A-A Gradient & Alveolar Gas Equation -
Laboratory Diagnostics

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A-A Gradient & Alveolar Gas equation are very evident to determine various causes of hypoxemia. Alveolar gas equation is useful for calculation of the partial pressure of oxygen in lung alveoli and A-A Gradient is the value that shows the difference between alveolar oxygen pressure and arterial oxygen pressure. The etiology of hypoxemia can be hypoventilation, diffusion impairment, and presence of shunt, V/Q mismatch and high altitude. The variation in the values of alveolar gas equation and A-A Gradient establish the laboratory diagnosis of the lung pathologies.

Alveolar Gas Equation

Alveolar gas equation helps to calculate the partial pressure of oxygen in alveoli

\[ P_{aO_2} = P_{iO_2} - \frac{(P_{aCO_2})}{R} \]

- \( P_{aO_2} \) = Partial pressure of oxygen in alveoli
- \( P_{iO_2} \) = Partial pressure of oxygen in inspired air
- \( P_{aCO_2} \) = Partial pressure of \( CO_2 \) in arterial blood
R = Respiratory quotient

This is the simplest form of the alveolar gas equation by Rossier & Mean. Other versions of the alveolar gas equation are:

- **West**: \[ PAO_2 = PO_2 - (P_aCO_2/R) + K \]

\[ K = F_iO_2 x P_aCO_2 x [(1-R)/R] \]

For most clinical conditions, the value of K is too small to make a difference in the value of \( P_AO_2 \) and hence can be neglected.

- **Riley**: \[ P_iO_2 = PO_2 - (P_aCO_2/R) \times [1 - F_iO_2(1-R)] \]

The difference between the values of \( P_AO_2 \) calculated by the above two equations is only due to inert gas exchange; hence, they can be used to calculate the concentration effect.

- **Selkurt**: \[ P_iO_2 = PO_2 - P_aCO_2 x [F_iO_2 + (1 - F_iO_2)/R] \]

- **Filley, MacIntosh & Wright**: \[ P_iO_2 = PO_2 - P_aCO_2 x ((P_iO_2 - P_aO_2)/P_aCO_2) \]

This equation allows for the disequilibria of inert gasses, therefore, it can be used during induction or recovery from anesthesia. Important assumptions for the above equation:

- **Metabolic minute production** of carbon dioxide is constant.
- \( P_aCO_2 = P_aCO_2 \), as the alveolar membrane is thin and carbon dioxide is highly diffusible.
- Alveolar and inspired gasses follow the ideal gas law (PV = nRT).
- Inspired gas contains no CO_2 or water.
- All other gasses except oxygen in the inspired gas are in equilibrium with their dissolved states in the blood.
- The alveolar gas is saturated with water.
- Note that \( P_iO_2 = (P_{atm} - PH_2O) \times F_iO_2 \).

\( P_{atm} \) = Atmospheric pressure (760 mm Hg at sea level)

\( PH_2O \) = Water vapor pressure (47 mm Hg at body temperature)

\( F_iO_2 \) = Fraction of inspired oxygen (0.21 in room air)

Thus, at normal body temperature, while breathing room air at sea level,

\[ P_{iO_2} = (760 - 47) \times 0.21 = 149.7 \text{ mm Hg} \]

Respiratory quotient is the amount of CO_2 produced divided by the amount of **oxygen** consumed by tissue metabolism.

- Normally, R is 0.8, when cells are using both glucose and free fatty acids as fuel.
- R is 1.0 when the fuel is only **glucose** (for example, patient on intravenous glucose).
- R is 0.7 when the fuel is only free fatty acids (for example, a **hypoglycemic** or a **diabetic patient**).

**Alveolar-arterial Gradient**

A-a gradient is the **difference between alveolar oxygen pressure and arterial oxygen pressure**. A-a gradient can be used to study the different causes of **hypoxemia**.

**Hypoxemia** is a decrease in arterial PO2, while hypoxia is decreased oxygen delivery to
the tissues. \( \text{PO}_2 \) can be calculated using alveolar gas equation (discussed above). The patient may develop hypoxia in the presence of normal \( \text{P}_a\text{O}_2 \), as in cases of carbon-monoxide poisoning or decreased hemoglobin (anemia).

\[
\text{A-a O}_2 \text{ gradient} = \text{P}_a\text{O}_2 - \text{P}_s\text{O}_2
\]

**Example**

For a patient with \( \text{P}_a\text{CO}_2 = 40 \text{ mm Hg} \), \( \text{P}_a\text{O}_2 = 97 \text{ mm Hg} \), \( \text{P}_s\text{O}_2 \) can be derived from alveolar gas equation (Rossier & Mean) as follows:

\[
\text{P}_s\text{O}_2 = \text{P}_a\text{O}_2 - \left(\frac{\text{P}_a\text{CO}_2}{R}\right) = 149.7 - (40/0.8) \text{ if } \text{P}_a\text{CO}_2 \text{ is 40 mm Hg}
\]

\[
= 99.7 \text{ mm Hg}
\]

Thus, A-a O\(_2\) gradient = \( \text{P}_s\text{O}_2 - \text{P}_a\text{O}_2 \)

\[
= 99.7 - 97 \text{ if } \text{P}_s\text{O}_2 \text{ is 97 mm Hg}
\]

\[
= 2.7 \text{ mm Hg}
\]

Assuming that the patient is breathing room air at sea level, with normal body temperature:

- Normal A-a O\(_2\) gradient suggests normal gas exchange between alveoli and blood. Values < 15 mm Hg are considered normal.
- Increased A-a O\(_2\) gradient (> 15 mm Hg) suggests abnormal gas exchange between alveoli and blood, which may be due to V/Q mismatch, shunting, or thickened diffusion barrier.

**Factors Affecting A-a O\(_2\) Gradient**

**Age**

A-a O\(_2\) gradient increases by 3 mm Hg for each decade over 30 years of age.

**Alveolar PO\(_2\)**

As the shape of oxygen dissociation curve is non-linear, greater the \( \text{P}_s\text{O}_2 \), greater the A-a O\(_2\) gradient, provided rest factors are the same.

**Magnitude of venous admixture**

Venous admixture reduces arterial O\(_2\) content and increases arterial CO\(_2\) content. As \( \text{P}_s\text{O}_2 \) is usually on hemoglobin dissociation curve, a small reduction in O\(_2\) content causes a large reduction in \( \text{P}_s\text{O}_2 \), therefore increasing A-a O\(_2\) gradient.

CO\(_2\) dissociation curve being steep and more linear increased arterial CO\(_2\) content does not cause a significant increase in \( \text{P}_a\text{CO}_2 \). In clinical settings, compensatory hyperventilation is more than enough to offset the small increase in \( \text{P}_a\text{CO}_2 \); therefore, \( \text{P}_a\text{CO}_2 \) is often reduced, rather than increased.

**Cardiac output**

Provided the same venous admixture, cardiac output is inversely proportional to A-a O\(_2\) gradient. However, a reduction in cardiac output is associated with a reduced venous admixture and reduced shunt fraction, therefore, \( \text{P}_s\text{O}_2 \) and A-a O\(_2\) gradient are almost
Hemoglobin

**Hemoglobin concentration** does not influence the arterial oxygen content, but increased hemoglobin concentration would slightly reduce the arterial oxygen tension.

Alveolar ventilation

Increased alveolar ventilation increases both $P_{a}O_{2}$ and A-a $O_{2}$ gradient.

**Different Causes of Hypoxemia**

Hypoxemia is a decrease in arterial $PO_{2}$, while hypoxia is decreased oxygen delivery to the tissues. There are five important pathophysiological causes of hypoxemia and respiratory failure, which are as follows:
Hypoventilation

The minute ventilation depends on the respiratory rate and the **tidal volume**, which is the amount of inspired air during each normal breath at rest.

\[
\text{Minute ventilation} = \text{Respiratory rate} \times \text{Tidal volume}
\]

The normal respiratory rate is about **12 breaths per minute** and the normal **tidal volume is about 500 mL**. Therefore, the minute respiratory volume normally averages about **6 L/min**.

**Hypoventilation** occurs when there is a decrease in the respiratory rate and/or **tidal volume** so that the decreased amount of air is exchanged per minute. There will be a decreased oxygen entry within the alveoli and the arteries leading to decreased \( P_{a}O_{2} \).

As already described, the \( P_{a}CO_{2} \) is inversely proportional to the ventilation; hence, the hypoventilation will lead to increased \( P_{a}CO_{2} \). The **alveolar-arterial gradient** will be normal and less than 10 mm Hg as there is no defect in the diffusion of gasses. In these cases, increasing the **ventilation** and/or increasing the oxygen concentration will correct the deranged blood gasses.

Diffusion impairment

In diffusion impairment, there is a structural problem within the lung. There may be a decreased surface area (as in **emphysema**), or increased thickness of alveolar membranes (as in **fibrosis** and **restrictive lung diseases**) that impairs the diffusion of gasses across the alveoli leading to an increased alveolar-arterial gradient. In increased A-a gradient, the alveolar \( PO_{2} \) will be normal or increased, but arterial \( PO_{2} \) will be decreased. The greater the structural problem is present, the greater the alveolar-arterial gradient will be.
Since the diffusion of gasses is directly proportional to the concentration of gasses, therefore increasing the concentration of inhaled oxygen will correct $P_aO_2$ but the increased A-a gradient will be present as long as the structural problem is present.
In a pulmonary shunt, also known as a **right-to-left shunt**, the **venous deoxygenated blood from the right side enters the left side of the heart and systemic circulation without getting oxygenated within the alveoli**. In simple words, a shunt refers to “normal perfusion, poor ventilation”.

The lungs are having a normal blood supply, but ventilation is decreased or absent that fails to exchange gasses with the incoming deoxygenated blood. The ventilation/perfusion ratio is or near to zero. This happens, for example, in **atelectasis** and cyanotic **heart diseases**. In atelectasis, the collapsed lung is not ventilated and blood within that segment fails to oxygenate. In cyanotic heart diseases, the blood from the right side bypasses (shunts) the lungs and enters the left side, causing **hypoxemia** and **cyanosis**.
The A-a gradient is increased as deoxygenated blood enters the arterial (systemic) circulation decreasing the arterial oxygen tension, $P_{aO_2}$.

Since venous blood does not oxygenate in the pulmonary shunt, therefore increasing the oxygen concentration does not correct the hypoxemia. The blood will bypass the lungs, no matter how much-increased oxygen concentration is used. **This failure to increase $P_{aO_2}$ after oxygen administration** is a very important point and helps to differentiate from the impaired diffusion and other causes of hypoxemia that correct with the supplemental oxygen.

**Ventilation-perfusion (V/Q) mismatch**

It is the ratio of alveolar ventilation (V) to pulmonary blood flow (Q). The matching of ventilation and perfusion is essential to achieve the adequate exchange of oxygen and carbon dioxide within the alveoli. The **V/Q ratio** in normal individuals is around 0.8, but this ratio alters in the presence of significant ventilation or perfusion defects.
Within the lungs, all the alveoli do not have uniform ventilation and perfusion; they tend to vary due to the effects of gravity.

At the apex of the lung, alveoli are large and completely inflated, while they are small at the bases. Similarly, the blood supply is more at the base of the lung, than at the apex. This creates physiological ventilation (V) - perfusion (Q) mismatch between different alveoli.
The **decreased V/Q ratio** (< 0.8) may occur either from decreased ventilation (airway or interstitial lung disease) or from over-perfusion. The blood is wasted in these cases and fails to properly oxygenate. In extreme conditions, when ventilation is significantly decreased and V/Q approaches to zero, it will behave as a pulmonary shunt.

The **increased V/Q ratio** (> 0.8) usually occurs when perfusion is decreased (pulmonary embolism preventing the blood flow distal to obstruction) or over-ventilation. The air is wasted in these cases and is unable to diffuse through the blood. In extreme conditions, when perfusion is significantly decreased and V/Q approaches to 1, the alveoli will act as dead space and no diffusion of gasses occur.

Therefore, the increased mismatch in ventilation and perfusion within the lung impairs the gas exchange processes and ultimately will lead to hypoxemia and respiratory failure.

**High altitude**

At high altitudes, the **barometric pressure (PB)** is decreased, which will lead to decreased alveolar PO$_2$ as in the equation:

$$P_{A}O_2 = FIO_2 \times (PB - PH_2O) - P_{A}CO_2/R$$

The decreased alveolar $P_AO_2$ will lead to decreased arterial $P_AO_2$ and hypoxemia but the A-a gradient remains normal as there is no defect within the gas exchange processes. In
these conditions, supplementing with additional oxygen (increasing the FIO₂) increases the PₐO₂ and corrects the hypoxemia.

When a person suddenly ascends to high altitude, the body responds to the hypoxemia by hyperventilation causing respiratory alkalosis. The concentrations of 2, 3-diphosphoglycerate (DPG) are increased, shifting the oxygen-hemoglobin dissociation curve to the right.

Chronically, the acclimatization takes place and the body responds by increasing the oxygen-carrying capacity of the blood (polycythemia). The kidneys excrete bicarbonates and maintain the pH within normal limits.

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<tr>
<td>High Altitude</td>
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Conditions Associated with Increased A-a O₂ Gradient

- Pulmonary atelectasis
- Pulmonary consolidation/infection/neoplasm
- Alveolar destruction
- Extrapulmonary shunting
- Drugs such as vasodilators and volatile anesthetics
- Hepatic failure
- Pregnancy

Review Questions

The correct answers can be found below the references.

1. Which of the following alveolar gas equations allows for disequilibria of inert gasses?

   A. PₐO₂ = PₐO₂ - (PₐCO₂/R)
   B. PₐO₂ = PₐO₂ - (PₐCO₂/R) + K  
     K = FₐO₂ x PₐCO₂ x [(1 – R)/R]
   C. PₐO₂ = PₐO₂ - (PₐCO₂/R) x [1-FₐO₂/(1-R)]
   D. PₐO₂ = PₐO₂ - PₐCO₂ x [FₐO₂ + (1-FₐO₂)/R]
   E. PₐO₂ = PₐO₂ - PₐCO₂ x [(PₐO₂ - PₐO₂)/PₐCO₂]

2. Which of the following best describes the effects of venous admixture on arterial blood gasses and A-a O₂ gradient in clinical settings?

   A. ↓ O₂ content, ↓ PₐO₂, ↑ CO₂ content, ↑ PₐCO₂, ↑ A-a O₂ gradient
   B. ↓ O₂ content, ↓ PₐO₂, ↑ CO₂ content, ↓ PₐCO₂, ↑ A-a O₂ gradient
   C. ↑ O₂ content, ↑ PₐO₂, ↑ CO₂ content, ↓ PₐCO₂, ↑ A-a O₂ gradient
   D. ↓ O₂ content, ↓ PₐO₂, ↑ CO₂ content, ↑ PₐCO₂, ↓ A-a O₂ gradient
E. ↓ O₂ content, ↓ PₐO₂, ↑ CO₂ content, ↓ PₐCO₂, ↓ A-a O₂ gradient

3. Which of the following is least commonly associated with an increased A-a O₂ gradient?

A. Lobar pneumonia
B. Liver failure
C. Renal failure
D. Pregnancy
E. Use of vasodilators

References


Costanzo, L. BRs Physiology (text only) 4th (Fourth) edition.

Correct answers: 1E, 2B, 3C

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