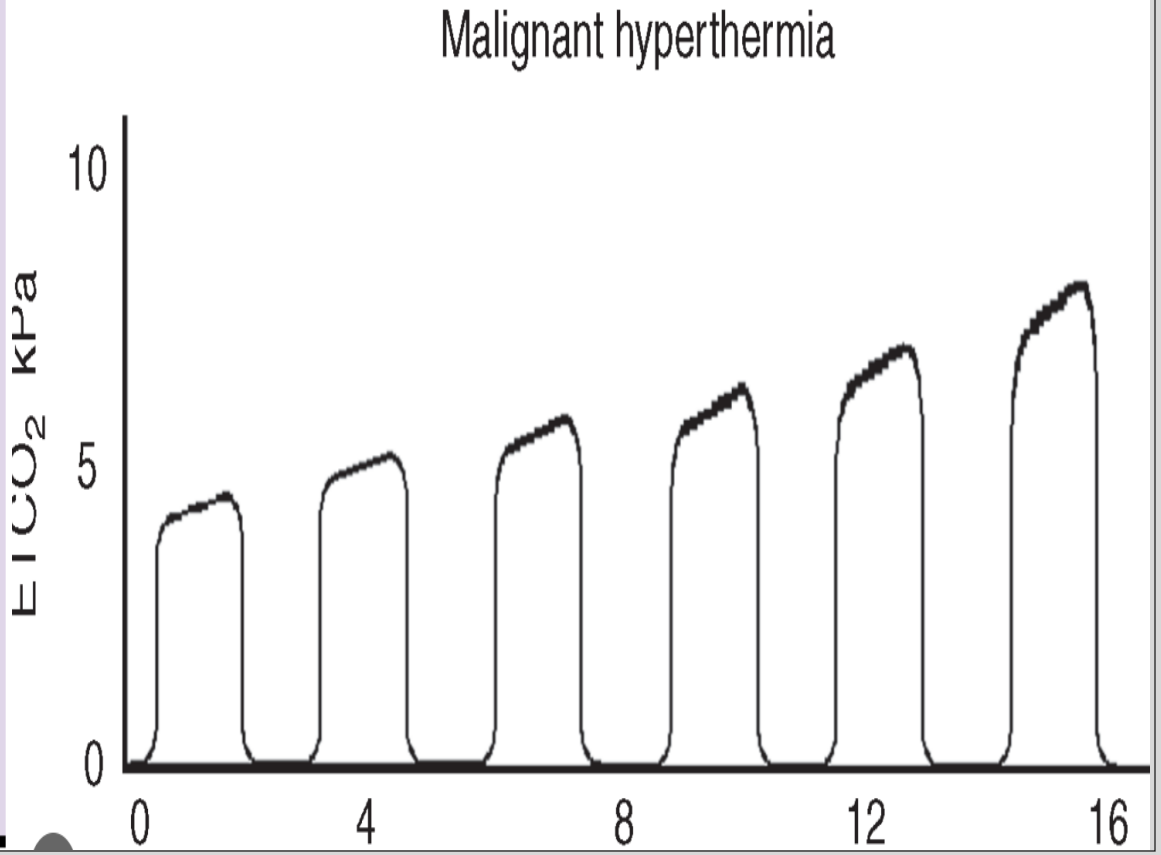
Myoglobinemia

Myoglobinuria

Hyperthermia

Fever

Sweating



Malignant Hyperthermia treatment and diagnosis

1. Discontinue volatile anesthetic and succinylcholine. Notify the surgeon. Call for help.
2. Mix dantrolene sodium with sterile distilled water, and administer 2.5 mg/kg intravenously as soon as possible.
3. Administer bicarbonate for metabolic acidosis.
4. Institute cooling measures (lavage, cooling blanket, cold intravenous solutions).
5. Treat severe hyperkalemia with dextrose, 25–50 g intravenously, and regular insulin, 10–20 units intravenously (adult dose).
6. Administer antiarrhythmic agents if needed despite correction of hyperkalemia and acidosis.
7. Monitor end-tidal CO_2 tension, electrolytes, blood gases, creatine kinase, serum myoglobin, core temperature, urinary output and color, and coagulation status.

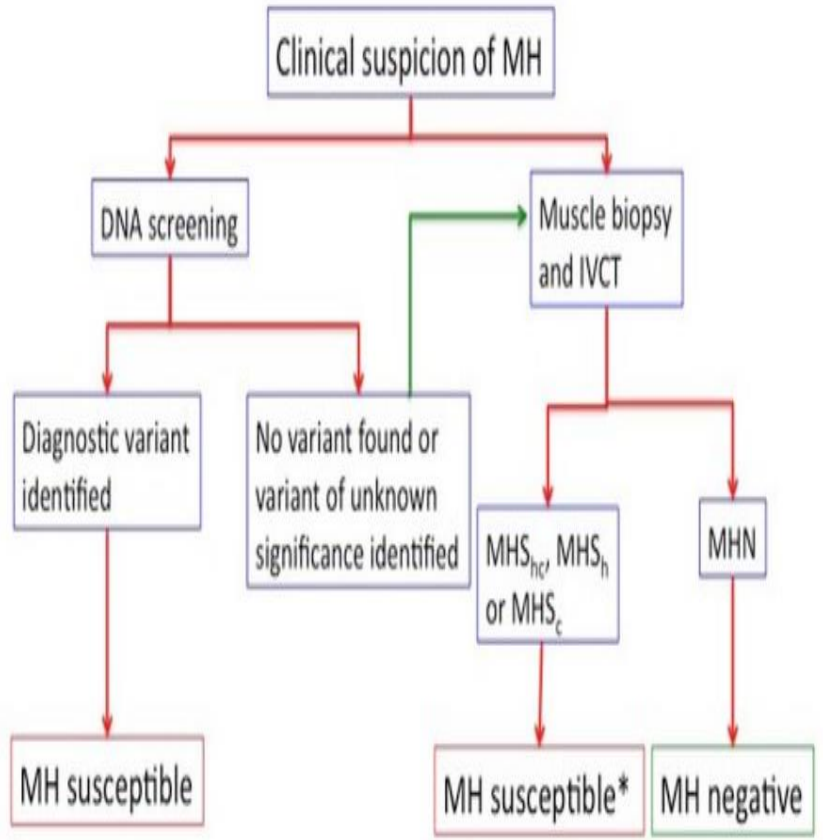


TABLE 8–6 Clinical pharmacology of inhalational anesthetics.

	Nitrous Oxide	Halothane	Isoflurane	Desflurane	Sevoflurane
Cardiovascular					
Blood pressure	N/C[1]	↓↓	↓↓	↓↓	↓
Heart rate	N/C	↓	↑	N/C or ↑	N/C
Systemic vascular resistance	N/C	N/C	↓↓	↓↓	↓
Cardiac output[2]	N/C	↓	N/C	N/C or ↓	↓
Respiratory					
Tidal volume	↓	↓↓	↓↓	↓	↓
Respiratory rate	↑	↑↑	↑	↑	↑
$Paco_2$					
Resting	N/C	↑	↑	↑↑	↑
Challenge	↑	↑	↑	↑↑	↑
Cerebral					
Blood flow	↑	↑↑	↑	↑	↑
Intracranial pressure	↑	↑↑	↑	↑	↑
Cerebral metabolic rate	↑	↓	↓↓	↓↓	↓↓
Seizures	↓	↓	↓	↓	↓
Neuromuscular					
Nondepolarizing blockade[3]	↑	↑↑	↑↑↑	↑↑↑	↑↑
Renal					
Renal blood flow	↓↓	↓↓	↓↓	↓	↓
Glomerular filtration rate	↓↓	↓↓	↓↓	↓	↓
Urinary output	↓↓	↓↓	↓↓	↓	↓
Hepatic					
Blood flow	↓	↓↓	↓	↓	↓
Metabolism[4]	0.004%	15% to 20%	0.2%	<0.1%	5%

[1]N/C, no change.
[2]Controlled ventilation.
[3]Depolarizing blockage is probably also prolonged by these agents, but this is usually not clinically significant.

Figure 29.5 Ranking of clinical properties of volatile agents. D = desflurane, H = halothane, I = isoflurane, S = sevoflurane

	Worst	Worse	Better	Best
Induction	D	I	H	S
Cardiovascular stability	H	I	D	S
Respiratory irritation	D	I		H & S
Ease of titration	H	I	S	D
Emergence	H	I	S	D
Metabolism/toxicity	H	S	I	D

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

	Halothane	Isoflurane	Desflurane	Sevoflurane
Pungency	●○○○	●●●○	●●○○	○○○○
Respiratory irritation	○○○○	●●○○	●●●○	○○○○
Respiratory depression	●●○○	●●●○	●●●●	●●○○
Cardiovascular depression	●●●○	●●○○	●○○○	●○○○
Coronary vasodilatation	●○○○	●●○○	●○○○	●●○○
Muscle relaxation	●●○○	●●●○	●●●○	●●●○
Intracranial pressure elevation	●●●●	●●○○	●●●○	●●○○

QUESTIONS !!!