Inhaled anesthetic

R1 Soravish Sirilertworakul
Wanwipha Malaithong, M.D.

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Introduction

Introduction

- Inhalation anesthetics are the most common drugs used for the provision of general anesthesia.
    - Rapid induction and recovery
    - The ability to quickly increase or decrease anesthetic levels
    - A fraction of a volatile anesthetic to the inspired oxygen results in a state of unconsciousness and amnesia.
    - When combined with intravenous adjuvants, such as opioids and benzodiazepines, a balanced technique is achieved

Physical Characteristic

Boiling Points of gas

- If volatile liquids reside in a closed container, molecules of the substance will equilibrate between the liquid and gas phases.
- At equilibrium, the pressure exerted by molecular collisions of the gas against the container walls is the vapor pressure (proportional to temperature)
- Boiling point of a liquid is the temperature at which its vapor pressure exceeds atmospheric pressure in an open container.

Gas in mixtures

- Partial pressure is the pressure that gas exerts proportional to its fractional mass.
- This is its The sum of the partial pressures of each gas in a mixture of gases equals the total pressure of the entire mixture (Dalton's law)
  - $P_{total} = P_{gas1} + P_{gas2} + \ldots + P_{gasN}$

Gas in Solutions

- Partial pressure of a gas in solution refers to the pressure of the gas in the gas phase (if it were present) in equilibrium with the liquid.
- It is important to talk of partial pressures, because gases equilibrate based on partial pressures, not concentrations.

Henry's law

$$C_g = kP_g$$

- C_g is concentration of gas in solution,
- k is a solubility constant
- P_g is the partial pressure of the gas.

Solubility coefficient (λ)

$$\lambda = V_{\text{dissolved gas}} / V_{\text{liquid}} \text{ at } 37^{o}C$$

- λ = Solubility coefficient (λ)
- V = Volume

Concentration

The concentration of any one gas in a mixture of gases in solution depends on two factors:

(1) Its partial pressure in the gas phase in equilibrium with the solution,

(2) Its solubility within that solution.

In summary

- Inhaled anesthetics equilibrate based on their partial pressures in each tissue (or tissue compartment), not based on their concentrations.
- The partial pressure of a gas in solution is defined by the partial pressure in the gas phase with which it is in equilibrium. Where there is no gas phase the partial pressure reflects a force to move out of solution.
- The concentration of anesthetic in a tissue depends on its partial pressure and the tissue solubility of the anesthetic.

Pharmacokinetics

Goal of delivering

- The goal of delivering inhaled anesthetics is to produce the anesthetic state by establishing a specific concentration of anesthetic molecules in the central nervous system (CNS), which is done by establishing the specific partial pressure of the agent in the lungs that ultimately equilibrates with the brain and spinal cord.

At Equilibrium

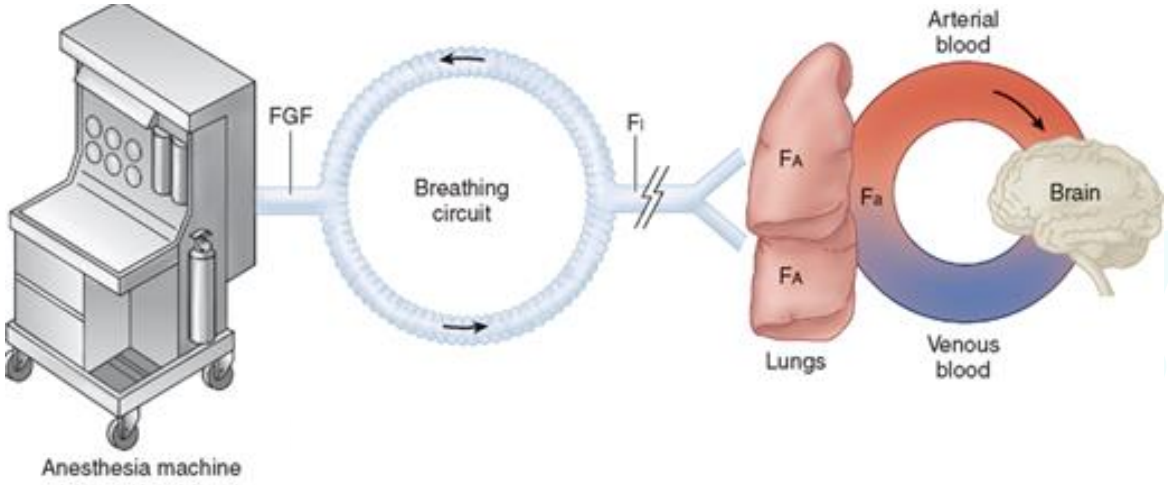
$$P_{CNS} = P_{blood} = P_{alveoli}$$

- Inhaled anesthetics are gases rapidly transferred bidirectionally via the lungs , bloodstream and CNS tissues as partial pressures equilibrate.
- Plasma and tissues have a low capacity to absorb the inhaled anesthetics.
- Metabolism, excretion, and redistribution of the inhaled anesthetics are minimal.

Anesthetic Transfer

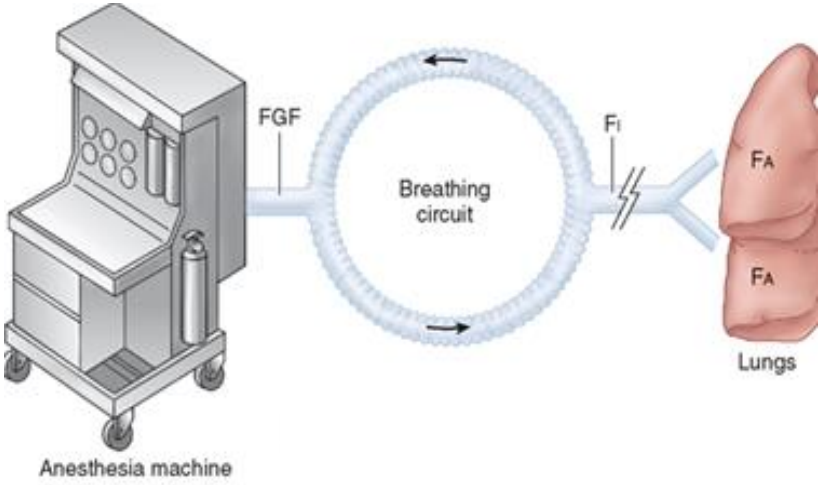
- Transfer of inhale anesthetic from anesthetic machine to alveoli.
- Transfer of inhale anesthetic from alveoli to arterial blood.
- Transfer of inhale anesthetic from arterial blood to brain.

Anesthetic Transfer



- FGF : Fresh gas flow
- F_I : Fractional concentration of anesthetic leaving circuit
- F_A : Fractional concentration of anesthetic present in the alveoli
- F_a : Fractional concentration of anesthetic present in arterial blood

Transfer of inhale anesthetic from anesthetic machine to alveoli



- FGF : Fresh gas flow
- F_I : Fractional concentration of anesthetic leaving circuit
- F_A : Fractional concentration of anesthetic present in the alveoli

Fractional concentration of anesthetic leaving circuit (F_I)

$$F_I = F_{FGO}(1-e^{-T/\tau})$$

- F_I = Fractional concentration of anesthetic leaving circuit
- F_{FGO} = Fractional of anesthetic in FGF
- T = Time
- τ = Time constant = Circuit capacity (V_c) / FGF

Fractional concentration of anesthetic leaving circuit (F_I)

$$F_I = F_{FGO}(1-e^{-T/\tau})$$

- $F_I \propto F_{FGO}$, FGF, 1/Circuit capacity
- Other factors : CO2 absorbent, solubility of inhaled anesthetics in plastic/rubber play a minor roles.

Fractional concentration of anesthetic present in the alveoli (F_A)

$$F_A = F_I(1-e^{-T/\tau})$$

- F_A = Fractional concentration of anesthetic present in the alveoli
- F_I = Fractional concentration of anesthetic leaving circuit
- T = Time
- τ = Time constant = Functional residual capacity (FRC)/ Minute ventilation (V_A)

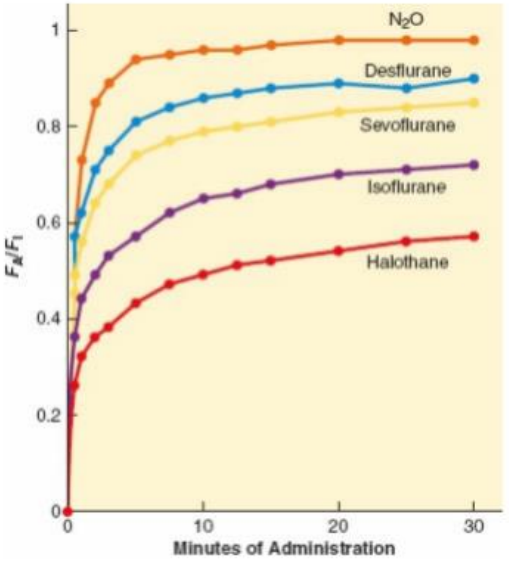
Fractional concentration of anesthetic present in the alveoli (F_A)

$$F_A = F_I(1-e^{-T/\tau})$$

- $F_A \propto F_I$, Minute ventilation (V_A), 1/Functional residual capacity (1/FRC)

F_A / F_I

- The ratio of fractional concentration of alveolar anesthetic to inspired anesthetic (F_A/F_I) over time common way to assess anesthetic uptake.
- The faster F_A rises relative to F_I, the faster the speed of induction since F_A is proportional to P_A



Transfer of inhale anesthetic from Alveoli to Arterial blood

- Since there is uptake from alveoli to blood, F_A is not solely a function of F_I and time.
- The greater the uptake, the slower the rate of rise of F_A/F_I, and vice versa.
- The most important factor in the rate of rise of F_A/F_I is uptake of anesthetic from the alveoli into the bloodstream.

Transfer of inhale anesthetic from Alveoli to Arterial blood

$$P_a = P_A(1-e^{-T/\tau}) \text{ where } P_A = F_A \times P_{B(\text{barometric})}$$

- P_a = Partial pressure of anesthetic present in arterial blood
- P_A = Partial pressure of anesthetic in alveoli
- T = Time
- τ = Time constant = Blood capacity (volume of anesthetic dissolved in blood)/Flow (volume of anesthetic delivered per unit time)

Fractional concentration of anesthetic present in the alveoli (F_A)

$$P_a = P_A(1-e^{-T/\tau})$$

- $P_a \propto P_A$, Flow, 1/Blood capacity (Blood uptake)
- The greater Blood uptake, The larger the capacity of the blood and tissues for that anesthetic, and the longer it takes to saturate at any given delivery rate.

Blood uptake (Fick equation)

$$V_B = \delta^{b/g} \times Q \times (P_A - P_V)/P_B$$

- V_B = Blood uptake
- $\delta^{b/g}$ = Blood/gas partition coefficient
- Q = Cardiac output
- P_A = Alveolar partial pressure
- P_V = Mixed venous partial pressure of anesthetic
- P_B = Barometric pressure

Blood uptake

$$V_B = \delta^{b/g} \times Q \times (P_A - P_V)/P_B$$

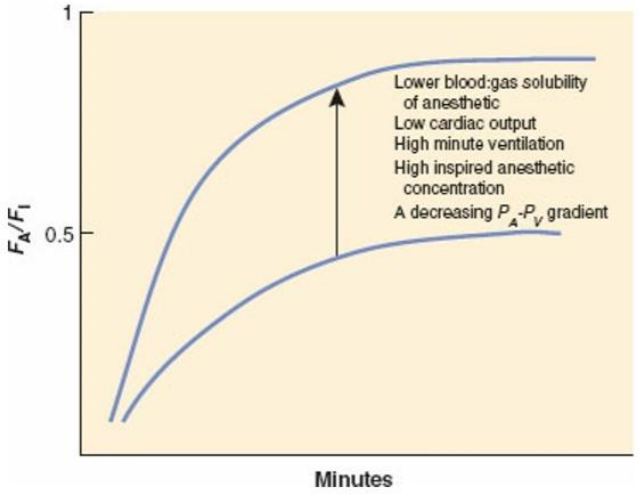
- $V_B \propto$ Blood/gas partition coefficient ($\delta^{b/g}$), Perfusion (Q), Alveolar and venous partial pressure different.
- The greater the value of V_B, the greater the uptake from alveoli to blood, and the slower the rise in F_A/F_I.

Transfer of inhale anesthetic from arterial blood to brain (Distribution)

- As blood is equilibrating with alveolar gas, it also begins to equilibrate with the VRG, muscle, and, more gradually, the fat compartments.
- Three factors :
  - Tissue Perfusion
  - Tissue/blood partition coefficient
  - Arterial to venous partial pressure difference

In summary

- Factors that effect F_A/F_I



	Increase
From anesthetic machine to alveoli.	- High conc. F_{FGO} - High Fresh gas flow - High Minute ventilation - Low anesthetic machine capacity
From alveoli to arterial blood.	- Low Blood/gas partition coefficient - Low Cardiac output - Low Alveolar partial pressure and mixed venous partial pressure different

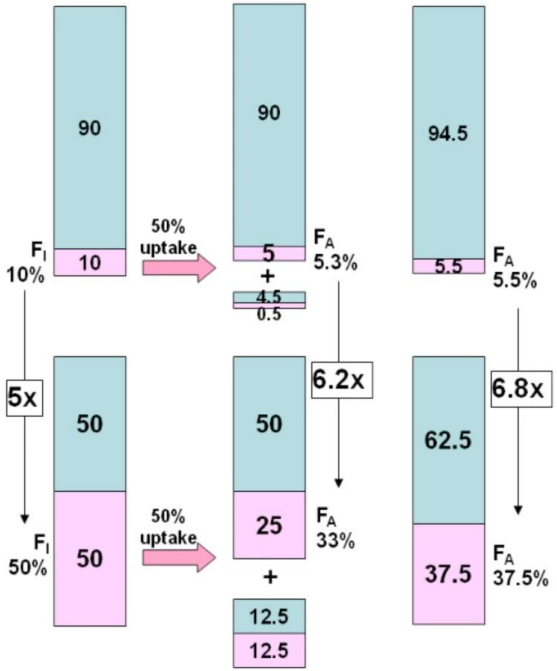
In summary

- Factors that effect P_{CNS}
  - Brain Perfusion,
  - Brain/blood partition coefficient
  - Arterial to venous partial pressure difference

Concentration effects (Overpressurization)

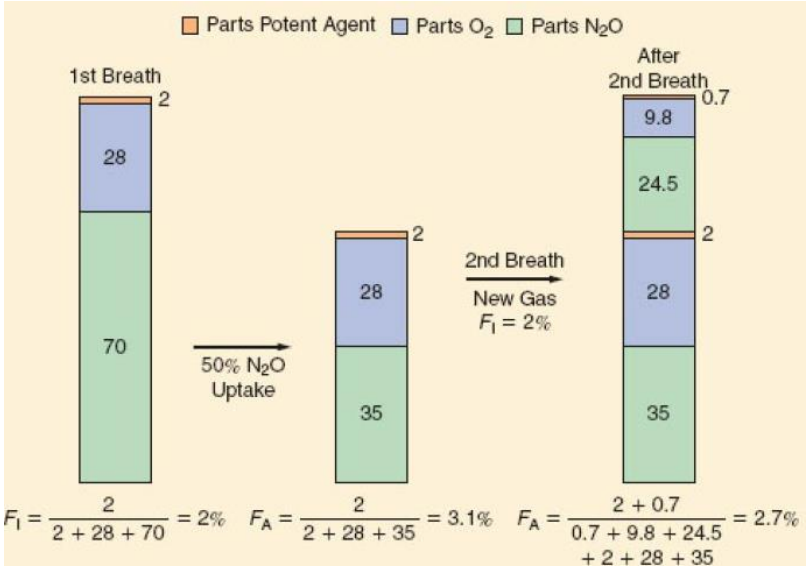
- This is the administration of a higher partial pressure of anesthetic than the alveolar concentration (F_A) actually desired for the patient.
- Inspired anesthetic concentration (F_I) can influence both F_A and the rate of rise of F_A/F_I.
- The greater the inspired concentration of an inhaled anesthetic, the greater the rate of rise.
- This concentration effect has two components: the concentrating effect and an augmented gas inflow effect.

The concentrating effect



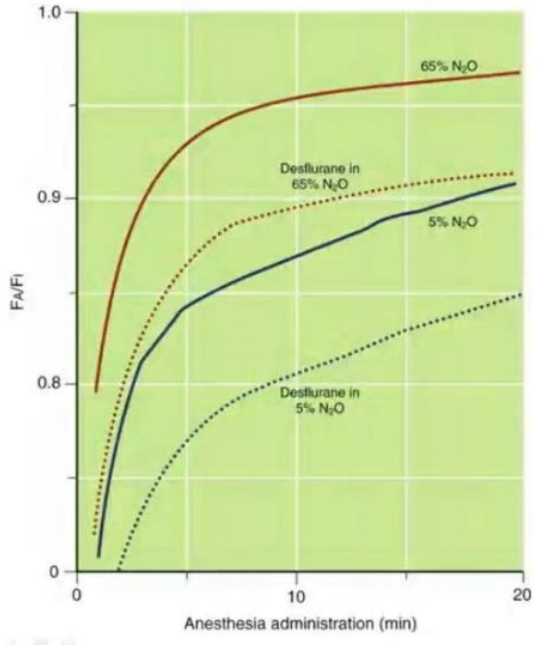
- This is the administration of a higher partial pressure of anesthetic than the alveolar concentration (F_A) actually desired for the patient.
- Inspired anesthetic concentration (F_I) can influence both F_A and the rate of rise of F_A/F_I.
- Two components :
  - The concentrating effect
  - Augmented gas inflow effect.

The Second gas effect



- Case of concentration effect applies to administration of a potent anesthetic with N_2O, that is, two gases simultaneously.
- Along with the concentration of potent agent in the alveoli via its uptake, there is further concentration via the uptake of N_2O, a process called the second gas effect.

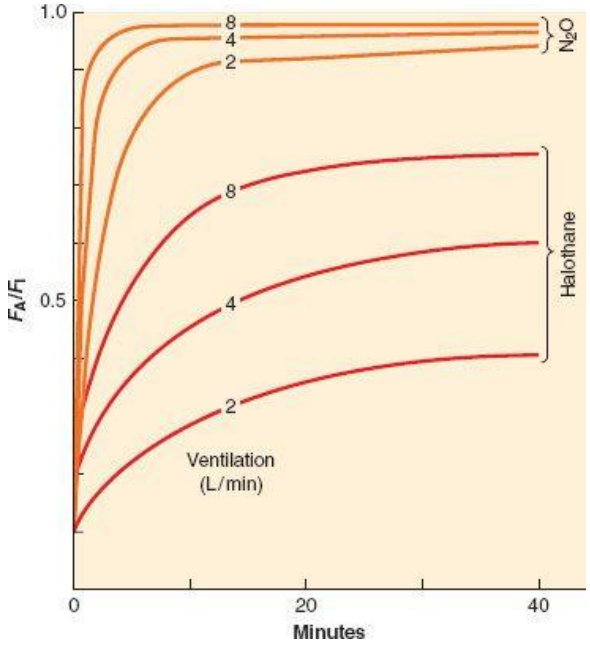
Both effects



- Concentration Effect
  - F_I = 65% N_2O
  - F_I = 5% N_2O

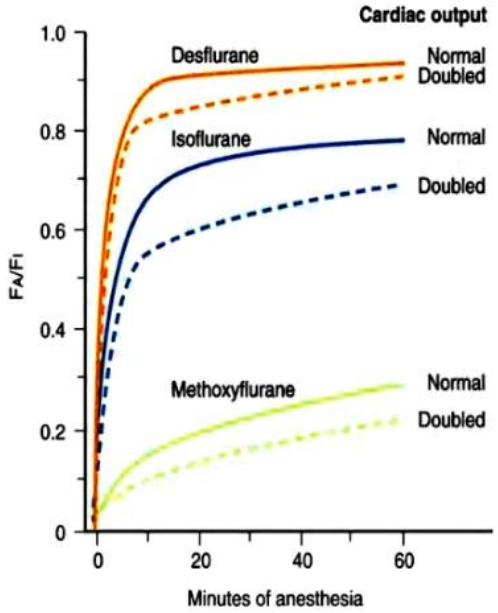
- Second Gas Effect
  - F_I = 4% desflurane in 65% N_2O
  - F_I = 4% desflurane in 5% N_2O

The Ventilation effect



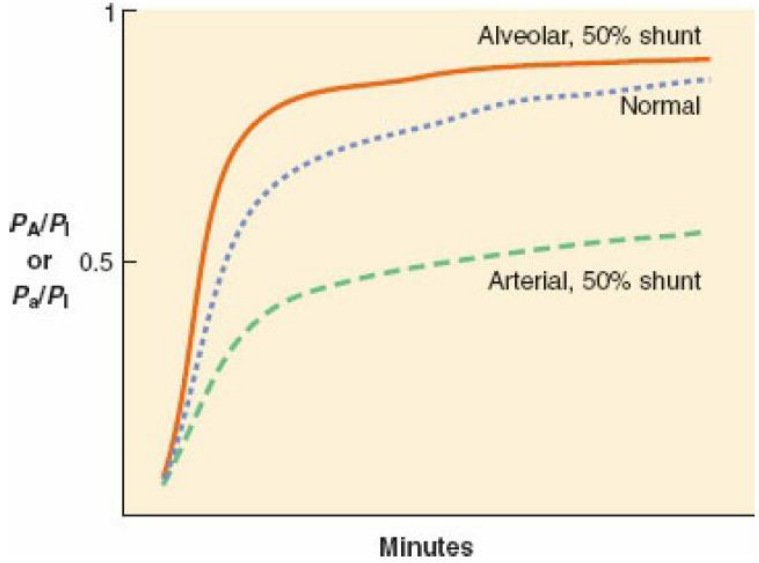
- The greater ventilation, The faster anesthetic replace in alveoli -> Rapid rise in F_A/F_I
- More significant effect with blood soluble agents
- Negative feedback :
  High Minute ventilation -> Rapid induction -> Lower Minute ventilation

The Perfusion effect



- The greater cardiac output, The greater uptake anesthetic gas to blood -> Delays rise In F_A/F_I
- More significant effect with blood soluble agents
- Positive feedback :
  Low cardiac output -> Rapid induction -> Lower cardiac output

Ventilation-Perfusion Mismatching



- In presence of V/Q mismatching (Shunt) e.g. One-lung intubation
  - P_A/P_I rising in intubated lung but P_A in non-intubated side is essentially zero
  - P_a/P_I is significantly reduced.
  - In Total, It's slow induction.

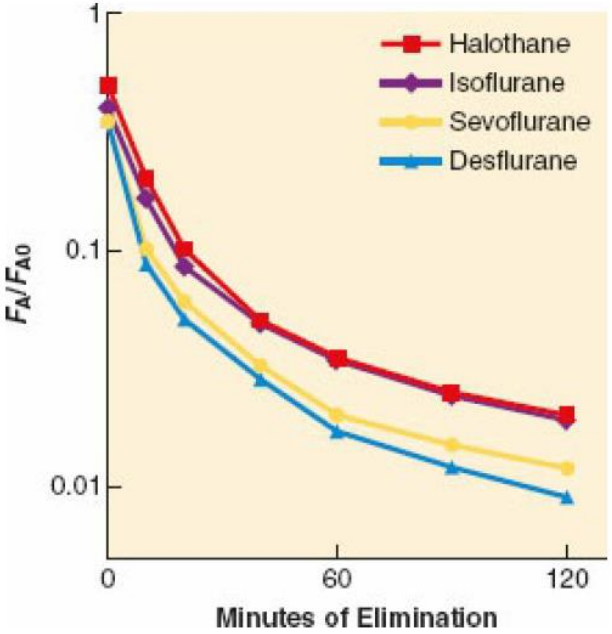
Metabolism

- Enzymes responsible for biotransformation of inhaled anesthetics become saturated at less than anesthetizing doses of these drugs, such that metabolism plays little role in opposing induction.

Elimination

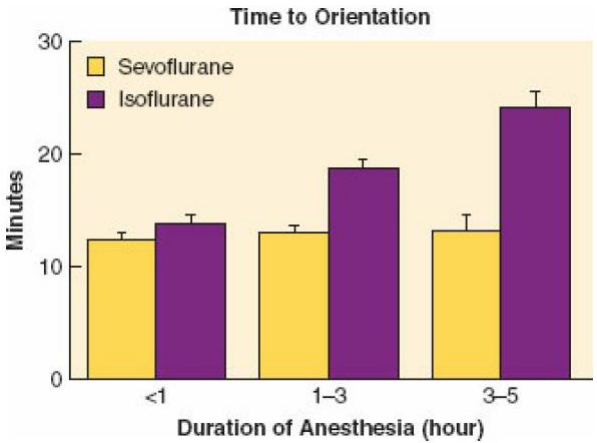
- Exhalation and Recovery
- Percutaneous and Visceral Loss
- Diffusion Between Tissues

Exhalation and Recovery



- Recovery from anesthesia, or “washout,” is usually expressed as the ratio of expired fractional concentration of anesthetic (F_A) to the expired concentration at time zero (F_{A0}) when the anesthetic was discontinued (or F_A/F_{A0}).
- Solubility is the primary determinant of the rate of fall of F_A.

F_A/F_{A0}



- The “reservoir” of anesthetic in the body at the end of administration depends on tissue solubility (which determines the capacity) and the dose and duration of anesthetic (which determine how much of that capacity is filled).
- Other factors include : cardiac output, minute ventilation

Percutaneous and Visceral Loss

- Although the loss of inhaled anesthetics via the skin is very small, it does occur and the loss is the greatest for N_2O.
- These anesthetics also pass across gastrointestinal viscera and the pleura. During open abdominal or thoracic surgery there is some anesthetic loss via these routes.
- Relative to losses by all other routes, losses via percutaneous and visceral routes are insignificant.

Diffusion Between Tissues

- Tissue compartments have derived to five-compartment model that are the alveoli, the VRG, the muscle, the fat, and one additional compartment.
- Current opinion is that this fifth compartment represents adipose tissue adjacent to lean tissue that receives anesthetic via inter- tissue diffusion.
- This transfer of anesthetic is not insignificant and may account for up to one-third of uptake during long administration.

In summary

Factors effect induction time	Factors effect recovery time
- High conc. F_{FGO}	- Low Blood/gas partition coefficient
- High Fresh gas flow	- Duration of anesthesia
- High Minute ventilation	- Low Fat solubility
- Low Blood/gas partition coefficient	
- Low Cardiac output	

Pharmacodynamics

Mechanism of action

- No theory to explains clearly mechanism of action.
- Majority theory : Exert their effect by binding diversity to ion channel to ligands binding to receptor
    - Enhance function of inhibitory ion channels e.g. GABA, Glycine
    - Blocking function of excitatory ion channel e.g. NMDA
    - Affect the release of neurotransmitter

Minimum Alveolar Concentration (MAC)

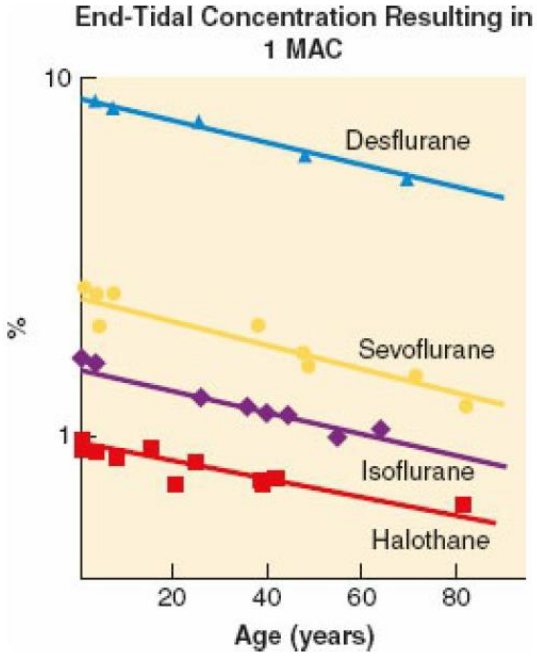
- MAC is the alveolar concentration of an anesthetic at one atmosphere (in volume%) that prevents movement in response to a surgical stimulus in 50% of patients.

0.15-0.5 MAC (MAC Awake)	patient opens his or her eyes to command
0.4-0.5 MAC	loss of self-awareness and recall
1 MAC	Prevent movement in response to a surgical stimulus in 50% of patients.
1.2-1.3 MAC	Prevent movement in response to a surgical stimulus in 95-99% of patients. (Recommend for surgery)
1.5 MAC (MAC BAR)	Blunts adrenergic responses to noxious stimuli.

Factors effects MAC

Increase MAC	Decrease MAC
Hypernatremia	Hyponatremia
Hyperthermia	Hypothermia
Pediatrics	Elderly
Chronic alcohol drinking	Acute alcohol drinking
Medication e.g. MAOI, Levodopa, Ephedrine	Medication e.g. Opioids, Barbiturate, Benzodiazepine, Ketamine
Drug abuse e.g. Cocaine, Amphetamine	Other metabolic cause e.g. Metabolic acidosis, Hypoxia, Hypotension, Anemia

Effects of Age on MAC



- The Highest MAC value are infants 1 to 6 months old. (Except Sevoflurane)
- A change in MAC of approximately 6% per decade.

Effects on CNS

- $CMRO_2$ is decreased only to the extent that spontaneous cortical neuronal activity (as reflected on the EEG) is decreased.
- Dose-dependent increase CBF “Metabolic uncoupling” (Desflurane, Sevoflurane at MAC < 1.5 have minimal effects on CBF)
- Dose-dependent diminish autoregulation of brain (vasodilatory effects)
- Increase ICP due to vasodilation (Desflurane > Sevoflurane)

Effects on CVS

- Dose-dependent decrease blood pressure, SVR
- Maintain Cardiac output
- No effects on myocardial contractility in healthy patients.
- Transient increase in HR (Desflurane, Isoflurane)
- Prolong QT_c interval (may predispose to VT)
- Ischemic preconditioning in brief coronary occlusion and ischemia

Effects on ANS

- Dose-dependent decrease in reflex control of sympathetic output (at 1 MAC or greater) -> earlier recognition of intraoperative blood loss.
- Desflurane increase in resting sympathetic nerve system activity and plasma norepinephrine (But in total decrease BP due to vasodilation)

Effects on RS

- Decrease V_T and increase RR -> minor effects on decreasing minute ventilation.
- The respiratory depression can be partially antagonized during surgical stimulation where respiratory rate and tidal volume have been shown to increase.
- Bronchodilation by directly reducing smooth muscle tone
- Reduced ciliary movement and alter the characteristics of mucus -> Inadequate clearing of secretion, mucus plugging, atelectasis and hypoxemia especially in smokers.

Effects on RS

- Dose-dependent depression of the ventilatory response to hypercarbia
- Dose-dependent attenuation of the ventilatory response to hypoxia -> significant in patients who depend on hypoxic drive to set their level of ventilation

Effects on Hepatobiliary system

- Halothane : cause hepatic arterial constriction and induced hepatitis
- Enflurane : increase hepatic vascular resistance
- Isoflurane : increase in microvascular blood velocity
- Modern volatile anesthetics undergo minimal liver metabolism, and minimally affect hepatic function.

Effects on Renal system

- Decrease GFR by decrease renal perfusion pressure.
- Can be exacerbated by hypovolemia, catecholamines and ADH

Effects on Neuromuscular system

- Dose-dependent relax skeletal muscle (most prominent for potent volatile anesthetics above 1.0 MAC)
- Potentiate the action of neuromuscular blocking drugs.
- Nitrous oxide does not affect skeletal muscle relaxation.

Malignant hyperthermia

- Malignant hyperthermia is a clinical syndrome of acute, uncontrolled, increased skeletal muscle metabolism resulting in heightened oxygen consumption, lactate formation, heat production, and rhabdomyolysis.

- The hallmark findings of MH are a rapidly rising temperature, increasing up to 1°C every 5 minutes along with increasing end-tidal CO2, arrhythmias, mixed respiratory/metabolic acidosis, and skeletal muscle rigidity

Overview of current Inhaled anesthetics

Isoflurane

- Halogenated methyl ethyl ether
- Clear, nonflammable liquid at temperature, pungent smell
- Most potent of volatile anesthetic in clinical use
- Disadvantages : - Controversy, using in coronary artery patient because possibility of “Coronary steal”

Desflurane

- Fluorinated methyl ethyl ether
- High vapor pressure -> Require an electrically driven, heated, pressurized vaporizer
- Lowest blood:gas solubility coefficient -> Fastest onset and recovery
- Low fat solubility -> Advantage in morbidly obese patient

- Disadvantages : - Most pungent of MAC equivalent volatile anesthetic -> Coughing, Salivation, Breath holding, Laryngospasm, activate Sympathetic nervous system

Sevoflurane

- Fluorinated methyl isopropyl ether
- Pleasant odor, lack of pungency
- Potent bronchodilator
- Low blood:gas solubility coefficient -> Fast onset and recovery
- Disadvantages : - Increase risk of post-operative agitation and delirium

Nitrous Oxide (N_2O)

- Sweet-smelling, nonflammable gas but support combustion
- Low potency
- No significant muscle relaxation effect

- Disadvantage : - Absorption and expansion into air-filled structures
  - Risk of diffusion hypoxia
  - Increased risk of PONV
  - Toxic effects on cell function (Inactivation of vit B_{12})
  - Teratogenic effect (Inactivation of vit B_{12})

Diffusion Hypoxia

- Washout of high concentrations of N_2O can lower alveolar concentrations of oxygen and carbon dioxide, a phenomenon called diffusion hypoxia.
- The resulting alveolar hypoxia can cause hypoxemia, and alveolar hypocarbia can depress respiratory drive, which may exacerbate hypoxemia.
- It is therefore appropriate to initiate recovery from N_2O anesthesia with 100% oxygen rather than less concentrated O_2/air mixtures.

Xenon

- Inert gas, nonexplosive, non-pungent, quick onset and offset
- NMDA receptor inhibition -> analgesia effect
- Minimal effect on cardiovascular and neural systems
- Not trigger malignant hyperthermia
- Disadvantage : - High cost
  - High MAC (MAC = 71%)

Anesthetic Degradation by carbon dioxide absorbers

Compound A

- Sevoflurane undergoes base-catalyzed degradation in carbon dioxide absorbents to form a vinyl ether called compound A.

- Factors enhance compound A production :
  - Low flow anesthesia (0.5-1 LPM)
  - Close circuit system
  - Warm or very dry CO2 absorbent
  - Baralyme > Sodalime

- No effects on renal function in humans

Carbon monoxide and heat

- Carbon dioxide (CO2) absorbents degrade sevoflurane, desflurane, and isoflurane to carbon monoxide (CO) as the result of an exothermic reaction
- Desflurane produce the most CO
- Sevoflurane produced the most exothermic reaction
- Factors enhance CO production :
  - Dry carbon dioxide absorbent
  - Heated carbon dioxide absorbent
  - Low flow anesthesia
  - Baralyme > Sodalime

TAKE HOME MESSAGE

TAKE HOME MESSAGE

- Inhaled anesthetics equilibrate based on their partial pressures
- At Equilibrium ; PCNS = P blood = P alveoli
- Induction time can be faster by High conc. F_{FGO}, High Fresh gas flow, High Minute ventilation, Low Blood/gas partition coefficient, Low Cardiac output
- Recovery time is affected by-Blood/gas partition coefficient, Duration of anesthesia, Fat solubility
- MAC is the alveolar concentration of an anesthetic at one atmosphere (in volume%) that prevents movement in response to a surgical stimulus in 50% of patients. A change in MAC of approximately 6% per decade.

TAKE HOME MESSAGE

- Volatile anesthetic decrease CMRO2 but increase CBF (metabolic uncoupling)
- Volatile anesthetic decrease blood pressure, SVR
- Volatile anesthetic decrease tidal volume but increase respiratory rate
- Volatile anesthetics are potent triggers for malignant hyperthermia in genetically susceptible patients.

TAKE HOME MESSAGE

- Isoflurane is the most potent of the volatile anesthetics in clinical use, desflurane is the least soluble, and sevoflurane is the least irritating to the airways.
- Nitrous oxide (N_2O) can expand close air-space and washout of N_2O can lower alveolar concentrations of oxygen and carbon dioxide, a phenomenon called diffusion hypoxia.
- For degradation by CO_2 absorbers, Sevoflurane produce compound A and the most exothermic reaction, Desflurane produces the most carbon monoxide (CO)

Table 18-1 Physiochemical Properties of Volatile Anesthetics

Property	Sevoflurane	Desflurane	Isoflurane	Enflurane	Halothane	N_2O
Boiling point (°C)	59	24	49	57	50	−88
Vapor pressure at 20°C (mmHg)	157	669	238	172	243	38,770
Molecular weight (g)	200	168	184	184	197	44
Oil:gas partition coefficient	47	19	91	97	224	1.4
Blood:gas partition coefficient	0.65	0.42	1.46	1.9	2.50	0.46
Brain:blood solubility	1.7	1.3	1.6	1.4	1.9	1.1
Fat:blood solubility	47.5	27.2	44.9	36	51.1	2.3
Muscle:blood solubility	3.1	2.0	2.9	1.7	3.4	1.2
MAC in O_2 30–60 years, at 37°C P_B 760 (%)	1.8	6.6	1.17	1.63	0.75	104
MAC in 60–70% N_2O (%)	0.66	2.38	0.56	0.57	0.29	—
MAC, >65 years (%)	1.45	5.17	1.0	1.55	0.64	—
Preservative	No	No	No	No	Thymol	No
Stable in moist CO_2 absorber	No	Yes	Yes	Yes	No	Yes
Flammability (%) (in 70% N_2O/30% O_2)	10	17	7	5.8	4.8	
Recovered as metabolites (%)	2–5	0.02	0.2	2.4	20	

MAC, minimum alveolar concentration; N_2O, nitrous oxide.

Thank you