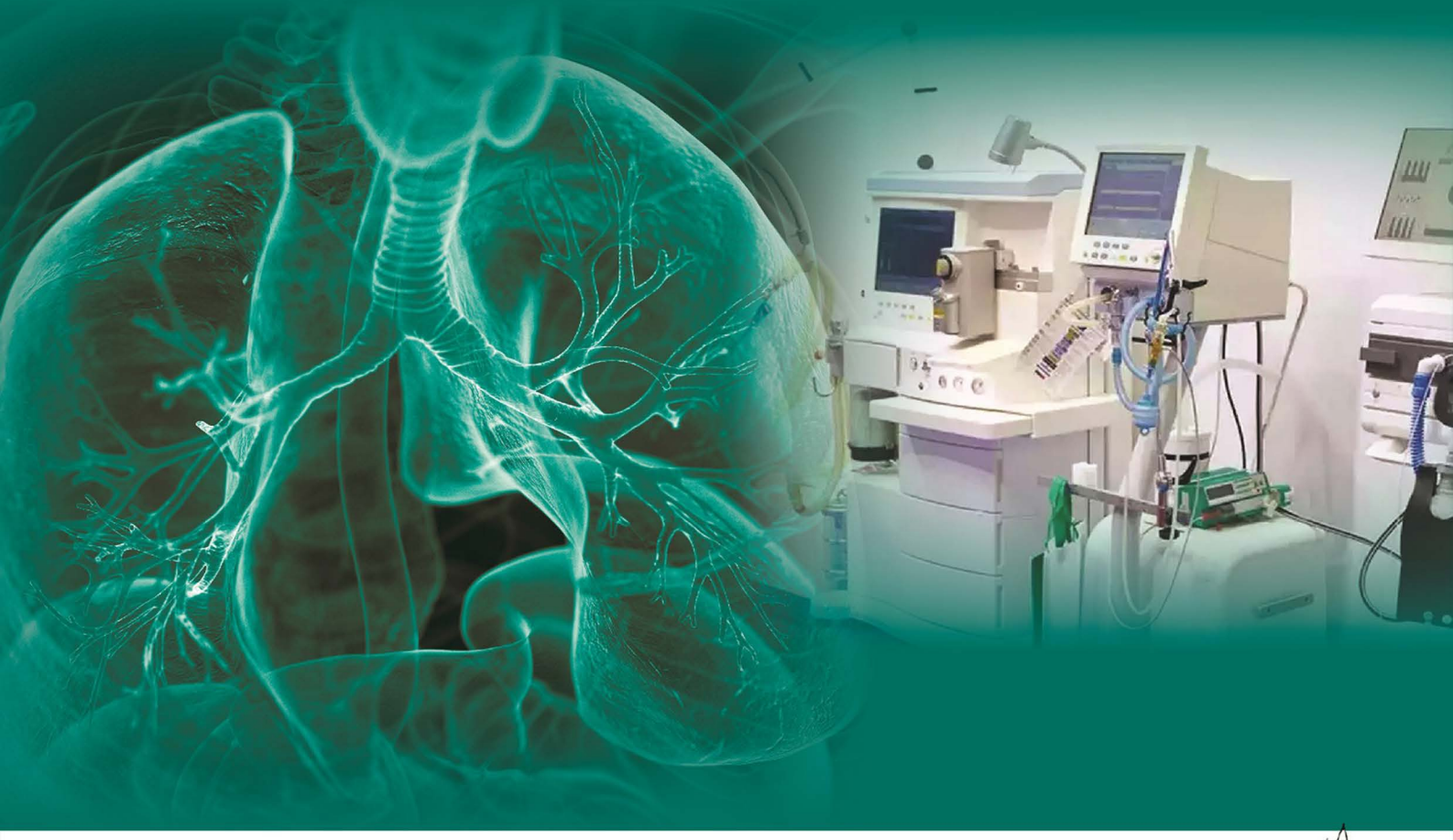
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Textbook of Mechanical Ventilation



Editors
Atul Prabhakar Kulkarni
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Subhal Bhalchandra Dixit

Foreword
Shirish Prayag

JAYPEE

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CHAPTER 6

Physiology of Gas Exchange

Sanjoli Singhal, Keerthana K, Vijaya Patil

SUMMARY

Gas exchange occurs in lungs between alveoli and pulmonary blood where the process involves uptake of oxygen (O_2) and release of carbon dioxide (CO_2). For efficient gas exchange alveolar ventilation should match with pulmonary circulation. Quality of alveolar–capillary membrane, surface area available for gas exchange, and partial pressure of oxygen in alveolar air are important determinants of oxygen diffusion. Gas exchange also occurs at tissue level between systemic capillaries and cells. Here oxygen is released to cells and CO_2 is picked up. Oxygen content of blood, adequacy of perfusion, and functioning mitochondria are crucial for cellular respiration. Energy in the form of adenosine triphosphate (ATP) is consumed for act of breathing, but gas exchange at both levels occurs by simple diffusion across pressure gradient.

INTRODUCTION

The four processes of gaseous exchange, i.e., O_2 delivery, CO_2 excretion, ventilation and perfusion (V/Q) matching, and diffusion maintain normal partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in the arterial blood. The concept of partial pressure is significant because the diffusion of O_2 and CO_2 molecules across the alveolar capillary membrane occur as a result of their partial pressure gradients, and the diffusion continues until their partial pressures are equal.

ALVEOLAR GAS EQUATION

The key factor which determines the rate of diffusion of oxygen through the alveolar capillary membrane is the partial pressure gradient of O_2.[1-3] With the use of alveolar gas equation (AGE) we can measure this partial pressure of oxygen in the alveoli.

The AGE states:

$$PAO_2 = FiO_2 (P_{atm} - P_{H_2O}) - PaCO_2/RQ$$

Where,

- *PAO_2:* Partial pressure of oxygen in the alveoli
- *FiO_2*: Fraction of inspired oxygen (for dry air it is 20.93%)
- *P_{atm}*: Atmospheric pressure (at sea level it is 760 mm Hg)
- *P_{H_2O}*: Water vapor pressure of fully humidified inspired air (47 mm Hg)
- *$PaCO_2$*: Partial pressure of CO_2 in arterial blood, which is 40 mm Hg
- *RQ*: Respiratory Quotient (volume of CO_2 eliminated from the lungs/volume of O_2 consumed from alveolar gas, which is taken as 0.8 for a balanced diet).

The three essential variables of this equation which affect the PAO_2 are:

1. FiO_2
2. P_{atm}
3. Alveolar ventilation

CLINICAL SIGNIFICANCE

- For a patient breathing room air at sea level, the alveolar pO_2 becomes:

  $0.21 \times (760 - 47) - (40/0.8)$, which is approximately 100 mm Hg.

  When we increase the FiO_2 to 100%, the PAO_2 becomes:

  $1 \times (760 - 47) - (40/0.8) = 663$ mm Hg

  Hence, increasing FiO_2 will increase the PAO_2 and result in a higher O_2 diffusion gradient across the alveolar capillary membrane.
- At higher altitudes the P_{atm} decreases, hence for any given FiO_2 there is a lower PAO_2 in the alveoli.

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For example, at 10,000 feet the P_{atm} is about 530 mm Hg. Putting these values in our equation:

$$0.21 \times (530 - 47) - (40/0.8)$$

So, our PAO_2 at that level will be around 51 mm Hg, thus decreasing the diffusion gradient.

Whereas in hyperbaric chamber at 2 P_{atm}, AEG will become:

$$0.21 \times (1520 - 47) - (40/0.8)$$

So, PAO_2 will be approximately 259, increasing the diffusion gradient.

- $PaCO_2$ is inversely proportional to alveolar ventilation. Hypoventilation leads to increase in $PaCO_2$, thus decreasing PAO_2 leading to hypoxemia.

  Applying this concept in a clinical scenario:
  In a postoperative patient with opioid overdose, residual neuromuscular blockade, etc., hypoventilation sets in leading to an increased $PaCO_2$. For example, if $PaCO_2$ becomes 70 mm Hg, using same equation PAO_2 will be:

$$0.21 \times (760 - 47) - (70/0.8) = 62.3 \text{ mm Hg.}$$

Thus, hypercarbia will decrease the PAO_2 and result in a lower O_2 diffusion gradient across the alveolar capillary membrane.

The AGE is also used to estimate the Alveolar–arterial gradient known as the A–a gradient.

$$\text{A–a gradient} = PAO_2 - PaO_2$$

This gradient helps us identify the cause of hypoxemia.

The normal A–a gradient increases with age and value ranges from 5–20 mm Hg (10 mm Hg) **(Table 1)**.[3]

OXYGEN CASCADE

The oxygen cascade describes the movement of oxygen down its partial pressure gradient from air to mitochondrion **(Flowchart 1)**.

TABLE 1: Factors affecting A-a gradient.

Increased alveolar–arterial gradient	***Normal alveolar–arterial gradient***
V/Q (ventilation and perfusion) mismatch, ARDS (acute respiratory distress syndrome), pneumonia, and atelectasis	Hypoxic mixtures
Right-to-left shunt—pulmonary arteriovenous malformations and intracardiac shunts	Low barometric pressure (high altitude)
Severe diffusion impairment—end-stage pulmonary fibrosis	Alveolar hypoventilation leading to hypercarbia-airway obstruction, neuromuscular disorders, and drug-induced respiratory depression

ANATOMY OF BLOOD–GAS INTERFACE

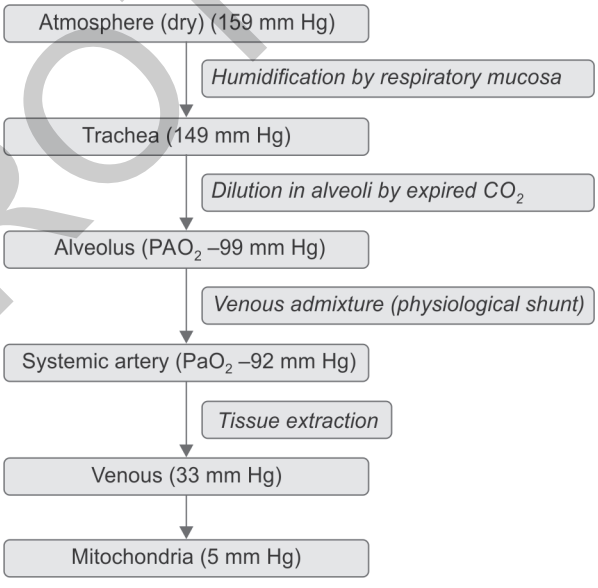
The blood–gas barrier (alveolar capillary membrane) is a thin unit with a surface area of around 50–100 m^2 in a normal adult **(Fig. 1)**.

The thickness of this membrane being 0.2–0.6 µm.[1]

Alveolar–capillary membrane is composed of:

- Layer of surfactant lining the alveolar epithelium
- The alveolar epithelium
- Epithelial basement membrane
- Interstitial space
- Capillary basement membrane
- Capillary endothelial membrane.

Flowchart 1: Oxygen cascade.



(PaO_2: partial pressures of oxygen in the arterial blood; PAO_2: partial pressure of oxygen in the alveoli)

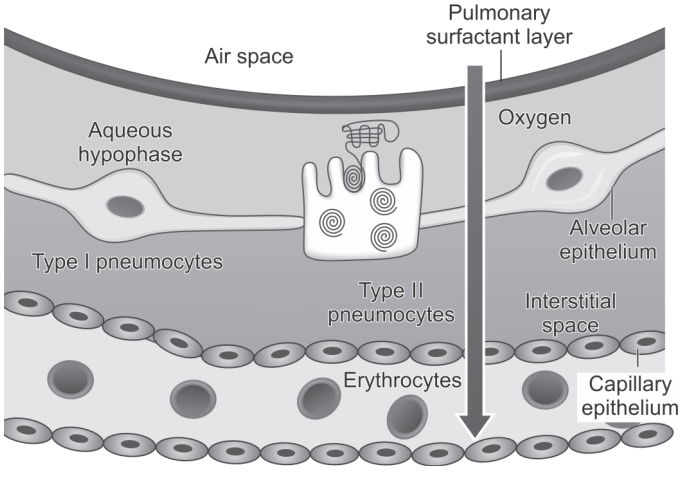


Fig. 1: Blood–gas interface.

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Pulmonary gas exchange occurs at this blood gas interface, i.e., alveolar–capillary membrane. The movement of oxygen and carbon dioxide across this interface occurs by simple diffusion across pressure gradient.

MOLECULAR BASIS OF DIFFUSION OF GASES

The movement of gas across any tissue is explained by "Fick's law of diffusion" **(Fig. 2)**.[1,2,4] According to this law, the net transfer of a gas (Vgas) through any membrane depends upon:

- The net difference between the partial pressure (pressure exerted by dissolved form of gas) of the two gases across the membrane (P1–P2)
- The surface area of the membrane (A)
- The thickness of the membrane (T)
- Diffusion coefficient of the gas (D) which is directly proportional to the solubility of the gas (Sol) and inversely proportional to the square root of molecular weight of the gas (MW).

$$\dot{V}_{gas} \propto A/T \cdot D \cdot (P_1 - P_2)$$
$$D \propto Sol/\sqrt{MW}$$

The above equation explains the difference in rate of transfer of gases and their implications in various clinical scenarios.

Comparing two gases such as oxygen and carbon dioxide for example, despite both of them having similar molecular weight, CO_2 diffuses 20 times more than O_2. This is attributed to its higher solubility coefficient. Hence in clinical conditions where there is an impaired diffusion such as in pulmonary fibrosis, the diffusion of oxygen gets affected more than CO_2 and hence, these patients more likely experience type 1 respiratory failure.

CONCEPT OF DIFFUSION AND PERFUSION LIMITATION

After the gas crosses the respiratory membrane, it enters the pulmonary capillary and causes a rise in partial pressure of that particular gas in the blood. If that gas binds to hemoglobin (Hb), the rate at which the partial pressure will increase in the blood will depend on the strength of the bond formed between the gas and Hb, i.e., its availability as dissolved form in blood (as pressure is exerted by dissolved gas). Stronger is the bond, lesser is the gas in dissolved form and lower is the rise in partial pressure.[5]

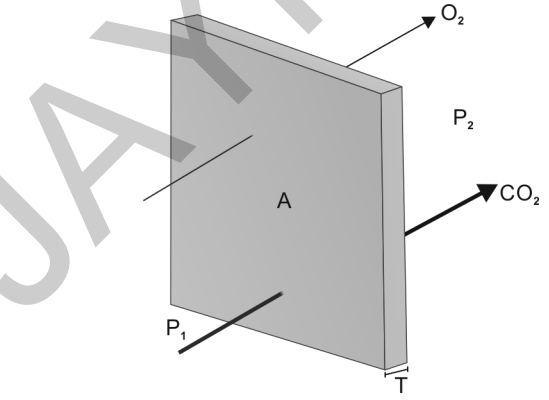


Fig. 2: Fick's Law of Diffusion. [A: area; ($P_1 - P_2$): difference in partial pressures; T: thickness]

For instance, carbon monoxide (CO) has very high affinity for Hb, 200–300 times more than with oxygen and forms a very strong bond. Hence when the gas moves from alveoli to pulmonary capillary, there is no increase in partial pressure of the gas and it continues to move freely across the membrane. Hence, CO uptake from alveoli to blood is said to be diffusion-limited, i.e., the transfer of CO depends upon the membrane properties and not by the blood flow. This is the reason why diffusing capacity of lung for CO (DLCO) is used to check for quality of alveolar–capillary membrane in various parenchymal and nonparenchymal lung diseases.[6]

On the other hand, there is another set of gases whose transfer depends on the amount of blood available and not on the diffusion properties of the membrane.

For example, nitrous oxide (N_2O) does not have any affinity for Hb[1], so as soon as it reaches the blood the partial pressure of the blood rises quickly and this increase in the partial pressure quickly equilibrates with alveolar partial pressure and limits its further absorption. Hence, it is said to be a perfusion-limited gas.

Oxygen shows both diffusion and perfusion limitations in different scenarios. Normally, it behaves like a perfusion-limited gas like nitrous, but under abnormal circumstances it shows some diffusion limitation as well.

When the red blood cell (RBC) moves across the pulmonary capillary, oxygen diffusion across the alveolar capillary membrane into the blood causes a rise in partial pressure of oxygen (pO_2) in the blood thus reaching an equilibrium with the alveolar partial pressure. Under normal circumstances where the RBC takes around 0.75 seconds to traverse the pulmonary capillary (pulmonary transit time), this equilibrium is reached just after 0.25 seconds.[1,2] After this, there is no net movement of oxygen across the membrane **(Fig. 3)**.

However, there are certain conditions where this equilibrium between the alveolar capillary membrane is not achieved until the RBC reaches the end of the pulmonary capillary. This occurs in conditions where there is thickening of alveolar capillary membrane resulting in delay in the time to achieve equilibrium leading to hypoxemia.

There are other conditions which decrease the RBC transit time in the pulmonary capillary. For example,

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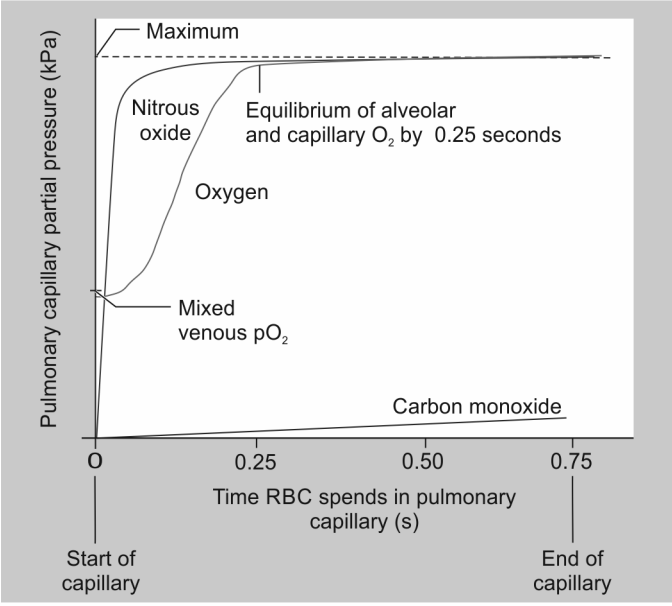


Fig. 3: Equilibrium of various gases across alveolar capillary membrane. (PO_2: partial pressure of oxygen; RBC: red blood cell)

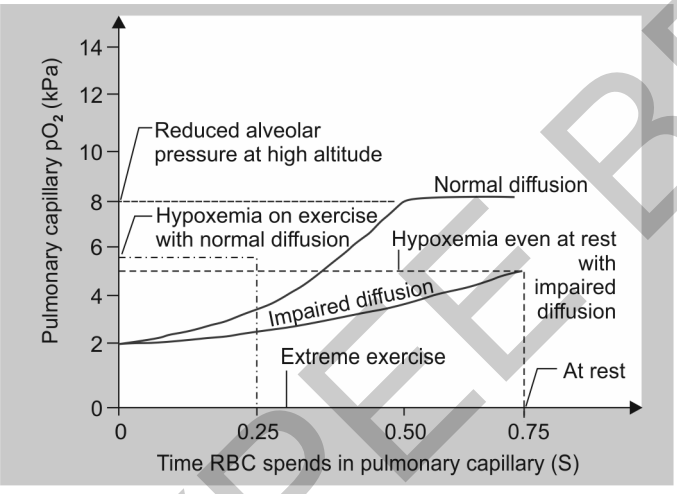


Fig. 4: Normal versus impaired diffusion. (PO_2: partial pressure of oxygen; RBC: red blood cell)

during strenuous exercise, the time spent by the RBC in the pulmonary capillary may reduce to 0.25 seconds or less. In patients with an intact alveolar capillary barrier, this does not affect the oxygen diffusion, but if the alveolar–capillary membrane is compromised this can lead to diffusion limitation resulting in hypoxemia and reduced exercise tolerance **(Fig. 4)**.

OXYGEN TRANSPORT

Around 2% of oxygen gets transported as dissolved form in the blood and the other 98% is bound to Hb.

Dissolved Form

The oxygen which is present as dissolved form follows Henry's Law.

Each 100 mL of blood contains 0.003 mL of O_2 for each mm of pO_2.

Using the above concept for arterial blood, in normal person the amount of O_2 carried in 100 mL blood becomes 0.3 mL.

Reaction with Hemoglobin

Apart from this dissolved form, a major proportion of oxygen gets carried along with Hb. The reaction of O_2 with Hb can be explained by oxygen dissociation curve (ODC) **(Fig. 5)**.

This ODC depicts the relationship between oxygen saturation and oxygen tension and explains how the loading and unloading of oxygen take place at different sites in the body.

Four oxygen molecules bind to each Hb (heme group) molecule in a reversible fashion.

This binding with Hb is termed as cooperative binding, i.e., with each successive binding the affinity of Hb to oxygen increases. This explains the sigmoid nature of the ODC.

The curve has a flat upper portion and a steep lower portion.

The flat upper portion implies that even if the pO_2 falls slightly, the oxygen saturation will not change significantly; hence, the loading of oxygen in the alveolar end will be least affected. But in a patient in which the PaO_2 is already low, for example in any pathological respiratory disease or say in a critically ill patient, the pO_2 lies in the steep part of the curve; hence, any further fall in PO_2 will result in a significant decrease in the oxygen saturation thus causing tissue hypoxia.

The steep part of the ODC best explains the O_2 offloading at the peripheral tissues, i.e., when pO_2 is low there is a significant fall in the saturation, hence favoring O_2 unloading.

It is the p50 value in the ODC which best describes the right or the left shift of the curve.

Right shift of the curve signifies more unloading so all the conditions where there is increased requirement of O_2 (acidosis, exercise, increased temperature, etc.) cause rightward shift favoring more O_2 to be delivered to the peripheral tissues. This enhanced unloading of oxygen in metabolically active peripheral tissues is explained by "Bohr effect."

Bohr effect is the reduced affinity of Hb to oxygen secondary to increase in pCO_2 or a decrease in pH.[1,7]

This effect is seen in peripheral metabolically active tissues where due to the increased muscle activity, the local pH decreases along with the increased CO_2. This causes a

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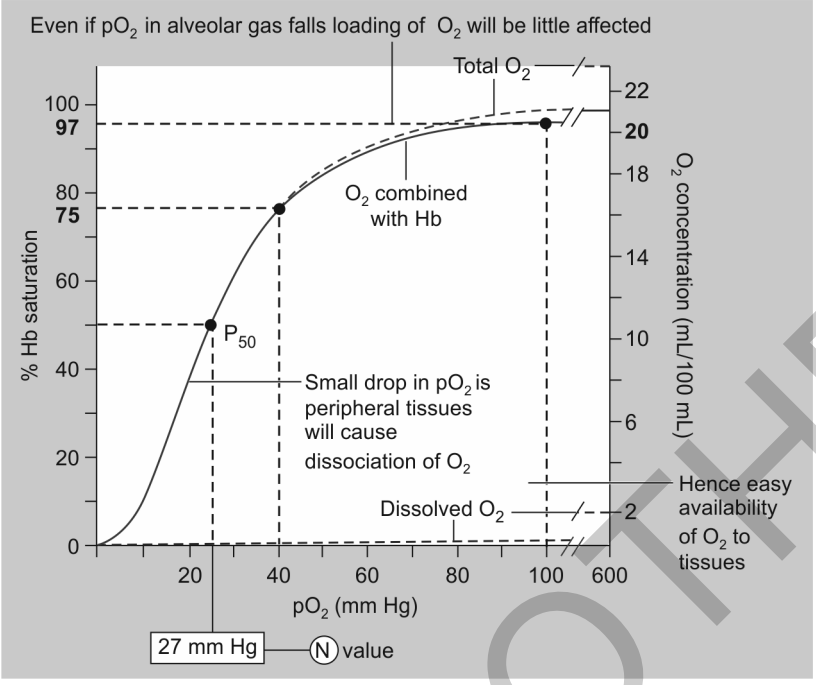


Fig. 5: Oxygen dissociation curve. (Hb: hemoglobin; pO_2: partial pressure of oxygen)

rightward shift of the ODC, hence increasing the availability of oxygen to these tissues.

DOUBLE BOHR EFFECT

This explains gaseous exchange at the level of placenta.

It is occurrence of Bohr effect twice; one at fetal end and other at the maternal end.

The deoxygenated blood which is carried by the umbilical arteries from the fetus has a high CO_2 content. On reaching the placenta this CO_2 diffuses into maternal blood. This decrease in the CO_2 content of the fetal blood makes it relatively alkaline, shifting the ODC toward left, hence favoring more oxygen uptake by fetal Hb. On the other hand, the maternal blood gains CO_2 making the blood more acidic and shifting the curve toward the right and hence causing more offloading of oxygen from the maternal blood.[7] This phenomenon is known as double Bohr effect. This effect aids in better transfer of oxygen from the maternal to fetal side thus improving fetal oxygenation.

CARBON DIOXIDE TRANSPORT

Carbon dioxide unlike oxygen is carried differently in three ways: in dissolved form in blood, as bicarbonate, and as carbamino compounds.

The solubility of CO_2 is about 20 times more that of oxygen (0.067 mL/dL/mm Hg).[1,2] About 10% of it is carried in dissolved form whereas majority of it, i.e., around 60% is carried as bicarbonate in the blood. This formation of bicarbonate in the body is catalyzed by an enzyme carbonic anhydrase.

$$CO_2 + H_2O \xrightleftharpoons{\text{Carbonic anhydrase}} H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

Carbon dioxide + water — *Carbonic acid* — *Bicarbonate + hydrogen ion*

This reaction takes place in the RBC where the presence of carbonic anhydrase enzymes favors the reaction and leads to generation of bicarbonate ions.

These bicarbonate ions are permeable across the RBC membrane and hence move out of the cell, but the H^+ ion being impermeable accumulates in the RBC. To maintain the electric neutrality, Cl^- ions from the plasma move into RBC, which is termed as the *chloride shift.*

The accumulated H^+ ions bind to the reduced Hb (since it is a better proton acceptor) thus favoring CO_2 loading at the peripheral tissues. This effect is called as the "Haldane effect."

The remaining 30% of the carbon dioxide is transported as carbaminohemoglobin. It reacts with globin protein in the Hb molecule and forms this compound. Since reduced Hb is a better acceptor of CO_2, this reaction is favored in the peripheral tissues causing more CO_2 loading.

VENTILATION–PERFUSION

Under ideal conditions, each alveolus should undergo the exact amount of ventilation in order to fully oxygenate all the

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blood passing through that alveolus. This is known as V/Q matching.

Ideally, V/Q = 1

However, normal alveolar ventilation is 4 L/min and normal perfusion of the lungs, i.e., cardiac output (CO) is 5 L/min.

Hence, the V/Q becomes 0.8.

This ratio is not uniform across the lung varying from three at the apices to 0.6 at the bases due to the gravitational effects on both ventilation and perfusion.

The perfusion of the lung increases from the apex to the base due to the effect of gravity on the pulmonary capillary pressure and slinky effect (gravitationally induced lung deformation and change in lung density). Similarly, the alveolar ventilation also increases from the apex to the base. However, gravity has a greater effect on blood flow than ventilation resulting in a higher V/Q ratio at the apex of the lung **(Fig. 6 and Table 2)**.

WEST ZONES OF THE LUNG

West's gravitational model of V/Q describes the uneven distribution of blood flow across the lung. This difference is based mainly due to:

- Hydrostatic forces due to gravity
- Airway pressure

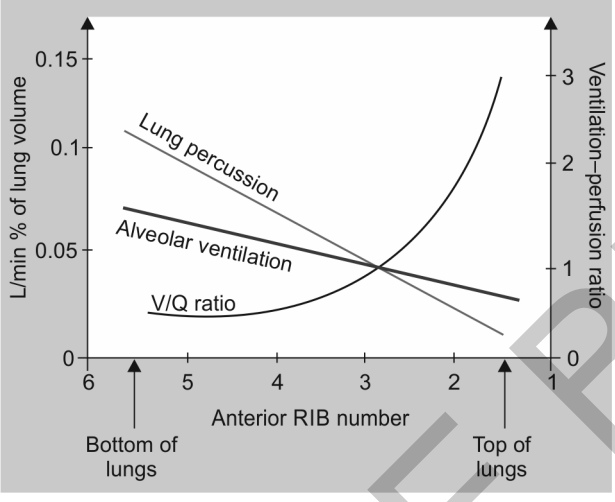


Fig. 6: Ventilation–perfusion (V/Q) relationship across lung.

TABLE 2: Etiology of ventilation perfusion mismatch.

Low ventilation–perfusion (ventilation-affected causing hypoxemia)	***High ventilation–perfusion (lung perfusion-affected)***
Upper airway obstruction	Pulmonary embolism
Pneumonia	Reduced stroke volume (hypovolemia and cardiac dysfunction)
Pneumothorax	
ARDS (acute respiratory distress syndrome)	
Emphysema	
Atelectasis, one-lung ventilation	

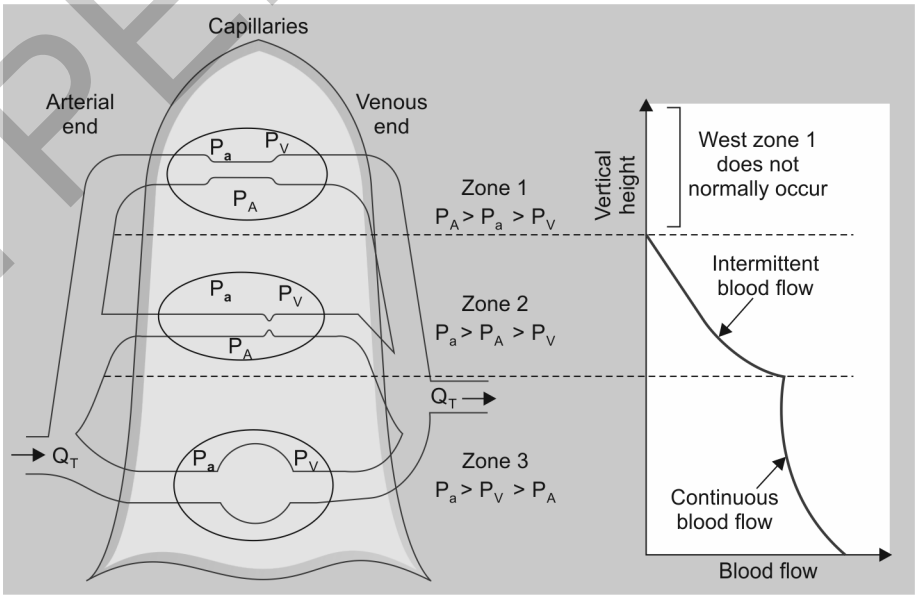


Fig. 7: West zones of lung. (P_a: pulmonary arterial pressure; P_A: alveolar pressure; P_V: pulmonary venous pressure)

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The upright lung is divided into three vertical zones **(Fig. 7)**:

1. *Zone 1—$P_A > P_a > P_v$:* In this zone, the alveolar pressure (PA) exceeds the pulmonary arterial pressure (P_a).

   Apical alveoli are more distended than the basal alveoli due to a more negative intrapleural pressure at the apex than the base. These distended alveoli cause compression of pulmonary vasculature resulting in a higher V/Q ratio at the apex.

   Normally, in a healthy individual this zone does not occur since the pressure in the pulmonary artery is sufficient enough to maintain the flow in the capillaries.

   West zone 1 becomes clinically significant only when:
   - The arterial pressure is abnormally low, for example in shock.
   - The pressure in the alveoli is abnormally high, for example in cases where is generation of high intrinsic positive end-expiratory pressure (PEEP) such as chronic obstructive pulmonary disease (COPD), asthma, or during positive pressure ventilation.
2. *Zone 2—$P_a > P_A > P_v$:* As we move to zone 2, the hydrostatic effect causes increase in the P_a, which exceeds the P_A. However, this PA is still higher than the venous pressure compressing the venous end of the pulmonary capillary. Hence, the blood flow in this zone is dependent on the arterial–alveolar pressure difference, which is seen in a normal lung between the apex and the hilum. Blood flow in this zone occurs only during the systole since the diastolic pressure is less than the P_A causing V/Q mismatch.
3. *Zone 3—$P_a > P_v > P_A$:* In this zone, under the effect of gravity, the arterial and venous pressures exceed the P_A leading to a continuous flow of blood in the capillary throughout the cardiac cycle.

   This arteriovenous pressure difference determines the blood flow below the level of hilum in a normal lung.

OXYGEN CONTENT IN BLOOD

Oxygen is transported in blood in two forms: dissolved and combined with hemoglobin.

It can be represented as:

CaO_2 = O_2 bound to Hb + O_2 in dissolved form

CaO_2 in each 100 mL of blood = [1.34 * Hb (g%) * SaO_2/100%] + 0.003 * PaO_2

For person with Hb of 15 g%, PaO_2 of 100 mm Hg and saturation of 100%:

CaO_2 = (1.34 * 15 * 100/100) + 0.003 * 100

= 20 + 0.3 = 20.3 mL O_2/100 mL of blood

OXYGEN DELIVERY TO TISSUES (DO_2 OR OXYGEN FLUX)

It explains the global oxygen delivery from the lungs to the tissues per minute.

Oxygen delivery = CO × arterial oxygen content (CaO_2)

DO_2 = CO × CaO_2 × 10 (conversion factor as CaO_2 is O_2/100 mL)

Thus, a normal adult male with a resting CO of 5 L/min has an oxygen delivery of 1,000 mL/min.

Oxygen flux decreases in presence of low Hb, low CO, and hypoxemia, whereas it increases with increase in CO as can happen during rigorous exercise.

However, in chronic conditions, compensatory mechanisms try to optimize oxygen delivery.

For example, in an anemic patient, we expect a decrease in the delivery of O_2 applying the above equation.

However, a decreased blood viscosity and increase in CO compensates for the decreased hemoglobin thus maintaining oxygen delivery to the tissues by increasing CO (provided there are no cardiac limitations).

GLOBAL OXYGEN CONSUMPTION (VO_2)

It is the volume of oxygen consumed by the tissues per minute.

It is calculated by reverse Fick principle and is given as:

$$VO_2 = CO \times (CaO_2 - CvO_2) \times 10$$

CO: Cardiac output (L/min)

CaO_2: Arterial oxygen content (mL/100 mL of blood)

CvO_2: Venous oxygen content (mL/100 mL of blood)

10: Unit conversion factor

Thus, for an adult male, resting VO_2 is 250 mL/min.

Using the above equations, we can calculate the percentage of oxygen extracted at the tissue level, called the oxygen extraction ratio (OER).

$$OER = VO_2/DO_2$$

For a resting adult male,

$$OER = 250/1{,}000 = 25\%$$

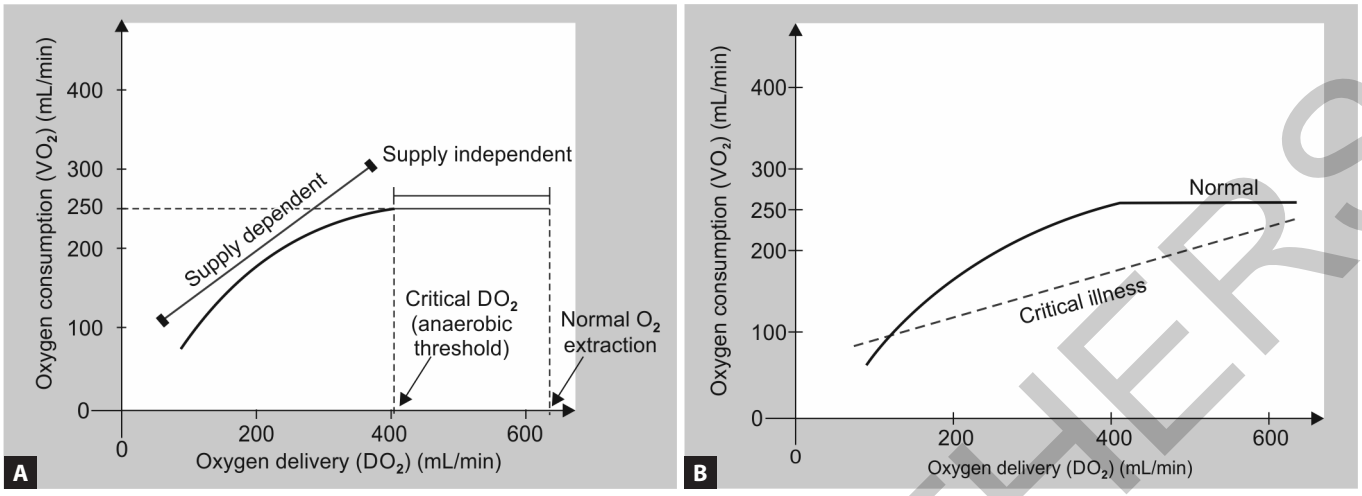
So, the tissues consume 25% of the delivered oxygen and the rest being circulated back to the venous blood in the lungs. Hence, a mixed venous O_2 saturation (normally 70–80%) corresponds to an OER of 20–30%.

Factors Affecting VO_2

Factors affecting VO_2 are shown in **Table 3**.

Figures 8A and B clearly explain the relationship between DO_2 and its consumption at the tissue level in a normal versus a critically ill patient.

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Figs. 8A and B: (A) Oxygen supply/demand in normal individual; and (B) Oxygen supply/demand in critically ill.

TABLE 3: Factors affecting oxygen consumption.

Increase in VO_2	***Decrease in VO_2***
Exercise	Sedation, analgesia (in case of pain), antipyretics (if fever), and antiepileptics (if seizures)
Trauma and hyperthyroidism	Skeletal muscle paralysis
Inflammation, sepsis, and pyrexia	Mitochondrial dysfunction and hypothyroidism
Shivering and seizures	Mechanical ventilation
Pain	Hypothermia
Agitation	Starvation

(VO_2: oxygen consumption)

In a normal patient, as the VO_2 increases (as mentioned in **Table 3**) or the DO_2 decreases initially, the tissues maintain their aerobic metabolism by increasing their OER.[8]

This OER is maximum at the critical DO_2 (which is 4 mL/kg/min).

Below the critical DO_2, any further increase in VO_2 or decrease in DO_2 will result in anaerobic metabolism and cause tissue hypoxia.

Each organ or tissue has its own critical DO_2. Tissues with higher OER (heart, liver, and brain) are more likely to be dependent on DO_2 (supply dependence).[2]

In a critically ill patient due to increased metabolic requirements, VO_2 increases and is dependent on the DO_2 over a wider range as compared to a healthy individual.

CONCLUSION

Movement of oxygen from air to tissues and that of CO_2 from tissues to lungs involves multiple steps and thus can get affected due to various reasons. It is important to understand this physiology in health and in disease so that appropriate corrective steps can be taken to improve outcome.

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