Ventilation – Perfusion Relationship

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Introduction

The lungs play an essential role in gas exchange between the blood and the external environment. They are composed of a system of airways that progressively branch out until reaching the respiratory bronchioles and alveoli, where gas exchange takes place. Most of the large airways and bronchioles form the conducting zone, whose main function is to transport air to the areas of alveolar exchange. This gas exchange occurs between the air contained in the alveoli and the blood flowing through the pulmonary capillaries.

For gas exchange to be efficient, the alveoli must be properly ventilated and perfused. Ventilation (V) refers to the flow of air that enters and exits the alveoli, while perfusion (Q) refers to the blood flow reaching the alveolar capillaries. The ventilation/perfusion ratio (V/Q) is used clinically to evaluate this balance, considering that different regions of the lung may present variations in ventilation and perfusion. Alterations in the V/Q ratio can negatively impact gas exchange and contribute to the development of hypoxemia.

This concept is fundamental in pulmonary physiology, as it describes how the amount of air reaching the alveoli is related to the blood flow in the pulmonary capillaries. Maintaining an adequate V/Q balance is crucial to ensure effective tissue oxygenation and proper carbon dioxide elimination. Deviations from this ratio are common in various pulmonary and systemic pathologies, highlighting the importance of understanding its mechanisms to design optimal ventilation and treatment strategies in clinical practice.

The ventilation/perfusion relationship and gas exchange at the pulmonary level are basic concepts that must be considered in all clinical scenarios. For each gas exchange unit, the partial pressure of oxygen and carbon dioxide (PO_2 and PCO_2) in alveolar blood are determined by the relationship between alveolar ventilation and blood flow ($V'A/Q'$) in each unit. Shunt and regions with low $V'A/Q'$ are two examples of $V'A/Q'$ mismatch and are the most frequent causes of hypoxemia. Diffusion limitation, hypoventilation, and low inspired PO_2 cause hypoxemia even in the absence of $V'A/Q'$ mismatch.
Unlike other causes, hypoxemia due to shunt responds poorly to supplemental oxygen. Gas exchange units with little or no blood flow (high $V'A/Q'$ regions) result in alveolar dead space and an increase in wasted ventilation, that is, less efficient carbon dioxide elimination. Due to the respiratory drive to maintain normal arterial PCO_2, the most frequent result of wasted ventilation is an increase in minute ventilation and respiratory workload, not hypercapnia.

Calculations of the alveolar-arterial oxygen tension difference, venous admixture, and wasted ventilation provide quantitative estimates of the effect of V′A/Q′ mismatch on gas exchange. The types of V′A/Q′ mismatch that cause impaired gas exchange typically vary with different lung diseases.

Gas exchange in The Lung

Oxygen (O_2) is essential for cellular metabolism in all multicellular organisms. In humans, the process begins with the lungs absorbing O_2 from the air. Simultaneously, carbon dioxide (CO_2), which is a metabolic waste product, must be continuously expelled through the lungs to maintain the body's internal balance. Blood plays a key role by delivering oxygen to tissues and carrying carbon dioxide back to the lungs for removal. Ventilation supports this process by supplying oxygen to the blood and removing carbon dioxide from it. For gas exchange to be efficient, there must be a close alignment between ventilation and blood flow in the lungs. Clinically, impaired gas exchange often results from a mismatch between these two processes—known as ventilation-perfusion ($\dot{V}A/\dot{Q}$) mismatch—where certain lung areas receive too much or too little air relative to their blood supply. This review focuses on how different types of $\dot{V}A/\dot{Q}$ mismatch impact the effectiveness of oxygen and carbon dioxide exchange. To understand this better, it first discusses gas exchange in an ideal lung without any mismatch, which closely resembles the situation in healthy individuals due to the minimal $\dot{V}A/\dot{Q}$ mismatch in normal lungs.

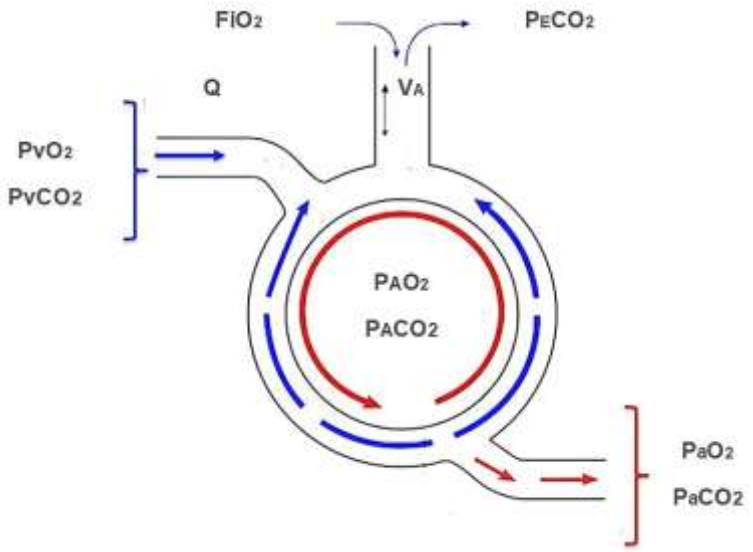


Figure 1: Model of single alveolus (gas exchanging unit) displaying the traditional nomenclature used to describe fractions (F), partial pressures (P) of gases (O_2 and CO_2) in venous blood (V), exhaled (E) gas, and alveolar gas (A). $\dot{Q}$ and $\dot{V}_A$ represent blood flow and ventilation, respectively.

Respiratory Physiology And Gas Transport

The blood gas transport system constitutes the final stage of respiratory function and requires the integration of the respiratory and circulatory systems (blood and cardiovascular system).

Oxygen Transport

Oxygen is transported physically dissolved in the blood and chemically combined with hemoglobin (Hb) inside red blood cells. Under normal conditions, with an arterial partial pressure of oxygen (PaO_2) close to 100 mmHg, the blood carries 0.3 ml of dissolved oxygen per 100 ml of blood per mmHg of pressure at 37°C (Henry's Law).

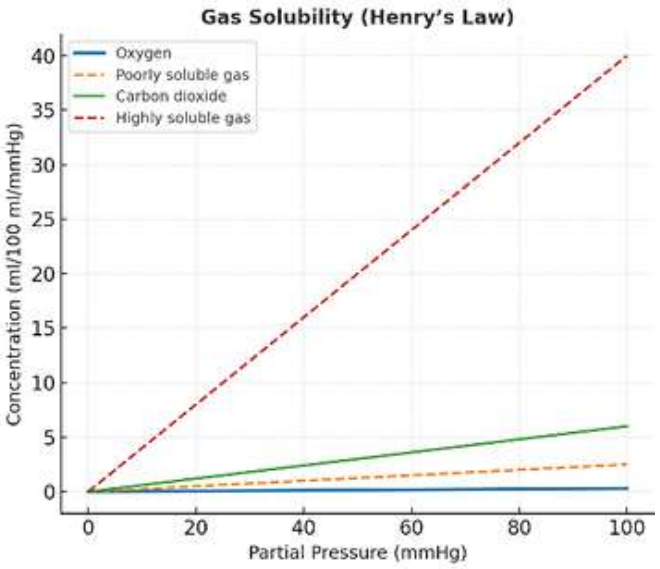


Figure 2**:** Henry's Law for gases physically dissolved in a liquid. There is a linear relationship between concentration and partial pressure, the slope of which defines physical solubility. Four examples are shown: O_2 in blue; poorly soluble gas in in orange (dashed line); CO_2 in green; highly soluble gas in red (dashed line). Solubility of CO_2 is more than 20 times that of O_2 in plasma/water. CO_2: carbon dioxide; O_2: oxygen.

Dissolved oxygen is physiologically significant, as its pressure determines the degree of hemoglobin saturation, the reversibility of oxygen binding, and the diffusion or movement of oxygen from blood to tissues.

Under normal conditions, each gram of hemoglobin binds to 1.34 ml of O_2. A person with 15 g of Hb per 100 ml of blood can transport approximately 20.1 ml of O_2 per 100 ml of blood. One way to express the proportion of hemoglobin bound to O_2 is the oxygen saturation percentage (SpO_2).

There is a relationship between plasma oxygen pressure (PO_2) and hemoglobin saturation, represented by the hemoglobin dissociation curve, which has a sigmoidal shape. The P50 is defined as the PO_2 required to achieve 50% hemoglobin saturation, and its approximate value is 26 mmHg. The higher the P50, the lower the affinity of Hb for O_2 (meaning a higher PO_2 is needed to saturate Hb at 50%). Various factors shift the hemoglobin dissociation curve to the right or left.

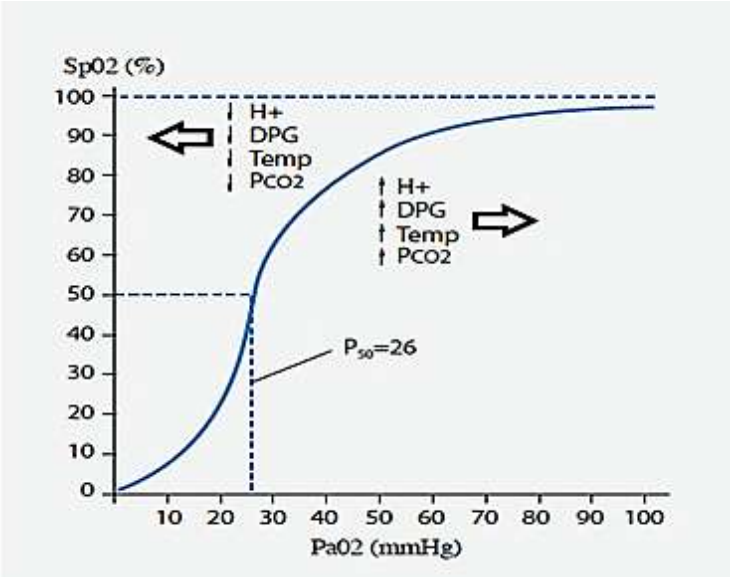


Figure 3**:** Hemoglobin Dissociation Curve. Relationship between the partial pressure of oxygen in plasma (PaO_2) and the hemoglobin saturation level (SpO_2). P50 indicates the partial pressure of oxygen at which hemoglobin is 50% saturated. The figure shows the factors that increase or decrease hemoglobin's affinity for oxygen. From reference 22.

Carbon Dioxide Transport

CO_2 is a final byproduct of aerobic metabolism and is produced inside the mitochondria.
In an adult, 200–250 ml of CO_2 is produced per minute on average. This CO_2 is transported from the cells into the blood and then reaches the lungs for elimination. A large portion of the CO_2 that reaches the blood diffuses into red blood cells; there, one fraction binds to the amino groups of hemoglobin, while another fraction reacts chemically with water to form bicarbonate and carbonate ions.

Therefore, CO_2 is transported in the blood in three forms:

1. Dissolved in plasma.
2. As bicarbonate and carbonate ions.
3. Combined with proteins (carbamino compounds).

CO_2 Dissociation Curve

The CO_2 dissociation curve is much more linear than the oxygen dissociation curve. This explains why the mixed arterio-venous oxygen pressure difference (PO_2) is typically greater (about 60 mmHg) than that of CO_2 (PCO_2), which is around 5–7 mmHg. The CO_2 dissociation curve depends on the degree of blood oxygenation to facilitate CO_2 release.

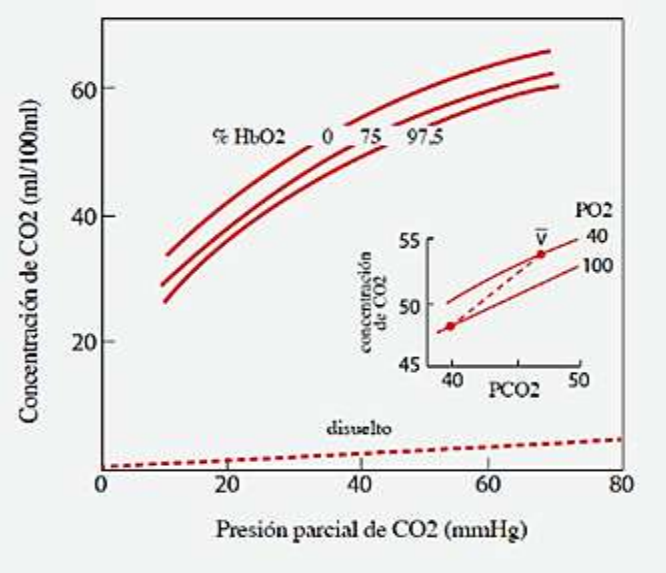


Figure 4: CO_2 Dissociation Curve in Blood with Different O_2 Saturation Levels. From reference 22.

Haldane Effect:

This phenomenon occurs in the pulmonary capillaries, where the high concentration of O_2 reduces the affinity of hemoglobin for CO_2, shifting the curve to the left. As a result, deoxygenated blood arriving in the lungs starts to bind oxygen and release CO_2. In this way, oxygenated blood has less buffering capacity than deoxygenated blood, and therefore, a reduced ability to carry bicarbonate ions.

Bohr Effect:

This occurs in the tissues and favors oxygen release by hemoglobin. It is caused by the protons (H^+) released from carbonic acid dissociation and the formation of carbamino compounds, which bind to specific amino acid residues in the globin chains, promoting oxygen release.

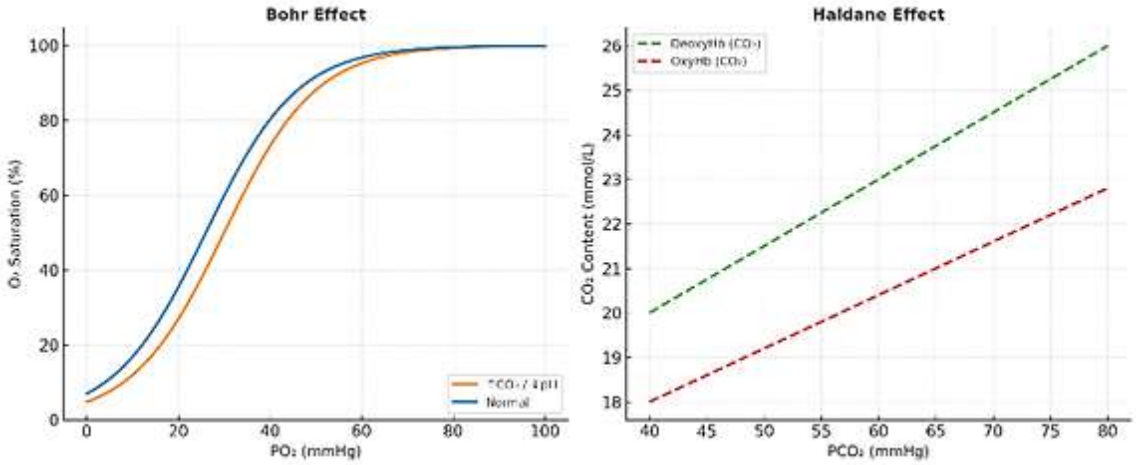


Figure 5: The Bohr and Haldane effects. (A) Bohr effect: the addition of CO_2 or a lower pH reduces O_2 affinity of Hb, shifting the ODC to the right (higher P50) and favoring O_2 release in tissue capillaries. Alkalosis has the opposite effects. (B) Haldane effect: the oxygenation of Hb reduces the CO_2 affinity of Hb, shifting the CO_2 dissociation curve to the right and favoring CO_2 release from Hb (a higher PCO_2 at a given CO_2 content of blood). Deoxygenation of Hb has the opposite effect. ODC, oxyhemoglobin dissociation curve.

Lung Structure

The lung is a specialized organ for gas exchange, whose primary function is to facilitate the movement of oxygen from air into blood and the removal of carbon dioxide in the opposite direction. Although it performs other functions, gas exchange is its essential process, which takes place at the alveolar-capillary membrane.

This exchange is made possible by the conductance of air and blood through the airways and pulmonary vasculature toward a vast alveolar capillary surface. In an adult, inhaled air travels through the trachea, which has a cross-sectional area of about 3 cm^2, and reaches the alveoli, which have a total surface area of approximately 140 m^2—equivalent to the size of a tennis court.

The pulmonary vascular system begins at the main pulmonary artery and repeatedly branches into arterioles and capillaries, which cover 85–95% of the alveolar surface. Between the gas compartment and the blood compartment lies the extremely thin alveolar-capillary membrane (about 1 μm thick), allowing for rapid gas diffusion.

The considerable volume of blood present in the alveolar capillaries slows down blood flow velocity, increasing the transit time of blood, typically between 0.25 and 0.75 seconds. This extended time favors efficient gas exchange between alveolar air and blood.

Alveolar–Capillary Membrane

Oxygen and carbon dioxide move between air and blood by simple diffusion, that is, from a region of high partial pressure to one of low partial pressure. Fick's law of diffusion states that the amount of gas that moves across a sheet of tissue is proportional to its surface area but inversely proportional to its thickness.

The alveolar-capillary membrane is extremely thin and has a surface area ranging between 50 m^2 and 100 m^2, making it highly suited for its role in gas exchange. Air reaches one side of the alveolar-capillary membrane via the airways, while blood reaches the other side via the pulmonary blood vessels.

Key characteristics:

- A large portion of this surface is extremely thin (0.2–0.3 μm).
- The total surface area is vast, estimated at 50–100 m^2.
- This large surface is due to the approximately 500 million alveoli.
- The membrane is so thin that significant increases in capillary pressure can damage it.

Airways and Air Flow

The airways consist of a series of branching tubes that become narrower, shorter, and more numerous as they extend deeper into the lungs. These are divided into a conducting zone and a respiratory zone.

- The anatomical dead space volume is approximately 150 ml.
- The volume of the alveolar region is around 2.5 to 3 liters.
- Gas movement in the alveolar region occurs primarily by diffusion.

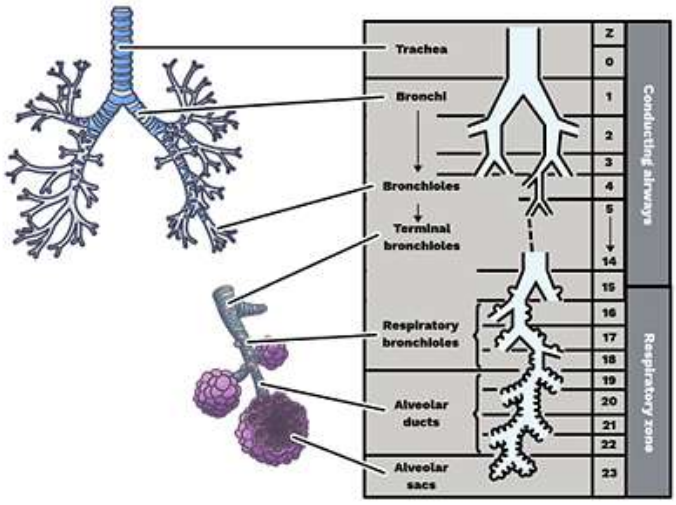


Figure 6: Idealization of Human Airways According to Weibel. Note that the first 16 generations (Z) make up the conducting airways, and the last seven comprise the respiratory zone (or transitional and respiratory zones).

Vessels and Blood Flow

The pulmonary blood vessels are a network of tubes that branch out from the pulmonary artery to the capillaries and then return via the pulmonary veins.

Initially, the arteries, veins, and bronchi run together, but as they approach the periphery of the lung, the veins separate and pass between the lobules, while the arteries and bronchi continue toward the center of each lobule. The capillaries form a dense network in the alveolar walls.

Key facts:

- The entire cardiac output from the right heart flows into the lungs.
- The diameter of the capillaries is approximately 7 to 10 μm.
- The thickness of most capillary walls is less than 0.3 μm.
- Blood spends about 0.75 seconds in the capillaries during its transit.

Pulmonary Circulation and Ventilation–Perfusion Relationship

Pulmonary Circulation

Pulmonary circulation refers to the path of venous blood from the right ventricle (RV) through the pulmonary artery, then toward the alveolar territory, where it becomes oxygenated. The oxygenated blood then returns to the left atrium (LA) via the pulmonary veins, entering the systemic circuit.

Although the pulmonary and systemic circulations differ significantly in terms of blood volume, vascular resistance, flow characteristics, and pressures, they share a similar anatomical and physiological organization.

Both systems include:

- A receiving chamber (atrial).
- A pumping chamber (ventricles).
- A vascular network responsible for distribution.

Due to their functional complementarity and series configuration, there is a strong interdependence between both circulations. Any alteration in one circuit can affect the other. Therefore, from a physiological perspective, the general circulation (including both pulmonary and systemic) must be understood as a single integrated system, interconnected through multiple conduits and coordinated by the action of the four cardiac chambers.

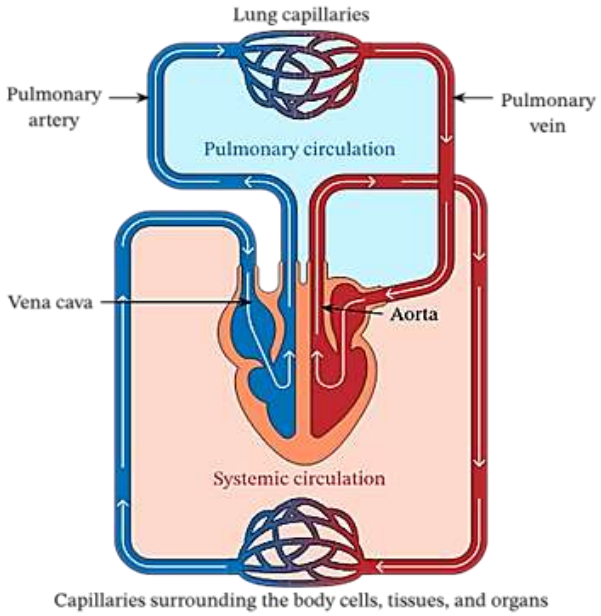


FIGURE 7. OpenStax. Figure 20.23: Pulmonary Circuit [image]. In: Anatomy and Physiology 2e [Internet]. Houston (TX): OpenStax; 2013

Functions of Pulmonary Circulation

- Gas exchange.
- Filtration.
- Nourishment of pulmonary parenchyma.
- Production and metabolism of humoral substances.

The V/Q ratio is not uniform throughout the lung. The pressure that keeps alveoli open—transpulmonary pressure—is determined by the difference between alveolar pressure and pleural pressure.

- At the lung bases, pleural pressure becomes less negative, resulting in smaller alveoli with greater compliance, which leads to relatively greater ventilation in those regions.
- Gravity creates a higher hydrostatic pressure in the blood descending to the bases and a pressure drop in the blood rising to the apices.

Taking an upright individual as a reference, West et al. divided the lung into three zones, based on the relationship between alveolar pressure and intravascular pressures. Later, Hughes et al. proposed a fourth zone at the lung bases.

Definitions: Shunt, Ventilation/Perfusion Mismatch, and Dead Space

Shunt, ventilation-perfusion mismatch (V/Q), and dead space refer to specific abnormalities of lung ventilation and perfusion.

• **Shunt:** represents the scenario where some regions of the lungs receive blood flow but no ventilation, resulting in a decrease in oxygen levels in the blood. The presence of shunt can be observed in ARDS patients, who typically exhibit extensive consolidations on computed tomography (CT) scan. From a pathophysiological perspective, there is a notable reduction in functional residual capacity (FRC); this reduction can be effectively treated with PEEP to restore end-expiratory lung volume (EELV).

• **V/Q mismatch:** is an imbalance between ventilation and blood flow. This ratio can be low (shunt-like) or high (dead space-like). Shunt-like mismatch results from reduced ventilation relative to blood flow, leading to decreased oxygenation. Dead space-like mismatch occurs when ventilation exceeds blood flow, leading to inadequate carbon dioxide removal.

• **Dead space:** refers to the regions of the respiratory system which do not participate in gas exchange. Total dead space (also known as physiological dead space) is the sum of the dead space of the airways and alveolar dead space. While the former is physiological, the latter occurs when alveoli are ventilated but not perfused due to pathological conditions, such as pulmonary embolism.

In summary, shunt, V/Q mismatch, and dead space are interrelated concepts that describe different aspects of impaired gas exchange in the lungs. Understanding these principles is crucial for the diagnosis and the management of respiratory disorders.

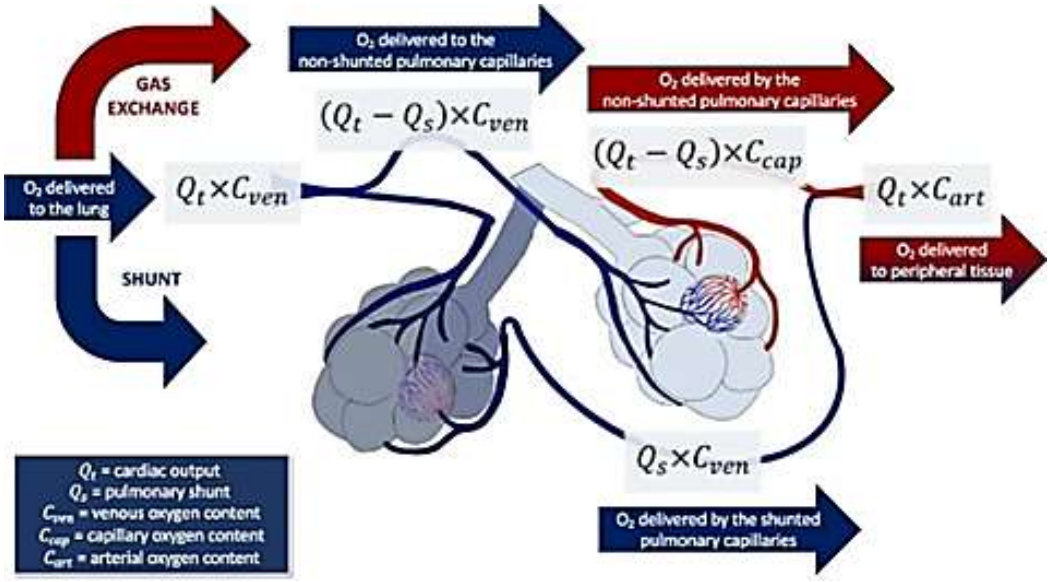


Figure 8: Graphical Abstract of Shunt. From reference 3

Ventilation

Inspiration occurs when the respiratory muscles, especially the diaphragm, contract and cause expansion of the thorax. This increase in thoracic volume allows air to enter passively through the tracheobronchial tree until it reaches the alveolar-capillary membrane, which spans approximately 70 m² of respiratory bronchioles and alveoli.

The concept of compliance refers to the capacity of the respiratory system to change its volume in response to a change in pressure (ΔV/ΔP). When referring to the compliance of the entire lung-thorax system, it is called respiratory compliance.
This parameter includes both:

- Lung compliance, which depends on the elastic recoil of connective tissue and alveolar surface tension.
- Chest wall compliance, which is determined by the musculoskeletal structure and the amount of adipose tissue in the thorax and abdomen.

Gravity affects the distribution of ventilation, as alveoli located in the lower (dependent) regions are compressed by the weight of the overlying lung tissue. As a result, these alveoli are less distended than those in the upper (non-dependent) regions and lie in a steeper part of the compliance curve.

During inspiration, this characteristic leads to a greater volume increase in dependent alveoli, meaning ventilation is more efficient in these areas compared to non-dependent lung regions.

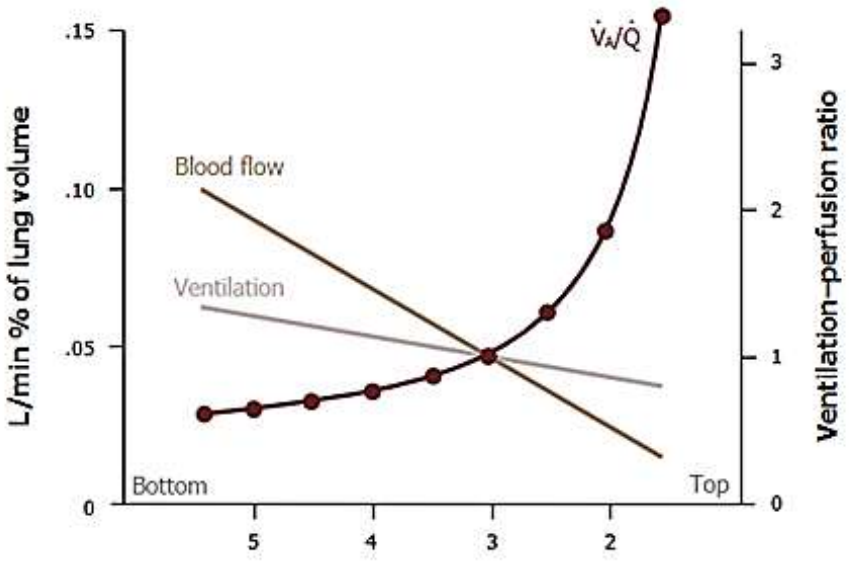


Figure 9: Distribution of V/Q. Andrew Binks (Virginia Tech Libraries' Open Education Initiative)

Pulmonary Compliance and Closing Capacity

Pulmonary compliance is greater when the lungs are near the functional residual capacity (FRC), which is the lung volume present at the end of a normal expiration. However, this compliance decreases at the extremes of lung volume, when alveoli are overdistended or compressed.

Due to the effect of gravity, the small airways in the lower lung regions may collapse during expiration. This phenomenon occurs when lung volume decreases to a level known as the closing capacity (CC).

- In young and healthy individuals, FRC is greater than CC throughout the respiratory cycle, preventing airway collapse.
- However, with advanced age or in the presence of pulmonary disease, CC may exceed FRC, causing small airway closure during expiration.

This results in an intrapulmonary shunt that reduces arterial oxygen partial pressure (PaO_2).

Perfusion

Gravity also significantly influences the distribution of pulmonary blood flow. In the upright position, capillary pressure in the lower lung regions is approximately 30 cmH_2O higher than in the upper regions, resulting in greater perfusion in the basal areas.

In addition to gravity, other factors affect pulmonary blood flow, including:

- The relationship between alveolar and vascular pressures (known as West zones).
- The tone of arteriolar smooth muscle, and Vascular conductance.

These factors help explain why, in the prone position, the dorsal regions of the lung tend to receive greater perfusion.

The pulmonary circulation is designed to facilitate efficient gas exchange. The mean pulmonary arterial pressure (mPAP) must be low enough to prevent fluid accumulation in the alveolar-capillary membrane, yet high enough to ensure adequate blood flow to less dependent regions of the lung.

During increased cardiac output (e.g., during exercise), capillary recruitment and dilation prevent a significant rise in mPAP.

Pulmonary vascular resistance (PVR) is lowest near the FRC, but increases at higher lung volumes due to capillary compression caused by alveolar distension.

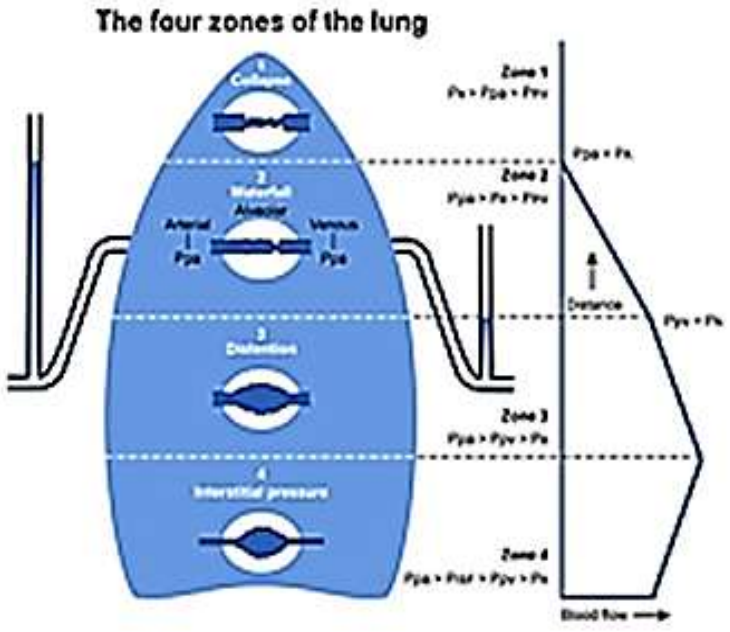


FIGURE 10. Regional Differences in Pulmonary Blood Flow Distribution Representation of West zones (I–III) and Hughes' zone (IV) in an upright patient. In zone I, there is no blood flow because alveolar pressure (PA) exceeds both arterial (Pa) and venous pressure (Pv). In zone II, blood flow depends on the Pa–PA gradient. In zone III, flow depends on the Pa–Pv gradient. In zone IV, interstitial pressure (Pin) adds to PA, which again reduces blood flow. From reference 24.

Ventilation–Perfusion Relationship

To fulfill its primary function of gas exchange, the lung requires two essential components:

- Adequate ventilation (V).
- Optimal perfusion (Q).

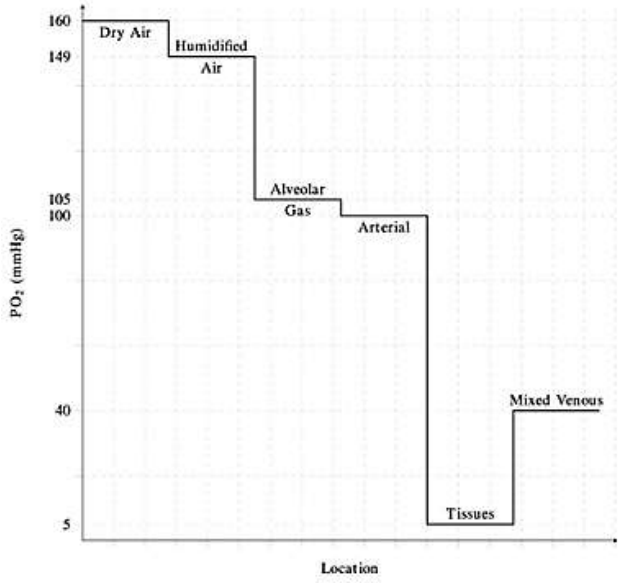
The interaction between these two parameters determines the V/Q ratio in different regions of the lung, which is crucial for understanding pulmonary physiology. Although the concept of V/Q ratio appears simple, it is influenced by various physical phenomena that can complicate its interpretation.

Considering that the V/Q ratio varies according to the West zones, the average V/Q ratio is approximately 0.8 to 1, which is considered normal, at least in terms of volume units.
In general, any alteration in ventilation or perfusion has the following characteristics:

- When the V/Q ratio deviates from its normal value, gas exchange is impaired.
- If the imbalance is due to decreased ventilation or increased perfusion, the V/Q ratio will be < 1.
- If ventilation is absent, the ratio will be zero.
- Conversely, if the imbalance is due to decreased perfusion or increased ventilation, the V/Q ratio will be > 1.
- If perfusion is absent, the ratio approaches infinity.

To maintain the V/Q ratio within normal ranges, compensatory mechanisms must adjust one parameter when the other changes. For example:

- If ventilation increases, perfusion should also increase.
- If perfusion increases, a physiological compensation should increase ventilation.
- The same applies in reverse: if ventilation decreases, perfusion should decrease, and vice versa.



Figures 11: Oxygen Cascade Representation of the progressive decline of oxygen from the atmosphere to the mitochondria.

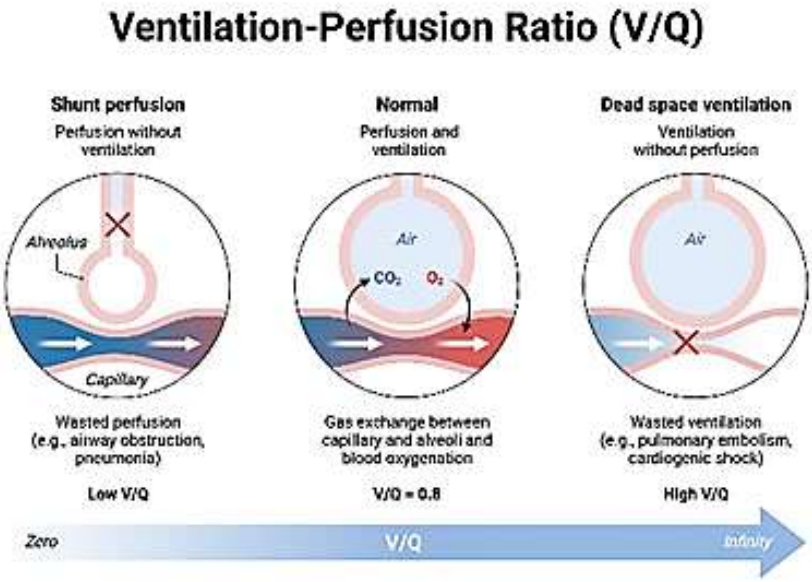


Figure 12: Ventilation/Perfusion Relationship. V: Ventilation. Q: Perfusion. First diagram: Ventilation defect → no gas exchange Second diagram: Normal V/Q → capillary and alveolar gases are equal Third diagram: Perfusion defect → no gas exchange

Causes of Arterial Hypoxemia

Cause of Hypoxemia	PAO_2	A–a Gradient	Response to Increased FiO_2
Diffusion limitation	Normal	Increased	Improves
Hypoventilation	Decreased	Normal	Improves
Decreased inspired PO_2 (PIO_2)	Decreased	Normal	Improves
Low V′A/Q′ ratio	Locally reduced	Increased	Improves
Shunt	Locally reduced	Increased	Minimal improvement

PAO_2: Alveolar oxygen partial pressure; A–a Gradient: Alveolar–arterial oxygen tension difference; PaO_2: Arterial oxygen partial pressure; FiO_2: Fraction of inspired oxygen; PIO_2: Partial pressure of inspired oxygen; V′A/Q′: Alveolar ventilation/perfusion ratio

Table 1: Five causes of hypoxemia.

V/Q Mismatch Alterations

Imbalances in the ventilation–perfusion (V/Q) ratio are the main mechanism responsible for gas exchange impairment and are therefore the leading cause of hypoxemia.

V/Q mismatch can lead to the following patterns:

1. Perfused but poorly ventilated areas (V/Q < 1)

The most extreme case is an intrapulmonary shunt, where alveolar units are not ventilated but are still perfused. This means that deoxygenated venous blood mixes with oxygenated arterial blood.

Characteristics:

- Presents with hypocapnia.
- Increased minute ventilation.
- Elevated alveolar–arterial oxygen gradient.
- 100% oxygen therapy produces minimal PaO_2 improvement.

Intrapulmonary shunting is found in common pathological conditions such as:

- Cardiogenic pulmonary edema.
- Pneumonia.
- Acute respiratory distress syndrome (ARDS).

2. Well-ventilated but poorly perfused areas (V/Q > 1)

This is known as dead space. If the increase in dead space is mild or moderate, wasted ventilation can be compensated by increasing minute ventilation, ensuring that alveoli with adequate perfusion continue to receive sufficient ventilation. In this case, arterial gas values remain normal, but at the cost of increased energy expenditure for ventilation. In healthy individuals, the normal physiologic dead space is 20% to 35% (2.2 ml/kg IBW) of tidal volume at rest.

Increased dead space can result from:

- Functional or anatomical reduction in vascular bed (e.g., pulmonary embolism, interstitial fibrosis, emphysema).
- Enlarged airspaces that only contact capillaries peripherally (e.g., bullae, air cysts).

When dead space becomes extensive, it can lead to hypoxemia and CO_2 retention.

3. V/Q impairment in asymptomatic regions

There is a third condition in which both ventilation and perfusion are impaired.

This occurs in severe scenarios like ARDS, leading to profound V/Q mismatches and compromised gas exchange:

- Hypoxemia in both early and late stages
- Increased $PaCO_2$ in later stages
- Elevated respiratory effort and minute ventilation
- Low or normal $PaCO_2$ in early stages due to respiratory alkalosis.
- Alveolar atelectasis from surfactant loss and edema worsens the shunt effect.

Effect of Ventilation–Perfusion Mismatch on Overall Gas Exchange

Although regional differences in gas exchange occur naturally in the lungs, it is important to assess whether uneven ventilation and blood flow affect the overall efficiency of pulmonary gas exchange—that is, the lung's ability to uptake oxygen (O_2) and eliminate carbon dioxide (CO_2).

A lung with ventilation–perfusion mismatch is less effective at transferring O_2 and CO_2 compared to a lung that is uniformly ventilated and perfused, assuming all other factors are equal.
If the same total amount of gas is exchanged (as determined by the body's metabolic demands), the mismatched lung will:

- Have lower arterial PO_2
- Have higher arterial PCO_2

This highlights the critical importance of a well-matched V/Q ratio for maintaining adequate oxygenation and CO_2 elimination.

Conclusions

Multiple factors can impair gas exchange in critically ill patients.
However, ventilation–perfusion (V/Q) mismatch is the most important pathophysiological mechanism involved in the majority of acute pulmonary conditions.

To optimize gas exchange, several strategies are used:

- Supplemental oxygen.
- Mechanical ventilation with PEEP.
- Proper patient positioning.
- Careful intravenous fluid management.

A deep understanding of the physiological basis of gas exchange disorders is essential to guide appropriate treatment.

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