INHALATIONAL ANESTHESIA

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General Anesthesia

- Global but reversible depression of CNS function
- Components of anesthetic state:
  - Amnesia
  - Immobility in response to noxious stimuli
  - Attenuation of autonomic responses
  - Analgesia
  - unconsciousness

Inhaled anesthetics

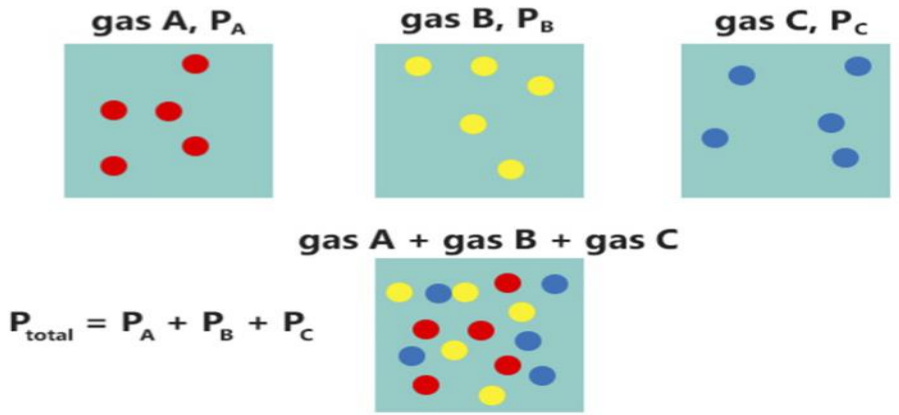
- Administered as gases
- Historically, ether and chloroform were in use
- Nitrous oxide was first successfully used gas, still in use
- Volatile liquids administered as vapors
  - Halothane, enflurane, methoxyflurane (rarely used)
  - Isoflurane, desflurane, sevoflurane
- All are halogenated ethers with flourine (to reduce flammability) except N2O and halothane

Table 1 – Inhalation anesthetic agents (Year available for clinical use).

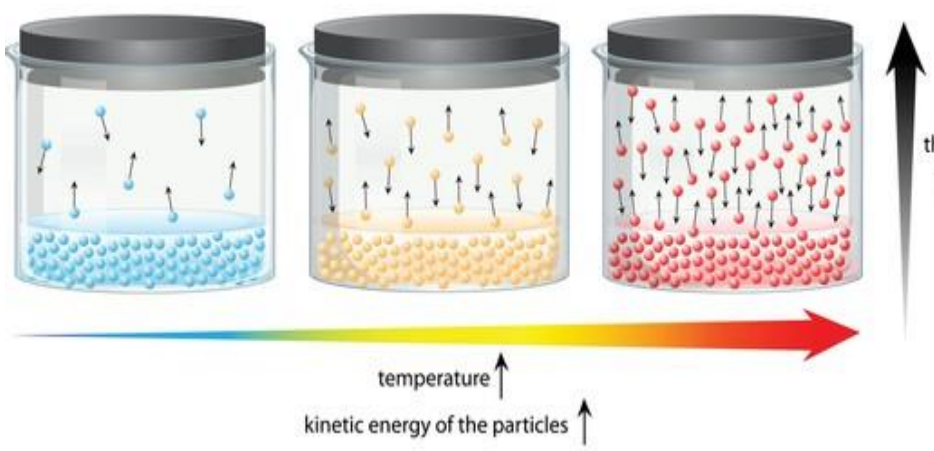
Agents in clinical use	New Agents	Agents of historical interest
Halothane (1956)	Desflurane (1992)	Chloroform (1847)
Isoflurane (1981)	Sevoflurane (1994)	Cyclopropane (1925)
Enflurane (1973)	Xenon (1997)	Diethyl ether (1846)
Methoxyflurane (1960)		Fluroxene (1951)
Nitrous Oxide (1844)		Trichlorethylene (1930)

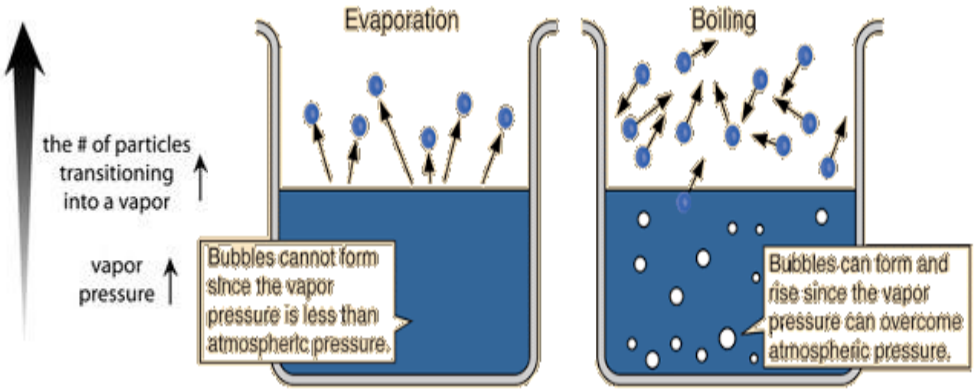
Terminologies

- Partial pressure



- Vapor pressure and Boiling point

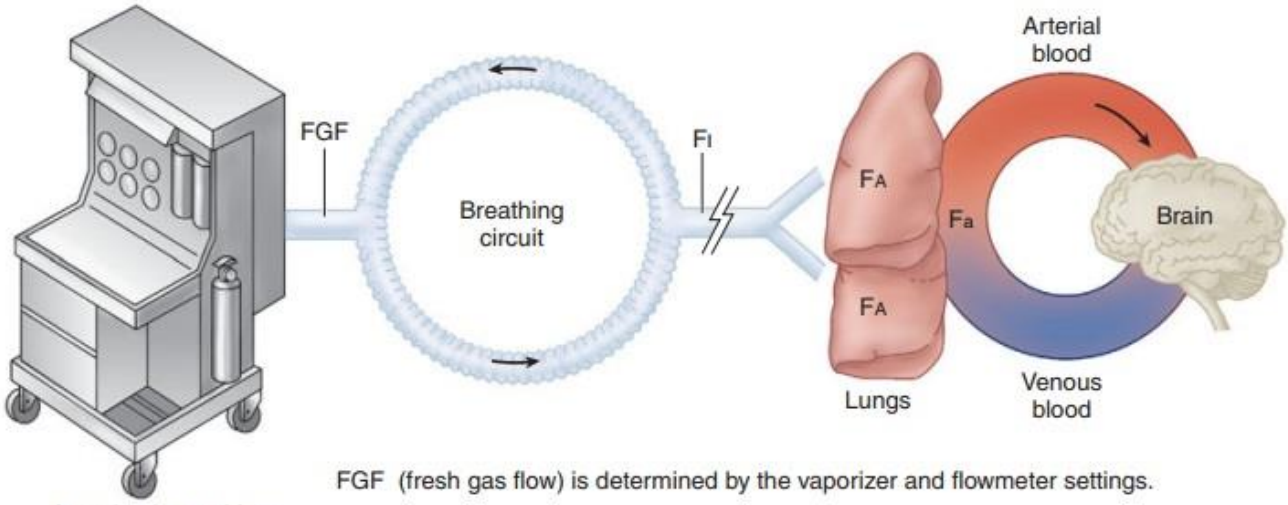




Physical properties

Anesthetic Agent	Molecular Weight (g)	Vapor Pressure mmHg at 20 ºC	Boiling Point ºC
Desflurane	168	600	22.8
Sevoflurane	200	170	58.5
Nitrous oxide	44	-	-
Isoflurane	184.5	240	48.5
Enflurane	184.5	172	56.2
Halothane	197.4	244	50.2

Pharmacokinetics



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

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

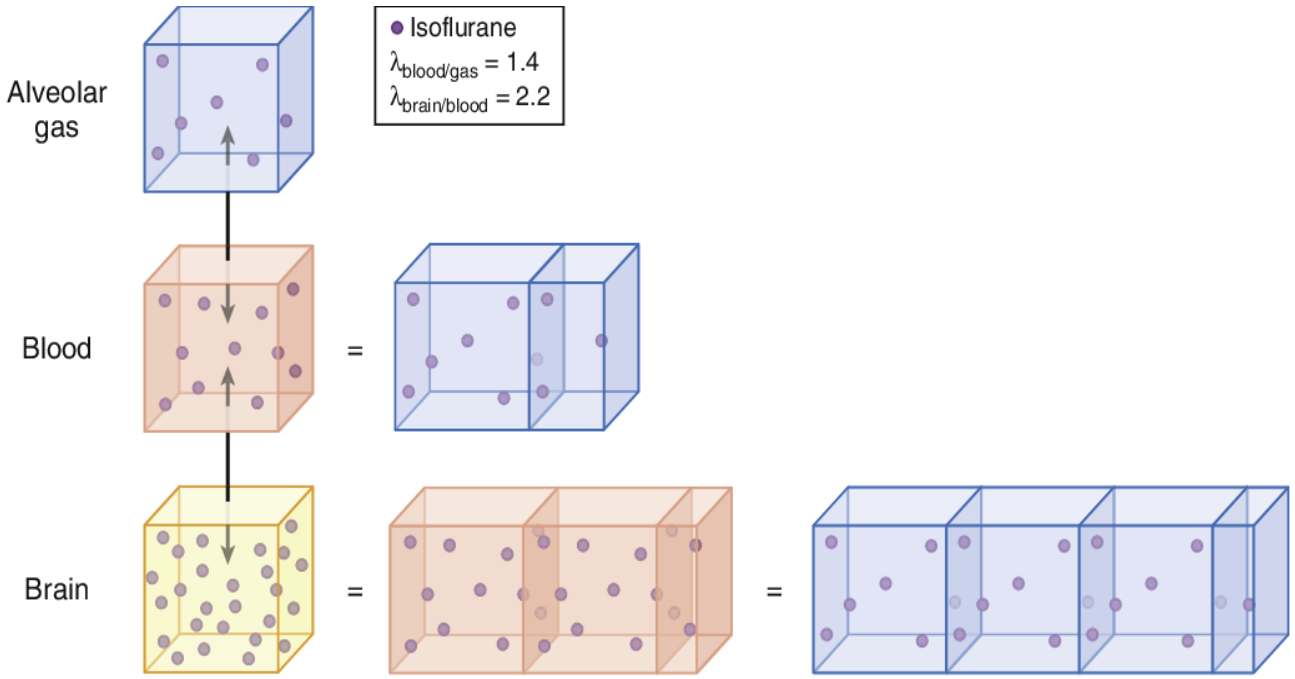
FA (aveolar gas concentration) is determined by (1) uptake (uptake = λb/g x C(A-V) x Q); (2) ventilation; and (3) the concentration effect and second gas effect:
- a) concentrating effect
- b) augmented inflow effect

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

FIGURE 8–1 Inhalation anesthetic agents must pass through many barriers between the anesthesia machine and the brain.

Partition coefficient

- Ratio of concentration of anesthetics in two phases at equilibrium (partial pressure is equal)
- Measures relative solubilities of anesthetic in two phases

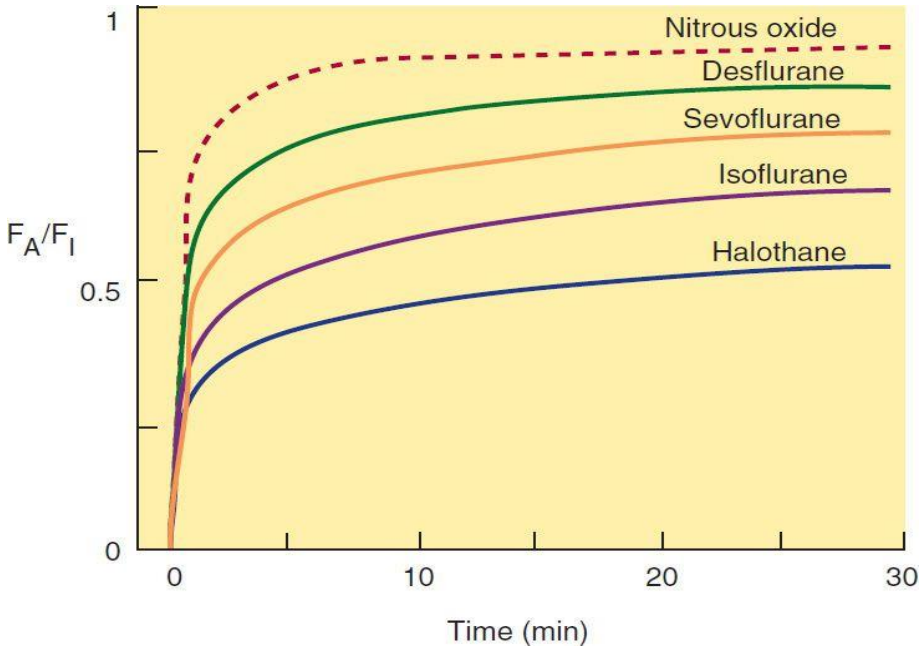


Blood gas solubility

Anesthetic Agent	Blood/Gas Coefficient	Brain/Gas
Desflurane	0.45	1.3
Sevoflurane	0.65	1.7
Nitrous oxide	0.47	1.1
Isoflurane	1.4	1.6
Enflurane	1.8	1.3
Halothane	2.4	1.9

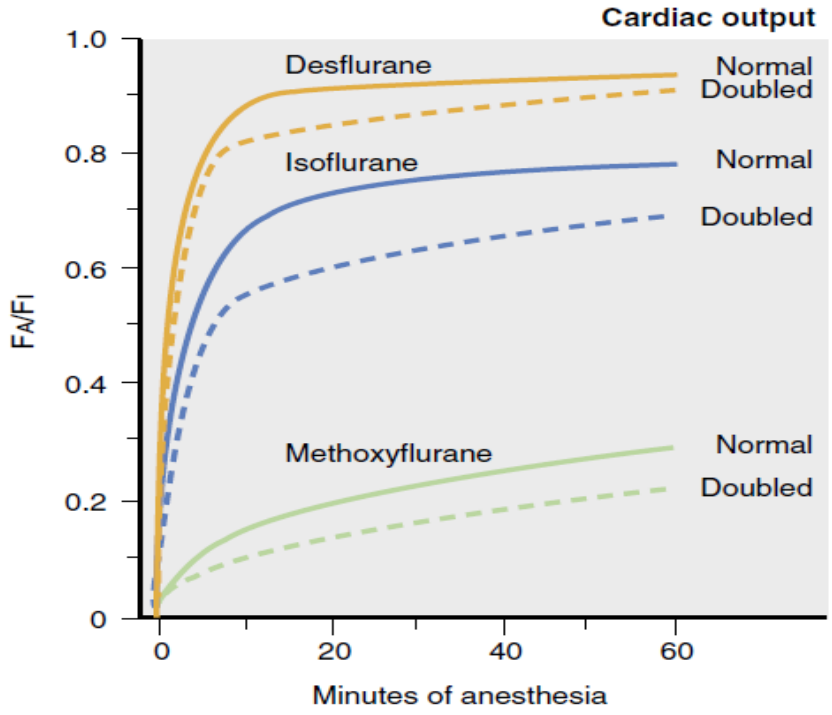
Inhaled anesthetic - Uptake

- Uptake
  - Blood gas solubility: Higher the solubility, longer time to achieve equilibrium and achieve desired concentration in brain, hence delay in induction
  - Faster FA rises to FI, faster the induction



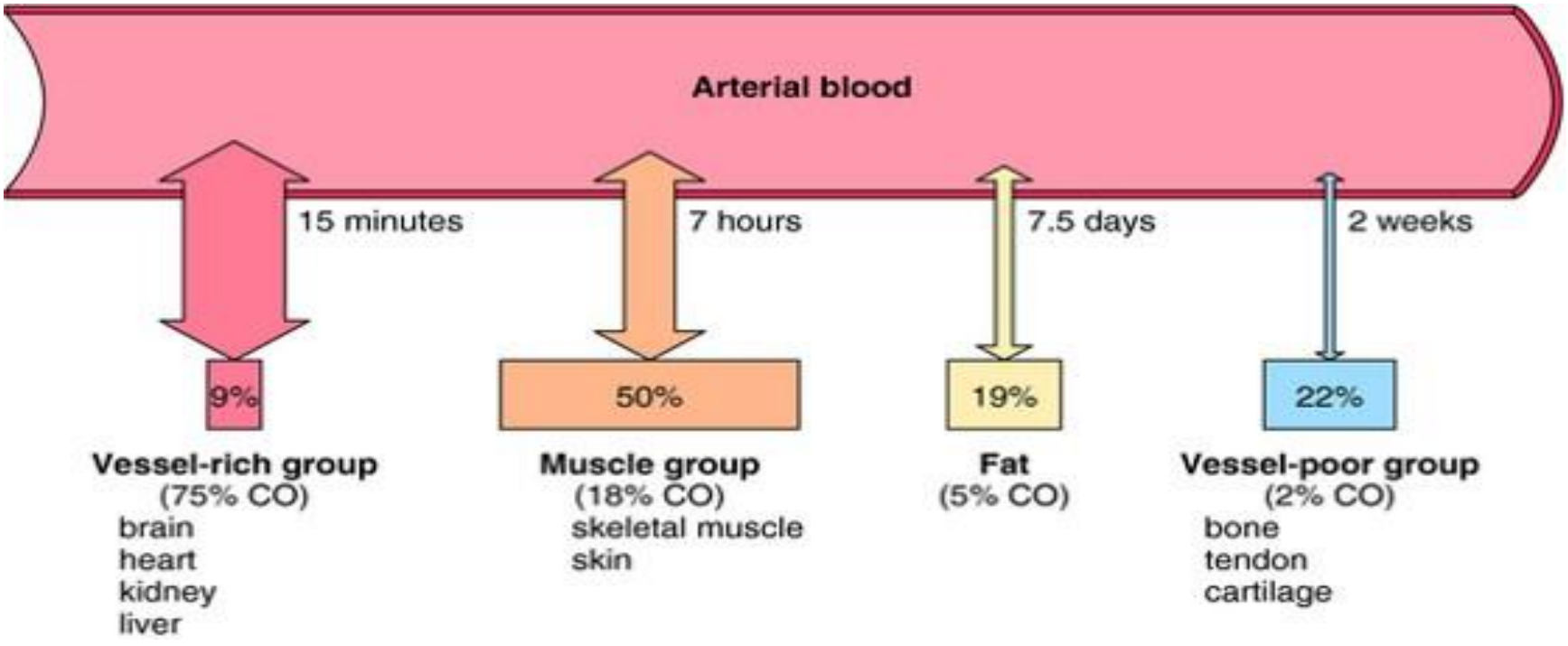
Inhaled anesthetic - Uptake

- Cardiac output
  - Increased pulmonary blood flow causes increased uptake, in turn decrease in alveolar concentration leads to delayed induction



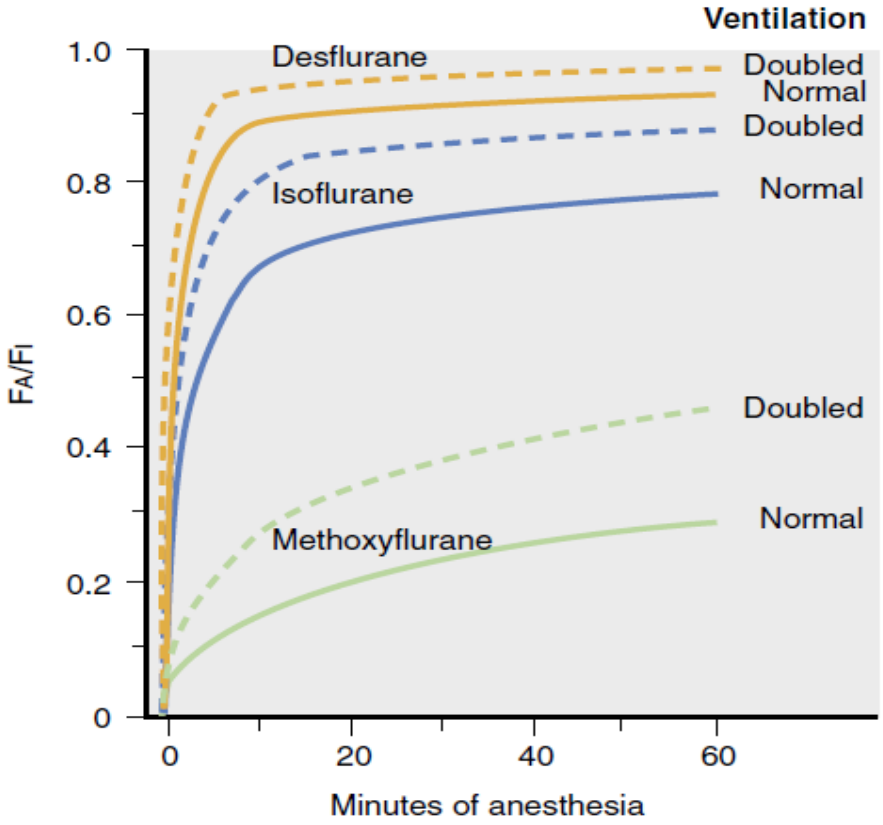
Uptake

- Partial pressure difference between alveolar gas and venous blood depends on tissue solubility, blood flow and partial pressure difference between blood and tissues



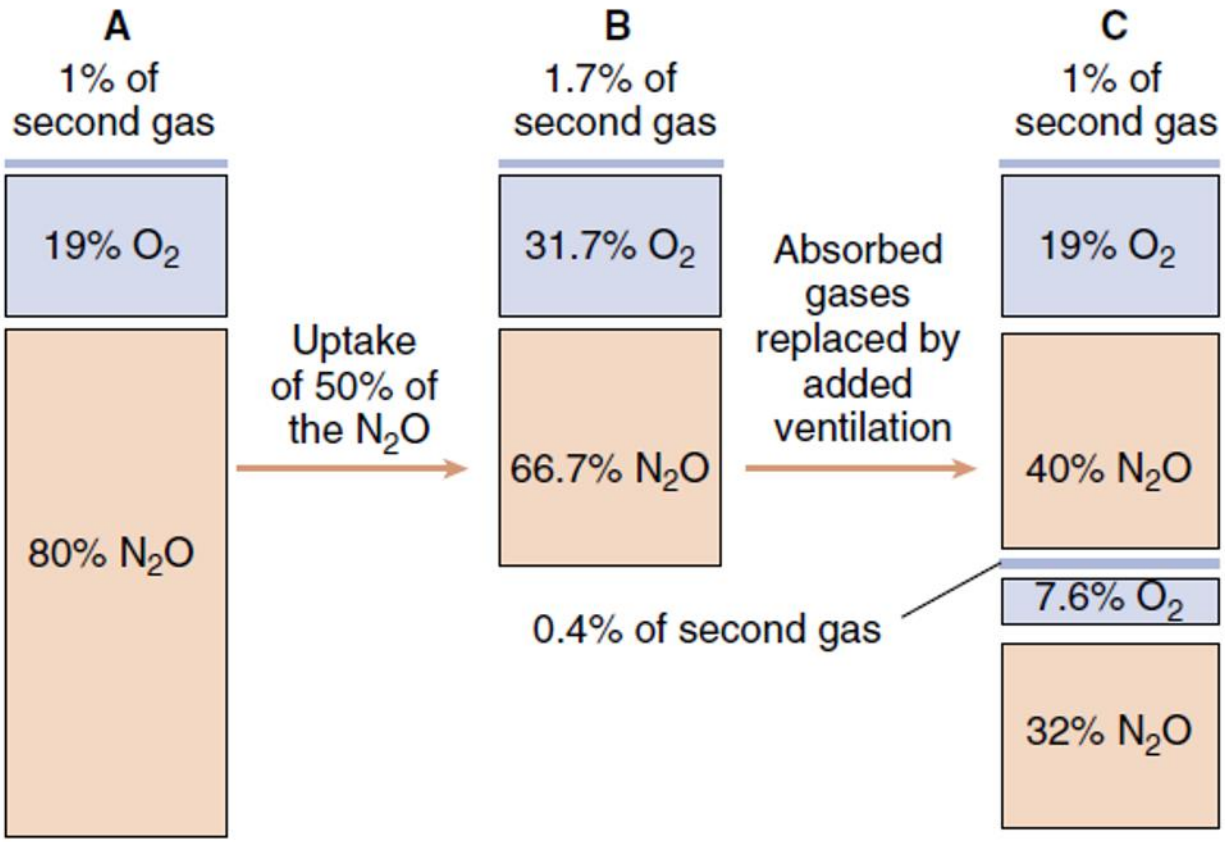
Inhaled anesthetic - Uptake

- **Ventilation:** higher the minute ventilation, rapid rise in FA and faster induction



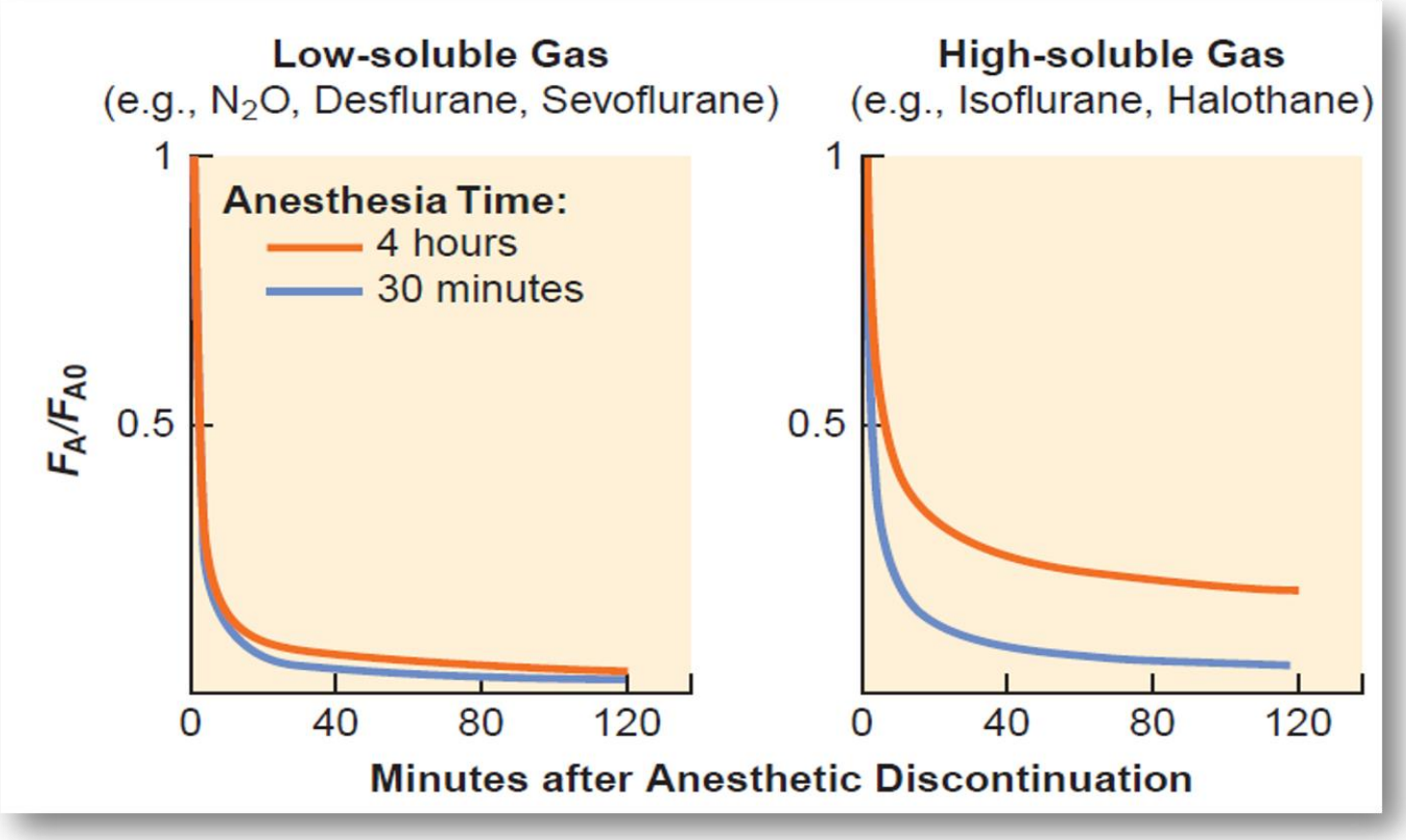
Inhaled anesthetic - Uptake

- Concentration and second gas effect



Recovery

- Recovery like induction, depends on anesthetic solubility, cardiac output, and minute ventilation.
- Solubility is the primary determinant of the rate of fall of FA
- The “reservoir” of anesthetic in the body at the end of administration depends on tissue solubility and the dose and duration of anesthetic


Low-soluble Gas
(e.g., N_2O, Desflurane, Sevoflurane)
High-soluble Gas
(e.g., Isoflurane, Halothane)
Anesthesia Time:
4 hours
30 minutes
F_A/F_{A0}
1
0.5
0
40
80
120
Minutes after Anesthetic Discontinuation

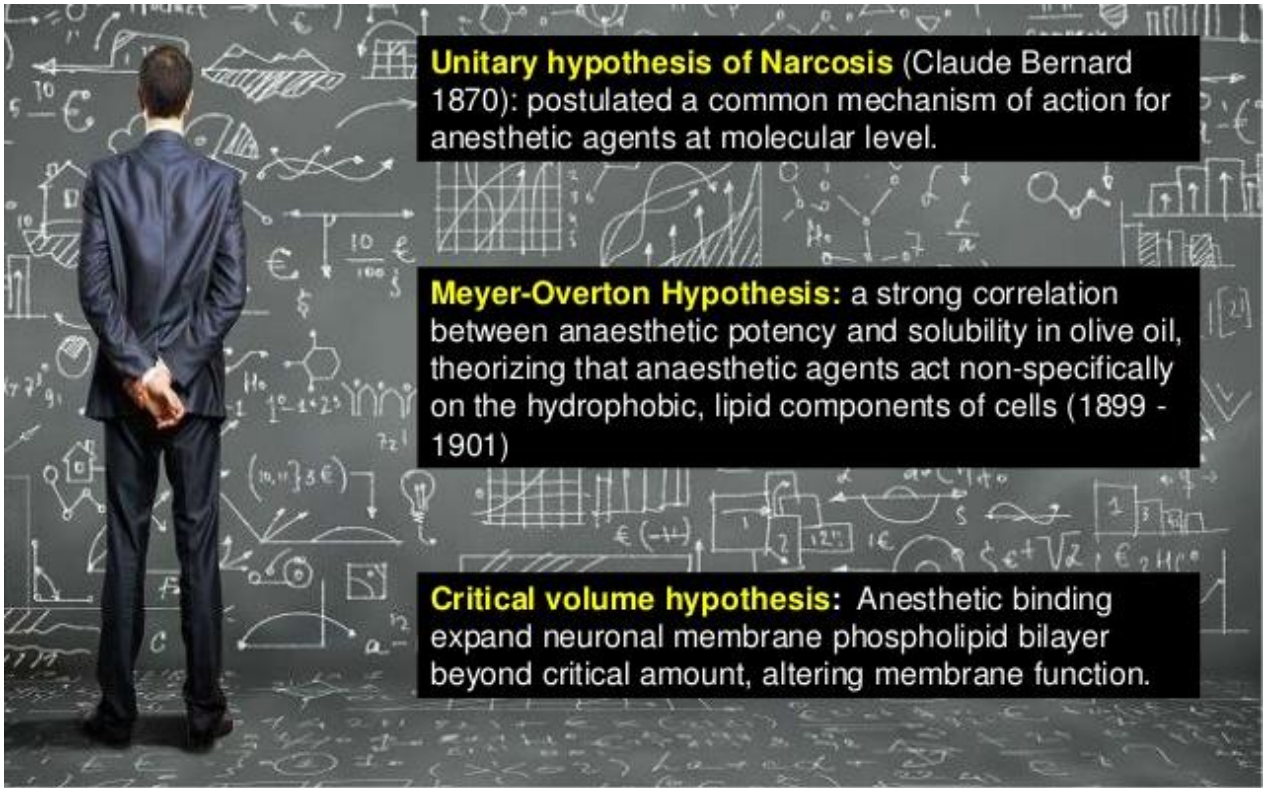
Measure of Anesthetic Potency

- **Minimum alveolar concentration (MAC) of agent that prevents skeletal muscle movement in response to noxious stimuli (surgical skin incision) in 50% patients.**

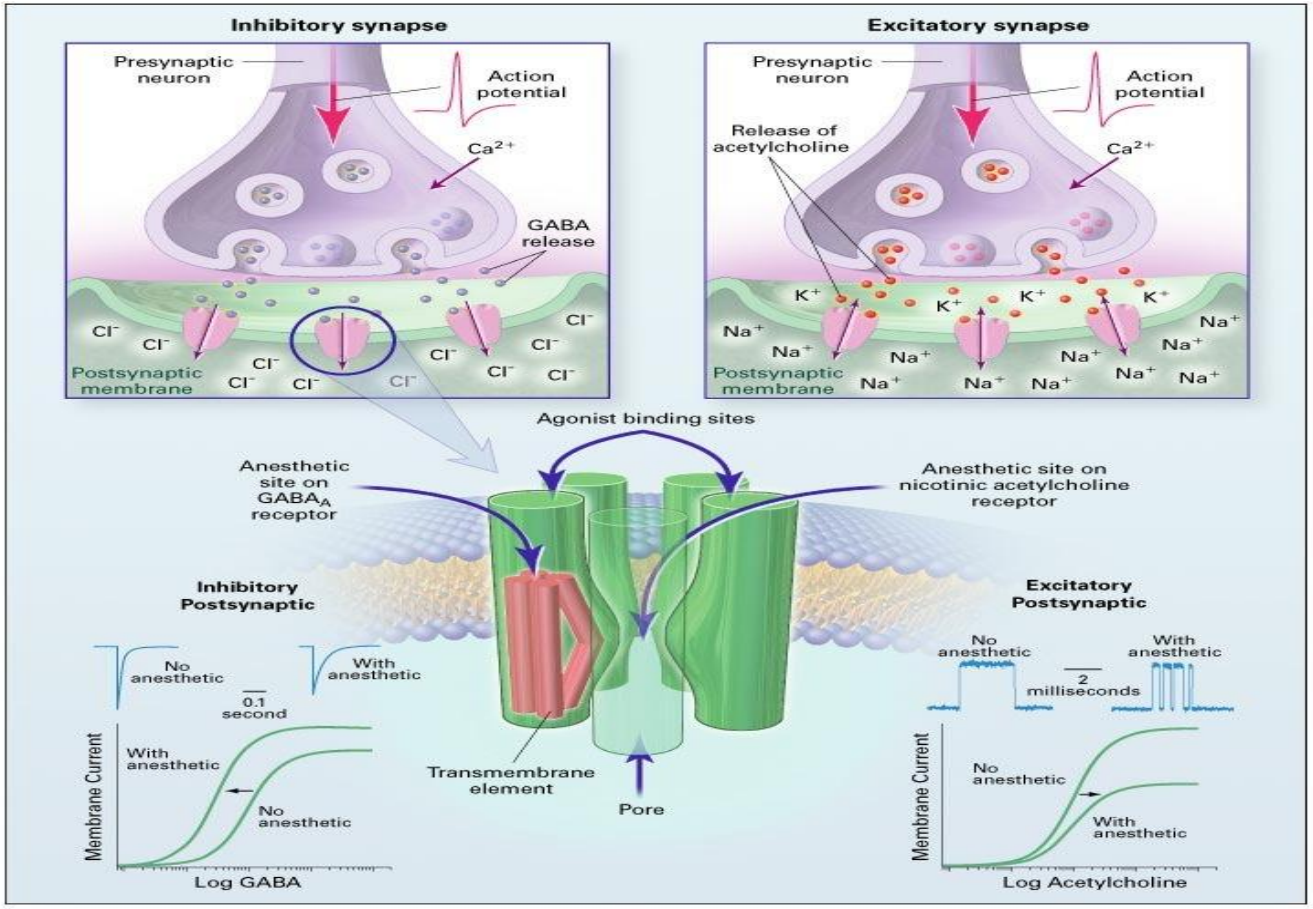
AGENT	MAC	POTENCY
Methoxy-flurane	0.16%	Most potent
Halothane	0.74%	
Isoflurane	1.17%	
Enflurane	1.7%	
Sevoflurane	2.05%	
Desflurane	6.0%	
Nitrous oxide	104%	Least potent

The lower the MAC– the more potent the agent!

Mechanism of anesthetic action



Mechanism of action



Pharmacodynamics

	Desflurane	Isoflurane	Nitrous Oxide	Sevoflurane
1 MAC	6.0%	1.2%	105%	2%
Vapor Pressure (mm Hg at 20°C)	681	240	Gas at room temperature	160
Blood/Gas Partition Coefficient	0.42	1.4	0.47	0.65
CNS Effects	↑ CBF ↓↓ $CMRO_2$ ↑ ICP	↑ CBF at >1 MAC ↓↓ $CMRO_2$ ↑ ICP at >1 MAC EEG suppression at >2 MAC	↑ CBF ↑ $CMRO_2$ ↑ ICP	↑ CBF ↓↓ $CMRO_2$ ↑ ICP
Cardiovascular Effects	↓↓ BP ↑ or N/C HR ↓↓ SVR ↓ or N/C CO Rapid ↑ associated with transient elevations in HR, BP, and catechols	↓↓ BP ↑ HR ↓↓ SVR N/C CO Rapid ↑ associated with transient elevations in HR, BP, and catechols	N/C BP N/C HR N/C SVR N/C CO Increases pulmonary vascular resistance due to constriction of pulmonary smooth muscle	↓ BP N/C HR ↓ SVR ↓ CO May prolong QT interval
Pulmonary Effects	↓ TV ↑ RR Depresses ventilatory response to ↑ $PaCO_2$	↓↓ TV ↑ RR Depresses ventilatory response to ↑ $PaCO_2$ Modest bronchodilation	↓ TV ↑ RR Depresses hypoxic ventilatory drive	↓ TV ↑ RR Depresses ventilatory response to ↑ $PaCO_2$ Mild bronchodilation
Hepatic Effects	↓ Hepatic blood flow	↓ Hepatic blood flow	↓ Hepatic blood flow	N/C Hepatic blood flow
Renal Effects	↓ Renal blood flow ↓ GFR ↓ UOP	↓↓ Renal blood flow ↓↓ GFR ↓↓ UOP	↓↓ Renal blood flow ↓↓ GFR ↓↓ UOP	↓ Renal blood flow ↓ GFR ↓ UOP

Effect on CVS

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Contractility	↓↓↓	↓	↓↓	minimal	↓
Heart rate	↓↓	↑↑	↑	↑ (↑↑ > 1.5 MAC)	nil
Systemic vascular resistance	↓	↓↓	↓	↓↓	↓
Blood pressure	↓↓	↓↓	↓↓	↓↓	↓
Coronary steal syndrome	no	possibly	no	no	no
Splanchnic blood flow	↓	unchanged	↓	unchanged	unchanged
Sensitization to catecholamines	↑↑↑	nil	↑	nil	nil

Effect on CNS

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Cerebral blood flow	↑↑↑	↑ (nil if < 1 MAC)	↑	↑	↑
Cerebral O_2 requirement	↓	↓	↓	↓	↓
EEG	burst suppression	burst suppression	epileptiform activity (3 Hz spike and wave)	burst suppression	burst suppression
Effect on uterus	some relaxation	some relaxation	some relaxation	some relaxation	some relaxation
Potentiation of muscle relaxation	some	significant	significant	significant	significant
Analgesia	none	some	some	some	some

Effect on RS

- Respiration
  - Bronchodilators except desflurane
  - Impair mucociliary clearance
  - Decrease in ventilatory response to hypoxia and hypercarbia

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Respiratory rate	↑	↑↑	↑↑	↑↑	↑↑
Tidal volume	↓	↓↓	↓↓↓	↓↓	↓
$PaCO_2$	unchanged	↑↑	↑↑↑	↑↑	↑

Effect on kidneys

- Renal
  - Decrease RBF, GFR, urine output

AGENT	PROPERTY	EFFECT
Halothane	Inorganic fluoride levels are less	No Neprotoxicity
Isoflurane	Inorganic fluoride levels are less	No Neprotoxicity
Desflurane	Inorganic fluoride levels are very less, highly stable & resists degradation by soda-lime & liver	No Neprotoxicity
Sevoflurane	Inorganic fluoride levels are less but not stable , degraded by soda-lime to compound A & undergoes liver metabolism.	Compound A is Neprotoxic
Enflurane	Biotranformed to inorganic fluoride levels after prolonged use (> 4hrs)	Nephrotoxic, after prolonged use
Methoxyflurane	Biotranformed to high inorganic fluoride levels	Highly nephrotoxic

Effect on liver

- Decrease portal blood flow but total hepatic blood flow maintained with compensatory increase in hepatic arterial blood flow (hepatic artery buffer response)
- HABR disrupted by halothane, cause hepatic arterial vasoconstriction and reduce flow
- Transient elevation of enzymes

Metabolism

TABLE 26-3 **METABOLISM OF HALOGENATED VOLATILE ANESTHETICS**

Anesthetic	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Extent of tissue metabolism (%)	25	70	2.5	0.2	0.02	5
Oxidating enzymes	CYP2E1, CYP2A6	CYP2E1, CYP1A2, 2C9/10, 2D6	CYP2E1	CYP2E1	CYP2E1	CYP2E1
Oxidative metabolites	F_3C-COOH, HBr, HCl	H_3C-O-CF_2-COOH, HCl_2C-COOH, HOOC-COOH, HF, HCl	HF_2C-O-CF_2-COOH, HCl, HF	HF_2C-O-CO-CF_3, F_3C-COOH, CF_2HOH, HCl	HF_2C-O-CO-CF_3, F_3C-COOH, CF_2HOH, HF	HO-$CH(CF_3)_2$, HF
Trifuoroacetylated hepatocellular proteins	+++++	n/a	++	+	+	none
Reducing enzymes	CYP2A6, CYP3A4	n/a	n/a	n/a	n/a	
Reductive metabolites	F^-, Br^- $F_2C = CHCl$ F_3C-CH_2Cl	—	—	—	—	—
Tissue toxicities	Hepatic	Renal, hepatic	Renal, hepatic	Hepatic	Hepatic	Hepatic
Fulminant hepatitis incidence	1:20,000	Reported, incidence unknown	1:300,000	Rare	Rare	Few case reports

Nitrous oxide

- Colorless, odourless gas
- Low blood gas solubility, least potent
- Analgesia even at 20% concentration
- Concentration and second gas effect
- Diffusion hypoxia
- Can expand air spaces like pneumothorax, pneumocephalus, middle ear, air embolus, etc
- Inhibit vitamin B12 (and in turn, methionine synthetase), can lead to megaloblastic anemia, subacute myelopathy, neuropathy, homocystinemia

Halothane

- 2 bromo-2-chloro-1,1,1-trifluoroethane
- 1956, first halogenated agent used
- Not pungent, tolerated for inhalational induction, especially in children
- thymol as preservative to prevent spontaneous oxidative decomposition
- Bradycardia and arrhythmias, seen more with epinephrine
- Halothane hepatitis
- Malignant hyperthermia

Enflurane

- 2 chloro-1,1,2-trifluoroethyl difluoromethyl ether
- Not in use presently
- Slow induction and recovery
- seizures in high concentrations
- Nephrotoxic with prolonged use

Isoflurane

- 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether
- Widely used, safe
- Coronary steal syndrome – insignificant
- Anesthetic preconditioning

Desflurane

- Difluoromethyl 1-fluoro-2,2,2-trifluoromethyl ether
- Highly volatile at room temperature
- Need special heated vaporiser
- Faster induction and recovery
- Airway irritant, hence not preferred for induction
- CO with dry CO2 absorbants

Sevoflurane

- Fluoromethyl 2,2,2-trifluoro-1-trifluoromethylethyl ether
- Faster induction and recovery
- Preferred agent for induction, especially paediatrics
- Compound A (nephrotoxic) and CO produced with dried co2 absorbers, more with low flows

Xenon

- Inert gas, identified in 1951
- Well tolerated, least side effects
- Low blood gas solubility 0.14
- MAC 71
- High cost of production, extracted from air by distillation of liquefied air
- Not used widely because of high cost, higher density (more resistance and work of breathing)

Thank you.