GAS EXCHANGE AND DIFFUSION

The composition of alveolar gas depends upon the composition of inspired gas, composition of gas in the functional residual capacity (FRC), minus the O_2 taken up by the blood plus the CO_2 added from blood. Details of how the listed composition arises are discussed in standard monographs of respiratory physiology on the topic of ventilation/perfusion defects

Diffusion takes place in the gas phase by the random motion of gas molecules.

Graham's law of diffusion (1833) states that the rate of diffusion of a gas is inversely proportional to the square root of its molecular weight. Thus, the relative rates of diffusion of CO_2 and O_2 are equal to $\sqrt{(32/44)}$ or 0.85.

Fick's Law of Diffusion

Fick's first law states that the amount of gas transferred per unit time ($\Delta N/\Delta t$) across a membrane of thickness Δx is proportional to the area (A) available for exchange and the partial pressure difference (ΔP) of the gas across the membrane. The constant of proportionality (K) is called Krogh's diffusion coefficient (see below) to distinguish it from D:

$$\Delta N/\Delta t = KA\,\Delta P/\Delta x$$

For gas exchange across an alveolus in the lung, A and Δx are the same for all gases; different transfer rates result from differences in K and ΔP. For the lung, Δx is about 0.5 μm—a very thin barrier; and A is about 70 m^2—a very large surface area. Krogh's diffusion coefficient ($K = aD$) is equal to the diffusion coefficient (D) times the solubility (a) of a gas in the fluid through which the gas diffuses. For example, CO_2 is 24 times more soluble than O_2 in water. Thus, the rate of CO_2 diffusion is 0.85 × 24 = 20 times as rapid as that for O_2 given the same partial pressure difference.

Oxygen transport

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In plasma

At physiological P_{O2} (40 < P_{O2} < 100 mm Hg), only a small amount of oxygen is dissolved in plasma since oxygen has such a low solubility.

In combination with haemoglobin

The protein haemoglobin is a molecule which is responsible for carrying almost all of the oxygen in the blood. It is composed of four subunits, each with a heme group plus a globin chain. The heme group is composed of a porphyrin ring which contains an iron (Fe) atom in its center. Normally, the Fe is in the +2 redox state (ferrous) and can reversibly bind oxygen. There are at least six genes that control globin synthesis in humans, resulting in the formation of six structurally different polypeptide chains that are designated α, β, γ, δ, ξ, and ς chains. All normal and most abnormal haemoglobin molecules are tetramers consisting of two different pairs of polypeptide chains, each chain forming a monomeric subunit.

Binding of Oxygen to Hemoglobin: Oxygen Saturation (Dissociation) Curve

The haemoglobin molecule has four binding sites for oxygen molecules: the iron atoms in the four heme groups. Thus, each Hb tetramer can bind four oxygen molecules. From the molecular weight of Hb, one can calculate that 1 g of Hb can combine with 1.39 ml of oxygen. Actually, some of the Hb normally in red blood cells cannot bind oxygen (it is either metHb or HbCO), and the empirically determined oxygen-binding capacity of haemoglobin (C_{Hb}) is 1.34 ml O_2 per gram Hb. In 100 ml of blood, there is about 15 g of Hb, so that 100 ml of blood has the capacity to bind 20.1 ml of oxygen. This quantity is called the oxygen-binding capacity of blood (C_B).

The curve is known as the oxygen saturation curve or the oxygen dissociation curve and expresses the relationship between P_{O2} and the bound oxygen content.

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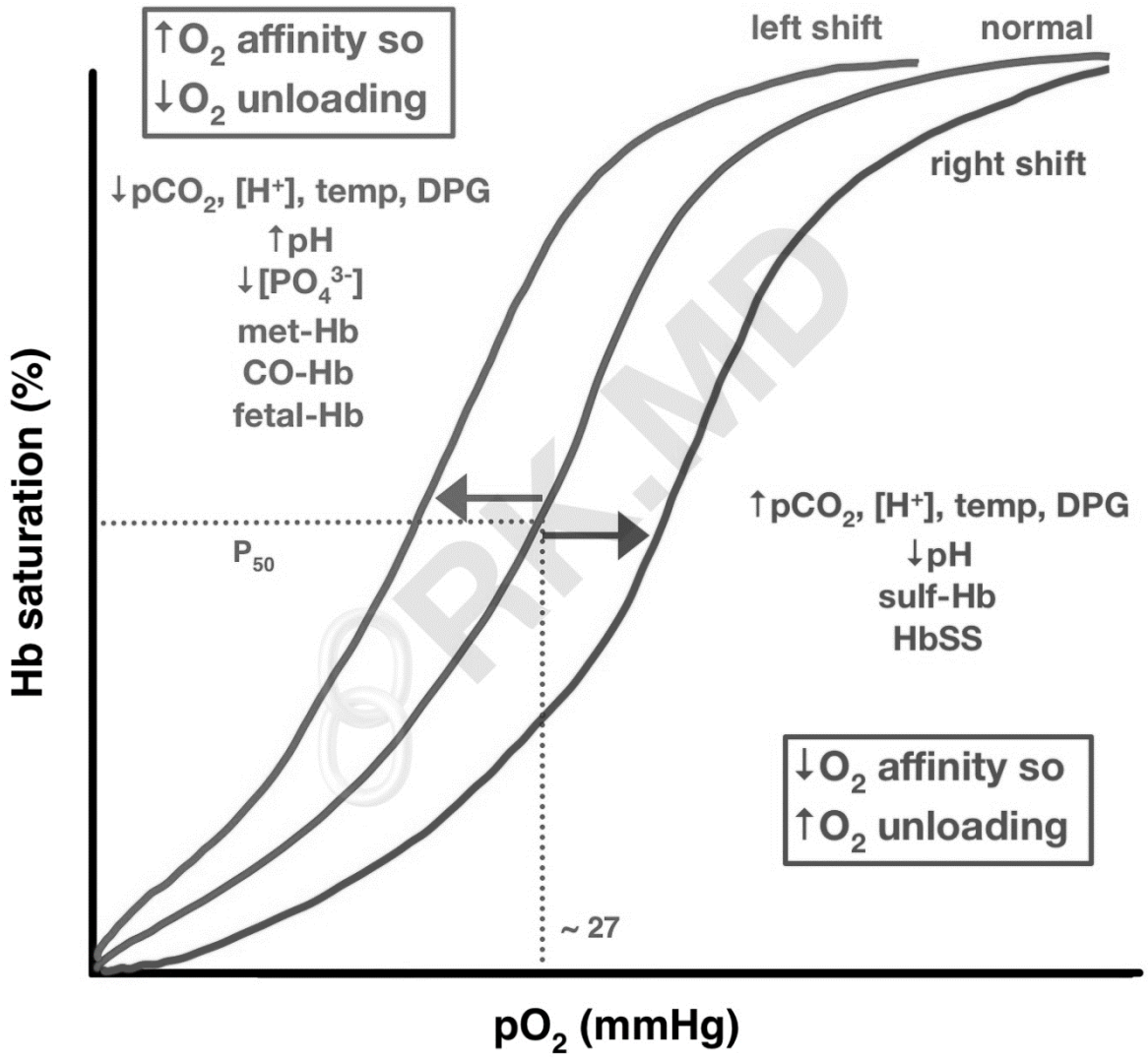
OXYHEMOGLOBIN DISSOCIATION CURVE



Oxygen dissociation curve-relating oxygen bound to hemoglobin (oxygen saturation, S_{O2}) as a function of partial pressure of oxygen (P_{O2}).

P_{50} is defined as the P_{O2} at which oxygen saturation is 50%. The standard conditions under which oxygen binding is measured are T = 37 °C, pH = 7.4 and P_{CO2} = 40 mm

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Hg. The fractional oxygen saturation of Hb is the amount of oxygen combined with Hb divided by the oxygen-binding capacity of the blood (20.1 vol% at normal Hct).

$$O_2 \text{ content in bound form} = O_2 \text{ saturation} \times O_2\text{-binding capacity}$$

The oxygen dissociation curve is said to have a sigmoid shape, which reflects the cooperative nature of oxygen binding to Hb. This curve is highly nonlinear in the normal physiological range of P_{O2} (i.e., 40 to 100 mm Hg). The middle portion of the curve (20–80% saturation) is steeper than the low P_{O2} and high P_{O2} segments. The affinity of Hb for oxygen increases steadily as oxygen saturation goes from 0% to 100% for a given oxygen dissociation curve.

Shift of curve to right

Increasing the temperature of Hb lowers its affinity for O_2 and shifts the oxygen dissociation curve to the right

Increased H^+ activity (decreased pH) also lowers the affinity of Hb for O_2. This was originally noticed by **Bohr (Bohr effect)** and his colleagues (1904) as an effect of increased P_{CO2}, but it has been shown to be primarily an effect of pH inside the red blood cell. CO_2 by itself, at constant pH, also affects the oxygen dissociation curve such that increased P_{CO2} shifts the curve to the right (i.e., lowers the affinity of Hb for oxygen).

2,3 DPG is a glycolytic intermediate produced within the RBC that affects the affinity of Hb for oxygen. Increases in RBC [H^+] cause decreases in [2,3 DPG], and decreases in RBC [H^+] cause increases in [2,3 DPG]. 2,3 DPG is a charged ion that cannot permeate the RBC membrane. Increases in its concentration shift the oxygen dissociation curve to the right.

The oxygen dissociation curve is shifted to the right to allow easier unloading of oxygen from Hb in the tissues. The rightward shift in the oxygen dissociation curve is more important at lower P_{O2}. Although the rightward shift interferes with oxygen loading in the lungs.

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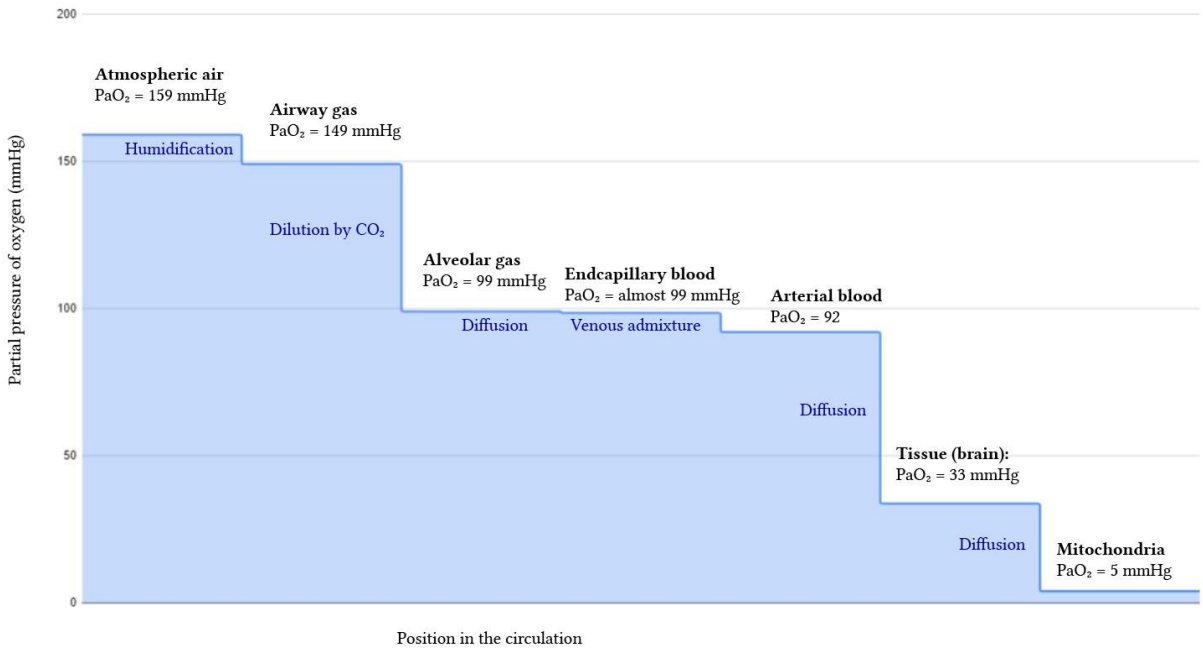
Shift of curve to left

Decreased Temperature

Decrease in 2,3 DPG

Decreased H^+ activity

Oxygen cascade



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Carbondioxide transport

There are three means by which carbon dioxide is transported in the bloodstream from peripheral tissues and back to the lungs:

(1) dissolved gas

(2) bicarbonate

(3) carbaminohemoglobin bound to hemoglobin (and other proteins).

As carbon dioxide diffuses into the bloodstream from peripheral tissues, approximately 10% of it remains dissolved either in plasma or the blood's extracellular fluid matrix, to a partial pressure of about 45 mmHg. Most of the carbon dioxide diffusing through the capillaries and ultimately into the red blood cells combines with water via a chemical reaction catalyzed by the enzyme carbonic anhydrase catalyzes, forming carbonic acid. Carbonic acid almost immediately dissociates into a bicarbonate anion (HCO3-) and a proton. Thus, bicarbonate is the primary means by which carbon dioxide is transport occurs throughout the bloodstream according to the equation

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$.

As carbon dioxide continues to be produced by tissues, this reaction is continually driven forward in the periphery, according to Le Chatelier's principle. The proton formed by this reaction is buffered by hemoglobin, while the bicarbonate anion diffuses out of the red blood cell and into the serum in exchange for a chloride anion through a special HCO3-/Cl- transporter.

Thus, venous blood has both a higher concentration of bicarbonate and a lower concentration of chloride thanks to this so-called chloride shift. In the lungs, this process reverses as both the HCO3-/Cl- exchanger and carbonic anhydrase enzyme reverse directions; this results in an influx of bicarbonate into red blood cells, an efflux of chloride ions, and the generation of first carbonic acid and then carbon dioxide. The carbon dioxide diffuses out of the red blood cells, through the capillary walls, and into the alveolar spaces f exhaled Finally, the remaining 10% of the carbon dioxide that diffuses into the bloodstream and, subsequently, into the red blood cells, binds to the amino terminus of proteins, predominantly hemoglobin, to form carbaminohemoglobin.

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Oxygen delivery and carbon dioxide removal intrinsically link with one another through processes described by the Bohr and Haldane effects. While not detailed here, the Bohr effect states that the increase of carbon dioxide in the blood in peripheral tissues causes a right shift in the oxygen-hemoglobin dissociation curve and, consequently, increased oxygenation of the tissues. Once the carbon dioxide-enriched blood reaches the lungs, however, the reverse of this reaction will also occur. As the influx of oxygen increases hemoglobin saturation, the carbon dioxide is more likely to become detached and diffused into the alveoli for exhalation; this is called the **Haldane effect.**

Specifically, the **Haldane effect** describes the difference in carbon dioxide carrying capacity in oxygenated blood compared with deoxygenated blood. At a consistent partial pressure of carbon dioxide, the Haldane effect states that oxygenated (arterial) blood will carry less carbon dioxide than deoxygenated (venous) blood due to a combination of an impaired ability of hemoglobin to buffer the excess carbon dioxide as well as a decreased capacity for carbamino carriage.

As oxygen binds to hemoglobin, the hemoglobin becomes more acidic, which has two effects. First, it reduces the binding affinity of the hemoglobin for carbon dioxide, making the carbon dioxide more likely to dissociate from the hemoglobin and diffuse out of the red blood cell into the alveolar space. Second, acidic hemoglobin can release a proton that will combine with bicarbonate to form carbonic acid. Again, Le Chatelier's principle drives the following reaction forward as blood passes through the alveoli: H+ + HCO3- --> H2CO3 --> CO2 + H2O. The carbon dioxide produced here continually diffuses into the alveoli and is exhaled, ensuring favorable kinetics for the reaction to proceed. Thus, the Haldane effect increases the quantity of carbon dioxide that can be eliminated during a given timeframe. **Graphically, the Haldane effect is represented by a right shift that occurs in the carbon dioxide dissociation curve**

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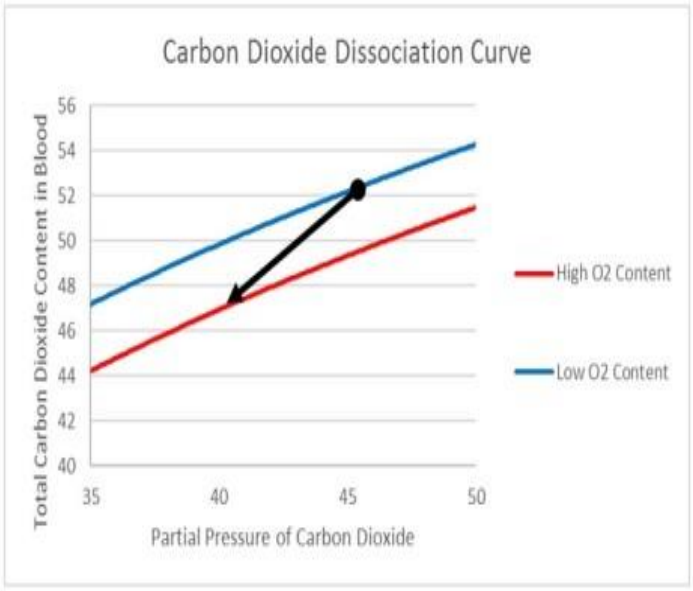

The Haldane Effect causes increased offloading of carbon dioxide upon oxygenation of the blood, as displayed above. As blood passes through the lungs, an influx of oxygen causes a right shift of the carbon dioxide dissociation curve while the partial pressure of carbon dioxide drops from 45-46 down to about 40mmHg. This serves to release a greater amount of carbon dioxide into the alveolar spaces.

The carbon dioxide dissociation curve shows a graphical representation of the Haldane Effect.

n peripheral tissues, where oxygen content is low, carbon dioxide binds to hemoglobin to form carbaminohemoglobin. As blood returns to the lungs and the partial pressure of oxygen increases, the carbon dioxide dissociation curve shifts right (seen by the arrow showing the offloading of carbon dioxide as oxygenation increases), lowering the total carbon dioxide content in the bloodstream. Thus, although the partial pressure of carbon dioxide only decreases from 45 or 46 mmHg on the venous side to 40 mmHg on the arterial side, the total amount of carbon dioxide in the bloodstream decreases by a much greater percentage.

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