Cardiac Muscle and Action Potential

Introduction: - after this lecture you need to:
1- Distinguish cardiac muscle microstructure.
2- Describe the cardiac muscle action potential.
3- Point out the functional importance of the action potential (the cardiac muscle action potential is too long compared with the skeletal muscle and also the absolute refractory period is much longer in the cardiac muscle that's why the cardiac muscle does not get tetanus).
4- Outline the intracellular calcium homeostasis.

The microstructure of the cardiac muscle:

The wall: - endocardium, myocardium, pericardium and the pericardium space.
We talked about the pericardial space, we talked about the structure of the shape of the cells in cardiac muscle is rectangular and these cells are connected with each other with intercalated discs and between them there are gap junctions they help in forming what we call it syncytium the heart beating pattern. In the heart there are two syncytium, one in the atria that means the two atria work together and one in the ventricles which also work together.

Gap junctions: connect one cell to the other electrically (between the intercalated discs which means that they are electrical couplers), they are low resistance area, and any change in the potential in one cell will be spreaded to the other cells very fast through these gap junctions. They are voltage gated channels, with hexagonal subunits.

T-tubules are shorter and wider in the heart than the ones in the skeletal muscles, they are located in the Z line or the Z disc. However, they are thinner and longer in the skeletal muscle and they are located in between the sarcomeres. There is one t-
tubule per sarcomere in the cardiac muscle but there are 2 T tubules per sarcomere in the skeletal muscle.

**Sarcoplasmic reticulum (SR)** that it's less developed in the heart (cardiac muscle) than in the skeletal muscle that's why an extra source of calcium is needed in the cardiac muscle (that extra source of calcium comes from the extracellular fluid surrounding the cardiac muscle).

That's why the extracellular fluid is very important because of the calcium ion in it, without the calcium of extracellular fluid the contraction of the heart will never occur.

Because of the presence of gap junctions in between the intercalated discs, once an action potential occurs in one cell, this action potential spreads to all cells and since the cells of the ventricles are connected to each other they are forming what we call it syncytium, so once one cell is stimulated all cells will get depolarized so all cells will contract at the same time if any pathology happened to this syncytium we will have **ventricular fibrillation**: which is a condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart (each cardiac muscle fiber will contract on his own) and it will cause death due to cardiac arrest.

Skeletal muscles don't have syncytium, each cell is separated from the other and there're no gap junctions. Gap junctions are only found in cardiac muscle. Poorly developed sarcoplasmic reticulum (SR) is in the cardiac muscle and well-developed SR is in the skeletal muscles, that's why we need an extra source of calcium in the cardiac muscles. Cardiac muscles are rich in mitochondria because the heart is always contracted (needs ATP), low nuclei.

**Action potential** in the skeletal muscles has two phases:

1. Depolarization phase due to Na$^+$ influx.
2. Repolarization phase due to K$^+$ efflux (out flux).

N$^+$ and K$^+$ channels that are involved in this action potential are voltage gated channels.

This action potential is very short (around 10 milliseconds maximum). But the cardiac muscle action potential is around 300 millisecond (much longer).

Comparing the absolute refractory period. The skeletal muscle's absolute refractory period is very short compared with the cardiac muscle which has very long refractory period. This means you can get another stimulus earlier in the skeletal muscle. Every electrical response must be followed by mechanical response (contraction and
relaxation), Contraction and relaxation takes longer than the action potential around 100 millisecond that means you can summate.

In cardiac muscle, the action potential starts from more negative resting membrane potential (-90mv) it has rapid depolarization phase (phase 0) due to opening of fast Na+ voltage gated channels, partial repolarization (phase 1) due to opening of Cl- Channels and/or some K+ channels, (phase 2) the plateau phase which is due to opening of slow Ca+2 channels, (phase 3) the repolarization phase due to opening of K+ voltage gated channels, (phase 4) is the coming back to the resting membrane potential.

(Conductance) of ions and change of their permeability during the cardiac muscle action potential: the permeability (conductance) is very high for sodium in phase zero because the Na+ channels are opened. At the end of phase zero and the beginning of phase 1 there is a decrease in the permeability of the membrane to K+ and this does not occur in the skeletal muscle (in the skeletal muscle there is only more sodium or more potassium) But here at the end of phase zero and the beginning of phase 1 there is a decrease in the permeability of potassium and during phase 2 which is the opening of slow calcium channels increase the membrane permeability to calcium. Now the permeability of potassium will increase in phase 3.

*phase 1 and phase 2 are only found in the cardiac muscle not skeletal muscle.

* What is the importance of having the permeability of potassium during phase 1 and 2 lower than the resting?

Considering the plateau (where the membrane is depolarized; the membrane potential is getting less negative). The factors that keeps this depolarization; first is the calcium influx maintains this depolarization, because calcium is positively
charged. Another thing may maintain this depolarization is the decrease in permeability for K+ in phase 1 and 2 if the potassium permeability is very high at the plateau phase potassium will leave out the membrane, so it might neutralise the calcium, which will result in having a more negative membrane potential and that will end the depolarization phase and there will be no plateau that's why it is important to have the permeability of the membrane for potassium low at phase 1 and 2.

The importance in having longer refractory period in cardiac muscles and shorter one in the skeletal muscle:
The absolute refractory period, extends to half of the repolarization phase. The absolute refractory period in the skeletal muscle is very short, and it’s much shorter than the contraction phase of the skeletal muscle, this means that you can give another impulse or stimulus before the muscle gets relaxed this means that the second impulse will cause another contraction In case that the muscle didn’t get relaxed before the second stimulus, the muscle will stay contracted causing tetanus or spasm in the skeletal muscle. The cardiac muscle, the refractory period is very long and the contraction phase of it is shorter than the refractory period so if the muscle receives another stimulus at the end of the absolute refractory period, the muscle will already be relaxed and it will never get tetanus so the importance of the long absolute refractory period is to prevent tetanus in cardiac muscle and the importance of it being shorter in the skeletal muscle is to help tetanus to occur to increase the power of the muscle.

Sodium channels:

They have two gates, they’re voltage gated.
(1) An outer gate in the extracellular matrix is called activation gate or M gate.
(2) The innermost gate is called inactivation gate or H gate.
So sodium channels have 2 gates; activation gate and inactivation gate. During rest, the membrane is polarized (resting membrane potential in the heart -90, or in the skeletal muscle -70) during this stage the activation gate is closed (the outside gate) and the inactivation (inside) gate is opened. It's like a fence with two gates; an outer one and an inner one, if only one of these gates is closed nothing will pass through that fence, The activation gate opens when the membrane potential becomes less negative (depolarization), and the inactivation gate closes when the membrane potential is becoming less negative. One opens the other closes. **But what makes the difference is the timing.** The activation gate responds very fast, the inactivation gate responds slowly. So when the membrane potential is getting less negative the activation gate opens before the inactivation gate closes and that will cause influx of sodium ion inside the cell and depolarization because the inactivation gate responds slowly. After a while time the inactivation gate closes and that will prevent the sodium from entering even though the activation gate is opened. (Keep this piece of information in your mind, it’s very important).

**The importance of having extracellular calcium ions during action potential:**

We said that we need extracellular calcium. During phase 2 calcium enters the cell through slow voltage gated Ca channel, the calcium that enters through the slow calcium channels it goes to the SR (sarcoplasmic reticulum) and induces or triggers release of calcium from the SR. The calcium that enters through the slow calcium channel plus the calcium that's released from the SR they initiate the process of contraction in the sarcomere. So the calcium that enters through the slow calcium channels is important because as we noticed it helps to trigger the increase in calcium ion in the sarcomere by inducing it's release from the SR.

Now when relaxation happens, we have to decrease calcium, because calcium is the ion that causes contraction if it increases, if it decreases it will cause relaxation. **How can we decrease it?**

**Firstly we bring it back to the SR (calcium uptake) by calcium pump** (which mean active transport). So the first thing calcium will be re-uptaken to the SR actively through the calcium pump (calcium ATPase), but a lot of calcium entered not only from the SR also from the extracellular fluid. Calcium is going to go outside the cell by a transporter, called **sodium - calcium counter transporter**, calcium goes out in exchange with sodium that goes in three sodium per one calcium (electrogenic process)T his is secondary active transport. The third method is the calcium pump
in the SL (Sarcolemma) it pumps calcium outside. So how many methods do we have for calcium to come back to the normal? **Three.**

1- Calcium pump in the SR (primary active transport)
2- calcium-sodium exchanger in the SL (Secondary active transport)
3- Calcium pump in the SL (primary active transport)

All of that happens normally, but now if there was too much calcium abnormally, there's another process which is the fourth process that happens abnormally (normal physiology), (Abnormal pathology).

In **pathological stage**, the mitochondria takes extra calcium with sodium-calcium exchanger

*Normal concentration of calcium during systole (contraction) is $10^{-5}$ M and during Diastole (relaxation) is $10^{-7}$ M and in the extracellular fluid is $10^{-3}$ M which is more than inside the cell that's why calcium influx happens during opening of calcium channel (concentration gradient)*

*but during relaxation calcium will go out from the cell against concentration gradient so that process will be active transport.*

**Conduction system of the heart:**

The heart is different from skeletal muscle If we take the heart out and put it in a solution that contains calcium a lot of contracting will occur but this contraction will
not occur unless there is an electrical change that means there must be an action potential. There are no nerves so there must be a source of action potential inside the heart not out because we have no nerves. But in the skeletal muscle if we cut the nerves it will be paralyzed. So there is an intrinsic system of producing action potential inside the heart, that intrinsic system we call it conduction system of the heart, that conduction system of the heart consist of modified (in term of structure and in term of function) cardiac muscle cells not nerves.

In term of structure they have very little myosin and actin so they are unable to contract, in term of function now we'll talk about it.

So our aim here is to list the parts that comprise the conduction system. The mechanism of the pacemaker potential (how the potential happened and spread).

The heart is supplied by autonomic nerves but these autonomic nerves are not the initiators of heart contracting they only regulate it during sympathetic (increase heart rate) parasympathetic (decreasing heart rate).

**Parts of the conduction system:**
The first part is called SA nodes (Sinoatrial node), it is a structure, it exists in the posterior aspect of the right atrium just below the superior vena cava.
The second part is AV node, it is in the right atrium, at the junction between the atrium and ventricle that's what we call it atrioventricular node. From this node a bundle continues called (AV bundle) or sometimes we call it Hess bundle referred to the scientist he discovered it.

Then this AV bundle divide into right bundle branch and left bundle branch, right bundle branch supply the right ventricle and left bundle branch supply the left ventricle. They end by fibers called purkinje fibers.

So, this system consist of:
(1) SA node.
(2) AV node.
(3) AV bundle.
(4) Bundle branches (left and right AV bundle branch).
(5) Purkinje fibers.
All these parts are modified cardiac muscle cells and they are able to produce automatic rhythmic impulses (without any stimulation) ... with different rates.

1- The SA node, it can produce impulses with rate of 70-80 impulses, pump (action potential) per minute.

2- The AV nodes is able to produce impulses with a rate of 40-60 impulses per minute.

3- The Purkinje fibers is able to produce impulses with a rate of 15-40 impulses per minute.

*It's noticed that the normal impulses rate of the heart is 70 Impulse/min according to the fastest node (SA Node) so that's why the SA node is considered as the pacemaker of the heart if this pacemaker was damaged the heart will beat with a rate of 40 impulse/min which is an ectopic pacemaker (abnormal)
Autonomic supply of the heart: 
The sympathetic nervous system that comes from sympathetic cardiac nerves supplies all parts of the heart atria, ventricle, SA node, AV node, AV bundle. The parasympathetic comes through vagus nerve which is the 10th cranial nerve, and supplies only the atria SA node and AV node, and it doesn’t supply the ventricles. The impulse travels from SA node to the AV node to the AV bundle then to the Purkinje fibers.

The mechanism:
how these nodes are able to produce automatic impulses? Let’s see their action potential of the them, we observe the action potential of the heart. The functional modifications (all cells with different variabilities) all of them are leaky to sodium (leaky channels not voltage-gated channels, no receptors) if they leak sodium this means that they will never reach the resting membrane (-90) because sodium is positive charged and it will enter because of the cardiac electrochemical gradient. So because these are leaky to sodium there resting membrane potential is less negative, and because they are leaky to sodium during phase 4 of the action potential they will get slow depolarization when they reach the threshold they will fire an action potential. Because we reached the threshold slowly the sodium gates as we mentioned before there’re two gates one is fast and the other is slow, so the inactivation gates will close before the activation gates open. So the inactivation gate closes before the activation gate opens, so no sodium will enter. The calcium gates will open so this will be phase zero, and there’s a slow depolarization phase, in phase zero the potential is caused by calcium not sodium because the sodium...
channels were closed because they reached the threshold slowly and the inactivation gates close before the activation gates open, after that comes phase 3 and there's no plateau, there are only phase zero 4 and 3. Slow depolarization (sodium leakage) we reach the threshold, calcium then potassium at the end we don’t reach -90 because of the leakage of sodium and it continues. So this is rhythmic and continuous. At the SA node this rate is around 70 to 80 per minute, in the AV node this rate is about 40 to 60, in the perkanje fibers it's slower, and they become slower because they're different in terms of leakiness to sodium, so we call it the pace maker potential or the slow response potential (slow depolarization, calcium and potassium).