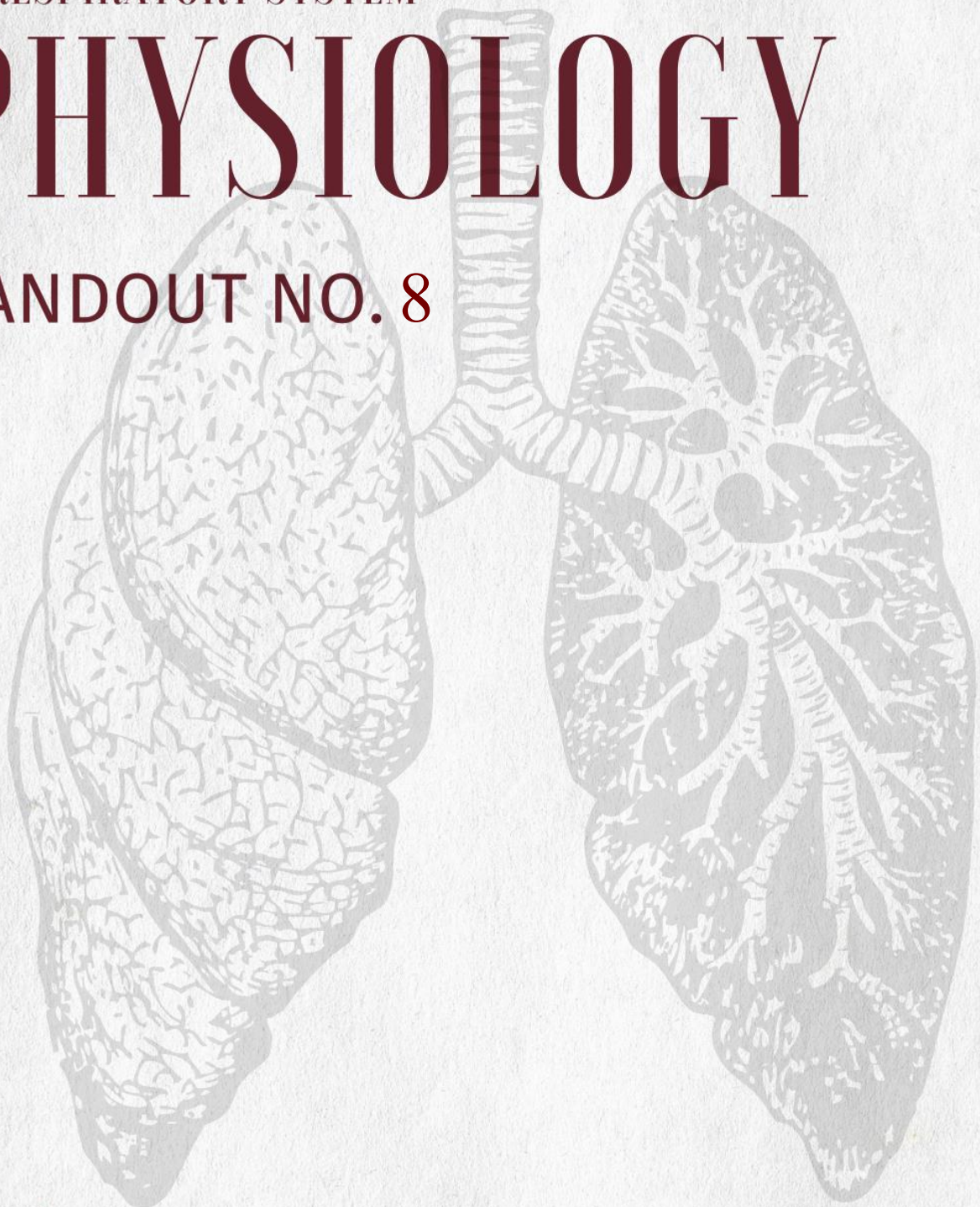
RESPIRATORY SYSTEM

PHYSIOLOGY

HANDOUT NO. 8



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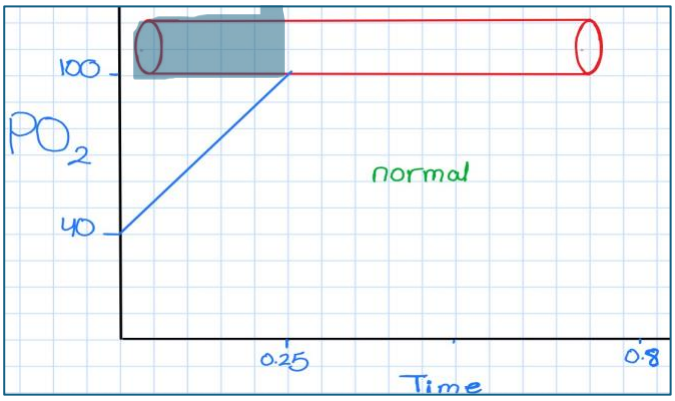
▪ Transporting O_2 & CO_2

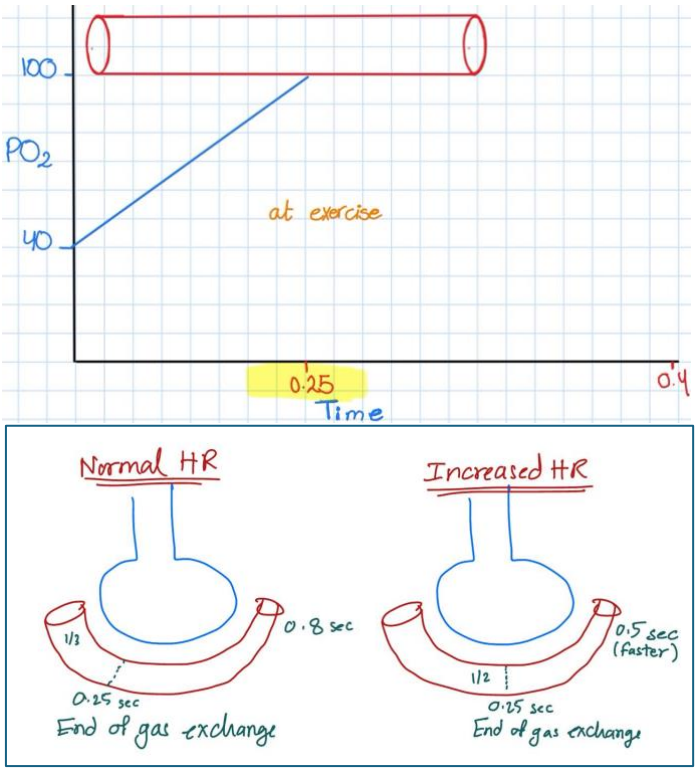
Let's recap some concepts from previous lectures:

- The diffusion capacity (DL) of the respiratory membrane refers to the amount of oxygen that can diffuse from the alveoli to the capillaries per minute per 1 mmHg of pressure difference. (we are gonna talk about this later)

- Recall that we said only 1/3 of the respiratory membrane is used <u>at rest</u> (grey colour in the picture below). Here, the heart rate =75 bpm, cardiac output (CO) is normal, & the cardiac cycle takes 0.8 sec. O_2 diffuses from alveoli (high PO2=100) to the capillaries (PO2=40)
- At a normal heart rate, it takes approximately 0.8 seconds for blood to pass through the entire length of one pulmonary capillary. Gas exchange occurs in the first third of the capillary length because oxygen diffusion requires only about 0.25 seconds.



- While during exercise, the velocity increases (V= Q/A) because flow (cardiac output) increases, so the cardiac cycle shortens to 0.4 sec. and the heart rate increases to 150 bpm. Notice that the body utilizes most of the respiratory membrane, OR as you can say, “the body utilizes most of the capillary length” (the grey colour in image below).
- When the heart rate increases, during exercise for example, gas exchange still requires about 0.25 seconds, but the blood takes a much shorter time to pass through the full length of the pulmonary capillary. If it takes, for instance, 0.5 seconds, gas exchange can still be completed within half the length of the pulmonary capillary. Therefore, during exercise, the proportion of the pulmonary capillary length utilized for gas exchange increases.



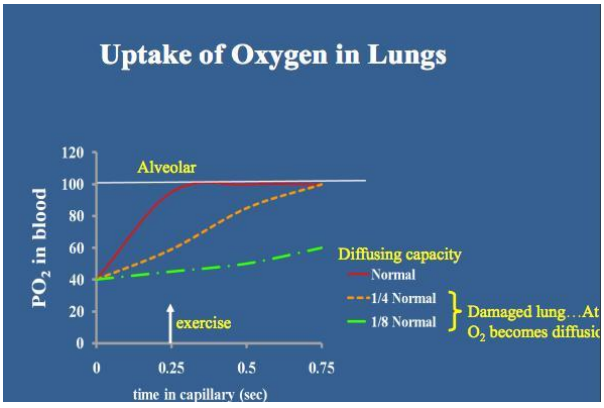
★ Kindly, make sure you understand this concept (it is a past paper Question!!)

Check the slides for the images above with their related concepts

O2 diffuses into the pulmonary capillaries because the PO2 in the alveoli is high.

Note: O2 utilizes less than one third of the respiratory membrane…perfusion limited

▪ PO2 in the pulmonary capillaries increased very fast (1/3 distance) it takes 0.3 sec (we said above 0.25, not a huge difference) leaving the rest 0.5 sec with no more exchange.



- ❖ In a normal person, PO2 increases from 40 to 100.
- ❖ If diffusion capacity becomes ¼ of its normal value, PO2 barely reaches 100

- If diffusion capacity becomes⅛ of its normal value, the patient's PO2 will hardly reach 60. (Mostly PaO2<60, this means that only 10-15% of the lung is functional).

Respiratory membrane

The gases of respiratory importance are highly soluble in lipids. Therefore, they can easily diffuse through tissues, including the respiratory membrane. The respiratory membrane is composed of 6 layers (some says they're 5 by forgetting about surfactant): Thickness is only 0.25 – 0.6 micro to allow rapid diffusion of gases

- A layer of slight fluid lining the alveolus and containing surfactant
- Alveolar epithelium
- Epithelial basement membrane
- Interstitial space
- Capillary basement membrane
- Capillary endothelial membrane.

After remembering respiratory membrane layers let's dive to the concept of this part of the lecture

Factors affecting the rate of gas diffusion through respiratory membrane:

- Diffusion capacity of respiratory membrane is how much O2 can diffuse from the alveoli to the capillaries per minute per 1mmHg (ΔP).
  - Why is it important? Because if any damage happens to the respiratory membrane, it helps determine the extent of that damage.
- So, if you take ABGs and you find PaO2= 100 mmHg & PCO2= 40 mmHg does this exclude lung disease? No. Why? Because of compensation. For example, if half of the lung was removed, the other half can compensate (بيمشي الحال). We can still oxygenate the blood adequately since we use only 1/3 of the respiratory membrane.
- However, keep in mind if PaO2 is low (e.g., 80 mmHg), it is a clear indicator of a problem. In such cases, most of the respiratory membrane has likely been damaged.
- Hence, to know if there's a lung disease or any related problem, we need a test that can assess the functionality of the respiratory membrane, regardless of blood gas values.

- This is why we use tests like Diffusion capacity of the Lung for Carbon monoxide (DLCO) to measure how much O2 diffuses from alveoli to the capillaries per minute per 1mmHg of pressure difference.

After playing with the equation

Let's tidy up the idea:

$$Flow\ (Q) = DF\ X\ K$$

$$dO2 = \Delta PO2\ X\ K$$

$$DL = K$$

$$K = \frac{dO2}{\Delta PO2}$$

$$\frac{dO2}{\Delta PO2} = K = DL = \frac{1}{R}$$

Where:

dO2 = Diffusion of O2, it represents Flow

K= Permeability

DL = Diffusion capacity of Lung

R= Resistance.

dO2/ ΔPO2 = how much O2 /min*1mmHg (ΔP).

- RECALL: DL= $DL = \frac{A}{dx}\ x\ \frac{SO2}{\sqrt{MW}}$
  - **DL**: diffusion capacity of the lung,
  - **A**; area (between 50-100 m2, we can't calculate it, I cannot tell exactly what is left after the damage).
  - **dx**; thickness (also not easy to calculate since it ranges between 0.2-0.6),
  - **SO2**; solubility of O2 (from physics),
  - **MW**; molecular weight (also from physics)
  - **diffusion coefficient** = $\frac{SO2}{\sqrt{MW}}$

To sum up; I can't directly find DL via the law above due to the absence of certain values about membrane

So how can I measure K??

$$K = \frac{\dot{V}\,O2}{\mathbf{\Delta PO2}}$$

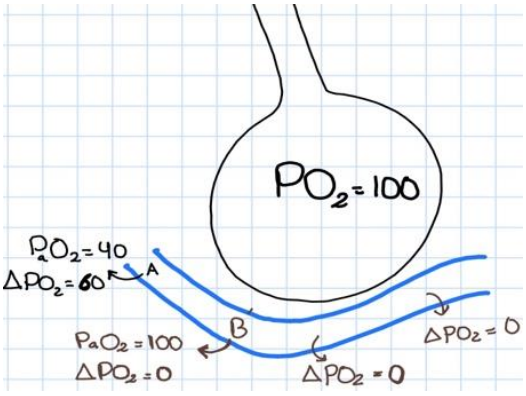
Vo2: rate of O2 consumption (O2 consumption/min), **ΔPO2**=P_AO2-P_aO2

➔And once we find K, we find DLO2 (diffusion capacity of the lung for O2)

- To determine the value of Vo2 (do2), we can use a straightforward method. We ask the patient to breathe into a closed bag that contains a known volume of oxygen. After 10 minutes of breathing, we can measure the concentration of oxygen in the bag. The calculation is done as follows: (final concentration - initial concentration) / 10 minutes. For example, if the result is 250 mL/min, it represents a normal value.

To sum up (Take-home message):

- DLO2 cannot be measured directly because we cannot measure the surface area or thickness of the respiratory membrane, BUT DLO2 can be measured **indirectly** using K.
- Remember: Flow (Q) = ΔPO2 x K, where (Q) represents the O2 consumption rate (250mL/min). Thus, so all we need to determine is ΔPO2
- Now how can we measure ΔPO2?



- As you can see in the image above, at point A, I know the difference. Also, at point B I can tell the difference. But how could I determine the difference at other points? Because the ΔPO2 would be zero (100-100) This is impossible!! Then how could we find K?! By DLCO, by finding ΔPCO, we will explain why CO within few seconds!

▪ DLCO

What is DLCO?

- DLCO is a test that measures the diffusion capacity of carbon monoxide in the lungs.
- It evaluates how well carbon monoxide (and indirectly, oxygen) moves from the air in the lungs into the bloodstream.
- We let the patient to inhale a small amount of CO (a very small amount- it's a dangerous gas that can lead to death!), the CO that enters the blood directly binds to Hb in RBCs forming carboxyhemoglobin.

CO (carbon monoxide) WHY do we use it?

- Normally, we don't have CO in our blood. Therefore, the PCO in the blood = 0
- Affinity for Hemoglobin: CO binding affinity is 250 times greater than that of O2, which ensures that there is no free CO in the blood at all, so

$$\Delta PCO = PACO - 0$$

To better understand affinity concept, check this example:

- If we have mixed gases with PO2 = 100 mmHg, then PCO= 100/250=0.4 mmHg
- Further explantion for the example:

CO is **250 times more likely** to bind to hemoglobin than O_2. To produce The same binding effect as PO2=100 mmHg, the PCO would need to be scaled down by a factor of 250: PCO =Po2/250 = 100/250=0.4mmHg.

A PCO just 0.4 mmHg creates the same hemoglobin saturation effect as PO2=100 mmHg. This highlights how incredibly potent CO is at binding to hemoglobin compared to O_2.

➔ HbO2 is 50%, HbCO is 50% ➔ so what we should give to the patient is much less than this.

Let's explain where it came from.

Binding Competition (HbCO vs. HbO_2): The relative binding of CO and O_2 to hemoglobin is determined by their:

1- Partial pressures (PCOPCO and PO2PO2)2-Affinity ratio (250:1 for CO:O_2).

The equation for the ratio of CO-bound hemoglobin (HbCO) to oxygen-bound hemoglobin (HbO2) is: HbCO/HbO2 = (PCO*CO affinity)/(Po2*O2affinity)

=0.4*250/100*1 = 1 , This means the ratio of CO-bound hemoglobin to oxygen bound hemoglobin is 1:1, or 50% HbCO and 50% HbO2

➔ what we get from all above is that we can calculate ΔPCO

e.g. K_{co} or DLco = 17mL/min*1mmHg

❖ From this, we can tell ΔPO2. By studying CO (and leveraging its high affinity Hb) we can:

1. Measure the diffusion capacity of CO (DLCO).
2. Use the relationship between CO and O_2 to estimate the diffusion capacity of O_2 (DLO2).
3. Use DLO2 to indirectly calculate ΔPO2.

❖ The diffusion coefficient **diffusion coefficient** = $\frac{SO2}{\sqrt{MW}}$

for:

- O2=1,
- CO=0.8,
- CO2=20.

$$\frac{DL02}{DLCO} = \frac{\frac{Area}{dx} x\ 1}{\frac{Area}{dx} x\ .8} = 1.25$$

So, the diffusion coefficient for O2 is greater than CO by 1.25x:

$$DL_{O2} = 1.25\ DLCO$$

❖ Or we can say, DL_{O2} =17/0.8 = 21mL/min*1mmHg (notice that 17 *1/0.8= 17*1.25)

$$DL_{co2} = 20\ DL_{O2} = 20\ X\ 21 \approx 400$$

You might ask, where did 17 come from? "The number 17 is a physiological constant that encapsulates the relationship between the partial pressures and diffusion coefficients of oxygen and carbon monoxide in alveolar and capillary environments. It simplifies the estimation of DO2 based on DCO.

Let's summarise all above 🤓:

- First, keep in mind all our work on CO since DLo2 cannot be measured directly because ΔPo2 cannot be found. Why CO? Due to its ↑ affinity which guarantee that all of it will enter RBCs directly (no CO found freely in blood => PaCO=0)
-

Step	Formula	Example Values
Measure ΔP_{CO}	$\Delta P_{CO} = P_{A_{CO}} - P_{C_{CO}}$	$P_{CO} = 0.4\,\text{mmHg}$
Calculate K_{CO}	$K_{CO} = \frac{d_{CO}}{\Delta P_{CO}}$	$K_{CO} = 17\,\text{mL/min/mmHg}$
Find DL_{CO}	$DL_{CO} = K_{CO}$	$DL_{CO} = 17\,\text{mL/min/mmHg}$
Convert DL_{O_2}	$DL_{O_2} = \frac{DL_{CO}}{0.8}$	$DL_{O_2} = 21.25\,\text{mL/min/mmHg}$
Find ΔP_{O_2}	$\Delta P_{O_2} = \frac{V_{O_2}}{DL_{O_2}}$	$V_{O_2} = 250\,\text{mL/min}$

- Notice that 4th row can be also measured via the ratio DLO2/DLCO => DLo2=1.25 * DLCO

- Diffusion Capacity of The Respiratory Membrane

It is the volume of gas that diffuses through the membrane each minute for pressure difference of one mm Hg.

- Normal value for O2 is 21 mL/min/mm Hg
- Normal value for CO2 is about 20 times greater than O2.
- During muscular exercise, increases 2-3 times due to:

  – recruitment and distention of capillaries to utilize more than 1/3.

  – Improvement in ventilation/ Perfusion ratio: The entire lungs will be at zone 3, which will lead to increasing the DLO2 to ≈ 60 (3x)

• Lungs receive blood from:

  – Pulmonary artery - deoxygenated blood

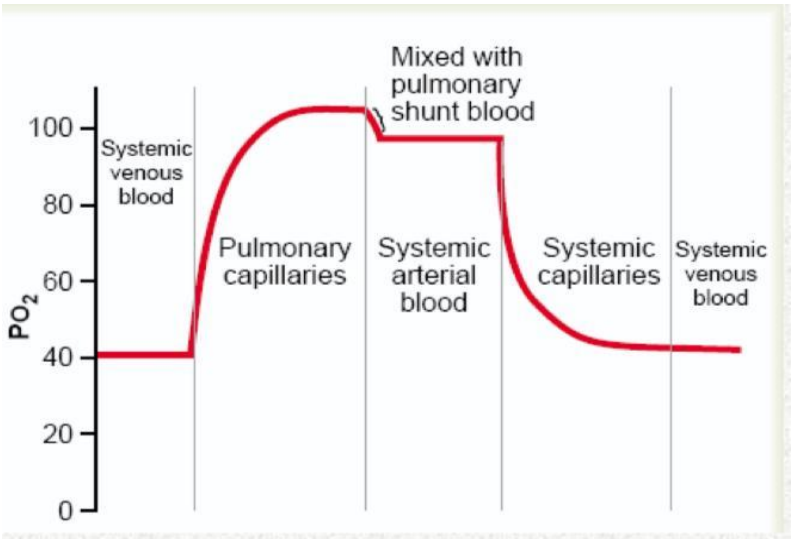
  – Bronchial arteries - oxygenated blood to perfuse muscular walls of bronchi and bronchioles

Now recall some info from previous lectures to build on it:

★ Why $P_aO2 < P_AO2$ (it is 95)?

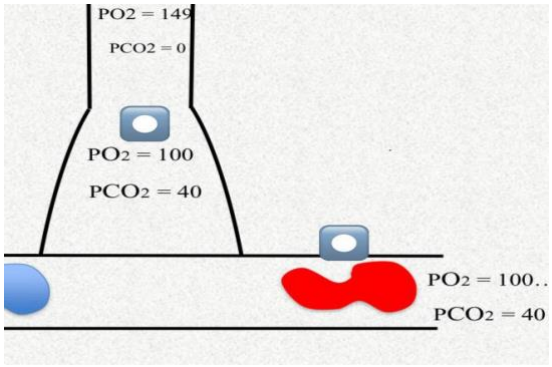
1- Venous admixture from the 3 sources:
-Bronchial circulation ↓ O2
- Cardiac veins ↓ O2
- Pulmonary circulation ↑ O2

2- Low V/Q ratio at the base of the lung because the base is lower than the apex, making it much more perfused, while the hyperventilated region (apex) cannot compensate for the hypoventilated region (base) in terms of blood PO2.

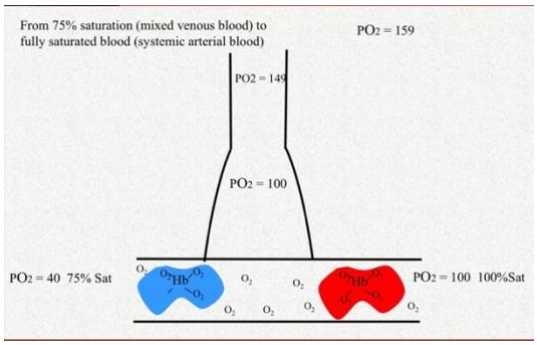


Let's discuss this graph:

- PO2 in systemic venous blood = 40mmHg
- PO2 in pulmonary capillaries
    1- at entry: 40mmHg
    2- at exit: **100** mmHg
- Once it reaches the arteries PO2 will drop to = 95mmHg, **why?**
    - Because of the two reasons mentioned before.
- At systemic capillaries:
    1- at entry: 95mmHg
    2- at exit: 40mmHg



- The doctor focuses on these sites (marked by dots in the image on the right). The red site has the same values as alveolar PO2 and PCO2.



- At the beginning (RBCs highlighted in blue), you can see that PO2=40mmHg, which means 75% saturated Hb, and 15mL of oxygen. The Hb is bound to three O2 molecules.
- While at the end of the capillary (RBCs highlighted in red), PO2=100mmHg, 100% saturated Hb, and 20mLof oxygen. The Hb is bound to four O2 molecules.

▪ Haemoglobin & oxygen transporting

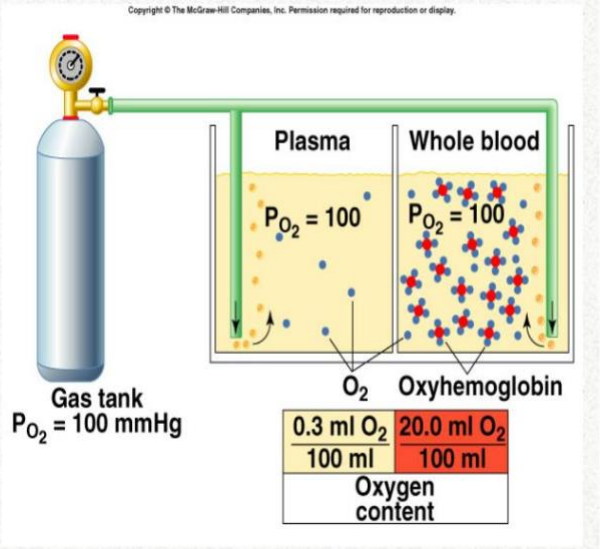
- If we say that blood makes 7% of human weight (assuming it is 70kg) then blood amount = 7% x 70 = 5L= 5000 mL= 5 x 10^6 **µL**
- In each 1µL of blood (which is a cube of 1mm x 1mm x 1mm = $1mm^3$), there are 5 x 10^6 RBCs
  - **Be careful!!** You can say we have 5 x 10^6 RBCs/mm^3 OR 5 x 10^6 RBCs/µL, BUT you should **never** say 5 x 10^6/L.
- In each RBC we have 280 million Hb molecules.
  - **Be careful!!** You should never say that each RBC can carry four O2 molecules ✕✕
  - **But you can say that one RBC can carry 280 x 10^6 x 4 (because one Hb can carry four O2 molecules, so we multiply 4 by the number of Hb molecules in one RBC)** ✓

RBC= 5 million per µl blood

280 million Hb/RBC.

Each Hb has 4 polypeptide chains and 4 hemes.

In the center of each heme group is 1 atom of iron that can combine with 1 molecule 0_2.



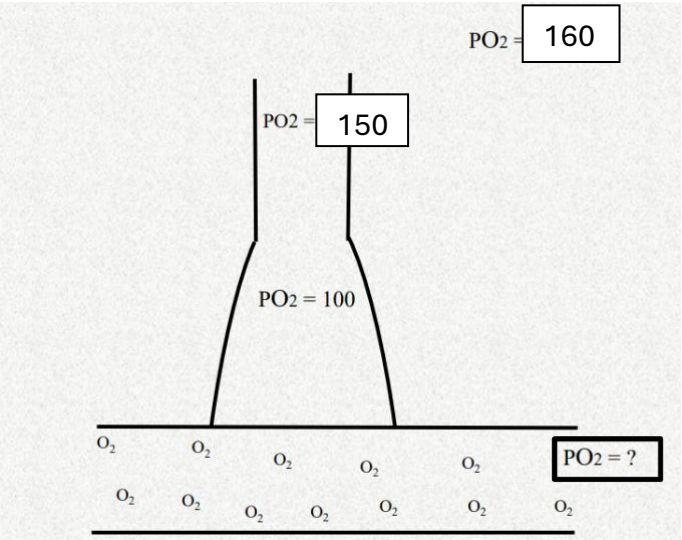
- Each Hb consists of two α chains (an α chain contains 141 AA) & two β chains (a β chain contains 146 AA).
- Each polypeptide chain has one heme group. So, 1 Hb contains 4 heme groups.
- Each heme has in its center a Fe^{+2} ion (ferrous, which can reversibly bind to & release O2, while Fe^{+3} or ferric, cannot).
- Fe^{+3} makes up only 1-2% of the total, with the remaining heme bound to ferrous.
- Ferric is converted to ferrous via **reductase** enzyme inside the RBCs.
- As you can see in the table above, O2 exists in the dissolved form at 0.3 mL, Where does this number come from? It is calculated as PO2 x So2 (solubility) =100 x 0.003 = 0.3 mL/dL.
- Meanwhile, in the RBCs, O2 exists as oxyhemoglobin at 20mL/dL.

★ In total, we have 20.3mL of O2/dL of blood.

Finally, lets revise this idea:

PO2 & ADS:

- PO2 at the end of the capillary is normally always equal to alveolar PO2 (unless there is some pathology affecting diffusion).
- In the picture below, the outside PO2 = 160, anatomic dead space PO2 = 150, and the alveolar PO2 = 100. So, what is PO2 at the end of the capillary?
- PO2 = 100 (same as alveolar)



Now, to understand PO2, O2 saturation, and O2 concentrations, we are going to solve some questions and explain each concept as we go through them (very important):

Question 1:

1. Arterial PO2 is 100 mmHg, and the oxygen content is 20mLO2/dL. What is arterial PO2 if ½ of all the red blood cells were removed?

A. PO2 = 0 mmHg

B. PO2 =30 mmHg

C. PO2 =50 mmHg

D. PO2 =60 mmHg

E. PO2 =100 mmHg

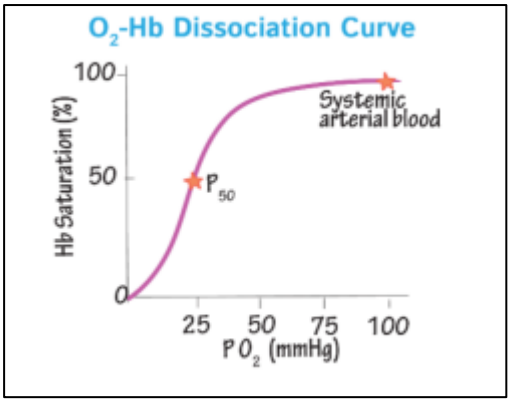
Let's break down the question:

- **Arterial PO2 is 100, what information does this provide us with?**
  Arterial PO2 means PO2 after gas exchange in the alveoli. An arterial PO2 of 100mmHg indicates normal alveolar function and normal diffusion through the respiratory membrane. It doesn't indicate anything else (remember this point, we will discuss it later, so don't worry).
- **O2 content is 20mLO2/dL, what does this mean?**
  This content results from the equation derived from the fact that each 1g of Hb can carry 1.34mL O2. (Since each heme group binds one O2 molecule).

The normal Hb concentration is 14-16 in males (assume15)

15 x 1.34 = **20mL O2/ dL.**

So, what does this value indicate? When all hemoglobin in RBCs is fully saturated with O2, the O2 concentration should be around **20mLO2/dL.** This is true in our question, meaning the **O2 saturation above is 100%.**

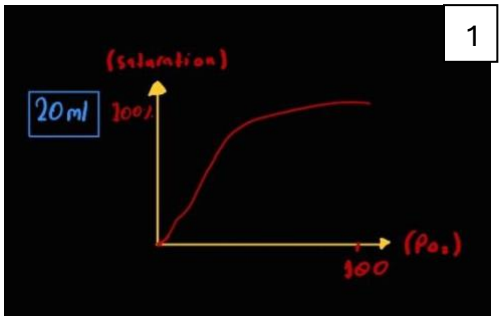


- **Now, the question states that 50% of all RBCs are removed. Let's see what changes happen regarding PO2, [O2], and O2 saturation:**

The first thing you should note is that as long as alveolar PO2 remains unchanged, arterial PO2 will also stay the same. Therefore, **PO2 after we remove half of the RBCs in our body is 100 mmHg.**

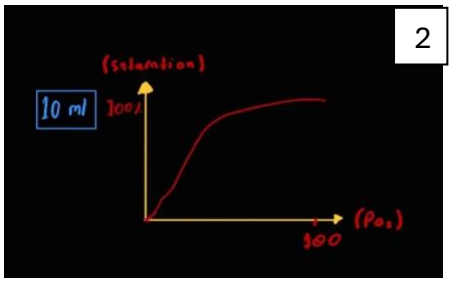
Now, to see what happens regarding saturation and [O2], recall the O2 saturation curve:

- At PO2 of 100, O2 saturation is 100%, meaning that all Hb is bound to O2.
- So, in a normal RBC count, a 100% saturation would be equivalent to **20mL of O2. (picture 1)**



However, in our case, when half the RBCs are removed, Hb content decreases from 15 to 7.5. This decreases the oxygen-carrying capacity of the blood. To calculate it, we use the same equation: 7.5*1.34 = **10mL of O2,** and this is logical, as half the amount of Hb would logically be able to only carry half the amount of O2, and any excess O2 would be useless, as only 0.3mLof O2 can dissolve in the plasma while the rest must be carried by hemoglobin.

So, according to this, 100% saturation in our example corresponds to **10mL of o2** (all the Hb we have is bound to oxygen, even if its amount is low, it is still fully saturated- **picture 2).**



To sum up:

At normal Hg: PO2 = 100, [O2] = 20mL, O2 saturation is 100%

After we remove half the RBCs: PO2 = 100, [O2] = 10mL, O2 saturation is 100%

Answer: E

Question 2:

2. What happens to mixed venous PO2 in an anemic person?

A. Normal

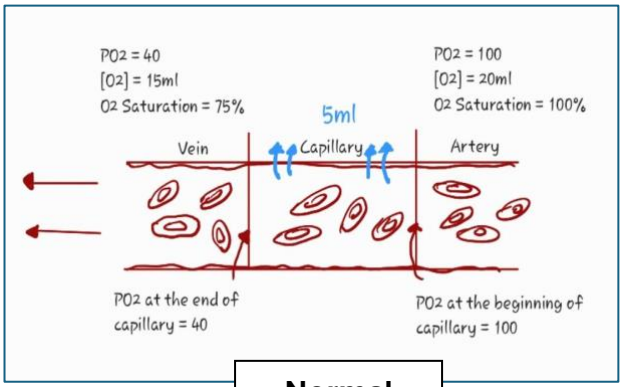
B. Lower

C. Higher

- An important thing to note in such questions is that arterial PO2 tells you nothing except the status of alveolar PO2 and gas exchange. In the absence of a pathological condition that affects alveolar PO2 or exchange, arterial PO2 remains 100 regardless of the oxygen status. Therefore, **the arterial PO2 in the question above would be 100 for both a normal and an anemic person.**

Now, let's dive into the oxygen exchange status in a normal person:

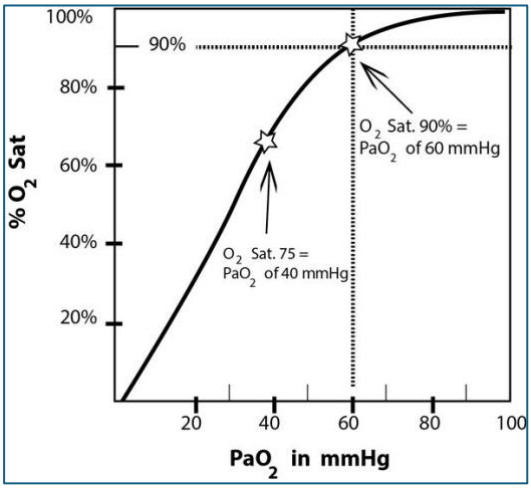
- In a normal individual, arterial PO2 is 100, [O2] is 20mL/dL, and O2 saturation is 100%.
- In systemic capillaries, PO2 at the arterial side of the capillary (beginning) is 100. As blood moves inside the capillary, oxygen diffuses through the capillary wall into the interstitium, the amount of diffused oxygen is usually constant at rest and is not affected by oxygen status in the body (the tissue



Normal

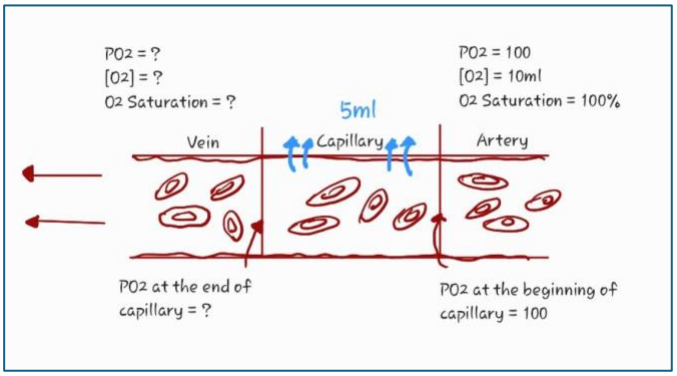
needs this amount of oxygen and is going to take it whether there is enough oxygen in the blood or not), this amount is **5mL/dL.**

- As a result of this diffusion, oxygen content in the capillaries gradually decreases until it reaches 15mL/dL (20-5=15) at the venous side of the capillary (end).
- To calculate oxygen saturation at the venous side, we use the formula: (O2 concentration ÷ maximum carrying capacity of oxygen of the blood), thus, (15÷20)=75%. **Oxygen saturation is 75%, and oxygen extraction ratio is 25% (5÷20).**
- From the oxygen saturation curve, **at 75% saturation, PO2 = 40** (you should've memorised this value from the previous lecture).
- So basically, as the blood moves inside the capillary, oxygen diffuses gradually, and PO2 decreases from 100 at the arterial side to 40 at the venous side.

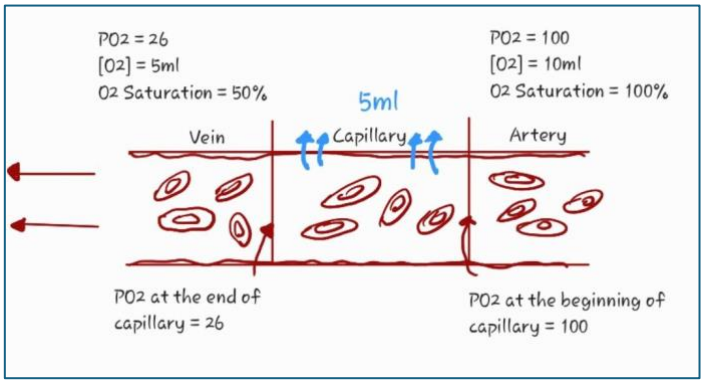


Now, we are going to do the same calculations for an anemic person and compare his venous PO2 to a normal person's venous PO2, is it the same (40), lower, or higher?

- In an anemic person, maximum oxygen-carrying capacity is reduced, the doctor assumed it to be 10 mL/dL.
- So, in an anemic person**, arterial PO2 is 100, [O2] is 10mL, and O2 saturation is 100%.**
- Regarding capillary exchange, the same steps apply, 5mL of oxygen/dL diffuses through the capillary wall (this amount is constant and only increases during exercise).



- As a result of this diffusion, oxygen content in the capillaries decreases gradually, until it reaches **5mL/dL** (10-5=5) at the venous side of the capillary (end). **Oxygen saturation is 50% (5÷10), and oxygen extraction ratio is 50% (5÷10).** (The maximum oxygen carrying capacity of the blood decreased from 20mL/dL to 10mL/dL. this is because a



low amount of hemoglobin, for example, 7.5, won't be able to carry more than 10mL of oxygen/dL).

- ❖ From the oxygen saturation curve, **at 50% saturation, PO2 = 26** (you should've memorized this value from the previous lecture).

So basically, **as the blood moves inside the capillary, oxygen diffuses gradually, and PO2 decreases from 100 at the arterial side to 26 at the venous side.**

Answer: B

Question 3:

A person is breathing from a gas tank containing 45% oxygen. What is the alveolar PO2?

A. 149 mmHg B. 250 mmHg C. 270 mmHg

D. 320 mmHg E. 340 mmHg

To calculate alveolar PO2, we use the formula:

$$PO2A = PO2i - \frac{PaCO2}{R}$$

Where: **PO2A** = alveolar PO2, **PO2i** = inhaled PO2,
PCO2a = arterial PCO2, **R**= respiratory exchange ratio.

- **PO2i** is the partial pressure of inhaled oxygen, usually 150 since O2 in atmospheric air is 21%, but in our example, the person is breathing from a tank containing 45% O2. So, we use the original formula we used in the first physiology lecture: 760-47= 713. (47 is PH2O, added to the gas in anatomic dead space). 713*45% = 321.

  ➔ **PO2i = 321 mmHg.**

- **Arterial PCO2** (which is the amount of CO2 in the pulmonary arteries, not systemic) is **40.**
- **R** is **0.8** (usually constant)

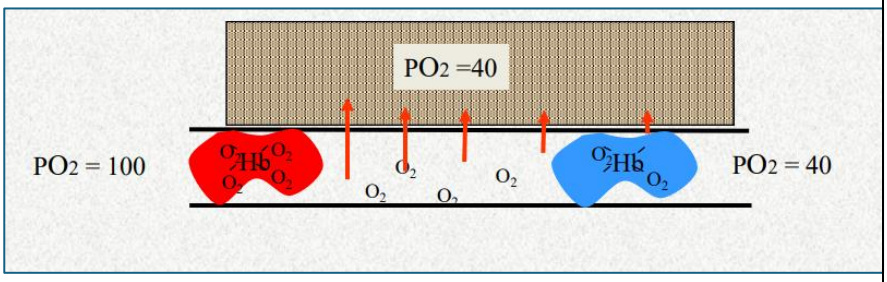
PO2A = 321 – (40/0.8) = 271 ≈ 270

Answer: C

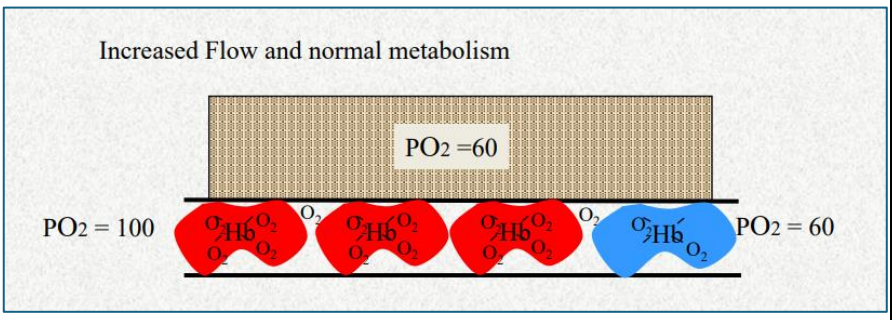
Question 4:

4. Blood and muscle PO2:

This is the normal exchange process that happens in the muscles. Muscle interstitial PO2 is the same as venous PO2 at the end of the exchange.



A. what happens to interstitial PO2 when we increase flow, but maintain normal metabolism?

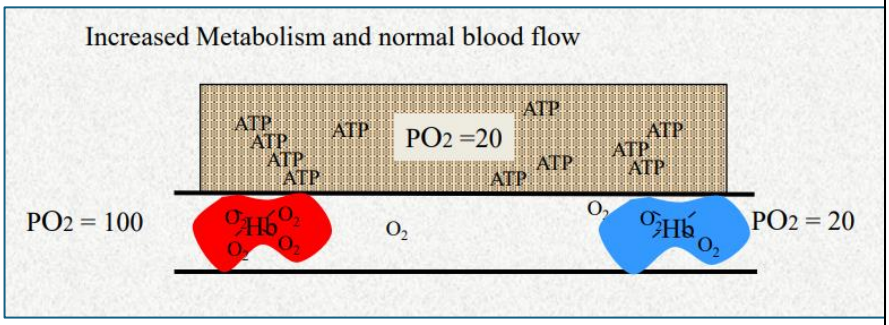


Answer: PO2 increases.

Why?

Blood flow is increased, and oxygen delivery is increased but O2 consumption remains the same. Please note that you cannot find the exact PO2 without specific numbers, it can only be stated as above or below 40. Note that **venous PO2 is always equivalent to interstitial PO2.**

B. What happens to interstitial PO2 when we increase metabolism, but normal blood flow?



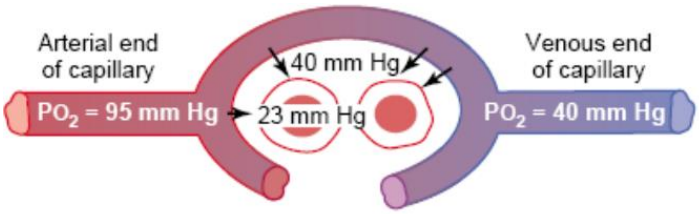
Answer: PO2 decreases.

Why? Because oxygen delivery and blood flow remain constant, but O2 consumption **increases**.

In a normal individual ([O2] =20mL/dL) O2 extraction ratio is 25%, but it can increase up to 50% or even 75%, reaching VO2max during exercise. This increased extraction ratio will cause the venous blood drained from the muscle to have **↓ PO2, ↓ O2 saturation, ↓ [O2]** (results similar to an anemic person, use the steps in the previous questions and you will see how).

*The doctor read the following slides very quickly and mostly didn't explain anything:

PO2 in systemic circulation (Diffusion from peripheral capillaries):



Oxygen is always being used by the cells. Therefore, the intracellular PO2 in the peripheral tissue cells remains lower than the PO2 in the peripheral capillaries.

Increased Blood Flow to Tissue:

• Normal blood flow

– 200mLO2 /lit of arterial blood * 5 lit blood/min= 1000 mL/min

– VO2 /min…250mLare consumed at rest (25%)

• Utilization Coefficient or (Extraction ratio):

• Is the % of blood that gives up its O2 as it passes through tissue capillaries. Normally is 25%. In exercise 75% - 85%. In some local tissues with extremely high metabolic rate → 100%.

O2 Uptake during Exercise:

• VO2 increases during exercise until it reaches VO2max…what limits VO2max…lung? CVS? number of mitochondria?

• Increased cardiac output and thus muscle blood flow and extraction ratio…all make more O2 available to the exercising tissues

• Decreased transit time…Normal lung can still oxygenate blood beside this issue

• Increased diffusing capacity

– Opening up of additional capillaries

– Better ventilation/perfusion match

• Equilibration even with shorter time

This is the last important topic in the lecture:

▪ VO2 Max

What limits VO2max?

VO2 max is the **maximum** O2 consumption during maximum exercise. (Remember, we said it is constant at 5mL/dL but only at rest, however, during exercise, it can increase).

Let's say that VO2 max is 40mL/dL. What limits this value? Is it the lungs? The heart? Or mitochondria? (The doctor said that this is an exam question.)

1. If we assume it is the **lung**, it means we are saying that the lungs cannot provide more than 40mL/min, how do we test if this is true?

   It was found that even after removing part of the lung, VO2 max can still be reached, indicating that the lungs normally can provide more than the needed O2, and some other factor must be limiting it.

2. What about **mitochondria**? Are mitochondria only able to consume 40mL/dL/min?

   Unfortunately, mitochondria are not the cause of this limitation, because simply, VO2 max can be reached without using all our muscle fibers. In fact, most of them may be resting and uninvolved.

3. This only leaves us with the **heart**, the only explanation left is that the heart's maximum cardiac output (which is 20L/min) is what limits VO2 max. But how do we confirm this?

   During exercise, both maximum cardiac output and VO2 max are reached. Since we cannot further increase the cardiac output to see whether it will increase VO2 max, we use a drug that lowers cardiac output. When such drugs were used, a resultant decrease in VO2 max was noticed. **We conclude that the CVS is what limits VO2max.**

Transport of Oxygen and Carbon Dioxide

• Oxygen transport

– Only about 1.5% is in the dissolved form (in plasma)

– 98.5% bound to hemoglobin in red blood cells

• Heme portion of hemoglobin contains 4 iron atoms – each can bind one O2 molecule

• Only dissolved portion can diffuse out of blood into cells

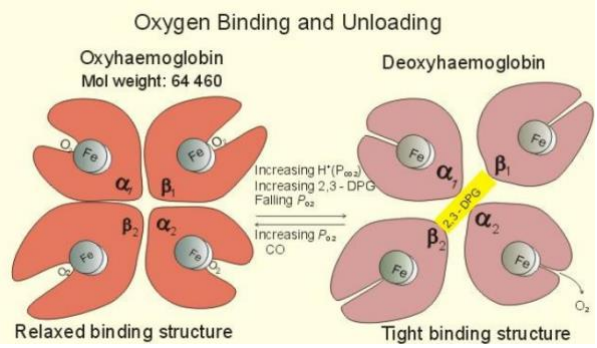
• Oxygen must be able to love (bind, associate, load, increase affinity) and hate dissociate (hate, unload • decrease affinity).

▪ Hemoglobin:

The total amount of Oxygen carried by Hb in blood depends upon:

❑ The percentage saturation of Hb.

❑ The amount of Hb in the blood.



- Hb exists in two forms, relaxed binding (oxyhemoglobin) and tight binding (releasing, deoxyhemoglobin).
- Four factors influence the shift from relaxed to tight state:
  1. **H+ (↓PH, acidosis).**
  2. **↑ PCO2.**
  3. **↑ 2,3 DPG.**
  4. **↑ Temp.**

  Three of these factors increase during exercise (acidosis, temp, PCO2).
- 2,3-DPG binds the beta subunit in the Hb molecule, fetal Hb has no beta subunit (2α, 2γ), and thus doesn't bind 2,3-DPG (less switch from relaxed to tight, causing the molecule to exist in the relaxed form mostly).

Oxyhemoglobin:

– Normal heme contains iron in the reduced form (Fe2+).

– Fe2+ shares electrons and bonds with oxygen.

Deoxyhemoglobin:

– When oxyhemoglobin dissociates to release oxygen, the heme iron is still in the reduced form.

– Hemoglobin does not lose an electron when it combines with 02.

Methemoglobin:

– Has iron in the oxidized form (Fe+++).

– Blood normally contains a small amount. but ferric Fe+3 which is useless because it does not release O2. NADH meth-Hb reductase can convert ferric to ferrous form

Carboxyhemoglobin:

– The reduced heme is combined with carbon monoxide.

– The bond with carbon monoxide is 250 times stronger than the bond with oxygen.

At a partial pressure of O_2 (PO_2) of 100 mmHg, hemoglobin (Hb) binds oxygen with the same affinity as it binds carbon monoxide (CO) at a partial pressure of CO (PCO) of 0.4 mmHg. This means that when these partial pressures are present in the blood, 50% of the hemoglobin will be bound to oxygen, while the other 50% will be bound to carbon monoxide. Using this concept, we can calculate the relative affinity of CO compared to O_2. Since a PO_2 of 100 mmHg is required to match the binding affinity achieved by a PCO of only 0.4 mmHg, the ratio of the two partial pressures is **100/0.4 = 250. This indicates that CO binds to hemoglobin 250 times more strongly than O_2.**

∴ Therefore, transport of O2 to tissues is impaired.

Carbaminohemoglobin:

- The reduced heme is combined with carbon dioxide.

Version 2: (highlighted in yellow)
- **P3:** editing the x-axis values in the first picture
- **P6:** VO2(dO2) instead of DLO2
- **P6+7+8+9:** extra explanation and paraphrasing