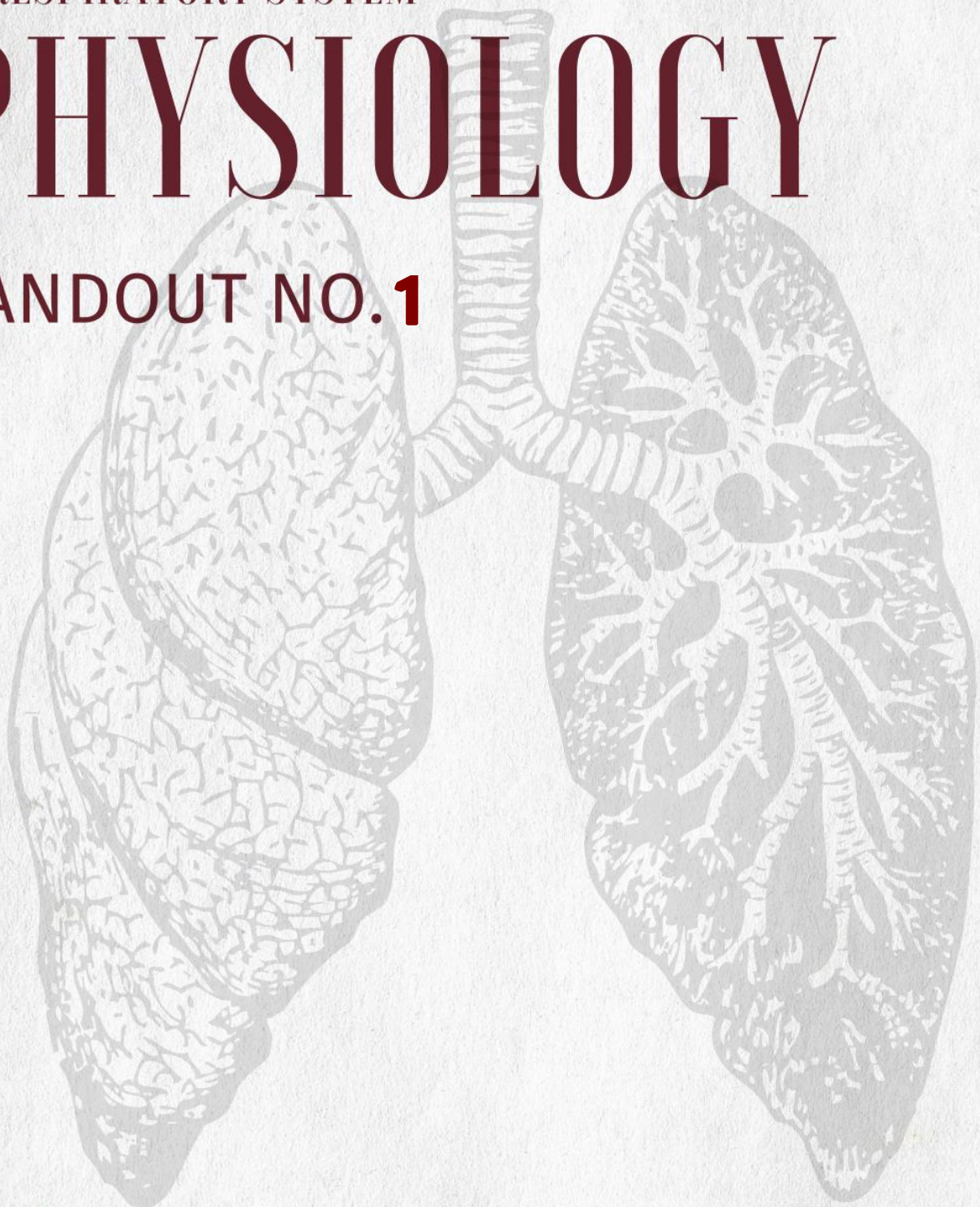
RESPIRATORY SYSTEM

PHYSIOLOGY

HANDOUT NO.1



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Additional

Overview: potential causes of hypoxia

🎯 **Let's take a look into Respiratory Physiology Lecture Topics (11 Lectures)**

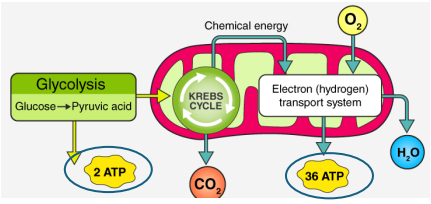
1. **Overview**: Causes of hypoxia (✔ covered in our topic today "**Handout 1**") – *1 lecture*.
2. **Mechanics of Breathing (Lung Ventilation)** – *1 lecture*.
3. **Airway Resistance and COPD** – *2 lectures*.
4. **Lung Compliance**: Includes conditions like lung fibrosis, IRDS, and ARDS – *1 lecture*.
5. **Pulmonary Circulation and Ventilation-Perfusion Ratio** – *1 lecture*.
6. **Gas Exchange and Transport** – *2 lectures*.
7. **Regulation of Lung Ventilation**: Topics include high altitude, exercise, etc. – *2 lectures*.
8. **Pulmonary Function Tests, Pathophysiology of Lung Diseases, and Clinical Applications** – *1 lecture*

The function of the respiratory system

The primary function of the respiratory system is to maintain **homeostasis** of oxygen (O_2), carbon dioxide (CO_2), and hydrogen ions (H^+). *(Note: Hydrogen ion homeostasis is discussed in greater depth later in the UGS section.)*

Oxygen serves as a critical electron acceptor in the mitochondria, enabling the production of a significant amount of ATP. Through oxidative phosphorylation, the breakdown of one glucose molecule generates approximately **36 molecules of ATP**. In the absence of oxygen, however, only **2 ATP molecules** are produced via anaerobic glycolysis.

Extra pic →



❓ What is hypoxia? Hypoxemia? And how do they differ?

- Hypoxia refers to a **decrease in the utilization of oxygen by the cells**. This means the cells are not receiving or using enough oxygen to meet their metabolic needs, which can impair cellular function.

- Hypoxemia, on the other hand, is **one of the causes of hypoxia** and specifically refers to a **decrease in the oxygen levels in the blood**. This condition results in reduced oxygen transport to tissues, potentially leading to hypoxia if severe or prolonged.

- **Extra Example**: A person with severe anemia may have normal oxygen levels in their blood (no hypoxemia), but their tissues may still experience hypoxia because there aren't enough red blood cells to deliver the oxygen effectively.

In simple terms, **hypoxemia** is about low oxygen in the **blood**, while **hypoxia** is about low oxygen **usage by tissues and cells**. Hypoxemia can lead to hypoxia, but hypoxia can also occur without hypoxemia.

The non-respiratory functions of the respiratory system

The non-respiratory functions of the respiratory system (Note: Most of these non-respiratory functions of the lungs will not be covered in this course)

(Read only not included in the exam)

- Helps blood and lymph flow (venous return) as we took in CVS
- Acid base balance. Regulation of pH which dependents on rate of CO2 release
- Pulmonary capillaries remove any air bubble which might otherwise reach systemic circulation
- Airways remove airborne particles
- Ventilation contribute to heat loss and water loss. Regulation of body temperature by evaporation of water from the respiratory passages to help heat loss from the body
- Important reservoir of blood
- Phonation

BP regulation by converting AI to AII with the help of ACEs

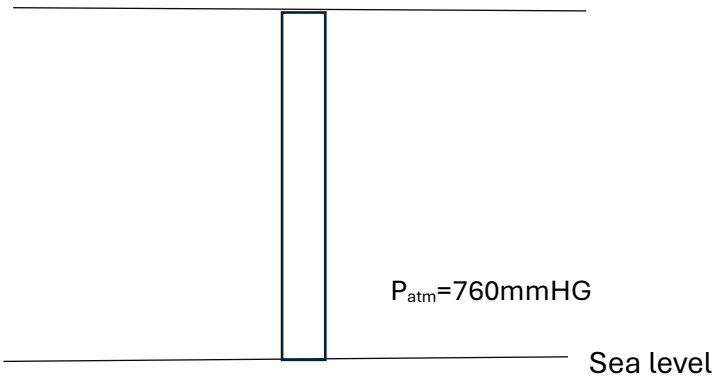
- **Metabolic functions such as:**
- Conversion of angiotensin I to AII
- Synthesis and removal of bradykinin and PGs
- Storage and release of serotonin and histamine
- inactivation of noradrenaline and adrenaline
- synthesis of peptides like substance P and opiates
- secretion of heparin by mast cells
- secretion of immunoglobulins in the bronchial mucus

Introduction

RS and CVS systems are **highly interconnected**: fact: lung disease probably will develop heart failure and vice versa; for example: left ventricular heart failure will result in pulmonary edema and decreased O2 supplied by the lung due to lung disease, will result in right heart failure (Cor pulmonale), which is a condition that causes the right side of the heart to fail

Potential causes of hypoxia

we have 10 causes, and we will start with cause 1: **unavailability of oxygen in the outside air.**



The right graph represents a column of air in the atmosphere. The weight of that column produces pressure. Remember that pressure is Force/Area.
$P = F/A$
At sea level, P_{atm} is equal to 760 mmHg. But, we consider it as reference and value it at zero. So that:
P=761mmHg is considered as +1, P=759 is considered as -1.

An arterial blood pressure of 100mmHg is actually 860mmHg. A venous blood pressure of 20mmHg is actually 780mmHg. That's why, arterial bleeding would be projectile whereas venous bleeding is not.

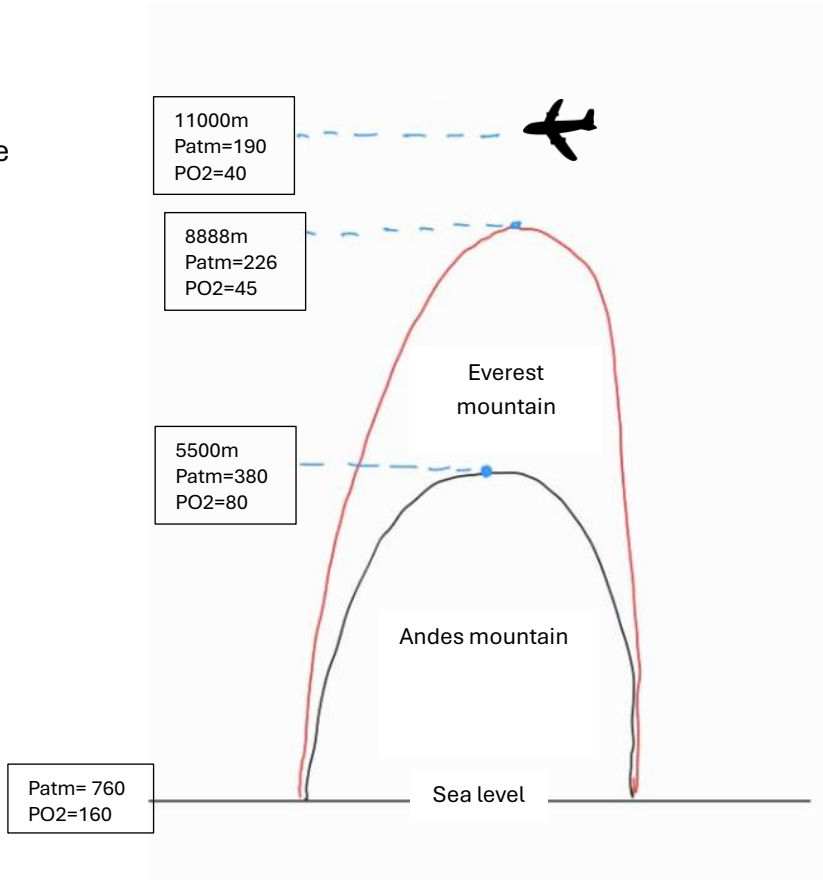
Atmospheric air is mainly composed of two gases: Oxygen and Nitrogen.
21% is oxygen. So, $PO2 = 21\% * 760 = 159 \approx 160\text{mmHg}$

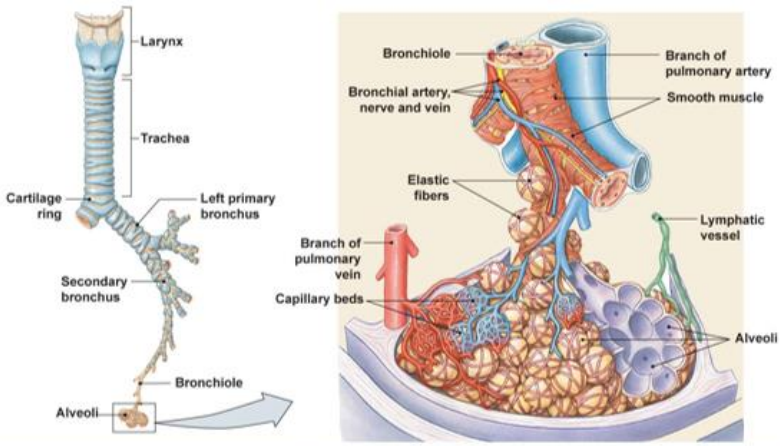
. $PN2 \approx 600\text{mmHg}$
For CO2, $PCO2 = 0.3$ which is considered as≈ **zero**.

🧗 Now, if you ascended to a high altitude like at the top of the Andes mountains in Peru which about 5500 m
P_{atm} is halved to about 380 mmHg.

❗ note: Keep in mind that the percentage of oxygen remains the same (21%), so PO2 would be 80Hg.

If you look at right graph you can see Patm and pO2 for different altitudes at sea level, Andes mount, Everest mount, and at flying altitudes.
At mount Everest, PO2 is very low and you can't survive for more than one hour without a source of oxygen.





	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		4	
		3			
		4	1-10		
		5			
		6-11		1×10^4	
Exchange surface	Bronchioles	12-23	0.5-1	2×10^4 ↓ 8×10^7	100 ↓ 5×10^3
	Alveoli	24	0.3	$3\text{-}6 \times 10^8$	$>1 \times 10^6$

Respiratory tract zone

Respiratory system is composed of 2 zones: <u>conductive and exchange zone</u>.

The tract goes as: Mouth and nose → Pharynx → Larynx → Trachea then it starts dividing into left and right primary bronchi → secondary bronchus → tertiary bronchus.
All that occurs in 23 divisions (branches) then an alveolus (pleural: alveoli)
We have 300-600 million alveoli with a surface area of 50-100 m^2 that is available for diffusion.

Look at the table above: 👀

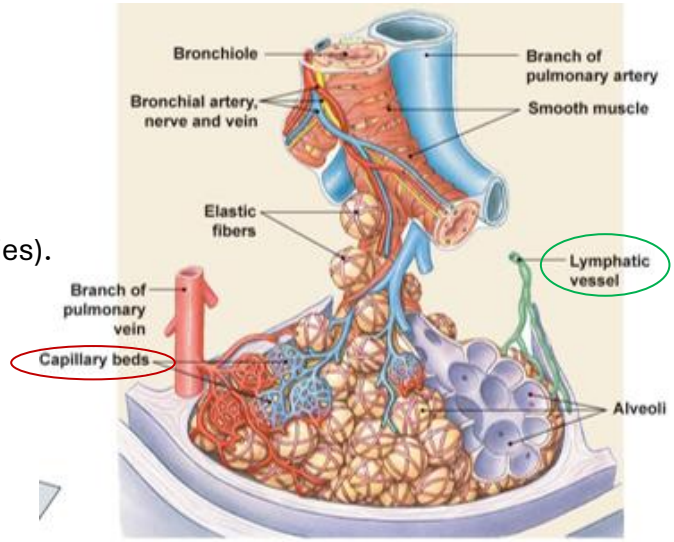
- **Trachea** is considered **Division 0**.
- **Primary (main or mother) bronchus** is **Division 1**.

- **Divisions 0–16:**

- These form the **conductive zone**, responsible for conducting air in and out without any gas exchange.
- The **terminal bronchiole** is **Division 16**, and it marks the end of the conductive zone. *(Bronchioles are characterized by a diameter of 1 mm or less.)*

- **Divisions 17–23:**

- These constitute the **respiratory (exchange) zone**, where gas exchange occurs.
- **Division 23** is the **alveolus**, the critical site for gas exchange, with a variable diameter ranging from **100–300 µm** (micrometers).



<u>As you can see from the right image:</u>
Each single alveolus is surrounded by a huge network of capillaries (about 100 capillaries). Also, it has a huge lymphatic vessel for lymphatic drainage which is very important to take back filtered fluid to the circulation to keep the lung dry. Lymphatics take care of accumulated fluid in the interstitial space.
Otherwise, pulmonary edema would interfere with gas exchange.

Anatomic dead space

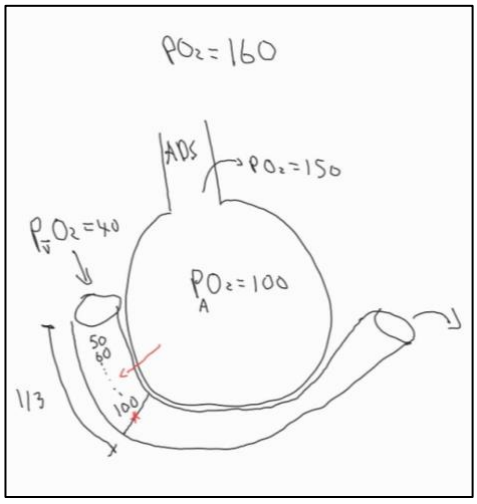
The **conductive zone** is sometimes referred to as the **anatomic dead space** because no gas exchange occurs in this area. The **anatomic dead space volume (ADSV)** is calculated as: **ADSV = 2 mL/kg .**

For example, a person weighing **75 kg** has an ADSV of approximately **150 mL**, which is often cited in textbooks as the typical adult ADSV.

Despite its name, the conductive zone plays an important role in preparing inhaled air for the respiratory zone. When dry air is inhaled

(containing $\mathbf{O_2}$ and $\mathbf{N_2}$, with $\mathbf{PH_2O = 0}$),

the conductive zone adds a third gas: $\mathbf{H_2O}$ **vapor**.



- This addition of **water vapor** ensures that inhaled air is fully humidified before reaching the lungs.
- As water vapor is added, it **displaces other gases** to maintain a total pressure of **760 mmHg**.
- At body temperature (**37°C**), $\mathbf{PH_2O = 47\ mmHg}$, meaning atmospheric air becomes **100% saturated with water vapor**

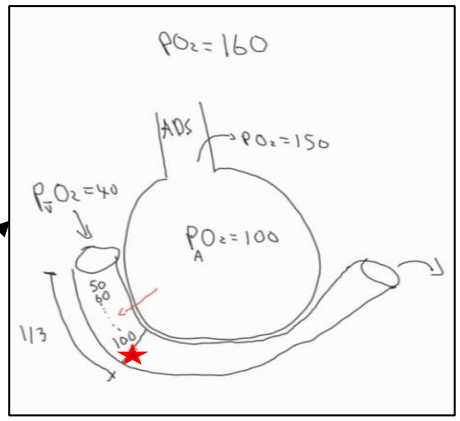
So now in the anatomic dead space,
$PO2 = (760 - 47) \times 21\% = 149 \approx 150 mmHg.$

PCO2 remains at zero, as there is no gas exchange occurring.

Gas exchange in the alveoli

Blood in the capillary comes from :

Systemic veins → Right atrium → Right ventricle → Pulmonary artery



The symbol $\mathbf{P_vO_2}$ (with "v bar" representing mixed venous blood) indicates the **oxygen level in mixed venous blood**. This oxygen level depends on the activity and function of the organs.

Reconditioning organs receives very high levels of blood not to meet its demand but for changing the composition of blood.
Ex: **Renal** blood flow arterial O2 conc =20, venous O2 conc =18.5 ,
meaning that kidneys extract only a small amount of oxygen.
Whereas the heart, arterial O2 conc=20, venous O2 conc=9.
Heart can't tolerate hypoxia because it consumes a lot of O2.

As we said, Venous blood reaching right atrium is mixes. Right ventricles are better representing the blood mixing, Pulmonary artery is the best because no blood is added to it.

PO2 outside=160, PO2 in anatomic dead space is 150 "similar to atmospheric air but slightly reduced due to mixing with residual air".

PO2 in Alveolar Air (PAO2) = 100 mmHg (due to oxygen uptake into the blood and CO2 removal.

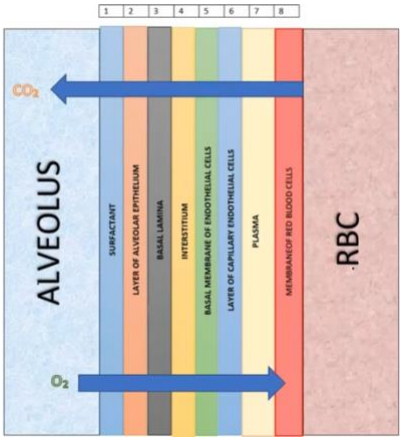
Oxygen diffuses from the **alveoli**, where the **partial pressure of oxygen (PO_2)** is high, into the **capillaries**, where the PO_2 is lower. This movement follows a **partial pressure gradient** and is not related to a concentration gradient.

In the capillary: Oxygen equilibrium is reached within the **first 1/3 of its length** (marked by red star in the image).

The barrier that separates the **alveolus** from the **capillary endothelium** is called the **respiratory membrane**.

- **Partial Pressure Gradient**: The driving force for gas diffusion in the lungs (related to gas pressure).
- **Concentration Gradient**: More relevant for solutes in liquids and solids (related to molecule quantity).

Respiratory membrane



The respiratory membrane is composed of 6 layers in which oxygen has to cross, starting from the alveolar side from the in inside, the surfactant→the epithelium→the basement membrane of the alveolous→the interstitium(fibrosis and edema - accumulation of fluids- can occur here) →the basement membrane of the endothelium→the endothelial layer.

The thickness of theses 6 layers is on average 0.5 micrometer. So as we said before, the area of all the alveoli is 50-100 square meters and the thickness is 0.5

Very important note:

oxygen can cross any biological membrane easily with no problems as if the membrane does not exist (not through channels, pores or carriers but directly through the phospholipid bilayer) so that in most cases the diffusion being a potential cause for hypoxia is very unlikely. Oxygen availability to tissues is not **diffusion-limited** but rather **perfusion-limited**. This means that oxygen delivery depends on blood flow, not the ability of oxygen to diffuse across membranes.

- **Perfusion Limitation**: Oxygen flow occurs only when there is a **partial pressure difference** between the alveoli and the capillary blood. This exchange happens efficiently in the first **third of the capillary length**.
- Once oxygen enters the **red blood cell ,** it binds to hemoglobin, forming **oxyhemoglobin**. Although the **concentration of oxygen** in the blood may increase, oxygen does not diffuse based on concentration differences but rather due to the **partial pressure gradient**.

Ohm's law

J O2 (flow)= DF (driving force)/R (resistance)

This is one of the most important laws in physiology and it indicates that "the flow is directly proportional to the driving force and inversely proportional to the resistance". Resistance -in simple terms - tells you how difficult this process is going to occur and actually nobody can measure the resistance directly , so we measure the driving force and the flow and consequently through the equation we know the resistance. (we don't use poiseuille's equation here, we only say that R is inversely proportional to the fourth power of the radius)

Oxygen crosses the membrane as if it does not exist, CO2 crosses the membrane 20 times easier than the O2, so when there is a lung disease, pulmonary fibrosis , for example -respiratory failure type 1- **O2** is affected **first** because CO2 is much more diffusable than O2 and it's affected later . (When referring to gases pressures in the

alveoli we won't mention H2O and N2, because we can't utilize the nitrogen and add it to our biological membrane (e.g. by making amino acids) as it's a spectator molecule. pH2O is always 47 because our body's temperature is 37 everywhere). Diffusion is flow which is quantity per unit time and flow of electrons is called current and the voltage difference is the driving force and the resistance is called ohm.

The permeability

K (permeability)=(A area/ dx thickness)*(S solubility/√mm)

Permeability is how easy to cross the membrane . In the context of ions we refer to it as conductance which is the opposite of resistance so instead of saying that flow is the driving force over the resistance we can say that it's the driving force times the permeability which is one over the resistance, so the unit of permeability was called moh-the inverse of ohm- J=DF*K /// K=1/R

$$J = \text{Driving Force (DF)} \times \text{Permeability (K)} \quad \text{where} \quad K = \frac{1}{R}$$

The permeability is a product of 2 things, one belongs to the membrane itself, and the other belongs to the molecule itself. In context of the membrane, we are interested in two things, the area and the thickness, the more the area, the more the permeability, and the more the thickness (fibrosis, pneumonia, infection, inflammation, edema) the less the permeability and the less the diffusion and in this case O2 becomes diffusion limited rather than perfusion limited. And in context of the gas, the factors are the solubility and the square root of the molecular weight. the more the solubility (the more it's attracted to water) we can build up more pressure because it becomes something different like when we add oxygen to hemoglobin it's not oxygen anymore, it's a different chemical composition, so we can still add more of it.

Related to membrane

$$K = \frac{Area}{membrane\ thickness} * \frac{Solubility}{\sqrt{Molecular\ weight}}$$

Related to gas

All gases cross the same membrane so that the differential factors are those related to the gas itself, and the **least** important factor among the four is the molecular weight because we take the square root of it.

To simplify gas-related factors, we combine solubility and molecular weight into a single value called the **diffusion coefficient** (D):

O2: Diffusion coefficient = 1 $CO2$ Diffusion coefficient = 20

CO: Diffusion coefficient = 0.8

All gases cross the same membrane, so differences in diffusion depend on the gas's **diffusion coefficient** , and for that reason, when any problem occurs diffusion of oxygen is affected first as its' coefficient is 1 while CO2's coefficient is 20.

- In respiratory failure type 1, pO2 drops to 50 instead of 100 and pCO2 stays the same. While in type 2, pO2 is 50 and pCO2 starts to rise due to severe damage to the respiratory membrane.

- ## Gas exchange between the capillaries and the cells

When blood reaches the capillaries, **oxygen (*O2*) exchange** occurs because the partial pressure of oxygen is lower in the interstitium compared to the capillaries. For oxygen to move from the interstitium into the cells, the pO2 in the cells must be **below 40 mmHg**.

Similarly, for **carbon dioxide (CO2) exchange**, the pCO2 inside the cells must be **above 45 mmHg** for CO2 to diffuse out of the cells into the interstitium and then into the capillaries. This movement follows the partial pressure gradient, ensuring efficient gas exchange at the cellular level

Expiratory air

When we inhale air, it's referred to as **tidal volume** (similar to the concept of stroke volume in the heart). It represents the volume of air inhaled or exhaled with each breath. At rest, the tidal volume is approximately **500 mL**, but it increases during exercise.

- **Before inhalation**, the lungs contain approximately **2200 mL of air** (the functional residual capacity).
- **After inhalation**, the lung volume rises to **2700 mL**.

Fresh air that is inhaled has pO2 equals to 160, and pCO2 equals to 0. Exhaled air in the anatomical dead space is alveolar type of air having the same composition of alveoli at the end of expiration, (pO2=100, pCO2=40).

The first 150ml of the 500 ml push the air in the anatomical dead space and replace it, the alveolar air receives the same air that it pushed out . As a result, the air in the alveoli is only partially renewed with fresh air during each breath. The remaining 350ml is then mixed in the alveoli. The composition of air at the end of inspiration is almost the same as the outside air but humidified so pO2 is not 100 but 150 ,and pCO2 is 0.

- so if you're asked what's the composition of air in the anatomical dead space? You say that **it depends whether it's at the end of inspiration or at the end of expiration.** At the end of inspiration: the same as the outside air,
- At the end expiration: the same as the inside air. This concept is important in the context of CPR, when you give the patient your expiratory air, you deliver:
- The first **150 mL of fresh air** from the anatomical dead space.
- **350 mL of alveolar air**, which still contains sufficient oxygen (pO2 =100mmHg) to be beneficial.

RMV (respiratory minute ventilation) = tidal volume*respiratory rate

for example, 500*12=6 L/min but in fact it's not right....as this is the total ventilation, which includes both the air that participates in gas exchange (alveolar ventilation) and the air that doesn't (anatomic dead space ventilation).

Alveolar ventilation = 350*12=4,2L and anatomic dead space ventilation=150*12=1,8L

PO2 mixed expired= ((150ml*150) + (350ml*100))/500ml=116

Where is PO2 the Highest?

- ✔ **Mixed Expired Air (116 mmHg)**: This is a mix of air from both the anatomical dead space and the alveoli.
- **Systemic Arterial Blood**: This has a PO2 around 95–100 mmHg, as it's oxygenated in the alveoli.
- **Pulmonary Veins**: This blood has a PO2 similar to systemic arterial blood since it's oxygenated by the lungs.
- **Alveolar Air**: The PO2 in the alveoli is typically around 100 mmHg at the end of a breath.

$$\text{PO2 (mixed expired)} = \frac{(150\,\text{mL} \times 150) + (350\,\text{mL} \times 100)}{500\,\text{mL}}$$

Extra explanation to this formula :

1. **Anatomical Dead Space** (150 mL):
   The first 150 mL of the tidal volume comes from the anatomical dead space, where the air doesn't participate in gas exchange. This air is similar to the outside air and has a **PO2 of 150 mmHg** in this example (a typical value for atmospheric air). This air gets exhaled first.
2. **Alveolar Air** (350 mL):
   The remaining 350 mL of the tidal volume comes from the alveoli, where gas exchange occurs. The **PO2 in the alveoli is around 100 mmHg** at the end of expiration, as oxygen has already been partially exchanged with carbon dioxide in the lungs.

The formula then calculates the **PO2** of the mixed expired air by using the contributions of these two volumes of air, considering their individual partial pressures of oxygen