The inspiration of oxygen and expiration of carbon dioxide are vital functions of the human body. A decrease in PO\(_2\) and increase in PCO\(_2\) can alter many normal physiologic processes, and may eventually be fatal. The human body has various reflex mechanisms to manage such changes. Understanding of these reflexes and identification and management of any impairment in them is essential in the management of many respiratory and renal diseases.
Atmospheric dry air is a mixture of many gases. At sea level, this air has a pressure of 760 mm Hg. The partial pressure that each gas contributes to this atmospheric pressure is based on the percentage of gas in the air.

\[ P_{\text{gas}} = F_{\text{gas}} \times P_{\text{atm}} \]

- \( P_{\text{gas}} \) = Partial pressure of gas
- \( F_{\text{gas}} \) = Fraction of gas in air
- \( P_{\text{atm}} \) = Atmospheric pressure

Taking the above formula, the PO\(_2\) will be:

\[ \text{PO}_2 = 0.21 \times 760 \text{ mm Hg} \]
\[ \text{PO}_2 = 160 \text{ mm Hg} \]

PCO\(_2\) is very low in the atmospheric dry air, and hence, is considered to have a partial pressure of 0 mm Hg. As the air is inspired, it is warmed to 37°C and completely humidified. The gases in the air have a slightly lower partial pressure, owing to the addition of water vapors. This air has not yet participated in gas exchange. In the alveoli, where gas exchange occurs, PO\(_2\) decreases and PCO\(_2\) increases considerably.

<table>
<thead>
<tr>
<th>Site of air</th>
<th>PO(_2) (mm Hg)</th>
<th>PCO(_2) (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atmosphere</td>
<td>160</td>
<td>0</td>
</tr>
<tr>
<td>Trachea (humidified)</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>Alveoli</td>
<td>100</td>
<td>40</td>
</tr>
</tbody>
</table>

In a normal healthy system, PO\(_2\) and PCO\(_2\) of the alveolar and pulmonary capillary compartments are the same. As some of the blood shunts through the lungs, the PO\(_2\) of the systemic arterial blood is slightly lower than that of the pulmonary capillaries.

<table>
<thead>
<tr>
<th>Site of blood</th>
<th>PaO(_2) (mm Hg)</th>
<th>PaCO(_2) (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arteries</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Pulmonary capillaries</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Systemic arteries</td>
<td>95</td>
<td>40</td>
</tr>
</tbody>
</table>

Alveolar-Arterial Gradient

The difference between PO\(_2\) of alveoli and PO\(_2\) of arterial blood is referred to as alveolar-arterial gradient (A-a gradient).

\[ \text{A-a gradient} = P_{aO_2} - P_{\text{a}O_2} \]
P\(_{\text{A}}\text{O}_2\) = Alveolar PO\(_2\) (calculated from the alveolar gas equation)

P\(_{\text{a}}\text{O}_2\) = Arterial PO\(_2\) (measured in arterial blood)

In a normal healthy non-smoker’s system, A-a gradient is 5-10 mm Hg.

### Alveolar Gas Equation

Arterial PO\(_2\) (P\(_{\text{a}}\text{O}_2\)) is measured from an arterial blood sample. Unlike P\(_{\text{a}}\text{O}_2\), alveolar PO\(_2\) (P\(_{\text{A}}\text{O}_2\)) cannot be measured directly by taking an air sample from alveoli. Instead, an equation is used to estimate P\(_{\text{A}}\text{O}_2\).

\[
P_{\text{A}}\text{O}_2 = P_{\text{I}}\text{O}_2 - \frac{P_{\text{a}}\text{CO}_2}{R} + \left[P_{\text{a}}\text{CO}_2 \times F_{\text{I}}\text{O}_2 \times \frac{1 - R}{R}\right]
\]

- \(P_{\text{A}}\text{O}_2\) = Alveolar partial pressure of oxygen
- \(P_{\text{a}}\text{O}_2\) = Partial pressure of inspired oxygen
- \(P_{\text{a}}\text{CO}_2\) = Arterial partial pressure of carbon dioxide
- \(F_{\text{I}}\text{O}_2\) = Fraction of inspired gas that is oxygen
- \(R\) = Respiratory exchange ratio

The above equation can be simplified when \(F_{\text{I}}\text{O}_2 < 1\)

\[
P_{\text{A}}\text{O}_2 = P_{\text{I}}\text{O}_2 - \frac{P_{\text{a}}\text{CO}_2}{R}
\]

### Alveolar PCO\(_2\)

Alveolar PCO\(_2\) depends on two factors:
- Alveolar ventilation
- Metabolic rate

**Alveolar ventilation** has an inverse relationship with \(P_{\text{a}}\text{CO}_2\).
- Hyperventilation decreases \(P_{\text{a}}\text{CO}_2\) as deoxygenated air clears away faster. If ventilation is doubled, \(P_{\text{a}}\text{CO}_2\) halves.
- Hypoventilation increases \(P_{\text{a}}\text{CO}_2\) as deoxygenated air remains in alveoli for a longer time. If ventilation is halved, PACO\(_2\) doubles.

**Metabolic rate** has a direct relationship with \(P_{\text{a}}\text{CO}_2\).
- Increased metabolic rate increases \(P_{\text{a}}\text{CO}_2\).
- Decreased metabolic rate decreases \(P_{\text{a}}\text{CO}_2\).

The body compensates for these changes in \(P_{\text{a}}\text{CO}_2\) by altering alveolar ventilation. In other words, to keep \(P_{\text{a}}\text{CO}_2\) constant, the body matches metabolic rate with equivalent changes in alveolar ventilation. For example, during exercise (increased metabolism), the respiratory rate also increases to expel the increased \(P_{\text{a}}\text{CO}_2\).

### Alveolar PO\(_2\)

Alveolar PO\(_2\) (P\(_{\text{A}}\text{O}_2\)) depends on \(P_{\text{a}}\text{CO}_2\), and therefore, on alveolar ventilation.
Hyperventilation decreases $P_A CO_2$, leaving more space for oxygen (increased $P_A O_2$).

Hypoventilation increases $P_A CO_2$, decreasing space for oxygen (increased $P_A O_2$).

**Arterial-Venous Gradient**

The **difference between $PO_2$ of arterial blood and $PO_2$ of venous blood** is referred to as arterial-venous gradient (a-v gradient). The arterial-venous gradient is highly dependent on the rate of metabolism. At higher metabolic rates, more $O_2$ is produced. Hence, the a-v gradient is high during exercise and in trained athletes.

**Tissue Hypoxia — Deprivation of Oxygen Supply**

Hypoxia is a state of the body or a region of the body when it is **deprived of adequate oxygen supply**. It results from the failure of oxygen delivery to cells.

**Etiology of Hypoxia**

Tissue hypoxia has many diverse reasons. The mechanisms behind these causes can be summarized as follows:

- General ischemia
- Localized ischemia
- Anemia
- Carbon monoxide poisoning
- Hypoxemia

Generalized ischemia results from a low cardiac output. Many heart diseases could contribute towards it. Localized ischemia, on the other hand, is caused by vascular dysfunction, as in cases of peripheral vascular disease and gangrenes.
Anemia decreases the capacity of blood to carry oxygen as lesser hemoglobin is available to bind to oxygen. This leads to a decreased supply of oxygen throughout the body.

Carbon monoxide binds to hemoglobin and keeps it from carrying oxygen. The binding of carbon monoxide to hemoglobin is 100 times stronger than that of oxygen to hemoglobin. Additionally, it keeps the already bound oxygen from releasing at tissues.

Hypoxemia refers to a decreased oxygen level in the blood (specifically arterial blood), as opposed to hypoxia which refers to the decreased oxygen level in tissues, organs and/or the body. Hypoxemia would eventually lead to hypoxia, but, as mentioned above, it is only one of the many causes of hypoxia.

Body’s Response to Hypoxia

The body has various compensatory mechanisms set in place to combat hypoxia. The immediate response includes:

- Shifting respiratory reactions from aerobic to anaerobic reactions, leading to lactic acid build-up
- Increasing ventilation in response to lower PO₂
- Systemic vasodilation to improve tissue perfusion
- Pulmonary vasoconstriction to shunt blood towards better-ventilated regions

If hypoxia remains for a longer duration (over 2 weeks), interstitial cells in the peritubular capillary bed of the renal cortex secrete erythropoietin. Erythropoietin will primarily target erythocyte progenitors to induce the production of red blood cells. This improves the oxygen supply. Therefore, erythrocytosis is considered to be an important clinical sign of chronic hypoxia.

Hypoxemia — Decreased Blood Oxygen

Air is inhaled into the alveoli where oxygen diffuses into the blood through the walls of the alveoli and capillaries. Hypoxemia, i.e. decreased oxygen in the blood, occurs due to dysfunction at any stage in this process.
Hypoventilation or Low $P_{O_2}$

The very first stage of respiration is inhaling an adequate amount of oxygen.

- In hypobaric conditions, the atmospheric pressure of air is lower, and hence, the constituent gases, including oxygen, have lower partial pressure.
- In closed compartments, oxygen is limited. Over time, its consumption can lead to decreased $F_{O_2}$.
- Hypoventilation causes decreased $P_{A O_2}$.

Diffusional Impairment

The exchange of gases ($O_2$ & $CO_2$) between the alveoli and blood occurs by simple diffusion.

- **Thicker alveolar or capillary wall** impairs diffusion of gases.
- **Pulmonary fibrosis** thickens the walls of the lungs. Fluid in the lungs can decrease the diffusion capacity.
- The measurement of the uptake of CO in mL/min/mm Hg is called the diffusing capacity of the lung (DLCO).

Right-to-left Shunt

Some pathological shunts can skip the pulmonary circulation.

- **Cardiac defects** allow the mixing of deoxygenated blood with oxygenated blood.
Uncorrected left-to-right shunts can progress to the right-to-left shunt. This phenomenon is known as Eisenmenger syndrome.

V/Q Inequality

The gas exchange across the alveolar-capillary barrier could either be diffusion-limited or perfusion-limited. **The diffusion-limited gas exchange** occurs when net diffusion into pulmonary capillary depends on a magnitude of A-a gradient. If the gradient is high, more oxygen will diffuse. **The perfusion-limited gas exchange** occurs when the gas exchange is limited by blood flow through pulmonary capillaries. People with heart diseases (reduced cardiac output) experience a perfusion-limited gas exchange.

Ideally, the **ventilation-perfusion ratio (V/Q) should be 1**. Physiologically, the apex of a lung is poorly perfused (decreased blood flow) and highly ventilated. The V/Q ratio is high and signifies that oxygen does not get a chance to properly diffuse from alveoli to blood. In contrast, the base of a lung is highly perfused (increased blood flow) and normally ventilated. The V/Q ratio is low and signifies that enough oxygen is not available to properly oxygenate the blood.

Hypercapnia — Increased Carbon Dioxide in Blood

Hypercapnia refers to an **increased carbon dioxide level in the blood**. Hypercapnia occurs when enough carbon dioxide is not being expelled from the body.

---

**Main symptoms of Carbon dioxide toxicity**

- **Visual**
  - Dimmed sight

- **Auditory**
  - Reduced hearing

- **Respiratory**
  - Shortness of breath

- **Muscular**
  - Tremor

- **Central**
  - Drowsiness
  - Mild narcosis
  - Dizziness
  - Confusion
  - Headache
  - Unconsciousness

- **Skin**
  - Sweating

- **Heart**
  - Increased heart rate and blood pressure

*Image: “Main Symptoms of Carbon Dioxide Toxicity” by Mikael Häggström. License: Public Domain*
- $P_{CO_2}$ directly depends on $P_{aCO_2}$. Expulsion of $CO_2$ in the alveoli is important to maintain a concentration gradient between alveoli and blood and facilitate the diffusion of $CO_2$ across the alveolar-capillary barrier.
- Poor ventilation decreases the V/Q ratio, stopping the adequate off-loading of $CO_2$ from erythrocytes.
- A higher metabolism produces more $CO_2$. Without proper reflex, this can lead to hypercapnia.

**Review Questions**

Solutions can be found below the references.

1. Analysis of expiratory gases of a patient reveals the following information. What is the explanation of such findings in the patient?

<table>
<thead>
<tr>
<th>Site of Air</th>
<th>$PO_2$ (mm Hg)</th>
<th>$PCO_2$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>Alveoli</td>
<td>140</td>
<td>10</td>
</tr>
</tbody>
</table>

   A. Normal alveolar ventilation and perfusion  
   B. Poor alveolar ventilation  
   C. Poor alveolar perfusion  
   D. Right-to-left shunt

2. A patient has the following arterial blood findings. Which of the following is the most likely cause of these findings?

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$PaO_2$</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>% Saturation</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Oxygen content</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

   A. Obesity  
   B. Carbon monoxide poisoning  
   C. High altitude  
   D. Asthma  
   E. Anemia

**References**


**Correct answers:** 1C, 2B

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