### RESPIRATORY PHYSIOLOGY

- Table of Normal Values
- Mechanics of Respiration
- Physiology of Respiration

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#### TABLE OF NORMAL VALUES

<table>
<thead>
<tr>
<th>ITEM</th>
<th>NORMAL VALUE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Stuff</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural Pressure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning of Inspiration</td>
<td>-5 cm H₂O</td>
<td>5 cm H₂O less than atmospheric pressure</td>
</tr>
<tr>
<td>(At Functional Residual Capacity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural Pressure:</td>
<td>-8 cm H₂O</td>
<td>With normal inspiration, the change in pleural pressure is very small.</td>
</tr>
<tr>
<td>End of Inspiration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Alveolar Surface Area for Gas Exchange</td>
<td>75 m²</td>
<td></td>
</tr>
<tr>
<td>Normal alveolar diffusion barrier</td>
<td>1 micron</td>
<td></td>
</tr>
<tr>
<td><strong>Airway Resistance and Flow</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Airway Resistance</td>
<td>0.5 - 1.5 cm H₂O / mL / sec</td>
<td></td>
</tr>
<tr>
<td>Fraction of Vital Capacity in the First second of a forced maximal exhalation</td>
<td>70% - 80%</td>
<td>The FVC test is used to measure airway resistance. Subnormal value indicates COPD.</td>
</tr>
<tr>
<td>(FEV₁ / FVC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gas Exchange</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atmospheric PO₂</td>
<td>21% of 760 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>160 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Inspired PO₂</td>
<td>= (21%) x (747 - 47 mm Hg)</td>
<td>Air becomes saturated with water which has partial pressure of 47 mm Hg.</td>
</tr>
<tr>
<td>P,O₂</td>
<td>= 147 mm Hg</td>
<td>Thus we take the PO₂ of dry air = (21%)(700)</td>
</tr>
<tr>
<td>Inspired PCO₂</td>
<td>Virtually 0</td>
<td>Atmospheric air contains virtually no CO₂</td>
</tr>
<tr>
<td>( P_A CO_2 )</td>
<td>( PAO_2 )</td>
<td>Alveolar ( PO_2 ) 100 mm Hg</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>( PA CO_2 )</td>
<td>( PAO_2 )</td>
<td>Alveolar ( PCO_2 ) 40 mm Hg</td>
</tr>
<tr>
<td>( PV CO_2 )</td>
<td>( PV O_2 )</td>
<td>Mixed Venous ( PO_2 ) 40 mm Hg</td>
</tr>
<tr>
<td>( PV CO_2 )</td>
<td>( PV O_2 )</td>
<td>Mixed Venous ( PCO_2 ) 46 mm Hg</td>
</tr>
<tr>
<td>( Pa CO_2 )</td>
<td>( Pa O_2 )</td>
<td>Arterial ( PO_2 ) 90 - 95 mm Hg</td>
</tr>
<tr>
<td>( Pa CO_2 )</td>
<td>( Pa O_2 )</td>
<td>Arterial ( PCO_2 ) 40 mm Hg</td>
</tr>
</tbody>
</table>

### Dead Space

<table>
<thead>
<tr>
<th>Tidal Volume</th>
<th>450 - 500 mL</th>
<th>Volume of air during normal inspiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical Dead Space</td>
<td>150 mL</td>
<td>The individual's weight in lbs = anatomical dead space in mL</td>
</tr>
<tr>
<td>( V_D / V_E ) Ratio</td>
<td>0.2 to 0.3, i.e. 20% - 30% of expired air is dead space.</td>
<td>High dead space occurs with pulmonary embolism, and with low ( V_A/Q ) ratios.</td>
</tr>
<tr>
<td></td>
<td>When ( V_D/V_E ) ( \rightarrow ) 0.6, patients are put on a ventilator.</td>
<td></td>
</tr>
<tr>
<td>Respiratory Quotient</td>
<td>0.8</td>
<td>The reciprocal is 1.2, the fudge-factor for the alveolar ventilation equation.</td>
</tr>
<tr>
<td>( VCO_2 / VO_2 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Gas Transport and Acid-Base Balance

| Plasma Solubility Coefficient of \( O_2 \) (\( SO_2 \)) | 0.003 mL \( O_2 \) / dL plasma, or 0.003 Vol-% | |
### Plasma Solubility Coefficient of CO₂ (SCO₂)

<table>
<thead>
<tr>
<th>Plasma Solubility Coefficient of CO₂ (SCO₂)</th>
<th>0.03 mL CO₂ / dL plasma, or 0.03 Vol-%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂(g) is thus 10x more soluble than O₂(g).</td>
<td></td>
</tr>
</tbody>
</table>

### O₂ Carrying-Capacity of Hemoglobin

<table>
<thead>
<tr>
<th>O₂ Carrying-Capacity of Hemoglobin</th>
<th>1.34 mL O₂ / g Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>One gram of Hb holds 1.34 mL of O₂.</td>
<td></td>
</tr>
<tr>
<td>Thus:</td>
<td>Maximum HbO₂ = (Hematocrit)(1.34)</td>
</tr>
</tbody>
</table>

### Hematocrit

<table>
<thead>
<tr>
<th>Hematocrit</th>
<th>15 g Hb / dL blood</th>
</tr>
</thead>
</table>

### HbO₂

<table>
<thead>
<tr>
<th>Normal O₂-Carrying Capacity of hemoglobin</th>
<th>20 vol-%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hematocrit)(1.34) =</td>
<td></td>
</tr>
<tr>
<td>(15 g Hb / dL)(1.34) =</td>
<td></td>
</tr>
<tr>
<td>20 mL O₂ / dL</td>
<td></td>
</tr>
</tbody>
</table>

### Arterial Hb-Saturation

<table>
<thead>
<tr>
<th>Arterial Hb-Saturation</th>
<th>100% saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Pₐ O₂ (Oxygen partial pressure)</td>
<td>Pₐ O₂ = 100 mm Hg</td>
</tr>
<tr>
<td>Arterial Cₐ O₂ (Oxygen Content)</td>
<td>Cₐ O₂ = 20 mL / dL</td>
</tr>
<tr>
<td>Arterial:</td>
<td>100% saturation ----&gt;</td>
</tr>
<tr>
<td></td>
<td>100 mm Hg ----&gt;</td>
</tr>
<tr>
<td></td>
<td>20 mL / dL O₂ content</td>
</tr>
</tbody>
</table>

### Venous Hb-Saturation

<table>
<thead>
<tr>
<th>Venous Hb-Saturation</th>
<th>75% saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous Pᵥ O₂ (Oxygen partial pressure)</td>
<td>Pᵥ O₂ = 40 mm Hg</td>
</tr>
<tr>
<td>Venous Cᵥ O₂ (Oxygen content)</td>
<td>Cᵥ O₂ = 15 mL / dL</td>
</tr>
<tr>
<td>Venous:</td>
<td>75% saturation ----&gt;</td>
</tr>
<tr>
<td></td>
<td>40 mm Hg ----&gt;</td>
</tr>
<tr>
<td></td>
<td>15 mL / dL O₂ content</td>
</tr>
</tbody>
</table>

### P₅₀

<table>
<thead>
<tr>
<th>P₅₀</th>
<th>50% saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P₅₀ = 26 mm Hg</td>
<td></td>
</tr>
<tr>
<td>P₅₀ is the PO₂ required to achieve 50% hemoglobin saturation</td>
<td></td>
</tr>
</tbody>
</table>

### Normal plasma HCO₃⁻

<table>
<thead>
<tr>
<th>Normal plasma HCO₃⁻</th>
<th>24 mM</th>
</tr>
</thead>
</table>

### Normal blood pH

<table>
<thead>
<tr>
<th>Normal blood pH</th>
<th>7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 0.1 decrease in pH corresponds to a 1 mM increase in HCO₃⁻, in healthy, uncompensated hypoventilation.</td>
<td></td>
</tr>
</tbody>
</table>

### Ventilation / Perfusion of the Lung

<table>
<thead>
<tr>
<th>Vₐ/Q Ratio, Lung Apex (Top)</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex of lung gets less ventilation and less perfusion, but perfusion is substantially less than at base.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vₐ/Q Ratio, Lung Base (Bottom)</th>
<th>0.5 - 0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base of lung gets greater perfusion and ventilation, but perfusion is substantially greater than at apex.</td>
<td></td>
</tr>
<tr>
<td>V_a/Q Ratio, Overall</td>
<td>1.0</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Overall Perfusion of Lung</td>
<td>5.0 - 6.0 L / min</td>
</tr>
<tr>
<td>Overall Ventilation of Lung</td>
<td>5.0 - 6.0 L / min</td>
</tr>
</tbody>
</table>

MECHANICS of RESPIRATION

PNEUMOTHORAX: A knife wound will equilibrate the pressure between the pleura and lung, making the chest expand and the lungs collapse.

NEGATIVE PRESSURE BREATHING: Lung pressures are usually measured in cm H$_2$O because they are relatively low pressures, and cm H$_2$O is a smaller quantity than mm Hg.

- **INSPIRATION:**
  - BEGINNING OF INSPIRATION: There is no movement of air.
    - Thus alveolar pressure is 0 (the same as atmospheric pressure).
    - Pleural Pressure is -5 cm H$_2$O
  - FORCED INSPIRATION: Rapid or forced inspiration causes pleural pressure to become much more negative than usual.
    - In normal unforced breathing, the diaphragm is the sole muscle responsible for inspiration.
    - Forced inspiration: Increase thoracic volume even more than just what the diaphragm can do alone.
      - **External Intercostals** can move the ribs up and outward.
      - **Sternocleidomastiod** can move clavicle upward with an extreme inhalation.
  - INSPIRATION: The pleural pressure changes from -5 to about -8 cm H$_2$O, but how much the pressure changes will be dependent on the compliance of the lung.

- **EXPIRATION:** Normal expiration is simple relaxation of the diaphragm --> lung-volume decreases due to its natural elasticity.
  - FORCED EXPIRATION: The pleural pressure can actually become positive as air is forced out of lungs.

PRESSURE AND FLOW:

- There are three pressures that determine airflow and volume of the lungs:
  - ATMOSPHERIC PRESSURE ($P_{ATM}$): Barometric pressure, normally about 747 mm Hg in Kansas.
  - ALVEOLAR PRESSURE ($P_{ALV}$): The pressure in the lung.
  - PLEURAL PRESSURE ($P_{PLU}$): The pressure in the pleura, between the lung and thoracic wall.

- **TOTAL DeltaPRESSURE** = ($P_{ATM}$ - $P_{ALV}$) + ($P_{ALV}$ - $P_{PLU}$) = Delta$P_{FLOW}$ + Delta$P_{TRANSPULM}$
  - ($P_{ATM}$ - $P_{ALV}$) = TRANSAIRFLOW PRESSURE: The pressure difference between the atmosphere and alveoli determines airflow.
    - DeltaP = ($P_{ATM}$ - $P_{ALV}$) = (Airflow) x (Resistance)
    - The higher the flow, the higher the pressure; the higher the resistance for an equivalent flow, the higher the pressure required to overcome that resistance.
  - ($P_{ALV}$ - $P_{PLU}$) = TRANSPULMONARY PRESSURE: Transpulmonary pressure determines the volume of the lung and is therefore dependent on the compliance of the lung.
- The lower the compliance of the lung, the higher the transpulmonary pressure necessary to achieve an equivalent tidal volume.
- **Asthma:** There is nothing wrong with compliance of the lung in this case, so the transpulmonary pressure is not affected by asthma. Instead, both the alveolar pressure and pleural pressure become more negative, and the transpulmonary pressure hence remains the same.

**LUNG VOLUMES:**

- **TIDAL VOLUME (TV):** The volume of air inhaled during a normal inspiration.
  - Normally about 500 mL
- **EXPIRATORY RESERVE VOLUME (ERV):** The maximum volume of air that can be exhaled after a normal expiration.
- **INSPIRATORY RESERVE VOLUME (IRV):** The maximum volume of air that can be inhaled after a normal inspiration.
- **VITAL CAPACITY (VC):** The maximum possible volume of air that one can expire in a single breath, after having taken a maximal inspiration.
  - Or: The sum of the Tidal Volume, Inspiratory Reserve Volume, and Expiratory Reserve Volume.
  - “Capacity” indicates that it is actually the sum of two separatable volumes.
- **FUNCTIONAL RESIDUAL CAPACITY (FRC):** The total volume of air contained in the lungs at the end of a normal expiration.
  - Or: The Expiratory Reserve Volume + the Residual Volume.
  - The Functional Residual Capacity is much larger than the tidal volume, i.e. the volume of air expired.
  - FNXN: It prevents dramatic changes in \(O_2\) and \(PO_2\) with each breath.
  - If Functional Residual Capacity becomes very low, then \(PO_2\) increases with inspiration and decreases with expiration. That isn’t good.
- **RESIDUAL VOLUME (RV):** The volume of air that remains in the lungs after a maximal expiration. It is the air that remains in the lung basically no matter what you do unless the lungs collapse.
  - This is normally about 20% of Total Lung Capacity.
- **TOTAL LUNG CAPACITY (TLC):** Defined as the Vital Capacity plus the Residual Volume.
  - “Capacity” indicates that it is actually the sum of two separatable volumes.

**STATIC PRESSURE-VOLUME CURVE:** A pressure-volume curve of the lung, where each point is measured when there is no airflow. This implies that the total pressure at that instant is equal to the transpulmonary pressure since there is no pressure gradient for airflow.

- The curve is made by having the patient incrementally inhale more air and then stop inhaling. At the instant the patient stops inhaling, airflow ceases and a measurement can be taken.
- Normal Shape: This curve is normally a sigmoid curve, with maximal pleural pressure when you have reached Total Lung Capacity, and with minimal pleural pressure occurring at Residual Volume.
- **HYSTERESIS:** Only after forced expiration, the phenomenon of not getting the same static pressure-volume curve. The observed change is variable.

**COMPLIANCE:** DeltaV / DeltaP, the slope of the Static Pressure Volume Curve. In other words, it is the slope of a P/V curve when there is no airflow and the pressure thus represents transpulmonary pressure.
Compliance decreases with lung volume. That is, an empty lung has a higher compliance than a filled lung. This is consistent with the P/V curve levelling off as it approaches Total Lung Capacity.

Factors that affect Compliance:
- Elastic Fibers in the alveoli.
- Pulmonary Surfactant in the alveolar fluid. Surfactant reduces the surface tension of the alveoli and prevents them from coalescing.
  - LaPLACE: PRESSURE required to keep alveoli inflated = \( \frac{2 \text{ Surface Tension}}{r} \)
    - The higher the surface tension, the more pressure required to inflate alveolus.
    - The lower the radius (size) of the alveolus, the more pressure required to inflate alveolus.

HIGH COMPLIANCE: The lungs have trouble deflating because they have lost their elasticity, as in Emphysema.
- Occurs with destruction of elastic fibers in lung, such as emphesema.
- There is great difficulty in exhaling but no inhaling.

LOW COMPLIANCE: Occurs with overproduction of collagen as in Restrictive Lung Disease.
- There is great difficulty in inhaling, expanding the lung.
- Also occurs with lack of surfactant as in Infant Respiratory Distress Syndrome (IRDS).

AIRWAY RESISTANCE:

- Relationships:
  - The lower the flow, the higher the airway resistance.
  - The higher the pressure difference required to maintain flow, the higher the airway resistance.

- Anatomy: Where is the region of greatest resistance?
  - Highest resistance always occurs in the nose and nasopharynx. Hence COPD, which affect the bronchioles first, may not be detected until it affect the upper respiratory tract.
  - The terminal bronchioles have low resistance because they have the highest total cross-sectional area. That is, if you add them in parallel (add their resistance), their combined resistance is lower than in the nose and nasopharynx.

- Measuring Airway Resistance: Have patient maximally exhale as quickly as possible. This means we are asking the patient to generate maximum possible flow during exhalation.
  - FORCED VITAL CAPACITY (FVC): The volume of air exhaled during a forced maximal expiration.
  - The SLOPE of the FVC curve indicates FLOW. The steeper the slope, the faster the flow, the lower the airway resistance.
  - FRACTION OF VITAL CAPACITY (FEV₁): The fraction of FVC that is exhaled in the first second. Normally this should be 80% of FVC.

- LUNG VOLUME vs AIRFLOW: As the lungs expand, the resistance to airflow decreases.
  - Fully expanded lungs have minimal resistance to airflow, because the total airway cross-sectional area increases with lung volume, decreasing total resistance.
  - Fully collapsed lungs (i.e. at residual volume) have maximal resistance to airflow.

- THE FVC CURVE: The curve of maximal exhalation of Forced Vital Capacity. It is used to diagnose airway resistance.
  - EARLY CURVE = EFFORT-DEPENDENT: The patient reaches a maximum envelope of how quickly he can exhale, indicating maximum possible airflow.
    - This region corresponds to FEV₁, or the first second of maximal exhalation. The slope of that portion of graph indicates maximum possible airflow.
LATE CURVE = EFFORT-INDEPENDENT: As the lung approaches residual volume, airflow decreases to a common value, regardless of effort.
- The slope of this part of the curve is fixed at each volume.
- SLOPE = AIRFLOW. The steeper the slope of the FEV₁ part of graph, the lower the resistance.

- Limit to Flow: Airflow cannot go beyond a maximum value for the following reasons:
  - The airways are compressible. This tends to compensate for increased flow, i.e. if we had rigid airways then flow would be higher.
  - The very action that creates maximal airflow, compression of the chest, also contributes to airway constriction. That is, forced exhalation is self-defeating in that the action of forced exhalation increases airway resistance.

- Equal Pressure Point (EPP): During a forced exhalation, the point in the airway at which airway pressure (tendency for airways to compress) is equal to pleural pressure (which is positive due to forced exhalation). Thus at that point transairway pressure is equal to zero and there is no net airflow.
  - Upstream Segment: Segment from alveoli to EPP. There is low airway resistance resulting in net outward flow.
  - Downstream Segment: Segment from EPP to mouth. The transairway pressure becomes negative in this segment due to high resistance and low airway pressure.
    - This tends to collapse the upper airways, except that Tracheal Collapse is prevented by the tracheal cartileges. The bronchi and bronchioles, however, do tend to compress from this phenomenon.

BRONCHIAL SMOOTH MUSCLE: Autonomic control of airway resistance.

- Sympathetic beta2-Receptors ———> Bronchodilation
  - Catecholamines and adrenergic drugs thus produce smooth muscle relaxation and can be used to treat asthma.
- Parasympathetic Cholinergic Receptors ———> Bronchoconstriction
  - Atropine, a cholinergic blocker, produces bronchodilation.
- Histamine: Produces very strong bronchoconstriction at low doses. Antihistamines are used to counteract that effect.
- Irritant Reflex: Various noxious stimuli, such as smoke and foreign chemicals, produce bronchoconstriction via irritant receptors on the bronchial smooth muscle. This reflex arc is carried by the Parasympathetic System.
- LOW CO₂ in the airways also produces bronchoconstriction. This could be a way to alleviate hyperventilation.

PHYSIOLOGY of RESPIRATION

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): Various pathologies will all lead to the common symptoms of COPD, which is caused by chronic increased airway resistance.

- Emphysema: Loss of elastic recoil and destruction of lung parenchyma.
  - Mechanism leading to COPD: Loss of elastic recoils ———> more effort is required to exhale ———> Upper airways constrict from the increased effort and increased thoracic pressure on exhalation ———> COPD.
- Bronchitis: Chronic inflammation of the bronchi lead to thickening of mucosa and decreased bronchial diameter.
- Asthma: The spasmodic contraction of bronchial smooth muscle, which occurs in episodes.
- COPD SYMPTOMS: In general exhaling is a bigger problem with COPD than inhaling.
Increased resistance can be seen with the Forced Exhalation test. The slope will decrease.

- Hypoventilation -----> high pCO₂
- More pressure will be required to generate equivalent airflow. The greater pressure in turn, leads to a greater tendency for the airways to collapse, which creates a downward spiral.
- Residual Volume increases to pathological levels. You can’t exhale all the air out of the lungs.
- Tidal volume may also increase, as the individual breathes an overall higher volume as a compensation for poor exhalation.

DYNAMIC Pressure-Volume Curve:

- The slope of the line AB is overall lung compliance.
- Along the line, that is the pressure required to simply maintain lung volume, i.e. transpulmonary pressure, the same pressure as in the static curve.
- Any pressure in excess of transpulmonary pressure (i.e. to the right of the line) is used to create airflow into the lungs (i.e. transairway pressure).
- If you were to inhale or exhale very slowly, the lines would converge on the central compliance-line. Little airflow is created and not much extra pressure is needed.

VENOUS ADMIXTURE: The pulmonary capillary (freshly oxygenated) blood leaving the lungs, combined with venous blood that did not perfuse the lungs.

- In a healthy lung, the venous admixture lowers PO₂ and increases PCO₂ by only a very little bit, as compared to pulmonary capillary blood.
- Arterial PO₂ (P̄ₐO₂) is almost the same as alveolar PO₂ (P̄A₂O₂) but slightly lower.
  - P̄₂O₂ = 90 - 95 mm Hg
  - P̄A₂O₂ = 100 mm Hg
- Arterial PCO₂ (P̄ₐCO₂) is almost the same as alveolar PCO₂ (P̄A₂CO₂) but slightly higher.
  - P̄ₐCO₂ P̄A₂CO₂ = 40 mm Hg

EXERCISE:

- Low to Medium Exercise Intensity: Alveolar gas levels do not change. O₂ consumption increases, but ventilation increases correspondingly to result in no net change.
- High Exercise Intensity: Behavior depends on fitness of individual.
  - Most People: HYPERVENTILATION occurs with high exercise intensity. Ventilation rate exceeds O₂ needs: P̄₂O₂ goes up and P̄₂CO₂ goes down.
  - Olympic Athletes: HYPOVENTILATION occurs instead, because athletes have lots of muscle mass and are conditioned to consumer more oxygen.

PHYSIOLOGICAL DEAD SPACE = ANATOMICAL DEAD SPACE + ALVEOLAR DEAD SPACE. Dead space is defined as inspired air that is not perfused by blood and thus "waisted" because it does not contribute to gas exchange.

- ANATOMICAL DEAD SPACE: The volume of air occupying the upper airways where there are no alveoli.
  - It is approximately equal to a patient's weight in pounds, i.e. a 150 lb individual would have 150 mL anatomical dead space.
- ALVEOLAR DEAD SPACE: The volume of air that reaches the alveoli but still doesn’t get perfused by blood.
• HEALTHY Individuals: Alveolar Dead Space should be virtually zero, so that physiological dead space = anatomical dead space.

• MEASURING DEAD SPACE: $V_D / V_E$ Ratio
  o BREATHING CYCLE:
    • INSPIRED AIR levels:
      - $PO_2 = 147$ mm Hg
      - $PCO_2 = 0$ mm Hg
    • EXPIRATION: The air from the dead space comes out first, so the alveolar pressures initially stay the same. Once the alveolar air comes out, expired air approaches the concentration of alveolar air.
      - $P_{\text{a}}O_2 = 100$ mm Hg
      - $P_{\text{a}}CO_2 = 46$ mm Hg
  o All expired CO$_2$ comes from the alveoli, and it is diluted by any air that is in the dead space.
    • The dilution factor represents a ratio of the volume of dead space to the volume of perfused alveolar air.
    • Thus, the larger the difference between $P_{\text{a}}CO_2$ and $P_{\text{e}}CO_2$, the more the CO$_2$ must be diluted by alveolar air.

• $P_{\text{a}}CO_2$ = Arterial PCO$_2$
• $P_{\text{e}}CO_2$ = PCO$_2$ in expired air.

ALVEOLAR VENTILATION:

• Alveolar Ventilation is inversely related to $P_{\text{a}}CO_2$.
  o Normal $P_{\text{a}}CO_2 = 40$ mm Hg
  o Hyperventilation of 2x normal $-------> P_{\text{a}}CO_2 = 20$ mm Hg
  o Hypoventilation of 2x less than normal $-------> P_{\text{a}}CO_2 = 80$ mm Hg

• ALVEOLAR VENTILATION EQUATION: $P_{\text{a}}O_2 = P_{\text{i}}O_2 - 1.2 (P_{\text{a}}CO_2)$
  o Derivation: Assuming we exchange O$_2$ and CO$_2$ evenly, then the partial pressure drop of O$_2$ should be equal to the pressure rise of CO$_2$.
    • That is: $P_{\text{i}}O_2 - P_{\text{a}}O_2 = P_{\text{a}}CO_2 - P_{\text{CO}}$
    • But, $P_{\text{CO}} = 0$
    • And, we actually take in a little more O$_2$ then we exhale CO$_2$ with each breath. Thus 1.2 is the fudge factor to account for this difference.
  o Meaning: The equation says that alveolar ventilation is dependent on two factors:
    • $P_{\text{i}}O_2$ = PO$_2$ in inspired air.
    • $P_{\text{a}}CO_2 = P_{\text{a}}CO_2$ = alveolar or arterial CO$_2$ concentration, both of which vary inversely with ventilation.

• Hyperventilation $------->$ PCO$_2$ goes down and PO$_2$ goes up.
• Hypoventilation $------->$ PCO$_2$ goes up and PO$_2$ goes down.

PULMONARY DIFFUSION:

• Variables:
  o $D =$ DIFFUSION COEFFICIENT
    • Diffusion Coefficient depends on the specific gas and the nature of the membrane. CO$_2$ is more soluble (i.e. higher diffusion coefficient) than O$_2$.
    • It depends on both the solubility of the gas in the membrane and the molecular weight of the gas.
- CO₂ is much more membrane soluble than O₂, thus a much smaller pressure gradient is required for CO₂ (46 - 40 torr) than for O₂ (100 - 40) to maintain nearly equal diffusion rates.
  - SA = SURFACE AREA available for diffusion
  - DeltaPressures = PRESSURE GRADIENT, the difference in partial pressure between blood and alveolar space.

- PULMONARY PERFUSION: It is a high velocity, low resistance system. Time-Course of Perfusion = RBC travels through capillary in 0.75 seconds.
  - 0.25 seconds = Time for RBC hemoglobin to get saturated with O₂ under normal conditions.
  - 0.50 seconds = Reserve Buffer for poor PₐO₂, poor diffusion, etc.

- DIFFUSION CAPACITY OF THE LUNGS FOR OXYGEN, DLO₂: It is a single constant that combines all of the non-measurable factors affecting gas diffusion, namely Diffusion Coefficient for O₂ (D), Surface Area (SA), and Membrane Thickness (T).

Thus:

\[ P_{A}O₂ - P_{Cap}O₂ = \Delta \text{Pressures} = \text{the pressure gradient across the membrane.} \]
\[ \text{The higher the pressure gradient required to maintain flow, the lower the diffusion capacity of the lungs for oxygen.} \]
\[ VO₂ = \text{Oxygen flow across membrane.} \]
\[ \text{The higher the VO₂, the higher the diffusion capacity of the lungs for oxygen.} \]

- MEASURING DIFFUSION CAPACITY: We use Carbon Monoxide (CO) instead of O₂ to measure diffusion capacity, since PₐCO₂ cannot be determined.
  - We use CO because it binds to Hb with such high affinity that we can infuse a very low quantity of CO, saturate the blood, and still maintain a PₐCO of approximately 0.

Thus we can measure DLO₂ in terms of DLCO:

- CO will give you different diffusion values but it is a good measure of lung disfunction (diffusion problems) when compared to normal values.

- DISEASE: Normally diffusion is not the limiting factor in gas transfer. But in disease states it can become the limiting factor. When diffusion is the limiting factor, \[ P_{A}O₂ \gg P_{Cap}O₂ \]. That indicates a diffusion problem.
  - Pulmonary Edema and Emphysema both result in diffusion problems bur for different reasons.
    - Pulmonary Edema = Membrane thickness becomes much greater, thus diffusion coefficient becomes smaller.
    - Emphysema = Coalescence of alveoli -----> lower surface area for diffusion.
  - DIFFUSION BARRIER: Arterial O₂ levels will go down and arterial CO₂ levels will go up, but oxygen levels are affected more than CO₂ levels. Thus O₂ availability is the limiting factor in diffusion problems, not CO₂ overload. O₂ is limiting because:
    - O₂ is less permeable and thus more susceptible to diffusion barriers.
The O₂ pressure gradient is much larger, thus the difference becomes proportionately more significant.

**HYPERVENTILATION:** Diffusion problem / disease ------→ hypoxia ------→ compensatory hyperventilation ------→ CO₂ levels GO DOWN while O₂ levels remain at or slightly below normal.

Thus low \( P_aCO_2 \) coupled with low (or slightly low) \( P_aO_2 \) is indicative of a diffusion problem.

**OXYGEN TRANSPORT:**

- **Volumes-% (Vol-%)** means mL gas / dL of blood, or mL gas per 100 mL blood.
- **TOTAL O₂-CONTENT = DISSOLVED O₂ + Hb-BOUND O₂**
  
  - **DISSOLVED O₂ = (PO₂) \times (0.003) Vol-%**
    - 0.003 is the solubility of O₂ in plasma.
    - This amount can normally be disregarded unless a patient is receiving 100% O₂ by mask, at which point dissolved O₂ increases considerably.
  
  - **Hb-BOUND O₂ = (HEMATOCRIT) \times (1.34) \times (Hb-Saturation)**
    - Hematocrit = Hemoglobin concentration of blood (g Hb / dL blood)
    - 1.34 = O₂ Carrying-Capacity of Hb (mL O₂ / g Hb)
    - Hb-Saturation = The percent of hemoglobin that is O₂-bound (%)

From above two equations:

**OXYGEN-DISSOCATION CURVE:** The relationship between Dissolved O₂ and PO₂ is linear, while the relationship between HbO₂ and PO₂ is alinear.

- We must remember THREE VALUES from this curve:
  
  - **ARTERIAL BLOOD:** Arterial Blood is 100% Hb-saturated and has a PO₂ of 100 mm Hg
  - **VENOUS BLOOD:** Venous blood is 75% Hb-saturated and has PO₂ of 40 mm Hg
  - **P50:** The PO₂ required to achieve 50% hemoglobin saturation. 50% Hb-saturation corresponds to PO₂ of 26 mm Hg

- Curve Shape:
  
  - **TOP PART OF CURVE:** Safety factor in case PO₂ levels fall below normal.
    - HYPERVENTILATION will not result in higher PO₂ in normal individuals because it's in top part of curve, **but in hypoxic patients** (PO₂ venous PO₂ 40 mm Hg), hyperventilation can make a bigger difference.
  
  - **STEEP PART OF CURVE:** Oxygen unloading to tissues. A small pressure difference of PO₂ creates a big difference in Hb-Saturation ------→ O₂ unloads to tissues.

- **Shifts in O₂-Dissociation Curve:**
  
  - **LEFT-SHIFT:** An increase in O₂-affinity and a decrease in the P50 value (less PO₂ required to achieve equivalent saturation)
Generally, DECREASED METABOLIC NEEDS shift the curve to the left, viz:
- DECREASED TEMPERATURE ------> SHIFT CURVE LEFT
- HIGHER (BASIC) pH ------> SHIFT CURVE LEFT
- LOWER PCO$_2$ CONCENTRATION ------> SHIFT CURVE LEFT

- RIGHT-SHIFT: A decrease in O$_2$ affinity and an increase in the P50 value (greater PO$_2$ required to achieve equivalent saturation)
  - EXERCISING MUSCLE generally demands more O$_2$ to the tissues, thus lower O$_2$-affinity. The following properties all indicate exercising muscle:
    - INCREASED TEMPERATURE ------> SHIFT CURVE RIGHT
      - Exercising muscle has higher temperature.
    - DECREASED (ACIDIC) pH ------> SHIFT CURVE RIGHT
      - Lactic acidosis in muscle.
    - INCREASED PCO$_2$ ------> SHIFT CURVE RIGHT
      - Higher CO$_2$ production in exercising muscle.
  - 2,3-BIPHOSPHOGLYCERATE (2,3-BPG) ------> SHIFT CURVE RIGHT.

THE FICK EQUATION: The net amount of O$_2$ taken up by the tissues is dependent on blood flow (Q) and the Arterio-Venous oxygen concentrations:

- The variables:
  - VO$_2$ = O$_2$-Ventilation of the tissues, i.e. the net amount of O$_2$ that the tissues get.
  - Q = Blood-flow
  - C$_a$O$_2$ = Arterial O$_2$-Content (or concentration), Vol-%
  - C$_v$O$_2$ = Venous O$_2$-Content (or concentration), Vol-%
- ARTERIO-VENOUS O$_2$ DIFFERENCE, (A-V)O$_2$ is inversely related to Cardiac Output and directly related to tissue oxygen consumption.
  - The higher the oxygen consumption, the greater the (A-V)O$_2$ difference.
  - The higher the CO, the less the (A-V)O$_2$ difference.
  - Normally, (A-V)O$_2$ = (100 - 40) = 60 mm Hg

Hypoxia / Hyperoxia:
- HYPOXIA: Caused by Hypoventilation.
  - This will lower the O$_2$-content of the blood, but not by very much. A PO$_2$ of 60 mm Hg still has Hb saturation of 90%
  - Arterial PO$_2$ changes a lot with hypoxia while Venous PO$_2$ changes hardly at all. In severe hypoxia, arterial PO$_2$ approaches the levels of venous PO$_2$ while venous PO$_2$ (i.e. 40 mm Hg) while venous PO$_2$ remains relatively constant.
    - The cause of this difference in arterial / venous levels in hypoxia is because of the shape of the O$_2$-dissociation curve (steep in venous range, and flat in arterial range).
- HYPEROXIA: Caused by Hyperventilation.
  - If you breathe 100% O$_2$ by mask, you get tremendous increase in Alveolar PO$_2$ (from 100 mm Hg ------> ~600 mm Hg), yet arterial PO$_2$ changes hardly at all.
  - Again, this is because of the shape of the O$_2$ dissociation curve.

CARBON DIOXIDE TRANSPORT:
- CO$_2$ is carried in blood plasma in a few forms:
  - Dissolved as CO$_2$(aq) in the plasma.
  - CARBAMINO COMPOUNDS: CO$_2$ can combine with the amino-terminus of plasma proteins to be carried as a Carbamino compound. This occurs in the plasma.
    - In the plasma, CO$_2$ + H$_2$O $\leftrightarrow$ H$_2$CO$_3$ $\leftrightarrow$ H$^+$ + HCO$_3^-$
      - In the plasma, this reaction is slow and uncatalyzed.
- CO$_2$ STORAGE IN ERYTHROCYTE:
o CO₂ is transported into RBC's, rather quickly, by simple diffusion through the membrane.
  - The CO₂ concentration gradient is maintained because CO₂ is quickly converted to HCO₃⁻ once inside the erythrocyte.

  o Once inside, **Carbonic Anhydrase** enzymatically catalyzes the reaction:
    - CO₂ + H₂O ⇌ H₂CO₃ ⇌ H⁺ + HCO₃⁻ (Carbonic Anhydrase)
    - The bicarbonate, HCO₃⁻, is then transported back **out into the plasma** by a Cl⁻-HCO₃⁻ Antiport on the RBC plasma membrane.
      - HCO₃⁻ out ----> into plasma
      - Cl⁻ in ----> into RBC.
    - The acid, H⁺, is taken up by Histidine residues on hemoglobins in the RBC. Hemoglobin His-Residues thus act as a pH buffer inside the RBC.

  • Thus, the majority of CO₂ in blood is stored as HCO₃⁻ in plasma, which originated from the RBC intracellular carbonic anhydrase system.

**ACID-BASE BALANCE:** Blood pH is determined by the HCO₃⁻:CO₂ ratio, according to a derivation of the Henderson Hasselbach Equation:

**Variables:**
- 6.1 = pKₐ of H₂CO₃ (3.5) + log 400 (because CO₂ is 400x more prevalent than H₂CO₃)
- 0.03 = Plasma Solubility of CO₂
- The normal ratio of (dissolved CO₂) : (H₂CO₃) is about 400:1. Carbonic Anhydrase favors the dissolved form of CO₂ at equilibrium.
- The above formula replaces CO₂ for H₂CO₃ because H₂CO₃ is in such low concentration.

**Blood-Buffer:** CO₂ + H₂O ⇌ H₂CO₃ ⇌ HCO₃⁻ + H⁺
- An increase in CO₂ (hypoventilation) will push the system to the right, causing increased acidity (lower pH) and increased plasma HCO₃⁻.
  - To an extent, the excess H⁺ will be taken up by non-carbonate buffers, the greatest contributor being Histidine residues on hemoglobin.
- A decrease in CO₂ (hyperventilation) will pull the system to the left, causing decreased acidity (higher pH) and decreased plasma HCO₃⁻.

**Non-Bicarbonate Buffers:** The blood has multiple buffers although the HCO₃⁻ system is the most predominant. The non-bicarbonate buffers are mostly the free amino and carboxy termini of amphoteric amino acids.

**ACID-BASE IMBALANCES:**

**RESPIRATORY ACIDOSIS:** Hypoventilation. **High PCO₂, low pH**
- Primary Abnormal Value: PCO₂ is too high, leading to a lower pH
- Compensation: Kidneys excrete more H⁺, bringing pH closer to normal range.
- NON-COMPENSATED RESPIRATORY ACIDOSIS: Falls within the prescribed relationship between HCO₃⁻ and pH. That is, the values can be explained by the buffer system alone.
  - A decrease of 0.1 pH (i.e. pH = 7.3) ------> increase in 1 mM HCO₃⁻ (i.e. HCO₃⁻ = 25 mM).
- COMPENSATED RESPIRATORY ACIDOSIS: It takes a while (hours-days) for the renal compensatory mechanism to kick in. Labs would show the following:
  - High PCO₂ and HCO₃⁻
  - Low / near normal pH from metabolic compensation.

**METABOLIC ACIDOSIS:** Acidosis caused by Non-Respiratory means, such as Diabetes, lactic acidosis, or shock. **Low PCO₂, low pH**
- Primary Abnormal Value: High H⁺ from a metabolic source.
- Compensation: Lungs, increased ventilation -----> lower CO₂ -----> restore pH
NON-COMPENSATED METABOLIC ACIDOSIS: Usually a trivial case, unless the patient also has COPD, because respiratory compensation occurs very quickly.
- CO₂ would be normal in this case, while HCO₃⁻ would be low because of the relatively high H⁺.

COMPENSATED METABOLIC ACIDOSIS: Labs would show the following:
- Low HCO₃⁻
- Low/near normal pH from respiratory compensation.
- Low PCO₂ from hyperventilation

RESPIRATORY ALKALOSIS: Hyperventilation. Low PCO₂; high pH
- Primary Abnormal Value: PCO₂ is too low, leading to a higher pH
- Compensation: Kidneys excrete more HCO₃⁻, increasing the relative concentration of H⁺ → lower pH.

NON-COMPENSATED RESPIRATORY ALKALOSIS: Falls within the prescribed relationship between HCO₃⁻ and pH. That is, the values can be explained by the buffer system alone.
- An increase of 0.1 pH (i.e., pH = 7.5) → decrease in 1 mM HCO₃⁻ (i.e., HCO₃⁻ = 23 mM).

COMPENSATED RESPIRATORY ALKALOSIS: Labs would show the following:
- Low PCO₂ and HCO₃⁻ due to original hyperventilation problem.
- High or near normal pH from metabolic compensation.

METABOLIC ALKALOSIS: Non-Respiratory abnormally low H⁺, as can occur from prolonged vomiting (i.e., loss of acidic stomach secretions) and Salicylate intoxication. High PCO₂; high pH
- Primary Abnormal Value: Low H⁺
- Compensation: Lungs, Decreased Ventilation
- NON-COMPENSATED METABOLIC ALKALOSIS: Trivial case. Respiratory hypoventilation compensates very quickly.

COMPENSATED METABOLIC ALKALOSIS: Lab values:
- High or near normal pH
- High PCO₂, HCO₃⁻ from compensatory hypoventilation.

VENTILATION / PERFUSION BALANCE:

- Blood/Air Distribution in Lung: The average V/Q ratio of the entire lung is 1. Blood supply and ventilation both increase from top to bottom of lung, according to gravity, but blood supply increases by a greater amount.
  - APEX OF LUNG: Relatively less air and less blood go to the apex.
    - Vₘ/Q 3.0
    - While both ventilation and blood supply are less than at apex, the blood supply is relatively less than ventilation, resulting in a higher overall Vₘ/Q ratio.
  - BASE OF LUNG: Relatively more air and more blood go to the base of the lung, primarily due to gravity.
    - Vₘ/Q 0.5
    - While both ventilation and blood supply are greater at base, the blood supply is relatively greater than the ventilation, resulting in a lower overall Vₘ/Q Ratio.
  - MIDDLE OF LUNG: In the middle of the lung near the hilus, the Vₘ/Q ratio most closely approximates 1.

- V/Q Balance Compensatory Mechanisms:
  - HYPOXIC PULMONARY VASOCONSTRICTION: Low PO₂ in the pulmonary circulation indicates poor ventilation. If we have poor ventilation, we don't want blood to flow to that region.
    - Thus Poor ventilation → Low PO₂ locally → local vasoconstriction diverts blood elsewhere.
    - This is the exact opposite of the systemic circulation, where low PO₂ in tissues leads to vasodilation to increase local flow.
- **COMPENSATORY BRONCHOCONSTRICTION**: The converse of above. If there is low blood flow to a region of lung, the corresponding bronchioles will bronchoconstrict.
  - Local low blood flow ------> local low PCO\textsubscript{2} -------> Regional bronchoconstriction --
    ----decreased ventilation to region

- **SHUNTED BLOOD: V\textsubscript{A}/Q TOO LOW.**
  o Shunted blood is defined as blood that goes through pulmonary circulation without getting ventilated (i.e. without taking up O\textsubscript{2}). This occurs when there is too little ventilation (hypoventilation) relative to perfusion.
  o The shunted blood constitutes VENOUS ADMIXTURE and lowers the resulting pulmonary capillary PO\textsubscript{2} accordingly.
  o More shunted blood ------> lower P\textsubscript{cap}O\textsubscript{2} ------> arterial gas composition (both CO\textsubscript{2} and O\textsubscript{2}) approaches the levels of venous blood.

- **CALCULATING BLOOD-GASES in Shunted Blood**: then there is a shunt, the PO\textsubscript{2} and C\textsubscript{a}O\textsubscript{2} of arterial blood depends on the relative quantity of shunted blood.
  - O\textsubscript{2}-CONCENTRATION can be calculated as the weighted average of arterial O\textsubscript{2}-concentration (C\textsubscript{a}O\textsubscript{2}, 20 vol-%) and venous O\textsubscript{2}-concentration (C\textsubscript{v}O\textsubscript{2}, 15 Vol-%).
    
    For example, with 50% shunted blood we have:
    - 50% of blood is like arterial = 20 mL O\textsubscript{2}/ dL blood
    - 50% of blood is like venous = 15 mL O\textsubscript{2}/ dL blood
    - Thus this blood is 50/50 average = 17.5 mL O\textsubscript{2}/ dL blood
  - O\textsubscript{2} PARTIAL PRESSURE: you cannot average PO\textsubscript{2} like you can O\textsubscript{2}- concentration, because of the shape of the O\textsubscript{2}-dissociation curve. PO\textsubscript{2} will actually decrease a lot more than this, and thus approach the PO\textsubscript{2} of venous blood.
  - CO\textsubscript{2} PARTIAL PRESSURE: Because the pressure-concentration relationship is linear, PCO\textsubscript{2} can be calculated by simply taking the weighted average of relative amounts of arterial (PCO\textsubscript{2} = 40) and venous (PCO\textsubscript{2} = 47) blood.
    - CO\textsubscript{2} values may actually decrease with Shunt, because of compensatory hyperventilation.
  - ETIOLOGY: Shunt can be an anatomical problem or a diffusion problem, as in Pulmonary Edema. Any blood that does not get oxygenated is considered to be shunted.

- **DEAD SPACE: V\textsubscript{A}/Q TOO HIGH.**
  o Dead Space is "waisted alveolar air," i.e. air that never contributes to gas exchange. Normally dead space should only be anatomical dead space (20-30% of tidal volume). Any dead space in excess is pathological.
  o Alveolar air that is not perfused has the same O\textsubscript{2} concentration as atmospheric air, 147 mm Hg
    - So, an alveolar P\textsubscript{A}O\textsubscript{2} of close to 147 is indicative of too much dead space.
  o ETIOLOGY: PULMONARY EMBOLISM can create a very large volume of dead space. If an upstream vessel is blocked (such as a pulmonary arteriole), all alveolar regions distal to the blockage will get no blood and thus will be functional dead space.
    - A small, isolated embolus will not affect arterial blood and may go undetected because blood will get shunted elsewhere and will get ventilated.
      - There is a great deal of RESERVE volume in the pulmonary capillary bed, to handle shunted blood.
  o DIAGNOSIS: With embolism and high pulmonary dead space, arterial PO\textsubscript{2} and arterial PCO\textsubscript{2} is likely to be normal, but expired PCO\textsubscript{2} will be decreased (again, because there is no CO\textsubscript{2} in atmospheric air).

REGULATION OF RESPIRATION:

- **Respiratory Centers** are in the medulla, floor of fourth ventricle.
  o **Inspiratory Neurons** fire rhythmically to generate inspiration. When inspiratory cease to fire, the diaphragm relaxes and expiration results.
- **Expiratory Neurons** can also fire during a forced expiration. They do not fire during a quiet expiration.

- Secondary Respiratory Centers:
  - **Apneuistic Center**: Upper medulla. Stimulation leads to continual inspiration.
  - **Pneumotaxic Center**: In pons. It inhibits inspiration, decreasing inspiratory volume ——> faster breathing rate secondarily.
    - *Stretch Receptors* in lungs are stretched as lungs inflate ——> send signals to Pneumotaxic Center to cease inspiration. This is modulated by higher centers in the brain and the details are unknown.

- **CHEMORECEPTORS**: Two pairs of them
  - **CENTRAL CHEMORECEPTORS**: Floor of the Fourth Ventricle.
    - They are *sensitive to pH in the surrounding CSF fluid*.
    - Low pH ——> Increase chemoreceptor firing rate ——> stimulate Central Controllers to increase ventilation.
  - **PERIPHERAL CHEMORECEPTORS**: Carotid Body and Aortic Arch.
    - Peripheral Receptors respond to low PO\(_2\) because of their inherently high metabolic rate. Low PO\(_2\) ——> increase chemoreceptor firing ——> increase ventilation.
      - There is a very high flow rate of blood across the Carotid Body and Aortic Arch. This means that anemia (low hematocrit) doesn't trigger chemoreceptors because there isn't time for O\(_2\)-unloading.
      - Thus only low PO\(_2\) triggers them.
    - **THRESHOLD**: Chemoreceptors kick in, full power, when the PO\(_2\) gets below 60 mm Hg. They are constitutively active before then but don't affect breathing rate significantly.
    - **pH-SENSITIVITY**: ONLY CAROTID BODY receptors are sensitive to pH -- not Aortic receptors. However, the relative contribution of Carotid Receptors with respect to pH change is small compared to the Central Receptors.