Respiratory System Physiology

Comprehensive File 1

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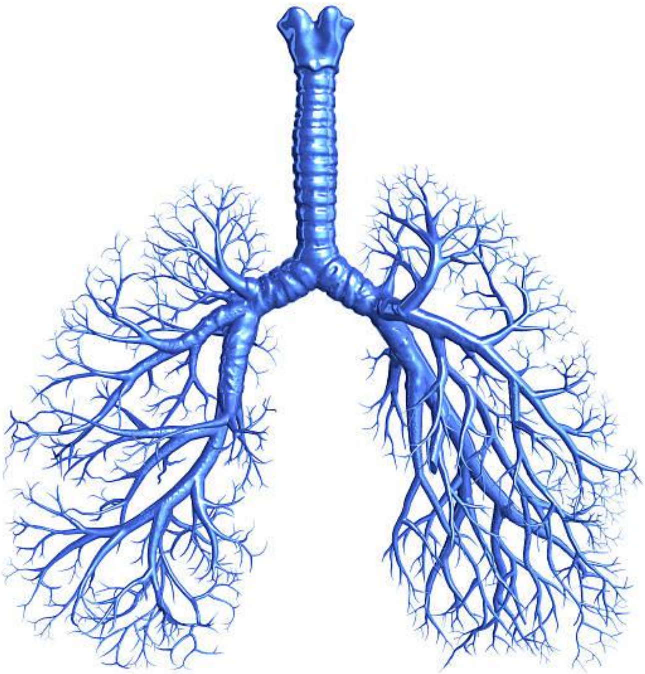

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Overview

The respiratory system is responsible for the homeostasis of oxygen (O_2), carbon dioxide (CO_2) and pH in our bodies. Normal physiological are around the following values:

- Arterial oxygen pressure (P_aO_2) = 100 mmHg
- Arterial carbon dioxide pressure (P_aCO_2) = 40 mmHg
- pH = 7.4 (the renal system also plays an important role in pH regulation).

These are collectively referred to as ABGs (arterial blood gases). Normal ABG values do not necessarily indicate a normal lung, as the lung has a good functional reserve that compensates in case of diseases. This will be addressed in the next lecture.

The lungs have a huge diversity of non-respiratory functions that include the aid in venous return through inspiration, regulation of arterial blood pressure through the conversion of angiotensin I into angiotensin II, acid base balance through the regulation of CO_2 levels that directly affect the levels of H^+ and therefore pH levels. These functions are not the scope of this module, and our main focus will be on the regulation of O_2 and CO_2 levels.

The lungs and the heart are interconnected, and this means that conditions that affect the heart will be reflected on the lungs, and vice versa. For example, left heart failure leads to pulmonary edema, while many lung diseases result in right heart failure (Cor pulmonale).

Oxygen

Cells require oxygen as the terminal electron acceptor in the oxidative phosphorylation process that is carried out by the mitochondria for the generation of around 36 ATPs from 2 pyruvate molecules that were generated by glycolysis. In the absence of oxygen, pyruvate can't be utilized to produce that amount of ATP, and the cell will end up with only 2 ATPs generated through anaerobic glycolysis.

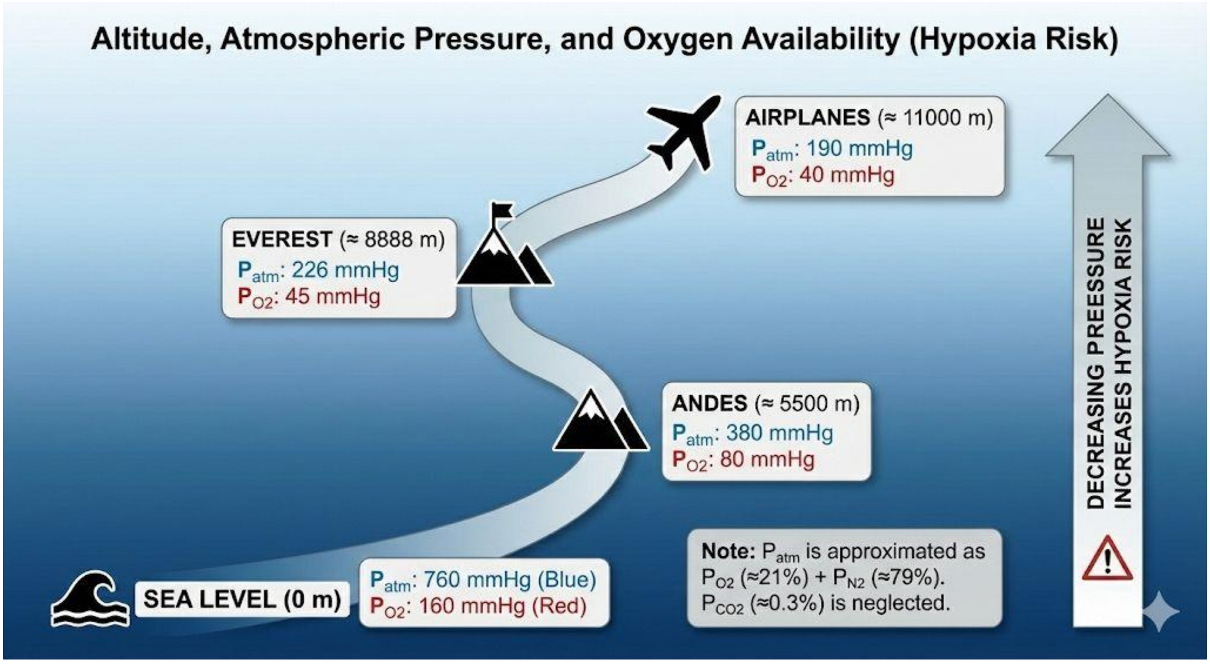
Hypoxia is defined as decreased oxygen utilization by the body cells.

Hypoxemia is defined as decreased oxygen concentration in the blood.

Note that hypoxia is not always due to hypoxemia as it could be due to the failure of the mitochondria to utilize oxygen even though normal oxygen concentrations are present in the circulation. This could be due to defects in the respiratory chain components or due to toxins, such as cyanide (CN^-) or some bacterial products.

One important cause of hypoxia in healthy individuals is the unavailability of oxygen in the air. This is seen in the case of altitude hypoxia. Atmospheric pressure is the weight of a column of air extending between the atmosphere and the ground over the area under it; at sea level, P_{atm} is 760 mmHg, and it starts to decline with increasing elevation. Take your time analyzing the picture below; notice how both the total P_{atm} and partial pressures of gases, such as PO_2, change. Beware that the relative composition of air remains the same, irrespective of the elevation ($PO_2 = 21\% * P_{atm}$).

Climbers develop acclimatization (أقلمة أو تأقلم) as they slowly climb the summit; detailed mechanisms will be discussed later.

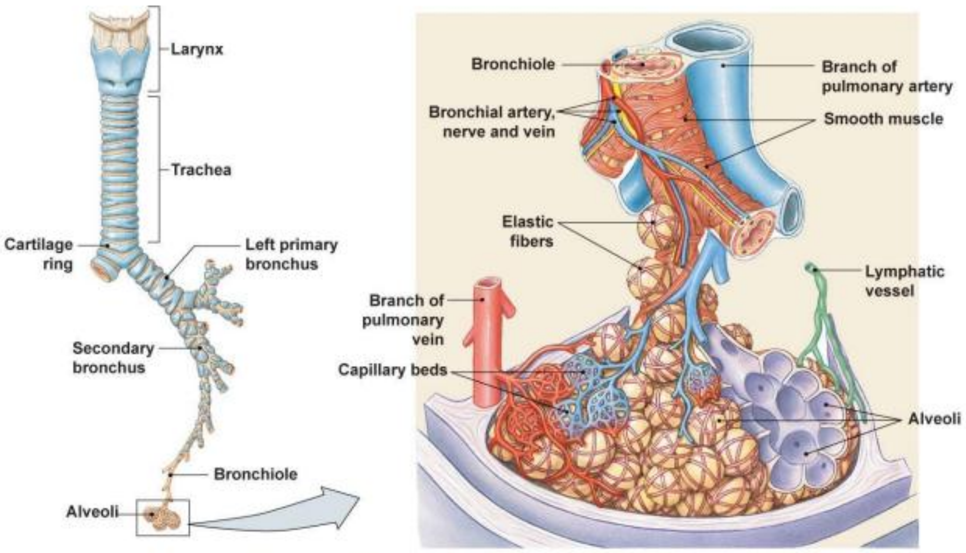


The Respiratory Tract

	Name	Division	Diameter (mm)	How many?	Cross-sectional area (cm^2)
Conducting system	Trachea	0	15-22	1	2.5
	Primary bronchi	1	10-15	2	↓
	Smaller bronchi ↓	2	1-10	4 ↓	
		3			
		4			
		5			
		6-11		1×10^4	
	Bronchioles	12-23	0.5-1	2×10^4 ↓ 8×10^7	100 ↓ 5×10^3
Exchange surface	Alveoli	24	0.3	$3\text{-}6 \times 10^8$	$>1 \times 10^6$

The respiratory system is composed of three components: **airways, alveoli, and vascular components**. Airways start with the nose and the mouth, then the pharynx, larynx, and trachea. At the end of the trachea, the first division occurs to give the left and right primary bronchi, and divisions of the airway continue, reaching the **16th division** also known as the **terminal bronchiole**. The **0-16th divisions** resemble the **conductive zone**, whose main function is allowing air to enter into subsequent divisions. The airway in general shows resistance to entering of air, and this resistance is highly influenced by its diameter; remember that $R \propto \frac{1}{r^4}$. Diseases of obstructive pattern affecting the conductive zone lead to increased resistance, which causes difficulty in expiration, giving a wheezing sound. Note that no gas exchange happens across this pathway as its wall is thick. The conductive zone (0-16th divisions) is also called **the anatomical dead space**, as no gas exchange happens across its wall. However, it is not dead functionally, as it has some other functions.

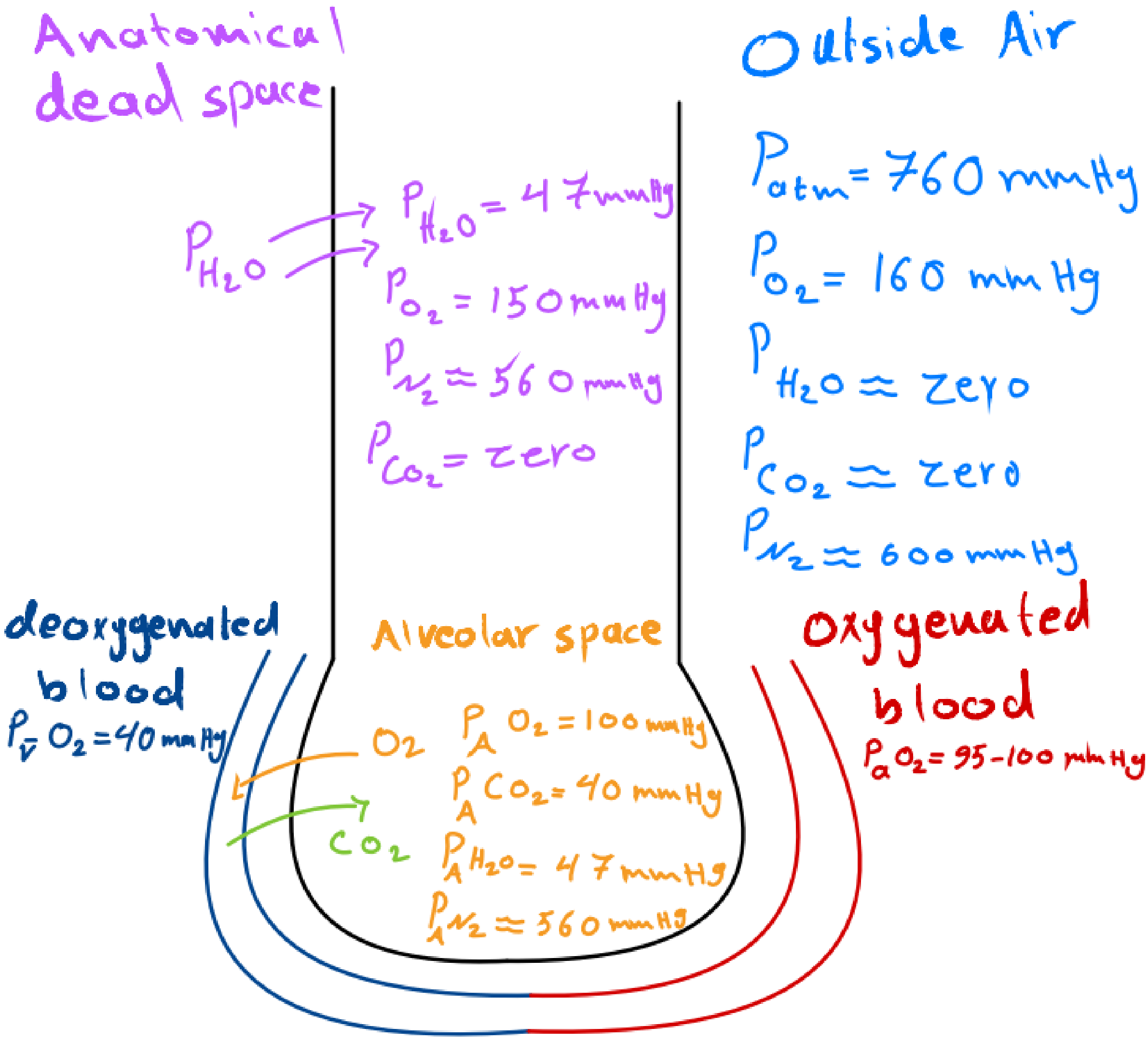
Divisions continue after the terminal bronchiole, starting from the **17th division,** which is called the **respiratory bronchiole**, until the **23rd** division (or 24th) that gives the **alveoli**. The **17th-23rd divisions** resemble the **respiratory zone**. The alveoli resemble balloons in shape; they are 600-800 million in number, each with a diameter of about 300 μm. They are inflatable and compliant with minimal resistance. Diseases of restrictive pattern that affects the alveoli lead to difficulty in inspiration. The figure below shows how the alveoli are extensively vascularized as hundreds of capillaries surround each alveolus.



Back to gas pressures, Dalton's Law, or the Law of Partial Pressures, states that the total pressure exerted by a mixture of gases is equal to the sum of the partial pressures of the gases in the mixture. At sea level, P_{atm} is around 760 mmHg, and oxygen contributes to around 21% of P_{atm} (160 mmHg), and nitrogen contributes to around 79% of P_{atm}. CO_2 contribution is about 0.3%, so it is neglected.

Partial pressure of water vapor (P_{H2O}) in the atmosphere is around zero, thus the air is considered dry. Our bodies cannot tolerate dry air as it is damaging to the airway, so once we breath in, the conductive zone will add water vapor that will have the pressure of 47 mmHg at a core body temperature of 37 Celsius. As the total pressure is the same in the outside air, airways, and alveoli, the added gas will displace gases from the inspired air, thus oxygen and nitrogen will contribute to 713 mmHg (760 – 47). This causes the airway partial pressure of oxygen to be equal to 150 mmHg (0.21 * 713).

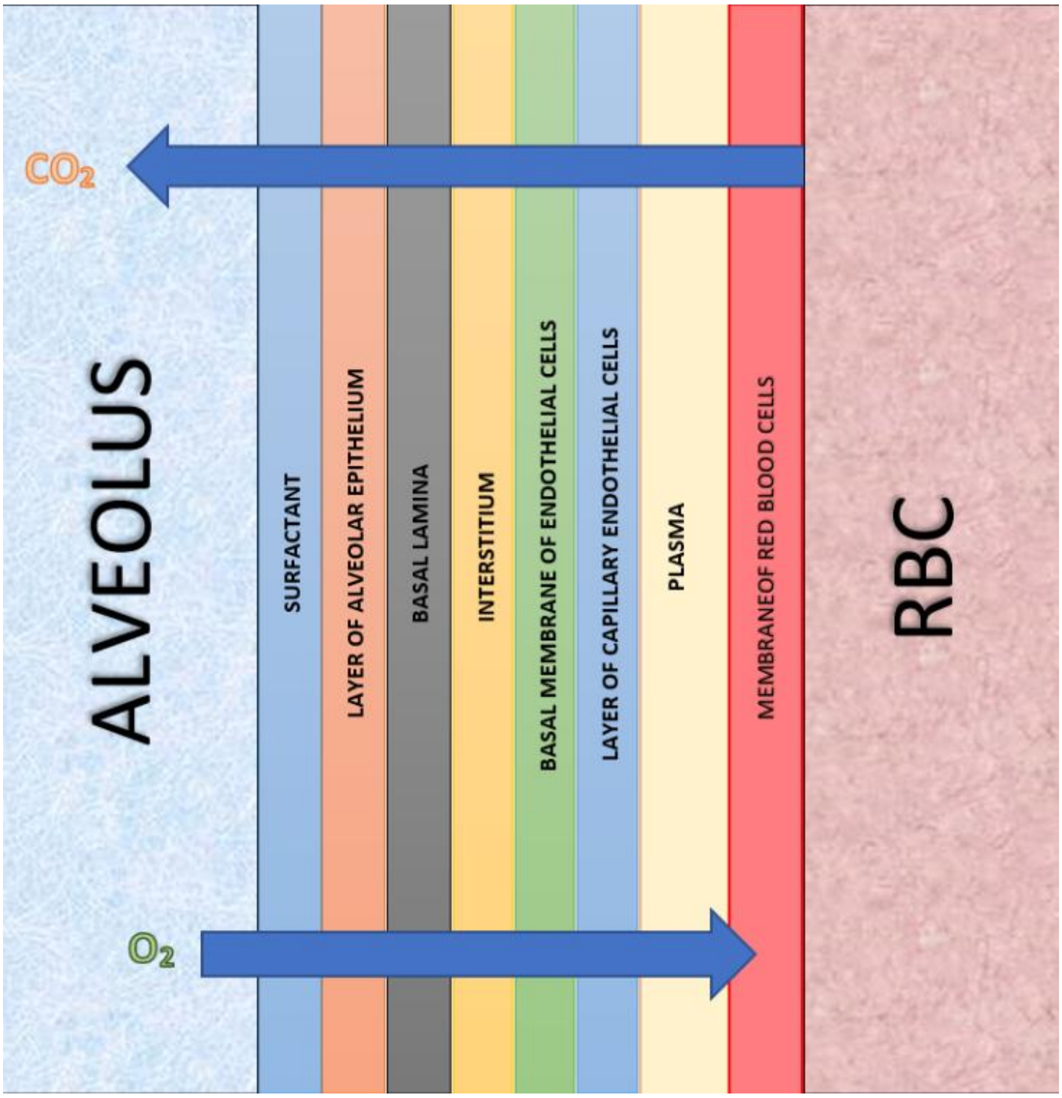
In the alveoli, oxygen starts to diffuse out down its pressure gradient to saturate the blood, thus $P\bar{v}O_2$ (the "v" stands for venous, and the bar stands for "mixed", as the venous blood that is drained from the systemic veins is mixed before going through the pulmonary artery) will have oxygen added to it, leading to a P_aO_2 (arterial partial oxygen pressure) of around 100 mmHg. Similarly, as CO_2 diffuses from the blood into the alveoli, its partial pressure in the blood will decrease. N_2 and H_2O are considered spectators; we are only concerned about O_2 and CO_2 pressure changes.



When oxygen diffuses from the alveoli to the blood, it has to cross 6 layers: (read the figure below from left to right)

1. The surfactant layer
2. The alveolar epithelium
3. The alveolar basement membrane
4. The interstitium
5. The basement membrane of the endothelium
6. The endothelial cell

Neglecting the plasma and the membrane of the RBCs, the 6 layers above are collectively called the **respiratory membrane**, spanning a thickness of 0.2-0.6 μm.



Although the respiratory membrane consists of 6 layers, oxygen can pass through all 6 layers, by simple diffusion, without being interrupted at all. In fact, oxygen can cross any biological membrane as if the membrane does not exist. It is thus said that oxygen availability for the cells is **not diffusion-limited**, meaning that if oxygen is not available for the tissues, diffusion-related concerns are not the cause in normal physiological conditions (in some pathologies, oxygen diffusion can be impaired).

However, oxygen availability is **perfusion-limited**, meaning that the availability of oxygen depends on the perfusion (amount of blood that arrives to the alveoli by the vasculature); the more the perfusion, the higher the amount of oxygen supplied to the circulation. In a normal person in normal conditions, the cardiac output is about 5 L/min, so oxygen availability to the tissues it determined by this amount of blood. If the person is an athlete in a marathon, up to 35 L/min may arrive to their alveoli, increasing gas exchange and thus oxygen availability.

Carbon dioxide holds the same property as oxygen, but it passes through membranes 20 times better than oxygen. The reason behind this will be discussed later in this file.

As discussed above, in some pathologies, the gas exchanged is impaired; this is called respiratory failure, and it is generally of 2 types. Carbon dioxide can still pass normally in type I respiratory failure. However, if the disease is severe enough (type II), both oxygen and carbon dioxide diffusion will be impaired. See the following table for comparison between the two types of respiratory failure.

Situation	***P_aO_2***	***P_aCO_2***
Type I Resp. Failure	↓	Normal
Type II Resp. Failure	↓↓↓	↑

Gas exchange has to occur across the respiratory membrane, and if it does not, blood composition of gases cannot be modified as the blood will return to the heart to be pumped to the systemic arteries, with the composition present after the alveoli.

Lung diseases are divided into 3 parts:

- 70% are of obstructive pattern – COPD (problems in expiration):
  Chronic bronchitis, emphysema, with or without asthma
- 20% are of restrictive pattern (problems in inspiration and expansion of alveoli)
- 10% are of vascular causes

At rest, oxygen consumption is about 250 ml/min. Oxygen consumption is the amount of oxygen that **flows** from the alveoli into the vasculature per unit time.

$$\boldsymbol{Flow} = \frac{\boldsymbol{DF}}{\boldsymbol{R}}\ [\boldsymbol{Ohm's\ Law}]$$

$$(DF\text{: } Driving\ Force;\ R\text{: } Resistance)$$

The flow is determined by DF (the oxygen partial pressure gradient between the alveoli and the capillaries) and R (the difficulty for oxygen flow).

Resistance is a vague term that largely depends on the context, so a better measure is typically used, namely permeability (or conductance when talking about ions).

Permeability (K) is essentially how easy the flow is. It is the reciprocal of resistance. When substituting into Ohm's law, the following equation emerges for oxygen flow:

$$\textbf{Oxygen Flow} = \Delta PO_2 * \boldsymbol{K}$$

Regarding permeability itself, it depends on both membrane and gas factors, summarized in the following equation:

$$\boldsymbol{K} = \left(\frac{\boldsymbol{A}}{\boldsymbol{dx}}\right) * \left(\frac{\boldsymbol{S}}{\sqrt{\boldsymbol{MW}}}\right)$$

$$(A\text{: } Surface\ area;\ dx\text{: } Thickness;\ S\text{: } Gas\ solubility;\ MW\text{: } Gas\ molecular\ weight)$$

Total surface area of diffusion is 50-100 m^2; respiratory membrane thickness ≈ 0.5 μm.

As you can see, the first two factors (A, dx) are related to the respiratory membrane, and the other two factors (S, $\sqrt{MW}$) are related to the gas itself that passes across.

Among the four factors, **MW is the least important** because it is not significantly different between gases. For example, oxygen MW is 32 g/mol, while carbon dioxide MW is 44 g/mol; when plugging in the numbers, the difference is negligible primarily because of the presence of the square root in the equation, which weakens the effect of this variable, at least when dealing with typically encountered gases (O_2, CO_2, N_2, CO).

For simplicity, the two gas-related factors are substituted by a single factor, named the diffusion coefficient. The diffusion coefficient is essentially the **solubility** divided by the square root of MW. This single factor summarizes the gas properties that are implicated in flow calculations. Since MW is not as important, diffusion coefficient depends more on gas solubility. Oxygen is designated as a reference with a coefficient of 1.

Gas	**O_2**	**CO_2**	**CO**
Diffusion Coefficient	1	20	0.8