Alveolar Gas Diffusion

You have heard discussions, and read text concerning gas diffusion, as this process obviously occurs during external and internal respiration. However, what determines the process of gas diffusion? Why does it occur? How can it be altered? Are some gases more effectively diffused than others? All of these questions have relevance to exercise physiology, regardless of whether the diffusive process occurs in the lung or in the peripheral tissues, such as contracting skeletal muscle. I am hoping that after reading this Topic you will know exactly what occurs when the word diffusion is mentioned, and in addition, you will gain in your understanding of connecting morphology to function to ensure optimal gas exchange.

To appreciate how the lungs and both internal and external respiration function, and sometimes dysfunction during intense exercise, there are some important features of **gas diffusion** that you must understand. Furthermore, such understanding will reveal that oxygen has such poor diffusive properties that exacerbate the **hypoxia** of high **altitude**, and even prevent complete external respiration in highly trained athletes during intense exercise at sea level.

Factors That Influence Gas Diffusion

To begin with, let's look at the factors that combine to determine how effective a gas can diffuse within the human body, and especially across one or multiple membranes. Such factors consist of the water solubility of the gas, the surface area for diffusion, the partial pressure gradient for diffusion, the hydration of the medium, the thickness of the membranes (if any) within the diffusion distance, the diffusion distance itself, and the gas molecular weight. These factors combine to form Equation 1.

$$Gas\ Diffusion \propto \frac{A}{T} \times D \times (P_1 - P_2);\ where\ D \propto \frac{Sol}{\sqrt{MW}}$$

$$A = Area;\ T = Thickness;\ D = Diffusion\ Constant;$$

$$P = Gas\ Pressure;\ Sol = Solubility;\ MW = Molecular\ Weight$$

Equation 1

Table 1 presents the **solubility coefficients** for gases of physiological relevance. The solubility coefficients are determined based on the volume of a specific gas that dissolves in water for a given partial pressure and water temperature. Note that the solubility coefficient for carbon dioxide is 23.75 times that of oxygen. Thus, oxygen diffusion is very dependent on the other components of Equation 1, such as the partial pressure gradient, surface area for diffusion, and thickness/distance over which diffusion must occur.

Table 1. Solubility coefficients for the main gases.

Gas	Solubility Coefficients
Oxygen	0.024
Carbon dioxide	0.57
Nitrogen	0.012
Helium	0.008

at 37 °C

The solubility coefficient can be used to calculate the concentration of gases dissolved in biological fluids. This is a simple calculation, being the product of the coefficient and the

partial pressure of the gas as shown in Equation 2. Despite the much higher partial pressure of oxygen in arterial blood (PaO_2), the CO_2 content of arterial blood is close to 8 times that for O_2.

$$Dissolved\ gas\ concentration = PPgas \times Sol$$
$$for\ O_2 = 104 \times 0.024 = 2.5mL/L \sim 0.3mL/100mL$$
$$for\ CO_2 = 40 \times 0.57 = 22.8mL/L \sim 2.3mL/100mL$$

Equation 2

Alveolar Gas Diffusion

Figure 1 is an electron micrograph of the cross section between a capillary and alveolus, often termed the **blood-gas interface**. Note the capillary endothelium, fluid interstitial space, and alveolus epithelium. The density of the capillaries within the connective tissue of the alveoli is enormous, as shown in Figure 2. As previously emphasized, there needs to be a match between lung inflation at the level of the alveoli and blood perfusion surrounding alveoli.

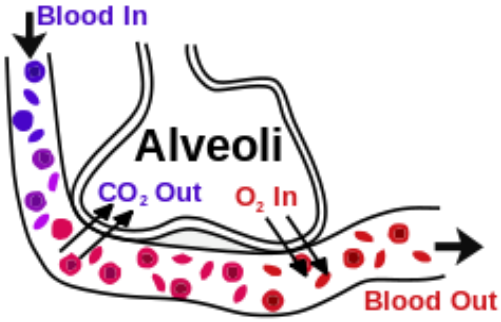

Figure 1. The blood-gas interface within the lung.

Figure 3 illustrates the time for equilibration between alveolar and arterial blood gas partial pressures for oxygen and carbon dioxide. The obvious difference between the two gases is that equilibration is faster for carbon dioxide than oxygen. There are a couple of reasons for this. First, the overall diffusability of carbon dioxide is greater than that for oxygen due in part to the 23 fold greater solubility of CO_2 vs. O_2. The second is that carbon dioxide has a lower partial pressure gradient. Of course, based on Equation 1, this slows diffusion, but the small diffusion gradient and the high diffusability of carbon dioxide make equilibration a quick event, both in the lung and at the level of the tissue. Compare this to oxygen, where the diffusion gradient is quite large, being 60 mmHg or 12 times larger than for carbon dioxide at rest within the lung, and increasing to perhaps 100 mmHg within intensely contracting skeletal muscle. I have provided this data for you in Program 1, along with extrapolations of exponential functions for both carbon dioxide and oxygen at the level of contracting muscle for different exercise intensities and different altitudes. This data is also presented in Figures 4 and 5.

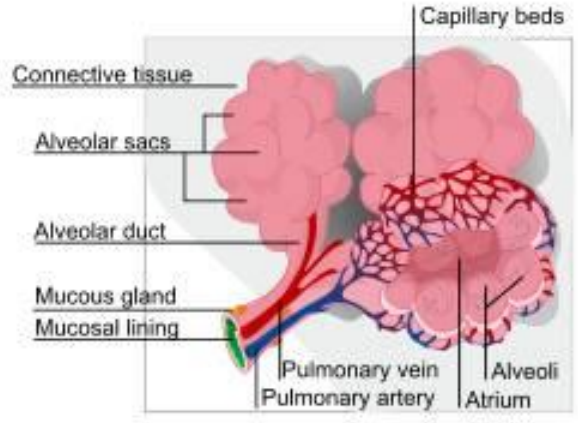

Figure 2. To support effective external respiration and gas diffusion, the density of pulmonary capillaries surrounding alveoli is enormous.

The other important variable in whether a physiological gas has time to equilibrate is the transit time for blood within the respiratory zone of the lung. For the peripheral tissues this would translate to the time within the capillaries of the muscle vascular bed. We are not sure what such transit times are for the peripheral muscle, but research has verified that **lung transit times** approximate 600 ms for rest conditions, and can decrease to close to 300 ms during high cardiac output conditions that accompany intense exercise. Note, for higher and higher cardiac outputs, the only way to maintain a constant transit time would be to open more and more arterioles and capillaries. Obviously, such acute increases in vascular density have clear limitations. Available research on this topic has revealed that pulmonary transit times do not decrease below the time for oxygen equilibration in the lung at near maximal exercise in trained subjects (based on the equilibration time known for rest conditions). Such results have been interpreted to indicate that any non-equilibration of a physiological gas within the lung must be due to other issues influencing gas diffusion (Equation 1). However, I find this interpretation to be over-simplistic. If there is non-equilibration between alveolar to blood PO_2 in the lung, then it is obvious that there is a mismatch between transit time and the required time for equilibration (assuming no physiological shunts are exacerbated during more intense exercise). Thus, factors must be involved that lengthen the required duration for equilibration (e.g mild edema). This could be a normal phenomenon in all subjects that only reveals itself in trained athletes due to their high cardiac output capacity.

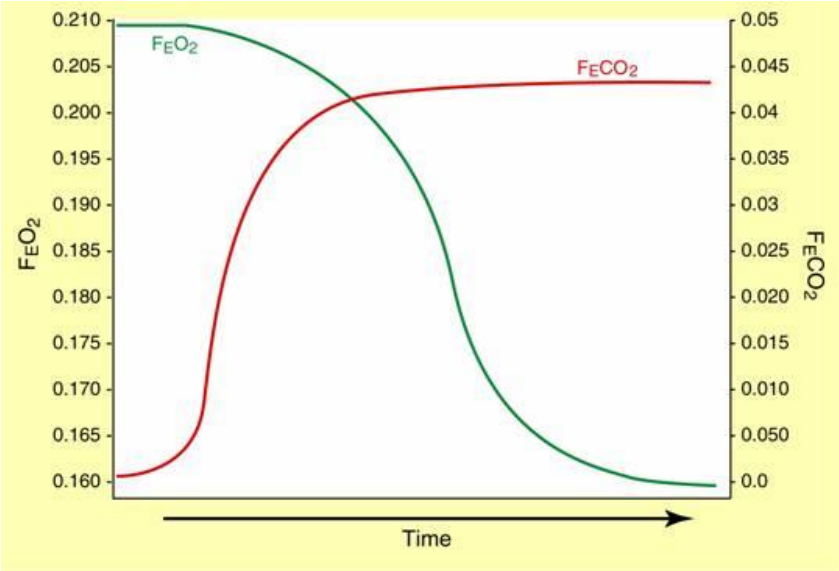

Figure 3. The relative times for equilibration between alveolar and arterial blood gas partial pressures for oxygen and carbon dioxide.

The bottom line is that oxygen is nearly at the limit of its diffusability to allow full equilibration at rest in the lung, let alone during exercise. We know that in some highly trained endurance athletes there is a limitation to oxygen equilibration in the lung even at sea level. We know this because measures of PaO_2 decrease during intense exercise approaching VO_2max, as shown in Figure 6 and termed **exercise-induced hypoxemia**. I repeat, this response does not occur in all trained subjects, and the most likely explanation for this response is a combination of small changes in all limits to gas diffusion in the lung, with perhaps greatest weight being placed on an increasing tissue thickness and diffusion distance within the blood to alveolar space caused by increased

pulmonary blood pressure, extravascular movement of water and therefore a slightly increasing edema of the blood-gas interface. Remember that such increased edema would oppose oxygen diffusion on two issues: greater hydration and greater diffusion distance. The higher the altitude, the greater the fall in PaO_2 during incremental exercise in all subjects.

Presumably the same concerns for oxygen diffusion occur to the peripheral tissues and internal respiration. However, we do not have the tools to study peripheral oxygen diffusion in humans. Certainly, data showing very low (< 3 mmHg) PO_2 conditions within muscle (based on **oxy-myoglobin** data) during intense exercise would indicate the ability for skeletal muscle to extraction almost all blood oxygen. This in turn implies that in the peripheral tissues there must be adequate time for oxygen unloading from **hemoglobin** to **myoglobin**, and then to the mitochondria. Research also shows that when added oxygen is present either in the form of increased hemoglobin, or increased PaO_2 from breathing **hyperoxic** gas, muscle can continue to increase its rate of oxygen extraction and metabolic consumption. Most physiologists are satisfied that the cumulative evidence suggests that muscle has a greater capacity for oxygen consumption than the capacity for muscle blood flow and oxygen delivery. This means that in healthy muscle, VO_2 is limited by oxygen delivery and not peripheral diffusion and cellular O_2 consumption.

Finally, it is worth noting that internal respiration gas diffusion kinetics would be muscle motor unit and fiber type specific, as a greater **mitochondrial density** would increase oxygen transfer from myoglobin to mitochondria, sustain a greater partial pressure gradient for oxygen and thereby facilitate diffusion.

Glossary Words

gas diffusion is the process by which a gas moves along its partial pressure gradient, resulting in its redistribution. The extent of diffusion is directly dependent on the cross sectional area exposed to the gas, gas water solubility and the partial pressure gradient, and inversely dependent on the thickness of membrane(s) separating the two gas regions and the gas molecular weight.

hypoxia refers to a reduction in the partial pressure of oxygen in air from standard conditions (P_IO_2 ~ 159 mmHg for clean and dry air at sea level).

altitude is the distance above sea level.

solubility coefficients are determined based on the volume of a specific gas that dissolves in water for a given partial pressure and water temperature.

blood-gas interface is the distance a gas must diffuse across to move from pulmonary blood in a capillary to within the alveoli.

lung transit times are the times it takes blood to move through the external respiration

zone of the lung.

exercise-induced hypoxemia refers to the lowering of the arterial partial pressure of oxygen that occurs in some athletes during intense exercise, and almost all individuals during exercise at increasing altitude.

oxy-myoglobin is the term for myoglobin bound with oxygen.

hemoglobin is the blood oxygen transport protein located on the surface of red blood cells.

myoglobin is the intramuscular oxygen binding protein.

hyperoxic refers to an increase in oxygen partial pressure above normal at sea level, or another reference altitude.

mitochondrial density refers to the mitochondrial mass expressed relative to tissue mass.