ANESTHESIA BASIC REVIEW: NATIONAL EDITION

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12/17/2022

DISCLOSURES

- I can only hope to one day have financial conflicts of interest.
- Goals of the Review Lectures:
  - (1) High Yield Points or Concepts
    - I will try to point out straight “memorization” topics and try to focus on concepts you can build on
  - (2) Mnemonics and Memory Techniques (Mnemonics) and Trick Question Alerts (TQA)
  - (3) Current and Future Study/Reference Material
    - Sincerest apologies for the very wordy slides

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VOLATILE ANESTHETICS

GAS LAWS, FA/FI, MAC & SIDE EFFECTS

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GAS LAWS

- (1) Ideal Gas Law:
  - PV = nRT
    - R = ideal gas constant (0.0821 atm*L/mol*K), n = moles of gas
- (2) Dalton's Law of Partial Pressures
  - Px = (Pb – Ph2o) * F
    - Px = partial pressure of gas X (mmHg), Pb = barometric pressure (mmHg), Ph2o = water vapor pressure at a given temperature (mmHg); F = fractional concentration of gas
    - Explains why at higher altitudes, a greater volume percentage of volatile anesthetics must be delivered to maintain the same anesthetic level as would be delivered at a lower altitude
- (3) Charles Law
  - V1 / T1 = V2 / T2
- (4) Boyle's Law
  - P1V1 = P2V2
- (5) Gay Lussac's Law
  - P1/T1 = P2/T2
    - ETT cuff expansion as the initial air injected which was at room temperature warms to body temperature and expands
- (6) Henry's Law
  - C(gas) = P(gas) * Solubility
    - Concentration of a gas is directly proportional to its partial pressure

Mnemonics:
- Prince Charles is under constant pressure.
- Water "Boyle's" at a constant temperature.

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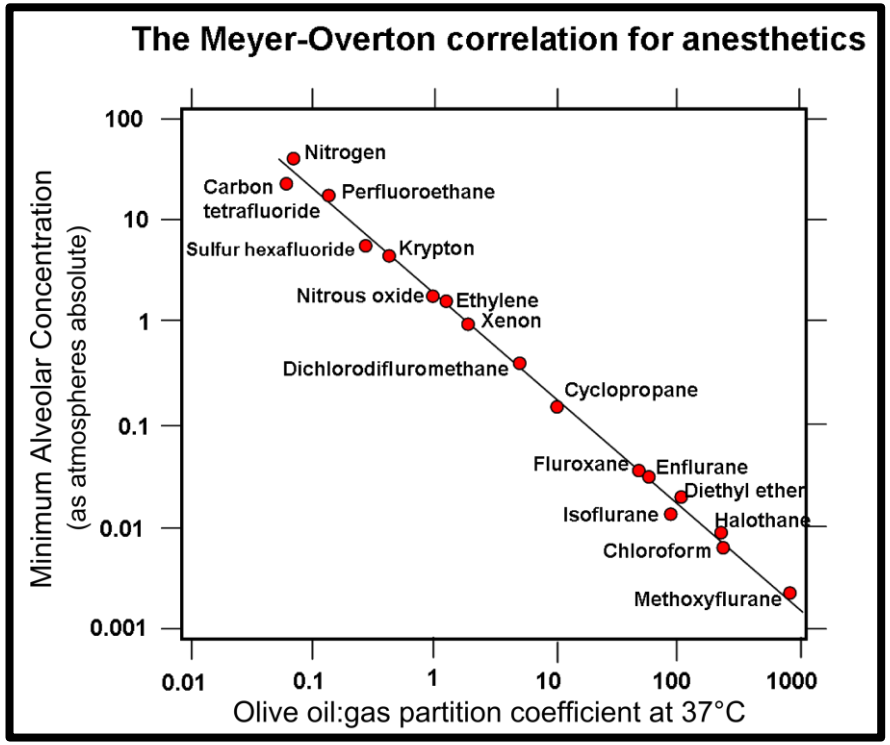
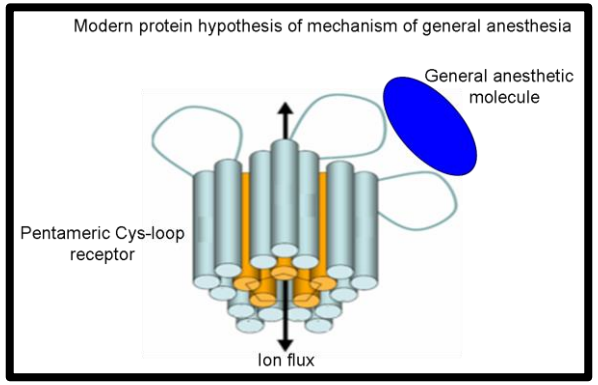
MECHANISM OF ACTION

- Mechanism of Action: Poorly Understood. Theories include:
  - (1) Meyer-Overton Correlation (Historical)
    - Potencies of general anesthetics are related to their hydrophobicity or solubility in olive oil, and linearly correlated with its oil/water partition coefficient
  - (2) Lipid Bilayer Expansion Hypothesis (aka: Critical Volume Hypothesis) (Historical)
    - Suggested that the molecular structure of the volatile anesthetic is not important, however bulk hydrophobic anesthetic molecules distort the lipid bilayer, reversibly altering the function of membrane ion channels
      - Pressure Reversal Effect: increased atmospheric pressure reverses the effects of anesthetic agents on the lipid bilayer
  - **(3) Protein-Based Theories**
    - Franks and Liebs noted volatile anesthetic inhibition of luciferases (enzymes that produce light when the oxidize their substrate) and cytochrome P450 directly correlate with anesthetic potency (follow Meyer-Overton Correlation).
    - General anesthetics may interact with the hydrophobic sites of proteins, rather than indirect effects through the lipid bilayer
- Site of Action:
  - Amnesia: higher brain structures (including hippocampus)
  - Sedation: tuberomammillary nucleus of the hypothalamus
  - Akinesia: mediated via spinal cord



Akuznetsova. (2009). *The Meyer-Overton Correlation*. Theories of general anaesthetic action. Wikimedia Commons. Retrieved November 11, 2021, from https://commons.wikimedia.org/wiki/File:The_Meyer-Overton_correlation.png.



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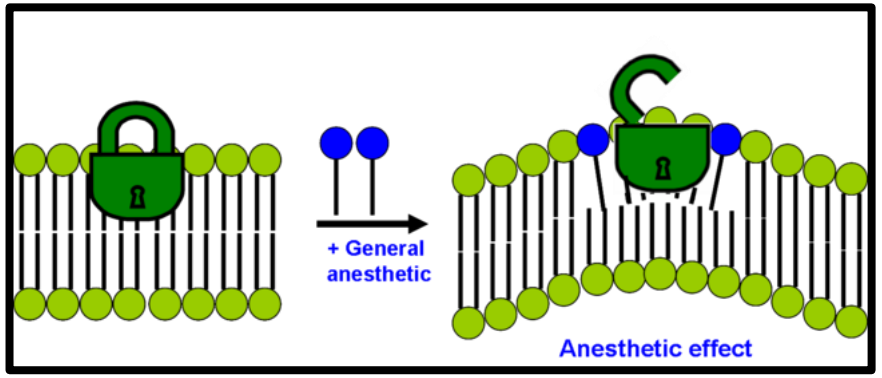

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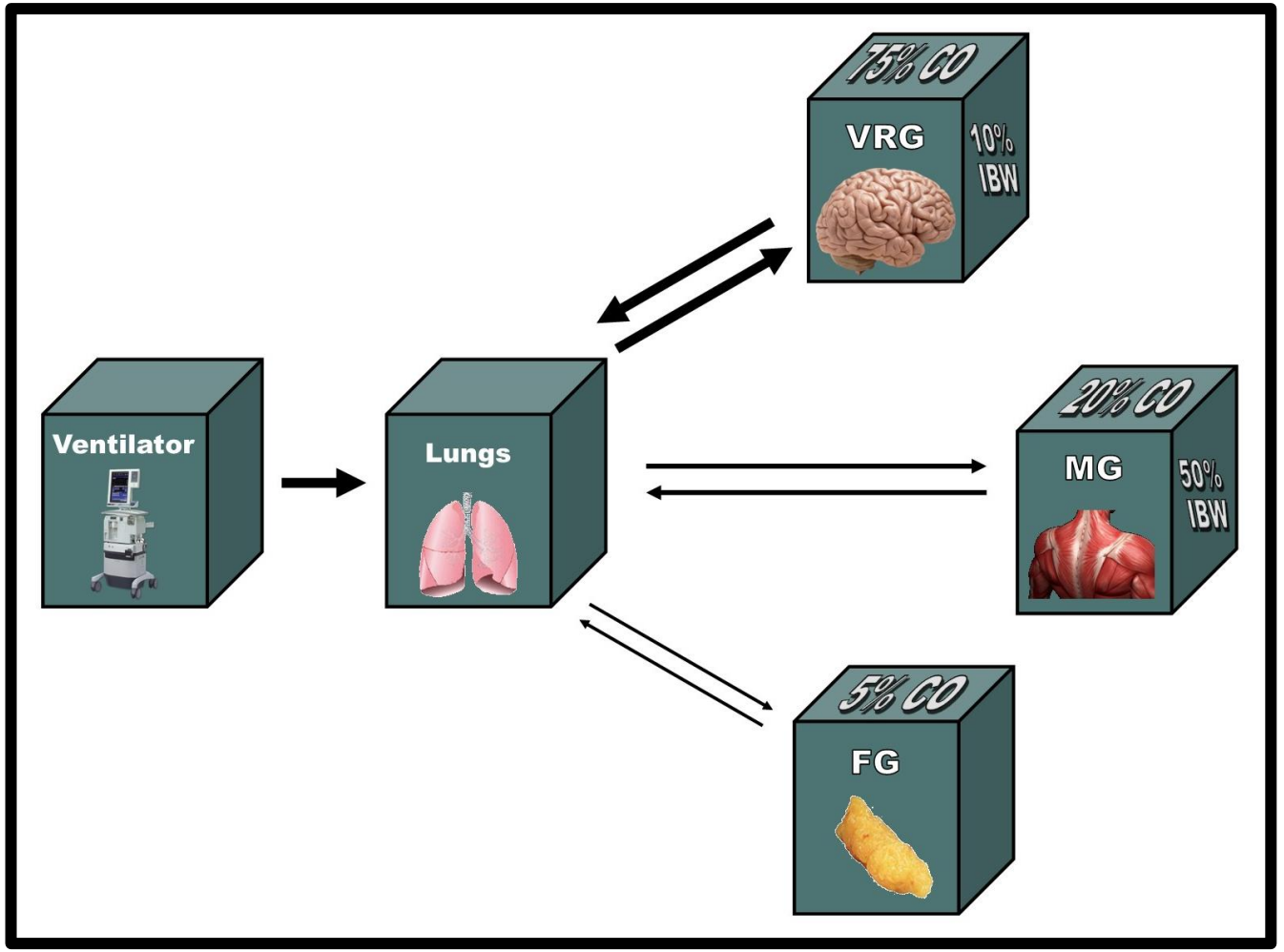
VOLATILE ANESTHETIC UPTAKE

- Tissue blood flow is the most important factor in determining inhalational anesthetic uptake into tissues since anesthetic solubility in different tissues (tissue-blood partition coefficient) does not vary widely compared to tissue blood flow.
  - Vessel-Rich Group (VRG): brain, heart, splanchnic bed and liver. Compromises <10% of body weight, but receives 75% of CO.
    - Equilibration: 4-8 minutes
  - Muscle Group (MG): muscle and skin. Compromises 50% of body weight, but receives 20% of CO.
    - Equilibration: 2-4 hours
  - Fat Group (FG): relatively poorly perfused, but has a great affinity for anesthetics, lengthening equilibration time.



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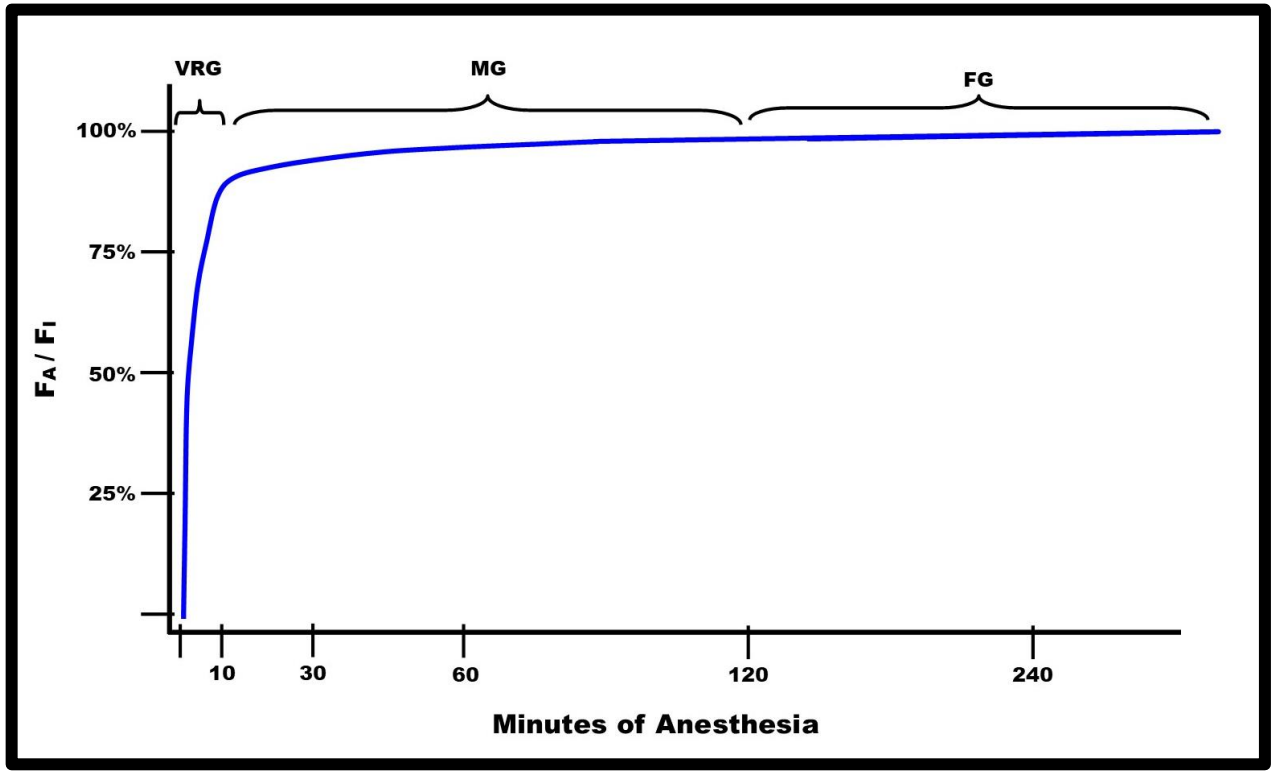
BASIC PRINCIPLES OF VOLATILE ANESTHETICS

- Pharmacologic effect of an inhalation agent is determined by the partial pressure of the anesthetic in the brain.
  - At equilibrium, the anesthetic partial pressure in the brain = blood = alveoli
  - Higher anesthetic gas solubility within a liquid results in lower gas partial pressure → greater solubility means that the gas molecules are more tightly bound to liquid molecules, resulting in less free active gas molecules available to exert pressure.
    - This explains why the partial pressure of highly soluble inhalational agents rises slowly in the blood despite the fact that it is taken up in large quantities by the blood.
  - Potency of inhaled anesthetic gas can be estimated by knowing solubility in olive oil (Meyer-Overton correlation, or lipid solubility-anesthetic potency correlation leading to the unity hypothesis, which notes that a common mechanism accounts for all anesthetic actions).
    - Higher oil:gas coefficient, the lower the MAC
      - Isoflurane OGC: 99 → MAC: 1
      - Desflurane OGC: 19 → MAC: 6



BASIC PRINCIPLES OF VOLATILE ANESTHETICS

- Factors Determining Alveolar Concentration (FA) of Anesthetic Gas
  - (A) Rate of Delivery of Inhalational Agent to the Lung
    - (1) Alveolar Ventilation
    - (2) Inspired Concentration
  - (B) Uptake of the Inhalational Agent by the Blood
    - (1) Solubility
    - (2) Cardiac Output
    - (3) Alveolar-to-Venous Anesthetic Partial Pressure
    - (4) Alveolar-to-Inspired Anesthetic Concentration Relationship (FA/FI)

$$Lung\ Uptake\ of\ Volatile\ Anesthetics = \frac{blood{:}\ gas\ partition\ coefficient\ * CO\ * (P_A - P_{venous})}{barometric\ pressure}$$

VOLATILE ANESTHETICS

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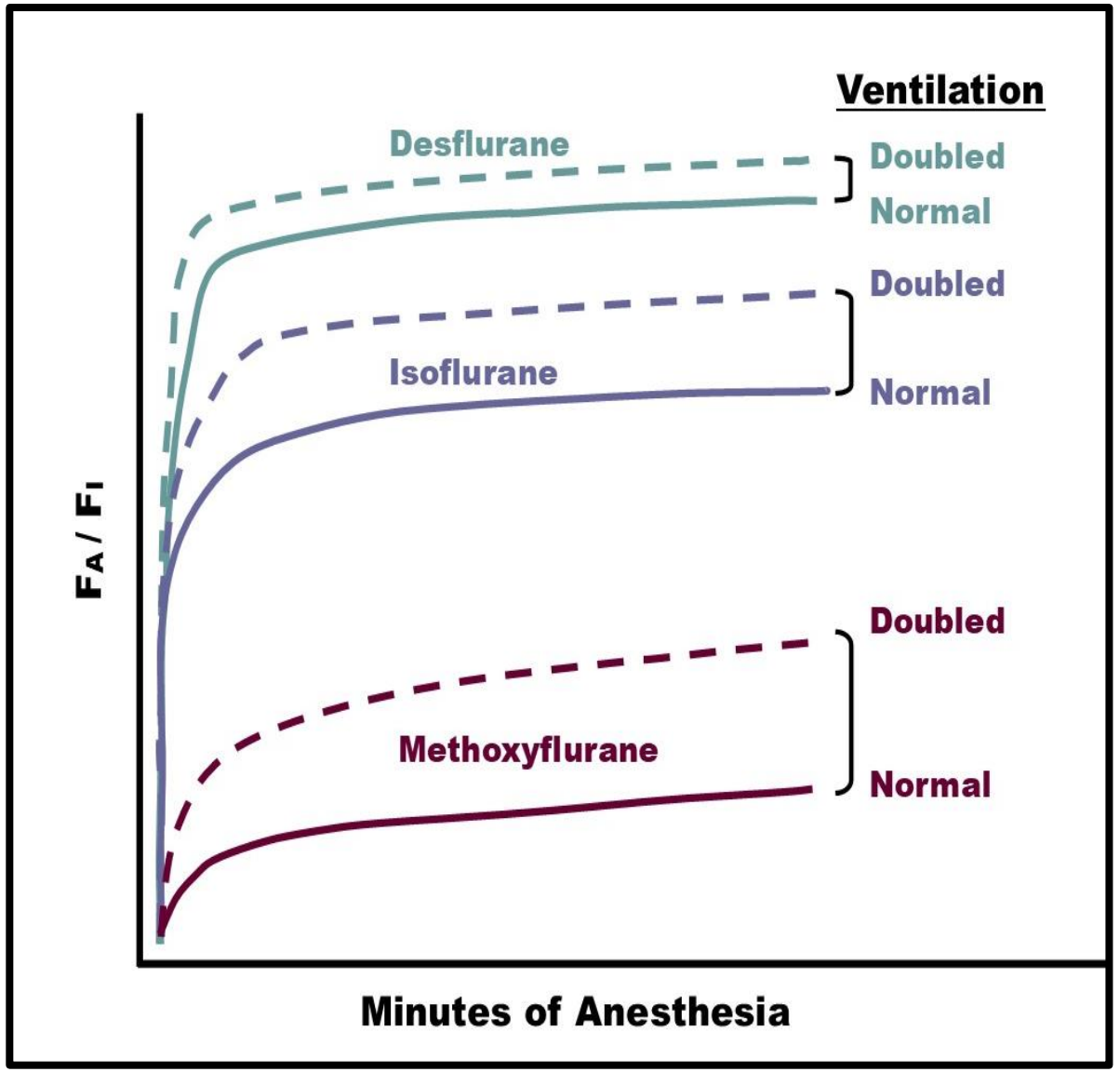
Rate of Delivery of Inhalational Agent to the Lung

- (1) Alveolar Ventilation
  - Increased minute ventilation affects highly soluble anesthetics the most because it replaces the large amount of anesthetic agent that is taken up by the blood.
  - Example: infants have a higher initial uptake of volatile anesthetics than adults due to their increased MV to FRC ratio.
- (2) Inspired Concentration
  - Overpressurization: brief use of higher vaporizer settings than the desired FA to shorten the time needed to reach the target FA.
  - FI is different from the concentration of the agent at the fresh gas outlet from the anesthesia machine, as the fresh anesthesia gas is immediately diluted by the gas in the circuit which is 7-8 L in volume.
    - The rate at which FI approaches the fresh gas concentration (wash-in time) is greatly influenced by the type of circuit and the FGF. Higher FGF leads to shorter wash-in time.



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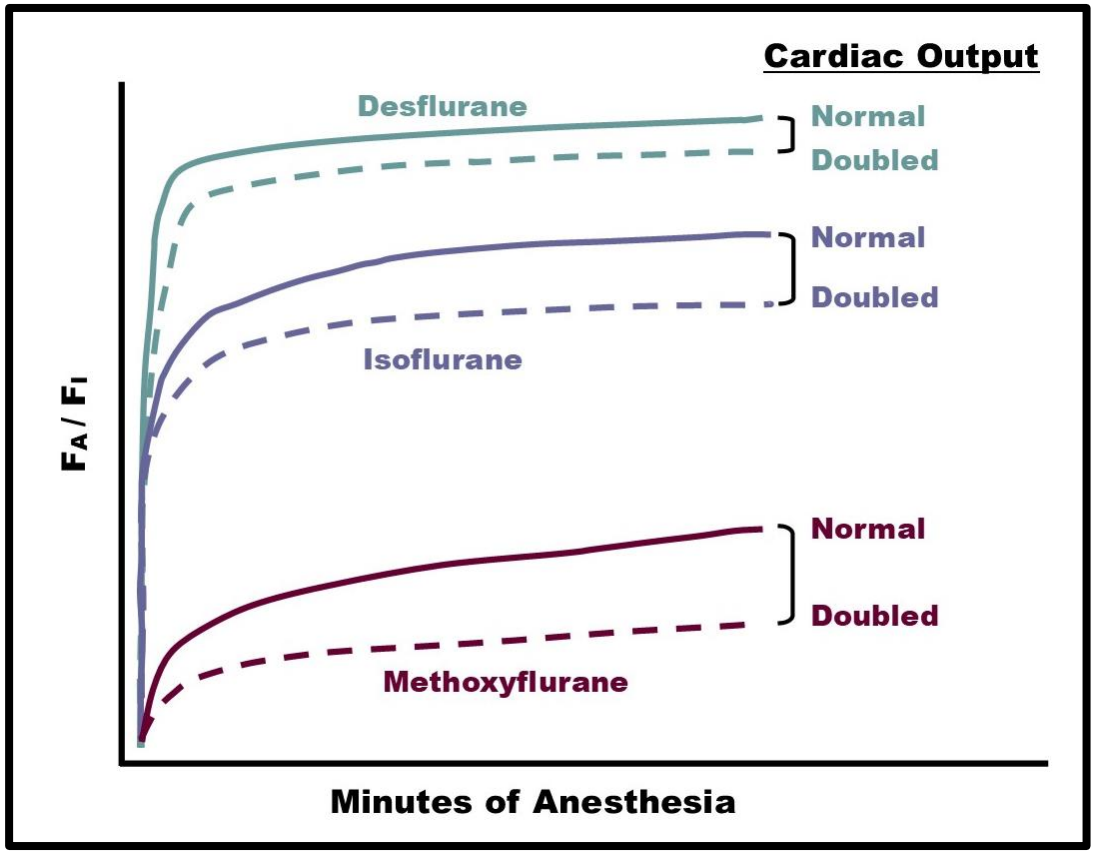
Uptake of the Inhalational Agent by the Blood

- (1) Solubility
  - The greater the solubility of an anesthetic in blood will lead to a higher rate of anesthetic from the lungs → in the case of highly soluble anesthetics, the enhanced blood uptake depletes the alveoli of the anesthetic and lowers their FA and partial pressure, hence a slower induction.
  - Blood-Gas Coefficient is often the most important factor in rise of FA/FI

Desflurane	Nitrous Oxide	Sevoflurane	Isoflurane	Halothane
0.42	0.46	0.69	1.46	2.54

Agent	MAC Value	Blood-Gas Coefficient
Methoxyflurane	0.16	12
Isoflurane	1.2	1.46
Sevoflurane	2.2	0.69
Desflurane	6.6	0.42

- (2) Cardiac Output
  - Higher CO results in slower induction due to increased inhalation agent taken up from the alveoli
    - Largest effect on highly soluble anesthetics



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- (3) Alveolar-to-Venous Anesthetic Partial Pressure Gradient
  - Rate of rise of mixed venous concentration depends on tissue uptake of the anesthetic
  - Tissue blood flow is the most important factor in determining inhalational anesthetic uptake into tissues since anesthetic solubility in different tissues (tissue-blood partition coefficient) does not vary widely compared to tissue blood flow.
    - Vessel-Rich Group (VRG): brain, heart, splanchnic bed and liver. Compromises <10% of body weight, but receives 75% of CO.
      - Equilibration: 4-8 minutes
    - Muscle Group (MG): muscle and skin. Compromises 50% of body weight, but receives 20% of CO.
      - Equilibration: 2-4 hours
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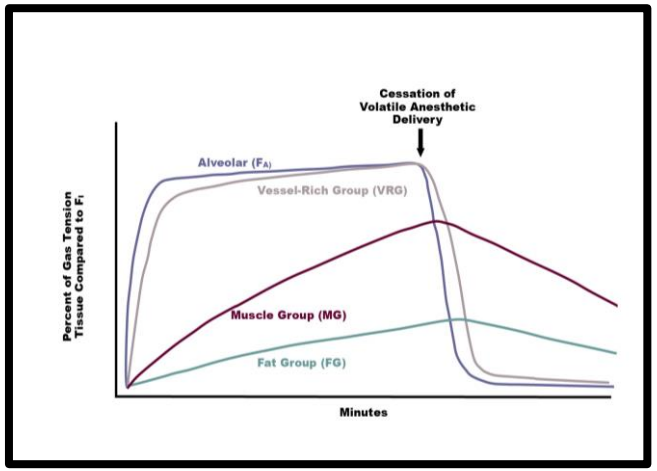

- (4) Alveolar-to-Inspired Anesthetic Concentration Relationship (FA/FI)
  - Initial rapid increase in FA/FI is due to initial absence of anesthetic agent into the blood
  - Height of the FA/FI curve is the ratio at which the balance between anesthetic delivery and uptake is achieved → depends on anesthetic solubility
  - After the first "knee", FA/FI continues to rise at a slower rate due to a progressive decrease in uptake by the VRG.
    - After about 8-minutes, 3/4th of the CO returning to the lungs contains nearly as much anesthetic as it did when it left the lungs.
  - With saturation of the VRG, the MG and FG become the main determinants of tissue uptake. The very slow uptake of these two groups produces the gradual ascent of the terminal portion of the FA/FI ratio.

Factors that Increase FA/FI:	Factors that Decrease FA/FI:
(1) Increased MV	(1) Decreased MV
(2) Decreased CO	(2) Increased CO
(3) Decreased blood solubility	(3) Increased blood solubility
(4) Low P arterial – P venous (less blood uptake)	(4) High Parterial – P venous (more blood uptake)

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V/Q MISMATCH AND FA/FI

- Dead Space (reduced CO, PE)
  - Speed of induction of inhalational agents is increased
  - More obvious for MORE SOLUBLE agents
- Intrapulmonary Shunt (mainstem intubation, foreign body in mainstem bronchus)
  - R → L shunt (either intrapulmonary or intracardiac): inhalational induction will be slower due to the dilution of the anesthetic agent when venous blood that has bypassed the lungs mixes with arterial blood.
  - More obvious for LESS SOLUBLE agents (desflurane, N2O) since the small amount of gas dissolved in the blood becomes almost nonexistent s/p mixing.

Shunt	Inhalational Agents	Intravenous Agents
Intrapulmonary (R → L)	Decreased Induction Speed	Minimal / No Effect
Intracardiac (R → L)	Decreased Induction Speed	Increased Induction Speed
Intracardiac (L → R)	Minimal / No Effect	Minimal / No Effect

VAPOR PRESSURE AND VAPORIZERS

- Vapor Pressure
  - Pressure exerted by vapor (gaseous) phase of a substance when equilibrium with the solid and/or liquid phase of the substance at a given temperature in a closed system.
    - Higher vapor pressure indicates the substance is more likely to evaporate at a given temperature than a substance with a lower vapor pressure.
      - Volatile anesthetics are liquids at room temperature but have relatively high vapor pressure and evaporate easily. Vaporizers are used to reliably convert the liquid phase into gas in an amount which may then be precisely delivered to patients.

HI-SE
- Halothane, Isoflurane have similar vapor pressures around 240 mmHg
- Sevoflurane, Enflurane have similar vapor pressures around 160-170 mmHg

Inhalational Anesthetic	Vapor Pressure (mmHg)
Nitrous Oxide	38,770
Desflurane	669
Halothane	243
Isoflurane	238
Enflurane	172
Sevoflurane	157

Q: What happens when you fill a sevoflurane vaporizer with isoflurane?
A: Deliver an overdose since isoflurane has a higher vapor pressure than sevoflurane; more isoflurane will be evaporated at the same pressure.

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EQUATIONS RELATED TO VOLATILES AND VAPORIZERS

- Volume of anesthetic that passes through a variable bypass vaporizer:
  - Volume (ml) = FGF * (Pvap / [Pbar – Pvap])
    - At higher altitude the barometric pressure is half that at sea level, the amount of isoflurane vapor output increases due to the lower barometric pressure. Therefore the settings that delivered 2% isoflurane now delivers 4% isoflurane. However, according to Dalton's law, the partial pressure of isoflurane delivered would be approximately the same at both altitudes since 2% isoflurane at 760 mmHg (15.2 mmHg) is the same as 4% isoflurane at 380 mmHg (15.2 mmHg).
- Anesthetic Uptake
  - Anesthetic Uptake = solubility * CO * (alveolar-venous partial pressure difference / barometric pressure)
- Time constant to reach a state of equilibrium in the anesthesia circuit
  - Time Constant (min) = Volume or capacity of the circuit (L) / FGF (L/min)
    - 63%, 84%, 95% and 99% of equilibrium will be reached after 1, 2, 3 and 4 time constants, respectively
    - Time constants also apply to the tissue-blood partition coefficients (3-time constants for complete equilibrium)
      - Isoflurane time constants: 3-4 minutes. Brain equilibrium: 10-15 minutes
      - N2O, desflurane, sevoflurane time constants: 2-minutes. Brain equilibrium: 6-minutes.
- Amount of liquid anesthetic consumed:
  - Short Answer
    - 1ml of liquid volatile agent ~200ml of vapor
      - Based on ideal gas law
      - Example: 4 L/min for 5-minutes = 20 L FGF. 1% isoflurane means diluting 200ml vapor in 20 L FGF and 200ml vapor is approximately 1ml liquid.
  - Medium Answer
    - Shortcut for calculating the volume of liquid anesthetic in 1-hour is as follows:
      - Liquid volatile anesthetic (ml/hr) ~ 3 * FGF (L/min) * volume % anesthetic vapor
        - Example: 3 * 4 L/min * 1% = 12 ml/hr → 1 ml in 5-minutes
  - Long Answer
    - To calculate the amount of liquid consumed, one must first calculate the volume of anesthetic vapor delivered:
      - %V = V / (V + FGF) → V = (%V * FGF) / (1 – %V)
        - Example: V = (0.1 * 4000) / (1 – 0.01) = 40.4 ml/min → 202 ml in 5-minutes → ~1ml liquid isoflurane

VOLATILE ANESTHETICS

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MAC

- Definition: alveolar concentration of an anesthetic gas at one atmosphere that prevents movement in response to surgical stimulus in 50% of patients. Analogous to ED50 for intravenous medications.
  - Standard deviation is 10% → 95% of patients should not move in response to 1.2 MAC and 99% should not move in response to 1.3 MAC.
- Types of MAC
  - MAC-BAR: alveolar concentration of anesthetic that blunts the adrenergic response to noxious stimulation (approximately 50% higher than standard MAC)
  - MAC-Awake: alveolar concentration at which a patient will open their eyes on command; typically 0.1-0.5 MAC

Stimulus	Isoflurane	Propofol
Direct Laryngoscopy	1.0% end tidal	9.8 mcg/ml
Endotracheal Intubation	1.76% end tidal	17.4 mcg/ml
Surgical Incision	1.16% end tidal	10.0 mcg/ml
Tetanus by Nerve Stimulation	1.03% end tidal	9.3 mcg/ml

Factors that increase MAC	Factors that decrease MAC
Hyperthermia	Hypothermia
Chronic EtOH Use	Acute EtOH Intoxication
Recreational Drugs (amphetamines, cocaine, ephedrine)	Anemia (Hb <5 g/dl)
Chronic Use of Sedatives (ex: BDZ)	Hypoxemia
Previous repeated exposures to anesthetics	Severe Metabolic Acidosis
Age (highest at 6-months)	Age (6% decrease per decade after age 40)
Hypernatremia	Hyponatremia
Magnesium (decreases MAC for TIVA)	Severe HoTN (SBP <50 mmHg)
Red Hair (melanocortin-1 receptor gene) – CONTROVERSIAL --	Pregnancy
	Drugs (next slide)

Factors that do NOT affect MAC
- Thyroid Function
- Hypo- or Hypercapnia
- Duration of Anesthesia
- Gender
- Hyperkalemia
- Metabolic Alkalosis

VOLATILE ANESTHETICS

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PHYSIOLOGIC EFFECTS

Table created from data in:
Torri, G. "Inhalation Anesthetics: a Review." *Minerva Anestesiologica*, vol. 75, no. 3, 27 Oct. 2009, pp. 215–228.
Butterworth, John F., et al. "Inhalation Anesthetics." *Morgan & Mikhail's Clinical Anesthesiology*, 6th ed., McGraw-Hill Education, New York, 2018.

		Isoflurane	Sevoflurane	Desflurane	Notes:
Cardiac	HR	Increase	Unchanged*	Increase	* Increased HR is noted for sevoflurane with concentrations >1 MAC
	SVR	Decrease**	Decrease	Decrease	SVR decrease is primarily related to peripheral vascular effects, NOT CO. Halothane primarily effects CO rather than SVR. ** Isoflurane may cause coronary steal phenomenon
	CO	Decrease	Decrease	Decrease	
Respiratory	Vt	Decrease ***			RR increase is reflex from decreased Vt. MV is NOT maintained as increased RR does not offset decreased Vt. *** Decrease in RR is greatest with isoflurane.
	RR	Increase			
Neurologic	CBF	Increase			Balance of decreased flow from decreased CMRO2 and increased flow from volatile-induced vasodilation.
	ICP	Increase			Increased ICP secondary to increased CBF from vasodilation. Can be offset by normocapnia.
	CMRO2	Decrease			
	Epileptiform Activity	None	Controversial	None	Light Anesthesia: EEG voltage increases and frequency decreases Deep Anesthesia: EEG activity decreases
Neuromuscular	NMB	Enhance			Decreased dose of NMB is required with volatiles.
Renal	RBF, GFR, UOP	Decrease			Secondary to systemic decreases in SVR.
Metabolism		0.2%	5%	0.1%	Halothane: 80% metabolism, Enflurane 2% metabolism

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CURRENTLY USED VOLATILE ANESTHETICS

- Sevoflurane
  - MAC: 2.2%
  - Blood-Gas Solubility: 0.69
  - Sweet smelling, minimal order, least amount of airway irritation among the volatile anesthetics.
  - Produces the largest concentration of fluoride ions following hepatic metabolism
    - 5-8% hepatic metabolism, results in an increase in serum fluoride concentration, however it does not cause a renal concentrating effect due to decreased solubility in blood and tissues.
      - Fluoride production rapidly decreases once anesthetic is no longer administered.
    - The degree of renal metabolism of inorganic fluoride ions, a process known as defluorination, contributes to nephrotoxicity (sevoflurane is minimally defluorinated within the kidneys)
      - Nephrotoxicity from inorganic fluoride is a high-output renal failure that does not respond to vasopressin. It is a result of direct fluoride ion toxicity to the collecting ducts, which inhibits the effect of antidiuretic hormone (ADH). Characterized by hypovolemia, polyuria, elevated BUN, elevated creatinine, serum hypernatremia and serum hyperosmolality

Opioids decrease RR but maintain Vt
Volatiles maintain RR but decrease Vt

- Isoflurane
  - MAC: 1.1%
  - Blood-Gas Solubility: 1.46
  - Great physical stability; undergoes essentially no deterioration during storage for up to 5-years.
  - Side Effects:
    - Isoflurane at MAC 1.0 increases HR by about 10-15 bpm and decreases SVR leading to a decrease in SBP
    - Coronary Steal Phenomenon (coronary vasodilation redirects blood flow away from fixed stenotic coronary branches)
    - Mild reduction in MV, reduced VT, increased RR
- Desflurane
  - MAC: 6.6%
  - Blood-Gas Solubility: 0.42
  - Most pungent of the volatile anesthetics → coughing, salivation, breath holding, laryngospasm
  - Degrades to form CO in desiccated CO2 absorbents
  - Increases HR and decreases SVR while maintaining CO
    - Rapid change in desflurane concentration leads to increased HR, thought to be due to the baroreceptor reflex
    - Dose-dependent depression of myocardial function; CO is maintained via increased HR
      - No effect on LV diastolic function

VOLATILE ANESTHETICS: TOXICITIES

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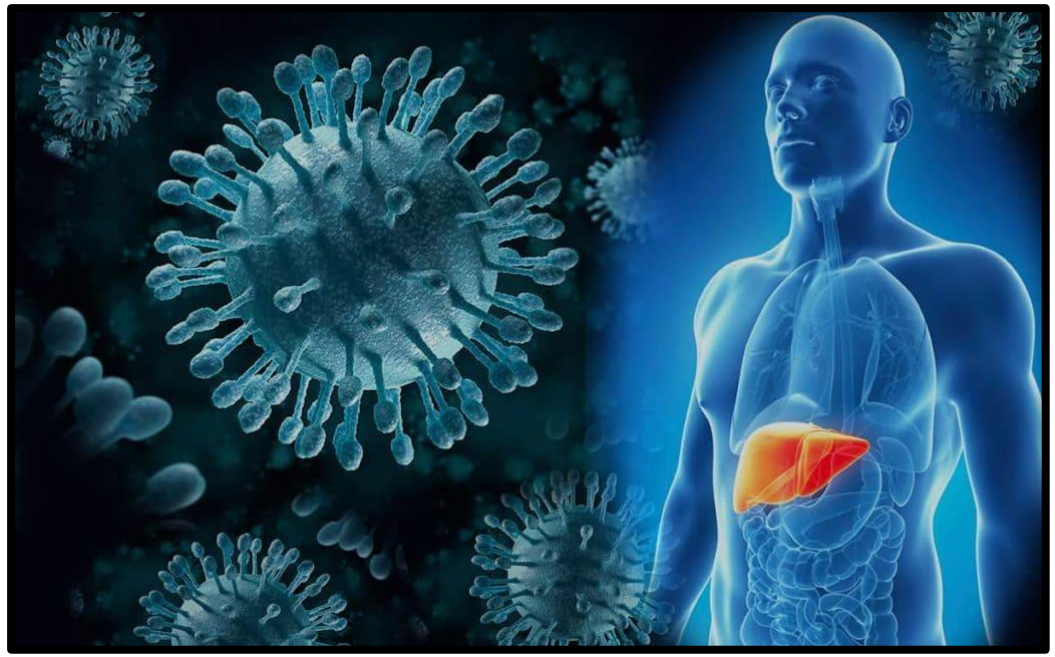
HALOTHANE HEPATITIS

- Incidence
  - 20% of adults develop subclinical hepatotoxicity that is reversible and innocuous
  - Fulminant hepatotoxicity (halothane hepatitis) develops rarely but is fatal 50-75% of the time (usually related to multiple exposures and is likely secondary to an immune response)
- Mechanism:
  - (1) Direct Hepatotoxicity from Halothane Metabolites
    - Halothane metabolites (trifluoroacetic acid, difluorochloroethylene) are free radicals which cause direct acute hepatic toxicity via irreversible binding and destroying hepatocellular structure
    - Halothane is the most extensively metabolized inhalational anesthetic (~20%)
  - (2) Immune-Mediated Sensitivity
    - Metabolites may act as haptens triggering immune-mediated sensitivity
    - Cross-sensitivity may occur with all volatile anesthetics except sevoflurane (no cases of immune-mediated hepatitis to date)
- Risk Factors: obesity (fat stores may act as “reservoir” for halothane), middle age, female (2:1), genetic factors



VOLATILE ANESTHETICS: TOXICITIES

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NEPHROTOXICITY

- Vasopressin-Resistant Polyuric Renal Insufficiency
  - Negative fluid balance, elevated serum sodium, elevated BUN, increased serum osmolality, fixed urinary osmolality similar to serum concentration (similar to nephrogenic diabetes insipidus)
  - Symptoms usually resolve within 10-20 days, though have been noted for up to 1-year
- Mechanism: fluoride-induced nephrotoxicity
  - Fluoride ions are released during biotransformation of **methoxyflurane, enflurane and sevoflurane**
  - Precise mechanism of nephrotoxicity is unclear. Hypothesis: fluoride inhibits adenylate cyclase, interfering with ADH activity on the nephron's DCT
- Methoxyflurane: creates the largest concentration of inorganic fluoride ions and fluoride-induced nephrotoxicity.
  - Methoxyflurane's extreme lipophilicity results in very long residence in tissues, which contributes to this toxicity.
- Enflurane: metabolized by CYP2E1.
  - Consider avoiding enflurane in patients on medications which chronically induce CYP2E1 (isoniazid, ethanol, phenobarbital, phenytoin, etc.)
- Sevoflurane:
  - Sevoflurane produces a larger amount of fluoride ions than enflurane, however the concentration of fluoride rapidly declines with cessation of administration owing to sevoflurane's low blood and tissue solubility.
  - Compound A: vinyl ether generated when the alkali in carbon dioxide absorbents, noted to be induce nephrotoxicity and hepatotoxicity in rats. Human studies have NOT noted Compound A-induced nephrotoxicity.
    - Low-flow sevoflurane has been noted to cause subtle transient changes in glomerular and tubular function in healthy individuals (mean duration: 6.7 hours). Clinical significance of these findings is unclear.

Fluoride Ion Production:
Methoxyflurane > Sevoflurane > Enflurane

Fluoride-Induced Nephrotoxicity
Nephrotoxicity >50 micromole/L
Moderate Renal Injury: 50-80 micromole/L
Severe Injury: >80 micromole/L

TQA:
Differential for postoperative renal failure includes vasopressin-resistant polyuric renal insufficiency secondary to volatile anesthetics, however more common etiologies are pre-renal causes from hypovolemia, decreased perfusion from increased intra-abdominal pressure, etc.

Pre-Renal	Vasopressin-Resistant Renal Insufficiency
Increased Serum Osmolality	Increased Serum Osmolality
Increased Urine Osmolality	**Decreased** Urine Osmolality

VOLATILE ANESTHETICS: TOXICITIES

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NEUROTOXICITY

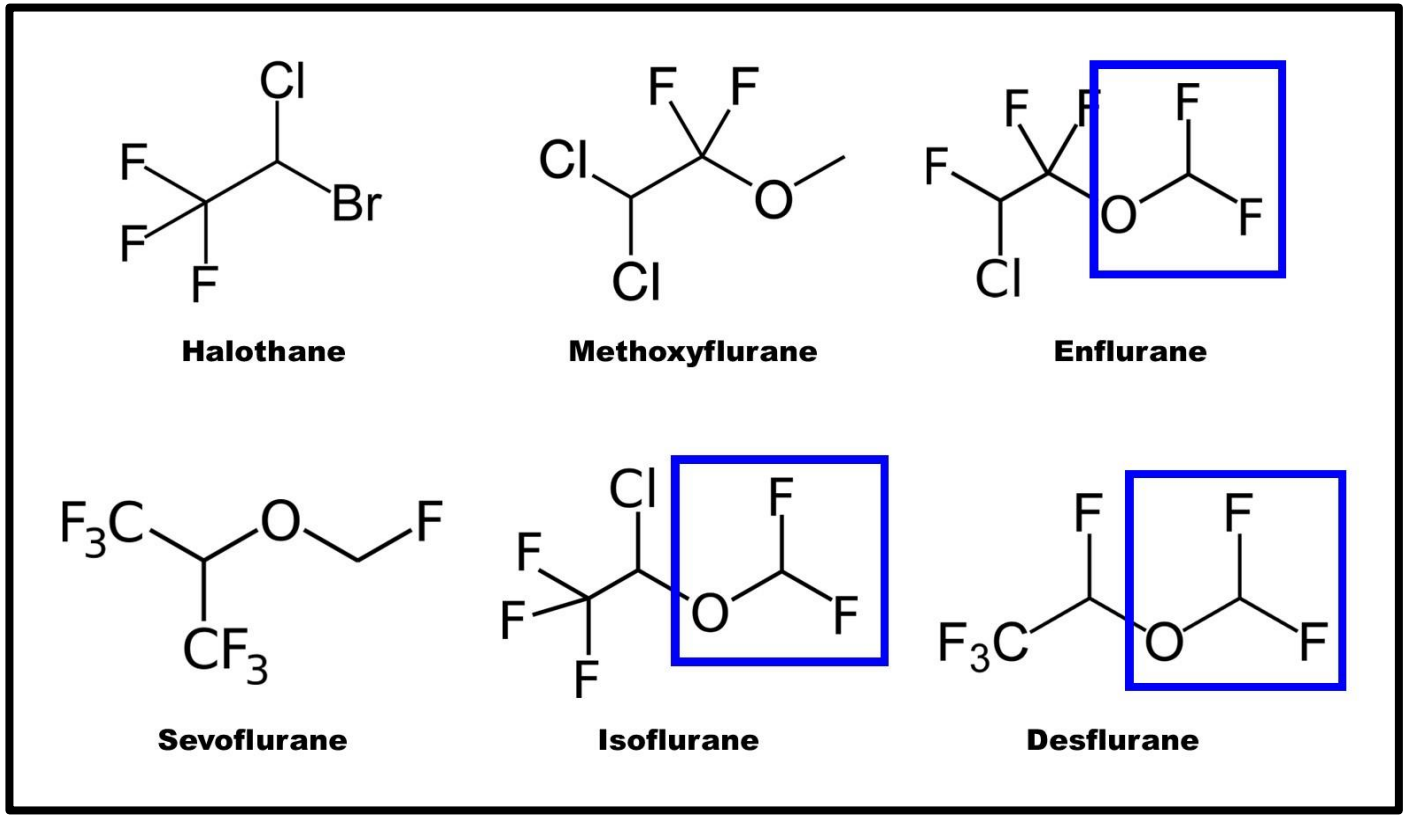
- Animal Data
  - Morphological and functional changes occur in the developing brain (rats, nonhuman primates, etc.) including accelerated neuronal apoptosis, deficits in learning and altered behavior
    - Effects are related to the dose and duration of exposure
    - Unclear if the functional deficits are related to the observed morphological changes
  - Difficulty in application of animal studies to human studies due to complexity and long duration of brain development in humans, extraordinary vulnerability to injury during specific times in development and neuronal plasticity allowing for recovery
- Human Data
  - 2016 PANDA (Pediatric Anesthesia NeuroDevelopment Assessment) Trial (Sun, et al)
    - No significant difference in neuropsychological testing in sibling-matched pairs between the sibling who had an anesthesia exposure prior to 36-months of age for inguinal hernia surgery (average anesthesia duration: 80 minutes), and the sibling without anesthesia exposure
  - 2016 GAS (General Anesthesia compared to Spinal anesthesia) Trial
    - Compared infants who underwent hernia repair with awake-spinal versus inhaled general anesthesia (<1-hour sevoflurane)
      - Age 2 = equivalent neurodevelopmental outcomes (Davidson, et al)
      - Age 5 = equivalent neurodevelopmental outcomes (McCann, et al)
  - 2018 MASK (Mayo Anesthesia Safety in Kids) Trial (Warner, et al)
    - Compared children without anesthesia exposure, single anesthesia exposure and multiple anesthesia exposures. Neuropsychological testing occurred at ages 8-12 years or 15-20 years.
      - IQ did not differ significantly based on exposure status (single exposure scored 0.5 points lower, multiple exposure scored 1.3 points lower)
      - Secondary outcomes noted decreased processing speed and fine motor abilities in children after multiple exposures, but not after a single exposure

VOLATILE ANESTHETICS: TOXICITIES

M. Jablonski, 2020-2021

CARBON MONOXIDE PRODUCTION

- Carbon Monoxide Production:
  - Generated from degradation of difluoromethoxy (CF_2O) moiety found in **desflurane, enflurane** and **isoflurane**
- Contributing Factors:
  - Water Content of Carbon Dioxide Absorbent
    - CO Production is inversely proportional to the water content of CO2 absorbents
    - Desiccated CO2 absorbents accelerate CO production
      - If fresh gas flows are left on overnight or over the weekend, CO2 absorbent should be changed. Monday mornings have the highest rate of CO2 absorbent desiccation.
  - Type of Carbon Dioxide Absorbent
    - Baralyme and Soda Lime contain strong alkalis (KOH, NaOH) which initiate the reaction that forms CO
  - Temperature
  - Anesthetic Concentration
- Detection
  - Co-Oximetry (rarely used in the OR)
  - Enflurane detected by mass spectrometry when using desflurane or isoflurane
    - Mass spectrometry cannot directly detect CO as the molecular weight is equivalent to nitrogen
    - Trifluoromethane produced by the degradation of isoflurane and enflurane causes false readings for enflurane



VOLATILE ANESTHETICS: TOXICITIES

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ENVIRONMENTAL EFFECTS

- Intergovernmental Panel on Climate Change (IPCC) Fourth Assessment Report Definitions:
  - **Ozone Depleting Potential (ODP):** ratio of integrated perturbations to total ozone relative to an equal emission of CFC-12
    - CFC-12, dichlorodifluoromethane, is a potent greenhouse gas previously used in air conditioners for automobiles and trunks
  - **Global Warming Potential (GWP):** cumulative radiative retention integrated over a period of time from the emission of gas relative to the reference gas (carbon dioxide)
    - GWP considers the heat-trapping efficiency and life-span of atmospheric gases
- Mechanism:
  - Exposure of anesthetic agents to intense ultraviolet radiation breaks the carbon-halogen bonds, creating halogen radicals that catalytically destroy the ozone
  - Ozone depletion by halocarbons depends on molecular weight, number and type of halogen atoms and atmospheric life span
    - Chemicals with a lifetime of >2-years are thought to reach the stratosphere in significant quantities

Compound	Lifetime (years)	GWP (20-years)
Carbon Dioxide	2-500	1
Nitrous Oxide	114	289
Isoflurane	3.6	1401
Sevoflurane	1.2	349
Desflurane	10	3714

Table Created from Data in:
United States, Congress, Forster, Piers, and Venkatachalam Ramaswamy. *Climate Change 2007: The Physical Science Basis: Summary for Policy Makers, a Report of Working Group I of the Intergovernmental Panel on Climate Change; and: Technical Summary, a Report Accepted by Working Group I of the IPCC but Not Approved in Detail; and: Frequently Asked Questions*, Intergovernmental Panel on Climate Change, 2007, pp. 129–234.
Ryan, S. M., & Nielsen, C. J. (2010). Global warming potential of inhaled anesthetics. *Anesthesia & Analgesia*, *111*(1), 92–98. https://doi.org/10.1213/ane.0b013e3181e058d7

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OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

AND ASSOCIATED DISEASE STATES

OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

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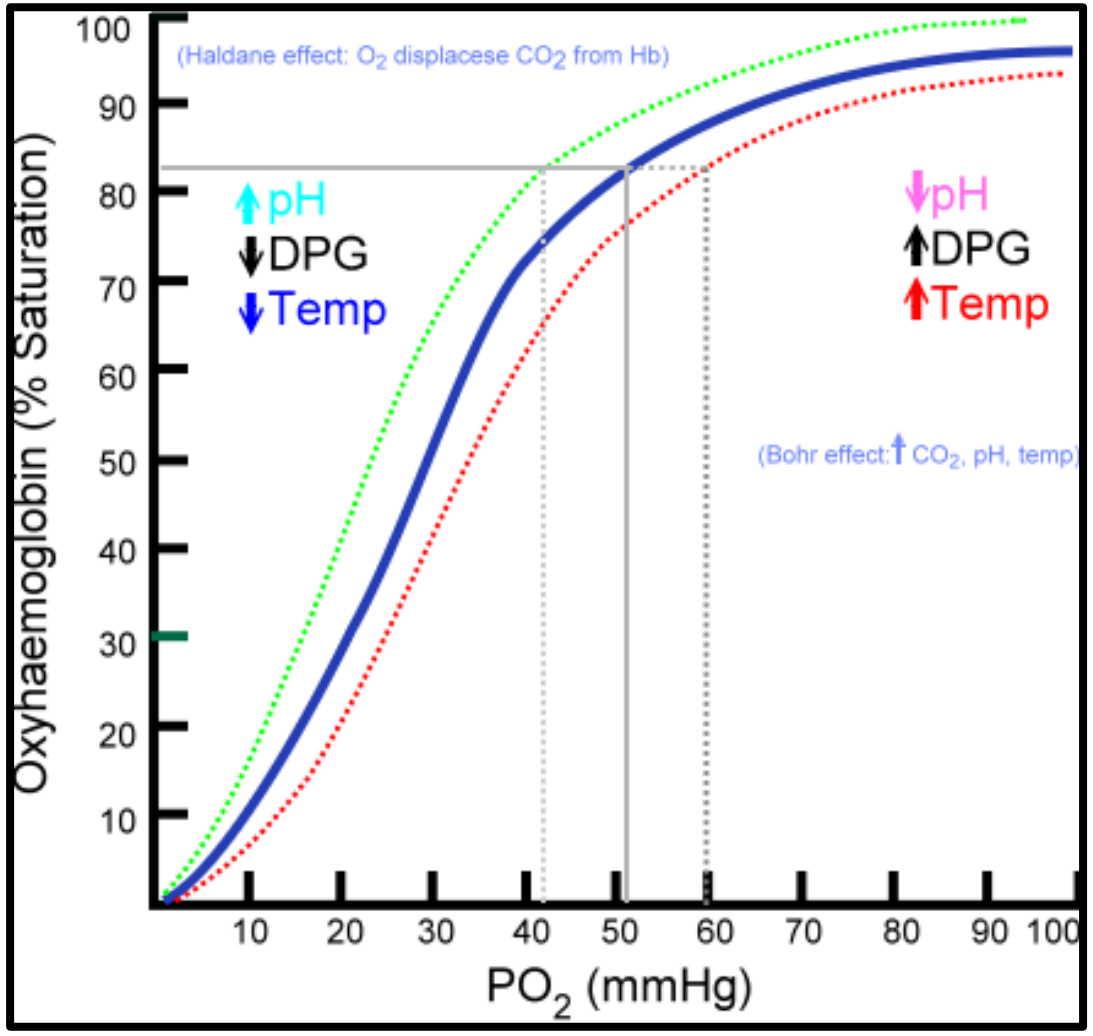
THE BASICS

- Hemoglobin P50: 27 mmHg
  - i.e. oxygen tension at which hemoglobin is 50% saturated
  - Fetal Hemoglobin P50: 19 mmHg
  - Maternal Hemoglobin P50: 30 mmHg
- Left Shift – i.e. Hb has an increased affinity for oxygen
  - HbF,
  - Carbon monoxide poisoning
  - Alkalosis
  - Hypocarbia
  - Hypothermia
  - Decreased 2,3-DPG (e.g. pRBC transfusions, septic shock, hypophosphatemia)
  - Methemoglobinemia
- Right Shift – i.e. Hb has a decreased affinity for oxygen
  - Acidosis and/or Hypercarbia (Bohr Effect)
  - Hyperthermia
  - Increased 2,3-DPG (hyperphosphatemia, thyroxine/hyperthyroidism, chronic anemia, cirrhosis, sleep apnea syndrome, CHF, high-altitude, hypoxia)
  - Propanolol in CAD



OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

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DISEASE STATES

- **Carbon Monoxide Poisoning**
  - Pathophysiology: carbon monoxide has an affinity for Hb that is 200-300x stronger than oxygen → COHb preferentially forms → LEFT shift of oxygen-hemoglobin dissociation curve →
    - Oxygen that does bind COHb does not dissociate
    - CO disrupts mitochondrial function, leading to less ATP production and uncoupled oxidative phosphorylation
      - Tissue hypoxia, anion-gap metabolic acidosis
  - Diagnosis: co-oximetry with elevated COHb (>15%) on ABG
    - ABG: metabolic acidosis with normal PaO2, falsely elevated SaO2 and SpO2
      - Note on ABGs: SaO2 is a derived number based on the measured PO2 and the assumption that all hemoglobin is normal (i.e. oxy- or deoxy- hemoglobin)
  - Treatment: High FiO2 (displaces CO), hyperbaric oxygen (for patients with COHb >30% and/or severe symptoms (obtundation, delirium, bradycardia, etc.)
- **Sulfhemoglobinemia**
  - Pathophysiology: rare condition believed to be caused by irreversible binding of a sulfur atom to the porphyrin ring of the heme moiety of hemoglobin
    - RIGHT shift of hemoglobin-oxygen dissociation curve
      - Better tolerated, often missed
  - Causes: sulfonamides, dapsone, metoclopramide, sumatriptan, some industrial chemicals
  - S/S: dark greenish-black color to blood
  - Treatment: none (must wait for new RBC synthesis)
- **Methemoglobinemia**
  - Pathophysiology: altered state of Hb in which the ferrous (Fe2+) iron molecules haves been oxidized to ferric (Fe3+), making them unable to carry oxygen
    - Methemoglobin must be converted back to its Fe2+ form by methemoglobin reductase (MHgbR), a NADPH dependent process (electron donor)
    - MetHb levels reach 15%, new oxygen is unable to bind → LEFT shift of oxygen-hemoglobin dissociation curve
      - Cyanosis develops when 1.5g/dl of MetHb are present in blood (compared to 5g/dl for normal deoxygenated blood)
      - Note on ABGs: SaO2 is a derived number based on the measured PO2 and the assumption that all hemoglobin is normal (i.e. oxy- or deoxy- hemoglobin)
        - Pulse oximetry reads 85%
  - Causes: congenital methemoglobinemia (deficiency in MHghR), G6PD (deficiency in NADPH production), medications (prolocaine (dose-dependent, > 500mg), benzocaine (NOT dose-dependent), quinine, metoclopramide, sulfonamides, dapsone, chloral hydrate, chloroquine, nitric oxide, nitroglycerin, benzene, analine dyes
  - Treatment:
    - Methylene Blue (1-2 mg/kg infused over 3-5 minutes)
      - Pulse oximetry transiently decreases (approaches 65% for roughly 10-minutes)
      - Monoamine oxidase inhibitor → can precipitate serotonin syndrome in combination with SSRIs with doses >5 mg/kg
        - Consider indigo carmine dye
    - Ascorbic Acid (Vitamin C) is used in G6PD-deficiency since methylene blue can cause hemolysis in G6PD-deficiency

Sulfhemoglobinemia verses Methemoglobinemia:
(1) Methemoglobinemia shifts hemoglobin dissociation curve to the LEFT. Sulfhemoglobinemia shifts to the RIGHT.
(2) Methemoglobinemia has a specific treatment (methylene blue, vitamin C). Sulfhemoglobinemia has no treatment.
(3) Methemoglobinemia blood is chocolate-brown color. Sulfhemoglobinemia blood is dark green-black color.

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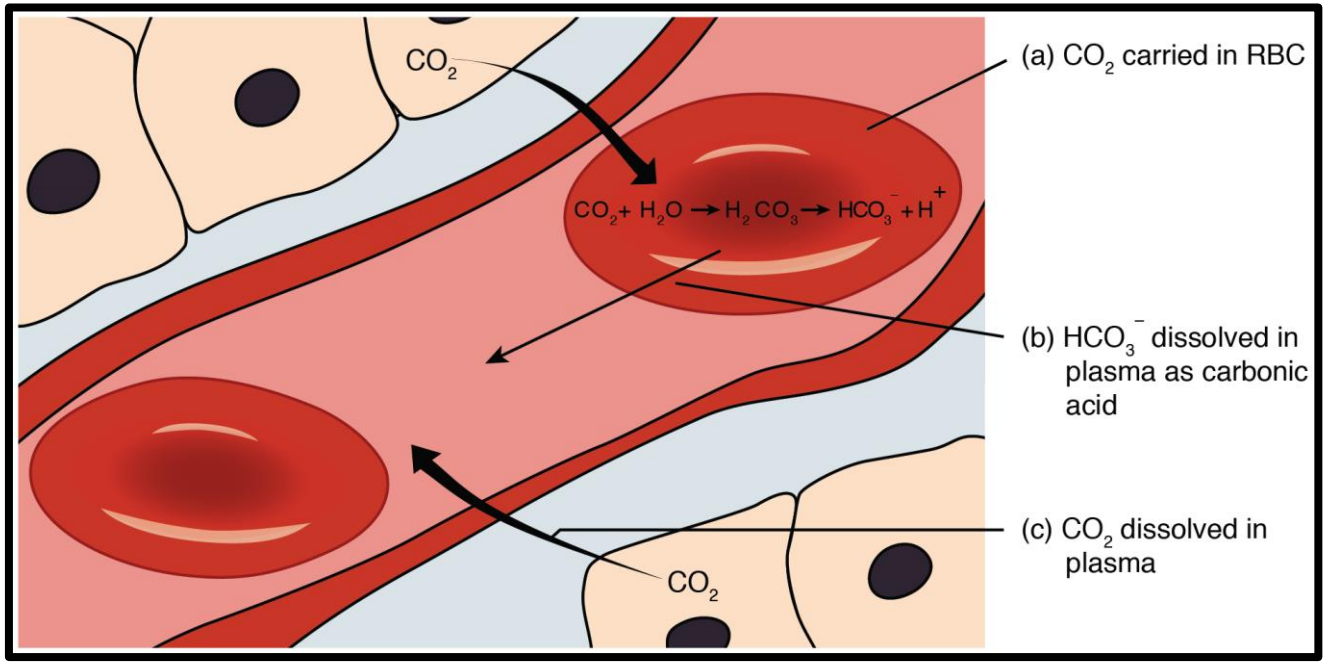
BOHR EFFECT, HALDANE EFFECT & CHLORIDE SHIFT

- Bohr Effect
  - Shift of the oxygen-hemoglobin dissociation curve caused by changes in the concentration of CO2 or pH of the environment → increases delivery of oxygen to acidotic and hypoxic tissues.
  - Binding of hydrogen ions to Hb chains leads to oxygen dissociation. Acidosis shifts the oxygen-hemoglobin dissociation curve toward the right → ultimately permits more CO2 to be transported from the tissue to the lungs during gas exchange.
- Haldane Effect
  - Hemoglobin's ability to increased amounts of CO2 in the deoxygenated state as opposed to the oxygenated state.
    - Deoxygenated hemoglobin has 3.5x more capacity for CO2 than oxygenated hemoglobin → explains the ability for Hb to carry CO2 from the tissues to the lungs for exhalation.
      - To maintain electrical neutrality, chloride replaces HCO3 which diffuses out of cells (chloride shift)
- Chloride Shift
  - Reaction in which bicarbonate is exchanged for a chloride ion across the RBC membrane. Bicarbonate is formed by the reaction of CO2 and H2O via carbonic anhydrase.



bOHR
Oxygen, Hydrogen Released in tissue

HAlDane
Hemoglobin's Affinity for carbon Dioxide

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NITROUS OXIDE

PHARMACODYNAMICS

CONCENTRATION EFFECT

SECOND GAS EFFECT

N2O AND CLOSED SPACES

NITROUS OXIDE

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PHARMACODYNAMICS

- MOA: Interaction with a variety of receptors:
  - Alpha-Adrenergic Agonism = analgesia, sympathomimetic effects
  - NMDA Antagonism = analgesia, CNS depression
  - CNS Dopaminergic Neuron Stimulation → release of endogenous opioids (analgesic properties)
    - Unlike volatile anesthetics, N2O does NOT affect the GABA receptor
- Characteristics:
  - MAC: 104%
  - Blood-Gas Solubility: 0.47 (N2O is approximately 34x more soluble than nitrogen)
  - Supports combustion; odorless
- Physiologic Effect:
  - Sympathomimetic (increases CO, SVR).
    - Does NOT inhibit hypoxic pulmonary vasoconstriction → increase PVR can be catastrophic in patients with PHTN
  - NO skeletal muscle relaxation; NO effect on uterine contractility
  - Increased PONV
  - Mild analgesic properties (30% N2O ~ 10-15mg morphine)
- Side Effects:
  - Megaloblastic Anemia: N2O oxidizes the cobalt atom within vitamin B12, inhibiting vitamin B12-dependent enzymes such as methionine synthetase (important for DNA synthesis and myelin production)
  - Chronic Exposure:
    - Polyneuropathy (indistinguishable from subacute combined degeneration of the spinal cord associated with pernicious anemia; symptoms include extremity numbness/paresthesia, weakness, truncal ataxia)
    - 2-3 fold increase in spontaneous abortion rates, infertility and higher rate of congenital abnormalities in offspring
    - 1.2-1.8 fold increase in liver, kidney and neurologic diseases

Physiologic Effect		Nitrous Oxide
Cardiovascular	SVR	Increase
	CO	Increase
Respiratory	RR	Increased
Neurologic	ICP	Increased
Neuromuscular	NMB	Unchanged
Renal	RBF, GFR, UOP	Decreased
Metabolism		0.004%

Table designed from data from:
"Nitrous Oxide." *Lexicomp*, UpToDate, Inc, 22 Nov. 2021, https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7366?cesid=2atkgdBJQiu&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dnitrous%252520oxide%26t%3Dname%26va%3Dnitrous%252520oxide#.

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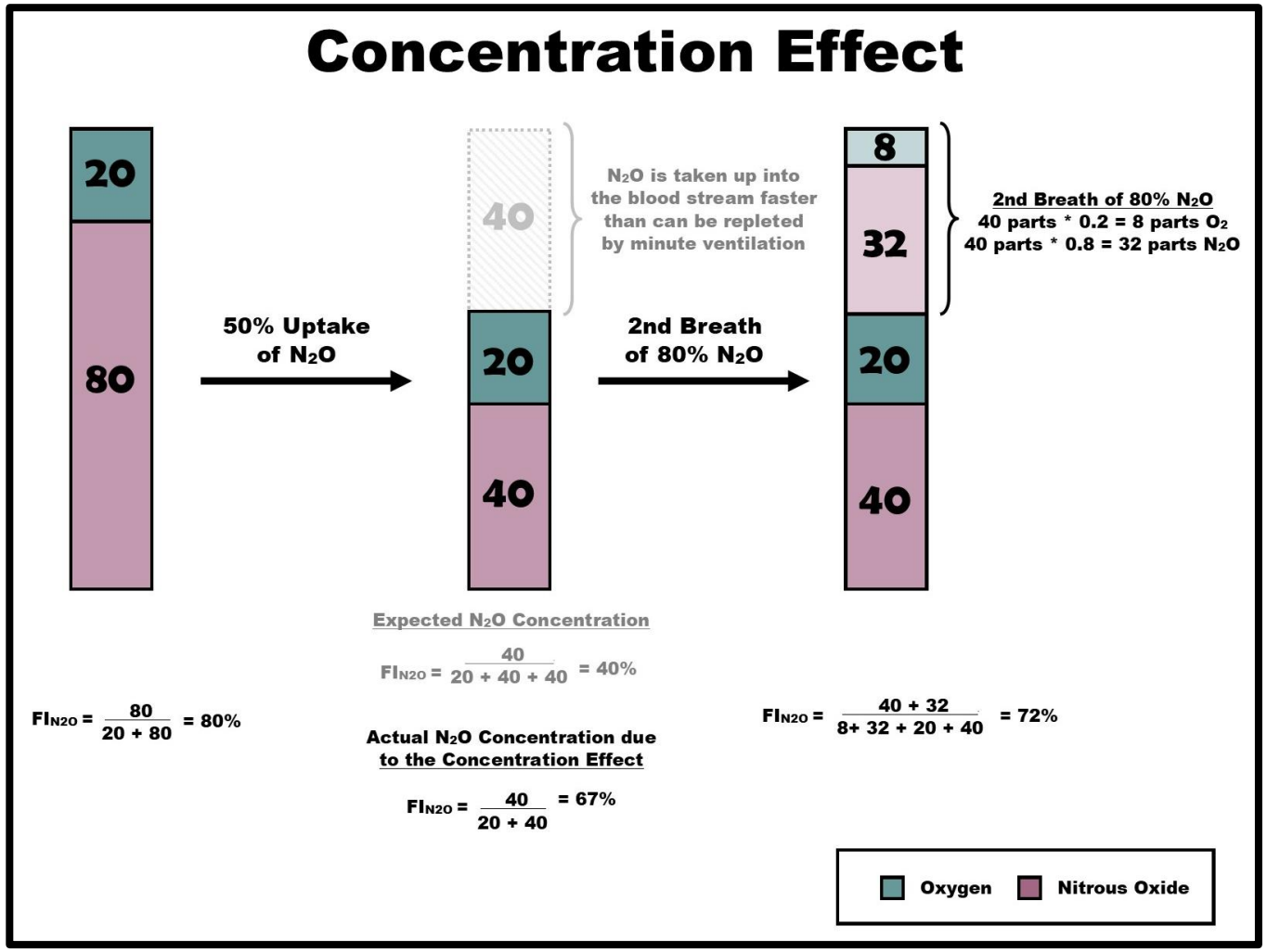
CONCENTRATION EFFECT & SECOND GAS EFFECT

- Concentration Effect
  - Increasing the FI of an inhalational anesthetic will more rapidly increase the FA of the agent.
    - (1) Concentrating Effect: the uptake of half of the nitrous oxide does not simply halve the concentration because the remaining gases are concentrated in a smaller volume
      - Concentration effect is why the curve of FA/FI rises more quickly for nitrous oxide than desflurane, despite their nearly equal blood-gas partition coefficients
        - Example: 80% N2O = 80-volumes N2O in 100. → 50% uptake yields 40 volumes N2O in 60 volumes, or 67% (40/60 = 67%)
    - (2) Augmentation of Inspired Ventilation: as gas leaves the lungs for the blood, new gas at the original FI enters the lungs to replace the volume taken up by the lungs .
      - Example: 80% N2O fills remaining 40 volumes of N2O that was taken up by the blood. 80% of 40 volumes = 32 volumes of N2O. The new 32-volumes is added to the previous 40-volumes of N2O to yield a final N2O concentration of 72%
- Second Gas Effect
  - N2O increases the rate of which FA reaches FI for other volatile anesthetics, using the same factors responsible for the concentration effect.



NITROUS OXIDE AND CLOSED SPACES

- Concept:
  - (1) Preoxygenation and denitrogenation of alveoli does NOT remove all of the nitrogen molecules from preexisting pockets of air in the patient.
  - (2) Nitrogen is highly insoluble (blood-gas partition coefficient: 0.015), therefore nitrogen is "trapped" in these gas compartments and does not easily dissolve into the blood.
  - (3) N2O readily transfers across membranes to enter these closed gas-filled spaces 30x faster than nitrogen will diffuse out, leading to an increase in volume that depends on:
    - (a) time
    - (2) FI, then FA concentration of N2O

Molecule	Blood:Gas Partition Coefficient
Nitrogen	0.015
Nitrous Oxide	0.47

- Contraindications to N2O
  - Intestinal Obstruction
    - Distended bowel makes surgical visualization more difficult and increased intraluminal pressure can significantly decrease bowel perfusion
  - PTX
  - VAE
    - Laparoscopy, spine surgery, hip arthroplasty, posterior fossa craniotomies
  - COPD
    - Blebs, intraoperative PTX
  - Laparoscopy
    - Okay for short laparoscopic procedures without bowel obstruction such as laparoscopic cholecystectomy
  - Intraocular Air
    - Retinal reattachment – air bubble is placed to tamponade the retina while adhesions develop that flatten the retina and promote healing; increased pressure from N2O can decrease retinal blood flow and cause central retinal artery ischemia and optic nerve ischemia
  - Tympanoplasty
    - Affect postoperative healing from displaced/ruptured tympanoplasty graft
  - Pneumocephalus
    - Increased ICP
  - ETT Cuffs/Swan-Ganz Catheters

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THE ANESTHESIA MACHINE

COMPONENTS, ALARMS, SAFETY FEATURES, BREATHING CIRCUITS

ANESTHESIA MACHINE

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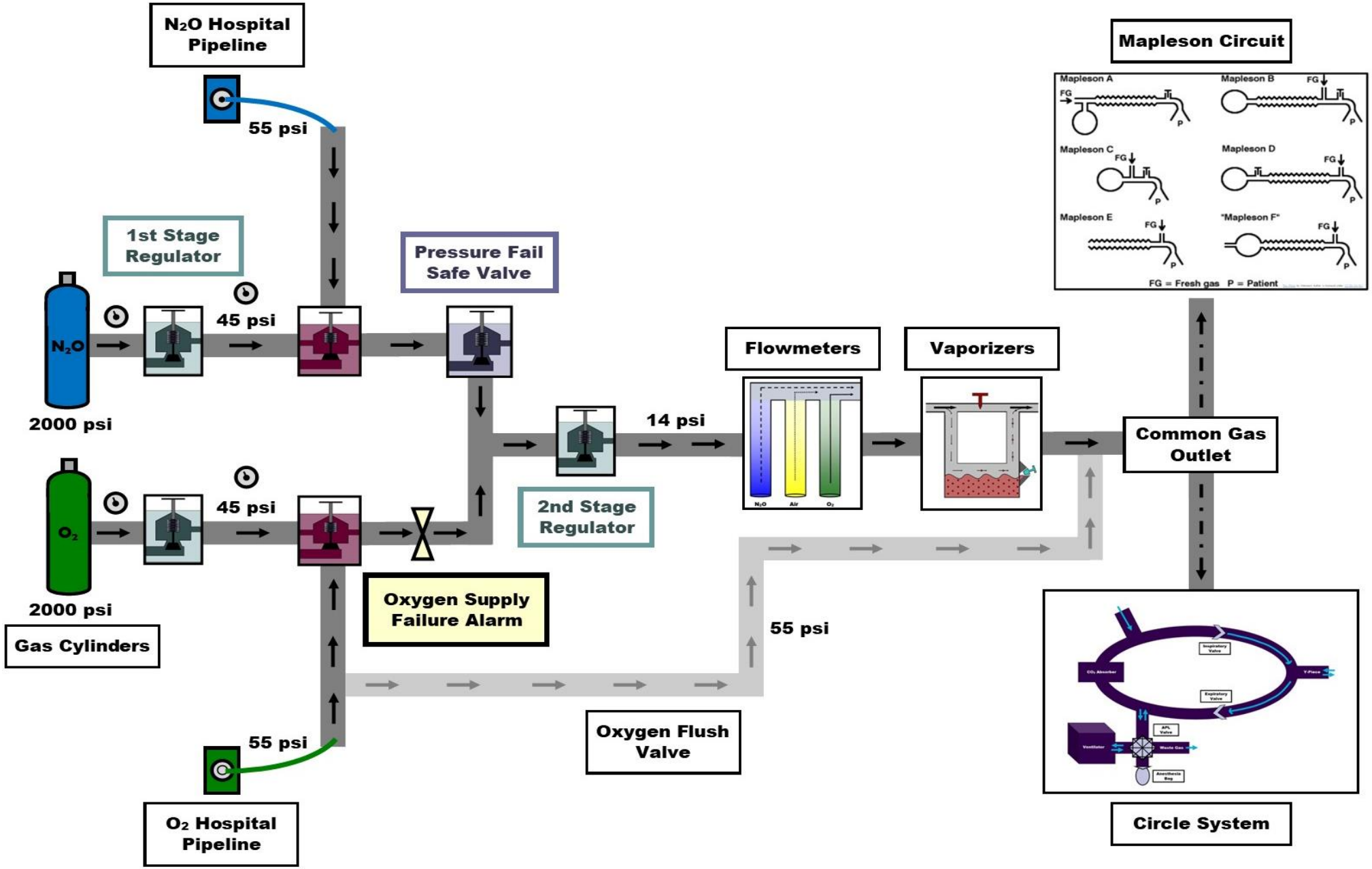

ANESTHESIA MACHINE

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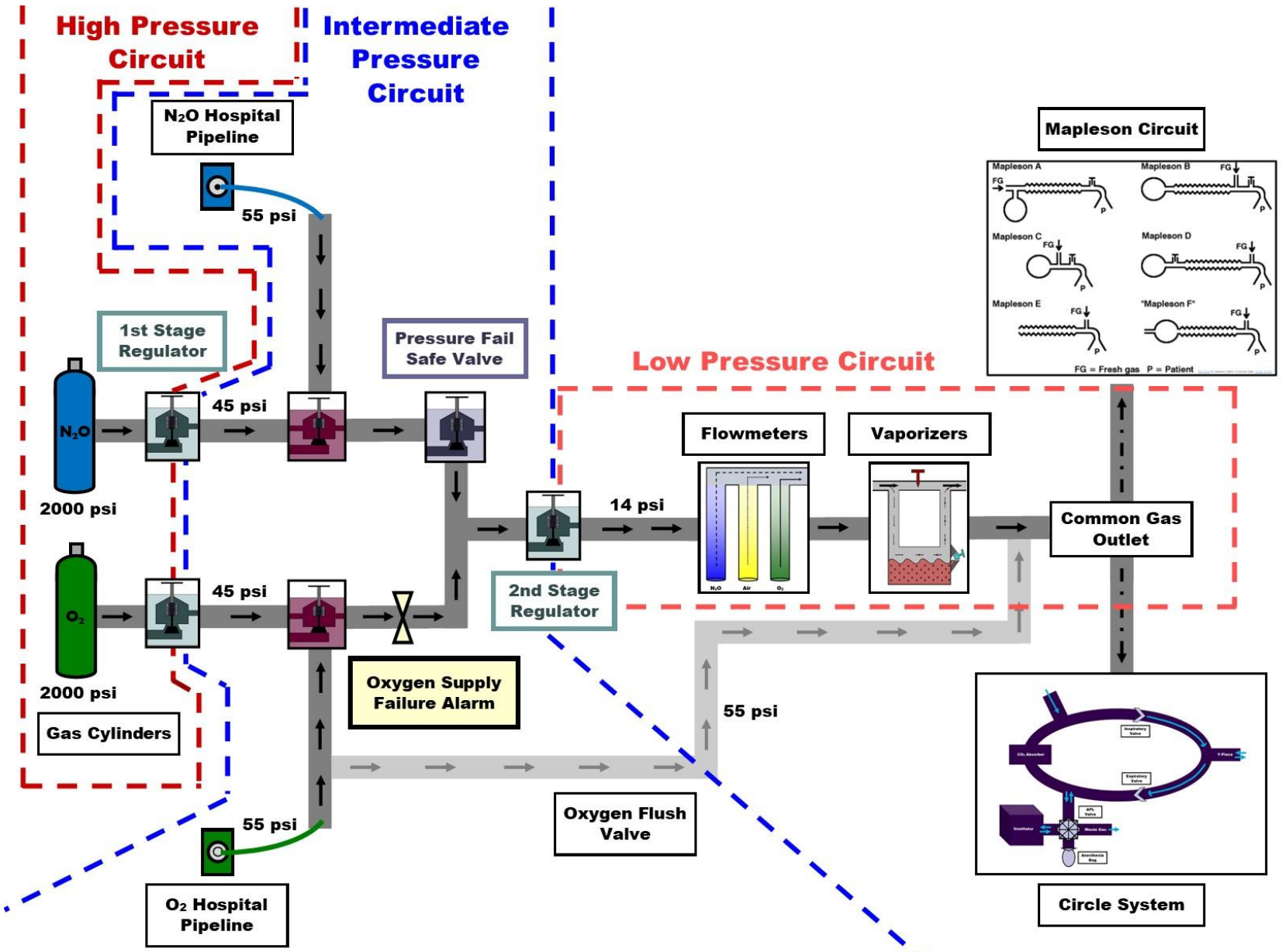
ANESTHESIA MACHINE DIAGRAM

- High Pressure Section
  - Gas cylinder
  - Pipes/connections to the inlet of the high-pressure regulator
- Intermediate Pressure Section
  - Hospital pipeline gas supply
  - Outlet of the high-pressure regulator
- Low Pressure Section
  - Flowmeters
  - Vaporizers
  - Fresh gas outlet



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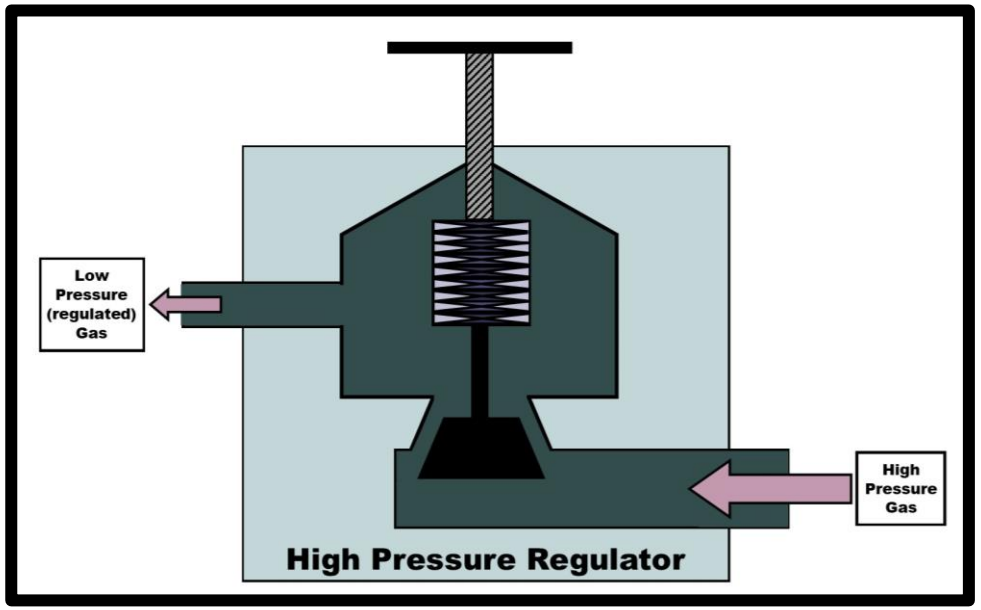
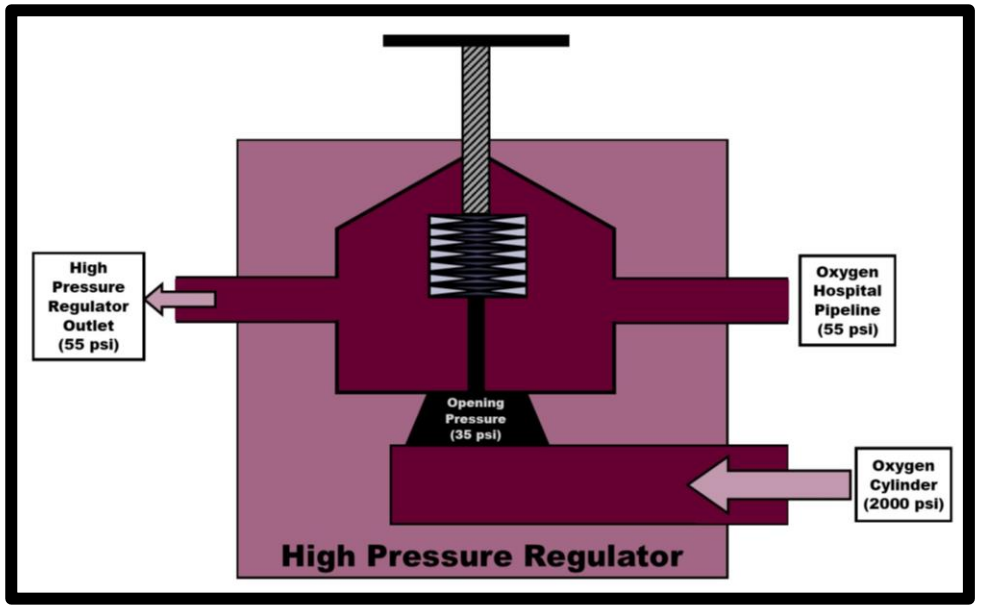
GAS SUPPLY SYSTEM

- High-Pressure Regulator
  - Designed to have an outlet pressure (35-45 psi) lower than that of the pipeline supply (~45-55 psi) → if the E-cylinder is left open while the anesthesia machine is connected to the hospital pipeline gas supply, the preferential supply will be from the pipeline
    - Cylinder is ONLY used if the pipeline pressure drops
      - If the oxygen cylinder is left open AND pipeline pressure is lost, the first alarm to sound would be when the oxygen cylinder is empty → close the oxygen cylinder after machine check
      - If the oxygen cylinder is closed AND pipeline pressure is lost, low-pressure alarm will occur and be the first indication of an issue → the oxygen cylinder can then be opened and the situation temporized while emergency planning is initiated.
- Gas Supply Pressures:
  - Gas Cylinders: 2000 psi
  - Medical Gas Outlets (Wall): 55 psi
  - 1st Stage Pressure Regulator → reduces to 45 psi
  - 2nd Stage Pressure Regulator → reduces to 14 psi
  - Oxygen Flush Valve: bypasses the flowmeters and vaporizers





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GAS CYLINDERS

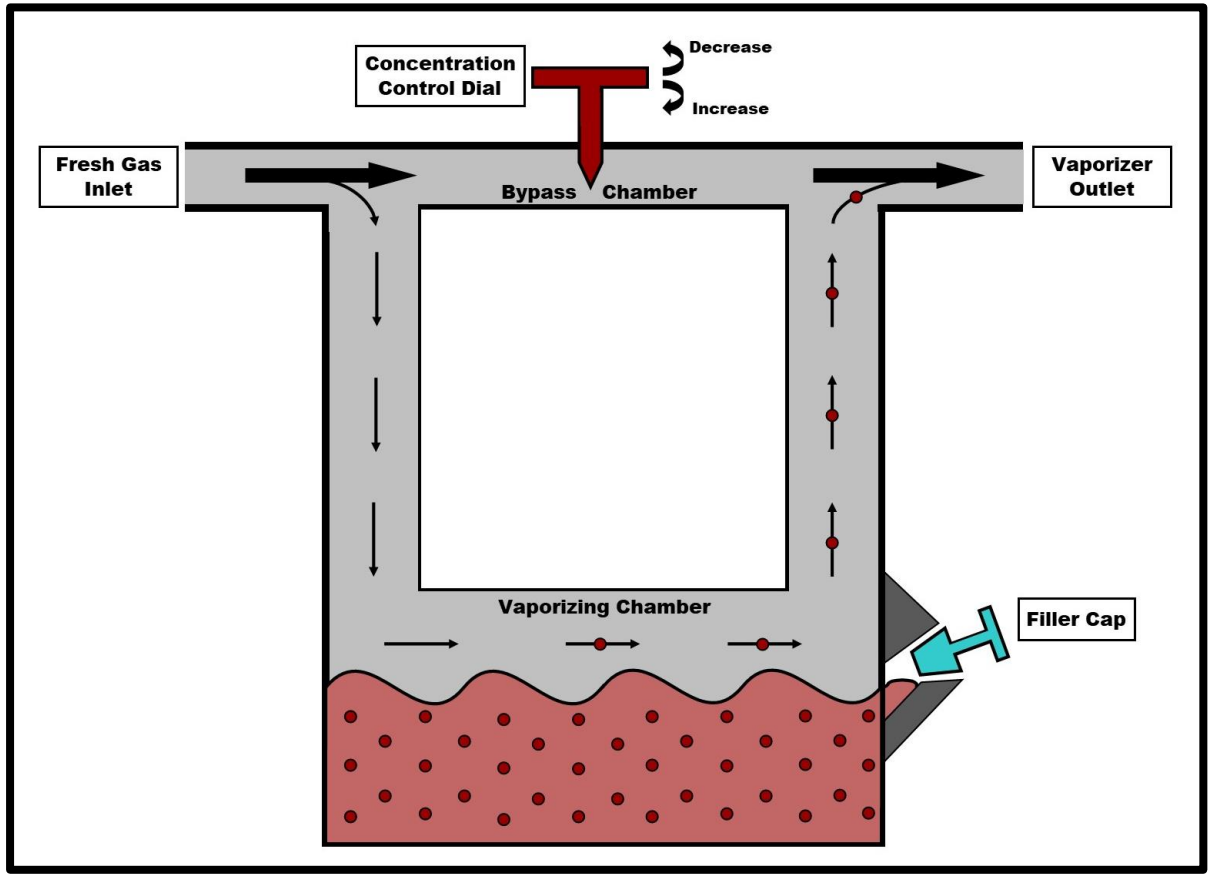
- Non-Liquefied Gases
  - Never become liquid at room temperature, even at high pressures
    - Air, Helium, Nitrogen, Oxygen
  - Oxygen Gas Cylinder
    - Full tank holds 660 L with a pressure of 1900 psi
      - Direct relationship between pressure and volume remaining
        - Time Remaining (hours) = cylinder pressure / (200 * oxygen flow rate)
          - Quick Method to Estimate Volume Remaining in an Oxygen Tank = Pressure / 3
            - Example: 900 psi would have ~300 L O2
- Liquefied Gases
  - Liquid at ambient temperature when stored under pressure in cylinders
    - Carbon Dioxide, Nitrous Oxide, Propane
  - Nitrous Oxide Gas Cylinder
    - Maximum of 1590 liters with a gauge pressure of 745 psi
      - Gauge pressure remains constant at 745 psi until the tank is 75% empty (approximately 253 liters remain), then it drops proportionally to the amount of remaining N2O
        - Volume Remaining (L) = [gauge pressure (psi) / 745 psi] * 253 L
      - Only reliable way to know the volume of gas left in a N2O tank when the gauge pressure reads full is to weigh the tank and compare it to the empty weight

Characteristics	Oxygen	N2O	CO2	Air	Helium
Physical State	Gaseous	Liquid/ Gaseous	Liquid/ Gaseous	Gaseous	Gaseous
Cylinder Color	GREEN*	BLUE	GRAY	YELLOW	BROWN
Full Cylinder (L)	660	1590	1590	625	500
Full Cylinder (psi)	1900	745	838	1900	1600

* Oxygen Cylinder Color:
- **Green** is the standard color in the United States.
- **White** is the standard international color.

VARIABLE BYPASS VAPORIZERS (SEVOFLURANE, ISOFLURANE)

- Mechanism: FGF is split:
  - (1) some of the FGF bypasses the vaporizer chamber
  - (2) some is diverted into the vaporizing chamber where it becomes saturated with volatile agent.
    - This gas then returns toward the outflow where a concentration dial controls how much of the saturated gas mixes with gas the bypassed portion.
- Agent-Specific
  - FGF splitting ratio is different for each anesthetic agent based on vapor pressure.
- Temperature Compensated
  - Increasing temperature will lead to increased anesthetic agent in the vapor or gas form.
  - Modern vaporizers utilize a bimetallic strip (two metals against each other) which bend with temperature changes → when temperature increases, the strip moves to allow more gas to bypass the vaporizing chamber.
    - Temperature-compensated from approximately 10-40 degrees Celsius



VARIABLE BYPASS VAPORIZER: APPLICATIONS

- Vaporizer Output = FGF * (Pvap / [Pbar – Pvap])
  - Decreasing barometric pressure → more volatile utilized
    - As barometric pressure falls, saturated vapor takes up more space or volume percent of the atmospheric pressure, increasing a vaporizer's output (partial pressure is constant!)
  - Variable bypass vaporizers deliver approximately the same MAC at higher or lower elevations due to proportional atmospheric change
- Agent Saturated Vapor Pressure = (Agent Vapor Volume / [Carrier Gas Volume + Agent Vapor Volume]) * Total Atmospheric Pressure
  - Example: 100ml/min FGF goes into the vaporizer and 145ml/min comes out. Assuming standard temperature and pressure, which volatile anesthetic is being delivered?
    - (45 ml/min / 145 ml/min) * 760 mmHg = ~238 mmHg which is approximately the saturated vapor pressure of isoflurane

Agent	SVP	SVP / (ATM – SVP)
Sevoflurane	160 mmHg	~ ¼
Enflurane	175 mmHg	~ 1/3
Isoflurane	238 mmHg	~ ½
Halothane	241 mmHg	~ ½
Desflurane	669 mmHg	N/A

Isoflurane
Isoelectric EKG leads have an equal amount of positive and negative charges → "half and half"

Sevoflurane
There are 4 seasons to remember sevoflurane is 1/4th atmospheric pressure

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DESFLURANE VAPORIZER

- Desflurane has a high vapor pressure and boils above 22.8-degrees Celsius, which is within the range of ambient operating room temperatures, therefore desflurane cannot be used with a variable-bypass vaporizer
  - Desflurane vaporizer is a dual-gas blender that heats to 39-degrees Celsius → creates a constant desflurane vapor pressure of 2-atm within the vaporizer, independent of barometric pressure, meaning the vaporizer delivers anesthetic at a fixed percent concentration, NOT fixed partial pressure.
    - At higher altitudes, the partial pressure of desflurane delivered to the alveoli is reduced due to the fall in atmospheric pressure due to Dalton's law of partial pressures
      - Since the potency of volatile anesthetics is a function of agent partial pressure (NOT inspired percent concentration), compensation for increases in altitude when using a desflurane vaporizer should be manually increased with the dial setting according to the following formula:
        - Required Dial Setting = Desired % * (760 mmHg / current atmospheric pressure in mmHg)

Reminder:
Dalton's Law of Partial Pressures

$$Px = (Pb - Ph2o) * F$$

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GAS ANALYZER

- Infrared Spectrophotometry is the most commonly used method for gas analysis within anesthesia machines.
  - Infrared light is passed through a gas sample taken from the anesthesia circuit and the amount absorbed by the gas at specific wavelengths (which helps determine the identify of the gas) is proportional to the partial pressure of the gas.
    - If ambient pressure is known, then the volume percent can be calculated by dividing the partial pressure of the measured gas by the partial pressure of the system → Dalton's Law of Partial Pressures
  - Infrared Spectrophotometry only works with gases that are <u>polar, have dissimilar atoms and are asymmetric</u>
    - CO_2, N_2O and volatile anesthetics can be measured with infrared light, but NOT O_2
- Severinghaus Electrode measures PCO_2
  - Based on the principle that pH and PCO_2 change in a linear fashion with temperature. Electrode contains an internal pH sensor which can also measure the partial pressure of CO_2.
- Techniques to Measure Oxygen Concentration
  - (1) Paramagnetic
    - Analyzer creates an electromagnetic field that attracts oxygen molecules. The gas sample is then compared to room air to calculate the concentration of oxygen in the sample.
  - (2) Galvanic
    - Oxygen molecules enter the electrode and react with the lead (pB) anode. The reaction produces electrons which move across the electrolyte fluid to the gold (Au) cathode. The amount of electrode (or current) moving across the fluid is proportional to the oxygen concentration.
      - Commonly utilized in SCUBA equipment to measure oxygen content in the breathing apparatus during dives
      - Electrodes become depleted by continuous exposure to oxygen, which limits the lifespan to ~1-year
  - (3) Polarographic (ex: Clark Electrode)
    - Oxygen molecules react with silver (Ag) anode producing electrons. These electrons move across the fluid to react with the platinum (Pt) cathode. The concentration of electrons (or current) moving across the "bridge" of fluid is proportional to the oxygen concentration.
      - Unlike the galvanic system, the polarographic analyzers have a battery which polarizes the electrode, allowing the reaction to occur much faster.
        - Lifespan is ~3-years due to Teflon membrane, which becomes coated with protein.
        - Commonly used in anesthesia machines and ABG analysis

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CIRCUIT TYPES

- Types:
  - (1) Semi-Open System
    - High FGFs, NO rebreathing
      - Absence of expiratory/inspiratory valves and CO2 absorbent → dependence on FGF to prevent CO2 rebreathing.
  - (2) Semi-Closed System
    - Lower FGFs, some rebreathing
  - (3) Closed System
    - FGF = patient consumption; complete rebreathing

Mode	Reservoir	Rebreathing	Examples
Open	No	No	Open Drop Ether
Semi-Open	Yes	No	Nonrebreathing circuit (Mapleson) or Circle system at high FGF (>MV)
Semi-Closed	Yes	Yes, partial	Circle at low FGF (<MV)
Closed	Yes	Yes, complete	Circle (if APL valve closed)

- Closed Circuit Anesthesia
  - Low-flow technique using a circle system in which the total FGF (oxygen and volatile anesthetic) is equal to oxygen consumption (3-3.5 ml/kg/min in adults) and inhalational anesthetic metabolism.
    - No gas is vented through the APL valve to the scavenger.
    - To minimize FGF, only O2 is used.
    - Exhaled CO2 is converted to a comparable volume of water vapor by the absorbent.
  - Benefits:
    - Decreased fresh gas and volatile anesthetic use
    - Conservation of heat and humidity
    - Improved mucociliary function
    - Decreased microatelectasis
  - Side Effects:
    - Hypoxic mixture (must closely monitor FIO2 and ETCO2)
    - Increased PONV due to rebreathing of noxious gases such as acetone or CO (see below)
  - Relative Contraindications:
    - Sevoflurane Use (increased risk of Compound A)
    - Alcoholism (increased acetone production)
    - Malnutrition (increased acetone production)
    - Cirrhosis (increased acetone production)
    - Ketoacidosis (increased acetone production)
    - Heavy Smokers (increased CO)

ANESTHESIA MACHINE

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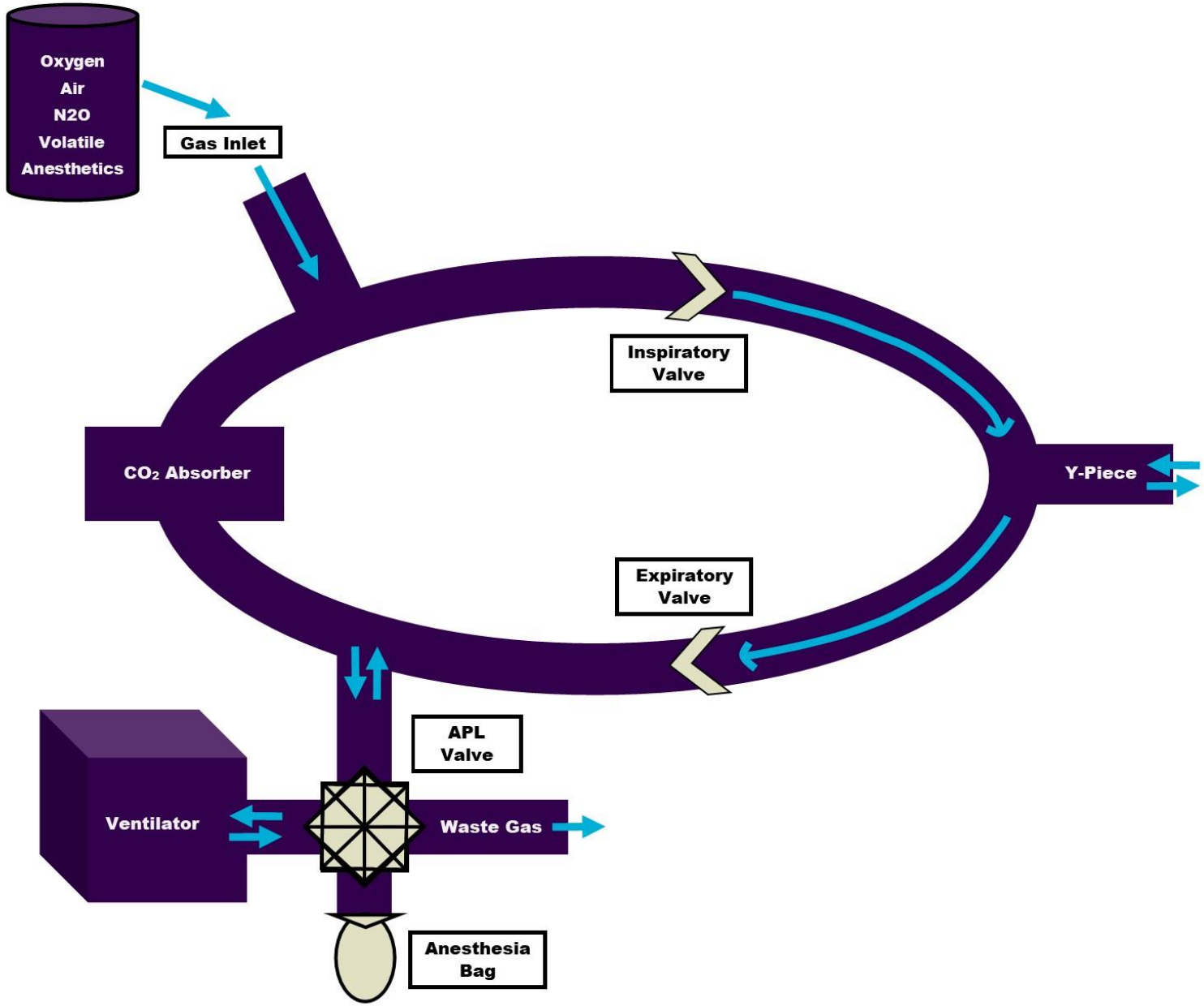
GAS FLOW THROUGH THE BREATHING CIRCUIT

- 1. Gas Inlet BEFORE the Inspiratory Valve
  - Rationale: prevents wasting fresh gas flow
- 2. Only device between the patient and inspiratory/expiratory vales are the flow sensors (occasionally) and the fresh gas sampling outlet
  - Rationale: prevents rebreathing and wasting fresh gas flow



ANESTHESIA MACHINE

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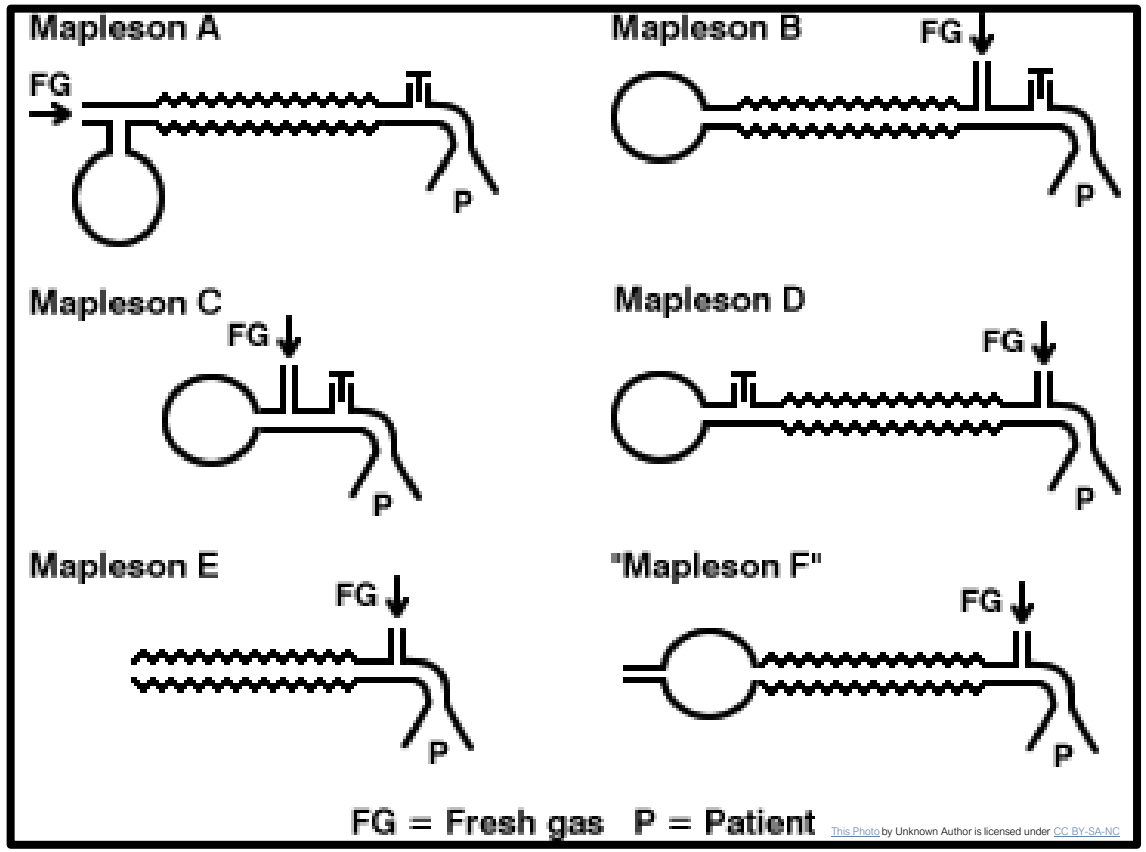
MAPLESON CIRCUITS

- Semi-open breathing circuits without carbon dioxide absorbents, expiratory/inspiratory valves and prevention of rebreathing is dependence on FGF
- Mapleson A (aka: Magill)
  - FGF must be equal to or greater than MV to prevent rebreathing.
    - Most efficient for spontaneous breathing.
  - FGF inlet is located at the site most distal to the patient, reservoir bag is located directly adjacent to the FGF inlet followed by a length of corrugated tubing followed by the APL valve, ETT and patient
    - Inspiration: FGF within the system is inspired by the spontaneously ventilating patient, the APL is closed and reservoir bag deflated.
    - Early Expiration: exhaled gas is eliminated from the system through APL valve. As exhaled gas I pushed distally, FGF travels proximally and facilitates further elimination of the exhaled gas.
      - The FGF (L/min) must equal the patient's MV in order to ensure that the exhaled gas is not inhaled during the next inspiratory cycle.
- Mapleson D (aka: Bain), E, F (aka: Jackson-Rees)
  - FGF during spontaneous ventilation must be equal to 2-3x MV
    - During controlled ventilation, FGF only 1-2x MV to prevent rebreathing (most efficient of the Mapleson circuits)
  - Bain Circuit is a modified Mapleson D circuit with coaxial delivery of FGF → allows for more rapid changes in inspired gas concentration compared to the circle system (one of the only advantages as circle system has a large dead space).



Mnemonic #1:
Mapleson A is better for spontaneous respiration.
Mapleson D is better for controlled ventilation.

Mnemonic #2
- All Dogs Can Bite (spontaneously): A > D > C > B
- Dead Bodies Can't Argue (controlled): D > B > C > A

M. Jablonski, 2020-2021

CARBON DIOXIDE ABSORBENTS

- Absorbents remove CO2 from the circuit's expiratory limb, allowing anesthetic gas to be recycled, making a closed system possible.
  - Desiccated absorbents, low fresh gas flows and warm absorbents increase risk for issues with CO2 absorbents
- Granule size has been engineered to maximize surface area for absorption while minimizing resistance
  - Ethyl Violet is the pH indicator (colorless when fresh, purple when pH falls below 10.3, indicating absorbent exhaustion)
- Problems with CO2 Absorbents:
  - (1) Absorbents can degrade volatile anesthetics into toxic byproducts
    - Sevoflurane = Compound A
  - (2) Volatile anesthetic degradation can generate CO
    - Desflurane > Isoflurane > Sevoflurane
    - Baralyme > Soda Lime > Amsorb
  - (3) Reactions generate heat which theoretically could contribute to a fire
    - Sevoflurane = most heat
  - (4) Degradation of volatile agents decreases agent FI

Risk of CO Formation:
KOH > NaOH >> Ba(OH)2, Ca(OH)2

- Types of CO2 Absorbents:
  - Soda Lime
    - Contents: calcium hydroxide, sodium and potassium hydroxide
    - Soda lime can absorb 23-26L of CO2 per 100g of absorbent
      - Higher moisture absorbents (e.g. soda lime) have more water content available to react with CO2, leading to an increased CO2 absorptive capacity
  - Barium Hydroxide (Baralyme)
    - Produces more CO than soda lime due to decreased content of barium hydroxide absorbents, increased Compound A production and increased heat (risk of fire)
      - Removed from US market
  - Amsorb/Sodasorb/Sodalime II/Spherasorb/Lithium Hydroxide
    - Contents: calcium hydroxide lime
      - Minimizes formation of compound A and CO because it lacks strong bases
        - Also has less CO2 absorption capacity per 100g

Calcium Hydroxide and Strong Base

$$CO_2 + H_2O \rightarrow H_2CO_3$$
$$H_2CO_3 + 2NaOH \rightarrow Na_2CO_3 + 2H_2O + Heat$$
$$Na_2CO_3 + Ca(OH)_2 \rightarrow CaCO_3 + 2NaOH$$

Calcium Hydroxide

$$Ca(OH)_2 + CO_2 \rightarrow CaCO_3 + H_2O$$

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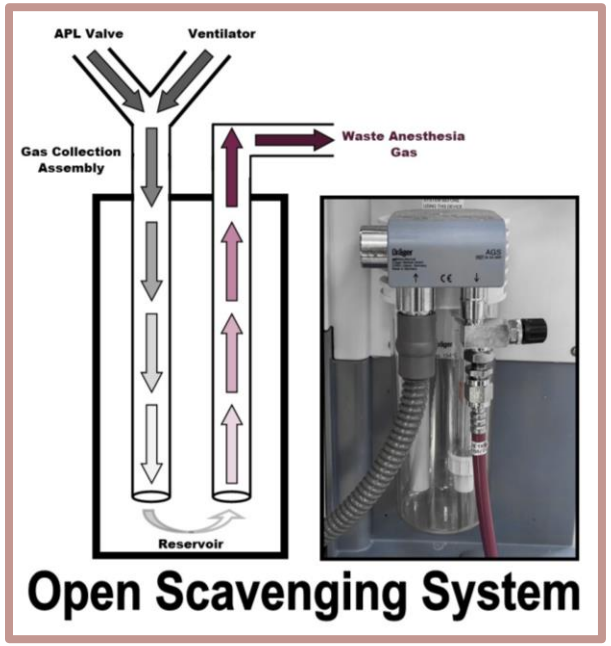
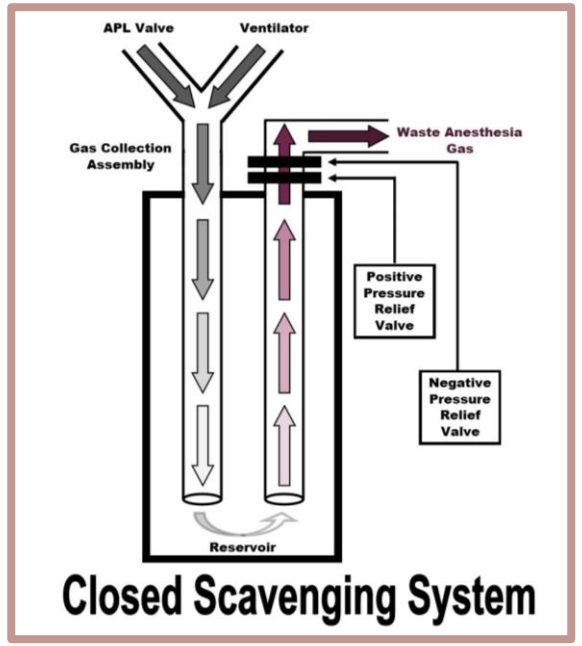
SCAVENGING SYSTEMS

- Purpose: collect and remove vented anesthetic gases from the OR, decrease OR pollution by anesthetic gases
- Methods: Scavengers and Operating Room Ventilation
- Types of Scavenging:
  - Active (suction applied) vs. Passive (passive movement of waste gasses down corrugated tubing through the room ventilation exhaust grill of the OR)
  - Open (to the atmosphere, no valves; new anesthesia machine models) vs. Closed (communicate with the atmosphere through valves; older anesthesia machine models)
    - Open systems have increased risk of occupational exposure to anesthetic gases.
    - Closed systems have increased risk of barotrauma
- Components:
  - Gas collection assembly (tubes connected to APL and vent relief valve)
  - Transfer tubing
  - Scavenging interface
  - Gas disposal tubing (carries gas from interface to disposal assembly)
  - Gas disposal assembly (active or passive; active is most common and utilizes the hospital suction system)
- Scavenging Interface
  - Protects against excessive positive pressure in a closed scavenging system, or against excessive negative pressure in an active scavenging system
    - Positive-Pressure Relief: in the absence of suction in a closed scavenging systems, excessive positive pressure can build up and cause barotrauma
    - Negative Pressure Relief: active scavenging systems have suction applied; excessive suction could cause negative pressure in the breathing circuit
- OSHA Standards
  - <2 ppm halogenated agents
  - <25 ppm nitrous oxide

TQA:
If halogenated anesthetic agents and nitrous oxide are used in combination, OSHA Standards are:
<0.5 ppm of halogenated agent





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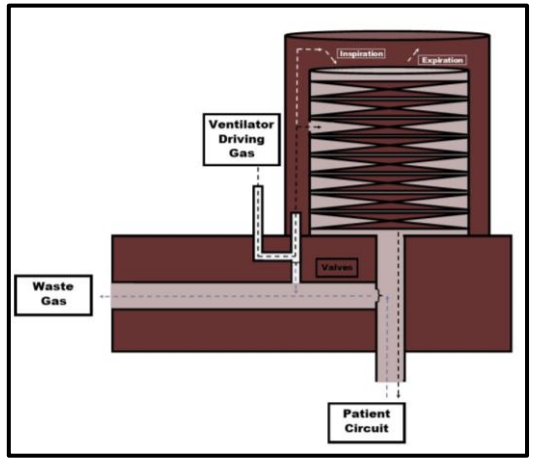
ADDITIONAL COMPONENTS

- Unidirectional Valves
  - Inspiratory and expiratory unidirectional valves direct gas flow and prevent rebreathing.
    - Allow for lower gas flow, however, add resistance to the system
    - Should be close to the Y-piece; in the event of a leak, which will limit the amount of back-flow that can occur
- Y-Connector
  - Connects ETT to inspiratory/expiratory limbs
  - Contributes to mechanical dead space of the circuit
- Fresh Gas Inlet (FGI)
  - Circle systems have the fresh gas inlet between the absorber and the inspiratory valve.
    - If FGI is downstream of the inspiratory valve, fresh gas can bypass the patient during exhalation → waste fresh gas
    - If FGI is placed between the expiratory valve and the absorber, the fresh gas would become diluted with exhaled gas
  - In older ventilators, FGF contributed to tidal volume; newer ventilators have a decoupling valve.
  - Rebreathing of exhaled gases will occur if MV > FGF
    - Vt breathing at normal RR (MV ~5 L/min). Increasing FGF from 5 → 10 L/min has no effect on end-tidal O2 concentrations.
    - Deep breathing, MV can exceed FGF
      - Example: 70kg patient with normal pulmonary function has ~5L VC. 4-VC breaths every 30-seconds, means MV ~40 L/min. Deep breathing can exceed 15 L/min O2 delivered by the anesthesia machine → rebreathing, lowering FiO2



- Reservoir Bag / Pneumatic Bellow
  - Stores oxygen and anesthetic gases
  - Leak in the high-pressure system of the ventilator will result in the inability of the bellow to rise
  - Hole in the bellows could result in barotrauma as pressurized oxygen or air that is used to compress the bellows would exit the hole and enter the breathing system
    - If medical air, rather than oxygen, is utilized to drive a pneumatic bellow, a leak in the bellows could cause a lower-than-desired inspiratory fraction of oxygen to be delivered to the patient
      - Oxygen is preferentially used for safety purposes, except in situations where the hospital's supply of oxygen must be preserved (i.e. COVID-19 emergency planning)
  - If there is failure of the pipeline supply of gas, the bellows can be driven by the E-cylinders, but this will consume more gas, so hand ventilation with low gas flows should be employed
  - Non-Compensating Pneumatic Bellow:
    - Does not take into account the added volume from FGF during inspiration when delivering a set tidal volume
      - Actual Vt is greater than the set Vt
        - Example:
          - O2 FGF 3 L/min + Air FGF: 3 L/min = 6 L/min → 100 ml/sec.
          - RR: 12 (each breath lasts for 5-seconds).
          - I:E ratio is 1:1.5, meaning 2-seconds for inspiration and 3-seconds for expiration.
            - FGF = 2-seconds * 100 ml/sec = 200ml
              - 200ml is added to the set tidal volume (800ml) to result in 1000ml that is actually delivered.

ANESTHESIA MACHINE

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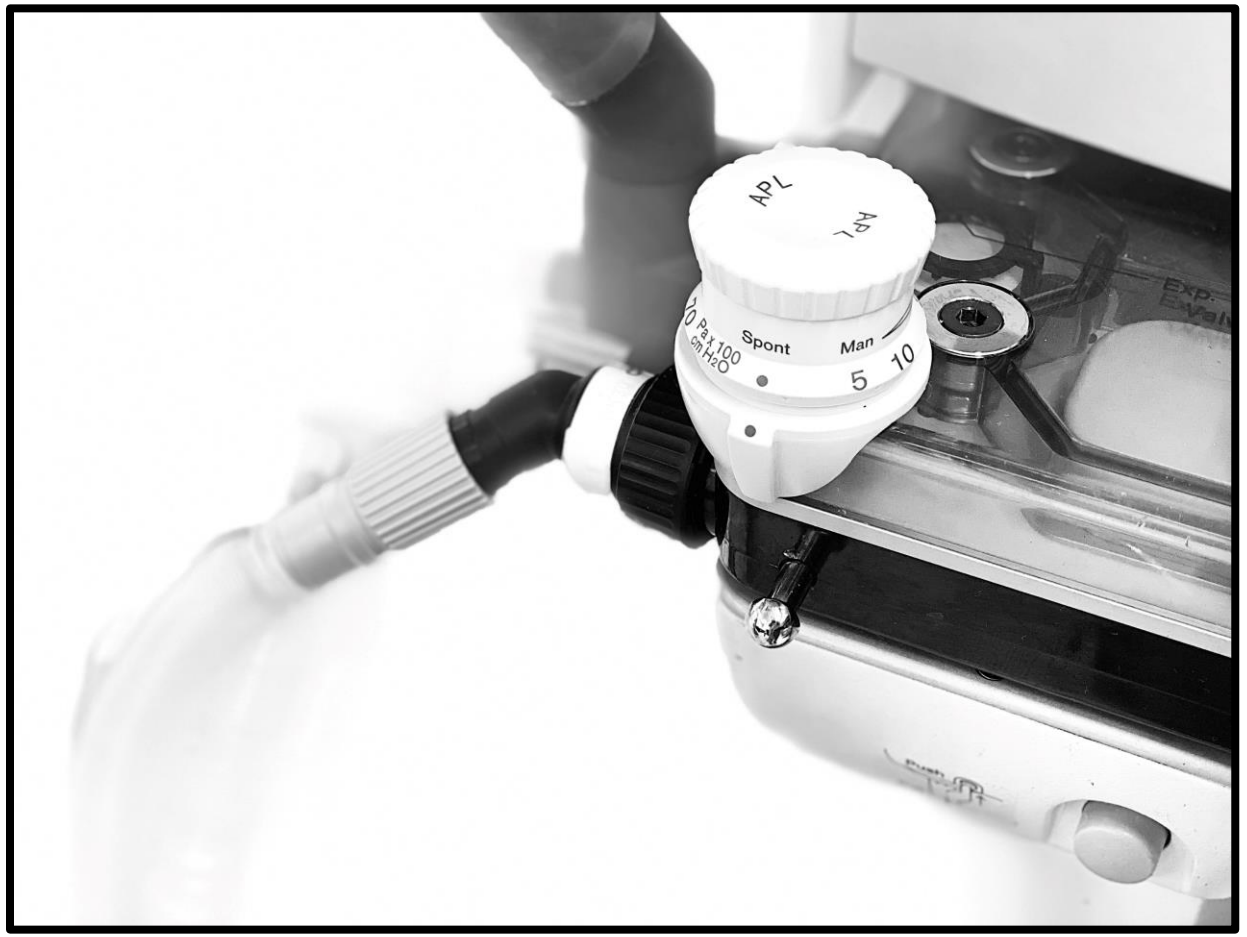
ADDITIONAL COMPONENTS

- Low Resistance Tubing
  - Ideal breathing system would have low resistance and low dead space, effective for both spontaneous and controlled ventilation with excellent humidification and scavenging system.
  - Large diameter minimizes resistance; corrugation increases flexibility but increases turbulent flow
  - Circle systems allow for economy of gas use, decreased pollution and conservation of heat and moisture.
    - Circle systems have higher resistance due to valves, longer tubing and CO2 Absorption
      - Older machines do not account for this dead space, which is problematic when using adult circuits for pediatric patients.

- Adjustable Pressure-Limiting (APL) Valve
  - Allows for exhaled gases and FGF to exit the system when the pressure exceeds the pressure limit.
  - Typically taken out of the circuit when the ventilator is switched to the mechanical ventilation mode, so the system will function regardless of whether the APL valve is opened or closed
  - When ventilator is on “vent” mode, waste gas is scavenged by “ventilator relief valve”
    - Violet/Purple tubing is for waste anesthesia gas



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SAFETY FEATURES

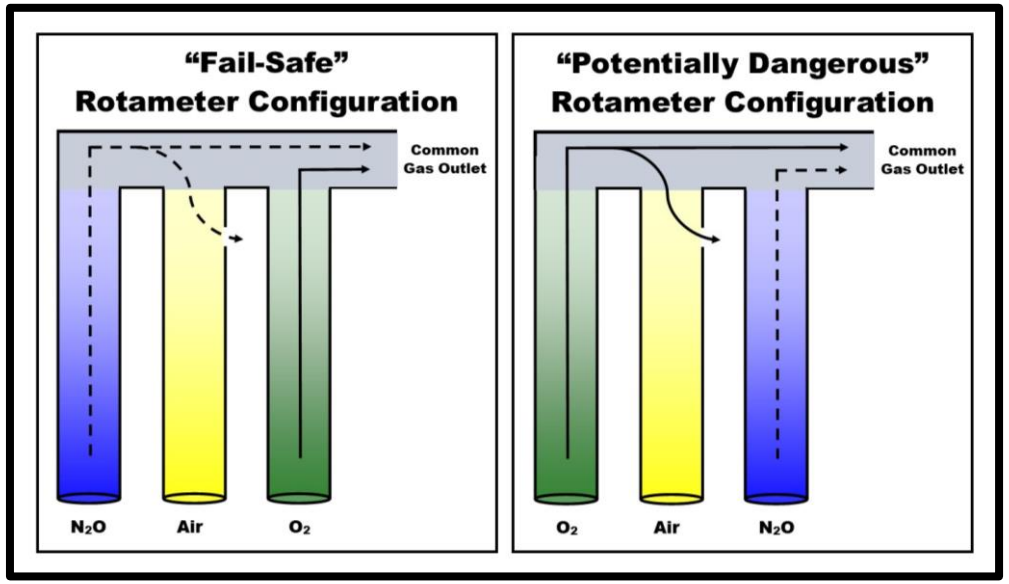
- **Pressure Fail-Safe**
  - Feature: prevents hypoxic mixtures if there is a decrease oxygen supply at the flowmeter level
  - Mechanism:
    - One system has a device present in all gas lines supplying all flow meters except for oxygen and interrupts the supply of other gases if the oxygen supply is reduced to a certain level (usually 30psi). This level is the opening threshold pressure for use of other gases
    - Another system causes a proportional decrease in all other gases as oxygen pressure is decreased. Oxygen opening threshold pressure: 12psi.
  - Notes:
    - Oxygen flush valve can provide high flows of oxygen (35-75 L/min) directly to the common gas outlet, bypassing the flowmeters (risk of barotrauma).
    - If there is a failure of the pipeline supply of gas, the bellows can be driven by the E-cylinders, though this will consume more gas so hand ventilation should be employed.
  - Management of Loss of Pipeline Pressure
    - (1) Disconnect the anesthesia machine from the pipeline
      - Pressure could be restored in the pipeline, but it may be an unexpected gas (e.g. N_2O into the O_2 line) or contaminated gas; if the pipeline pressure returns, the oxygen cylinder would no longer deliver gas since the supply line had a higher pressure.
        - Simply increasing FGF could delivery a hypoxic mixture and further deplete the oxygen supply.
    - (2) Open the emergency oxygen cylinder fully
    - (3) Ventilate by hand with the anesthesia breathing circuit
      - Old ventilator bellows were driven by oxygen and would deplete the oxygen supply

- **Pipeline Pressure Color Coding**
  - Green = oxygen
  - Blue = nitrous oxide
  - Yellow = air
  - Gray = carbon dioxide
  - White = vacuum
  - Violet = waste anesthesia gas

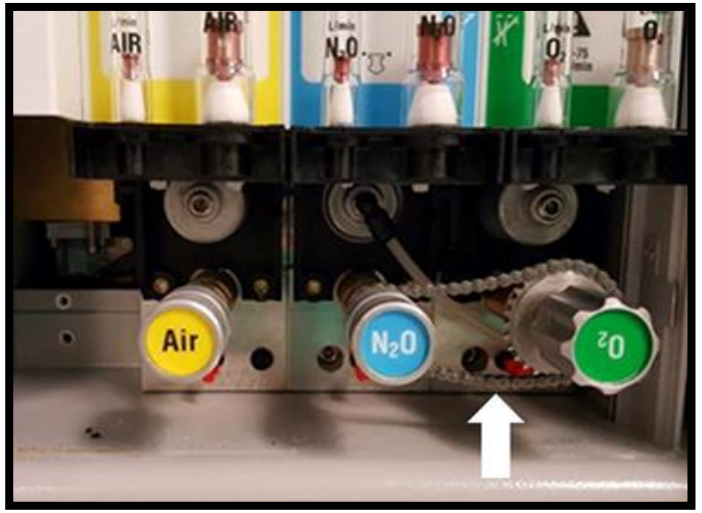
SAFETY FEATURES

- Flowmeter Configuration
  - Feature: controls gas proportions and gas flow to the common gas outlet
  - Mechanism:
    - Gas flow enters at the base of a glass flow tube which is tapered in that its diameter increases with height and a small metal bobbin or ball rides the gas jet. As the bobbin rises, the space around it, known as the annulus, increases (i.e. variable orifice). Greater flow jets are required as the orifice widens to keep the bobbin afloat at that level. The top of the bobbin or middle of the ball indicates the flow in liters per minute.
      - Viscosity is important in low flow states (laminar) and density is important in high gas flows (turbulent)
      - Flow meters are effected by temperature and altitude
        - Increased altitude decreases barometric pressure, therefore increasing flow. In low flow states, viscosity is the key and does not alter much with altitude. In high flow states, density is the most important; the flow meters will delivery higher flows but read lower than the actual rate.
    - Oxygen is the most distally positioned because this arrangement decreases the likelihood that leaks proximal to the oxygen will result in a hypoxic mixture.
- Oxygen Ratio Proportioning Device
  - Feature: N2O-to-O2 proportion device links the two flows to prevent a final inspired oxygen concentration of <25%.

Flowmeter Configuration



Oxygen Ratio Proportioning Device



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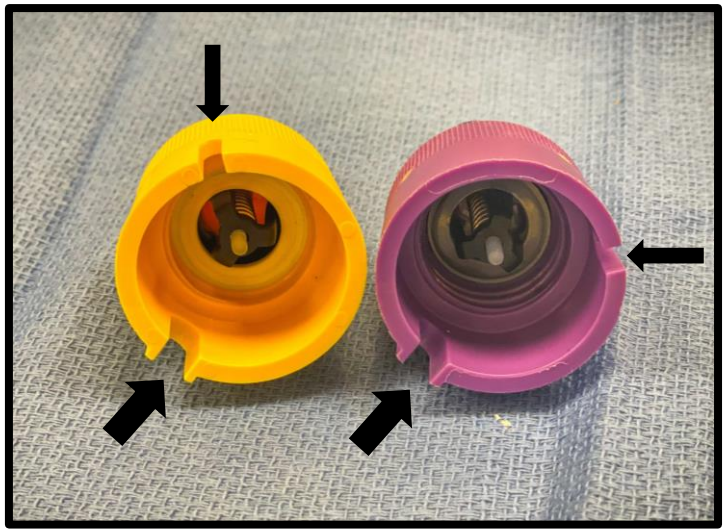
MECHANICAL SAFETY COMPONENTS OF THE ANESTHESIA MACHINE

- Diameter Index Safety System
  - Threaded non-interchangeable connections on the anesthesia machine; wrong hose cannot be connected to wrong wall pipeline or machine port.
    - This does NOT protect against a pipeline crossover at the hospital level (i.e. newly constructed operating suite) as this error is upstream of the operating room
      - First indication of a pipeline crossover at the hospital level would be the results of the gas analyzer measuring inspired gas
- Pin Index Safety System
  - Two metal pins on the anesthesia machine correspond to holes on the cylinder; pins are different sizes and have different orientations for the specific gas cylinders; prevents the connection of the wrong cylinder to the wrong inlet
- Vaporizer Interlock System
  - Ensures that: (1) only one vaporizer is turned on at a time; (2) fresh gas only enters the vaporizer which is turned on; (3) trace vapor output is minimized when the vaporizer is off; (4) vaporizers are locked into the gas circuit to ensure the vaporizer is seated correctly
- Keyed Vaporizer Filling
  - Keyed filling of vaporizer bottles to the vaporizer cassettes prevent filling of the vaporizer with the wrong gas.

Diameter Index Safety System

Keyed Vaporizer Filling



ANESTHESIA MACHINE

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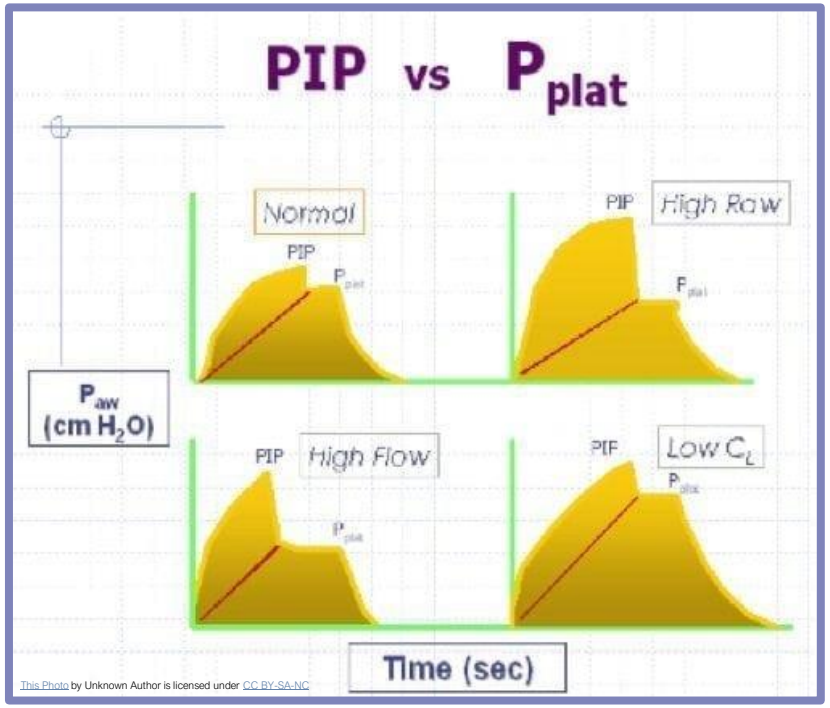
ALARMS

- **Sub-Ambient Pressure Alarm**
  - Triggered when the pressure in the breathing circuit falls below a predetermined amount (typically below -10 cmH2O for >1-second).
    - Meant to protect against obstruction in safety valves used in the gas scavenging system → protects against profound vacuum pressures that can be delivered to the anesthesia machine by an active gas scavenging system
    - May be triggered during spontaneous or controlled respiration
      - Low pressure alarm is NOT active during spontaneous ventilation
  - Location: most circuits have the pressure sensor just proximal to the inspiratory valve to prevent interference of condensation.
  - Causes:
    - Accidental placement of NG-tube or endoscope within the trachea and using suction → loss of volume and negative pressure alarm is triggered
    - Patient inhalation against increase resistance in the circuit
    - Patient inhalation against a collapsed reservoir bag
    - Malfunctioning active closed scavenging system (excessive vacuum or valve dysfunction)
    - Blocked inspiratory limb during exhalation

- **Peak Pressure Alarms**
  - Lung Resistances
    - Airway resistance affects airflow into the lungs. Peak inspiratory pressure (Pip) directly varies with flow resistance from the ventilator tubing to the segmental bronchi.
      - Increased Pip and unchanged Pplateau occur in situations with increased airway resistance → bronchospasm, kinked ETT, airway secretions, mucus plugs
    - Elastic resistance affects the expansion of the lungs (aka: pulmonary compliance). Changes in elastic resistance causes changes in BOTH peak inspiratory pressure (Pip) AND plateau pressure (Pplateau)
      - Increased PiP AND Pplateau occur in situations with decreased lung compliance → intrinsic pulmonary diseases, ascites, abdominal insufflation, tension PTX, Trendelenburg position
        - Peak and Plateau Pressures usually differ by ~4-10 cmH2O
  - Continuous pressure for >15-seconds that is NOT programed as PEEP → prevent elevated intrathoracic pressure from impeding venous return and decreasing cardiac output

VCV > PCV waveforms provide diagnostic clues regarding patient's respiratory mechanics

Airway Resistance	Pulmonary Compliance
Increased Pip Unchanged Pplateau	Increased Pip Increased Pplateau
Airway Compression Bronchospasm Foreign Body Kinked ETT Mucus Plug Secretions	Abdominal Insufflation Ascites Intrinsic Lung Disease Obesity Pulmonary Edema Tension Pneumothorax Trendelenburg Position



ANESTHESIA MACHINE

ANESTHESIA MACHINE CHECK

- (1) Oxygen Analyzer Calibration
- (2) Low Pressure Leak Test
  - Differentiates between leaks in the machine and leaks in the breathing system
    - Low pressure circuit includes all components from the flow control valve to the common gas outlet, including vaporizers.
      - Loose filler caps on the vaporizer and fragile flow tubes are susceptible to leaks/cracks, which can result in hypoxia and awareness.
  - Suction bulb is placed on the common gas outlet and bulb squeezed until a vacuum is created.
- (3) Circle System Leak Test

SUMMARY OF ANESTHESIA MACHINE ALARMS & SAFETY FEATURES

M. Jablonski, 2020-2021

Alarm or Safety Feature	Feature or Trigger	Purpose
High-Pressure Regulator	Pressure in hospital gas pipeline	Preferentially utilize gas from hospital pipeline rather than E-cylinder
Sub-Ambient Pressure Alarm	Pressure in the breathing circuit falls below -10 cmH2O for >1-second	Protects against profound vacuum pressures that can be delivered to the anesthesia machine by an active gas scavenging system
E-Cylinder Oxygen Supply Check Valve	Prevents the backward flow of oxygen from the anesthesia machine into either an empty E-cylinder or the operating room environment if E-cylinder is removed	Assists in preferential use of pipeline oxygen supply instead of E-cylinder oxygen supply
Low Oxygen Pressure Sensor	Detects low pressure within the intermediate pressure oxygen system within the anesthesia machine	Help to prevent hypoxic gas mixture. ** Note: does NOT detect FiO2, will NOT detect oxygen pipeline contamination or crossover
Peak Pressure Alarm	Airway pressure above predetermined set pressure, or continuous pressure for >15-seconds that is NOT programed as PEEP	Prevent elevated intrathoracic pressure from impeding venous return and decreasing cardiac output
Diameter Index Safety System	Threaded non-interchangeable connections on the anesthesia machine	Prevents hospital gas supply hose cannot be connected to wrong wall pipeline or machine port
Pin Index Safety System	Two metal pins on the anesthesia machine correspond to holes on the cylinder; pins are different sizes and have different orientations for the specific gas cylinders	Prevents the connection of the wrong cylinder to the wrong inlet on the anesthesia machine
Keyed Vaporizer Filling	Specific notch design on vaporizer filling key which are different for each inhaled anesthetic agent	Prevent filling of the vaporizer with the wrong gas.
Vaporizer Interlock Mechanism	Reciprocal pins and pivotable lever that interconnect two vaporizers on anesthesia machines which feature secured vaporizers	Only one vaporizer can be turned on at a time.
Pressure Fail-Safe	Device present in all gas lines except for oxygen that interrupts the supply of other gases if the oxygen supply is reduced <30psi, which is the opening threshold pressure for other gases	Prevents hypoxic mixtures if there is a decrease oxygen supply at the flowmeter level
Oxygen Ratio and Proportioning Devices	N2O-to-O2 proportion device links the two flows to prevent a final inspired oxygen concentration of <25%.	Prevent hypoxic mixture

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ANESTHESIA MACHINES AS ICU VENTILATORS

- ASA/APSF Recommendations:
  - (1) Removal and drainage of all anesthetic vaporizers (unless anesthetic gas is to be used as ICU sedation)
  - (2) Removal of the nitrous oxide cylinder and hoses from the machine
  - (3) Modifying alarms to match those of other ICU ventilators
  - (4) Disconnecting gas scavenging
    - Exceptions: (1) inhaled anesthetics are planned sedation, (2) gas analyzing system is not filtered
      - If gas analyzing system is between the filter and the patient → contaminate entire anesthesia machine and ICU room
    - Removal of scavenger reservoir bag if a closed scavenging system is utilized
  - (5) Changing the bellow drive gas to compressed air if oxygen supplies are limited
  - (6) Using higher than normal fresh gas flows to prevent excess humidity in the circuit and clogging of airway filters
  - (7) Placement of a "high quality" viral filter between the breathing circuit and the patient's airway with the capability to sample gas from the machine side of the filter.
    - HME/HMEF (heat and moisture exchangers (filters)) are recommended due to simplicity, low labor costs, option to filter bacterial components
      - Humidification prevents desiccation of orotracheal secretions, decreases caloric expenditure and heat loss in pediatric populations.
      - Goal humidification >50% (preferably 100%). Approximately 1-hour is required to achieve 80% humidification with a passive HME device.
    - HME Disadvantages: increased airway resistance (including catastrophic obstruction), circuit disconnection, less efficient humidification (compared to active humidification devices), increased dead space

- Oxygen Supply
  - Liquid oxygen has a greater capacity than compressed cylinders
    - Portable liquid oxygen systems are rare and expensive
- Oxygen Concerns with Excessive Mechanical Ventilation
  - Fall in oxygen line pressures, damage to inline regulators due to excessively cold temperatures generated during gas cylinder depressurization, potentially insufficient oxygen delivery
- Minimizing Oxygen Consumption
  - (1) Utilizing electrically-powered ventilators
  - (2) Converting ventilator drive gas to medical air instead of oxygen for ventilators with pneumatically-driven bellows
    - Inspiration features injection of gas roughly equal to the patient's tidal volume to compress the bellow → gas is evacuated into the gas scavenging system during exhalation
      - Utilizes approximately 5-7 L/min of oxygen (approximately patient's minute ventilation)
  - (3) Low fresh gas flow
    - Complications: excessive airway humidity (clogs viral filters), increased CO_2 absorbent utilization
      - ASA/APSF recommends fresh gas flows of 1.5x patient's minute ventilation when an anesthesia machine is used as an ICU ventilator
        - Ability to change and manipulate fresh gas flow is a key distinguishing feature of anesthesia machines when compared with ICU ventilators
  - (4) Limit Therapies Requiring High Oxygen Flows
    - High-flow nasal cannula can use up to 70 L/min whereas ventilators usually use <10 L/min

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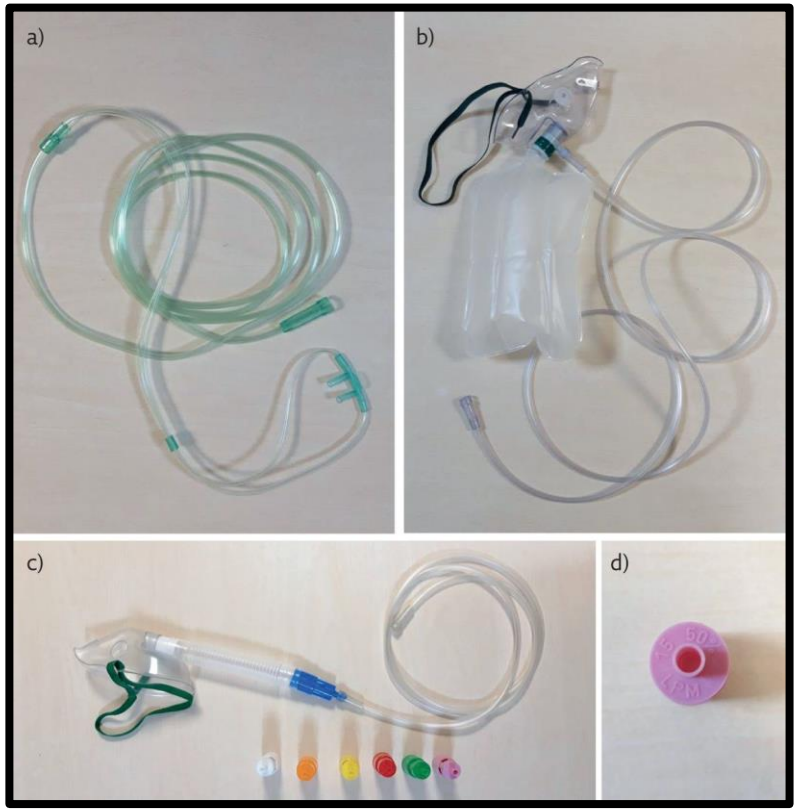
MONITORING OF ANESTHESIA MACHINES DURING ICU VENTILATION

Task	Monitoring Frequency
Alarms	Continuously
CO2 Absorbent	q1h
Monitored Parameters (FiO2, FiCO2, ETCO2, insp. Pressure, Vt, spirometry)	q1h
Filters/Water Traps	q1h
Increase FGF to >/= MV if humidity is present until insp. hose dries	q4h
Filter/HME Replacement	q4-24h
Perform Self Test	q24h

LOW FLOW OXYGEN DELIVERY DEVICES

- Delivers 100% oxygen at flows less than the patient's inspiratory flow rate → oxygen is diluted with room air and thus FiO2 can be increased by increasing the oxygen flow rate, though each system has a maximum FiO2 that can typically be provided.



Device	FiO2	Flow Rates
Nasal Cannula	25-40%	6 L/min
Simple Face Mask	35-50%	>5 L/min
Partial Rebreathing Mask	40-70%	> 6 L/min
Nonrebreathing Mask	60-80%	>10 L/min