Gas Transport By The Blood

How Gases Are Moved To And From Peripheral Tissues

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Introduction

The primary function of the cardio-respiratory system is to extract oxygen from the atmosphere and deliver it to the mitochondria of cells. At the cellular level, mitochondria utilize oxygen as the terminal electron acceptor for the production of ATP through the electron transport chain via the biochemical process of oxidative phosphorylation. Together, the series of physiological events that connect environmental oxygen to cellular metabolism is termed the oxygen transport cascade. This cascade is composed of four primary steps:

- Pulmonary ventilation, mostly a convective process, brings O_2 from the air to the alveoli and simultaneously returns CO_2 from the alveoli to the air.
- Alveolar-lung capillary diffusion. Diffusion is responsible for the movement of both O_2 and CO_2 between the alveolar gas and the capillary blood.
- Circulation, a convective process, transports blood containing O_2 and CO_2 from the lungs to the tissues and back to the lungs powered by the heart as a pump.
- Tissue capillary-mitochondrial diffusion is responsible for O_2 and CO_2 movement between the tissue capillary blood and the tissue mitochondria.

Gas Laws and Air Composition

Understanding the underlying principles of gases and their behavior is important for understanding the mechanisms of gas exchange in the lungs and at the level of body tissues.

Gas molecules exert force on the surfaces they are in contact with; this force is called pressure. In a mixture of gases, the total pressure is the sum of the contributions of each constituent, with the partial pressure of each gas representing the pressure that gas would exert if it alone occupied the entire volume occupied by the mixture. Dalton's law describes this concept in a mathematical equation which states that the total pressure (P) exerted by a mixture of gases "n" is the sum of the partial pressures of the gases in the mixture, such as:

$$P\ total = P1 + P2 + P3 + ...Pn \quad \text{(Equation 1)}$$

Furthermore, the partial pressure of a gas "n" is equal to its fractional concentration in the gas mixture (Cn) multiplied by P total:

$$Pn = [Cn] \times P\ total/100 \quad \text{(Equation 2)}$$

For example, atmospheric air is a mixture of gases consisting of oxygen (O_2), nitrogen, carbon dioxide (CO_2), and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure (PB) (Table 1). In the atmosphere, O_2 exerts a certain partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen.

Table 1: Partial Pressures of Atmospheric Gases

Gas	Percent of total composition	Partial pressure (mm Hg)
Nitrogen (N_2)	78.6	597.4
Oxygen (O_2)	20.9	158.8
Water Vapor (H_2O)	0.04	0.3
Carbon dioxide (CO_2)	0.004	0.03
Others	0.0006	0.005
Total composition/total atmospheric pressure	100%	760.0

As the air is inhaled, it becomes humidified within the respiratory tract. As water vapor exerts its own pressure (PH_2O = 47 mmHg at body temperature, 37°C), it reduces the partial pressure for oxygen and other gases. In the case of O_2, its partial pressure (PIO_2) in inspired air at sea level (PB = 760 mm Hg), before any gas exchange occurs, is given by the following equation, which is an application of Dalton's law:

$$PIO_2 = FIO_2 \times (PB - PH_2O) / 100 = 0.21 \text{ x } (760 - 47) = 149.7 \text{ mmHg} \quad \text{(Equation 3)}$$

Where: FIO_2 = Fraction of inspired O_2 (≈ 21% in room air), PB = Barometric pressure (760 mmHg at sea level), PH_2O = Water vapor pressure (47 mm Hg at body temp).

Within the alveolus, air composition differs from that in the atmosphere (Table 2). This is mainly due to the enrichment of CO_2 from venous blood, which enters the alveolus due to gas exchange. In yet another application of the same principle (Dalton's law) the partial pressure of O_2 in the alveolar gas mixture (PAO_2) is given by the alveolar gas equation:

$$PAO_2 = FIO_2 \times (PB - PH_2O) - (PACO_2 / R) \text{ (Equation 4)}$$

Where: $PACO_2$ = Alveolar CO_2 partial pressure (~ 40 mmHg), R = Respiratory quotient (~ 0.8, varies with diet/metabolism).

Table 2: Composition and Partial Pressures of Alveolar Air

Gas	Percent of total composition	Partial pressure (mmHg)
Nitrogen (N_2)	74.9	569
Oxygen (O_2)	13.7	104
Water (H_2O)	6.2	47
Carbon dioxide (CO_2)	5.2	40
Total composition/total alveolar pressure	100%	760.0

Partial Pressure and Concentration Of A Gas In Blood

Suppose we have a closed system within which we have combined a volume of blood and a volume of inert gas, i.e., a gas that does not combine chemically with any other molecule in the liquid or transform chemically into another molecule or ion (Figure 1).

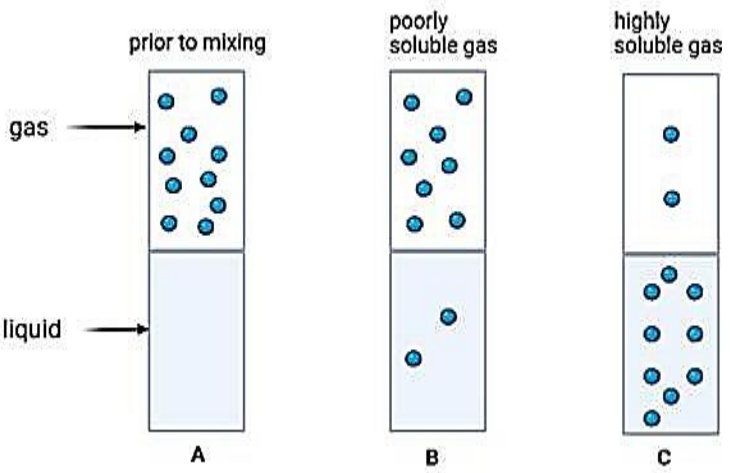

Figure 1: Moving from left to right (A-C), the panels show the gas molecular movement from gas to blood until equilibrium is reached. Panel B depicts a highly soluble gas, panel C depicts a poorly soluble gas.

The inert gas molecules, initially present only in the gas phase (Figure 1A), will start to move into the blood within the closed system. In this way, the inert gas concentration in the gas phase must fall while that in the blood phase must rise. After a few minutes of agitation, an equilibrium will have been established between the blood and gas phases, meaning that there will no longer be a net movement of inert gas molecules between the gas and blood phases (Figure 1B and 1C).

The partial pressure of the gas in the gas phase is known and given by Equation 2 above. What about the partial pressure of the gas dissolved in the blood? This pressure is equal to the partial pressure of the gas in the gas phase above it when the blood-gas system is in equilibrium. Is the partial pressure of gas in the liquid the only parameter we need to know when determining the gas concentration in this liquid? The answer is provided by Henry's law, which states that the concentration of an inert gas in a liquid (expressed as units of ml of gas per 100 ml of liquid) is equal to the product of the partial pressure of the gas in the liquid and the physical solubility of that gas in that liquid:

$$Cs = S \times P \quad \text{(Equation 5)}$$

Where S: solubility commonly expressed as mL gas/ 100mL liquid/mmHg partial pressure.
Cs: concentration of gas in a liquid (i.e., solution), expressed in mL gas / 100mL liquid. P: partial pressure of gas in a liquid, expressed in mmHg.

If we combine equations 2 and 4, taking into consideration that all calculations are done at sea level where atmospheric pressure PB = 760 mmHg and partial pressure of water vapor PH_2O = 47 mmHg), we have:

$$Cs = S \times C \times (PB - PH_2O) / 100$$

Where C is the concentration of the gas in the gas phase. The equation can be rearranged as:

$$Cs/C = S \times (PB - PH_2O) / 100.$$

Substituting for the known quantities we have:

$$Cs/C = S \times 7.13 = \lambda \text{ (gas partition coefficient)} \quad \text{(Equation 6)}$$

The blood gas partition coefficient is a dimensionless ratio of the concentration of an inert gas in the blood to that in the gas with which it is in equilibrium. Figures 1B and C represent two different gases with different solubility in the blood, the λ values of which are quite different. In the case of the more soluble gas (Figure 1B), 2 molecules of gas have dissolved into the blood, whereas 8 remain in the gas, giving a λ value of 0.25 and a solubility of 0.25/7.13 or 0.035 ml gas/100 ml blood/mmHg. In the case of the more soluble gas (Figure 1C), 8 gas molecules have dissolved, whereas 2 remain in the gas phase. This corresponds to a λ of 4 and a solubility of 0.56 ml gas/100 ml blood/mmHg.

Oxygen Transport In The Blood

The above discussion pertains to the physical solution of inert gases in blood. Neither O_2 nor CO_2 are inert gases; hence, their transport in blood involves more mechanisms than those discussed. More specifically, O_2 is carried in the blood simultaneously in two forms: as physically dissolved molecules (just as described above for inert gases) and as molecules bound to hemoglobin (Hb) within the red blood cells (RBC), with these two forms considered to be in equilibrium.

The solubility of O_2 in blood at normal body temperature is generally accepted to be 0.003mL/100mL blood/mmHg partial pressure of O_2 (PO_2). Arterial PO_2 in a normal young subject at rest is about 90 to 100 mmHg, breathing air at sea level. Thus, using Equation 5, the amount of O_2 physically dissolved in the arterial blood is 0.003 x 100, or 0.3 mL O_2/100 mL blood, which is equivalent to 3mL/L blood. This means that, in the case of a normal cardiac output of about 6 L/min, 18 ml O_2 (i.e., 3 ml/L x 6 L) is delivered to the entire body per minute in physically dissolved form. Given that the O_2 consumption at rest is about 300 mL/min, it becomes evident that physically dissolved O_2 cannot come close to supporting the metabolic need for O_2. During exercise or increased metabolic demands due to sepsis for example, the inadequacy of physically dissolved O_2 to address tissue metabolic demands becomes even more apparent. However, some interventions in clinical practice can increase the amount of O_2 dissolved in blood. Inhalation of 100% O_2, commonly occurring in the intensive care unit, will increase dissolved O_2 to 20 mL/L or 120 mL for a cardiac output of 6 L/min, assuming inhalation at sea level and normal lungs. This is about 40% of resting O_2 consumption, with the caveat that the conditions that necessitate inhalation of 100% O_2 are rarely associated with normal lungs or resting metabolic rates (think sepsis).

Hyperbaric oxygen is much more efficient in this regard. Routinely used to treat post-diving decompression sickness and carbon monoxide toxicity, and to promote skin wound healing, pure O_2 at 2.3 atmospheres would suffice to fully support the resting metabolic rate, assuming that all the O_2 delivered could be extracted from the blood.

Given the above, it becomes clear that additional O_2 carrying mechanisms are necessary and, indeed, have evolved primarily in the form of Hb. Hb binding of O_2 is essential as the principal mechanism for cellular access to O_2. As its name implies, it is a molecule with a heme group bound to globin proteins (Figure 2).

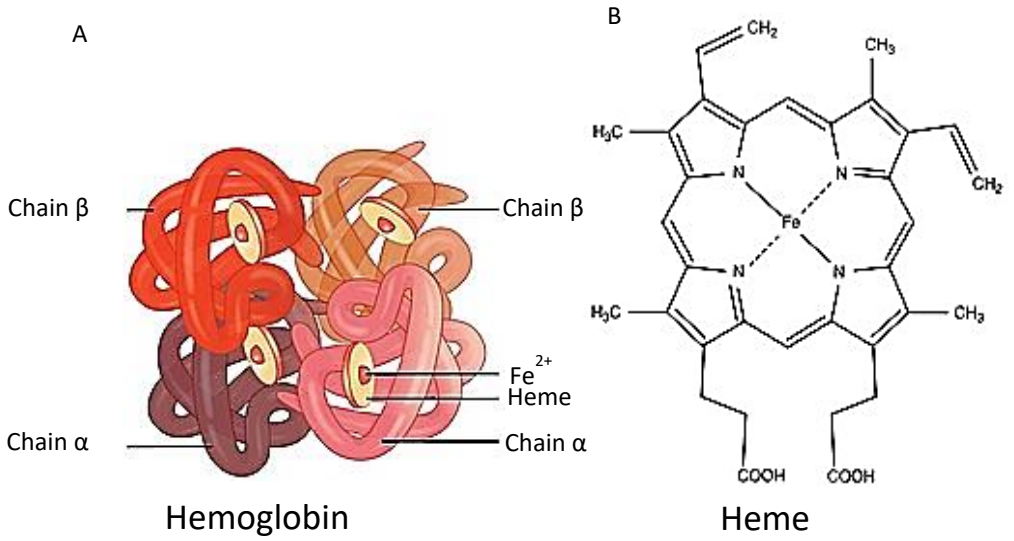

Figure 2: A. Hemoglobin is a tetrameric protein composed of four symmetrical subunits (two alpha and two beta subunits) and four heme groups that bind iron in its ferrous (Fe^{2+}) form. B. Heme molecule: A central iron atom is held inside a large porphyrin ring made of four interconnected pyrrole rings, which are small, five-sided (pentagonal) molecules made of four carbon atoms and one nitrogen atom. Adapted from reference 4.

The globin of normal adult Hb (i.e., Hb A) has two alpha chains, each consisting of 141 amino acids, and two beta chains, each consisting of 146 amino acids per molecule, and these four subunits form the scaffolding that holds four heme complexes each one of which is a porphyrin ring containing iron (Fe) ions that are the reversible binding sites for O_2. Each Hb molecule can bind four O_2 molecules. However, the affinity of Hb is not equal for all four of these molecules. It takes a higher PO_2 for the first O_2 molecule to bind to Hb than for the second molecule, and even less for the third and fourth. This phenomenon is called cooperativity and is explained by the two-state allosteric model of Monod, Wyman, and Changeux, published in 1965, which postulates that cooperative proteins are symmetric oligomers stable in at least two alternative quaternary conformations (i.e., allosteric confirmations, from the word allostery, which means another three-dimensional shape) with different ligand affinity. Ligand binding to subunits in the oligomer tends to stabilize the whole protein into a high-affinity quaternary conformation, which, in turn, tends to force the remaining unbound subunits into the same tertiary structure as the bound ones. The "interaction" between subunits is not direct. However, it is mediated by the all-or-none quaternary conformational change that keeps all subunits in the same affinity state, be it high or low. This cooperative mechanism also facilitates oxygen release: as each oxygen molecule is released, hemoglobin's affinity for the remaining oxygen decreases, promoting further oxygen unloading.

Each gram of Hb can bind 1.39 mL O_2 when every O_2 binding site is occupied, i.e. when Hb is fully saturated with O_2. In a subject with normal Hb concentration, this corresponds to about 20 mL of O_2 bound to Hb per 100 ml of arterial blood (as Hb concentration is measured in g/100 ml) and 1,200 ml O_2 per minute, assuming a cardiac output of 6 L/min. This is well over the resting metabolic requirement of 300 mL/min, and some 70-fold more than available by dissolved O_2 alone.

Significantly, only ferrous (Fe++) and not ferric (Fe+++) iron can bind O_2 reversibly. In the case of methemoglobinemia, the ferrous Fe of Hb is oxidized to ferric Fe, resulting in allosteric changes that lead to irreversible binding of O_2. This, in turn, hinders O_2 release to the tissues, causing "functional anemia" without Hb decrease. Methemoglobinemia can result from either inherited or acquired processes. Acquired forms are the most common, mainly due to exposure to substances that cause oxidation of the Hb both directly and indirectly. Inherited forms are due either to autosomal recessive variants in the CYB5R3 gene or to autosomal dominant variants in the globin genes, collectively known as HbM disease.

It is important to note that Hb is not distributed uniformly in the blood. Instead, all the Hb is confined within red blood cells, whose volume usually is 40 to 45% of the blood.
The remaining 55 to 60% of the blood is Hb-free plasma. The red blood cells carry O_2 bound to Hb and in physical solution, whereas the plasma carries O_2 only in physical solution.
An equilibrium exists between Hb-bound and physically dissolved O_2 molecules inside and outside the red blood cell, meaning there is no net movement of O_2 molecules from dissolved to Hb-bound and vice versa. Therefore, the PO_2 exists in the plasma as inside the red blood cells, even though the O_2 concentration [O_2] is much higher inside the red blood cell than in the plasma because of Hb binding inside the red cell.

Whereas the relationship between the PO_2 and the O_2 concentration of the physically dissolved O_2 obeys Henry's law (see equation 5), the same relationship for the Hb-bound O_2 is described by the oxygen–hemoglobin (O_2Hb) dissociation curve (ODC) (Figure 3).

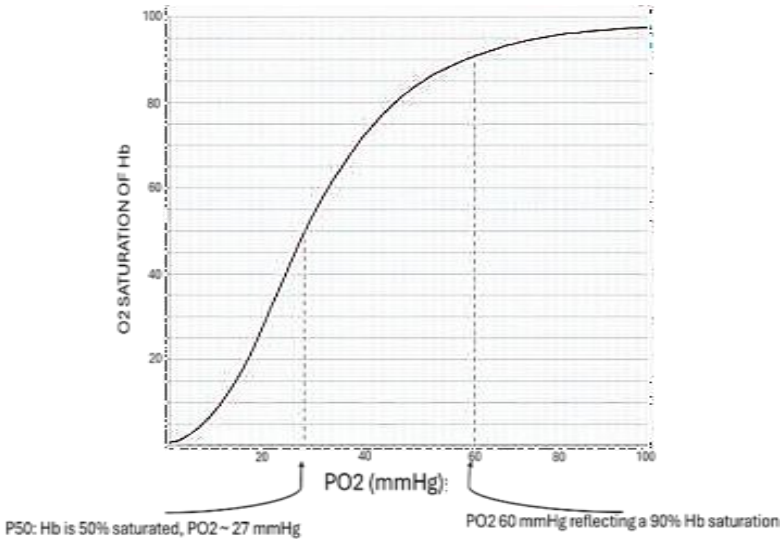

Figure 3: Oxygen-hemoglobin dissociation curve. Adapted from: https://derangedphysiology.com/main/cicm-primary-exam/respiratory-system/Chapter-112/oxyhaemoglobin-dissociation-curve.

This relationship is nonlinear. It is steeper at low PO_2 and less steep as PO_2 increases due to the cooperativity phenomenon described above. Eventually, when PO_2 is high enough that every Hb molecule contains four O_2 molecules, there can be no further increase in Hb-bound O_2 no matter how high the PO_2 goes, and the relationship becomes horizontal. In practice, about 97 to 98% of heme binding sites are occupied with O_2 molecules at a normal arterial blood PO_2 of 90 to 100 mmHg, and > 99% are occupied with O_2 molecules above a blood PO_2 of 200 mmHg, such as can be achieved upon 30% supplemental inspired oxygen in a normal lung.

The Hill equation is the most widely used mathematical expression to describe the ODC and is depicted below:

$$O_2 \text{ saturation} = PO_2^n / [PO_2^n + P50^n]$$

The parameter n is called the Hill coefficient and carries a value of about 2.7 for normal Hb.
P50 is the PO_2 when 50% of heme binding sites are occupied with O_2. In normal adult subjects, it averages about 27 mmHg under standard conditions (760 mmHg barometric pressure, 37°C temperature, and partial pressure of CO_2 [PCO_2] 40 mmHg).

Genetic variants in Hb can result in quite different values for P50. For example, normal fetal Hb (Hb F) has a P50 of about 19 mmHg, which means 50% more O_2 is carried by fetal than Hb A at this PO_2, making more O_2 available to fetal tissues despite their relatively low PO_2 environment.
It is important to stress that the Y axis in the usual presentation of the ODC represents the arterial oxygen

saturation as an overall percentage of binding sites on hemoglobin occupied by oxygen. Of more pertinent clinical significance, however, is not the Hb saturation but the arterial [O_2] as an indicator of how much O_2 is there for delivery to tissues or returning to the lungs after passing through the tissue capillaries (Figure 4).

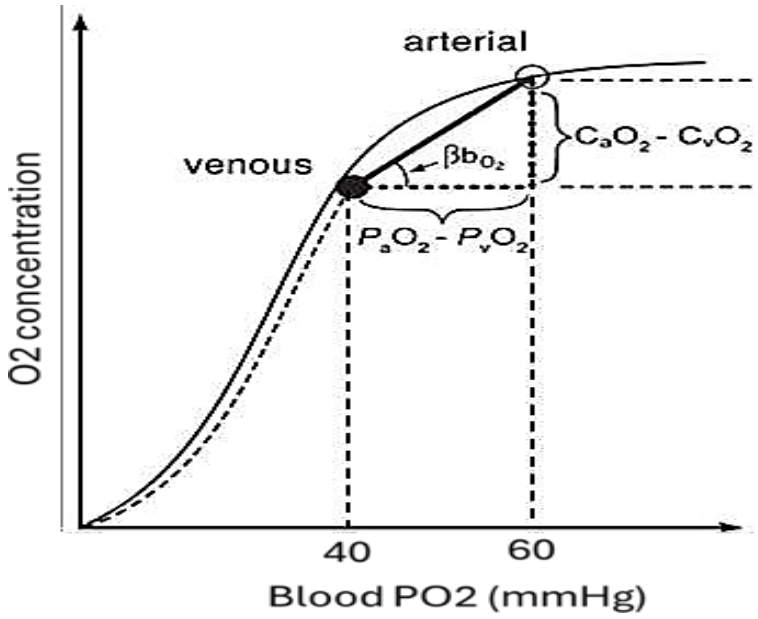

Figure 4: Schematic illustration of blood O_2 transport. Arterial (solid curve) and venous (dashed curve) ODC curves are shown. The curve is a plot of blood O_2 concentration (y-axis) versus PO2 (x-axis), with paired values for arterial and venous blood connected by a solid line. CaO_2 - CvO_2 denotes the arterial–venous difference in blood O_2 content, PaO_2 - PvO_2 denotes the corresponding difference in PO_2, βbO_2 (in the text denoted simply as β) denotes the blood O_2 capacitance coefficient (see text for details). Adapted from reference 12 with permission.

This requires multiplying the concentration of Hb in g/100 mL by the 1.39 mL of O_2 that 1 g of Hb can carry when fully saturated with O_2 and by the fractional O_2Hb saturation, as per the following equation: [O_2] = 1.39 x [Hb] x fractional O_2 saturation. Therefore, the units of [O_2] are mL O_2/100mL of blood.

As depicted in Figure 4, the slope of the ODC curve is drawn between an arterial PO_2 (60 mmHg) and a venous PO_2 (40 mmHg) and, thus, describes the change of [O_2] in the arterial and venous blood as a function of the PO_2. This slope is denoted by the letter β and is commonly called blood oxygen capacitance coefficient (or oxygen content coefficient) as it describes the amount of oxygen that can be carried per unit volume of blood per unit change in partial pressure of oxygen (PO_2). However, β can be calculated for every part of the ODC both in the venous and the arterial part of the curve. It is evident that [O_2] is not a linear function of PO_2. The relationship is close to linear in hypoxia but becomes much flatter in normoxia. For CO_2, the same relationship is much more linear (see below).

In cases of anemia, the arterial oxygen saturation would not change, whereas the arterial [O_2] would change significantly. The importance of showing the dissociation curve as a function of the [O_2] becomes evident when comparing normal and anemic subjects as shown in figure (Figure 5).

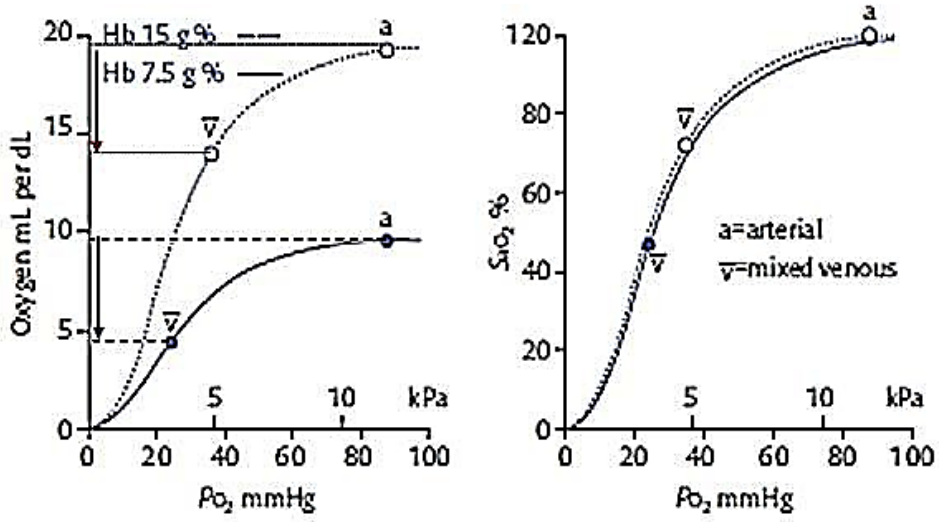

Figure 5: Left panel: ODC plotted as PO2 against oxygen concentration in two subjects with Hb of 15 g/100 ml vs.7.5 g/100 ml. Compare to right panel where ODC is plotted as PO_2 against oxygen saturation (SaO_2%). The normal and anemic curves are superimposed. Adapted from reference 13 with permission.

Assuming that both subjects have the same normal arterial PO_2 (white and blue dots denoted a) and the same tissue oxygen consumption (i.e. arteriovenous difference, which in the graph is approximately 5 ml O_2/100 ml of blood, observe green and blue arrows), the anemic subject has a lower venous PO_2 than the nonanemic one (white and blue dots denoted $\bar{v}$). This may not matter at rest when the O_2 supply remains in excess of metabolic needs despite anemia. However, the significance of this limited O_2 "reserve" is in exercise when, compared to rest, much more O_2 must be extracted from the blood and delivered to the tissues to sustain that exercise. Of course, the exact shape of the anemic curve will depend on the chronicity of anemia, which determines the presence or absence of compensatory mechanisms as well as, very importantly, on the co-presence of additional factors that are known to affect the relationship between O_2 concentration and PO_2 in the blood. At a given Hb concentration, these are:

- pH
- PCO_2
- Blood temperature
- 2,3-Bisphosphoglycerate (2,3-BPG) - also known as 2,3-Diphosphoglycerate
- CO

Decreases in the affinity of Hb for O_2, and, thus, rightward shifts in the dissociation curve, result from a reduced pH, increased PCO_2, and increased blood temperature. Increases in affinity and, thus, leftward shifts in the dissociation curve result from an increased pH, decreased PCO_2 and decreased blood temperature. Most of the shift induced by changes in PCO_2 is due to the associated changes in pH, resulting from CO_2 in blood forming carbonic acid, which dissociates into protons and bicarbonate ions.

As PCO_2 increases, pH falls (and vice versa), and this pH change causes most of the rightward shift from PCO_2. The Bohr effect is the decrease in the affinity of Hb for O_2 induced by the physical binding of CO_2 to amine groups in the Hb molecule. It results from allosteric changes in the quaternary structure of the Hb tetramer. The Bohr effect plays a small role in enhancing O_2 transport both at rest and during exercise. 2,3-BPG is ordinarily present in the red cell at about 5 mmol/L and is considered a metabolite of glycolysis. 2,3-BPG increases in concentration in anemia, at high altitudes, and in chronic lung disease when arterial PO_2 is reduced, as it mainly stems from a hypoxia-induced increase in ventilation. Conversely, 2,3-BPG is depleted in stored bank blood. Elevated 2,3-BPG levels decrease Hb affinity for O2, whereas decreased 2,3-BPG has the opposite effect.

A rightward shift of the ODC impairs O_2 loading in the lung capillaries (which is then reflected in arterial blood) because, at a given PO_2, there is less O_2 bound to Hb. Correspondingly, a leftward shift enhances O_2 loading in the lung capillaries, because at a given PO_2, there is more O_2 bound to Hb. Conversely, a rightward shift enhances O_2 unloading in the tissue capillaries because at a given PO_2 there is less O_2 bound to Hb, allowing more O_2 release to the tissues at any PO_2. In contrast, a leftward shift has the opposite effect.

The physiological consequence of such shifts in the O_2Hb dissociation curve becomes evident during exercise. Exercise (1) increases muscle vascular PCO_2 because of higher CO_2 production; (2) reduces muscle vascular pH both because of that higher PCO_2 and because of lactate efflux into the blood; and (3) increases muscle vascular temperature due to the high metabolic rate. As a result, the ODC rapidly shifts rightward within the muscle blood vessels, enhancing O_2 unloading from the muscle microvascular blood. When that warm, acidic, and hypercarbic venous blood returns to the pulmonary capillaries, the ODC rapidly shifts leftward as (1) lung capillary PCO_2 falls, and pH rises; (2) vascular temperature cools due to fresh air being inhaled at high rates. The leftward shift enhances O_2 loading into the pulmonary capillaries. Thus, the normal physiological responses to exercise lead to constant oscillation of the P50 in the lungs and tissues, favoring both O_2 loading in the lungs and unloading at the muscles, allowing for greater O_2 availability and exercise capacity than if those shifts did not occur.

Effect of hypoxia on the Oxygen–Hemoglobin Dissociation Curve

In humans and other mammals, hypoxia induces a reduction in Hb-O_2 affinity (as measured by the 'standard P50', pH 7.40, PCO_2 = 40 mmHg, 37°), which is attributable primarily to an increase in the red cell concentration of 2,3-BPG. The respiratory alkalosis accompanying hypoxia stimulates red cell glycolytic activity, which, in turn, increases 2,3-BPG synthesis. 2,3-BPG acts as an allosteric effector by preferentially binding and stabilizing deoxyHb, thus shifting the allosteric equilibrium in favor of the low-affinity (deoxy) state.

The hypoxia-induced stimulation of erythropoiesis can also reduce Hb-O_2 affinity as newly produced red cells have a higher 2,3-BPG concentration than older cells. Interestingly, this 2,3-BPG effect is counterbalanced by the increased pH due to respiratory alkalosis. This has been experimentally verified in human climbers reaching high altitudes. During the 1981 American Medical Research Expedition to Everest, blood gases and ODC curves were measured in climbers over several weeks at various stages of the ascent and subsequent descent. At elevations above ~ 6000 m, the affinity-increasing effect of respiratory alkalosis more than counteracted the 2,3-BPG effect. On the summit, (8848 m), extreme $PaCO_2$ (7.5 mmHg) and arterial pH (> 7.7) yielded an estimated blood P50 of 19.4 mmHg, indicating a significant leftward shift. According to the first author of the seminal 1984 paper, "Without this striking increase in O_2 affinity, it is likely that Everest could not be climbed without supplemental O_2.

Effects of Carbon Monoxide on the Oxygen–Hemoglobin Dissociation Curve

CO affects tissue O_2 availability in multiple ways. The molecule binds competitively to the same Fe++ sites in heme as O_2, but with about 200 to 270 times the affinity compared with O_2. This means that extremely low PCO is enough to quickly make Hb binding sites unavailable to oxygen. Even more important, however, is the fact that the presence of CO on Hb increases the affinity of the remaining non-CO bound heme sites for O_2. The main effect of the higher affinity is to impair tissue unloading of O_2 as, at a given venous PO_2, O_2 saturation remains higher than normal, and less O_2 is released to supply the tissues. This leftward shift of the ODC demands a higher-than-normal fall in venous PO_2 to achieve adequate unloading of O_2, which impairs O_2 movement by diffusion from the blood vessels to the mitochondria. Additional factors that further increase the toxic effects of CO are its binding to intracellular heme proteins (e.g., myoglobin, cytochromes), further interfering with O_2 transport and utilization, as well as oxidative stress causing cell damage. Elimination of CO from the body is very slow, with a half-time of about 5 hours if a subject is breathing ambient air but can be substantially accelerated by about a factor of 4 if 100% O_2 is breathed.

Carbon Dioxide Transport In Blood

The tissues produce CO_2 as a byproduct of oxidative phosphorylation. It must be continuously eliminated from the body at the rate at which it is produced to keep blood and tissue PCO_2 constant. The ultimate physiological goal in maintaining homeostasis of CO_2 is the maintenance of pH levels within a narrow range ensuring cellular metabolic stability and function. At rest, a typical normal subject produces 240 mL CO_2/min. Elimination involves moving, by diffusion, the CO_2 from the tissue cellular sites of production into the venous blood draining the tissues. That venous blood must then flow to the lungs, where some of its CO_2 will diffuse from the capillaries into alveolar gas to be eliminated by ventilation. At rest, only about 10% of the CO_2 carried in the venous blood is eliminated, leaving 90 % in the pulmonary venous (and thus also arterial) blood sent back to the tissues so that the acid-base balance is not continuously and seriously disrupted. Total CO_2 concentration in normal arterial blood is about 48 mL/100 mL blood, and that in mixed venous blood is 52 mL/100 mL. Correspondingly, arterial PCO_2 is typically 40 mmHg, whereas mixed venous PCO_2 is about 45 mmHg.
CO_2 is carried in blood in three forms:

- Physically dissolved.

  The solubility of CO_2 in blood at normal body temperature is about 0.067 mL CO_2/100 mL blood/mmHg, which is more than 20 times the solubility of O_2. However, with arterial blood typically having a PCO_2 of 40mm Hg, the concentration of dissolved CO_2 is 40 x 0.067, or 2.7 mL/100mL blood or 27 mL/L, whereas the concentration of dissolved CO2 in venous blood (PCO_2 of 45 mmHg) is 45 x 0.067, or 3.0 mL/100mL blood or 30mL/L. With a standard resting cardiac output of 6 L/min, the volume of CO_2 eliminated from the dissolved pool of CO_2 would be 6 x (30 - 27) mL/min, which is just 18 mL/min. This is only 8% of the 240 mL/min in need of elimination. As with O_2, the physical solution of CO_2 is not a very efficient transport mechanism of the molecule. However, it provides the means by which CO_2 molecules enter the red blood cell to participate in the other two forms of CO_2 transport mentioned below.

- Bound to blood proteins and mostly Hb as carbamino complexes.

  CO_2 does not compete with O_2 for heme-binding sites. Instead, CO_2 is chemically combined with terminal amine groups on the protein molecule. This reaction is swift in both directions and does not require enzymatic facilitation. Carbamino complexes account for approximately 10 % of the CO_2 present in arterial blood. The affinity of CO_2 for hemoglobin increases at lower oxygen saturation, a phenomenon known as Haldane effect. This makes sense since the unloading of oxygen in the

peripheral capillaries enhances the loading of CO_2 produced by the cells, thereby increasing the CO_2-carrying ability of the venous blood. In the lung capillaries, the opposite phenomenon occurs as oxygenation enhances the unloading of CO_2 from hemoglobin and thus facilitates the pulmonary excretion of CO_2. Indeed, the Haldane effect accounts for about 30 % of the amount eliminated from the lung per minute during rest but much less during exercise.

- As bicarbonate ion, HCO_3-

About 85 to 90% of the CO_2 in blood is present as HCO_3- ion, representing the pool from which most CO_2 eliminated by the lungs comes. CO_2 molecules are generated within tissue cells by oxidative phosphorylation. Due to the difference in PCO_2 between the intracellular milieu and the adjacent capillaries, a net movement of CO_2 ensues by diffusion out of the cell and into the plasma in the capillary. From there, most of the CO_2 diffuses into the RBC interior.

The CO_2 molecules that remain in plasma undergo two main reactions:

1) Some of the dissolved CO_2 molecules in the plasma react with water to form carbonic acid (H_2CO_3), which then dissociates into protons and bicarbonate ions according to the following reaction:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad \text{(Equation 7)}$$

2) Some dissolved CO_2 reacts with terminal amines on plasma proteins, rapidly forming carbamino compounds.

The CO_2 molecules that diffuse into the RBC undergo the following reactions:

1) Some remain physically dissolved.
2) A more considerable amount combines with terminal amine groups in Hb.
3) Most of the CO_2 undergoes the same transformation into carbonic acid and then into protons and bicarbonate ions that occur in plasma as per the reaction above. The critical difference between this reaction inside the RBC is that it is facilitated by the enzyme carbonic anhydrase, which is present only inside the RBC and not in the plasma and speeds up the reaction by more than 10,000-fold. Due to this much faster HCO_3- production inside the RBC, the intracellular HCO_3- concentration exceeds that in the plasma, which causes the movement of HCO_3- ions from inside the RBC into the plasma. Protons, which are also produced by the same reaction, do not follow HCO_3- ions in their outward movement due to their positive charge. The overall effect is a charge inequality between RBC and plasma, which is balanced by the movement of negatively charged chloride ions

from the plasma into the RBC through the activity of the Band 3 anion membrane transporter, a phenomenon known as chloride shift. (Figure 6). At the same time, the protons produced by the same reaction are accepted by deoxygenated Hb as it releases O_2 for diffusion to the tissue cells (one proton for each molecule of O_2 released). This reaction reduces the proton number, accelerating the conversion of CO_2 to bicarbonate and the continued release of O_2 from Hb. The same scenario plays out in the pulmonary capillaries in the opposite direction.

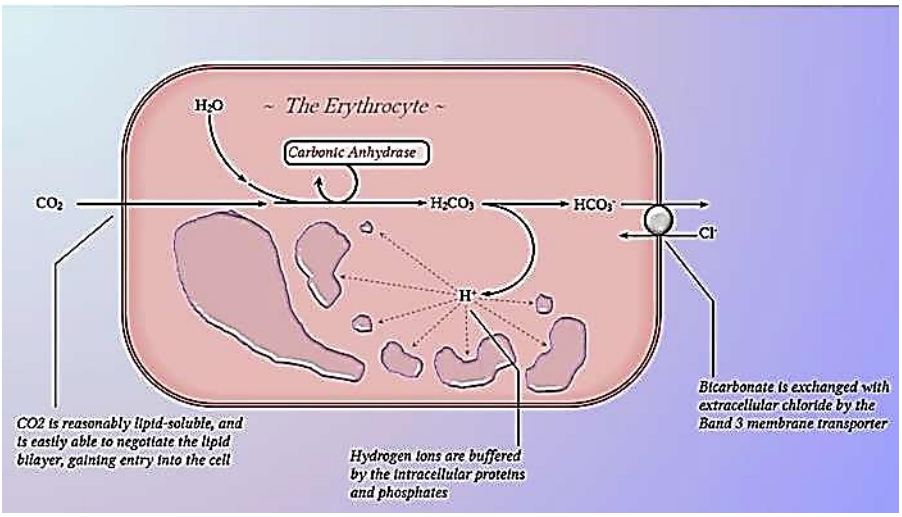

Figure 6: Chloride shift is the mechanism through which chloride is exchanged for bicarbonate inside the RBC as the blood transitions from arterial to venous partial pressure of oxygen. This exchange is complete within 700 milliseconds due to the extremely high enzyme concentrations within the RBC. Adapted from https://derangedphysiology.com/main/cicm-primary-exam/respiratory-system/Chapter-1144/erythrocyte-chloride-shift-hamburger-effect.

In this manner, CO_2 added to the tissue capillary blood ends up in all three transported forms (dissolved, carbamino bound, and bicarbonate ions) inside and outside the RBC. The composite CO_2 dissociation curve reflecting the sum of all 3 forms of CO_2 in plasma and RBC is depicted in Figure 7.

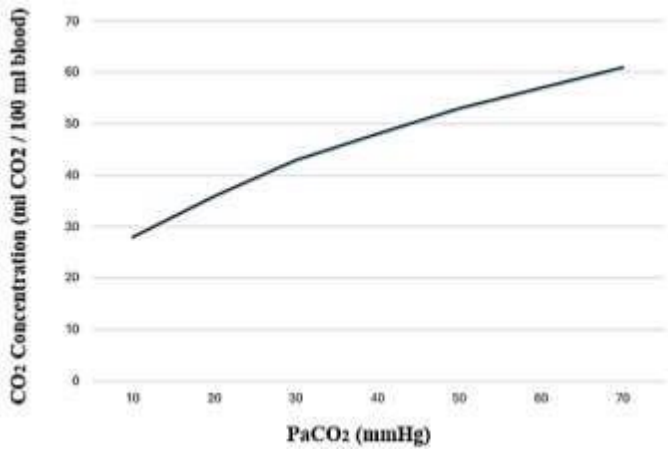

Figure 7: The CO_2 dissociation curve with total CO_2 concentration plotted against PCO_2. The curve shows the sum of the contributions to CO_2 carriage that come from all 3 forms of CO_2. The CO_2 curve is both more nearly linear and 10 times steeper than that for O_2. Adapted from reference 3.

The following observations can be made about the differences between the O_2 and CO_2 dissociation curves (Figure 8).

- The ODC is more curvilinear in shape than that for CO_2 in the physiological and even pathophysiological range. The ODC is steeper at low PO_2 and less steep at high PO_2.

- The average slope of the CO_2 dissociation curve in the physiological range at rest at sea level is some 10-fold more than that for O_2. This means the blood CO_2 capacitance coefficient (β) is higher than that for O_2 and does not change with hypoxia because of the nearly linear CO_2 dissociation curve.

- About 2.5 times as much CO_2 as O_2 (mL/100mL) is present in arterial blood.

- Other than for the minor contribution of physically dissolved O_2, there is a limit to how much O_2 can be carried per 100 mL blood because of the finite number of heme binding sites in hemoglobin (Hb). In contrast, the amount of CO_2 that can be carried in the blood in physical solution and as bicarbonate ion can, in concept, rise without limit as PCO_2 is increased, despite a limit on the number of terminal amine binding sites for CO_2.

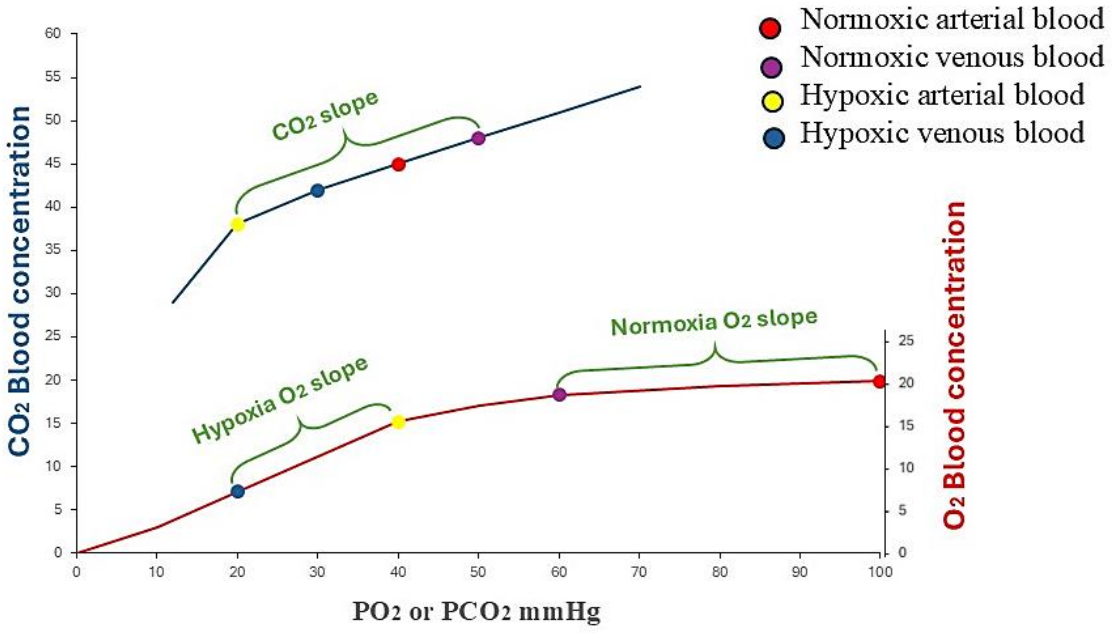

Figure 8: the ODC and CO_2 dissociation curves are compared in the same graph to illustrate the significant differences between O_2 and CO_2 in the shapes and slopes of their respective dissociation curves both in normoxia and hypoxia. The two properties (shape and slope) drive most of the differences between O_2 and CO_2 exchange at every step of the O_2 and CO_2 transport pathway. Adopted from reference 8.

Like the ODC, the CO_2 dissociation curve does not represent a static relationship: it is affected by the O_2 saturation of Hb, temperature, and, most importantly, pH (i.e., acidosis and alkalosis). Removal of protons by alkalosis drives the carbonic anhydrase reaction in Equation 7 rightward by mass action. This causes the bicarbonate ion, the central CO_2 transport molecule, to increase in concentration. The reverse occurs during acidosis, where less bicarbonate exists as the equation is driven leftward by excess protons.

Diffusion equilibration in the lung and peripheral tissues

Fresh gases and venous blood are delivered to and removed from a large alveolar capillary surface area through the airway and vascular trees. In an adult, inhaled air enters the trachea with a cross-sectional area of 3 cm^2 and is delivered to the alveoli with a surface area of 140 m^2, roughly the size of tennis court . Similarly, the pulmonary vascular tree begins as the main pulmonary artery and repeatedly bifurcates into arterioles and capillaries that cover 85–95 % of the alveolar surface. An exceptionally thin membrane of only 1 mm separates the alveolar gas and blood compartments, allowing gases to diffuse rapidly between them (29,30). Due to the large blood volume within the alveolar capillaries, blood flow slows, and the transit time for blood increases, typically to 0.25–0.75 s, allowing more time for gas exchange. The capillaries surrounding the alveolus deliver mixed venous blood with a low partial pressure of O_2 ($P\bar{v}O_2$). The PO_2 in the alveolar gas (PAO_2) is much higher than in the capillary blood.
As a red cell with a $P\bar{v}O_2$ (normally 40 mmHg) enters the pulmonary capillary, the much higher PAO_2 (normally 100 mmHg) results in a rapid diffusive flux of O_2 from gas to blood. A simple diffusion equation, the Fick law of diffusion, can express that initial diffusive flux:

$$\text{Initial } O_2 \text{ flux} = DL \times [PAO_2 - PvO_2] \quad \text{(Equation 8)}$$

In the equation above, DL denotes the diffusion coefficient (commonly called diffusing capacity), which is the rate of movement of (dissolved) O_2 molecules through the alveolar blood: gas barrier from the alveolus into capillary plasma. This is proportional to the total pulmonary capillary surface area available for O_2 diffusion and the physical solubility of O_2 in the alveolar wall, which is equal to that in plasma, i.e., 0.003 mL O_2/100 mL blood/mmHg PO_2, and inversely proportional to the alveolar wall thickness which is the distance O_2 must traverse from gas to plasma. In other words, DL can be expressed by the following equation:

$$DL = K \times A \times \alpha/T \quad \text{(Equation 9)}$$

where A is the capillary surface area, α is the O_2 solubility in the alveolar wall, T is the alveolar wall thickness, and K is a constant of proportionality.

As O_2 moves from the alveolar gas into the capillary, the capillary PO_2 increases and its difference from the PAO_2 becomes less; thus, the flux rate falls. At a certain time t during the flow of blood through the capillary, the flux of O_2 into the capillary can be described by:

$$O_2 \text{ flux } (t) = DL \times \{PAO_2 - PcO_2 (t)\} \quad \text{(Equation 10)}$$

where PcO_2 is the capillary partial pressure. At the same time, the O_2 flux does not only depend on the oxygen concentration gradient over time between the alveolus and capillary, but also the capillary blood volume Vc, and this relationship can be described by the following equation:

$$O_2 \text{ flux } (t) = Vc \times [O_2] \text{ change/time} = Vc \times d[O_2] / dt \quad \text{(Equation 11)}$$

Combining all the above equations, we have:

$$d[O_2] / dt = [K \times A \times \alpha / (T \times Vc)] \times [PAO_2 – PcO_2 (t)]$$

Recalling that $d[O_2]/dt$ can be expressed as $dPO_2/dt \times \beta$ where β is the slope of the ODC curve, the above equation can be rewritten as follows:

$$dPO_2 / dt = L \times \alpha/\beta \times [PAO_2 – PcO_2] \quad \text{(Equation 12)}$$

where L is a compound term equal to K x A / (T x Vc) and, thus, unrelated to any particular gas.
Let us now focus on two specific time points: the time right before the capillary blood comes in contact with the alveolus (when the capillary PO_2 is equal to the $P\bar{v}O_2$) and the time point when the blood has just left the lungs and is on its way to the left atrium (we will call the PO_2 at that time $PecO_2$ for "end-capillary"). The time difference between these two points is called transit time (tt) and is given by the ratio between the capillary blood volume and the cardiac output. With this consideration, the dPO_2/dt becomes $PAO_2 - P\bar{v}O_2 / tt$, and the equation above takes one last iteration:

$$PAO_2 - PecO_2 / PAO_2 - P\bar{v}O_2 = \exp (-L \times \alpha/\beta \times tt) \quad \text{(Equation 13)}$$

The maximum value the right-hand side of this equation can attain is 1, and the minimum is 0. If the value is 0, the PAO_2 is equal to the $PecO_2$, and thus, there is complete diffusion equilibration, whereas when the value is 1, the $PecO_2$ is equal to $P\bar{v}O_2$, and thus, there is no diffusion.

Inert gases, which are present in blood and tissues only in physical solution, have an α/β ratio equal to 1. This means that their diffusion only depends on the structural characteristics of the alveolar-capillary barrier and the cardiac output and is accomplished very quickly; thus, it is never diffusion-limited.
O2, however, has an α much less than β. At rest and in normoxia, α/β is 0.003 / 0.08 = 0.04, making O_2 much more vulnerable to diffusion limitation than inert gases. In hypoxia, the α/β ratio falls further because of the steeper slope of the ODC and becomes 0.003 / 0.3, which is only 0.01.

The above has important clinical implications: during exercise at sea level, some people may experience a small degree of diffusion limitation while others will not. Typically, athletes with high cardiac outputs and, thus, short blood capillary transit times develop diffusion limitation on exercise. In hypoxia, typically, diffusion limitation will not be observed at rest because the transit time remains around 0.75 seconds. However, during exercise in hypoxia (i.e., high altitude), some degree of diffusion limitation is expected in all healthy humans.

In the tissues, the same principle applies. The O_2 α/β ratio remains the same at rest. The equivalent of lung L for the tissues has higher values due to 1) the much larger distance the RBC must cross between the capillary lumen and the mitochondria and 2) the smaller surface available for diffusion when individual tissues are considered. This does not matter at rest when no diffusion limitation of O_2 unloading in the tissues is thought to occur. However, such limitations seem to be present during normoxic and hypoxic exercise as demonstrated by two facts: One is that the venous blood draining the contracting muscles is never fully depleted of O_2 even during maximal exercise, even though in trained athletes, the muscle venous O_2 saturation may be as low as 20%. The second observation is that when trained athletes undertake maximal exercise breathing 100% O_2, maximal external work and maximal O_2 uptake increase, even if by only small amounts.

For CO_2, on the other hand, α is 0.067 ml/100 ml blood/mmHg PCO_2. In contrast, β is 0.8 ml/100 ml blood/mmHg PCO_2 at rest and 0.5 ml/100 ml blood/mmHg PCO_2 during exercise, giving a ratio of 0.08, which further increases to 0.13 during exercise and no notable change during hypoxia due to the nearly linear chape of the CO_2 dissociation curve. This, in turn, suggests that diffusion limitation is not an issue for CO_2 either in pulmonary or tissue exchange. This is the case at rest, during exercise, and in both hypoxic and normoxic conditions.

Changes in convective O_2 and CO_2 transport mediated by changes in the shape and position of the respective dissociation curves.

The cardiovascular system is responsible for the convective O_2 transport from the lungs to the peripheral tissues, where the O_2 is consumed. The Fick Principle states that the rate of O_2 consumption by the perfused tissues is equal to the product of blood flow to the tissues and the difference in O_2 content between the arterial blood entering the tissue capillary bed and the venous blood leaving the capillary bed. Accordingly, the rate of O_2 consumption ($\dot{V}O_2$) is the product of cardiac output (Q) and the difference in the O_2 contents of arterial and venous blood (CaO_2 and CvO_2, respectively):

$$\dot{V}O_2 = Q \times CaO_2 - CvO_2 \quad \text{(Equation 14)}$$

The HbO_2 dissociation curve graphically depicts the Fick principle when the vertical axis is expressed in terms of blood $[O_2]$ (Figure 9).

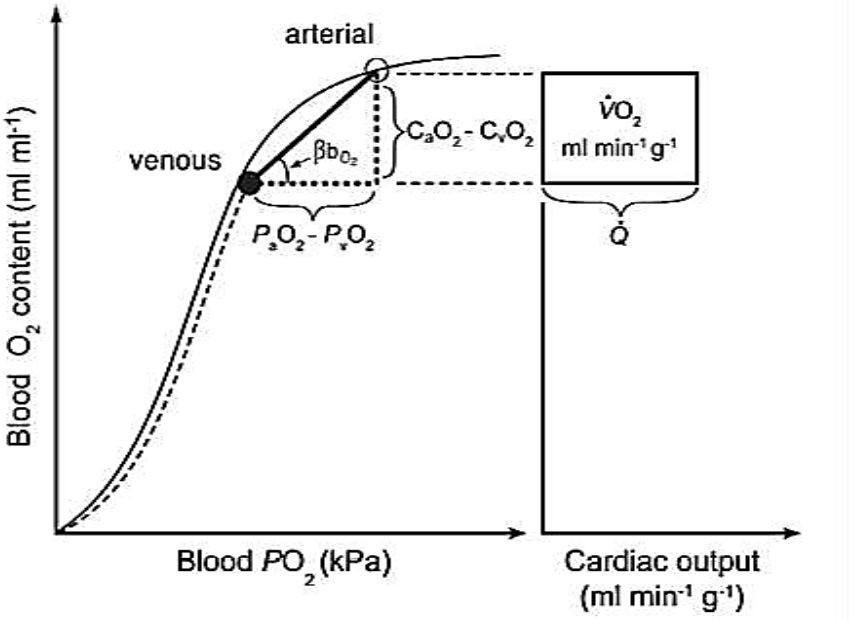

Figure 9: Total O_2 consumption is proportional to the cardiac output Q as well as the product of β, and PaO_2 - PvO_2 and can be enhanced by increasing Q and/or increasing β. Increases in β produce a corresponding increase in CaO_2 - CvO_2 through shifts in the shape of the ODC. From reference 12 with permission.

As discussed earlier, the slope β represents the change in $[O_2]$ for a given change in PO_2 and, for the point in the curve where the venous blood transitions into arterial blood, it represents the arterial-venous difference in O_2 content ($CaO_2 – CvO_2$) for a given arterial-venous difference in O_2 tension ($PaO_2 – PvO_2$). An increase in the slope of the line increases $CaO_2 – CvO_2$ for a $PaO_2 – PvO_2$. This, in turn, means that equation 14 can be re-written in terms of PO_2, PVO_2, and the blood-O_2 capacitance coefficient, which quantifies the amount of O_2 that is unloaded for a given arterial-venous difference in PO_2:

$$\dot{V}O_2 = Q \times \beta \times (PaO_2 - PvO_2) \quad \text{(Equation 15)}$$

In other words, the partial pressure of O_2 in the venous blood from a tissue (region) with a given VO_2 / Q ratio does depend on the slope of the ODC and increasing β (via changes in Hb concentration and/or changes in Hb-O_2 affinity) increases the quantity of O_2 transported to the tissue for a given difference in PO_2 between the sites of O_2 loading and unloading.

For CO_2, the equation becomes:

$$\dot{V}CO_2 = Q \times \beta \times (PvCO_2 - PaCO_2)$$

where $\dot{V}CO_2$ is the CO_2 production by the tissues, $PvCO_2$ is the venous blood partial pressure for CO_2, and $PaCO_2$ is the arterial partial pressure for CO_2.

From this equation, it becomes clear that venous PCO_2 is significantly associated with the slope β of the CO_2 dissociation curve, which is much higher for CO_2 than for O_2. This difference explains why the fall in PO_2 from arterial to venous is much higher than the increase in PCO_2 from arterial to venous for the same $\dot{V}O_2$, $\dot{V}CO_2$ and Q.

Conclusion

This chapter provided a review of the standard descriptions of how O_2 and CO_2 are carried in the blood and exchanged between alveolar gas and blood, on the one hand, and between tissue blood and tissue cells, on the other hand, emphasizing the integrated nature of these processes and their critical role in maintaining physiological homeostasis. Furthermore, the fact was highlighted that the differences in these dynamic processes between the two gases are due to differences in their dissociation curves, especially in their different overall shapes and slopes. Finally, how the slope of these curves explains the diffusion and convection dynamics of the two gases was briefly discussed. Understanding these mechanisms is essential for advancing clinical interventions and improving outcomes in conditions affecting gas exchange.

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