Human Physiology
Prof. Nishikant Subedar
IISER-Pune

Lecture – 19
Hemodynamics & Regulation - Part 3

So, we are now wondering as to how does the, how does what, how does what blood circulation, blood circulation. We are wondering as to how does blood circulation ensure that the different cells of the body keep on getting their steady and required supply of the blood, that is what we are doing. We have only 5 liters of blood that we keep on circulating and all and we have to make sure that all the cells have their supply and not that all cells have equal requirement, they have different requirements and the requirements keep on changing. Therefore, the system has got to be extremely dynamic, but we have already recorded so far that some of the mean like, well, when you need more blood you make the heart beat faster, you make the heart beat stronger and this is the first thing that you can do with reference to, but that will send the blood everywhere ok. Then whenever you want to make sure that you want to send it in this part or on that part then we have other tools ok.

Like in the in the blood vessels particularly in the in the larger arteries and in the smaller arteries and in the arterioles everywhere other than the capillaries you have the smooth muscles, ok. And with those smooth muscles you can either constrict and reduce the diameter so that you reduce the blood supply here or you can dilate them and increase the supply. So, that is these are the these are the different tools which our systems have evolved to make sure that a particular organ gets more blood depending now here and a little after somewhere else. So, so we have continuous covering of smooth muscles so very important is smooth muscles ok.

Then there was one other very interesting point that we noted in the earlier one and I will tell you the phenomenon and ask you and find out if you remember the name of the scientist. The active and inactive capillaries August Krogh.

What does it represent? Model organism. That there is always a model organism. Model organism. So, whenever before you before you embark on your research make sure that you have that you have selected ok.

So, so one point is how does the heart determine or how does an aorta determine? Ok. Here is a tissue that tissue is going to need more oxygen now, how does it know, the answer to that question is because the tissues are demanding oxygen ok. So, when you want anything you demand and when you demand ok then you may get ok. So, how to demand is a thing ok. So, how do you demand ok the answer is very simple you do some exercise with your left hand not with your right hand keep on doing it for 5 minutes then obviously the cells in the left hand all the muscles and all the types of cells they will undergo they will suddenly start what wanting more oxygen ok they will start wanting more oxygen they will demand and you will soon find that the blood flow in that part is increasing ok. So, so ok I will ask you to undertake an experiment the experiment is and this experiment is based on whatever we have done in the class.

So, here is a human subject for you before you sitting on a chair and then you are supposed to reduce the blood supply to the left hand for a period of 30 seconds maybe 1 minute maybe 2 minutes maybe 5 minutes ok and then you are supposed to track the blood flow track the blood flow ok. So, within the confines of what we have done in the class, can anyone design an experiment did you get the problem? You are sitting here and what is the problem assigned to you? Reduce the blood pressure. Reduce the blood pressure ok maybe now up for 30 minutes wait for half an hour maybe 1 minute maybe different periods different length of time and during that period ok during that period. So, before that during that period after that ok measure the amount of blood flow this is within the now I am testing you as your capability to think independently as a scientist and this is the framework of everything that I have taught you in this class. He has crossed one hurdle you put a cuff here and then you take the pressure to how much? 140.

140 more than 120 presumably 140. So, step number 1. He has answered one question very correctly step number 2. Then use the peizoelectric doppler flow meter. Then he absolutely correct. Then you know we talked about the Doppler's principle ok. So, you keep it pressed for 30 seconds once, then with the Doppler's principle will tell you the flow and if you know the volume of the of the blood vessel that you are occluding you can actually work out the amount of blood that is actually flowing.

Are you with me? Did you get the answer now? We have worked out how you can get some interesting data. I got this a very interesting picture can you take a look at the blood flow on the left and on the y axis there is blood flow through your hand ok. And then you put the cuff and blue one is for how many seconds you put the cuff there tell me. 30 seconds. 30 seconds then the another is 1 minute 2 minutes ok and then you follow and you track the amount of blood that is flowing and what do you get is the is the correlation very clear. There you followed or you are not following. What is the difference between the curve of 30 seconds and 5 minutes? Blood flow is what? Increasing.

It is more you do not look at it as if this is something I do not care no this is your problem

ok. You have to tell me what this is? You are tracking the amount of blood that is flowing and you find that over the period the cuff was tied, you get more flow of blood supply ok. Means that part of your left hand which was deprived of the blood flow for a certain length of time depending on the length of time you release it and suddenly more blood will flow ok. So the hungry tissue, you understand my language, hungry for oxygen, the hungry tissue the moment you tie, the tissue starts getting hungry ok. The mitochondria are not getting enough oxygen ok. The metabolism is stalled ok. And then that tissue immediately take steps to make sure that ok. So, here for the second time the supply of blood doing resting conditions and doing the exercise ok. The resting is green and exercise is yellow are you with me. And all I want you to do is to look at the striking result it at the level of what and what? Skeletal muscle. Skeletal muscle and there is some values also given by the author in the skeletal muscle can somebody read what is written here here here what is this? 1035.
1035 what what? ml per unit time. Whatever it is this is in the resting stage and in the exercising stage how much? 10,000. 10,000 just see the drama there ok. Just during exercise how much how much blood is being sent to the muscle and we have seen just now. So, the moment you start doing exercise the exercising muscle, it starts drawing more oxygen, now it is depleted of this. In that sense, that demand is in form of what? It can be in many forms. One of the forms is you give a signal to the smooth muscles, to the smooth muscles of the blood vessels of the arteries and you relax them you what you relax them. So, that you increase the blood supply of course, it must begin when you are doing exercise. So, the heart rate has gone up hello the force of has gone up and the blood vessel that is going to become more. Now it is relaxed ok or dilated all these factors will end together and then you can see about the response of the different organs under resting conditions, but the most dramatic of course, but to understand a little better we are planning the experiment in a different way.-

I take blood blood, ok. I have 4 bottles of blood ok. This is not possible ok. We are just imagining 4 bottles of blood A B C D. A thing is completely saturated with oxygen, ok. Second was 75 percent. 50 percent, 25 percent. Are you there look at this. So, I have 4 bottles ok and I am sending the blood that blood A blood B blood C blood D blood through that ok and then what I am monitoring I am monitoring the blood flow ok and what response do I get. Blood flow increases as the percent of oxygen is decreased. The message is very clear ok if my blood is fully saturated the blood flow is, but if the oxygen in the blood is low ok why would the oxygen in the blood be low well. I will put you from here and straight we put you in Leh or Ladakh or somewhere and I do not give you any time to acclimatize. What happens to you? Are you with me? There oxygen is rare. So, you start breathing fast ok. Not only you start breathing fast ok to compensate for the rarity of oxygen in that area, but you will also get this response ok or or have you all heard of carbon monoxide poisoning ok.

So, in case of carbon monoxide poisoning what will happen to the amount of blood in your system from 100 it will go to 75 if more it will go to 50 more than that you will die. Simple ok, not quite simple though. So, previous slide is this an effect of the oxygen itself in the blood or is it some changes in the body that causes the poisoning. Two slides down the lane, but I will answer your question right now. These tissue that is starving of oxygen, it sends certain chemical signals upstream, ok upstream and give the signal to the smooth muscles ok that you relax.

So, that I can get more blood you understand what I mean by I ok. So, this is signaling that -actually right now what I am doing is preparing the stage to give you that part of the drama. Are you with me? Now I will I am coming to that. In which case, it does, but it is not so simple, carbon monoxide you see I will tell you what happens. Our rate of breathing depends on the amount of carbon dioxide and not on oxygen. I have not talked that because we have not done the respiratory system as yet. So, if you wait till the respiratory system ok. I will tell you that the rate at which we are breathing hello your respiratory rate it may be 6, 7, 8 or 8 times per minute breathe in breathe out ok that does not depend on oxygen, it depends on what? Carbon dioxide. How it depends on carbon dioxide and how it is impacted by carbon monoxide wait for that lecture ok.

Who will tell me what is there on the what is there in the image on the right. The glomerulus. The bowman's capsule and there is a very familiar, we have drawn this figure with our pencil and we know what this is this bowman's capsule. And there is an afferent vessel there is an efferent vessel ok. Now what is the physiology happening there - most important is ultrafiltration. So, you give pressure how do you give pressure how do you give pressure blood is coming with pressure and from the heart ok.

And then you make sure that the afferent vessel by which the blood gets into - has slightly more diameter than the other one efferent one beauty of anatomy just by making a tube bigger and another tube smaller the bowman's capsule has ensured that you raise the pressure ok. And then because of the rise in pressure the ultrafiltration happens and lot of things are filtrated what happens to that we will see when we talk about excretory system. But you would appreciate one thing - that if there is one thing extremely critical for filtration to happen in the kidney that is heart and soul of the kidney pressure, ok. It is also clear that you cannot manipulate you do not have much room to manipulate with the pressure, are you with me why because continuously ultrafiltration is happening ok. Well what do I mean by that, I will make one statement to make it very simple our blood pressure is oscillating between what and what you tell me 120, 80, 120, 80, 120, 80 ok supposing you have a problem with low blood pressure and it goes from 80, 70, 60, 50, 50, 50 the moment you reach 50 the blood stops filtering there hello what happens filtration does not happen here in the filtration does not happen and filtration does not happen ok. Do not ask me questions I will answer them when we talk about excretory system. Filtration does not happen if filtration does not happen then you can imagine ok. and then all the metabolic waste products accumulate. We finished we are going towards death it is so important why am I making this point you better make sure that the pressure through which the blood is flowing the kidney is definitely much above 50, 60 ok 70, 80 is normal is perfect ok. So how do you make sure about that? For that the nature has provided muscles around these two vessels by which afferent vessel which takes the blood and efferent vessel which takes the blood away ok. You can see the smooth muscles there are you with me.

So for any reason if the blood pressure goes up ok then these smooth muscle on the afferent vessel will what contract ok. So it will make sure that the pressure at which ultrafiltration is happening is not influenced by the rise in the pressure elsewhere. So actually kidney is such an organ in our body that in a to a large extent is insulated from, if I can use that phrase, insulated from the pressure changes elsewhere you get it that is beautiful phenomenon. You have the kidney has to ok. So this is just one example where, we call it auto regulatory ok. How that auto regulation happen that also we will see sometime, ok. The other two functions are, I will talk about heart and about the muscles. We have already seen that the cells of the heart - and I am trying to answer your question. The tissue which is now starved of oxygen why you just do exercise do not even if you do not put a cough you suddenly do exercise, the tissue is going to require more oxygen. Now those tissues which are starved of oxygen - they start releasing different compounds, the cells themselves and here is the list of compounds - carbon dioxide makes sense ok, H ions, ADP, AMP, adenosine and potassium ions. This is a small list of ions and molecules tiny, tiny molecules which will be released by all the cells. Heart will use this sort of molecule like ADP molecule there is a different molecules, but this is a very small list of molecules. So every cell will release one of at least one of them ok if it is starved it will release one of them ok. And these substances then will go, they will diffuse outside they will diffuse outside and in the periphery they may encounter - now they have two options - one option is go and act on the nearest arteriole ok that nearest arteriole will have a receptor for one of these and under the influence of this signal that is coming from the oxygen starved cells it will dilate. So have you appreciated the logic the cell that needs more oxygen has been given the control of the smooth muscles which can bringing the blood to it got the message there ok. Very nice this is what is mainly happening in heart and brain. In what heart and brain this is the mechanism that happens also in the skeletal muscle this is the mechanism that happens there is yet another mechanism again I will again talk to you about August Krogh. What did August Krogh teach us that there are active capillaries and there are what is it that makes the active capillary inactive and other way round? Smooth muscles or sphincter muscles ok. So if some of these molecules could go and directly talk to the sphincter muscle and if the muscle could dilate you could get it very good idea and it happens in many tissues but active - inactive capillary strategy is not adopted in the heart. Because heart being an organ that is working 24 by 7 has all the capillary which are always active again get the beauty of the nature, ok. Can heart, does heart I will use my our language have the luxury of having some capillaries close now, no, it does not have does not have ok? So as far as heart is concerned, it operates by sending the message in that language what language that is the language it will send where to the smooth muscles of what arterioles and that the arterioles will dilate and increase and draw the blood supply to the cells. So these are the two organs which you can - I just put this slide - so there are two ways either you can do the smooth muscles of the arterioles or the smooth muscles of the sphincters - that is the phenomena you get, say in the alimentary canal. Follow this slide - adenosine this is purine or pyrimidine, purine it is a purine ok. Tt is a purine ok. Now here we are in a cell and this is a plasma membrane hello can you see the plasma membrane there ok. So if that is the plasma membrane ok then the author has written here intracellular and that is extracellular and what is this cell - this is a cell that is now needing more oxygen. It is doing exercise or work or whatever it needs more oxygen it is not getting enough oxygen as a result of that what it would do is it would let some ATP molecules to pass through this specialized kind of channel which is called as - I cannot read panaxin - it is a protein panaxin. It will allow the what molecule ATP molecule ok to go out from the intracellular side. So what is actually cell doing it is sending a message sending a message a chemical message and that is now that ADP molecule if you follow carefully those three blue circles - they get converted into two red circles they get converted into green circles you follow the story you know the story ATP ADP AMP ok that AMP or AMP - loses that one phosphate and becomes just what just becomes what just becomes what adenosine ok. You are following the story. You know it is getting the adenosine ok. Now this adenosine will interact with the receptors what receptor I will give you a very clear answer this is one very simple question will you find a smooth muscle in heart look, yeah. I am setting a trap for you so will you find smooth muscles in the heart yeah because there is this is the heart tissue heart there is a capillary and these are smooth muscles and you can see the bunch of RBCs there so you will you will see the coronary blood vessel it is a blood vessel ok. The blood vessel will have the smooth muscles ok. So now we are constructing a situation in which the heart cells are not getting adequate oxygen and therefore the heart cells are releasing the, as we have seen in the previous slide, a molecule which we identify as what adenosine. We are going ATP ADP AMP adenosine. Now what that adenosine does is presented in this cartoon. And the molecule is what molecule is here what it does - ADO stand for adenosine so adenosine molecule is coming from where heart muscles heart muscles coming source is heart muscle in the form of adenosine where is there now it is moving adenosine is moving extracellularly in the heart tissue. Are you with me some of it will go and talk to the vascular smooth muscle, means it will talk to the coronary arteries or arterioles there are smooth muscles and those smooth muscles on their plasma membrane they will have a receptor for adenosine. I will call that receptor as purinergic receptor why am I calling it as purinergic receptor? It is a purine, it is combining with what purine I can also call it as adenosine receptor no problem. Actually, this author is calling it as adenosine receptor adenosine receptor what kind A2, ok. Now the beauty is, even the cardiac muscle, which are actually the source of adenosine. Where did it come from - heart muscles even those cells themselves will have purinergic receptors which are sensitive to adenosine ok. Therefore you would appreciate that, once let us appreciate the cartoon here. The author says that the vascular smooth muscles which are here and here the author is particularly focusing on the cardiac muscles, which are located, where please we are doing that because we have specifically studied. Therefore author draws our attention to what? Go to plasma membrane and on the plasma membrane you will find a purinergic receptor ok on which adenosine can serve as a ligand ok. And then what does it do? Let us see it has adenosine receptor is of two types you can look at the look at you can look at the cartoon and you know what are the two types called as A1 and where is A1 located A1 is on the SA and AV node let us follow the diagram and where is A2 type of receptor for adenosine located on the on the smooth. If you take a single cell here on the plasma membrane you will get A2 type of receptor now what it does is acting adenosine acting via A2 receptors now that the receptor is 7 transmembrane protein G protein coupled ok. It is of the G_S type it is of the stimulatory type and then it will give rise to cyclic AMP ok. And there is a cascade of biochemical events and it will give rise to what? read the final effect – relaxation, at the same time, the same molecule acting via A1 receptor, it acts on G_I now G protein which is inhibitory type. It acts on adenine cyclase ok where cyclic AMP opposite effect cyclic AMP goes down and this net results is the going down of chronotropy - chronotropy refers to what? hmm chromo is color and chrono is time ok. The timing goes down means the heart which was beating at 72 will now start beating at 65 are you with me. Negative chronotropy done. Dromotropy is another interesting word which we are using in which negative dromotropy.

Dromotropy means if you remember when we talked about the conducting pathway hello SA-node, internal pathway, AV node, bundle of His, Purkinje fibers and each fiber has its specificity with which it conducts the action potential the speed goes down. What happens is speed goes down ok speed goes down. Means each action potential from here to there will take a longer time which means less number of beats per minute hello ok which means negative chronotropy ok. But dromotropy negative dromotropy negative why am I using the word negative going down so when I say negative dromotropy ok. I will ask you very simple question. You take two electrodes you take two electrodes put one electrode on the SA-node and put another on the AV node ok. And then the heart is beating and you see how much time it has taken from here to there and it has taken I am just making a figures - 0.1 point one second. I am just making up I do not know point one second ok. Now you give adenosine there what will happen to the time go up or go down or remain same. Time will go up time will go up the speed is reduced speed is what so it was if original was 0.1 it may be 0.12 1 2 3. The point is very clear so what are we talking how does the heart tissue respond when some of the heart muscles ok get let less oxygen so are you good.