Respiratory System
Physiology
Lecture - 8 -
Gas Transport

Chronic bronchitis is part of the COPD and its due to smoking.

There are certain differences between emphysema and chronic bronchitis.

PCO2 is increased in chronic bronchitis more than emphysema
there is always an overlap between emphysema and chronic bronchitis.

Clinical diagnosis: productive cough for 3 months continuously for 2 successive years -chronic bronchitis-

Emphysema diagnosis depends more on the pathological findings, chronic bronchitis diagnosis depends on lab tests.

In emphysema, pneumonia, fibrosis, tuberculosis, asbestosis... there is less respiratory membrane (less area)

Continuation of the previous lecture:
There are some tests that diagnose restrictive diseases, others that diagnose obstructive diseases. Also, we have tests to diagnose if there is diffusion limitation in the lungs We do a test to measure the diffusion capacity of the lung, before signs and symptoms manifest, we don't do it directly but rather through CO (carbon monoxide), because if we know the diffusion capacity of CO which is equal to 17ml/min for every mmHg pressure difference, you can figure out what's the diffusion capacity of oxygen as long as u know the diffusion coefficient which is 0.8 for CO compared to 1 for oxygen.

Now O2 consumption= 250ml/min at rest, this value is "FLOW" which equals "change in pressure/ resistance", resistance reflects the difficulty of respiration. Reciprocal of resistance if we are talking about ions is conductance, for glucose we call it permeability, here we are calling it _diffusion capacity_

Flow = $\frac{\Delta Pressure}{Resistance}$ Resistance = $\frac{1}{diffusion\ capacity(K)}$ So **Flow = Δ Pressure (ΔP)*diffusion capacity**

ΔP = PO2 alveolar - PO2 capillary

So unit of diffusion capacity is ml/min $mmhg^{-1}$ (volume of gas exchanged per minute for each mm mercury difference in pressure)

Diffusion capacity depends on 2 factors: 1) the respiratory membrane, cause if it gets thicker or reduced surface area, diffusion reduces and 2) the gas molecule itself

thicker through: fibrosis, edema and silicosis for example.

diffusion coefficient= solubility/ square root of M.W. and the solubility is more important cause square root of M.W. of different gases is not that different.

Diffusion Capacity = diffusion coefficient * $\frac{Area}{Thickness}$

Remember : **Diffusing capacity** of the lung (D_L) measures the diffusion of gas from alveoli in the lung, to the <u>red blood cells</u> in lung blood vessels per minute for every 1mmHg pressure difference.

Solubility for O2= 1 unit, solubility for CO2= 20, for CO=0.8, for N2=0.5

Our aim is find the diffusion capacity (amount of functioning respiratory membrane):

So we need to find, the flow and change in pressure of oxygen to calculate the diffusion capacity.
The flow can be easily measured for any gas however, the oxygen pressure difference (ΔP) between the alveoli and capillary varies along its length (equilibrates with the blood around the third of the capillary), and the same thing applies to CO2 so we can't use either gas to find ΔP and hence can't find their diffusion capacities directly.

However, we can use another gas CO (Carbon Monoxide), which directly binds hemoglobin and doesn't unbind, (constant partial pressure in capillary throughout = 0), so the ΔP is constant and can be measured and used to calculate diffusion capacity. The diffusion capacity of CO can be then be used to calculate diffusion capacity of oxygen since the membrane area and thickness

is same for both gases (same lung) so we simply divide by the diffusion coefficient which is already known from physics.

CO has 250 times higher affinity to Hb than O2, so when PO2 is 100mmHg and PCO is 0.4mmHg 50% of your Hb will bind to CO and if PCO was 0.8 almost all of your Hb will bind to CO2 ending up with anemia.

Give one single breath of CO (small amount), CO is taken by the blood immediately and is bound to Hb, CO in alveoli is 0.1 (as in example), so 'delta P' is equal to PCO alveoli and flow of CO is measured. Diffusion capacity typically is 17ml/min for every mmHg pressure difference for **CO.**

Diffusion coefficient for CO = 0.8, so diffusion capacity of oxygen = 17/0.8 = 21-23
We said that the diffusion capacity is a product of membrane (which is the same for all gases) and the diffusion coefficient.

Diffusion capacity is 21-23 for oxygen, around 400 for CO2 from here we can notice that in lung diseases the oxygen will be affected first , we'll see normal PCO2 and low PO2

Today's Lecture Topic : Gas Transport.

What information do we need to determine if the cardiovascular pulmonary system is working well or not?

Check the following scenario:
- we have two individuals A, and B, PaO2 for both equals 100

We can't determine which one between them has a better functioning cardiovascular pulmonary system from this single information.
Note: when PaO2 (ABG) is normal → lung is normal (we exclude it as the cause of the disease)

-O2 saturation for both 100%

We still need more information, because Hb concentration in individual B can be half the Hb concentration in A and still be 100% saturated, so now we need the concentration.

-Hemoglobin concentration 15g/dl for both
we still can't determine which is better yet.

What we need to know more is the hemoglobin **TYPE, if we have some sort of hemoglobinopathies.

One of the students asked: what's the point of knowing Hb concentration if we know that the partial pressure of O2 is 100.

Well, partial pressure of oxygen refers to its amount in the plasma, it doesn't necessarily mean that it is carried by Hb. you might for example have PO2 100 , and not have any Hb and this will totally be useless , oxygen won't be transported efficiently to the tissues.

Conclusion: we need to know Hb concentration and type in order to have an idea about the system's efficiency.

So, what we actually need to know if there were 20mL O2/ dL blood (in arterial blood) this is called **oxygen carrying capacity** , and it is the only information we need to decide whether the system is functionally efficient or not. So, as long as you can maintain 20ml O2/dL blood, we won't ask about anything else, because this is the end target that we want to reach. This will be explained in this sheet.

Oxygen is carried in two forms in the blood

1) Dissolved in the plasma

the concentration of oxygen in its dissolved form is governed by henry's law which states: Concentration of a gas in a solution is a product of its partial pressure multiplied by its solubility

PO2 = 100

solubility of O2 = 0.003

[O2] = PO2 * O2 sol

= 100 * 0.003 = 0.3mL/dL blood

i.e per each 100 mL (1dL) blood we have 0.3 mL O2 dissolved in plasma.

<u>*Blood volume is 7% of your body weight (males)</u> (5 liters in 70 kg male)

in females 6%, in newborns 8%

2) Carried by hemoglobin in RBCs: THE FOLLOWING DIAGRAM IS VERY IMPORTANT:

5 LITERS BLOOD

⇩

5000 mL

⇓

5 million µL

In each µL ⇓

5 million RBCs

In each RBC ⇓

280 million Hb

Each Hb can maximally bind ⇓

4 O2 molecules

~~ Question: true or false: 1 Hb molecule can maximally carry 8 Oxygen atoms. FALSE, they bind as molecules not as atoms.

*1g Hb can bind reversibly 1.34mL O2

Hb normal concentration for males: 14-16g/dL blood   avg:15
                                    females: 12-14g/dL blood

1g Hb → 1.34mL O2
15g Hb → ??

19.5 mLO2/dL blood bound to Hb → this is the maximum carrying capacity of the Hb in blood assuming the hemoglobin is fully saturated
in 100mL (1 dL) blood → 0.3 mL dissolved O2
                          19.5mL bound O2
                           total = 19.8 O2 in 1dL blood, we consider it 20 ml/dL (to make it easier)
the fraction of the dissolved O2 : 1.5% of the total O2 in blood → very small → negligible
While the bound O2 is 98.5%, so oxygen is carried mainly in the bound form.

if you put a person under a high PO2, PO2 = 200 , bound O2 is fixed it stays as it is because we have fixed amount of Hb in 1dL blood , whereas dissolved O2 is doubled → 0.6 (because [O2] = PO2 x O2 so → 200 x 0.003 → 0.6 mL)
which is almost nothing compared to the total amount of O2 in blood
So by increasing PO2 , you are exposed to oxygen free radicals , oxygen toxicity , oxygen poisoning , without adding any significant amount of oxygen to your blood.

-If we gave a person pure (100%) oxygen under atmospheric pressure, PO2=650 almost, [O2]= 2 ml, which is still not enough. If we gave this pure oxygen under 3 times the atm pressure, [O2]=6ml/dL, this is enough so we don't need RBCs anymore, but this is just hypothetical, we can't do it because it is extremely dangerous, this means that we will always need RBCs.

-The most important function of the cardio-respiratory system is to guarantee **normal oxygen carrying capacity in the blood** 20ml O2/dL. This means you should have a normal PO2, oxygen saturation, Hemoglobin concentration and normal type of Hemoglobin to have 20ml O2/dL. Having a normal Oxygen carrying capacity means that everything else is normal because for example if you had normal Hemoglobin, but it is bound with CO and not oxygen (for example)… you will end up with hypoxia. So if someone has normal hemoglobin concentration which is 15g/dl but 50% of his hemoglobin is occupied by carbon monoxide, he will have 10ml/dl of oxygen and not 20 ml/dl in the arterial blood.

So the arterial blood coming to the cell carries **20mL O2/dL**, also known as **20%volume to volume** (if you convert the dL to 100mL then multiply the result with 100% you will get the percentage of oxygen in the blood: (20ml O2/100 ml) *100% = 20%).
But cells utilize only 5 mL O2, leaving 15mL O2 going back to the heart through the venous system. So the venous system doesn't contain deoxygenated hemoglobin, but rather partially deoxygenated Hb.
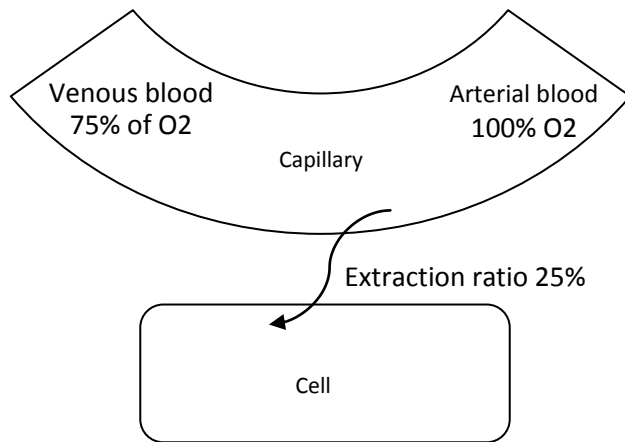
So the extraction ratio = [(O2 arterial – O2 venous) / O2 arterial] x 100%

= (20-15) / 20 x100%

=25%

Now if I want to calculate oxygen consumption by cells from the <u>cardiac output</u>:

The heart pumps 5L of blood, which equals 50 dL of blood, from every dL of blood the cell extracts only 5mL O2→

oxygen consumption = blood volume x extraction volume

= 50dL x 5 mL/ dL= | 250ml O2 | <u>OXYGEN CONSUMPTION</u>

Now the question is; why does the blood carry 20ml/dl of oxygen if only 5ml/dl is extracted and needed while 15ml/dl is sent back to the heart? This is simply because if any moment you need more oxygen (during exercise, hemorrhage etc.) then you can extract more, for example cells can extract 10ml/dl (50% extraction ratio), 15ml/dl (75% extraction ratio) or 20ml/dl (100% extraction ratio; the venous drainage here would contain no oxygen from that specific highly metabolic tissue) according to their needs of oxygen. Assuming there is no change in blood distribution.

So during rest, oxygen consumption is 250 ml, while the maximum oxygen consumption (during exercise for example) increases to 5L, 20 times more than the normal resting oxygen

consumption. Can the cardiac output increase 20 times? Of course not, the maximum cardiac output, which is found in marathoners, is 30 L/min (which 6 time more than the resting CO), while the max. CO in normal people is only 20 L/min (4 times the resting CO), so CO can never increase 20 times. Then how can we manage this increase in oxygen consumption (20 times)? By increasing the extraction ratio.

The doctor mentioned some notes about cardiovascular system and said that he might ask about them in the exam:

*Note: how do we diagnose heart failure? heart failure TRIAD : 1- dyspnea 2- fatigue 3- palpitation
if these symptoms appear during :
- severe exercise → HF stage 1
- moderate exercise → HF stage 2
- mild exercise → HF stage 3
- at rest → HF stage 4
 we can also use ejection fraction or cardiac reserve to classify heart failure.

*Note: Ejection fraction is the best method to determine the efficiency of the heart.

*Note: CO= 5L/min, at rest:
GI tract → 1400 ml
kidneys→1.2 liter
skeletal muscles →1.2 liter (almost 20%)
brain→750 ml liter
others →1 liter
-others: include coronary arteries (the heart) and skin, skin takes 0.5 liters while coronary arteries takes 250 ml (this number is very important).

During mild exercise: CO= 12 L/min:
Skeletal muscles→ 8L (66%)
Kidney→ 0.5 L
Brain→ 0.75 L (doesn't change)
GI→ 0.6

Skin→ increases
Coronary→ doubles

The dr. said that these numbers are approximate.
End of CVS notes.

Hemoglobin:

Hb is composed of 4 chains, it is an allosteric protein.

-HbA $2\alpha2\beta$→ (the most favorable type of Hb , because it's the one that can both bind and release O2), we have other types of Hb that might bind O2 without releasing it. And this is not efficient in transporting O2

-HbS → has valine instead of glutamic acid, so it loses one negative charge

-HbF $\alpha_2 \gamma_2$

-HbA2 $\alpha_2 \delta_2$

Note: alpha chain has 141 a.a. while beta has 146 a.a.
The molecular weight of Hb molecule= 64500 daltons, since it is less than 70000 it is in danger because it can be filtered by the kidney and lost in the urine. Normally, we don't have Hb in the urine because it is not free in the blood, it is found in the RBCs, this is one of the advantages of having Hb inside RBCs.
Note: average mass of one amino acid in a protein is 110

Now hemoglobin contains Heme group (non-protein moiety) and an apoprotein. The heme has an iron in its ferrous form (can bind oxygen reversibly), and when this hemoglobin is bound to oxygen then it's called Oxyhemoglobin. If the Heme group has Ferric iron then it can't bind oxygen, and this is called Methemoglobin or oxidized hemoglobin. Inside the RBC there is an enzyme called methemoglobin reductase which reduces the iron back to its ferrous form if Methemoglobin is present. This is a second advantage of having Hb inside the RBCs and not free in the plasma.

Therefore, there are different forms of hemoglobin that may be present are: Deoxygenated hemoglobin, oxyhemoglobin, carbaminohemoglobin, carboxyhemoglobin (bound with carbon monoxide).

If CO_2 binds then oxygen is released and this is called <u>Bohr effect,</u> and when H+ binds oxygen is released and this is also <u>Bohr Effect</u> (in tissues). If O2 binds then CO2 is released and this is called <u>Haldane effect</u> (in lung).
CO2 binds in a different binding site than oxygen so there is no competition, and H+ binds to a different site as well (so 3 binding sites).

2,3 BPG is a very important compound. It is produced in the RBC form 1,3diphosphoglycerate (a glycolytic intermediate) which becomes 2,3 Diphosphoglycerate (more correctly called 2,3 Bisphosphoglycerate) by a mutase enzyme in the RBC. For each molecule of hemoglobin we have one molecule of BPG in the RBC.

Now let us take a look at the Oxyhemoglobin dissociation curve:
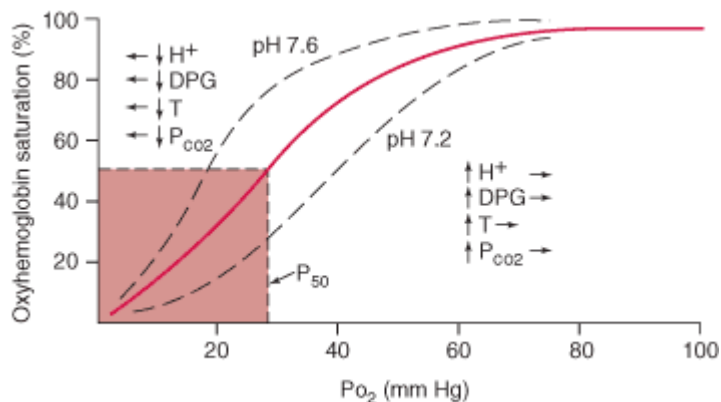
- When PO2 is 100mmHg, this means that that the partial pressure of oxygen is 100mmHg in the surrounding solution (Note: Be careful, here we are not talking about the oxygen bound to hemoglobin, but logically if the PO2 in the surrounding solution is 100 then hemoglobin is 100% saturated with oxygen or a little bit less).
- The saturation is almost 75% when PO2 is 40mmHg (in the venous blood).
- When PO2 is 60mmHg the curve starts declining very steeply, while from 100-60 the decline is only 10%.

- P50 is 26mmHg which is the partial pressure of oxygen when hemoglobin is 50% saturated.

Now in the Y-axis at 100% Oxyhemoglobin saturation, this does not necessary mean that you have 20ml/dl of oxygen which is conditional if you have normal hemoglobin concentration of about 15g/dl. If someone is anemic with 7.5g/dl hemoglobin concentration then you would have 10ml/dl oxygen with 100% saturated hemoglobin as well.

Now we have two sites that we should explain:
1. The capillaries approaching the lungs. Hemoglobin here must carry oxygen so it must switch to <u>high affinity form</u> to carry oxygen from the lungs.
2. Capillaries approaching the cells in the systemic circulation. Here hemoglobin must switch to <u>low affinity form</u> to release oxygen to the tissues.

When we say **high affinity hemoglobin** this means that at any PO2, the oxygen carried by the hemoglobin is more, and the curve shifts <u>upwards and to the left</u> as it is seen in the graph above.

When the curve is shifted <u>downward and to the right</u> this means that this is **low affinity hemoglobin**, the amount carried at a certain PO2 is less; so the amount released is more.

During exercise, the cells need more oxygen (5 ml/dL is not enough anymore), so the Cardiac output increases by 5X from 5L to 25L, but this is not enough. So the working cells force Hb to release more oxygen by producing an <u>increase</u> in 3 important factors which are **CO2**, **Hydrogen ion concentration, lactic acid** and **local Temperature**. These factors will decrease the affinity thus forcing the hemoglobin to release its oxygen, so the curve will be <u>shifted to the right</u>. Hemoglobin will <u>shift to the left</u> when these factors <u>decrease</u>. Now if we increase the release of oxygen by 2X then it will release 10ml/dl, by 3X then 15ml/dl is released and if the cells extract oxygen by 4X then 20ml/dl is released.
Also having a high concentration of 2,3BPG will shift the curve to the right.

So this means that oxygen consumption depends on two things:
1. The blood delivered to the tissue
2. The extraction ratio of oxygen

In relation to Fetal Hemoglobin (HbF):

   The lung of the fetus is the placenta which is a membrane that separates the fetus blood from the mother's blood. The fetal hemoglobin is exposed to oxygen at a partial pressure of 40 which is the partial pressure of oxygen in the interstitium of the mother, unlike our normal hemoglobin which is exposed to a PO2 of 100. So the fetus is exposed to a very low PO2 (not enough), but remember HbF does not bind 2,3 BPG so it has a higher affinity to oxygen. Remember, 2,3 BPG is a negative factor to oxygen binding (shifts the curve to the right) that is why HbF has a higher affinity to oxygen than HbA (the curve is shifted to the left), so the amount carried by HbF at a certain PO2 is higher . After delivery hemoglobin F (HbF) is replaced by Hemoglobin A (HbA) because the baby will be exposed to high PO2.

Extra Notes mentioned in the other record:

If the CO2 concentration increases in the blood due to a problem in ventilation in part of the lung, the respiratory center will sense this increase and stimulate hyperventilation. The hyperventilating parts of the lung will correct this increase in pCO2 however they won't be able to correct the decrease in pO2 that also occurs, that is because the under ventilated area of the lung (the one with the problem) is responsible for this decrease in pO2 (as well as the increase in pCO2 which is corrected).
So, CO2 is a **self compensatory gas** that can be sensed by the respiratory center however oxygen isn't.
pCO2 can be sensed in **two** tails (increase or decrease), however the pO2 sensed only in **half tail** (decrease below 60)

Good Luck ☺

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