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Physiology

Doctor 2019 | Medicine | JU

◉ Sheet ○ Slides

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Contributed in the Scientific Correction

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Doctor

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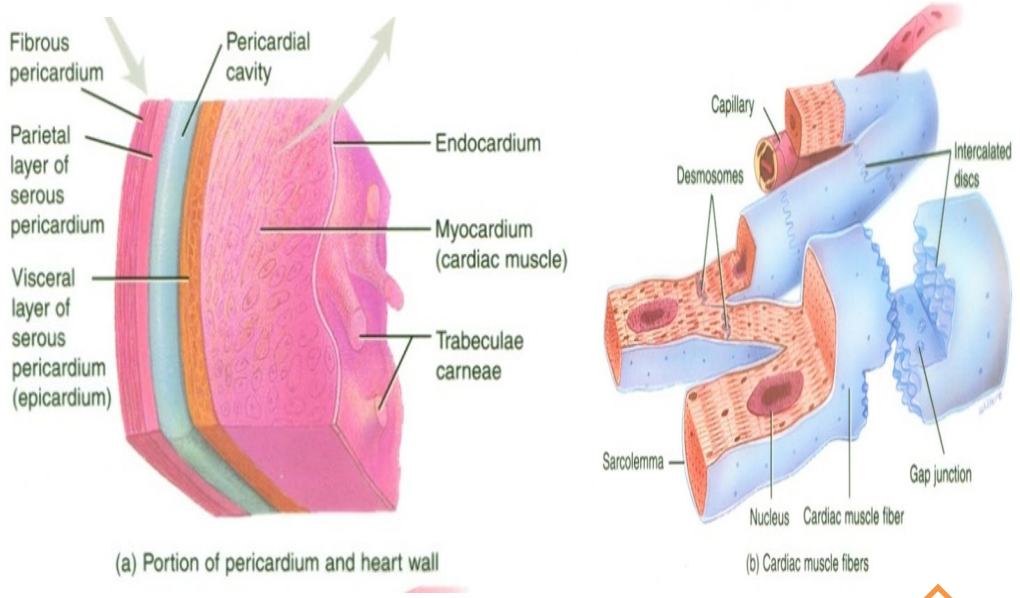
In this sheet we are going to talk about cardiac muscle, it's structure, function and action potential.

When we talk about the heart wall, we mean it consists 3 layers:

1. The innermost layer is called endocardium which is the epithelial layer of the heart and they are different of the other epithelial layers of all cavities in our body because the endocardium besides it's protective function of the inner of the heart, it releases hormones and these hormones are important in controlling the flow of the blood
2. Myocardium: the major layer of the heart wall
3. The outermost layer is the pericardium and it divides into 2 parts:
    a. Parietal layer lies outside
    b. Visceral layer lies inside

Between these 2 layers there is a space called pericardial space has a fluid inside about 50-100 ml works as shock absorber which protect the heart from damage that could occur from any movement or shock.



(a) Portion of pericardium and heart wall

(b) Cardiac muscle fibers

The cardiac muscle cell is rectangular in shape and interconnected with each other, forming a holo-organ

The cardiac muscles are called syncytium because of their interconnection

How they are interconnected with each other?

- They are interconnected by desmosomes and intercalated discs which allow the cell to continue with the other cell

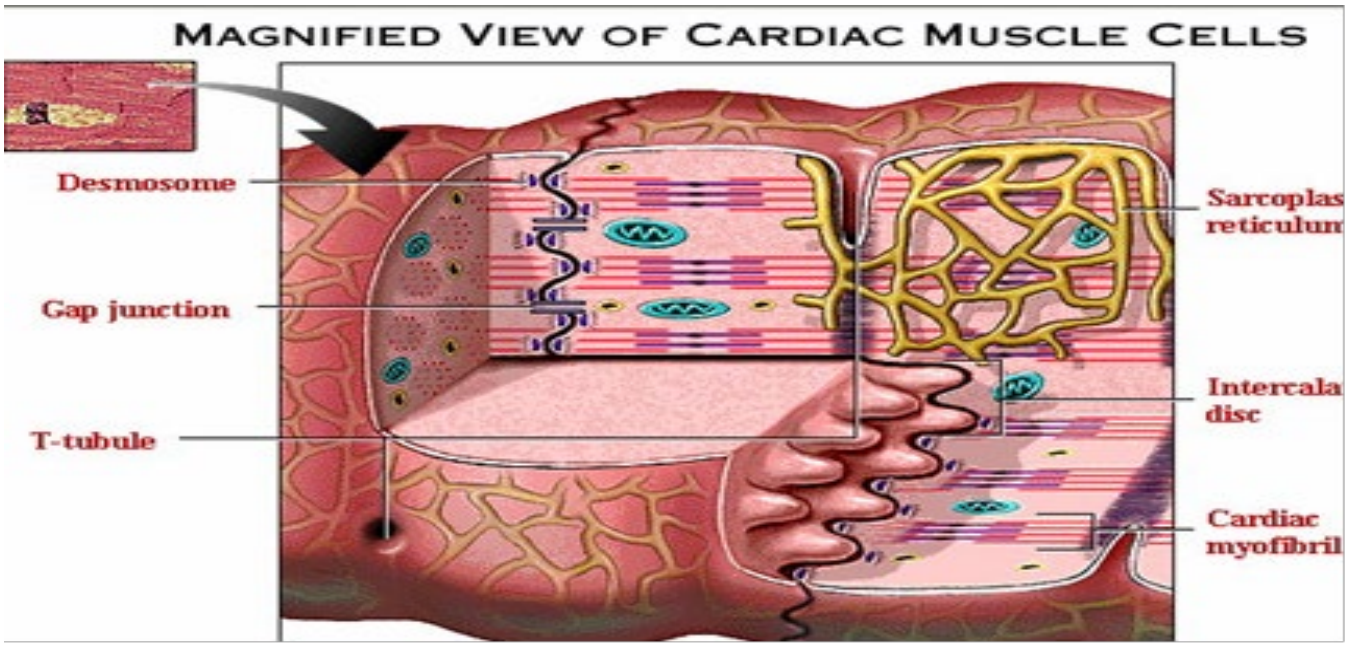
In few words: cardiac muscle cells differ from the skeletal cells in shape, the interconnectivity, the transition of the action potential and the intracellular organelles.

Inside the desmosomes we have a channel like structure called **"gap junctions"** which are channels open and close due to the change in voltage, so when the channel between 2 cells opens, ions will flow between these 2 cells according to the potential difference, these gap junctions work as couplers.

They are low electrical resistance area so once we have electrical difference in a cell, this difference moves to the all cells in the ventricle or the atria immediately.

The atrial cardiac cells are separated from the ventricular cells by inter-atrioventricular septum

The cardiac cells in the ventricle are interconnected with each other while the atrial cells are interconnected with each other



What follows the action potential?

- While the action potential is electrical change, so it is usually followed by mechanical change appear as contraction

If we have action potential for each cell it will contract separately which is dangerous especially in the heart; because it leads to heart fibrillation which eventually leads to DEATH.

The most dangerous complication of the myocardial infraction is the ventricular fibrillation

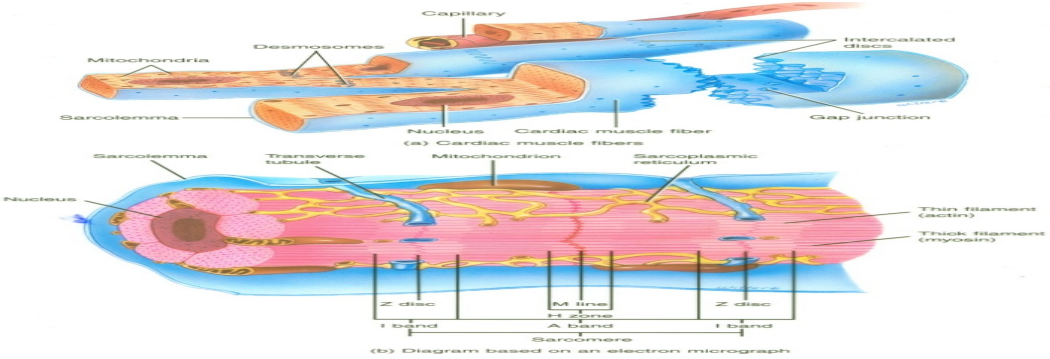
Both ventricles must contract at the same time "simultaneously" to initiate a pressure inside the ventricles to pump the blood to the atria.

Cardiac muscle cells:

It is surrounded by a texture called sarcolemma this structure has an invagination in it called transverse tubules.

Inside each cell we have the organelles:

1. The sarcoplasmic reticulum or the endoplasmic reticulum: it's less developed than the skeletal endoplasmic reticulum , it's function is to store calcium for contraction .if the sarcoplasmic reticulum doesn't store enough calcium it will need another source of calcium to contract which is the calcium in the extra cellular fluid around the cardiac tissue .
2. Mitochondria: because of the continues contraction of the cardiac muscle cells we have a lot of mitochondria in them and their function is to produce ATP.
3. 2 microfibrils consist of thin like structure, striated areas (light and dark) this striation is due to the structure of the cardiac muscle they are called sarcomeres (the contractile unit) in both skeletal and cardiac muscle cells
   The area that lies between 2 Z lines is the sarcomere "A" band is the thick area in the sarcomere consists of myosin protein and we have intercalated thin bands.



In skeletal sarcomeres we have two transvers microtubules inside the sarcomere, while in the cardiac the transvers tubules are located exactly on the Z lines each sarcomere in the cardiac muscle cell has only one transvers tubules.

in skeletal muscle cells we have less mitochondria but more nuclei than the cardiac muscle cells
In the cardiac the transvers tubule is wider and shorter in the skeletal its thinner and longer.

	cardiac	Skeletal
Sarcolemma	Less developed	More developed
# of nuclei	Less	More
# of mitochondria	more	Less
Transvers tubules	1 per sarcomere and it is wide and short	2 per sarcomere and are thin and long

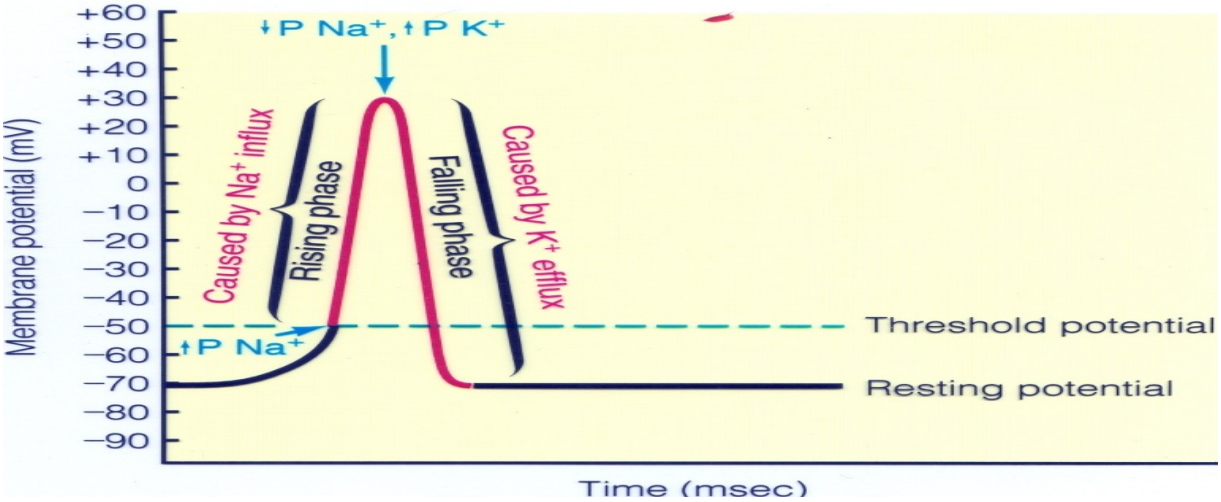
Gap junction: 6 protein subunits, when one cell has a change in its membrane immediately all cells will get the same change

Action potential of the skeletal muscle cells:

The resting membrane potential is around -90 mv (minus means the charge inside the cell is negative compared to the outside because of the higher membrane permeability to potassium than sodium.

When we have a stimulus and this stimulus reaches the threshold causing a depolarization to the membrane due to the opening of the sodium channels (Na+ influx, rising phase) and it moves inside until it reaches the overshot which is about +30 mv and it is followed by an opening of the potassium voltage gated channels (k+ efflux, falling phase)causing a repolarization.

The whole skeletal muscle action potential matter takes at most 10 milli second, usually it takes 2 milli second.



CARDIAC MUSCLE ACTION POTENTIAL:

Resting membrane potential is more negative equals around -90 mv which is due to the higher permeability to potassium ions much more than sodium ions.

It goes under five phases:

Phase 0: is the fast depolarization due to the opening of the voltage gated Na+ channels.

Phase 1: partial repolarization due to opening of cl- channels and other transient k+ channels and they are not voltage gated.

Phase 2: slow opening of voltage gated calcium channel and the calcium will enter the cell slowly the entrance of ca+2 ions is due to the difference in the concentration in and outside the cell.

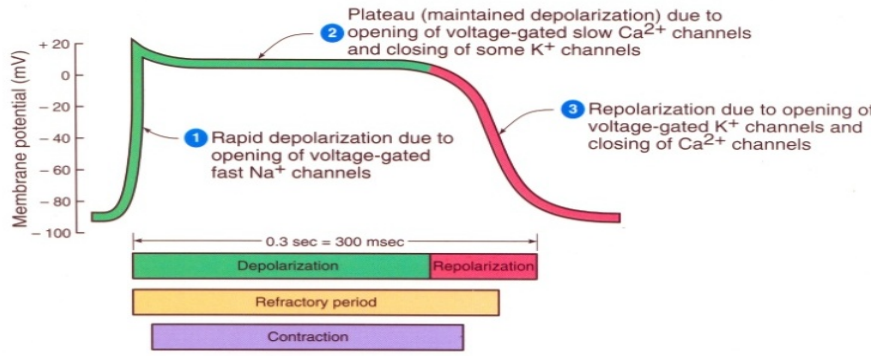
Plateau phase: due to the opening of voltage gated slow ca+2 channels and closing some k+ channels.

Phase3: opening of voltage gated k+ channels.

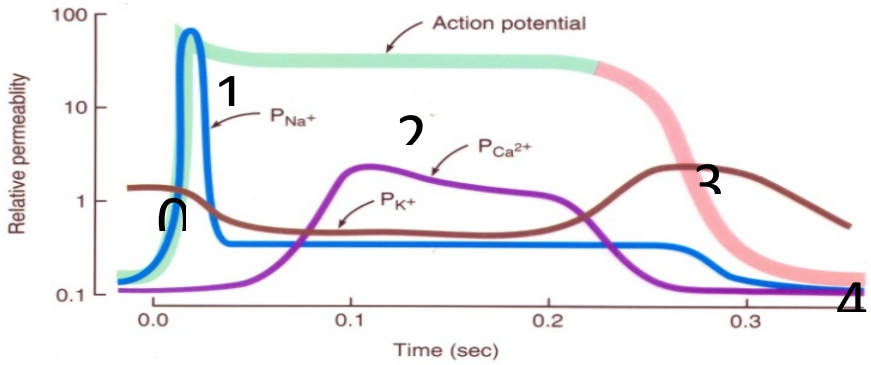
Phase 4: the membrane back to the resting state and the ions are rearranged by the contribution of the phase k+-Na+ pump.

The cardiac muscle action potential is very long, about 300 milliseconds in comparison with the action potential of the skeletal; muscle which is less than 10 milliseconds.

As we said the action potential is electrical response and each electrical response should be followed by mechanical response such as contraction and relaxation.



(a) Action potential, refractory period, and contraction



(b) Membrane permeability (P) changes

Let's talk about the **permeability of the membrane** for ions (the higher permeability the higher conductance).

Na+: very high during phase 0 and then it decreases.

K+: between phase 0 and phase 1 there is a decrease in the permeability (under the level of resting state) and it's called potassium rectification, and at the end of phase 2 an increase in the permeability occur.

Ca+2: in phase 2 an increase of permeability takes place and then it decreases.

NOTICE, the decrease in the permeability of potassium in phase 0 and 1.

Why is this decrease in the k+ permeability?

The decrease in conductance (permeability) of potassium at phase 0 and 1 of the cardiac action potential contributes to the maintenance of depolarization in phase 2 (plateau)

Let us suppose that the k+ permeability is still increased and the potassium **still exit** the cell (k+ efflux) while the ca+2 ions **enter** the cell, a **counter balance** will occur, so it **decreases** or polish the plateau, **so no plateau for this cell will take place**.

Each ion has a peak in the duration of action potential period as follows:

The ion	Ca+2	K+	Na+
The peak	In phase 2	In phase 3	In phase 0

NOW, let's talk about the refractory periods and their importance in the conduction system:

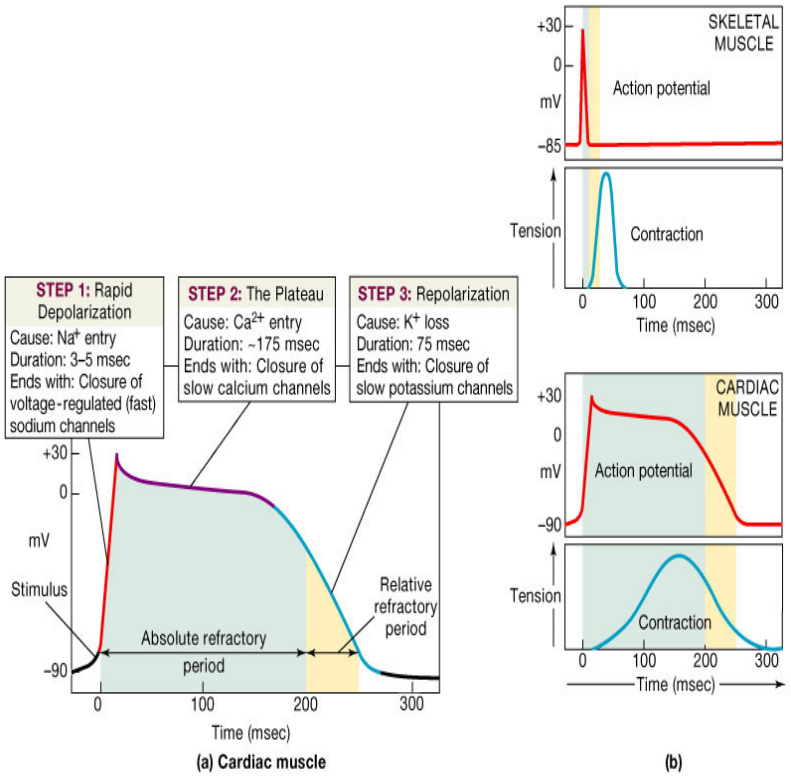
Absolute refractory period is very long; higher than 150 milliseconds while in the skeletal muscle is very short, but what is the importance of this difference?

During the relative refractory period you might have another action potential.

The action potential of **the skeletal muscle** occurs before the mechanical response starts in a period called **latent period** so I can have other action potentials which leads to several contractions which eventually leads to constant contraction which is called **Tetanus**.

In the cardiac muscle, the absolute refractory period **is truly long** so when another action potential occurs there is no way the muscle stays contracted because it goes in some period of relaxation.

When someone is subjected to electrical shot he dies but not from the maintained contraction of the heart muscles, but from the tetanus of the skeletal muscle of the diaphragm which leads to conclude that **whatever the stimulus is strong the cardiac muscle won't be tetanized.**



in the skeletal muscle, the mechanical response occurs after the end of the action potential, so it allows another contraction to take place before the muscle relaxes.

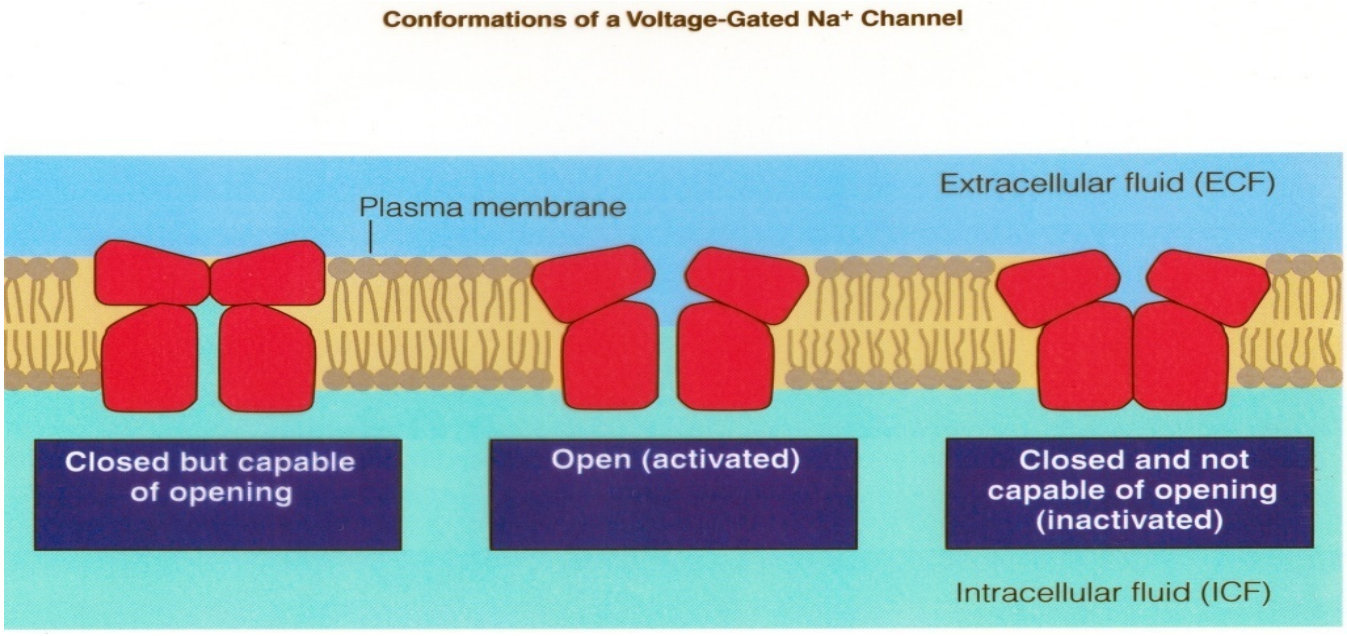
In the cardiac muscle, the long refractory period provides some relaxation phase before other action potential takes place.

NOW, let's move on and talk about the conformational changes of Na+ channel:

Na+ voltage gated channels has 2 transmembrane subunits:

1. Inactivation gate (H gate) intracellular, slow responding, closes when the potential becomes less negative.
2. Activation gate (M gate) extracellular, fast responding, opens when the membrane potential becomes less negative.

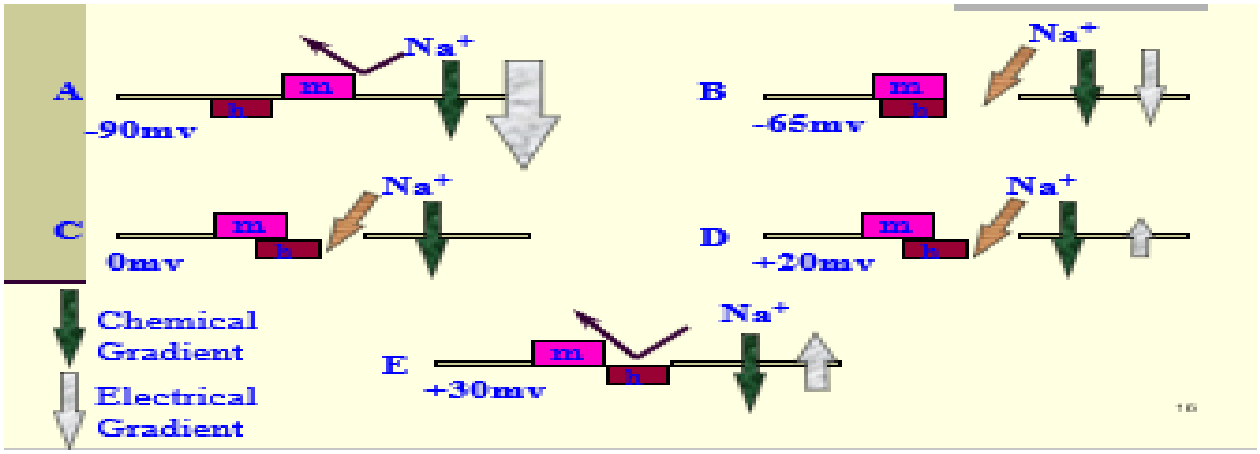
Less negative means near the threshold



The mechanism is as follows:

Normally at rest the activation gate is closed, and the inactivation gate is opened**; closed but capable of opening.**

When we have an electrochemical gradient for Na+ across the membrane and that makes the membrane potential closer to threshold; the activation gate opens fast before **the slow closure of the inactivation gate**, so the sodium influxes to the cell, the membrane becomes more negative, inactivation channel **is closed and not capable of opening.**



The mechanism through which (M, H) gates act during action potential:

▪ At RMP external gate (m gate) closes the Na channel (A)

▪ Upon reaching a stimulus, there is a fast moving of m gate to open the Na+ channel (it takes only 0.2 mSec to move) (B), this phase is called phase 0.

▪ Na+ ions enter the cell by simple diffusion.

▪ When 1 Na+ enters the cell, it brings 2 Na+, and 2 Na+ bring 4 Na+ and so on (amplification). Thus, the entrance of Na+ ions represents a positive feedback mechanism.

▪ When the membrane potential becomes less negative (-75 and less negative), this causes the movement of H gate (C, D)

▪ h gate takes 1 mSec to close (5 times slower than m gate).

▪ So, at the end of depolarization, the h gate is close and m gate is open (E)

▪ Upon reaching second stimulus, h gate will not move no matter how strong the stimulus is.

▪ h gate will reopen only when the membrane restores its RMP.

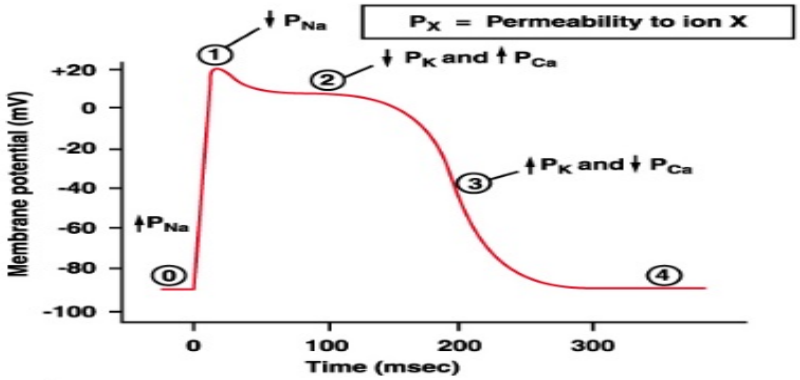
▪ m gate is called activation gate, while h gate is called deactivation gate.

So, during the action potential, the Na channels have 3 states:

1. Closed and active (when activation gate (M) is closed).

2. Open (when both gates are open).

3. Closed and inactive (when deactivation gate (H) is closed).



Phase	Membrane channels
⓪	Na^+ channels open
①	Na^+ channels close
②	Ca^{2+} channels open; fast K^+ channels close
③	Ca^{2+} channels close; slow K^+ channels open
④	Resting potential

There is a difference between skeletal and cardiac muscle during action potential:

In the skeletal muscle: when the action potential takes place on T-tubule, an electrostatic transfer occurs between the sarcoplasmic reticulum and the sarcoplasm which leads to the opening of ca+2 channels and releasing calcium from sarcoplasmic reticulum to the sarcoplasm through **Ryanodine receptor calcium release channel**.

In the cardiac muscle: during phase 2 the slow voltage gated ca+2 channel opens, then calcium enters **during plateau phase**, the calcium that enters causes release of the calcium from the SR.

The entrance of ca+2 triggers release of ca+2 from sarcoplasmic reticulum (calcium induced- calcium released) the released ca+2 goes and bind to **Troponin** to initiate contraction.

How we can initiate relaxation?

To cause relaxation you must reach resting level of calcium intracellular 10^{-7} M, **how?**

1. By calcium ATPase in the **sarcoplasmic reticulum**, which pumps calcium against gradient to get rid of it.
2. by Na+- ca+2 exchanger (3 Na+ in,1 ca+2 out), (its secondary cotransport, so it depends on the energy that energies k+- Na+ pump) it works bidirectionally; if Na+ inside is higher it works to get rid of sodium and vice versa.
3. by the calcium ATPase in the **sarcolemma**.

NOW, we will discuss how catecholamines (beta agonists, epinephrine) cause increase in the heart rate "positive chronotropic effect"?

EXTRA INFO: Chronotropic drugs may change the heart rate and rhythm by affecting the electrical conduction system of the heart and the nerves that influence it.

Catecholamines bind to β1 receptors which binds to G-protein receptor, so it increases cAMP.

cAMP with the stimulation of adenylyl cyclase will activate cAMP-PK, in which it will phosphorylates the sarcoplasmic reticulum proteins producing phospholamban.

When it is phosphorylated it activates ca+ pump which will sequester more and more ca+2 into the sarcoplasmic reticulum.

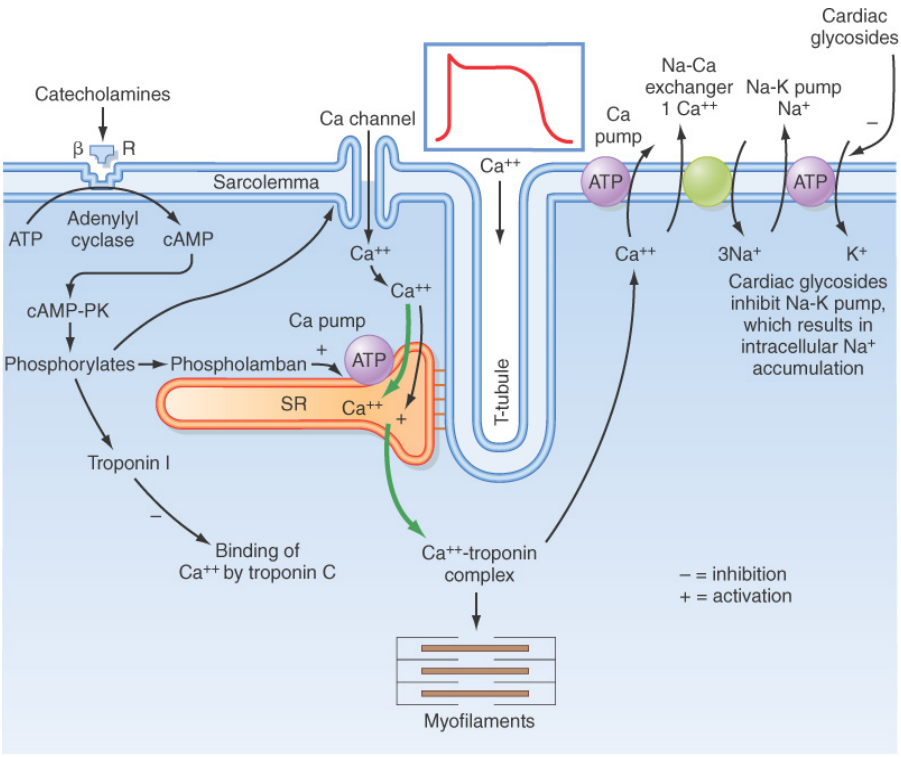
When ca+2 go back to the SR faster it means that the ca+2 sarcoplasmic levels are back to the resting level so the diastole phase is shorter and if it's shortened; we will have more systole- diastole so an increase in the heart rate will occur.

NOTE:

Phospholamban could be phosphorylated by any kinase not only cAMP-PK.

Systole= contraction

diastole= relaxation



Medical application:

Cardiac glycosides (digoxin):

is a positive ionotropic agent which increases contractility, how?

They inhibit Na+- k+ pump; sodium will accumulate inside the cell, so sodium will efflux from the cell as a result of exchanging with calcium.

Then it increases the concentration of calcium inside the cell which leads to more contractions.

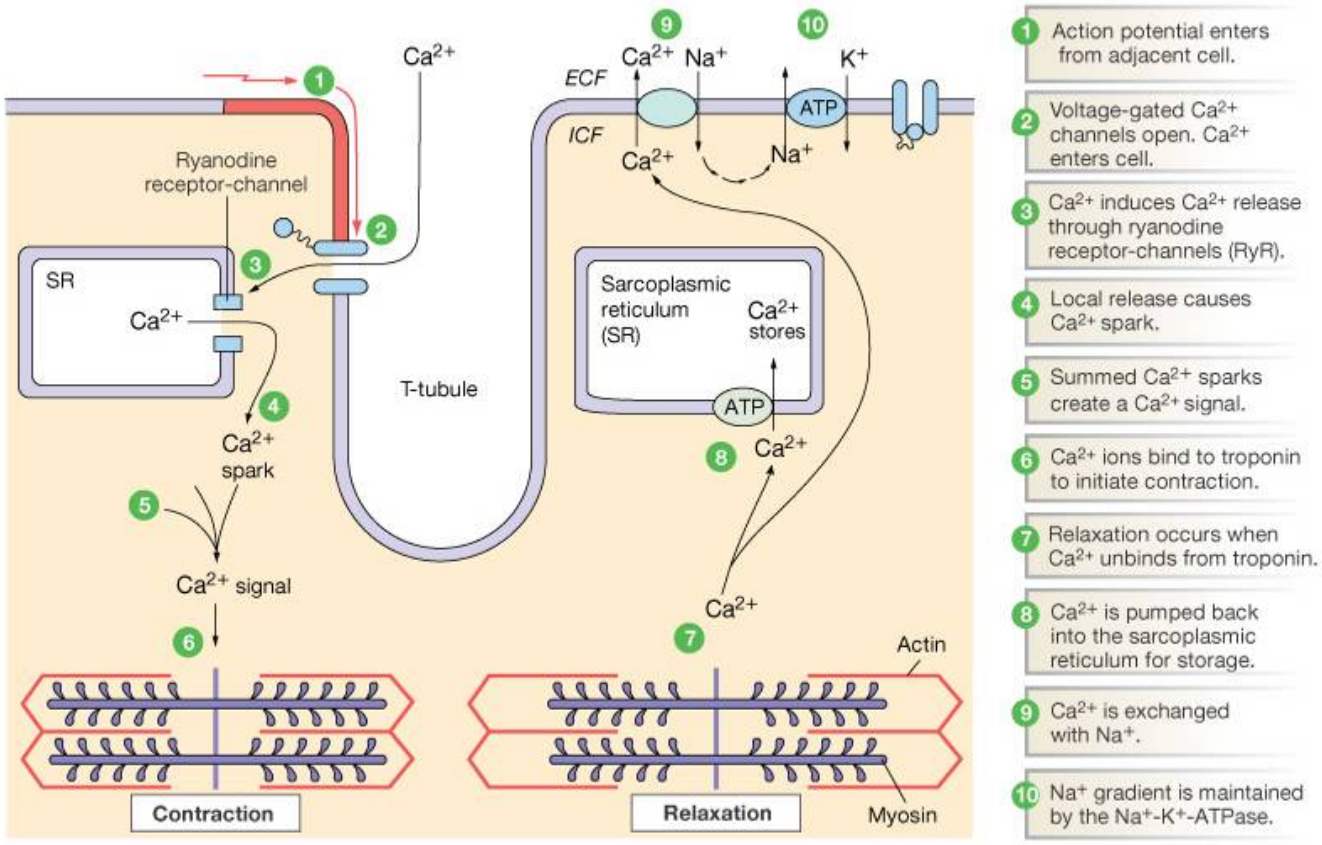
So, if you asked yourself, why we do have ca+2 ATPase and ca+2 exchanger?

> Calcium pump in the sarcolemma has high affinity; it works with very little increase in calcium but low capacity; it doesn't expel much ca+2 outside.
> Ca+2 exchanger has low affinity but high capacity so when it is stimulated it will expel more and more calcium outside the cell.

If we have pathological increase of ca+2 this will stimulate mitochondrial ca+2 exchanger which will pump ca+2 inside the mitochondria and Na+ to the cytosol

This pump is not active in normal conditions.

The figure below Summarize the function of the three pumps to produce relaxation:



A table summarize the difference between skeletal and cardiac muscles action potentials and their phases:

	Skeletal muscle	Cardiac muscle
Phase 0	Exists	Exists
Phase 1	Not existed	Exists (partial repolarization)
Phase 2	Not existed	Exists (plateau)
Phase 3	Exists (fast repolarization phase)	Exists (fast repolarization phase)
Phase 4	Resting potential	Resting potential

Act as if it is impossible to fail.