Human Physiology
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Lecture – 08
How does the heart muscle work? Part : 1

So, does this image strike you as something familiar? It should, ok. It is a section through a muscle, almost we have done it, ok. So you can identify the I band, and the A band, ok. At the centre of the I band you have the Z line, ok. So you have a sarcomere, from the Z line you will have the actin filaments and then the myosin filaments and then the sliding will happen and the muscle will contract. But this is not the skeletal muscle, this is the picture of a cardiac muscle.

So what we will do now is we will move on from the skeletal muscle, we will move on to the cardiac muscle and you will find that there are great deal of similarities. But some very relevant differences and I will try to underscore them in due course of time. So this is, this is the aim of this slide is to basically emphasize that it is a very very similar structure. We have seen this slide, we know smooth muscles that at the end we will talk about it, skeletal we have done and today we are trying to focus on the cardiac muscle.

So here is the heart. It is very familiar structure, you have studied on several occasions, ok. We will talk more about it. It is made up of certain cells which we call as cardiomyocytes. Myo refers to muscles, cardio- refers to heart, cardiomyocytes ok. And these cardiomyocytes are, are arranged in a very interesting way. See this, whereas the cells in the skeletal muscle were simple guys, you know straight cell, straight cell goes to one end, communicates with the other connects to the ligament ligament talks to the bone, very simple state.

And the architecture is slightly different, here is a cell, ok and then it branches, it branches and it then communicates with another cell, that's another cell and then branches again. So you will have a structure in which you have the cells which are bifurcating and joining and they form a sort of lattice work, ok. So this is a very interesting structure and it is very relevant. And to exemplify that point, we have this image where you can clearly see what, you can clearly see that this is a cell, this is a cell but this cell divides and then this cell meets yet another cell and that cell again divides. So they go on, they go on, form a sort of lattice work.

The second point that you would notice is that in the cell, ok, so you know there is a nucleus and there is a nucleus and there is a sort of a partition which we call as intercalated disc. Now this word is coming for the first time, we did not have it in the skeletal muscle. What word am I using now? Intercalated disc. These intercalated discs are very interesting because, gap junctions, hello, gap junctions, ok. Gap junctions are proteins, ok, they are made up of 6 subunits.

How many? 6. Six subunits and they are the junctions by which one cell can just communicate to another cell, ok. So I am sure you have learnt the purpose and the functioning of the gap junction. If one cell is stimulated, the ions will simply pass from one cell to another cell to another cell. So it is actually an electrical synapse. What is gap junction? It is an electrical synapse.

So if this cell is stimulated then it can stimulate that cell, it can stimulate that cell, it can stimulate that cell. But if it goes in that order, hello, if it goes in that order then the next cell, next cell, follow the line, next cell will fire a little later. And the next cell will fire a little later, and the next cell will fire a little later, ok. So in that way, in that way in I can program as to which cell should fire before which next which and the next which and the next which, ok. Please keep this thought with you because that will be very helpful when we understand, when we try to understand the process of systole and diastole. Now whereas in the case of the skeletal muscle it was very simple, the bone would anchor on ligament and on the bone.

Now here with the heart, ok, it is not a skeletal muscle, ok. So it does not go on any bone, ok. It goes on as if it goes on itself, ok. And to highlight that point we have, I am sure you can identify the heart, so this is an auricle, that is another auricle, so these bands or the fascicles of muscles they go this way, this way and one of the most interesting point is look at this fascicle, you know, this fascicle, this fascicle is what is making up the ventricle, hello, making up the ventricle. It goes like this, look at the arrow and then it folds on itself and it goes this way, ok. So because of that particular architecture, when the whole muscle contracts, you are going to get the reduction in the volume of the ventricle, increase in the pressure, that is how the blood will be pumped out of the ventricle. Are you with me? So it is a sort of a bag, ok, but that bag can relax and the bag can contract. Now it is possible because of this particular arrangement and then of course it is involuntary. Another major difference from that of the skeletal muscle, ok, skeletal muscle you can control these muscles, you can control them. But who controls the heart muscles, the answer to that question is the heart muscles control themselves, how do they do it, we will see a little later, ok. They have a particular rhythm and they keep on beating in a particular rhythm and that is possible because they have a very specialised tissue within themselves which call as, pacemaker, what do you call them as? What

pacemaker? Sinoatrial and AV-node, we will talk about it little later. But this image is again very interesting because there is a heart, I take a tiny piece of the heart, I can blow it up and I can see the cells, I can see the intercalated disc and along the intercalated disc I can see the gap junctions, here the gap junctions are what? What you see in the magnified view? So there is one cell, there is another cell, there is intercalated cell, there is gap junction and if this cell is depolarised, depolarised means there are more ions, more ions going in, ok, inside as discussed earlier, inside earlier was how much, let us see, minus 85 millivolts, what did I say? Minus say that again, minus what is this minus 85 millivolts, I will take a single cell, single cell, single cell from the heart and put an electrode in it, ok and try to measure what is the potential difference between inside to outside? I will find that the inside potential difference is how much? Minus 85 millivolts, how much it is? In comparison to the outside which I will consider as 0, so outside 0, inside is minus 80 and if one cell is depolarised, it means there is increase in the positive ions inside, the positive ions can flow from one cell to another cell by way of the gap junction and the other cell will also respond and then the other and then the other. And they can sequentially go on in a definite order. So we are again looking at a single cell and this looks again very familiar and what is most familiar is the occurrence of ok, you can see the actin myosin filaments, they are there, from here to here is a Z disc or it is a sarcomere, absolutely no problem and then you have the mitochondria there and the endoplasmic reticulum, hello, same structure, same structure but here I will draw your attention to two major issues.

Number one, the T tubules, they are there, ok but these T tubules are much bigger in diameter, ok, how much bigger? Bigger with reference to what? With reference to the T tubules which you will encounter in the skeletal muscle, these are almost 5 times larger in diameter than in skeletal muscle. This is 5 times larger in diameter means the total volume will be about 25 times more, hello, ok, so volume will be more. So these T tubules are much larger as compared to those that we encounter in the skeletal muscle. So when you are in the T tubule, you are extracellular, hello, you are extracellular, so if you are in the T tubule, you will encounter lot of large number of glycoproteins and those glycoproteins can bind to large number of calcium ions, so there is a huge supply of calcium ions where extracellularly, much more than you will encounter in the T tubules in the skeletal muscle, ok. And the second difference that you find is the endoplasmic reticulum, ok, which played a very important role in the case of skeletal muscle, why it would suddenly release, it would suddenly release the calcium ions whenever the information will come, how by way of the action potential along the plasma membrane, ok. Then DHPR, hello, DHPR and then the DHPR talking to the RYR, what am I talking about? Ryanodine and receptor, ok, and then it will open this endoplasmic reticulum and the calcium ions will will flow out and that is, here again the endoplasmic reticulum is much less developed. so I find a clear difference between the skeletal muscle

and the cardiac muscle. Here the T tubules are very large and the endoplasmic reticulum is little too small, so main source for calcium ions, source, main, I am not drawing a hard and fast line, the main source for calcium ions in the case of skeletal muscle is endoplasmic reticulum, done. But in the case here, ok, endoplasmic reticulum plays a little subsidiary role, mostly large volume comes from outside and for that reason we will find that the T tubules are much larger, ok. so there is a fundamental difference between the organization of what and what, the T tubules and endoplasmic reticulum that you will find in the case of the cardiac muscle. So, here we have again, I have put the image of cardiac muscle, you can see that and I will take single cell from here, ok, single cell from single compartment and I will impale, I will use the right word, I am going to impale an electrode, can you see that image. There, impale an electrode and what is that electrode, actually it is a glass capillary, ok.

In earlier days we used to use metal electrodes but metal electrodes have a problem that the ions leach and they damage your preparations. So these days we do not use metal electrodes, we simply use glass capillary and glass capillary is filled with, when you say glass capillary I was so happy, I thought you will answer my second question also, it is filled with a conducting solution which is nothing but concentrated KCL, what did I say, say that again, a capillary which is open at the tip, it is open at the tip and you know these days the techniques are so fine that the tip is less than a micron, hello, less than a micron. Ok and then you fill it up with potassium chloride solution strong and then you put in that a wire and then you connect that wire to oscilloscope or whatever you have, whatever. So you have one electrode, one electrode we will use the right word, impale it across the plasma membrane, inside so you are comparing the potential difference across what is just below the plasma membrane and what is outside the plasma membrane and you find that the difference across. The difference happens to be how much? Minus. Minus. 85 milliwatts. Ok, and now I am going to record it and this muscle cell, let us presume that it is behaving like a full heart and it is what? It is beating, it is beating, it is mechanically beating, ok. And it is beating because it is showing a rhythmic change in the potential, a rhythmic change in the potential, how many on an average, how many beats would you expect in this preparation of mine? 72 let us say, 72, 72, average 72, ok you can debate, you feel like but it is 72, it is what? 72, 72 beats average. Ok because that is the number of beats we have. Now when we find that - when you see what am I doing? I have impaling an electrode in a single heart muscle, ok and I keep on looking at my oscilloscope. Or my whatever instrument I have there. And I find that to begin with the potential difference here is about 80 here, 85, 80 whatever it is here and then suddenly it shoots, suddenly it shoots, ok and it goes how far? It goes almost to plus 20.

So inside for a very short period of time plus 20 which means there is a reversal of polarity, cell is completely depolarized and then, I find that it remains, there is a slight

decline but almost remains like a plateau and then suddenly it drops and goes back to the baseline. That plateau remains for about 0.2 to 0.3 seconds, how long does it remain? Now remember these words, 0.2 to 0.3 seconds, actually if you have taken a cell from the atria the plateau is for a period of 0. 2 seconds, you got the point? If I take that single cell from the ventricle then the plateau remains for a little longer it is about 0.3 seconds. Now this happens to be extremely slow if I compare it with the electrical response of a skeletal muscle. I am going to our yesterday's talk, in which we do the same experiment. We impale an electrode into a skeletal muscle and we find that resting potential is about how much here? Skeletal muscle, this skeletal muscle how much is it? Minus 90 millivolts and if you excite it, if you excite - what should be your method of exciting it? How can you excite it? Conductance. Yeah, say that again.

Conductance. Conductance, simple in the light of what we did in the previous lecture, you see the skeletal muscle cell will not respond on its own unless you stimulate it and one way to stimulate it is to go to the nerve that goes to the skeletal muscle, put your electrode and stimulate the nerve. Once you stimulate the nerve then the nerve will release what neurotransmitter at the terminal? Acetylcholine. Good or I can directly give acetylcholine works beautifully. Acetylcholine stimulates, okay so you can give acetylcholine and I find that then the cell responds so cell is going to show the depolarization. It goes to about almost plus 35. Look at that image, how far does it go? Inside will become, inside will go to plus 35 and then it rapidly comes down. Okay now I want you to look at that image - the lower one where I am showing you the tracing of the skeletal muscle and you tell me what time period does it take for the up shoot to happen and for it to come back to the resting position? Point what? 0.

3 what? 0.3 what? Milliseconds. Now can you compare this with this? This was how much? 0.3 seconds, okay have you let it go deep in your brain that there is huge difference. That whereas the nerve and the skeletal muscle work in terms of milliseconds, the cardiac muscle works in terms of 0.2 – 03 seconds.

So you can see how many fold, how many fold the response of the cardiac muscle is slower as compared to that of the skeletal muscle, okay. Now let us see why this response, why are we finding this response from the cardiac muscle to be slow. The plasma membrane of the cardiac muscle is equipped with different kinds of ion channels, got the point? Different kinds of ion channels and some of them are called as fast sodium ion channels, say that again - fast sodium ion channels and these are really fast because they open and close within the time frame of 1 upon 10,000th of a second. Hello, 1 upon 10,000th, are you with me? Open and close, open and close, you cannot even think, how quickly that happens we cannot even imagine as to how much is that.

And that means what? The cell has been stimulated, those sodium ion channels will open and the sodium will go so fast that and so much sodium will go that within a period of so much time. Hardly any time it just shoots and from starting from minus 85 mV inside it will go to how much? It will go to about plus 20 or so mV. Step number one, okay, opening of the fast sodium ion channels, okay. Well, this is followed by second type of channels which we call as calcium channels or slow sodium calcium ion channels or DHPR. Hello, DHPR, they are very familiar, we know them.

What does DHPR stand for? - dihydropyridine, okay, yeah receptor, very good. Slow and therefore calcium channels - we also have another name for this, L type. Why did we give the name L? Long lasting, which means they are slow. So, whereas the sodium ion channels open and they immediately depolarize the cell, okay, then a little later the L type calcium ion channels will open, they will allow as - they are voltage gated, they will allow the calcium ions to go through and it is a slow process and because of that the cell inside - it remains depolarized for about 0.2 seconds if you are in atria, 0.3 seconds if you are in the ventricle, okay.

Meanwhile those sodium ion channels have already closed because they are open for very transient period. And over a period of 0.2 or 0.3 seconds, the L type calcium ion channels are also closed. Yes, which one? To begin with how much was the potential inside? Minus 85, sodium ions came in as a result of that it went where? Plus 20, inside is plus 20, okay and then calcium ions keep on pouring, they also have positive charge, so the positivity remains there for a period of 0.2 to 0.3 seconds.

Does it go even higher? No it does not go higher. If the answer to that, if your answer to that question is, sodium ion channels have closed, sodium ions are already inside but the pump is also working at the same time. I cannot answer your question but say that whole thing put together, okay. If the sodium ions shoot there then the calcium ions come, actually calcium ion is also not able to make an absolute flat plateau, it keeps on going down and then potassium ions start opening, okay. And now the reverse will happen, okay. In what direction will the potassium ions travel? From inside to outside they will take the positive charge and as a result of that, this will again fall to the base level. So what are we essentially seeing? We are seeing the interplay of kinds of 3 ions, okay.

Sodium will take it up, calcium will maintain there or slowly drop and the potassium will bring the potential difference inside again to minus 85. Are we okay so far? Which one? What is, that is a very interesting question, what is making the potassium ion channel open? At that particular time. These are all voltage gated ion channels and their operation depends on the typical voltage which you provide to the membrane. So when the cell goes to that particular membrane, as a result of what? As a result of closing of

the calcium ion channels, whatever potential difference develops at that moment, that is good enough trigger for the potassium ion channels to open and when they open the rest of the story will follow, okay. So never forget, why are these channels responding? They are only responding to the voltage, voltage, voltage, okay.

So voltage will determine whether the channel will open or not, okay. Alright, alright. Now I will superimpose on this. Let us take a look at this image. What does this image tell? We are, this is very interesting image, follow this image.

Let us try to understand. We are trying to trace the transport of ions across the membrane, okay. Now we already know or may be if you do not know I will inform you. The plasma membrane, whether as a skeletal muscle or as a nerve cell, it has a large number of, I am using a different term leakage channels. What channels? Leakage channels. So what am I talking now? I am talking of potassium ion leakage channels.

What am I saying? Are these channels sensitive to voltage? No, they are not sensitive to voltage. These channels, when they open, they allow the flood of ions to go through? No. These are the channels which allow one ion to pass through at a time, one ion, okay, one ion. And since it is a leakage channel, the name itself means - in which direction will the potassium ions leak? Inside to outside, hello? No confusion there. It will leak from inside to, it will leak from inside to outside, okay.

Now whatever is the amount of sodium ions leaking because of the presence of sodium, I made a mistake, because whatever is the, let me recompose my sentence, whatever is the rate at which the potassium ion channels are leaking, whatever it is, I will call it as 1. What will I call it as? 1. If I call that as 1, then I want you to look at is the graph and tell me whether there is a leakage channel for sodium, are they there? And if they are there, are they as efficient as that of the potassium ion channels? It is here 0.1, what does it mean? In a resting stage, the rate at which, the number of sodium ion leakage channels is far less, is far less. Now this is a universal truth, remember this everywhere, okay, in any given nerve cell, in any given muscle cell, the rate at which potassium ions are leaking out is much more compared to the rate at which. In what direction will the potassium ions leak? Outside.

Now as a result of this cell being stimulated, you suddenly have, what is the first response? Opening of the fast, use the word fast, opening of what? Voltage gated fast sodium ion channels, okay. As a result of that, can you see that yellow spike there? It is fast, it goes beyond our graph, okay, and it rapidly comes down because sodium ion channels are open for a very short time. Are these leakage channels? No, no, no, they will just open and 50,000 to 100,000 ions will very rapidly go in with the milliseconds,

okay. A little later, I am drawing your attention to the red line. Look at the image and tell me what does the red line represent there? Calcium.

We are talking about the calcium conductance. As long as the cell was in resting stage, the calcium conductance was very low, okay. As a result of the entry of the sodium ions and as a result of that whatever voltage has changed that has stimulated the DHPR, as a result of that DHPR open and as a result of that you can see the conductance of the calcium ions across the plasma membrane which goes so far. Why do you think calcium ions are flowing in? More outside. More outside.

Calcium ions are far more outside. Does anyone remember as to how much of calcium ion, what is the ratio of the calcium ions outside to inside? It is too important, you just cannot ignore.
Listen to this. If we just compare the ionic concentration of calcium outside to inside, outside may be 1000 to 10,000 times more than inside. Do I have to shout more to emphasize? What did I say just now? Outside calcium ion concentration is 1000 to 10,000 times more. This is enormous gradient, enormous gradient. And you know one of the reasons why the gradient is so large? Because in the cell, in the cell, when I say in the cell I am excluding the endoplasmic reticulum. Are you with me? In the cytosol, a calcium ion is an extremely rare commodity.

You do not find it. The concentration is extremely low, 10 to the power of minus 7 M, very low calcium ion. Now can somebody please stand up and tell me as to what is the physiological significance of keeping the calcium ion concentration so low in any cell, endocrine cell, nervous cell, muscle cell, low. It is so low.

Why is it so low? You know the answer. That is the part of the answer but you are not hitting the nail on the head. Why, why? You are right, you are right. It is such a critical molecule. What is such a critical molecule? Calcium is such a critical molecule that you better control its concentration.

Hello, are you with me? So if you want to control anything you give calcium. But does it mean that you can allowed the concentration to rise? No, everything in the cell will go haywire. No. You have to make sure that such a critical molecule like calcium which has such an important role in hundreds of biochemical reactions, you better make sure that it is not freely available. In the cytoplasm, it must be in very low concentration. So, when you want something to be done, okay, you allow a little calcium.

When you want to actin and myosin, or when you want insulin to be released, you want saliva to be released, you go to any cell, any cell okay. Whenever you want to change

its, change its physiology, you want to release a little calcium. But a little calcium, little calcium may mean it has gone up by 1000 fold. Why has it gone 1000 fold? Because initially the calcium ion concentration was so low, so low, that a little could mean 100 times, 1000 times. Are you with me? Okay, so the beauty of the biology is to make sure that the calcium ion concentration in the cells keep it extremely low.

When you want anything, give a little. That little, little, maybe 1000 fold more, 1000 fold increase, okay. And then you can, okay. So here you have voltage-gated calcium ion channels which will open and they will stay open for some time and then they go down. Something very interesting is happening with the potassium ion channels, voltage-gated. Because of this, because of this depolarization, the, okay, so we have already seen what? The potassium ions are leaking.

At what rate? I do not know, I will call it as 1. So when the sodium ion channels open, okay, that very moment, the voltage-gated potassium ion channels are inhibited. Therefore, the conductance of potassium ion, therefore the conductance of potassium ion goes down, okay. And it goes a little up and then it goes a little beyond and when it goes a little beyond, this will come down and the cell is now completely repolarized. So the cell goes through the cycle of getting depolarized, going to the peak, assume a plateau where the cell remains depolarized while the potassium ions will go out, they will take with them the positive charge so that the positivity outside is again restored and the cell will, the cell will come back to the resting potential. Does voltage-gated channels only depend on voltage or do they have an additional factor along with voltage? No, they depend only voltage.

This is not potassium. No, this total. This we mean, this you mean? Okay, this one, the blue, the purple one you are talking, tell me about purple, yeah. The blue one. Yeah, tell me. So then let us say it gets opened at zero.

Its openings like twice then. Twice means I am not getting? In the front also at zero seconds also it gets stimulated once and once also at one second. You are talking about calcium ions, right? Potassium. You are talking about potassium ions? Yeah. Okay. So in this we do not talk about potassium ions, right? I am not getting his argument.

In this or that one? Starting to fall, then potential, voltage gets channel opened or closed. So that is the threshold voltage being reached even before that point.

Threshold for potassium. Yeah. Okay. Crossing the threshold which the potassium ions are later opening up. The answer to that question - I got your question now. The answer to that question is that the calcium ions, voltage-gated calcium ion channels do take a

little time to open. They are slow to start, continue to remain open and then go, okay? That is their nature.

So, if the calcium ions channels are slow to open, why does the potassium ions open? Because it is the same instead of the calcium. So here because calcium is opening, the potassium is getting, like permeability is getting decreased. Why did this open? Look, it is the dynamics of all these proteins, okay? And actually at that moment, the potassium ion channels are actually closing. Just see the potassium conductance here. What is happening to the potassium conductance? That is because the calcium is opening.

Yes, it is all put together. It is all put together. Okay, okay. The answer lies somewhere in the response of the channel, voltage-gated channel proteins to open, open with reference to time. It is voltage plus time, okay, means the same, I can give the same answer which I gave there. So when would the potassium, what would be the response of the potassium ion channels? First, first they will get inhibited at that, okay? And then eventually, and then eventually, so we have to look at the proteins of the sodium ion channels, potassium ion channels and the chemistry of which with reference to how and when they respond to the voltage and at what time scale? Your answer is hidden somewhere in what time scale. Are you getting the argument? Yes.