

Pulmonary Physiology

Control of Breathing

- Keep PCO_2 40 mmHg awake
- Neural Control
- Chemical Control

Pulmonary Physiology

- Control of Breathing
- Mechanics/Work of Breathing
- Ventilation
- Gas transport (including pulmonary circulation)
- Gas Exchange (including diffusion of gas/gas transfer)

Neural Control

- Inspiratory inhibition reflex (Hering Breuer); irritant, mechano, j receptors: stimulation in patients with, e.g., interstitial fibrosis, pulmonary embolism, atelectasis
- Stimulation of mechanoreceptors in airways: can cause tachypnea, bronchoconstriction

- “When you can’t breathe, nothing else matters.”

Chemical control

- CO_2 stimulation
- Hypoxemic stimulation
- H^+ stimulation

Chemical Control: CO₂ stimulation

- Rise in PaCO₂ = increase in [H⁺] concentration in ECF and ventrolateral surface of the medulla, stimulating ventilation (hyperventilation)
- In turn, dilation of CNS blood vessels by increased CO₂ leads to increased removal of CO₂ and decrease in central CO₂ stimulation; also, the hyperventilation results in lower CO₂ to stimulate. Then, lower CO₂ = brain vessel constriction = buildup in ECF CO₂ again
- **Chronically elevated PaCO₂ = increased ECF [HCO₃⁻] so acute increase in PaCO₂ will induce less of a change in [H⁺] and therefore less stimulus to ventilation

Chemical Control of Breathing

- When WOB elevated, PCO₂ not as potent a stimulus to breathe
- Sleep depresses ventilatory stimulation; PaCO₂ rises by several mmHg in sleep (most in REM sleep)

Chemical Control: Hypoxemic Stimulation

- Peripheral chemoreceptors (carotid body, aorta) respond primarily to low PaO₂; also can respond to PCO₂ and [H⁺] as well as decreased blood flow and increased temperature
- Low PaO₂=increased V_E, then decreased arterial and CNS CO₂ and [H⁺] = less central stimulus to breathe
- Hypoxic ventilatory depression may be seen early after initial stimulation (10-30 minutes) at altitude

Mechanics of breathing

- Total mechanical work of breathing=overcoming elastic-resistive work+ flow-resistive work; in normal individual this applies to INSPIRATION.
- Severe airway obstruction: may need expiratory work to overcome EXPIRATORY flow resistance
- Asthma= normal elastic resistance, high flow resistance
- Pulmonary fibrosis/stiff lungs (eg ARDS)= normal flow resistance, high elastic resistance and need for work to overcome this.

Chemical Control: Hydrogen ion stimulation

- Metabolic acidosis stimulates; alkalosis inhibits breathing primarily through peripheral chemoreceptors, ~7.30 to 7.50
- Acute metabolic acidemia = increased ventilation; then decreased PaCO₂ and CNS PCO₂, decreased [H⁺], decreased [HCO₃⁻], and after 24 hours normalization of CNS [H⁺].
- So, chronically low [HCO₃⁻] = easier to stimulate by CO₂. Conversely, met alkalosis = low VE; eventual increase in CNS [HCO₃⁻] = more difficult to stimulate by CO₂

Mechanics of breathing

- Elastic forces: recoil of lungs and recoil of chest wall =equilibrium at FRC (functional residual capacity)
- *Elastance*= $\Delta P / \Delta V$; this is the distensibility of the respiratory system (lungs, chest wall)
- *Compliance*= $\Delta V / \Delta P$
- Lung volume dependent
- Healthy: Lung compliance~0.2 L/cmH₂O: eg, change inspiratory pressure 5 cmH₂O, 1.0 L air is inspired,=1 L/5 cmH₂O=0.2 L/cmH₂O

Mechanics of breathing

- Emphysema: increased compliance due to loss of elastic recoil pressure: e.g., change in inspiratory pressure 5 cmH₂O/2.0 L inspired air, or 0.4 L/cmH₂O compliance
- (Sounds like a good thing for inspiration, but less efficient expiration..)
- Pulmonary fibrosis: increased elastic recoil pressure (stiff lungs): 5 cmH₂O inspiratory pressure change with 0.5 L air inspired; compliance=0.1 L/cmH₂O

Mechanics of Breathing

- Inspiratory airway resistance=pressure difference across airways between mouth and alveoli= $P_{dynamic}-P_{plateau}/flow$ (normal=<4 cmH₂O/L/sec)
- Maximal inspiratory flow rate depends primarily upon muscular effort
- Expiration: higher volumes=higher flow rates, but once ~50% TLC, rate declines with greater effort because of dynamic airway compression
- Dynamic airway compression=more collapse of airways in expiration in emphysema (loss of elastance/increased compliance) as effort increases=gas trapping

Mechanics of Breathing

- Transpulmonary pressure: difference between pleural pressure (usually measured as esophageal pressure) and mouth pressure static=no airflow
- Static compliance: relationship of transpulmonary pressure under static conditions (no airflow) to different degrees of lung inflation (volumes)
- Static inspiratory compliance= $V_T/P_{plateau}-PEEP$

Mechanics/Work of Breathing

- Note that low and high respiratory rates cause increased mechanical work of breathing:
- High rates=low lung volumes=need to increase total ventilation (by increasing flow rate) to maintain alveolar ventilation, since there is increased wasted (dead space) ventilation, so increased work necessary to overcome flow resistance
- Slow rates=little flow resistive work because of low flow rates but must increase VT to maintain alveolar ventilation; thus must use increased work to overcome elastic resistance

Mechanics of Breathing

- Dynamic compliance: compliance determined during breathing
- Dynamic compliance= $V_T/P_{dynamic} (peak)-PEEP$ (recall that static inspiratory compliance= $V_T/P_{plateau}-PEEP$)

Mechanics/Work of Breathing

- Elastic resistance high (low compliance) = increased respiratory frequency; V_T usually low, so rapid, shallow breathing=least work
- eg, pulmonary fibrosis = low lung compliance; obesity, kyphoscoliosis = low chest wall compliance
- Flow resistance high= decreased respiratory frequency ; generally deeper and slower breathing (eg, chronic airflow limitation)
- Note, however: with lung hyperinflation, volume pressure curve changes with decreasing compliance and the patient may breathe more rapidly and shallowly as well

Mechanics/Work of Breathing

- Metabolic work:
- Oxygen consumption (VO_2) in normals~1.0 ml/liter of ventilation; O_2 cost of breathing increases in patients with respiratory disorders due to the increased work required

Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

- Pulmonary capillary blood volume increases during inspiration and exercise
- Reduced when patients receive mechanical ventilation (intrathoracic pressure is raised, thus impeding venous return to the heart)
- Patients with increased pulmonary pressure (eg pulmonary hypertension, pulmonary embolism)=cardiodynamic consequences as well as disturbance of gas transfer

Ventilation

- $PACO_2 = VCO_2/VA \times K$ (the constant is actually 863 mmHg, derived from ideal gas laws).
- The ratio of VCO_2/VA for normal people at rest, at sea level, is about 1/21.6; thus, normal $PACO_2 = 1/21.6 \times 863 \text{ mmHg} = \sim 40 \text{ mmHg}$.

Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

- Transfer of O_2 and CO_2 between alveolar gas and pulmonary capillary blood is entirely passive, with the *rate of diffusion* of gas across alveolar-capillary barrier determined by (1) solubility of gas in liquid, (2) density of gas, (3) partial pressure difference between alveolar air and pulmonary capillary blood, and (4) surface area available for diffusion
- CO_2 diffusion not a clinical problem because CO_2 much more soluble and diffusible than oxygen between air and blood
- Total diffusing capacity includes uptake by hemoglobin and rate of flow

Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

- Conduction of blood coming from the tissues through the alveolar capillaries so that O_2 can be added and CO_2 removed.
- Pulmonary vessels=low pressures and low resistance to flow (thin walled)
- Resistance=driving pressure/flow (Q)
- Most resistance in the arterioles and capillaries
- Driving pressure=pressure at the beginning of the pulmonary circulation (the pulmonary artery) and other end (left atrium); normally, eg, blood flow 6 L/min and mean driving pressure of 9 mmHg, resistance is 9mmHg/6 L/min, or 1.5 mmHg/L/min (~10% of systemic pressure).

Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

- Low diffusion capacity not necessarily low PaO_2 , since so much redundancy:
- Complete exposure of alveolar PO_2 to capillary blood=no decrease in end capillary PO_2 , even if there is less volume, or Hgb, and no change in $AaDO_2$ (
- But incomplete transfer = decrease in end capillary PO_2 and widened $AaDO_2$

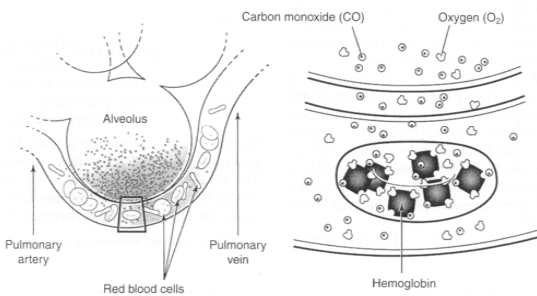
“Diffusion Capacity” vs Diffusion

- Note that: decreased diffusing capacity/gas transfer abnormality can result from numerous abnormalities not having anything to do with diffusion block itself

Gas Transport: CO₂

- CO₂ in physical solution: most carried in RBCs either as bicarbonate, or bound to Hgb (carbaminoHgb)
- Some is dissolved in plasma

Diffusing Capacity (Transfer Factor)



Gas Transport:Oxygen

- O₂ combined with Hgb in RBCs, and dissolved O₂ in physical solution in the plasma
- Normal: 1 gm of Hgb able to combine chemically with 1.34 ml O₂
- Thus: O₂ capacity=1.34 ml O₂/gmHgb
- If 15 gm Hgb/100 ml blood, O₂ capacity=20 ml O₂/100 ml blood=200 ml O₂/liter blood
- Dissolved O₂ = .003 ml O₂/100 ml blood/mmHg PaO₂
- $CaO_2 = SaO_2 \times [O_2 \text{ capacity}] + \text{dissolved } O_2$
- If PaO₂ =100 mmHg, and Hgb=15, then O₂ content = 200 ml O₂/liter blood + 3 mlO₂/liter blood= \sim 203 mlO₂/liter blood \times SaO₂

“Diffusion Capacity” vs Diffusion

- So when we say diffusion abnormality=cause of hypoxemia, we mean those abnormalities which involve some form of diffusion block, or other inability to transfer gas completely (eg, low PIO₂+ **decreased** circulatory time) so that insufficient transfer of alveolar PO₂ occur
- Low alveolar volume, low Hgb, may result in low diffusing capacity as measured by transfer of CO, and low O₂ content, but not low PaO₂

Hypoxemia

- Low partial pressure of O₂ in blood (PaO₂)
OR low O₂ content

Hypoxia

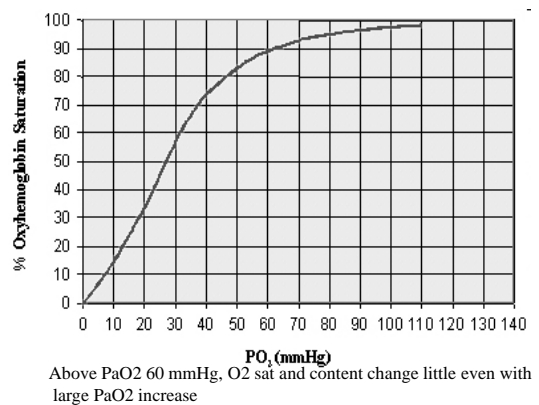
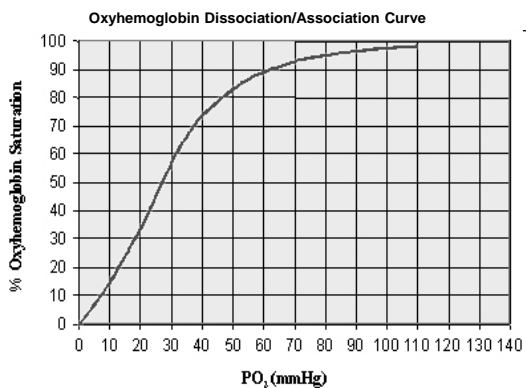
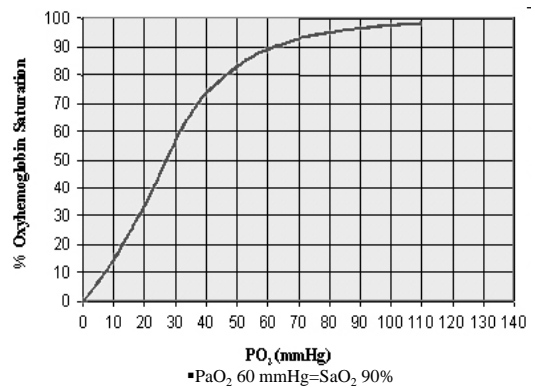
- Metabolic O₂ deficiency Unable to meet tissue demands)
- Hypoxia causes are:
 - “stagnant”, as with impaired blood flow; normal PaO₂ and SaO₂
 - “histocytotoxic”, as with metabolic impairment using O₂, such as cyanide poisoning; normal PaO₂ and SaO₂
 - “anemic”, as with low Hgb or carbon monoxide poisoning; normal PaO₂ and SaO₂
 - “hypoxic” or “hypoxemic”, as with impaired oxygenation such as low V/Q, shunt, diffusion block, or low PIO₂ such as high altitude; PaO₂ and SaO₂ decreased

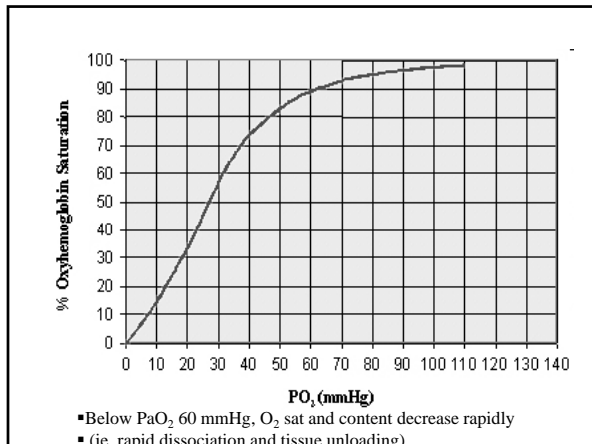
Oxyhemoglobin Dissociation/Association Curve: Key Points

- O₂ saturation=O₂ bound to Hgb/O₂ carrying capacity; degree of O₂ bound depends upon PO₂ Hgb is exposed to

Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

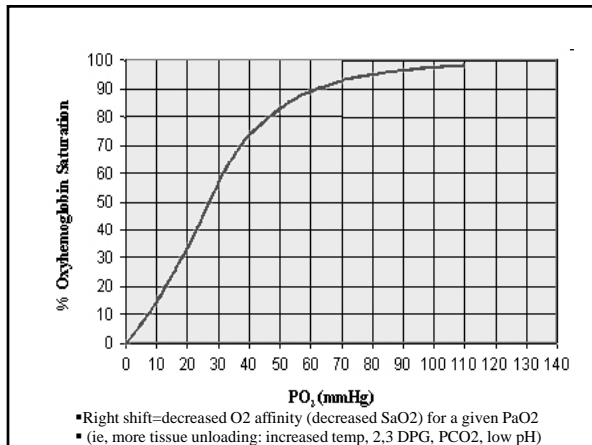
- Hypoxemia: hypoventilation, low PIO₂, diffusion abnormality (must be severe if at rest), V/Q mismatch, shunt (note that shunt and diffusion block manifest similarly in corresponding areas of lung; but diffusion abnormality (if not block) does NOT equal shunt)
- Note that low V/Q does not=shunt
- Degree of O₂ saturation depends on O₂ tension





Physiologic Causes of Hypoxemia

- Alveolar Hypoventilation
- Decreased P_{iO_2}
- Diffusion Abnormality
- V/Q mismatch
- Shunt



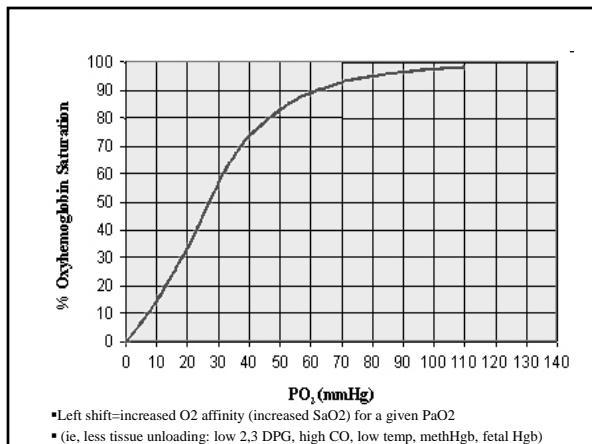
Physiologic Causes of Hypoxemia

Widening of $AaDO_2$:

- Diffusion Abnormality
- V/Q mismatch
- Shunt

No widening of $AaDO_2$:

- Hypoventilation
- Low P_{iO_2} (may contribute to widening if impaired diffusion)



Gas Exchange

- Alveolar Gas Equation:
- $PAO_2 = FIO_2 \times (P_B - PH_2O) - PCO_2/R + [PACO_2 \times FIO_2 \times 1 - R/R]$ (full)
- $PAO_2 = FIO_2 \times (P_B - PH_2O) - PCO_2/R$ (simplified)
- R=Respiratory Exchange Ratio: (gas R= CO_2 added to alveolar gas by blood/amount of O_2 removed from alveolar gas by blood; low V/Q=low R; normal=0.8)

Two patients breathing room air at sea level:

1. $\text{PaO}_2=40$ mmHg, $\text{PaCO}_2=90$ mmHg:

2. $\text{PaO}_2=40$ mmHg, $\text{PaCO}_2=22$ mmHg:

Ventilation and Gas Exchange

- Objective: to achieve adequate tissue oxygenation and remove metabolically produced CO_2 .
- Ventilation: concerned with delivery of fresh volume of air to gas exchanging units, and the removal of a sufficient volume of mixed gas out
- Gas Exchange: the ability to move gas across the alveolar-capillary membrane

Ventilation and Gas Exchange

- The failure of either or both results in impaired arterial blood gases and ultimately *respiratory failure*.
- Ventilatory failure: *Hypercapnic respiratory failure*
- Gas exchange failure: *Hypoxemic respiratory failure*
- *Hypoxemia is the inevitable result of both*

Abnormal Ventilation, Abnormal Gas Exchange

Hypoxemia

- Low partial pressure of O_2 in blood (PaO_2)
OR low O_2 content ($\text{CaO}_2:\text{SaO}_2 \times \text{O}_2$
carrying capacity+.03 ml O_2 /l/mmHg PaO_2)

Hypoxemia

- Hypoxemia is not synonymous with:

Hypoxemia

- Hypoxemia is not synonymous with:
 - Low O_2 delivery ($Ca O_2 \times C.O.$)

Hypoxemia

- Hypoxemia is not synonymous with:
 - Hypoxia, which is metabolic O_2 deficiency
 - Hypoxia causes are:
 - “stagnant”, as with impaired blood flow;
 - “histocytotoxic”, as with metabolic impairment using O_2 , such as cyanide poisoning;
 - “hypoxic”, as with impaired oxygenation such as low V/Q, or low PIO_2 such as high altitude;
 - “anemic”, as with low Hgb or carbon monoxide poisoning

Physiologic Causes of Hypoxemia

Alveolar Hypoventilation

Decreased PIO_2

Diffusion Abnormality

V/Q mismatch

Shunt

Hypoxemia

- Hypoxemia is not synonymous with:
 - Low O_2 carrying capacity (1.34 ml O_2 /gm Hgb; if 15 gmHgb/100ml blood, then 20 ml O_2 /100ml blood, or 200 ml O_2 /liter of blood)

Ventilation

- Minute Ventilation (VE)=tidal volume (VT) x respiratory frequency (“dead space” volume not accounted for)
- Alveolar ventilation (VA)=that part of minute ventilation which participates in gas exchange (that volume of fresh gas entering the respiratory exchange zone each minute)
- Alveolar ventilation=alveolar volume (tidal volume-dead space volume) x respiratory frequency

Ventilation

- Alveolar PCO₂ (PACO₂)=VCO₂/V_A x K
- VCO₂=CO₂ production
- V_A=alveolar ventilation
- Normal: VCO₂/V_A=1/21.6; K=863 mmHg, so PACO₂≈40mmHg)
- Alveolar PCO₂=CO₂ leaving lungs after gas exchange; directly reflects arterial PCO₂
- e.g., halving alveolar ventilation with constant CO₂ production will double the alveolar PCO₂
- e.g., doubling the alveolar PCO₂ reflects halved alveolar ventilation

Alveolar Hypoventilation: 2 Clinical Pearls

- Does not widen the AaDO₂
- The hypoxemia may be readily ameliorated with supplemental O₂
- Challenge: Write a proof for this latter statement

Hypoventilation

- Inability to inspire and expire a volume of air/gas sufficient to meet metabolic demands
- Inability to bring a fresh volume of O₂ with each breath to the gas exchanging unit, and inability to remove CO₂ produced by metabolism.
- *Sine qua non*: Increased arterial PCO₂ (PaCO₂); decreased arterial PO₂ (PaO₂) breathing room air (*parallel changes!!*)

Alveolar Gas Equation

- $PAO_2 = PIO_2 - PACO_2/R$
- $PAO_2 = PIO_2 - PACO_2/R + [PCO_2 \times FIO_2 \times 1-R/R]$

Hypoventilation/ Alveolar hypoventilation

- All hypoventilation concerns either :
- increased dead space/tidal volume ratio (anatomic or physiologic), ie “wasted” ventilation; or
- Decreased MINUTE ventilation (decreased tidal volume, and/or decreased respiratory rate)
- Each may result in alveolar hypoventilation (PaCO₂ elevated)

Alveolar Gas Equation

- $PAO_2 = PIO_2 - PACO_2/R$
- $PIO_2 = FIO_2 (P_{atm} - PH_2O)$

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- $PACO_2 = PaCO_2$

Case History

- Room air: $PaO_2 = 30$ mmHg, $PaCO_2 = 90$ mmHg, $pH = 7.08$
- $PAO_2 = 0.21 (760 - 47) - 90/0.8$
- $PAO_2 = 150 - 112.5 = 37.5$

Alveolar Gas Equation

- $PAO_2 = PIO_2 - PACO_2/R$
- $PIO_2: FIO_2 (P_{atm} - PH_2O)$
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- $R =$ Respiratory Exchange Ratio: (gas $R = CO_2$ added to alveolar gas by blood/amount of O_2 removed from alveolar gas by blood; low $V/Q =$ low R); normal = 0.8

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- $AaDO_2 = 7.5$ mmHg

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Alveolar Hypoventilation

- CNS: central hypoventilation; infectious, traumatic, vascular damage to medullary centers; pharmacologic and sleep suppression of ventilatory drive

Alveolar Hypoventilation

- CNS: central hypoventilation; infectious, traumatic, vascular damage to medullary centers; pharmacologic and sleep suppression of ventilatory drive
- Peripheral nervous system/myoneural junction: poliomyelitis, Guillain-Barre, myasthenia gravis

Alveolar Hypoventilation

- Respiratory muscles: muscular dystrophy, increased inspiratory loading (eg emphysema)
- Chest wall/mechanical restriction: kyphoscoliosis, trauma, splinting, obesity
- Airway obstruction: upper airway, lower airway

Alveolar Hypoventilation

Respiratory muscles: muscular dystrophy, ALS, increased inspiratory loading (eg emphysema)

Hypercapnic Respiratory Failure

- Primary deficit=hypoventilation without gas exchange abnormality
- Hypoxemia MUST result if patient breathing room air
- AaDO₂ not widened if no supervening gas exchange abnormality

Alveolar Hypoventilation

Respiratory muscles: muscular dystrophy, increased inspiratory loading (eg emphysema)

Chest wall/mechanical restriction: kyphoscoliosis, trauma, splinting, obesity

AaDO₂ and Hypoxemia

- Widened in diffusion disorder, V/Q mismatch, and shunt
- Not widened in alveolar hypoventilation and decreased PIO₂
- Normal AaDO₂ ~10-15 mmHg in young adult at sea level breathing RA

Climbing Everest (Decreased PIO₂)

- P_{atm}= 250 mmHg
- PaCO₂=18 mmHg; R=1
- PAO₂=PIO₂-PCO₂/R
- PAO₂= .21 (250-47)-18/1=24.6 mmHg
- Recent data: altitude 8400m, mean PaO₂=30 mmHg, Mean AaDO₂ 5.4 mmHg (wider than expected): Grocott et al, NEJM 2009, 360:2: 141

What happened?

- PAO₂=PIO₂ – PACO₂/R
- 0.21 FIO₂, PaO₂=50 mmHg, PaCO₂=28 mmHg
- PAO₂=0.21(713)-28/0.8=150-35= 115 mmHg
- AaDO₂=115-50= 65 mmHg

Case History

- RA: PaO₂=70, PaCO₂=30 mmHg

Hypoxemia

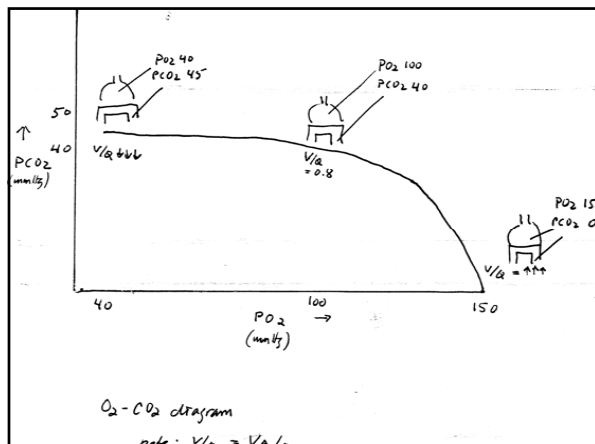
- No widening of AaDO₂: hypoventilation, low PIO₂.
- Widened AaDO₂: shunt, low V/Q, low diffusing capacity
- Hypoxemia of each may be overcome with supplemental O₂ *except: shunt*.
- Note: no gas exchange=no amelioration of hypoxemia with O₂, whether dead space, shunt, or no diffusion.

Case History

- RA: PaO₂=70, PaCO₂=30 mmHg
- No treatment: RA PaO₂=50 mmHg, PaCO₂=28 mmHg
- What happened? Did AaDO₂ change?

Low V/Q

- “Venous admixture”
- Alveolar filling: pneumonia, pulmonary edema (cardiogenic/non-cardiogenic)
- COPD a common situation of low V/Q
- Usually will involve some infinitely low V/Q (shunt) and decreased diffusion.



Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

- Low gas transfer and measured diffusing capacity may also result from processes not clearly blocking diffusion, such as low Hgb, or increased rate of flow disallowing adequate gas transfer
- All diffusion abnormalities do not typically = low PaO₂, or low O₂ content, since so much redundancy

Low V/Q

- Low relationship of V to Q; NOT low ventilation in all alveolar capillary units
- That is, Low V/Q is NOT hypoventilation (unless all units see the same lowering of V/Q)

Gas Transport: Pulmonary Circulation and Diffusion of Gas (Gas Transfer)

- Diffusing capacity, measured diffusing capacity (DLCO), and diffusion of gases differ
- Low diffusion will cause low measured diffusing capacity, possibly low PaO₂, and widened AaDO₂, low diffusing capability because of non-diffusion reasons (eg low Hgb, low volumes) will cause low measured diffusing capacity and low O₂ content but not necessarily decreased PaO₂ or widened AaDO₂

Diffusion Abnormality

- Alveolar-capillary membrane thickening (pulmonary hypertension, pulmonary vasculitis, pulmonary embolism)
- Alveolar-capillary membrane destruction (emphysema)
- Pulmonary interstitial thickening (pulmonary fibrosis)
- Alveolar filling (pulmonary edema, pneumonitis)

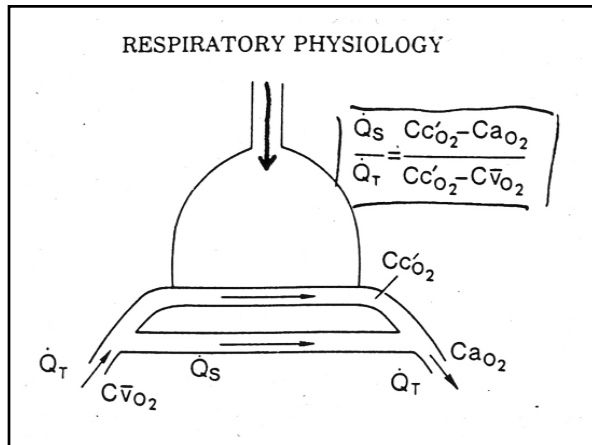
Shunt

- Infinitely low V/Q (but NOT low V/Q)
- Supplemental O₂ will not raise PaO₂ with large shunt
- Clinical examples: ARDS, other severe pneumonia, cardiogenic pulmonary edema
- May also be cardiogenic R-L shunt

- Shunt Fraction (Q_s/Q_t): $Cc'O_2 - CaO_2 / Cc'O_2 - CvO_2$ (normal <5%)
- Where CaO_2 is arterial O_2 content;
- $Cc'O_2$ is end capillary oxygen content;
- CvO_2 is mixed venous (pulmonary artery) O_2 content

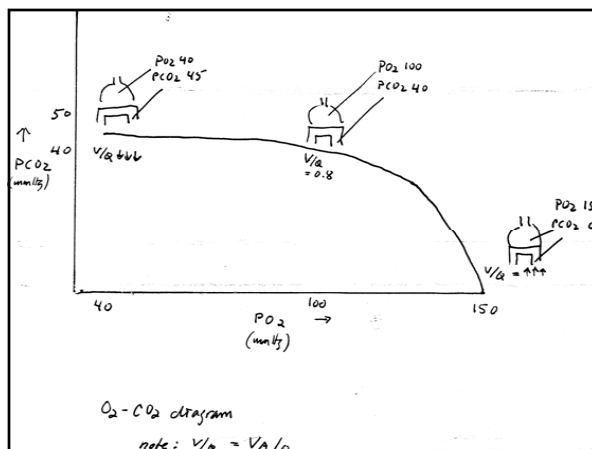
Hypoxemic Respiratory Failure

- Primary deficit=hypoxemia without hypoventilation, until late (?)
- Gas exchange abnormality: shunt, low V/Q , low diffusing capacity, all...
- Widened $AaDO_2$



SUMMARY

- Hypoventilation: High $PaCO_2$, Low PaO_2 , no widening of $AaDO_2$
- Gas exchange abnormality: Low PaO_2 , normal or low $PaCO_2$, widened $AaDO_2$
- Hypoxemia of all hypoventilation and gas exchange abnormalities may be sufficiently overcome by supplemental O_2 unless gas exchange abnormality is *absolute* (eg shunt)



Two patients breathing room air at sea level:

$PaO_2=40$ mmHg, $PaCO_2=90$ mmHg:

Severe alveolar hypoventilation; no gas exchange abnormality: ventilate, give oxygen if necessary to prevent severe hypoxemia; find and treat cause (s) of hypoventilation

$PaO_2=40$ mmHg, $PaCO_2=22$ mmHg:

Severe gas exchange abnormality: oxygenate; find and treat cause (s) of gas exchange problem (or low PIO_2)