RESPIRATORY SYSTEM

PHYSIOLOGY

HANDOUT NO.10

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Color code
slides
doctor
important
Extra info

Transport of Co2:

- There are two forms of oxygen transport, and 3 forms of co2 transport, **for CO2:**
  1. 70% are transported as **bicarbonate** (HCO_3^-)
  2. 20% are transported as **carbaminohemoglobin**
  3. 10% are transported **dissolved in plasma**
  - These percentages can differ according to the source

❖ Fate of CO2 in blood

- In plasma
  1. Dissolved
  2. Formation of carbamino compounds with plasma protein

     Very small, negligible
  3. Hydration, H+ buffered, HCO3 - in plasma (70%)
- In red blood cells
  1. Dissolved
  2. Formation of carbamino-Hb (20%)
  3. Hydration, H+ buffered, 70% of HCO3 - enters the plasma
  4. Cl shifts into cells; mosm/L in cells increases

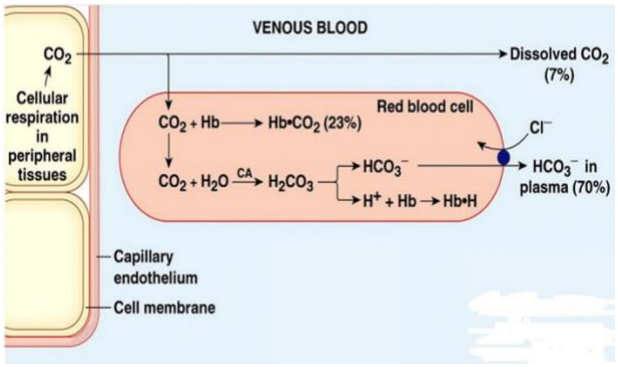
At the tissue level:

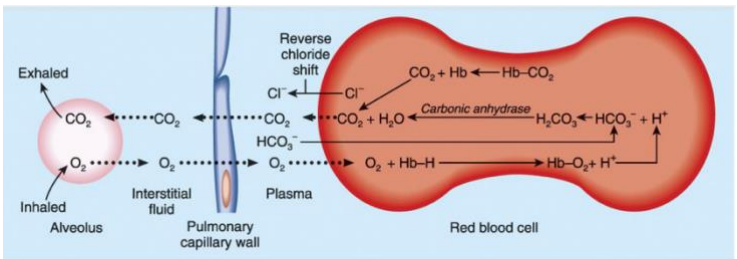
- In the tissue CO2 diffuses to the interstitium and then diffuses to the plasma (pass through the membranes easily as if they do not exist), the CO2 then enters the RBCs, CO2 will combine with H2O producing H_2CO_3 that will be cleaved into H^+ and HCO_3^-, inside the RBCs there is carbonic anhydrase that accelerates this reaction 6000 times, which is important since the RBCs keep moving and the time available for binding CO2 is limited, in addition to CO2 inhibitory effect if accumulated
- When HCO_3^- goes outside the RBCs to the plasma, the charge in the plasma will be more negative and inside the RBC will be more positive, to keep the balance of charges, chloride will enter the RBCs (chloride shift), resulting in the concentration of chloride inside the venous plasma is less than arterial plasma
- The H^+ product of the reaction, will bind with hemoglobin, forcing it to release oxygen (**Bohr effect**)

- Converting CO2 into HCO_3^- , gives the space to take more CO2 (keeping a gradient of CO2 between the interstitium and the plasma, thus enhancing its washout from cells, since we convert it into a non-CO2 compound: HCO_3^-)
- The Pco2 normally is 40 with the presence of carbonic anhydrase, if it's absent, the rxn will be much slower and the Pco2 will increase to 100 in intersitium, this increase is enough to inhibit and stop the function of the cells
- Co2 has an inhibitory effect, so the accumulation of co2 will kill the cells
- Co2 stimulates the neuronal cells only through hydrogen ions!
- Controlled amount of Co2 was used in anaesthesia in surgeries in the past (due to its inhibitory effect on neurons)

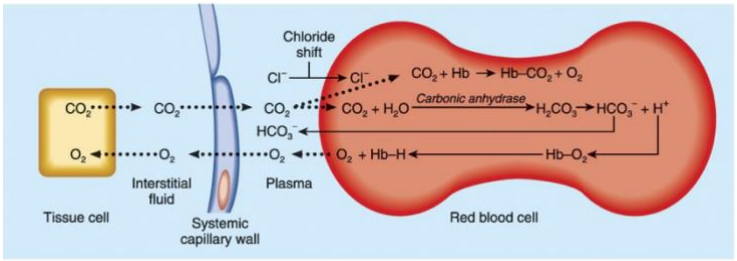
In the lung:

- The pO2 in the lung is 100, so the oxygen diffuses and goes eventually to the RBCs, binds to hemoglobin forming oxyhemoglobin, and resulting in Co2 and hydrogen ion release (that were bound before at the tissue level), this is called **Haldane Effect** (reversed Bohr effect)
- 1)The hydrogen released from (Hb-H) will bind with HCO_3^- reforming H_2Co_3, causing a shift to the left in the reaction, reproducing H2O and CO2, CO2 will diffuse and eventually reach the lung
- 2)Another mechanism of releasing CO2 is that HCO_3^- will return to inside the RBCs from plasma and bind the hydrogen inside reforming CO2
- 3)When oxygen enters the RBC, it will bind hemoglobin releasing the CO2 (carbaminohemoglobin → oxyhemoglobin)
- Eventually CO2 will go to the plasma and then to the Lung

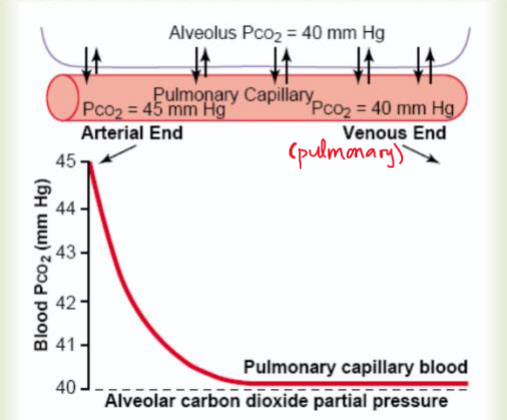




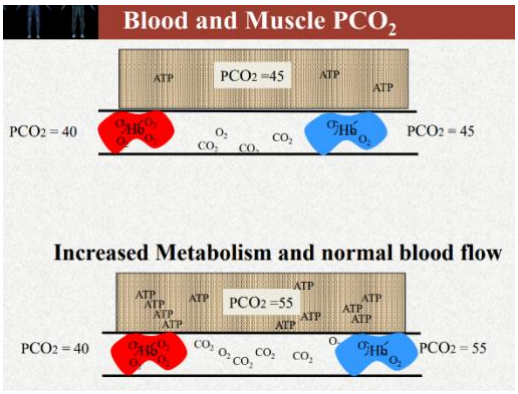
(a) Exchange of O_2 and CO_2 in pulmonary capillaries (external respiration)



(b) Exchange of O_2 and CO_2 in systemic capillaries (internal respiration)



→In alveoli, pCo2 is 40, pulmonary artery is 45 (mixed systemic venous), and after reaching 1/3 of the capillary length the pCo2 will be 40 (pulmonary venous end)



➔In muscles, the arterial Pco2 is 40 and the venous is 45

➔ In case of increased metabolism and normal blood flow, Pco2 in the muscles is increased, for example 55, then the venous will also be increased to 55

A-V difference

- ***The numbers are not for memorization!***
- The total co2 in arterial end is 48 ml/dl, venous is 52 ml/dl, and Arterial venous difference is 4 ml/dl
- For every dl of blood in tissues, we add 4 ml of co2, and we extract 5 ml of oxygen
- The dissolved arterial CO2 is 2.4, venous 2.8, the A-V difference is 0.4 (10% of dissolved CO2), the 0.4 is from the total A-V difference 4 ml/dl (calculated before)
- The Hb bound arterial is 2.4, venous is 3.6, and A-V diff is 1.2 (30%)
- Bicarbonate A-V diff is 2.4 (60%)
- The percentages here are different from what we said before, but the doctor said that to pay attention to highest (bicarbonate) and the lowest (dissolved).

CO_2 TRANSPORT

	Arterial	Venous	A-V difference
Bicarbonate	43.2 (90%) 22.73 mM/l	45.6 (88%) 24 mM/l	2.4 (60 %)
$HbCO_2$	2.4(5%)	3.6 (7 %)	1.2 (30%)
Dissolved CO_2	2.4 (5%)	2.8 (5%)	0.4 (10%)
Total	48 (100%)	52 (100%)	4 (100%)

Increased oxygen delivery to the tissue

Q: Two means by which oxygen delivery to tissue can be increased. Name them….

– 1: redistributing the blood flow to go to the muscles (by the 10 local vasodilators, most imp one is decreased PO2) (Most imp)

– 2: increasing the extraction ratio (by increasing H+, CO2.. curve shifting to the right)

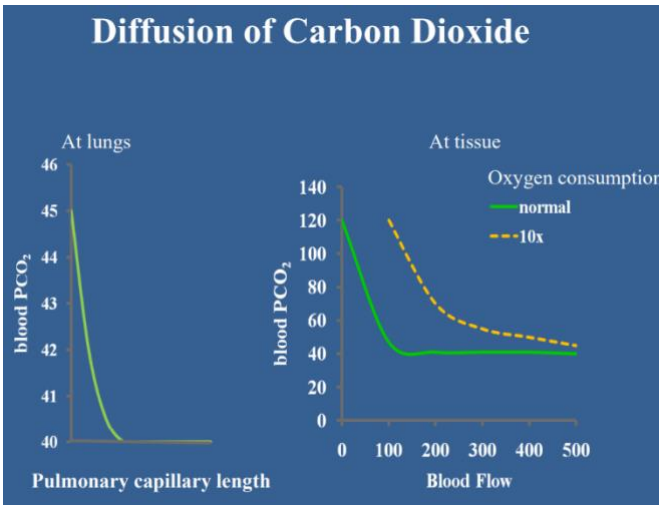
Also: increasing the cardiac output, but increased CO increases the oxygen delivery for all tissues, and in this question, we want to increase oxygen delivery for some tissues (like the muscles) and decrease it for others.

Sympathetic stimulation causes **vasoconstriction** for the GI and the kidney, but the effect on the vessels of the skeletal muscles is **vasodilation** (the local factors overcome the sympathetic stimulation on the muscles causing this vasodilation).

Arterial Blood Gas (ABG) during exercise

During exercise, ABGs stay the same, because co2 production increases (e.g., 4 times) and alveolar ventilation increases (e.g., 4 times) leading to the same $P_{alveolar}CO_2$ (=40) without change

$$P_{alveolar}CO_2 = \frac{\text{VCO2 (production)}}{\text{VA (alveolar ventilation)}} x\ k(constant, 0.863)$$



➔ ***Right pic:*** notice the green line is the normal, and the yellow intermitted line is 10 times the normal O2 consumption (increased O2 consumption indicates an increase in the metabolic rate, and a concurrent increase in CO2 production)

➔ . Green curve: when blood flow is 100%, the blood Pco2 is =40
When blood flow is increased, the Pco2 is still 40, because you also increased the production of co2

But when blood flow is less than CO2 production, PCO2 will be markedly increased.
Yellow curve: when CO2 production is increased 10 times, we need a much higher blood flow to reach the 40mmHg of PCO2

- ***Left pic:*** represents the capillary length utilised in gas exchange (1/3 of the total capillary length), entering with PCO2=45 at the pulmonary arterial end and ending with PCO2=40 at the pulmonary venous end after gas exchange

Respiratory Control System Overview

Purpose of the Respiratory Control System

The primary goal of the respiratory center is to maintain normal **arterial** blood gases (ABG) levels:

- **PO2** = 100 mmHg
- **PCO2** = 40 mmHg
- **pH** = 7.4

Feedback Mechanism of the Respiratory Center

The respiratory center operates via a feedback system that monitors and responds to changes in blood gases and pH. The effects of these changes are as follows:

1. **Increase in PCO2**
    - Stimulates the respiratory center (indirectly through H+).
2. **Decrease in PCO2**
    - Inhibits the respiratory center (indirectly through H+).
3. **Increase in H+ (Acidosis)**
    - Stimulates the respiratory center.
4. **Decrease in H+ (Alkalosis)**
    - Inhibits the respiratory center.
5. **Decrease in PO2 (below 60 mmHg)**
    - Stimulates the respiratory center.
6. **Increase in PO2**
    - Does not produce any effect.

Key Insight: Each factor (PCO2 and H+) has a two-tailed effect (stimulation or inhibition), while PO2 has a single-tail effect (decrease causes stimulation; increase has no effect).

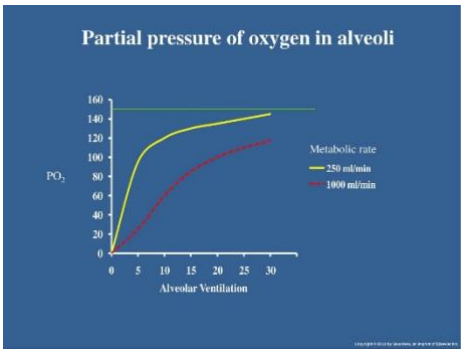
Tools Used by the Respiratory Center

The respiratory center adjusts **ventilation** to achieve its goal:

- **Increased Ventilation**
    - Aims to make alveolar air resemble outside air (higher PO2, lower PCO2).
- **Decreased Ventilation**
    - Aims to make alveolar air resemble venous blood (lower PO2, higher PCO2).

- Q: What is the controller system going to do?
- A: Homeostasis of O2, CO2, H+…Normal ABGs
- Q: How? What are the tools?
- A: by: ↑ventilation or ↓ventilation
- Q: What is the feedback system…nature of the receptor?
- A: ↓ PaCO2 , ↑PaCO2 , ↓ PaO2 (below 60 mmHg), ↓ H+, and finally ↑H+
- Note: ↑PaO2 has almost no effect on the controller system

Understanding Alveolar Ventilation and PO2



- **Baseline**: At an alveolar ventilation level of 1 (approximately 4.2 L/min), PO2 = 100 mmHg.
- **No ventilation**: PO2 drops to 40 mmHg.
- **Increasing ventilation**: PO2 increases and can reach a maximum of 150 mmHg (approximating the PO2 of inspired air).

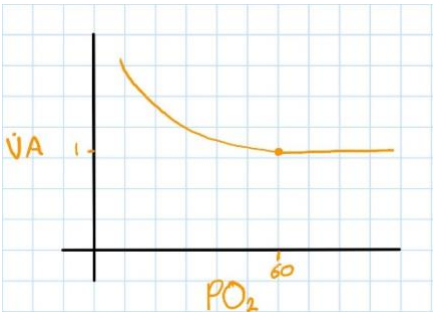
Graph Interpretation

Axes Selection for Variables

- When analyzing relationships:
    - If focusing on how **ventilation affects PO2**, plot:
        - **X-axis**: Ventilation
        - **Y-axis**: PO2

- If focusing on how **PO2 affects ventilation**, plot:
  - **X-axis**: PO2
  - **Y-axis**: Ventilation

Graph Analysis: PO2 vs. Ventilation



- **PO2 > 60 mmHg**:
  - Alveolar ventilation remains constant (approximately 1 or 4.2 L/min).
- **PO2 < 60 mmHg**:
  - Ventilation increases to compensate for the drop in oxygen levels.

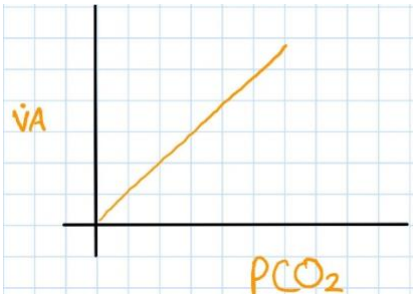
Example for Clarity

Usually, we put the independent variable on the X-axis and the dependent variable on the Y-axis. For example, with venous return and cardiac output, it actually depends:

- If the heart's function is to pump the received blood:
  - **Venous return** on the X-axis and **Cardiac output** on the Y-axis. This means the heart says, "As much as you return blood, I will pump."
- If the heart's function is to empty itself:
  - **Cardiac output** on the X-axis and **Venous return** on the Y-axis. This means the more cardiac output, the more chance for blood to return to the heart.

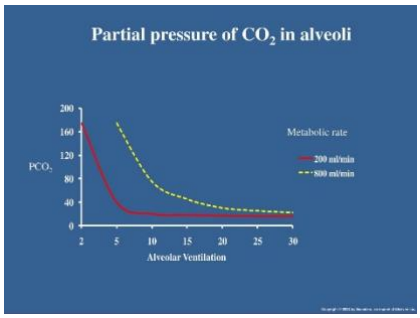
Application to the Respiratory System: Similarly, the axes depend on the focus of analysis—whether studying the effect of ventilation on PO2 or vice versa.

Understanding CO2 and Ventilation



Effect of PCO2 on Ventilation

- At **PCO2 = 40 mmHg**, ventilation is at a normal level.
- **Increasing PCO2** causes ventilation to increase.
- **Decreasing PCO2** causes ventilation to decrease.



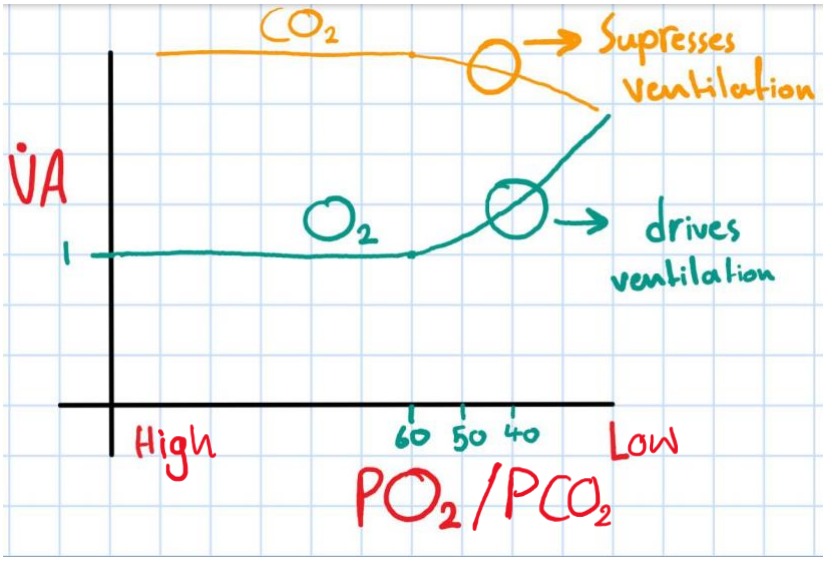
Effect of Ventilation on PCO2

- Using the equation **PACO2 = (VCO2 / VA) * K**:
  - When alveolar ventilation (**VA**) = 1 (4.2L/min), **PACO2 = 40 mmHg**.
  - Increasing ventilation decreases PACO2.

Simultaneous Changes

- Increasing ventilation affects **O2**, **CO2**, and **H+** levels.

High Altitude and Ventilation



- In such cases of high altitudes, I have problems during the acute phase (first day); both PO2 and PCO2 decrease, a decrease in PO2 drives ventilation, while a decrease in PCO2 suppresses ventilation.

  But it's not the effect of CO2 directly as you can see in the graph; it's the effect of H+, which means pH (indirect effect of CO2). (If we can adjust the pH to be constant despite the decreased PCO2, the opposing effect of suppressing hyperventilation by decreased PCO2 would be minimised, leaving the decreased PO2 to be the main driver of ventilation. But how can we do this?)

- **Equation**: pH = 6.1 + Log (HCO3- / CO2)

How did we calculate 1.2? By multiplying PaCO2=40 with the molar solubility coefficient of CO2=0.03mmol/L/mmHg (40*0.03=1.2)

But the numbers are not for memorisation, the doctor just mentioned them quickly!

Normal Situation:

- pH = 6.1 + Log (24 / 1.2) = 6.1 + Log (20) = 6.1 + 1.3 = 7.4

Effect of Decreased CO2:

- Decreased CO2 causes an increase in pH (**alkalosis**).

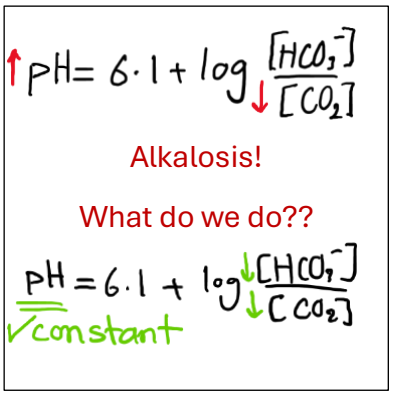
Role of Bicarbonate (HCO3-) normally

- Bicarbonate is vital and cannot be easily lost.
  - Normally, bicarbonate in urine = 0.
  - We cannot tolerate losing bicarbonate in the urine.
  - The kidney's primary function is to filter out harmful substances, but we also ask it to perform another important task. Bicarbonate enters the kidney through the renal artery and exits through the renal vein in larger amounts, meaning the kidney performs two functions in this process:
    1. Return bicarbonate that enters.
    2. Add more bicarbonate.

Why is bicarbonate so important?

- Bicarbonate binds with H+ to form carbonic acid (H2CO3), which converts to CO2 and is exhaled by the lungs.
- If H+ remains unattached, the body forms acids (e.g., lactic acid, sulfuric acid), which suppress CNS enzymes, causing coma and death.

Key Point: The body cannot tolerate acidosis.



Compensation at High Altitude

If a doctor asks: **What happens when you ascend to high altitude?**

- The urine is full of bicarbonate.

Explanation:

- When you ascend to high altitude, there is less O2, causing hyperventilation.
- Hyperventilation leads to hypocapnia (low CO2).
- Hypocapnia causes alkalosis, and as the body cannot tolerate acidosis, it cannot also tolerate alkalosis, because enzyme overactivity caused by alkalosis can lead to diaphragm spasms and death.
- To compensate for the loss of CO2, the kidneys excrete bicarbonate into the urine to maintain the HCO3-/CO2 ratio.
- So hypocapnia causes an increase in the excretion of bicarbonate in urine to keep pH somehow constant.

Why the Body Cannot Tolerate Alkalosis or Acidosis:

- **Alkalosis:** High blood pH can impair normal cellular function and enzyme activity. For example:
    - **Enzyme Overactivity:** Some enzymes, especially those involved in neuromuscular function, are highly sensitive to pH changes. Alkalosis can cause overactivity, leading to **tetany** (involuntary muscle contractions).
    - **Diaphragm Spasms:** Severe alkalosis can induce spasms in the diaphragm and other muscles, which may impair breathing. If breathing is significantly disrupted, it can result in hypoxia (low oxygen levels) and potentially death.
- **Acidosis:** it's worth noting that acidosis (low blood pH) is also life-threatening. It can suppress enzyme activity and disrupt cellular metabolism.

In short, the body has very tight control mechanisms to prevent significant shifts in pH because both alkalosis and acidosis can have dire consequences, including death.

Version 2:

- **P5:** deleting a sentence and adding more explanation to the graph