RESPIRATORY SYSTEM

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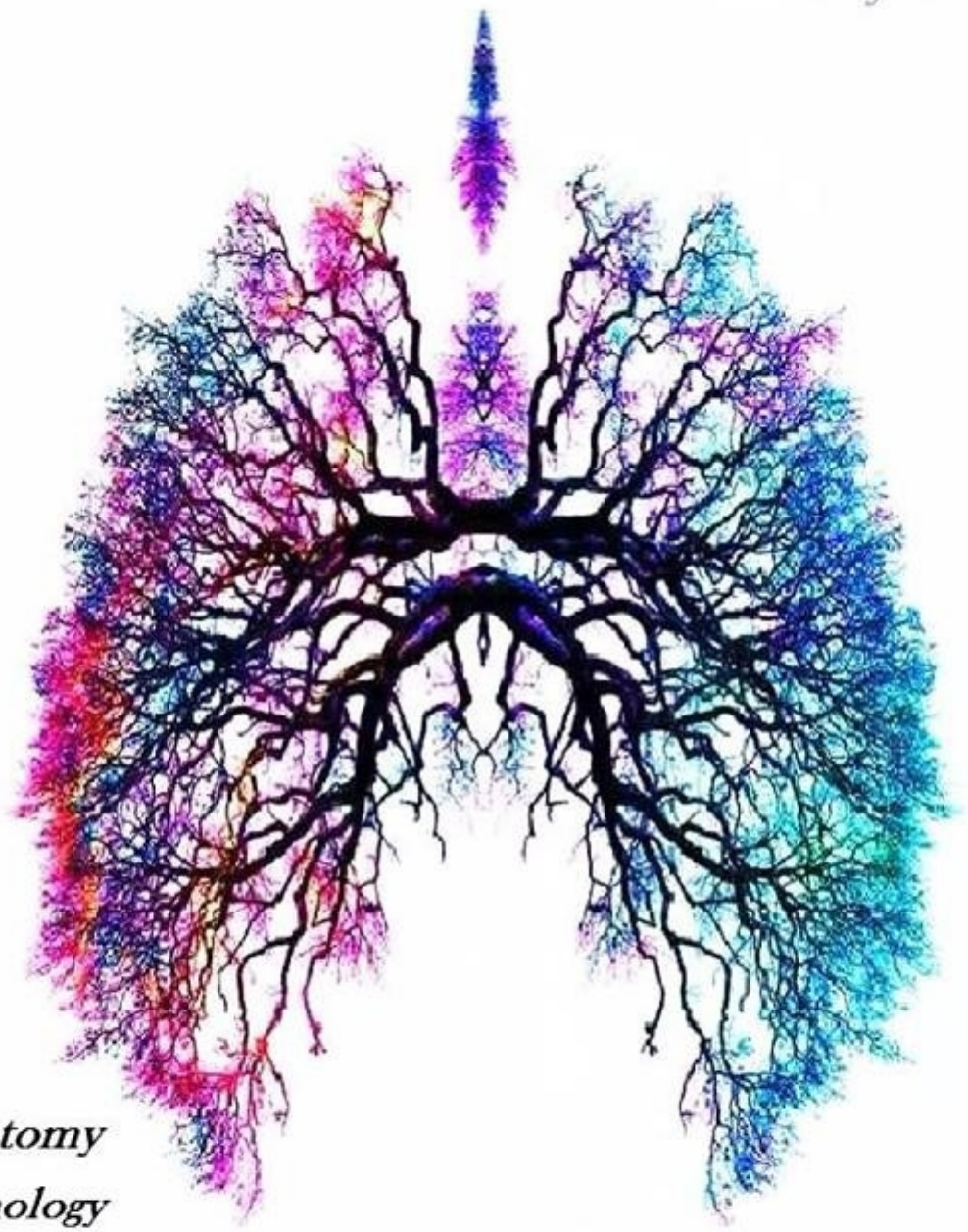

- ○ Anatomy
- ○ Pathology
- ● Physiology
- ○ Pharmacology
- ○ Microbiology
- ○ PBL

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Lecture # 7
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Gas Exchange

We expect from the CVS to achieve the main goal and deliver **20ml of O2 per each 1dl of arterial blood.** While the lungs are expected to maintain normal levels of ABGs; **PO2= 90 mmHg, PCO2= 40 mmHg, and a pH of 7.4**. However, normal levels of ABGs don't afford those 20ml of O2/1dl blood, thus another mechanism of carrying O2 should be used.

1 dl of arterial blood contains 20 ml of O2. Knowing the cells usually extract only 5ml; the extraction/utilization ratio can be calculated = 25%, leaving 15 ml of O2 in each 1 dl of venous blood "75%".

- The extraction ratio during training increases (50%, 75%, etc) and may reach to 100%, meaning you are utilizing the whole 20ml of O2 found in each dl of blood.

The heart pumps 5L/min or 50dl/min, from each dl we extract 5ml of O2 → O2 consumption (at rest)= 50*5= 250ml/min. [This consumption may increase 20 folds in a training athlete.]

- Supposing we consume only carbohydrates " Glu+6 O2 → 6 CO2+H2O", for each O2 molecule consumed, you will be producing 1 CO2 molecule.
- Actually we also use fats and proteins, making the glucose less metabolized, and the consumption of O2 higher than the production of CO2. This gives a

$$\text{Respiratory Exchange Ratio} = \frac{\text{CO2 production/min}}{\text{O2 consumption/min}} = \frac{200}{250} = 80\%$$

It is: How much CO2 you produce for the whole O2 consumption.

The plasma contributes to 55% of blood volume.
The plasma is composed of 92% water + 8% others.

- O2 diffuses to plasma. It has a low solubility in plasma, thus its partial pressure there will go up high rapidly. If it's more soluble then you can still add more O2 due to its rapid consumption and low PO2.
- PO2 in arteries= PO2 in alveoli= 100 mmHg.
- To know how much O2 is soluble in plasma, you apply:
- Henry's law → [O2] in plasma= PO2 * Solubility of O2
  = 100*0.003 = 0.3 ml/dl → very low!
- We need at least 5 ml/dl, thus we need a very huge Cardiac output which can't be provided by the heart to deliver the needed O2 with this low solubility, and this is not the case!

➔ Hb is enrolled in the delivery of O2, as well as many other systems, to achieve proper oxygenation of tissues .

The blood forms 7% of body weight in males, 6% in females (more fat and unused volumes of fluids), and 8% in infants. We take an average of 7%.

➔ 7% * 70 kg = 5 L of blood in an avg man.
➔ = 5000 ml = 5 million micro liter.
➔ Each micro liter of blood contains 5 million RBCs; each of which carries about 280 million Hb molecules.
➔ Each RBC carries 280 million * 4 = 1120 million O2 molecule.
➔ 1 Hb molecule has a MW= 46.5 Kilodalton *important to know*
Any molecule with a MW < 70 Kdalton can be filtered through the kidneys and may be lost in urine. So Hb, potentially, can be lost in urine ONLY IF it's swimming freely in the plasma . Actually it's trapped in RBCs (large cells → not filtered), thus Hb is not lost.

- A normal Hb molecule is composed of 2 Alpha + 2 Beta chains; Alpha= 141 aa, Beta=146 aa. Normal Hb → Alpha2-beta2.

- Other variants include :
  - HbF → Alpha2-Gamma2 (only appropriate in fetus), 1-2%.
  - HbS → Alpha2-BetaS2 (abnormal Beta chains; Valine instead of Glutamate in position #6.)
  - Hb1A → Alpha2-Delta2 , 1-2%.

➔ So normal Hb (HbA) concentration is not 100%.

- Hb amount: in Males = 14-16 g, in Females = 12-14 g. Average = 15 g/dl.
- Each Hb chain has a heme moiety with Fe+2 in its center. Ferrous Fe (+2) can share electrons, bind O2, and release it, unlike Ferric Fe (oxidized, +3) which cannot bind O2. It needs to be reduced by (NAD-H Meth-Hb Reductase) to Ferrous Fe to be able to love and hate O2 reversibly.
  ➔ This Reductase is found in the RBCs to assure that Hb doesn't leave the cells, thus not cleaved by plasma enzymes. When Hb goes to plasma, it also increases its viscosity making it harder for the heart to pump the blood.

- With 100% saturation, 4 O2 molecules are bound to the heme molecule. Sat% can be less than that, for example: 75%; meaning that the Hb molecule is carrying only 3 O2 molecules. 50%, 25%, or 0%.
  ➔ However, for billions of Heme molecules, the Sat% collectively can be any value from 0-100 (including decimal fractions).
  ➔ You can never over saturate Hb; NO 105% saturation!
- When Hb is saturated, 1g of Hb can reversibly bind 1.34 ml O2.
- For the 15g Hb in avg individual: 20 ml O2 are carried. **Remember the numbers!**
- Hb completes the mission; 20 ml carried O2 + previously dissolved 0.3.

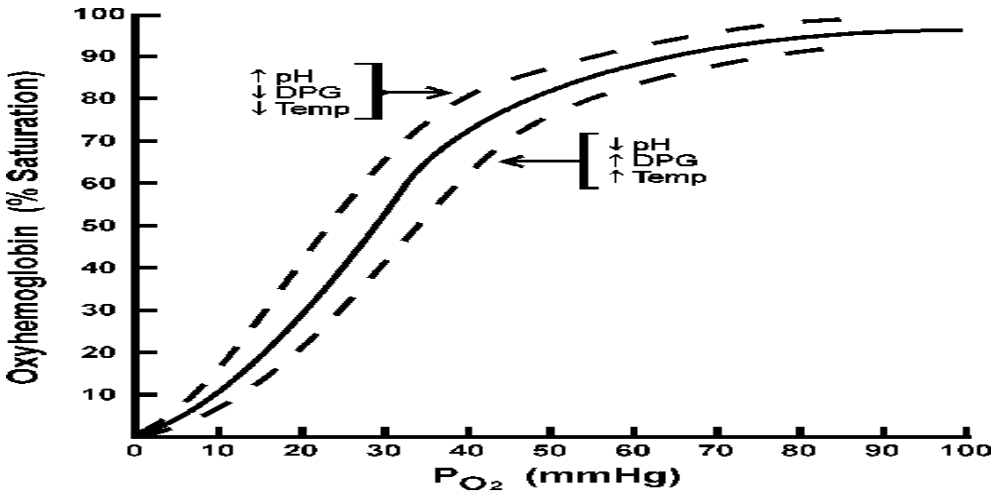
Although the O2 dissolved in plasma is neglected, it can help in cases of decreased Hb only if we increase [O2] in inspired air; when you give pure O2 to a patient (760 mmHg O2), it will be mixed with H2O in the airways (47 mmHg), resulting in a net of 713 mmHg O2 enter the lungs and go to the blood.

➔ CO2 will give 40 mmHg in arterial blood. You divide PCO2 on the respiratory exchange ration "R" (0.8). → 40/.8= 50
➔ Now, 713-50 = 663 mmHg, and this is the final arterial PO2.

Go back to Henry's low → O2 dissolved = 663 * 0.003 = 2ml (not enough alone)

➔ If you let the patient breath at 3 atm of pure O2 → 2*3= 6ml
Here you have enough O2 without the need of Hb, but this is actually lethal → O2 poisoning, so you can't do it.

You can also apply these calculations to predict the arterial PO2 if you give the patient an air with PO2 = 42%.



Hb-O2 dissociation curve.(please refer to the figure while studying the rest of the sheet)

- Sigmoidal in shape.
- The availability of O2, expressed as PO2, on X-axis → (Independent variable)
- The binding of Hb to O2, expressed as saturation (0-100%), on Y-axis → (Dependent variable)
- If O2 is available, it can bind Hb. However, it's not a linear relationship, due to the *Cooperative* binding of O2 to Hb. The 1st O2 to bind needs to overcome many bonding forces, so it's harder to it to bind, making the curve more horizontal initially (phase1). The 2nd O2 finds it easier to bind, and so forth, making the curve steeper (phase2). The curve finally goes back to platue after 100% saturation is achieved (phase3).

- 4 important "PO2"s concern us mostly, assuming Hb=15g;
  - PO2= 100 mmHg → Arterial PO2, tells that sat% = 98-100%, with 20ml O2/dl concentration .
  - PO2= 60 mmHg
  - PO2= 40mmHg
  - PO2= 26mmHg

  → If a patient has Hb=7.5 (Anemic): His arterial PO2=100 (or even more if he hyperventilates), Sat%= 100%, BUT [O2] conc. = only 10ml/dl *[7.5*1.34=10].*
  The lungs have completed their job, they gave you your normal ABGs levels, but this didn't guarantee that you won't develop hypoxia; you're Hb and blood should be normal too!

➔ *Normal individuals, with normal ventilation, Hb levels, and blood circulation, who enter the hospital for unrelated causes (e.g:appendectomy), this doesn't really need an O2 mask (PO2=42%), he won't benefit due to the fact that his blood is already normally saturated. You will only increase the dissolved O2 in plasma to become 0.6 ml rather than 0.3, and this again is negligible and not needed. You are only exposing him to more free radicals and O2 poisoning!*

- *While patients with pneumonia, pulmonary edema, or CO poisoning actually require O2 masks.*

If PO2 = 200 mmHg, you would expect the respiratory center to sense this increase and directly act to oppose it and depress it back to 100. However, this doesn't occur. The body knows that this 200 mmHg means nothing, thus the ventilation won't be suppressed!

- When PO2 = 60 mmHg, decreases by 40 degrees from normal, this still doesn't mean that much to your bodily responses. The Sat% becomes 90%, meaning you now have around 18ml of O2/dl, and your cells can take their needed 5ml/dl calmly without being affected.
  ➔ The respiratory center won't be stimulated too.

- When PO2 < 60 mmHg, the curve becomes very steep, the neurons start firing causing the respiratory center to stimulate **hyperventilation. Hyperventilation: I'm trying hard to make the composition of my alveolar air closer to that of the atmospheric air**.
  I need to increase PO2 + saturation%, & decrease PCO2.

- At PO2 = 40 mmHg, at the interstitial PO2, the Sat% is 75%.
  ➔ A 60-degree *fall in pressure, decreases the sat% by only 25%, this is the benefit of the sigmoidal curve.*

- **During exercising**, the PO2 drops to 15 mmHg, making the sat%= 25%, and increasing the extraction ratio to 75% (instead of normal 25%) because the cells need too much O2. The cells during exercising may need up to 4000 ml/min (16 times more than the normal 250 ml/min).
  ➔ The extraction ratio is increased by 3X only; so how can we achieve the 16X increase in consumption?
  By increasing the blood flow to tissues; the blood flow to MSS actually increases from 1L (at rest) to over 8L (upon exercising);

➔ O2 consumption = Blood Flow * Extraction Ratio
= ↑ 8-10 times * ↑ 2-3 times = ↑ 16-20 times increase!

- During exercising, the cells will ask the Hb to release/unload/hate its bound O2 (decreases the affinity), and should force it to do so, by:
  - Increasing <u>CO2</u> + <u>protons</u> production (due to increased work in the cell). CO2 & H+ will go the Hb chains and bind them at a specific site for each (not the same binding site for O2, it's not competitive inhibition). When CO2 binds to its site on the chain, conformational changes occur, resulting in O2 release, and this is known as "Bohr's effect". Also when H+ binds to its site, the O2 is released from the chain, again: "Bohr's effect too".
  - Increasing <u>temp</u> makes R-Hb → T-Hb, thus the O2 is released.
  - Increasing <u>2,3-BPG</u>; 2,3-BPG is a peripheral product of the anaerobic glycolysis occurring in the RBC, converted from 1,3-BPG by mutase.
    # Remember: RBCs carry O2 but can never utilize it for it don't have mitochondria.
    # It's an advantage to have the mutase enzyme inside the RBCs, so you can form the 2,3-BPG there.

  ➔ What 2,3-BPG does actually, is binding to Alpha/Beta chains and decreasing their affinities to O2 → Unloading*(forcing them to lose their Hb). It binds in the center between the 4 chains of the Hb molecule; each 2,3-BPG binds 1 Hb molecule.*
  - *At any PO2 value, the sat% will be less**. (The curve is shifted downward, and to the right.)***

  ➔ 2,3-BPG doesn't bind Gamma chains.

- A decrease in any of these factors [CO2, H+, Temp, 2,3-BPG] will cause the curve to be shifted to the left; increased affinity.

Finally, The doctor asked you to take a couple of minutes thinking about all these miracles in your cells, and saying سبحان الله .