Oxygen TRANSPORT, CYANOSIS – An Overview

UNIVERSITY OF PNG
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DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
PBL MBBS YEAR V SEMINAR

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• Transport of O$_2$ and CO$_2$ are vital components of all body functions including maintenance of Acid-Base balance;

• Let us briefly review Oxygen transport in relation to Acid-Base balance
What is the significance of PO$_2$?

- Partial pressure of O$_2$ (pO$_2$) is an indirect measure of O$_2$ content of arterial blood;
- pO$_2$ is measure of tension (pressure) of O$_2$ dissolved in blood plasma;
- It determines force of O$_2$ to diffuse across Pulmonary Alveoli membrane;
- It is use to determine the effectiveness of O$_2$ therapy;
What conditions can result in decrease levels of pO\textsubscript{2}?

Some conditions likely to cause decreased pO\textsubscript{2}:

- Patients that are unable to oxygenate arterial blood because of O\textsubscript{2} diffusion difficulties, Examples:
  - Pneumonia,
  - Shock Lung,
  - Congestive failure
- Patients in whom venous blood mixes prematurely with arterial blood, e.g.: Congestive heart disease;
- Patients with under-ventilated and over-perfuse Pulmonary Alveoli, Examples:
  - Pickwickian syndrome: i.e., Obese patients who cannot breath properly when in the supine position or
  - Patients with significant Atelectasis
What is the significance of O₂ saturation?

• Percentage of Hb saturated with O₂ is indicated by O₂ saturation;

• Tissues are adequately provided with O₂, when 92 – 100% of Hb exist as OxyHb;

• Decrease in the level of pO₂ causes decrease in percent saturation of Hb (OxyHb-dissociation curve);

• When O₂ saturation of Hb falls below 70% some tissues are unable to extract enough O₂ to function normally;
What is $O_2$ content?

- $O_2$ content is the calculated amount of oxygen in blood;
- The $O_2$ content is calculated thus:
  $$O_2 \text{ content} = (O_2 \text{ saturation} \times Hb \times 1.34) + (pO_2 \times 0.03)$$
- Total $O_2$ content in blood is the sum of dissolved $O_2$ and OxyHb;
- Total $O_2$ capacity of blood = 20ml of $O_2$ per 100ml blood;
- Normally, 97 – 98% of $O_2$ is transported as OxyHb from Lungs to tissues;
- About 0.33ml of $O_2$ is dissolved in 100ml of blood;
Question: The Hb level in a male subject is 12.5g/dl;
(a) Calculate the amount of $O_2$ present as OxyHb in blood;
(b) Calculate the % $O_2$ carried in the blood of this individual;

• Answer:

(a) 1.0g Hb, when fully saturated, carries 1.34ml $O_2$
  • Given that Hb level = 12.5g/dl of blood,
  • Amount of $O_2$ that can be transported as OxyHb equal to:
    \[ 12.5 \times 1.34 = 16.75\text{ml of } O_2 \text{ per 100ml of blood}; \]

(b) Total $O_2$ capacity of blood = 20ml of $O_2$ per 100ml blood;
  • In this individual total $O_2$ capacity of blood = 16.75ml /100ml
  • Thus, % $O_2$ carried = \( (16.75 / 20.0) \times 100 = 84.0\% \)
  • Thus 84.0% of oxygen can be transported as OxyHb;
How can $O_2$ composition of blood be characterized?

• Ability of blood to carry $O_2$ to tissues can be assessed by estimating % of total Hb present as OxyHb (blood $O_2$ Saturation);

• Blood $O_2$ saturation depends on: relative amounts of $O_2$ and Hb, and their ability to bind together;

• Characterization of $O_2$ composition of blood requires Measurement of $pO_2$, Hb level and % $O_2$ saturation;

• Measurement of $pO_2$ in Arterial blood are important and valuable in assessing efficiency of $O_2$ therapy;
• Result of only pO$_2$ may be misleading in conditions where O$_2$-carrying capacity of blood is grossly impaired, as in patients with either:
  • Severe Anemia,
  • Carbon Monoxide poisoning,
  • High amount of Methemoglobin,
  • Smokers;

• PO$_2$ may be within normal limits but O$_2$ saturation may be severely reduced because:
  • Carbon Monoxide binds Hb (CarboxyHb) with greater affinity than Oxygen
  • CarboxyHb concentration in blood of some smokers may be greater than 10%, which reduces supply of O$_2$ to tissues;
• In this group of patient measurement of Hb and % O₂ saturation are required in addition to pO₂
  • Significant of these assessment is that when metabolic needs exceeds supply of O₂, cells obtain energy via Anaerobic Glycolysis, leading to production and accumulation of Lactic acid (Lactic acidosis);
• Assessment of Lactate level in plasma can provide additional evidence of adequacy of O₂ supply to tissues;
• Delivery of O₂ to tissues also depends on blood flow, which is influenced by several other factors, such as Cardiac Output and Peripheral Perfusion;
What is the significance of PCO$_2$?

• pCO$_2$ (partial pressure of CO$_2$) in a measure of the pressure of CO$_2$ dissolved in blood;
• The faster and more deeply a patient breathes, the more CO$_2$ is passed out and the pCO$_2$ level in blood drops;
• pCO$_2$ is the respiratory component in Acid-base balance, because it is controlled by Lungs;
• Increase in the level of pCO$_2$ in blood leads to decrease in pH of blood (Respiratory Acidosis);
• pCO$_2$ in blood and CSF is a major stimulant to breathing center in the Brain;
• As level of pCO$_2$ in blood increases (Acidosis), breathing is stimulated, ventilation is increased to pass out more CO$_2$

• If pCO$_2$ level in blood increase too high, breathing cannot keep up with the corresponding demand to further increase ventilation;

• Further increase in level of pCO$_2$ in blood may depress brain function, resulting in significant decrease in rate of ventilation, causing coma;
• pCO₂ in blood are increased in Primary Respiratory Acidosis:
  • Some conditions resulting in increased PCO₂ include:
    • Airways obstruction;
    • Sedatives,
    • Anesthetics,
    • Respiratory Distress Syndrome,
    • Chronic Obstructive Pulmonary Disease

• pCO₂ in blood are decreased in Primary Respiratory Alkalosis:
  • Some conditions resulting in decreased PCO₂ include:
    • Hypoxia (resulting in hyperventilation) due to Chronic Heart Failure,
    • Edema,
    • Neurological disorders,
    • Mechanical Hyperventilation
Is the $\text{pCO}_2$ the same as $\text{CO}_2$ content in blood?

- $\text{pCO}_2$ in blood is not the same as $\text{CO}_2$ content in blood
- $\text{pCO}_2$ is a direct measurement of the pressure (tension) of $\text{CO}_2$ in blood;
- $\text{pCO}_2$ is regulated by the Lungs;
- $\text{pCO}_2$ is the respiratory component in Acid-base balance;

- $\text{CO}_2$ content in blood is an indirect measurement of Bicarbonate ion ($\text{HCO}_3^-$) in blood,
- $\text{HCO}_3^-$ is the metabolic component in Acid-base balance;
- $\text{HCO}_3^-$ is regulated by the Kidneys;
- Carbonic Anhydrase catalyzes the reversible reaction linking $\text{CO}_2$ and $\text{HCO}_3^-$
BICARBONATE BUFFER SYSTEM

Carbonic Anhydrase

\[ \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \]

\[ \text{pH} = \text{pKa} + \log_{10} \frac{[\text{HCO}_3^-]}{\text{PCO}_2} \]

\[ \text{pH} = \text{pKa} + \log_{10} \frac{\text{Kidneys}}{\text{Lungs}} \]
What is the significance of $\text{HCO}_3^-$?

- Most of the $\text{CO}_2$ content in blood is present as $\text{HCO}_3^-$
- $\text{HCO}_3^-$ is an indicator of buffering capacity of blood;
- $\text{HCO}_3^-$ is a measure of the metabolic (Renal) component in Acid-base balance;
- $\text{HCO}_3^-$ can be measured directly or calculated thus:
  $$ [\text{HCO}_3^- ] = \text{pCO}_2 \times 0.03 $$
- $[\text{HCO}_3^- ]$ in blood is directly proportional to pH level in blood;
• \([\text{HCO}_3^-]\) in blood is decreased in Primary Metabolic Acidosis;

• Some causes of primary metabolic acidosis:
  • Ketoacidosis,
  • Lactate acidosis (Hypoxia),
  • Diarrhea,
  • Renal failure

• \([\text{HCO}_3^-]\) in blood is elevated in Primary Metabolic Alkalosis;

• Some causes of primary metabolic alkalosis:
  • Prolonged vomiting,
  • Antacid treatment,
  • Nasogastric drainage
What is Base Excess (deficit)?

• Base Excess is the amount of $H^+$ ions required to return the pH of blood to 7.35 if $pCO_2$ were adjusted to normal;
• Base Excess is usually calculated by blood gas machine using pH, PCO$_2$ and Hematocrit;
• Base Excess represents the amount of buffering Anions ($HCO_3^-$, Hb, Proteins, Phosphates, etc) in the blood;
• Base Excess provides an estimate of the metabolic component of Acid-Base Balance;
• Negative-Base Excess (deficit) indicates Metabolic Acidosis
  • Base Excess < – 3

• Positive-Base Excess indicates Metabolic Alkalosis or Compensation to prolonged Respiratory Acidosis
  • Base Excess > + 3
**Arterial Blood Gas (ABG) data obtained in a patient with uncompensated primary acid-base disturbances**

**Acidosis** pH < 7.35 (note that pH less than 6.8 is incompatible with life)

**Alkalosis** pH > 7.45 (note that pH more than 8.0 is incompatible with life)

<table>
<thead>
<tr>
<th>Acid-base disturbance</th>
<th>pH</th>
<th>PCO₂ (mm Hg)</th>
<th>HCO₃⁻ (m Eq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Normal Values)</td>
<td>7.35 – 7.45</td>
<td>35 – 45</td>
<td>22 – 26</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>Low ↓</td>
<td>Normal</td>
<td>Low ↓</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>Elevated ↑</td>
<td>Normal</td>
<td>Elevated ↑</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>Low ↓</td>
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<td>Normal</td>
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<tr>
<td>Respiratory Alkalosis</td>
<td>Elevated ↑</td>
<td>Low ↓</td>
<td>Normal</td>
</tr>
</tbody>
</table>
How can the ABG data from a patient with compensatory acid-base disturbance be interpreted?

<table>
<thead>
<tr>
<th>Acid-base disturbance</th>
<th>pH</th>
<th>$\text{PCO}_2$ (mm Hg)</th>
<th>$\text{HCO}_3^-$ (m Eq/L)</th>
<th>Mode of compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Normal Values)</td>
<td>7.35 – 7.45</td>
<td>35 – 45</td>
<td>22 – 26</td>
<td>None</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>Low ↓</td>
<td>Low ↓</td>
<td>Low ↓*</td>
<td>Increase ventilation to reduce CO$_2$ in blood to raise pH</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>Elevated ↑</td>
<td>Elevated ↑</td>
<td>Elevated ↑*</td>
<td>Decrease ventilation to increase CO$_2$ in blood to lower pH</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>Low ↓</td>
<td>Elevated ↑*</td>
<td>Elevated ↑</td>
<td>Kidneys will retain HCO$_3^-$ to increase pH</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>Elevated ↑</td>
<td>Low ↓*</td>
<td>Low ↓</td>
<td>Increase excretion of HCO$_3^-$ by Kidneys to lower pH</td>
</tr>
</tbody>
</table>

*Primary Event
Interpretation of ABG data can be separated into steps (Table 2)

- **Step 1: Check the pH values:**
  - Acidosis is present if pH < 7.35
  - Alkalosis is present if pH > 7.45

- **Step 2: Check the PCO$_2$ values:**
  - If in step 1 the patient has Acidosis (pH < 7.35) then:
    - If pCO$_2$ is elevated: patient has Respiratory Acidosis;
    - If pCO$_2$ is low: patient has Metabolic Acidosis and is compensating for that situation by blowing off CO$_2$
  - If in step 1 the patient has Alkalosis (pH > 7.45) then:
    - If pCO$_2$ is low: patient has Respiratory Alkalosis;
    - If pCO$_2$ is elevated: patient has Metabolic Alkalosis and is compensating for that situation by retaining CO$_2$
Step 3: Check the HCO$_3^-$ values

• Expected [HCO$_3^-$] outcomes in each of the four situations are as follows:
  • Patient with Respiratory Acidosis, as compensatory mechanism, [HCO$_3^-$] is expected to be elevated;
  • Patient with Metabolic Acidosis, [HCO$_3^-$] is expected to be low;
  • Patient with Respiratory Alkalosis, as a compensatory mechanism, [HCO$_3^-$] is expected to be low;
  • Patient with Metabolic Alkalosis, [HCO$_3^-$] is expected to be raised;
What is Anion gap and how is it calculated?

- Anion gap is the difference between commonly measured Cations and Anions;
- Physiologically the Plasma is electrochemically neutral $[\text{Cations}] = [\text{Anions}]$
- Anion gap is used as a diagnostic parameter to detect organic acidosis due to increase in Anions that are difficult to measure;
- An increase Anion gap indicates increase in unmeasured Anions in plasma;
- By calculation: Anion gap $= [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$
- Normal Anion gap $= 12 - 18$ m Eq/L
How is metabolic acidosis classified using Anion gap?

- Anion can be used to classify Metabolic Acidosis:
- Increased Anion gap metabolic acidosis
- Normal [Cl-]; Normal or Low [HCO$_3^-$] (Increased Anions)
- May be due to:
  - Diabetic Ketoacidosis,
  - Uremic acidosis (Sulfates, Phosphates, Fixed acids)
  - Starvation (Ketoacids)
  - Alcoholic ketosis (Ethanol metabolites, Lactate)
  - Lactic acidosis (Lactate Hypoxia/ Hypoperfusion)
  - Exogenous poisons (Ketones, Lactate, Salicylates, Alcohols)
• Normal Anion gap metabolic acidosis,
  • Hyperchloremic Acidosis
• May be due to:
  • Diarrhea,
  • Renal Tubular Acidosis,
  • Early Renal Failure
What is Cyanosis?

• Condition that causes Skin, Lips, Mucous Membrane and/or Fingernails to appear bluish in color or (in severe cases) purple-magenta;

• Higher than normal Deoxygenated Hb (HHb) in small superficial blood vessels;

• Higher than normal MetHb in blood;
What are some of the causes of Cyanosis?

Several causes of Cyanosis:

• Some basic mechanisms that can cause Cyanosis are:
  
  • $O_2$ saturation of Arterial blood is lower than normal;
  
  • Circulation may be slowed causing more extraction of $O_2$ per gram of Hb, thus increasing the concentration of HHb in capillaries;
A variety of diseases and factors may cause Cyanosis:

- Lack of $O_2$ (such as in suffocation or Cyanotic Heart disease),
- Congenital Heart disease,
- Pulmonary disease,
- Terminal event as in Cardiopulmonary Arrest
- Abnormal Hb (such as, Met-Hemoglobinemia)
- Toxins (such as Cyanide, Carbon Monoxide)
- Exposure to Cold Air or Cold Water,
- High Altitude,
- Shock,
- Breath holding,
- Asthma,
- Seizures,
- Drug Overdoses (Narcotics, Sedatives), etc.
When can cyanosis be observed?

• Cyanosis may be observed when:
  • $O_2$ saturation of blood is below 80%;
  • Mean capillary concentration of HHb in blood is greater than 50g/L;

• Bluish color characteristic of Cyanosis is due to the presence of more than 50g/L of HHb in Capillary Blood;

• In “Healthy” Individuals ($Hb \geq 150g/L$) Cyanosis occurs when more than One-third of their Hemoglobin is Deoxygenated;
Can signs of Cyanosis be seen in severely Anemic Patients?

• In anemic individuals with lower Hb levels:
  • Greater proportion of their Hb would have to be deoxygenated before there would be 50g/L of HHb in their blood,
• Thus, anemic individuals are not easily cyanosed;
• For example:
  • If an anemic patient had only 75g/L of Hb, cyanosis would occur when greater than Two thirds (50g/L) of their Hb was deoxygenated;
Furthermore, if an anemic patient is exposed to Hypoxic Hypoxia, such patient will become cyanosed only at a much more severe degree of hypoxia than would a normal individual;

**IMPORTANT TO NOTE:**

- Presence of Cyanosis indicates that Hypoxia is present,
- Absence of Cyanosis does not mean that there is no Hypoxia,
- Absence of Cyanosis in a patient is not a guarantee of the absence of Hypoxia,
How is Met-Hemoglobinemia (Met-Hb) related to Cyanosis?

• Met-Hb is formed when $\text{Fe}^{2+}$ ion in Heme is converted to $\text{Fe}^{3+}$ ion;
• Met-Hb is incapable of binding and releasing Oxygen;
• Cyanosis can be due to increased Met-Hb in blood;
• Cyanosis may occur when over 10% of total Hb in blood is Met-Hb;
What are the major classes of Met-Hemoglobinemia?

• There are Two major classes:
  • Inherited Met-Hemoglobinemia
  • Acquired Met-Hemoglobinemia
What are the different types of Met-Hemoglobinemia?

Types of Inherited Met-Hemoglobinemia:

• **First type:**
  • Is due to deficient activity or absence of **Methemoglobin Reductase** that converts **Met-Hb to Hb**;

• **Second type** called **Hemoglobin M (Hb M)** disease:
  • Autosomal dominant trait characterized by production of an abnormal Met-Hemoglobin;

• **Hemoglobin M (Hb M):**
  • Mutation changes the Amino Acid residue to which Heme is attached thus altering its affinity for Oxygen and favoring its oxidation;
What are some causes of Acquired Met-Hemoglobinemia?

Acquired Met-Hemoglobinemia can be due to:

• Ingestion of certain drugs and chemical:
  • Sulfonamides,
  • Aniline dyes (in brightly colored cloths),
  • Nitrobenzene,
  • Nitrites (used commonly to prevent spoilage of meat),
  • Nitrates (present in food and water), etc.

• Met-Hb is produced when Nitric Oxide or other Oxidants converts Fe$^{2+}$ ion in Heme to Fe$^{3+}$ ion (Fig. 1)
Fig. 1: Diagram showing formation of Met-Hemoglobin by Oxidants and action of Methemoglobin Reductase that converts MetHb back to Hb.
How can acquired Met-Hemoglobinemia be controlled?

• Methylene Blue (Red-Ox Dye) and Ascorbic Acid (both are Reducing Agents) can be used to control Acquired Met-Hemoglobinemia;

• Ascorbic Acid can be used to control Mild forms of Met-Hemoglobinemia due to enzyme deficiency (Figs. 2)
Fig. 2: Diagram showing non-enzymatic action of Ascorbate (Vitamin C) in the conversion of MetHb to Hb. Dehydroascorbate is soluble and can be passed out in the urine.

Role of Reduced Glutathione (GSH) in the conversion of Dehydroascorbate to Ascorbate, and actions of enzymes involved are shown. Note that NADPH is obtained from G-6-Phosphate Dehydrogenase reaction in HMP-shunt.
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