Course: Electrophysiology of Heart

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Lecture 6: Action potential of cardiac muscle -2

Hello everyone. So, today we will start our next topic that is Action Potential of the Cardiac Muscle part 2. In the last lecture we had discussed the action potential of the myocardium that is atrial and the ventricular muscle. So, today we will discuss the action potential and various phases and the ionic basis of those phases of the nodal tissue or the pacemaker tissue. Now, a brief recap of what we had discussed in the previous lecture that is action potential of the ventricular muscle. So, there are various phases of ventricular muscle action potentials, so 4 phases.

Now, the first phase of the action potential is mainly because of the opening of the sodium channels. So, the fast sodium channels open and already I had discussed that what are the various characteristics of the sodium channels. They open very fast, they are very rapid in opening and also rapid in closing, they get inactivated very quickly. Then we have the slight or the early repolarization that is mainly because of the potassium channels.

Then we have the plateau phase that is mainly because of the calcium channels. Now, the plateau phase is usually because of both the calcium channels opening and the potassium channels opening. The influx of the calcium channels or the positive ions is usually counter balanced with the influx of the potassium ions. So, that usually maintains the plateau phase of the ventricular muscle potential. Then we have the complete repolarization or the late repolarization phase which is much compared to the early repolarization which it is much faster.

So, that is mainly because of the potassium channels opening more. More importantly because of the closing of the calcium channels and opening of the potassium channels. And then we have the final resting membrane potential that is this resting membrane potential is further maintained by the various channels that is so we had already discussed. That is sodium, potassium, ATPS pump as well as sodium calcium exchanger. So, these are the two important pumps that is one is primary active transport mechanism, the other one is secondary transport mechanism which mainly restores the membrane

potential.

So, this is all about your ventricular action potential. Now, before moving on to the nodal tissue potential few electrophysiological terms or mechanics we need to know that is when we correlate the electrical event and the mechanical events. Now, electrical event is your action potential generations. The same happens in case of your skeletal muscles also and smooth muscles also. The mechanical event is your contraction.

The electrical events will always occur first and then your mechanical events will occur. So, the electrical events precedes the mechanical events. The contraction of the muscle will only occur whenever there is electrical event occurring. So, the electrical event which is occurring that is the action potential we have seen in ventricular muscle. So, this is the electrical event and this is the mechanical event that means the contraction of the muscle.

So, here we can see the whenever there is this depolarization this is the zero phase depolarization, this is the phase 1, this is the plateau phase, this is the repolarization phase, final repolarizations and the phase 4 is the resting membrane potential. So, if we correlate this with the mechanical event we can see the contraction which is starting this is not starting at the level of the phase 0 or the depolarization phase. This is usually coinciding with the plateau phase. Now, the simple reason is in the plateau phase only we can see the calcium entering. Before that the calcium were not entering.

The sodium influx was there that has set the depolarization. Because of the depolarization further the L type of calcium channels got activated and so the calcium channels opened and the calcium influx has same. With calcium influx only contraction will start before that contraction will not start. So, the peak of this contraction phase or the mechanical phase the contraction begins whenever there is entry of this calcium channels not at the entry of sodium channels. So, again with the repolarization the relaxation phase occurs that is whenever repolarization is occurring that is phase 3.

The repolarization phase or the phase 3 coincides with the relaxation phase and the plateau phase or the phase 2 coincides with the contraction phase. So, with this we can see there are two phases we are getting in the mechanical event. We get the absolute refractory period and the relative refractory period. The absolute refractory period extends from the beginning of the contraction till the two third of this total action potential durations or the total mechanical event durations. Now, in this absolute refractory period means even if you apply any stimulus the second stimulus there would not be any absolute refractory means there would not be any action potential generated.

But, in case of relative refractory period means even if you apply a stimulus which is stronger than the first stimulus there can be generation of a second action potential. That is why the terms relative has occurred over here that is relative refractory period. So, absolute refractory period and the relative refractory period. So, this coincides if you just coincide with the electrical event we can see two third of this action potential is constituted by the absolute refractory period and the last one third is constituted by the relative refractory period. So, the duration of this action potential is therefore 250 to 300 milliseconds.

So, the duration in a ventricular muscle action potential is 250 to 300 milliseconds. Now, this action potential this we have taken from the cardiac muscle. So, cardiac muscle has got a long refractory period mainly because of the plateau phase mainly because of the plateau phase. And this absolute refractory period has already been told this extends from the phase 0 to the first half of the phase 3 of the action potentials and the later one third is the relative refractory period that is 50 milliseconds and 180 to 200 milliseconds. In this absolute refractory period no action potential will occur because already the ionic basis has already been discussed in the voltage physiology of the voltage gated channels the sodium are already in the inactivation phase.

So, it has to move to the closed state for reopening again, but in case of relatively relative refractory period since already the potassium channels had begun opening. So, there is a chance of second action potential generation provided the stimulus is stronger than the first one. So, now, this action potential which we have taken recorded this is from a single cardiac muscle right and so, the mechanical event. Now, if we the heart consists of various cardiac muscles. So, if we take the summation of all the action potentials of all the cardiac muscles then what we will get we will get nothing, but the ECG that is electrocardiographic recording.

Now, the details of ECG we will learn in the further slides, but till for today's topic for today's lecture since we are correlating the electrical in the mechanical events. So, this much you have to remember in an ECG we have the PQRST wave. So, the R wave of the ECG coincides with the depolarization phase of the action potential because this R wave is nothing, but the ventricular depolarization. So, this and action potential phase 0. So, action potential phase 0 is nothing, but the depolarization which occurs because of the influx of the sodium ions.

So, this will constitute the this will coincide with the R wave of ECG whereas, T wave will constitute the repolarization phase not the early repolarization obviously, the late repolarization phase or the phase 3. So, phase 3 will constitute the T wave that is the repolarization phase of the relaxation phase of the muscle. So, this ECG recording is

nothing, but the summation of the action potentials of all the cardiac muscle fibers. So, this is all about ECG and this duration from R to T since we talk about interval. So, we have to include the wave over here.

So, we do not take R T interval we take Q T interval over here. So, this duration Q and T interval as you can see 300 milliseconds it is nothing, but the action potential duration. So, this Q T interval of ECG is nothing, but your action potential duration which ranges between 250 milliseconds to 300 milliseconds more specifically 300 milliseconds for the ventricular muscle. So, this much you have to remember with the correlation of the electrical events and the mechanical events. Now, autorhythmicity heart can initiates its own impulse at constant rhythmical intervals.

Now, this beating of the heart at its own rhythm is mainly possible because of the pacemaker cells. The pacemaker cells or the P cells which are present in the acenode nodal tissue avinode and purkinje fibers. This P cells are small surrounded cells with few organelles they are connected by the gap junctions. Gap junctions I had already told you they are low resistance junctions they are the electrical synapse which is made by the connexion protein and they are mainly responsible for the sensation formation. So, the pacemaker potential this I had already told you that they have unstable resting membrane potential.

Because of the continuous change in the membrane permeability. So, minus 65 to minus 40 millivolt more specifically minus 50 for acenode minus 60 for avinode. So, this there are various phases for the pacemaker potential for the acenode and the avinode nodal tissue. We will come across the ionic basis of various phases. So, the ionic basis of various phases we can see this phase is nothing, but the pre potential or the diastolic depolarization.

So, this pre potential or diastolic depolarization or pacemaker potential is mainly because of the two reasons. The first part of the pre potential as you can see this is occurring at the level of minus 60 to minus 65 millivolt. Now, the opening of the pre potential the opening of the first channels in case of pre potential will occur at the level of minus 65 millivolt. I had told you usually the resting membrane potential lies in between minus 65 minus 60 minus 50 millivolt. So, when the resting membrane potential is below that minus 60 millivolt that means hyper polarization is occurring the channels present over here in the nodal tissues they get activated and they open up which causes influx of the sodium ions and that will cause the raise in the membrane potential.

Now, it is a very peculiar type of sodium channel which is opening at hyper polarization right because normally the sodium ions get influx or the sodium channels open at

depolarization. But this peculiarity we see in case of nodal tissue this type of channels are also present in the brain and also it is present in the retina. So, these are nothing, but known as funny channels. Funny channels means they are occurring funny they are acting funny because they are opening at hyper polarization they are not opening at depolarization they are opening when the membrane potential or the change in the voltage of the membrane is below the resting membrane potential. So, the initial part of the pre potential is mainly because of the H channel also known as funny channels.

This H channel comes from HCN channels that is hyper polarization cyclic AMP nucleotide HCN channels hyper polarization cyclic AMP nucleotide based channels or H channels or funny channels they cause influx of sodium channels. Now, this sodium channels are not fast sodium channels as you can see the pre potential slope is very slow it is not the steep. So, here this sodium channels open very very slow as compared to the sodium channels which used to get opened in the depolarization phase of the ventricular muscle potential. So, this H channels they pass slow sodium channels it is very important MCQ. And second the another important criteria of the pre potential is reduced potassium permeability whenever there will be reduced potassium permeability there will be hyper polarization and thus this H channels will obviously get open.

Now, the second part of the pre potential this is usually the first part of the pre potential by H channel. The second part of the pre potential or the pacemaker potential is mainly because of the T channels T channels means T type of calcium channels or transient calcium channels. Now, as it has already been discussed various types of calcium channels the long lasting calcium channels L type of calcium channels which generates L type of current. And T type of calcium channels are the voltage guided calcium channels which open at more negative voltage and here we can see the negative voltage over here it is opening below minus 40 milli volt and it is causing the rise in the membrane potential. So, this pre potential or pacemaker potential is mainly because of two reasons the third reason is obviously reduced potassium permeability.

Now, coming to the next phase that is the depolarization this phase is the depolarization. This depolarization phase is mainly because of the opening of the fast type of calcium channels that is L type of calcium channels or long lasting calcium channels or high voltage calcium channels and this calcium channels will cause the contraction. Now, the next phase is mainly the repolarization phase that is the potassium channels opening phase. So, this repolarization phase this is the repolarization phase which is mainly due to opening of the potassium channels. So, here the pacemaker potential or the resting membrane potential is phase 4 the depolarization phase is phase 0 the repolarization phase is phase 3.

So, I had already told you we do not have phase 1 and phase 2 over here like we have seen in the ventricular muscle action potential. So, we can see that the pre potential or the pacemaker potential or the diastolic depolarization is mainly because of the three reasons that is sodium channel opening which is slow and which is funny which is which gets opened at hyper polarization. The second thing is the reduced potassium permeability and the third is the transient calcium channel opening. Then we have the depolarization phase that is mainly the L type of calcium channels opening and then we have the repolarization phase that is the opening of the potassium channels. So, the action potentials in the SA node and AV node are mainly due to different mechanism ok.

So, in case of the nodal tissues SA node and AV node the action potential is mainly because of the calcium, but in case of the ventricular muscle it is mainly because of the sodium influx that is the main difference in the mechanism of the action potential. We can to see different phases where phase 1 and phase 2 is not these are 2 are not present in case of the pacemaker potential. So, the action potentials then the nodal tissue is mainly because of the calcium influx whereas, the action potential in the ventricular muscle is mainly because of the sodium influx. Now, this peaks are mainly determining the heart rate interval. So, interval that is the heart rate interval between these 2 peaks are nothing, but they give you the heart rate and the pre potential or the pacemaker potential slope that means, this is the slope this usually increases or decreases based on the stimulation of the system or body system.

Whether we give sympathetic stimulation or whether we give parasympathetic stimulation, the stimulation is mainly done by exogenously drugs. So, based on the stimulation exogenously or endogenously it can also happen. So, the slope changes the pre potential slope changes whether it can decrease or increase and the interval between this 2 peaks that gives you the heart rate and based on that the heart rate changes or increases or decreases. Now, we will see what are the factors which influence the pre potential.

The first factor is sympathetic stimulation. Sympathetic stimulation in our body means whenever there is increase in the epinephrine or non epinephrine secretions in our body. It can be endogenously occurring whenever there is fright or anxiety or stress or it can be done exogenously also by giving drugs. So, whatever in whatever way it occur this non epinephrine or the beta agonist they usually act on the beta 1 receptors. There are various types of adrenergic receptors specifically beta 1 receptors are present primarily on the heart and they are mainly responsible for the cardiac activity. And whenever there is action of this beta 1 receptors there is increase in the heart rate as well as force of conduction.

Now, we can see here sympathetic stimulation when we give this is the initial slope of the pre potential, but whenever we have given sympathetic stimulation we can see the slope has increased. That means, the pre potential slope has become steep. So, because of this steep or increase in the pre potential slope the heart rate gets increased. The heart rate gets into increased means the interval between the 2 peaks will the interval between the 2 action potentials will get decreased or the action potential duration will get changed or decreased. So, that is why sympathetic stimulation causes increase in the heart rate.

The opposite occurs whenever there is a parasympathetic stimulation. That means, there is stimulation of the M 2 receptors at that time vagal stimulation or the parasympathetic stimulation vagal stimulation here means acetylcholine. The vagal stimulation we give we can see there is very much increase in the pre potential slope. Increase in the pre potential slope means the slope got increased. So, obviously, the steepness of the slope we cannot see rather it is very much delayed or gradual progress of the pre potential slope is seen.

So, there is in the vagal stimulation there is not increase or a decrease in the pre potential slope. So, decrease in the pre potential slope means it will not become that steep which is seen in case of sympathetic stimulation. So, this is the if this is the curve of your pre potential. So, if this is the slope there will be here vagal stimulation if we give the slope will further get decreased. And in case of sympathetic stimulation if we give this slope will increase.

So, this increase slope means the increase from the in terms of the membrane potential it is talking about. So, how the sympathetic stimulation is occurring how this parasympathetic stimulation is occurring. Now, whenever the beta agonist is binding to the beta 1 receptors there is stimulation of adenyl cyclase enzyme there is stimulation of adenyl cyclase enzyme. This adenyl cyclase enzyme will cause activation of cyclic AMP. Now, this cyclic AMP will cause further activation of various protein kinases and this protein kinases will cause influx of the calcium ions and hence contraction will take place.

Now, at this level if we give any beta blocker that means, they will block the beta 1 receptors activity. Obviously, there will be no adenyl cyclase enzyme activity, no cyclic AMP generation, no protein kinase activity, no influx of calcium and hence there will be no contraction of the muscle. So, that is the role played by the beta blockers. So, this is the already been told that is the factors influencing pre potential of the parasympathetic stimulation where the slope gets decreased because of the activation of the acetylcholine on the M 2 receptors. Because of the hyperpolarization of the membrane that means, the more negativity of the membrane occurs and hence there is decrease in the heart rate and

the force of contraction.

The mechanism of action is just the opposite of the beta agonist activity there is decreased activity of cyclic AMP. There is decreased activity of cyclic AMP. So, that will cause decreased in the calcium influx. So, hence there is decrease in the calcium influx will cause obviously, no contraction of the muscle. So, this is the factors of these are the factors which influence the pre potentials.

Now, with this mechanism of actions with this various phases mechanism of action of various antiarrhythmic drugs are very important. Now, antiarrhythmic drugs play a very important role in controlling the abnormal heart rate and rhythms. So, we have generally 4 traditional classifications of antiarrhythmic drugs. We have class 1, we have class 2, we have class 3, we have class 4. Class 1, we have sodium channel blockers further the sodium channel blockers get divided into ABC.

This ABC division is based on moderate we can strong how strongly or how weakly or how moderately the sodium channel blocker happens block happens. This sodium channel blockers division of ABC is mainly because of the dissociation or association of the speed how the speed of the Purkinje fibers occur, how the speed of conduction of the Purkinje fibers occur, how we could modulate the activity, how does the sodium channel blockers could modulate the activity of the speed of the impulse transmission to Purkinje fibers. So, this we have quinidine, we have lidocaine, mexilatine, flaconate. So, these are the various types of drugs quinidine is very specifically used in case of Brugada syndrome. So, these are the drugs which mainly block the sodium channel that means, phase 0.

Now, coming to the plateau phase that means, calcium channel blockers. Now, I had already discussed the calcium channel blockers means here we are talking about L type of calcium channels. So, L type of calcium channel blockers we have verafamil and diltiazem. This L type of calcium channel blockers we also have amlodipine which is dihydropyridine blocker, but they are that is not used for anti arrhythmic drugs that is mainly used for anti angina and for and as anti hypertensive drug. For anti arrhythmic drugs diltiazem and verafamil is used which is a non dihydropyridine calcium channel blocker which acts on the L type of calcium channels.

Then we have class 3 that is potassium channel blockers. Potassium channel blockers we have amiodarone, sotalol. These class 3 potassium channel blockers and the main side effects of this potassium channel blocker is QT prolongation. Now, this QT prolongation occurs because of the slowing down of the conduction velocity which is done by this potassium channel blocker or prolonging the action potential duration. For

that this QT prolongation occurs usually.

Then we have class 2 beta blockers. The role of beta blockers I had already told you decrease the force of contractions and the heart rate. So, we have propanolol, metaprolol, labetalol. Now, these are all propanolol is a non cardio selective beta blocker. Cardio selective beta blocker we have atenolol and metaprolol.

So, in this way the anti arrhythmic drugs are in use. One very important anti arrhythmic drug is there known as Eva-bradine. Now, this Eva-bradine they mainly play a very important role in case of acting on the HCN channels or the funny channels. HCN channels or the funny channels what happens we can use beta blockers ok. We can use beta blockers and we can just reverse the rhythm or abnormalities in the rate and the rhythms, but beta blockers beta receptors actually they are present in various parts of our body.

So, that is why beta blockers poses various side effects. So, but if we could block the instead of the beta receptors if we could block the funny channels or HCN since this receptors present at very particular sites in our body as I told you it is present in the cardiac nodal tissues, then brain and in case of retina. So, the side effects are very less. So, that is why Eva-bradine is a newly classified anti arrhythmic drug which is used which block the funny channels or the HCN channels and can be used as an anti arrhythmic drug. So, with this we conclude today's lectures and the various points we have to remember that the fast action potentials we have 0 to 4 phases, that is 5 phases and slow action potentials we have 3 phases. The action potentials in the SN node and AV node is mainly because of the calcium channel influx while the action potential in the myocardium is mainly because of the sodium channel influx.

The sympathetic stimulations mainly done with the help of beta 1 receptors stimulator that increase the pre potential slope and hence increase the force of contraction and increase the heart rate. Whereas parasympathetic stimulation which acts on the M 2 receptors they mainly act on the M 2 receptors and they decrease the pre potential slope and hence decreases the heart rate and the force of contraction. So, with this I would like to conclude today's lecture. Thank you.