A-A Gradient & Alveolar Gas Equation – Laboratory Diagnostics

See online here

A-A Gradient & Alveolar Gas equation are very evident to determine various causes of hypoxemia. The 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 the alveolar gas equation and A-A Gradient establish the laboratory diagnosis of the lung pathologies.

Alveolar Gas Equation

The partial pressure of **oxygen in the alveoli** can be calculated using the following alveolar gas equation:

$P_AO_2 = P_iO_2 - (P_aCO_2/R)$
P_AO_2 = Partial pressure of oxygen in alveoli
PiO_2 = Partial pressure of oxygen in inspired air

P_aCO_2 = Partial pressure of CO_2 in arterial blood
R = Respiratory quotient

where PAO2 is the partial pressure of oxygen in the alveoli, PiO2 is the partial pressure of oxygen in inspired air, PaCO2 denotes the partial pressure of CO2 in arterial blood, and R represents the respiratory quotient.

This is the simplest form of the alveolar gas equation provided by **Rossier and Mean**. Other versions of the alveolar gas equation are as follows:

- **West:** $PAO_2 = P_iO_2 – (P_aCO_2/R) + K$

where $K = F_iO_2 \times P_aCO_2 \times [(1–R)/R]$

Under most clinical conditions, the value of K is not large enough to make a difference in the value of PAO2, and hence can be neglected.

- **Riley:** $P_AO_2 = P_iO_2 – (P_aCO_2/R) \times [1 – F_{i2}(1–R)]$

The difference between the values of PAO2 calculated using the above 2 equations is only due to inert gas exchange; hence, they can be used to calculate the concentration effect.

- **Selkurt:** $P_AO_2 = P_iO_2 – P_aCO_2 \times [F_iO_2 + (1 – F<_iO_2)/R]$
- **Filley, MacIntosh & Wright:** $P_AO_2 = P_iO_2 – P_aCO_2 \times [(P_iO_2 – P_{\bar{E}}O_2)/P_{\bar{E}}CO_2]$

This equation facilitates the disequilibria of inert gases. Therefore, it can be used during induction or recovery from anesthesia. Important assumptions for the above equation are:

- **Metabolic minute production** of carbon dioxide is constant.
- PACO2 = PaCO2, 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 CO2 or water.
- All other gases 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 PiO2 = (Patm – PH2O) x FiO2.

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,

$$\mathbf{P_iO_2 = (760 – 47) \times 0.21 = 149.7 \text{ mm Hg}}$$

Respiratory quotient is the amount of CO2 produced divided by the amount of **oxygen** consumed by tissue metabolism.

- Normally, R is 0.8, when cells use 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 includes 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 investigate the different causes of **hypoxemia.**

Hypoxemia is defined as a decrease in arterial PO2, while hypoxia indicates decreased oxygen delivery to the tissues. PO2 can be calculated using the alveolar gas equation (discussed above). The patient may develop hypoxia in the presence of normal PaO2, as in carbon monoxide **poisoning** or decreased hemoglobin (**anemia**).

$$\text{A-a } O_2 \text{ gradient} = P_AO_2 - P_aO_2$$

Example

For a patient with P_aCO_2 = 40 mm Hg, P_aO_2 = 97 mm Hg, P_AO_2 can be derived from alveolar gas equation (Rossier and Mean) as follows:

$$P_AO_2 = P_iO_2 - (P_aCO_2/R) = 149.7 - (40/0.8) \text{ if } P_aCO_2 \text{ is 40 mm Hg}$$
$$= 99.7 \text{ mm Hg}$$

Thus, A-a O_2 gradient = $P_AO_2 - P_aO_2$
= 99.7 – 97 if P_aO_2 is 97 mm Hg
= 2.7 mm Hg

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

- Normal A-a O2 gradient suggests a normal gas exchange between the **alveoli and blood**. Values < 15 mm Hg are considered normal.
- Increased A-a O2 gradient (> 15 mm Hg) suggests an abnormal gas exchange between alveoli and blood, which may be due to V/Q mismatch, shunting, or thickened diffusion barrier.

Factors affecting A-a O2 Gradient

Age

The A-a O2 gradient increases by 3 mm Hg for each decade over 30 years of age.

Alveolar PO2

As the shape of the oxygen dissociation curve is non-linear, greater the PAO2, greater is the A-a O2 gradient, provided the rest of the factors remain the same.

Magnitude of venous admixture

Venous admixture reduces arterial O2 content and increases arterial CO2 content. As PaO2 is usually based on the **hemoglobin dissociation curve**, a small reduction in the O2 level induces a large reduction in PaO2, thereby increasing A-a O2 gradient.

The CO2 dissociation curve is steep and a further linear increase in arterial CO2 content does not significantly increase the PaCO2 level. Under clinical settings, compensatory hyperventilation is more than adequate to offset the small increase in PaCO2. Therefore,

PaCO2 is often decreased, rather than increased.

Cardiac output

The cardiac output is inversely proportional to A-a O2 gradient provided the venous admixture remains the same. However, reduced cardiac output is associated with a reduction in venous admixture and shunt fraction. Therefore, PaO2 and A-a O2 gradient remain almost unchanged.

Hemoglobin

Hemoglobin concentration does not affect the arterial oxygen content, but increased hemoglobin concentration slightly reduces the arterial oxygen tension.

Alveolar ventilation

Increased alveolar ventilation increases both PAO2 and A-a O2 gradient.

Etiology of Hypoxemia

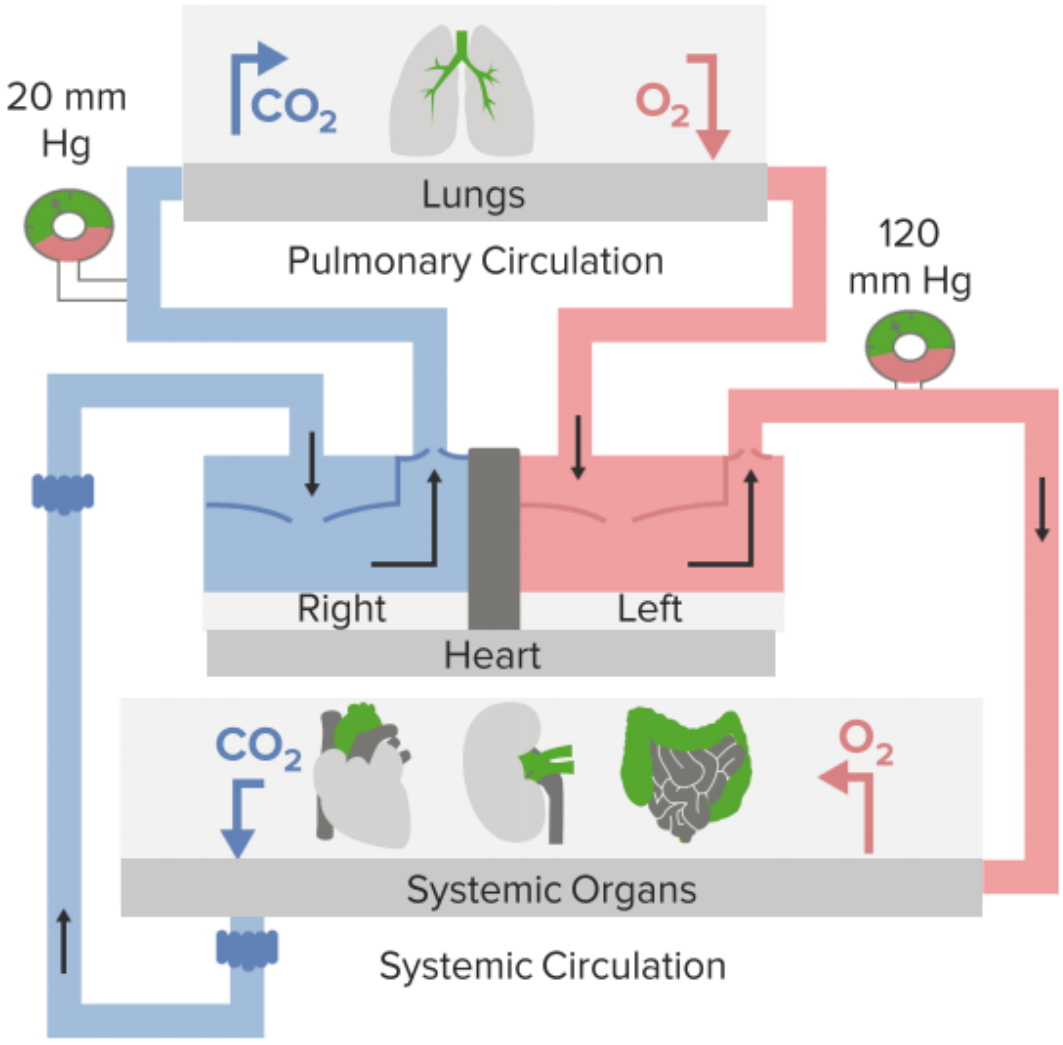

Image: Different Causes of Hypoxemia. By Lecturio

There are 5 important pathophysiological causes of hypoxemia and respiratory failure.

Hypoventilation

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

Minute ventilation = respiratory rate x 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 **the respiratory rate and tidal volume are decreased** so that the amount of air exchanged per minute is decreased. A decreased oxygen entry within the alveoli and the arteries leads to decreased PaO2. As already described, PaCO2 is inversely proportional to the ventilation; hence, hypoventilation increases PaCO2. The **A-a gradient** is normal and less than 10 mm Hg in the absence of abnormal diffusion of gas. In these cases, ventilation or the oxygen concentration can be increased to correct the abnormal behavior of blood gases.

Impaired diffusion

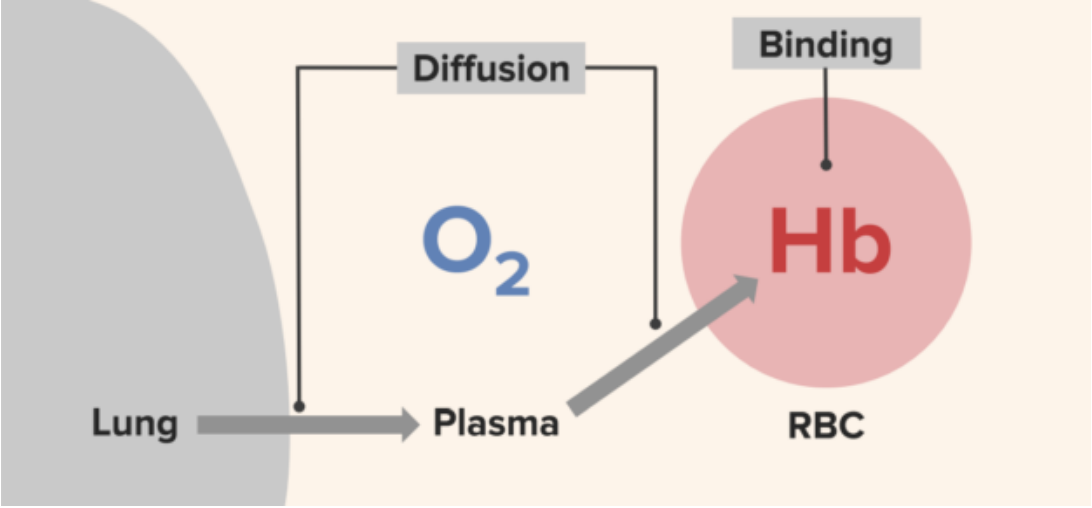

Image: Overview of Diffusion in the lung. By Lecturio

Impaired diffusion is attributed to structural defects within the lung. 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 gases across the alveoli increases the A-a gradient. Under increased A-a gradient, the alveolar PO2 is normal or increased, but the arterial PO2 is decreased. A greater structural defect leads to higher alveolar-arterial gradient.

$$\dot{V}_{gas} \propto \frac{A}{T} \cdot D \cdot (P_1 - P_2)$$

$$D \propto \frac{Sol}{\sqrt{MW}}$$

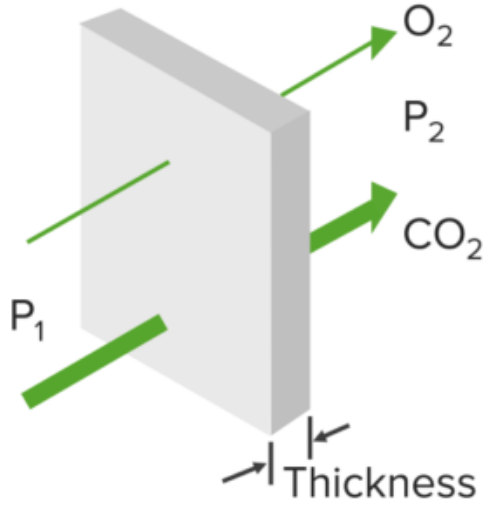

Image: Calculating diffusion. By Lecturio

Since the diffusion of gases is directly proportional to the gas concentrations, increasing the concentration of inhaled oxygen corrects PaO2. However, the increased A-a gradient persists as long as the structural problem remains.

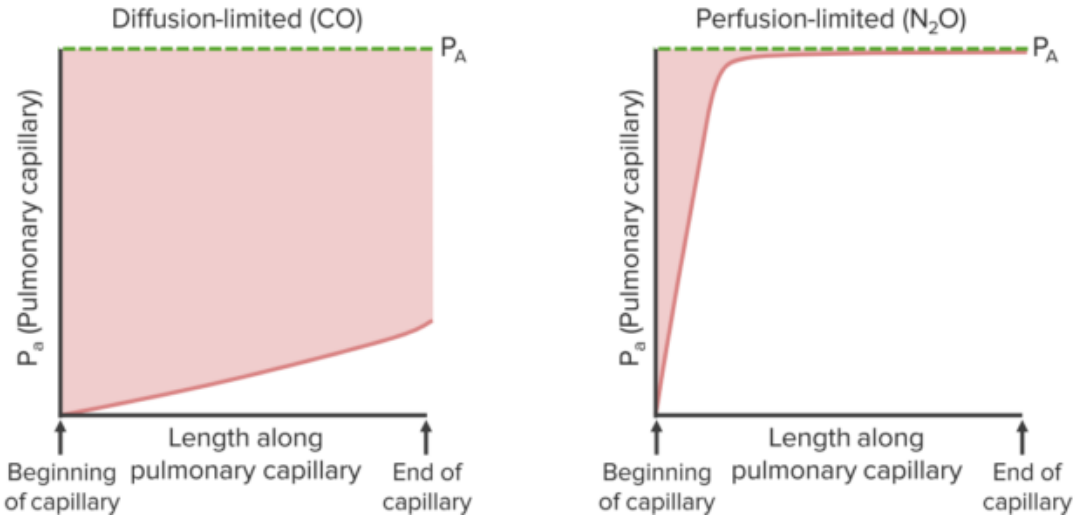

Image: Diffusion and perfusion limited gases. By Lecturio

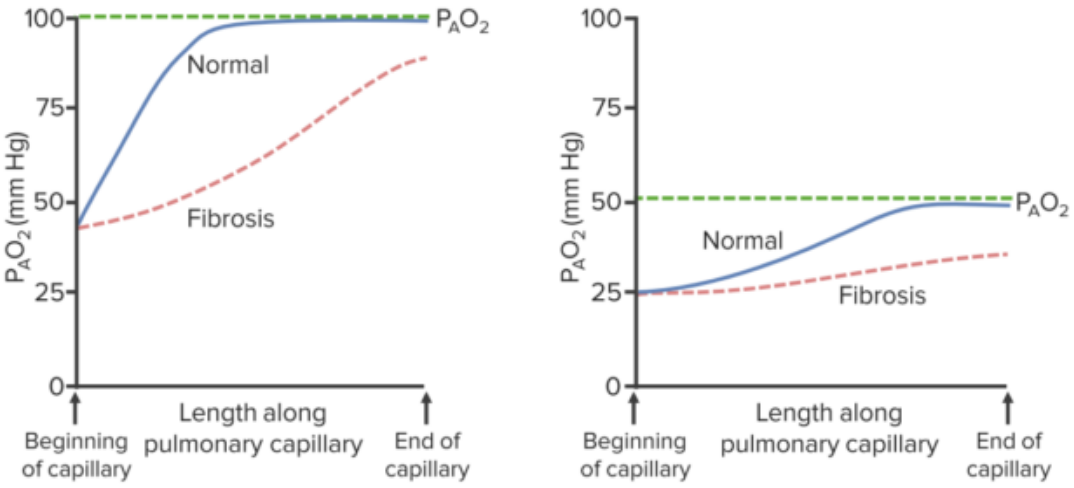

Image: Diffusional impairment. By Lecturio

Right-to-left shunt

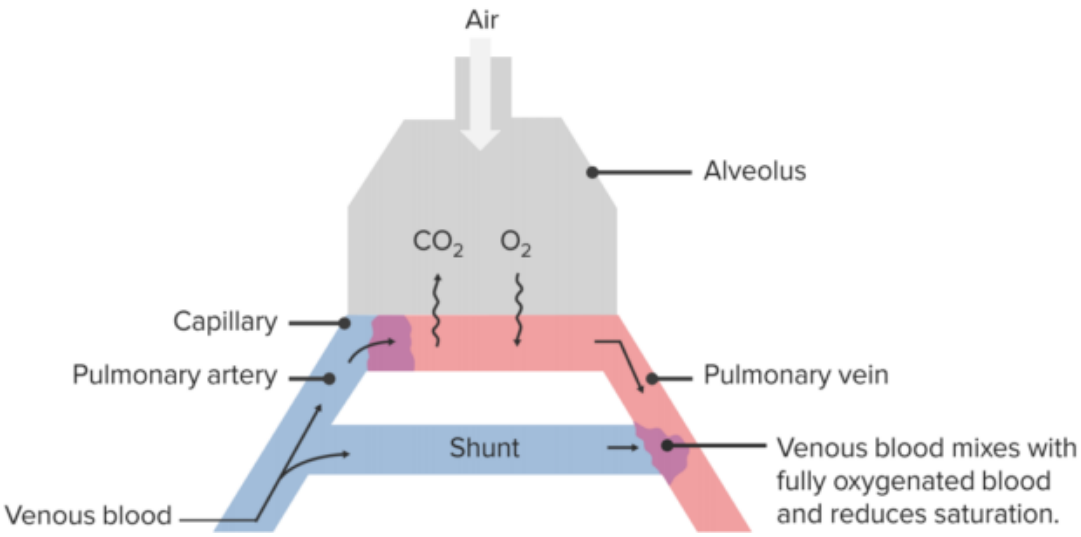

Image: Right to left shunt. By Lecturio

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**. Thus, a shunt refers to ‘normal perfusion, poor ventilation’.

The lungs carry a normal blood supply, but under decreased or zero ventilation no gas exchange occurs with the incoming deoxygenated blood. The ventilation-perfusion (V/Q) ratio is close to zero, especially 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**.

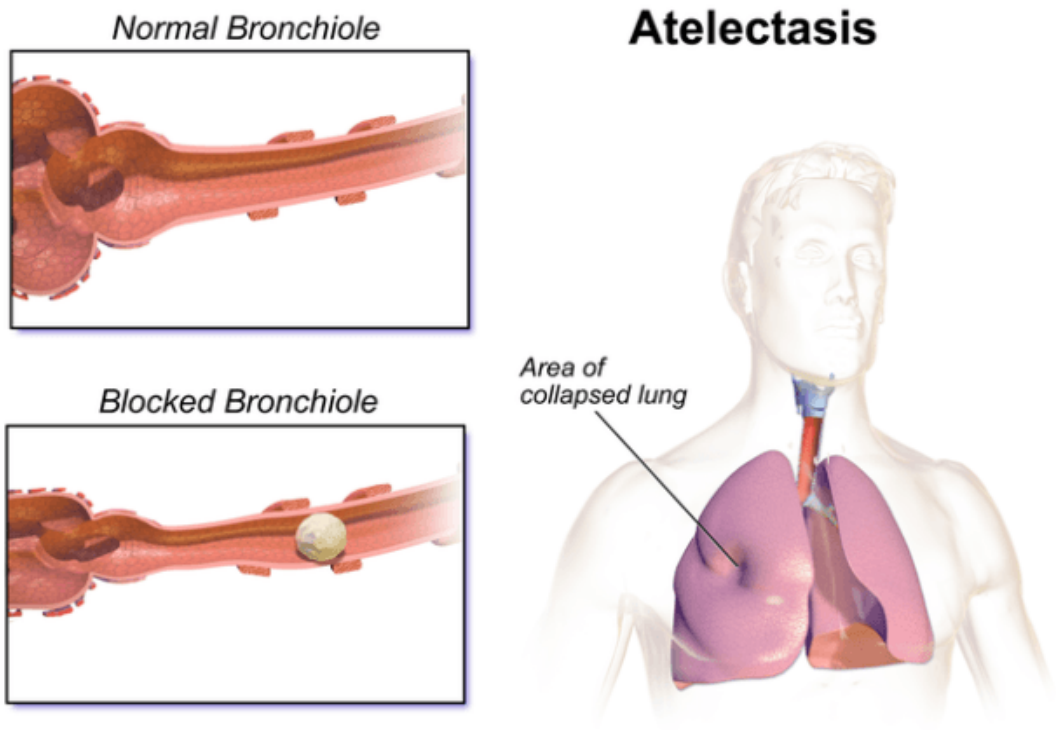

Image: Atelectasis. By BruceBlaus, License: CC BY-SA 4.0

The A-a gradient is increased as deoxygenated blood enters the arterial (systemic) circulation, which decreases the PaO2.

Since venous blood does not oxygenate in the pulmonary shunt, increasing the oxygen concentration does not correct the hypoxemia. The blood will bypass the lungs regardless of the increased oxygen concentrations. **This failure to increase PaO2 after oxygen administration** is very important in distinguishing impaired diffusion from other causes of hypoxemia that are corrected with supplemental oxygen.

Ventilation-perfusion (V/Q) mismatch

V/Q is the ratio of alveolar ventilation (V) to pulmonary blood flow (Q). A V/Q match facilitates adequate exchange of oxygen and carbon dioxide within the alveoli. The **V/Q ratio** in normal individuals is **around 0.8**, but this ratio is altered in the presence of significant ventilation or perfusion defects.

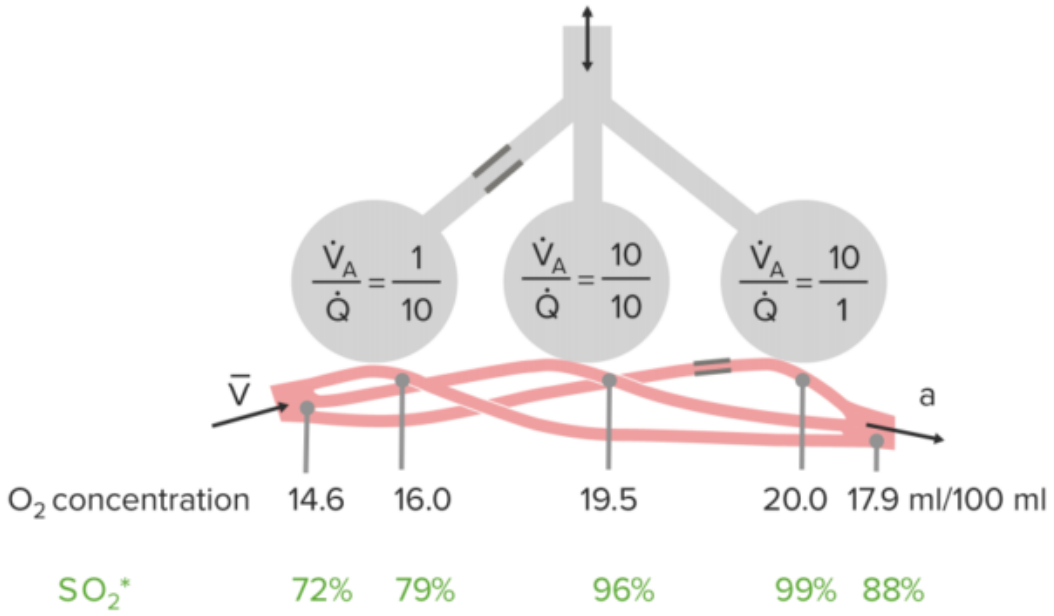

Image: Ventilation to perfusion inequality – theoretical examples. By Lecturio.

Within the lungs, all the alveoli do not exhibit uniform ventilation and perfusion due to the effects of gravity.

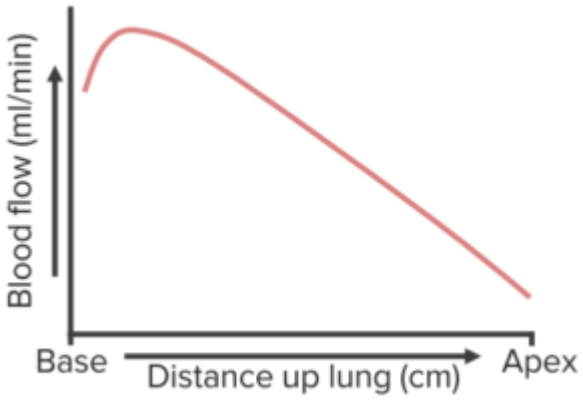

Image: Perfusion of the Lung. By Lecturio

At the apex of the lung, the alveoli are large and completely inflated, while they are small at the base. Similarly, the blood supply is higher at the base of the lung than at the apex, which creates physiological ventilation (V) – perfusion (Q) mismatch between different alveoli.

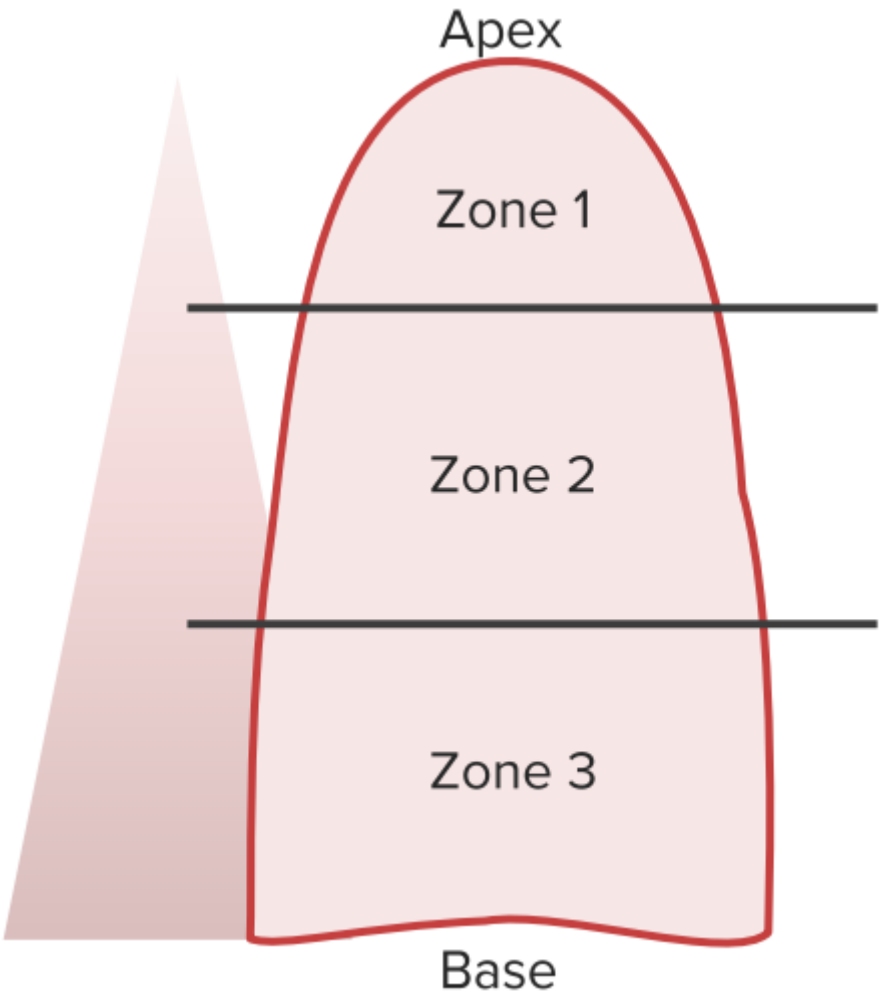

Image: Perfusion of the upright lung – apex and base. By Lecturio

The **decreased V/Q ratio (< 0.8)** may occur either due to decreased ventilation (airway or interstitial lung disease) or as a result of over-perfusion. The blood is wasted in these cases and fails to oxygenate adequately. In extreme conditions, when ventilation is significantly decreased and the V/Q approaches zero, it behaves as a pulmonary shunt.

The **increased V/Q ratio (> 0.8)** occurs when perfusion is decreased, for e.g., in pulmonary **embolism** preventing blood flow distal to obstruction or under excessive ventilation. The air is wasted in these cases and fails to diffuse through the blood. In extreme conditions, when perfusion is significantly decreased and V/Q approaches 1, the alveoli act as dead space and no diffusion of gases occurs.

Therefore, the increased V/Q mismatch within the lung impairs the gas exchange mechanisms and ultimately leads to hypoxemia and respiratory failure.

High altitude effect

At high altitudes, the **barometric pressure (PB)** is decreased, which leads to decreased alveolar PO2 as in the following equation:

$$\mathbf{P_AO_2 = FIO_2 \times (PB - PH_2O) - P_ACO_2/R}$$

The decreased alveolar PAO2 leads to decreased arterial PaO2 and hypoxemia but the A–a gradient remains normal as there is no defect within the gas exchange mechanism.

Under these conditions, supplemental oxygen therapy (elevated FIO2) increases the PAO2 and corrects the hypoxemia.

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

Under chronic conditions, acclimatization occurs and the body responds by increasing the oxygen-carrying capacity of the blood (**polycythemia**). The kidneys excrete bicarbonates and maintain the pH level within normal limits.

Causes of Hypoxemia			
Cause	**P_aO_2**	**A-a gradient**	**Response of P_aO_2 to supplemental oxygen**
Hypoventilation	Decreased	Normal	Increases
Impaired diffusion	Decreased	Increased	Increases
Shunt	Decreased	Increased	Does not increase
V/Q Mismatch	Decreased	Increased	Increases usually (depends on V/Q mismatch type)
High Altitude	Decreased	Normal	Increases

Factors 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

References

Cruickshank, S., & Hirschauer, N. (2004). The alveolar gas equation. *Continuing Education in Anaesthesia Critical Care & Pain, 4*(1), 24–27. http://doi.org/10.1093/bjaceaccp/mkh008

Martin, L. *THE FOUR MOST IMPORTANT EQUATIONS IN CLINICAL PRACTICE*. Retrieved March 12, 2018, from http://globalrph.com/martin_4_most.htm

Karius, D. R. *Respiratory Adaptations in Health and Disease: Calculating the Alveolar Oxygen & the A-a O2 gradient.* Retrieved March 12, 2018, from https://courses.kcumb.edu/physio/adaptations/alveolar%20oxygen.htm

Walker, B. R., Colledge, N. R., Ralston, S., & Penman, I. D. (2015). *Davidsons principles and practice of medicine*. Edinburgh: Churchill Livingstone/Elsevier.

Kaynar, A. M. (2017, October 23). *Respiratory Failure.* Retrieved March 12, 2018, from https://emedicine.medscape.com/article/167981-overview

Feller-Kopman, D. J., & Schwartzstein, R. M. *The evaluation, diagnosis, and treatment of the adult patient with acute hypercapnic respiratory failure.* Retrieved March 12, 2018,

from
https://www.uptodate.com/contents/the-evaluation-diagnosis-and-treatment-of-the-adult-patient-with-acute-hypercapnic-respiratory-failure

Costanzo, L. (2013, July 24). *Physiology.* Retrieved March 12, 2018, from https://www.elsevier.com/books/physiology/costanzo/978-1-4557-0847-5

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

Notes