Human Physiology
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Lecture - 02

Hello everyone, welcome to another new class on human physiology. In the last class, we discussed lung anatomy, and we saw what the different types of lung cells are, and briefly we discussed the respiration process. But in this class, we will thoroughly discuss how gas exchange happens and how the steps of respiration, inhalation, and exhalation occur. So, let us stay with it. What different content will be covered in this class? So, we will see what the different anatomical parts of the respiratory system are. We will discuss the uptake of the oxygen by the pulmonary blood.

Then we will discuss in detail about oxygen transport in the blood, right? Then we will discuss the oxyhemoglobin versus deoxyhemoglobin. We will discuss the cooperative binding of oxygen in hemoglobin. We will then discuss the oxygen dissociation curve for myoglobin along with hemoglobin. Finally, we will discuss the oxygen release to tissues and oxygen delivery.

So, we already discussed that we are not going to thoroughly mention the whole respiratory system again, but in the last class, you remember that we said that there are certain components of the respiratory system, right? So, we basically have the primary organ, which is the lung, that has a bilobular shape, and this lung has alveolar sacs or alveolar cells that consume oxygen, which is inhaled from the air. This upper part includes the nasal cavity, nostrils, oral cavity, epiglottis, and larynx; all these components, along with the thoracic cavity and the trachea, are involved. So, this entire upper component, including the trachea and the nasal cavity, contributes to the process of inhalation, right? So, we have already discussed this. So, basically, during inhalation, what happens is that the oxygen reaches the air we consume, and once this oxygen reaches the lungs, it goes through the trachea to the bronchus to the bronchioles and eventually to the small alveolar sacs. Here, basically, it gets kind of consumed by this oxygen, and there are a lot of microcapillaries present in the last two classes.

Also, we discuss the microcapillaries, which are basically small blood vessel chains, right? So, basically, oxygen diffusion happens here, right? So, basically, in this microcapillary, oxygen diffusion, or the oxygen exchange, or the gas exchange happens right from these lung cells to the blood cells, and eventually, once this oxygen or gas exchange happens, the oxygen either, like in passive transport or in active transport, basically gets circulated and distributed to different parts of our body. So, this is like the overall kind of detail of respiration. And eventually, after cellular metabolism and cellular respiration, what it does is generate a lot of carbon dioxide. This carbon dioxide eventually comes back through the blood via the venules and the veins. And again in this lung, the gas exchange happens so that the carbon dioxide, through the process of respiration, can go out.

Carbon dioxide can eventually move out from the body through a process of expiration and exhalation. So, what are the different respiratory units we already discussed? We have the upper respiratory units, which include the nose, right nostrils, and all. Then we have the trachea, and inside, near the lung, we have respiratory bronchioles, alveolar ducts, antrum, alveolar sacs, and eventually the small lung cells, which are also called alveoli. Basically, there are about 700

million alveoli, or lung cells, which are present in the lungs, where the exchange of oxygen and carbon dioxide eventually happens. So now let's see how the uptake of oxygen occurs in the case of pulmonary blood.

A pulmonary alveolus that is mostly adjacent to the pulmonary capillary. So, basically, in cases of this lung where the alveoli are present exactly beside these pulmonary-like alveoli, what we have is pulmonary arteries. Right inside this pulmonary-like alveoli, the partial pressure of oxygen is too high; it is about 104 millimeters of mercury, whereas in cases of the venous side of the blood, the pressure is very low at about 40 millimeters of mercury, which means you can see there is a huge pressure difference. So, as we are saying, inside this pressure, in the initial pressure, where the difference in pressure is about 64 millimeters of mercury, which is a positive pressure, and using this positive 64 millimeters of mercury, oxygen diffusion happens very rapidly. So, fully understanding again, we will kind of brush up.

So, the alveolar partial pressure of oxygen is about 104 millimeters of mercury, and on the venous side, the partial pressure is about 40 millimeters of mercury. Due to this positive 64 millimeter difference in mercury pressure, a rapid diffusion of oxygen occurs from the alveolus to the arteriole. Right, or like to the arterial side or the venous side, okay? So, eventually, when this happens, like a rapid diffusion of oxygen from the alveolar side to the arterial side, the pressure builds up slowly due to the rapid diffusion of oxygen. So, as you go slowly to this side, you see that there is a rapid rise in blood oxygen pressure, right? So, as we go from one side to the other side of this, like an overall artery, such as the pulmonary artery, what we will observe is that there is a rapid increase in blood pressure from about 40 millimeters of mercury to 104 millimeters of mercury. Then, as the blood oxygen is kind of infused inside the arteries, what happens is that there are basically two different ways the oxygen can be distributed or transported across our body.

So, scientist Krogh first laid the foundation, and he mentioned that oxygen could actually be transported via a passive diffusion pathway. So, there is basically Krogh, who first proposed the theory that oxygen can be transported via a passive diffusion mechanism. And in this way, oxygen can eventually get inside the fluid content that is inside the blood and then be diffused to various cells and tissues. But in this way, passive transport can only contribute to 3 percent of the oxygen transport in the body. So basically, the dissolved form of passive transport can only contribute about 3% of the total oxygen transport in the body.

And this basically follows Henry's law, which states that the dissolved oxygen is directly proportional to the partial pressure of oxygen. So as the partial pressure of oxygen increases, the amount of dissolved oxygen also increases. That means the concentration of oxygen is directly proportional to the partial pressure of oxygen. But as we said, only about 3 percent of the oxygen, which is basically only 0.3 ml, is transported in its diffuse form.

So, basically, if we consider that at a given time about 5 ml of oxygen is getting transferred in the body, only 0.3 ml of the oxygen can eventually get transported by the diffuse form. Now, what is basically the active form, right? So, the active transport, the active oxygen transport, basically happens with the help of hemoglobin, right? So, oxygen basically actively binds with the hemoglobin, which is present in the RBCs in the blood, we know. So, hemoglobin has a structural beauty that allows it to bind oxygen, and in this active binding form, oxygen is basically distributed to the body, mostly about 97 percent. So, what we just said is that hemoglobin, which is an iron-containing metalloprotein present in the RBCs of red blood cells,

can bind with oxygen and carry and distribute about 97 percent of it in an active transport manner.

It is basically like an octahedral complex of iron(II). So, basically, in cases of deoxyhemoglobin, iron is present in an octahedral complex where the iron oxidation state is Fe^{2+}. In the fifth position, which is bound to the nitrogen atom of an imidazole ring, if you see, it is bound to an imidazole ring, and in the sixth position, it is generally empty. So, in the fifth position, it is bound to the imidazole ring, and in a deoxyhemoglobin condition, the sixth position is empty. In this case, iron is in the plus 2 oxidation state, or you can also say it is in a high-spin oxidation state.

And basically, in these cases, it is in a tense condition or a tense state. A tense state of a hemoglobin octahedral structure, where there is no oxygen, is generally highly unfavorable for binding with any oxygen. So, basically, in cases of tense state, the hemoglobin structure is not ready to bind with any oxygen. Then what happens, basically, as you know, is that hemoglobin can bind with a total of four residues of oxygen. Why so? Because hemoglobin has two alpha protein residues and two beta protein residues, and each of these cassettes can bind with one oxygen.

But these four oxygen bindings do not happen at the same time, right? So what basically happens is that first one oxygen molecule gets bound to the hemoglobin, and you see whenever there is one oxygen molecule that binds with the deoxyhemoglobin, eventually there is this bond formation with the oxygen and the distal histidine residue of the hemoglobin, and that kind of gives a stable or relaxed state. So, basically, it creates a relaxed state of hemoglobin structure, which is also called a hard state. In these cases, the iron oxidation state is about Fe +3, or it is like a low-spin kind of situation. Right, so in this case, once the first oxygen binds, the hemoglobin structure eventually opens up, becomes stable, and enters a relaxed state. After that, the remaining three oxygens rapidly start to bind.

So, what we just said is that the deoxyhemoglobin structure, in a high-tension state, is not favorable for binding with any oxygen. But whenever there is fast oxygen binding, it eventually comes to the relaxed state, and in the relaxed state, the hemoglobin structure becomes highly favorable for binding with oxygen. So, what we just said, let's briefly discuss again, is that we have a total of 2 alpha residues and 2 beta residues for every hemoglobin. These alpha chains have about 141 amino acids, while the beta chains have about 146 amino acids. So, in cases of normal, like the deoxyhemoglobin state, we stated that it stays as a high-spin iron(II) complex, which is a 10-state, and it is not favorable for oxygen binding.

Whenever a single oxygen binds to either of these alpha or beta residues. So, whenever there is one oxygen that binds with an alpha or beta residue, the iron 2 from a high spin eventually converts to iron 3 in a low spin. inorganic coordination complex where the tense state becomes a relaxed state and it influences the rapid oxygen binding thereafter. So this process is also called cooperative binding of oxygen to hemoglobin. So, as you see initially, there is no oxygen present in any of the protein-like cassettes.

That means it was initially in a tense state where no oxygen was present; it was empty, but whenever a single oxygen binds to either the alpha or beta chain, Slowly, the tense state of the hemoglobin converted to the hard state or the relaxed state through conformational changes, and eventually, like the next three, the second, third, and fourth oxygen molecules bind rapidly. This process is called cooperative binding of oxygen to hemoglobin. Okay, hopefully, it is clear

how, kind of like the hemoglobin structure, they change from the tense state to the relaxed state through conformational changes, such as changes in the iron's valency state, and eventually, the cooperative binding of oxygen occurs. Now, let us see what the oxygen dissociation curve is like, and we will also discuss different conditions that influence oxygen binding to hemoglobin or may reduce oxygen binding to hemoglobin. The oxygen dissociation curve is nothing but a plot of the partial pressure of oxygen against oxyhemoglobin saturation or percentage saturation.

On this side, if we move along the x-axis, it will represent the partial pressure, which indicates how much partial pressure of oxygen is needed to saturate hemoglobin. So, as we go up, that means more and more oxygen is getting saturated in the hemoglobin, and to achieve maximum saturation of oxygen, what is the amount of partial pressure that is required? This is basically like the plot of PO2 versus the percent saturation, which is called the oxygen dissociation curve. And as you can see, this kind of shows this type of sigmoid geometry where initially the saturation happens very slowly, right? So, initial saturation, like the initial binding of oxygen, happens very slowly, and we have already discussed the reason, right? Because once there is no oxygen to any of these four alpha-beta protein cassettes, the hemoglobin structure is in a tense state. So, initially it takes a lot of time for such a lot of actually partial pressure to eventually bind oxygen to the blood. But once the few oxygens get bound, like when the first oxygen gets bound, the conformational changes happen, and eventually you see that there is this sharp increase, right? There is a sharp increase in the partial pressure of oxygen, along with the percent saturation.

So, at the initial time point, there is only very little saturation of the oxygen happening. But once the fast oxygen gets bound, there is a sudden increase in the saturation of the oxygen. And you can see that the partial pressure of oxygen, which is about 50% of the oxygen saturation, is about 30 to 35 mm of Hg, right? So, 30 to 35 millimeters of mercury pressure corresponds to about 50% oxygen saturation. So, about this much partial pressure is needed to saturate the hemoglobin with 50% oxygen. Now, what happens if, for example, in cases of temperature increase or decrease, in cases of carbon dioxide release, in cases of acidity increase, or in the case of H+ ion increase, what happens to this oxygen dissociation curve? We have to discuss them one by one.

So let us start with the pH first, and pH is also correlated with carbon dioxide secretion because after cellular respiration, carbon dioxide is produced, as we all know, and this carbon dioxide, once it binds with water, produces carbonic acid. This carbonic acid can dissociate to form H plus proton ions. So, basically, like H plus proton, in cases of it, basically decreases the pH. So, in cases of decreasing pH or in cases of increases in CO2, what it does is basically disfavors the binding of oxygen to hemoglobin. So, that means it will take more pressure; it will take more partial pressure to bind the oxygen.

So what we just said is that in cases of carbon dioxide secretion, it will basically influence a decrease in the acidity of the blood, which means there will be more and more H plus ions. And what this H plus ion does, you know, let me go back to the hemoglobin structure for a second. So, what this H plus ion does is that this H plus ion basically stabilizes this histidine ratio. So, you can see that there is this distal histidine-like molecule here, a distal histidine molecule. So, if we have a lot of H plus ions freely moving in the blood, these H plus ions will eventually bind with this distal histidine to make it stable.

And in that case, if it gets sterilized, what will happen is that oxygen binding will not occur. So what was just said is that in cases of increased H plus ions, the pH will decrease, and that will create an unfavorable oxygen binding condition for hemoglobin, causing the right shift of the oxygen dissociation curve. So in cases of pH decrease, H plus increase, or CO2 increase, we will observe a right shift of the oxygen dissociation curve. That means the oxygen will be released from the hemoglobin, or alternatively, you can say that it would take more pressure, like more partial pressure, to bind oxygen to the hemoglobin.

This is also called the Bohr effect. Then there is another condition; if the temperature is increased during exercise, what happens is that the temperature rises in our body, and if the temperature rises in the body, it unfavors the binding of oxygen with hemoglobin. Similarly, if the temperature goes higher, the oxygen dissociation curve will show a right shift, which means oxygen will be released from hemoglobin. The next condition is if 2,3-DPG, or 2,3-diphosphoglycerate, concentration goes higher in the body, what will happen is that 2,3-DPG, or 2,3-diphosphoglycerate, will increase. It is basically a chemical that is found in red blood cells, and sometimes the concentration goes higher through the glucose metabolic pathway. So, as this glucose metabolic pathway basically activates or happens rapidly, the concentration of this chemical, 2,3-DPG, increases.

And eventually what happens is that the 2,3-DPG binds with the beta chains of the hemoglobin residue. So, as you can understand, if 2,3-DPG binds with the beta chain residue, it is basically competitive binding, right? So it will basically capture the spaces where oxygen can eventually bind. So if the 2,3-DPG or DPG concentration goes higher, what will happen? Basically, the oxygen dissociation curve will have a rightward shape. And what is the meaning of the rightward shift of the oxygen dissociation curve? Again, that means oxygen will have a lower affinity to bind with hemoglobin. That means oxygen release will be observed from hemoglobin.

So, these are some of the conditions recapitulated. If the pH decreases or the H plus or the CO2 concentration increases in the blood, a right shift of the oxygen dissociation curve will be observed, which is also called the Bohr effect because this H plus will eventually stabilize the distal histidine, causing unfavorable oxygen binding to hemoglobin. So, in cases of 2,3-DPG or DPG, as it is a metabolic product of glucose, if it goes high, it competitively binds with the beta residues, right? So, DPG completely binds with the beta residues, and if DPG completely binds with the beta residue, what will happen? The oxygen will not be able to properly bind with the hemoglobin, causing the right shift of the oxygen dissociation curve. So, basically, oxygen will be released from the hemoglobin, or it will take a lot more partial pressure to bind oxygen to the hemoglobin. Okay, so in the same way, if the temperature goes high, there would be a right shift of the oxygen dissociation curve, which means a lack of oxygen binding to the hemoglobin.

Contrary to that, there are other conditions here. So, this is very important, right? Like, you can expect a lot of different questions from this oxygen dissociation curve. And as we said, the oxygen dissociation curve is very simple. It is basically a plot of the oxygen saturation versus the partial pressure of oxygen. So, it is a sigmoid curve, and in certain unfavorable cases, it will have a right shift, and a right shift means oxygen is not favorable to bind.

In cases of the contrary to the opposite condition, the oxygen will bind favorably to hemoglobin. So, this is a very interesting topic. And let us also discuss what happens to myoglobin. So, in cases of hemoglobin, we said that it has 4 kinds of protein subunits, which

are 2 alpha and 2 beta, and it is in a cooperative binding condition. So, initially because hemoglobin is in a 10 state.

So, fast oxygen takes a lot of time and a lot of high partial pressure to bind. But once the first oxygen binds to the hemoglobin moiety, the iron conformation changes, and the overall conformation of the hemoglobin changes from the T state or tense state to the relaxed state. And in that case, after the first oxygen, the second, third, and fourth try to bind more rapidly. But in the case of myoglobin, it is mostly kind of a monomer; it has just one pocket to bind oxygen. So, basically, it has only one pocket in case it binds with oxygen.

In cases of hemoglobin, what did we say? In cases of hemoglobin, it has four pockets, right? So in cases of myoglobin, you know, myoglobin is mostly present in our muscle cells. So in cases of myoglobin, it has only one pocket to bind with oxygen, and mostly oxygen binds in a much more linear fashion to the myoglobin, which is mostly thermodynamically favorable for binding oxygen to the myoglobin in a much more linear fashion. Where the oxygen binds to hemoglobin in an angular way, and as we have already discussed this cooperative binding many times, it is not favorable. So basically, the partial pressure required to mostly saturate the myoglobin to about 50% is very low. So you can see about three to four millimeters of mercury pressure, you can basically half-saturate the muscle cells or the blood near the muscles.

Right, mostly myoglobin is present in the cases of heart muscles or other muscle cells. So, myoglobin can bind with oxygen, and half saturation can occur at a pressure of 3 to 4 millimeters of mercury because it has, first of all, only one pocket for oxygen binding. Secondly, it binds with oxygen in a more thermodynamically favored manner in a linear fashion. But in the case of hemoglobin, as we said, cooperative binding happens; it binds oxygen in a slightly angular manner. Along with that, there are four residues that can bind oxygen, and it takes a little more time with higher partial pressure of oxygen.

So, basically, hemoglobin binding, like myoglobin binding, is more thermodynamically favorable than hemoglobin binding. So if we just mention the partial pressure of oxygen to bind to the half saturation of oxygen to myoglobin, it is around 3 to 4 millimeters of mercury pressure, but in cases of half saturation of oxygen for hemoglobin, it is about 30 to 35 millimeters of mercury pressure. This is very important. I hope you understand why myoglobin, which is mostly present in the muscles and tissues, has a rapid affinity for oxygen, because another reason is that biologically, muscle cells, including heart cells, need a lot of oxygen. So they cannot really afford a slow saturation of oxygen to those cells.

They need rapid oxygen all the time for muscle contraction, muscle function, and heart function, and that's why myoglobins are highly abundant in those tissues, helping with quick oxygen binding and maintaining proper muscle function. And then, once the oxygen gets bound to the muscle and tissue, we first have to discuss how this oxygen is released. Initially, it is bound with the hemoglobin, and then we will explain how the oxygen is released in the cells. So, various conditions happen that we already discussed; for example, if you do some exercise, the right temperature will go high, right? So, if we do some exercise, the temperature can go high, and the cells perform a lot of metabolic activity. And once cells perform a lot of metabolic activity, what do they do? It generates carbon dioxide, and we already discussed that carbon dioxide can also generate or increase the proton concentration.

Also, lactic acid can be generated. So all this carbon dioxide, protons, and everything is present in the interstitial fluid, right? These are present between the blood capillaries and the cells,

which are mostly called interstitial fluid. So when blood carries the oxygen near this interstitial fluid, near the cells, what happens? They experience high carbon dioxide and high protons. And as we already discussed in the environment of high proton concentration, high carbon dioxide, high temperature, or high lactic acid, what it does basically disfavors oxygen binding to hemoglobin. So, eventually, oxygen will get dissociated. So, oxygen will basically get dissociated from the hemoglobin or the oxyhemoglobin, and this oxygen will eventually be transported inside the cells.

So, oxygen will eventually be diffused from the blood to the cells via a diffusion process. So, I hope you understood how the oxygen is released from the oxyhemoglobin to the cells and tissues. So let's think about it. Hopefully, you understood how oxygen transport happens in the body overall. We thoroughly discussed the passive transport, which actually contributes only about 3% of the oxygen transport in the body.

Right, and it follows the Henry's law. We also discussed the active transport; basically, oxygen actively binds with hemoglobin in a cooperative manner. We also discussed how oxygen can bind with myoglobin in different muscle cells, which is more thermodynamically favorable. So, we fully understand how this oxygen transport happens in the body. Let's think about it: what is the role of the diaphragm in respiration? What are the two main phases of respiration? How do the exchanges of gases take place in the lungs? What is the role of hemoglobin in respiration? So, you can refer to a different book. If you have further questions, please discuss them with us during the live sessions.

You can also drop the questions to us in the email. So hopefully, you are enjoying the human physiology class. We will meet with you very soon to discuss another new class of human physiology. Thank you again.