Lecture Outline

- Basics of the Respiratory System
  - Functions & functional anatomy
- Gas Laws
- Ventilation
- Diffusion & Solubility
- Gas Exchange
  - Lungs
  - Tissues
- Gas Transport in Blood
- Regulation of Ventilation & Impacts on
  - Gas levels, pH

Ventilation & Gas Exchange

Relationship

- Net effect of ventilation is to exchange air within the alveoli to
  - Maintain a partial pressure gradient which is required for gas exchange in the tissues and in the lungs!
- Blood flow and ventilation rate are optimized to ensure a usable gradient remains despite changing conditions, this is mainly controlled at the local (lung) level by
  - the pulmonary capillaries collapse at low bp, diverting blood to areas of the lung with higher bp (away from the apex, towards the base)
  - Bronchiole diameter is affected by CO₂ levels
    - \( P_{CO_2} \) in expired air = \( P_{CO_2} \) in bronchiole diameter (and vice versa)
  - Arteriole diameter in the lungs, controlled by blood gas levels
    - With a \( P_{CO_2} \) and a \( P_{O_2} \), the pulmonary arterioles constrict
    - With a \( P_{CO_2} \) and a \( P_{O_2} \), the pulmonary arterioles dilate weakly

Gas Exchange

External Respiration

- The exchange of gases
  - Diffusion between the alveolar air and pulmonary capillary blood
  - Driven by
    - partial pressure (P) gradients for O₂ and CO₂
    - Solubility of gas which is affected by
      - Pressure gradient
      - Solubility coefficient for the particular gas
      - Temperature
      - Given the same pressure gradients and temp, O₂ will reach equilibrium at a lower dissolved content than will CO₂… Why?
**Solubility**

- The exchange membrane components and organization

**Gas Exchange**

**External Respiration**

- PO2 = 100 mm Hg
- PCO2 = 100 mm Hg
- [CO2] = 5.20 mmol/L
- [O2] = 5.20 mmol/L

**Internal Respiration**

- PO2 = 100 mm Hg
- PCO2 = 100 mm Hg
- [CO2] = 3.00 mmol/L
- [O2] = 0.15 mmol/L

**Gas Exchange**

**External Respiration**

- PO2 = 40 mm Hg
- PCO2 = 46 mm Hg
- PO2 = 100 mm Hg
- PCO2 = 40 mm Hg

**Internal Respiration**

- PO2 = 40 mm Hg
- PCO2 = 46 mm Hg
- PO2 = 100 mm Hg
- PCO2 = 40 mm Hg

**Inspired air**

**Expired air**

**Alveolus**

**Venule end**

**Arteriole end**

**Pulmonary capillary**

**RBC**

**Surfactant**

**Alveolar epithelium**

**Fused basement membranes**

**Nucleus of endothelial cell**

**Plasma**
Gas Exchange

• What happens when alveolar P\textsubscript{O\textsubscript{2}} drops?
  – Solubility rules indicate that
    • If P\textsubscript{O\textsubscript{2}} drops, then the amount dissolved in blood also drops!
    • Creating a hypoxic condition
• Factors that may cause low arterial P\textsubscript{O\textsubscript{2}}
  1. Not enough O\textsubscript{2} reaching alveoli
  2. Exchange between alveoli and pulmonary capillaries has a problem
  3. Not enough O\textsubscript{2} transported in blood

Gas Exchange

Hypoxia classifications

<table>
<thead>
<tr>
<th>Hypoxic hypoxia</th>
<th>Low arterial P\textsubscript{O\textsubscript{2}}</th>
<th>↑altitude, hypoventilation, ↓lung diffusion capacity, altered ventilation-perfusion ratio, asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemic hypoxia</td>
<td>↓Total O\textsubscript{2} bound to Hb</td>
<td>hemorrhage, low Hb, CO poisoning, altered Hb binding</td>
</tr>
<tr>
<td>Ischemic hypoxia</td>
<td>Hypoxia from reduction in blood flow</td>
<td>heart failure (systemic anemia), shock (peripheral hypoxia), thrombosis (single organ hypoxia)</td>
</tr>
<tr>
<td>Histotoxic hypoxia</td>
<td>cells being poisoned, and can’t use O\textsubscript{2}</td>
<td>Cyanide, H\textsubscript{2}S, alcohol, narcotics</td>
</tr>
</tbody>
</table>

Gas Exchange

Hypoxia Problems

1. Not enough O\textsubscript{2} in alveoli…
   – High elevation
     • Denver (5,280 ft above San Diego) where atmospheric pressure = 628 mm Hg
     – P\textsubscript{O\textsubscript{2}} then must be 132 mm Hg, instead of the 160 mm Hg here
     – A nearly 17.5% decrease in available oxygen in the blood!
     • What about top of Mt. Everest at 29,029 ft above San Diego?
       – Atmospheric pressure = 30kPa or 225 mm Hg
       – P\textsubscript{O\textsubscript{2}} then must be 47.25 mm Hg
       – A nearly 71% decrease in available oxygen in the blood!
       » To compensate ventilations increase from 15 per minute to between 80-90 ventilations per minute
   – Other ideas?

Gas Exchange

Which is harder?

• To breath at the top of the world’s tallest mountain, or second tallest mountain?

Which is harder?

– Peak of Mauna Kea – some 33,476 ft. above its base
– Peak of Mt. Everest – some 29,029 ft. above its base
Gas Exchange
Hypoxia Problems

2. Interference with alveolar capillary exchange
   - Alveolar air is normal but the exchange isn’t
   - Caused by
     • Less surface area for exchange (b)
     • Increased thickness of alveolar membrane (c)
     • Increased distance between alveolar membrane and capillary membrane (d)

Gas Transport
General Process

- Oxygen once in blood will
  - A. remain as dissolved oxygen
  - B. Bind to hemoglobin (Hb) to make HbO₂

Gas Transport
General Process

- TOTAL blood O₂ content = quantity dissolved in plasma + amount bound to Hb (HbO₂)
- Why have hemoglobin?
  - To ensure enough systemic O₂!
    • Dissolved oxygen content in blood volume
      - 15 ml O₂/min reaching the systemic tissues
    • O₂ requirement at rest = ~250 ml O₂/min
  - Oxygen bound to hemoglobin, allows the total amount of oxygen in the blood to exceed 250 ml O₂/min
Gas Transport

General Process

• O₂ in blood quickly associates with hemoglobin (Hb), forming oxyhemoglobin (HbO₂)
  – allows for blood to carry an extra 985 ml of oxygen/min in an average blood volume of 5L
  • Dissolved = 15ml O₂/min transported
  • Associated with Hb = 985 ml O₂/min
  – Total Oxygen carrying capacity = 1000ml/min or 1L/min
  • 4x’s greater than “at rest” demand

Gas Transport

Hemoglobin

• Why is hemoglobin so effective?
  – Each subunit of the quaternary structure has a binding site for oxygen
    • The heme group of each subunit contains a prophyrin ring with an iron atom (Fe²⁺) at the center
    – This Fe²⁺ reversibly binds O₂ in accordance with the law of mass action
    – Typically PₐO₂ drives this reaction

Gas Transport

oxygen binding to Hb

• What is the driving force for oxygen to bind to Hb?
  – Plasma PₐO₂

Gas Transport

Hemoglobin

• Hb structure can vary
  – Adult Hb
    • The subunits are alpha, beta, gamma, delta
    • Most common arrangement is 2 alpha, and 2 beta units (HbA) >95%
    • Also some where:
      – 2 alpha & 2 delta subunits present (HbA₂) ~2.5%
      – 2 alpha & 2 gamma subunits present (HbF) rare
  – Fetal Hb (HbF)
    • Gamma chains in place of the beta chains.
    • Creates Hb molecules with a higher affinity for oxygen

Hydroxyurea treatment in adults with sickle cell anemia stimulates development of more HbF than HbA
Gas Transport
Oxygen-hemoglobin dissociation curve

- The binding (association/dissociation curve) is NOT linear, it is rather a sigmoid (S shaped) curve.

Gas Transport
Oxygen-hemoglobin dissociation curves

- What would create a left-shift?
  Which curve would represent HbF?

Gas Transport
Oxygen-hemoglobin dissociation curves

- The binding of O2 on Hb is influenced by
  - Temperature
  - P_{CO_2}
  - pH
  - 2,3-DPG (BPG)

Effect of pH (Bohr Effect)  Effect of temperature

Effect of P_{CO_2}  Effect of 2,3-DPG (BPG)
Gas Transport

Oxygen Summary

- Why be concerned with CO₂ transport?
- Transports three ways:
  - Dissolved in blood (~7%)
  - Converted to bicarbonate ions (~70%)
  - Attaches to Hb (~23%)

\[
\text{CO}_2 + \text{Hb} \leftrightarrow \text{Hb} \cdot \text{CO}_2 \text{(carbaminohemoglobin)}
\]

Important things to consider:
1. The H⁺ created during bicarbonate ion formation
2. The transport of HCO₃⁻ out of the cell occurs with the movement of Cl⁻ into the cell called the chloride shift
   Both must reverse in the lungs!

Gas Transport

Carbon Dioxide

External Respiration (review)
Regulation of Ventilation

- Ventilation is controlled in the brain stem by a neural network
  - It is influenced by
    - Gas levels
    - pH
    - Emotions
    - Voluntary efforts
      - Tend to be very temporary!

Regulation of Ventilation
Brain Stem

- Control Model
  1. Rhythmic ventilation is due to spontaneously discharging neurons
     - Pre-Bötzinger complex (pacemaker)
  2. Respiratory neurons in medulla (DRG & VRG) control inspiratory & expiratory muscles
  3. Neurons in the Pons (PRG) integrate sensory input and influence activity of the medullary neurons
  4. Ventilation is under continuous modulation by reflexes and higher brain centers

Regulation of Ventilation
Neural Output Levels

- CO₂, O₂ and pH levels all influence ventilation
  - CO₂ has the biggest influence on ventilation rates
  - O₂ and H⁺ (pH) are influencing factors as well, but to a smaller extent

- Monitored by
  - peripheral and central chemoreceptors
    - Peripheral in the carotid and aortic bodies
    - Central in the medulla oblongata

Regulation of Ventilation
Influencing Factors

- Peripheral and central chemoreceptors
  - Peripheral in the carotid and aortic bodies
  - Central in the medulla oblongata
Regulation of Ventilation

Peripheral & Central Chemoreceptors

Ex. Chemoreceptors responses to plasma CO$_2$

Protective Measures

- Irritant receptors in airway cause
  - bronchoconstriction
  - coughing
  - sneezing

- Hering-Breuer inflation reflex
  - Prevents over-inflation of lungs
    - Stops inspiration
      - Rare in adults, infants may use this to limit ventilation volumes… why?

Higher Brain Center Influence

- Higher brain function NOT required for normal ventilation and regulation of respiratory cycles

- Conscious and unconscious controls
  - Emotional state
    - Fear/anxiety/excitement = increased respiratory cycle rate
    - Depression…
  - Holding your breath?
  - Hyperventilation before breath holding… good or bad?