Cardio-Vascular System

2.1

Physiology

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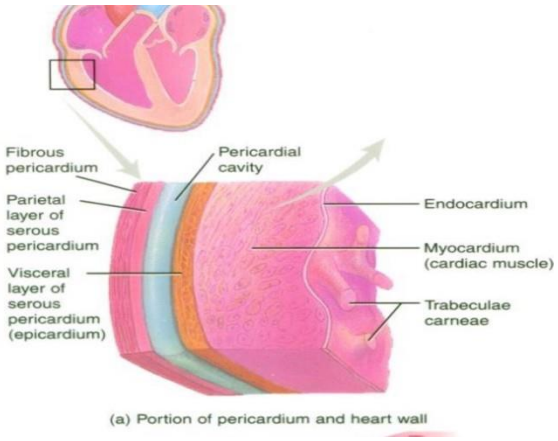
Notes from the first lecture;

The cardiovascular system consists of the heart and the vessels. Also, we said that we have 2 circulations, the lesser (pulmonary circulation) and the systemic circulation that distributes the blood to almost every part of our body.

we are going to talk about the first part of the cardiovascular system which is the heart.

Layers of The Heart

1. **Endocardium**: the inner most layer of the wall of the heart, it is an epithelial layer that has another function which is → secreting hormones that play a part in controlling the blood flow through these cells.
2. **Myocardium;** the middle layer and it is the thickest layer of the heart wall, it is a muscular layer that's composed of cardiac muscle fibers.
3. **Pericardium;** which has 2 parts:
   A. **Visceral layer:** close to the cardiac muscle
   B. **Parietal layer :** the outermost layer



(a) Portion of pericardium and heart wall

in between they form the pericardial cavity this cavity contains protein substances and the importance of it comes from the fact that sometimes it gets filled with fluid (pericardial effusion) which might limit the contraction of the heart and interfere with filling of the heart with blood [If it is not filled with blood it will not pump blood to the outside] . An increase in the pericardial cavity fluid is called **cardiac tamponade (could be caused by bacteria)

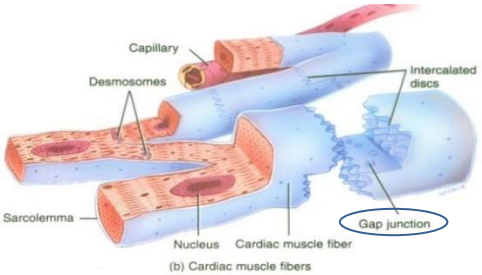
The amount of fluid could be small and doesn't interfere too-much with contraction and relaxation, but in case it was severe it might cause death.

So if you see someone with cardiac tamponade especially after a cardiac accident which can cause pericardial-cavity to be filled with blood 🩸 , the treatment is to release pressure , the fluid is drained through a needle or a knife to restore normal conditions quickly, otherwise that person might complain of suffocation and this case is lethal .

Cardiac Muscle: Myocardium

located between the pericardium and endocardium, it differs from the skeletal muscles in:

1. The skeletal cells are spindle in shape, while the **myocardial cells are rectangular in shape**.



(b) Cardiac muscle fibers

- Between these rectangular cells we have **intercalated discs**, these discs connect the cardiac muscle cells together, inside these intercalated discs we have gap junction.

- **Gap Junctions:** are proteins that are voltage-sensitive, acting like voltage gated channels. So they open and close according to the change in voltage. They allow action potentials to spread between cardiac cells by permitting the passage of ions between cells. They are called 'couplers' since they couple the cells together as they provide low electrical resistance areas between the myocardial cells through which ions can move. In case one cell has any change in the membrane potential this change will spread to almost all cells forming a physiological **syncytium**.

The heart contains 2 syncytia: Atrial and Ventricular Syncytium because the atria and the ventricles are separated from each other by a fibrous tissue.

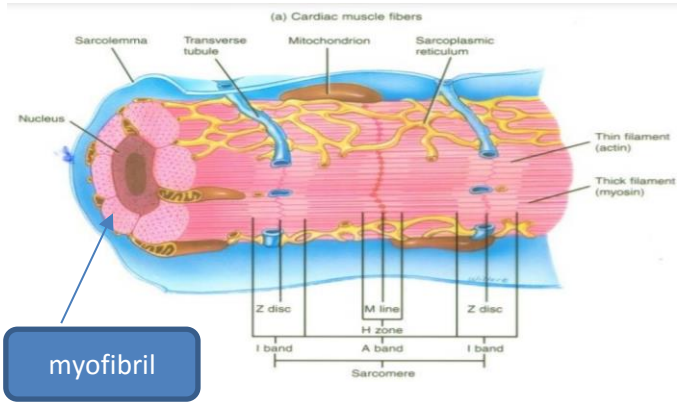
Atrial syncytium means: when there is an electrical change in one cell in the atrium this change will spread to all cells in both atria and both atria will contract as one unit , the same thing happens in the **ventricular syncytium**: electrical change in one cell →spread to all cells → spread to both ventricle causing them to contract at the same time.

This forms what we call an **effective pump**, otherwise if each cell contracts by itself regardless of the other cells this will cause loss of the coordinated contraction and what's called **Fibrillation** , if this fibrillation happens in the ventricle, we call it *Ventricular Fibrillation* and V fib. means death☠

What is the treatment of ventricular fibrillation? DC shock (direct-current shock) (defibrillation)

2. Superiorly to skeletal muscles, the myocardium cells are **rich in mitochondria** since these cardiac muscles never stop contracting and they **need energy** which they get from **aerobic respiration**. *Cardiac muscle cells have only one nucleus.
3. Cardiac muscle has poorly developed endoplasmic reticulum called **sarcoplasmic reticulum.** compared to the skeletal muscle that stores enough calcium, cardiac muscle capability for calcium storage is less, and accordingly it takes calcium from the extracellular fluid to accomplish proper contraction.
4. The outermost layer of the cardiac muscle cell is **sarcolemma** which sends transverse tubules (T-tubule). the transverse tubules in the cardiac muscles are **shorter and wider** than the one in the skeletal muscles as the T-tubules in skeletal muscles are slender and longer.

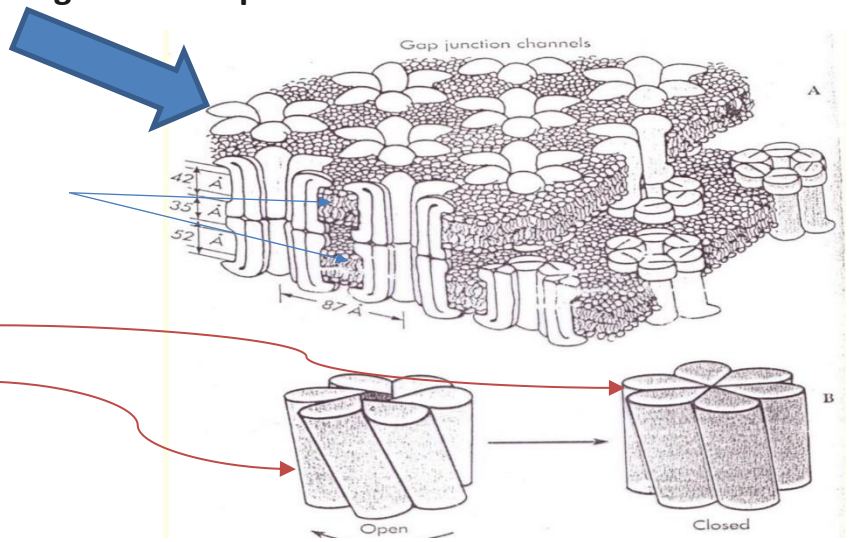
- **The T-tubules** in the cardiac muscle occur at the z disc, so each sarcomere has **only one t-tubule**. In contrast to skeletal muscles where t-tubule occur at the I – bands meaning they have 2 tubules for each sarcomere.



**the structure of the cardiac sarcomere (I-band, thick filaments, thin filaments, a-band, h-zone and m-line) they're the same as skeletal muscles.

These are the gap junctions, they're hexagonal in shape

**** 6 subunits of protein that connect two cells together**



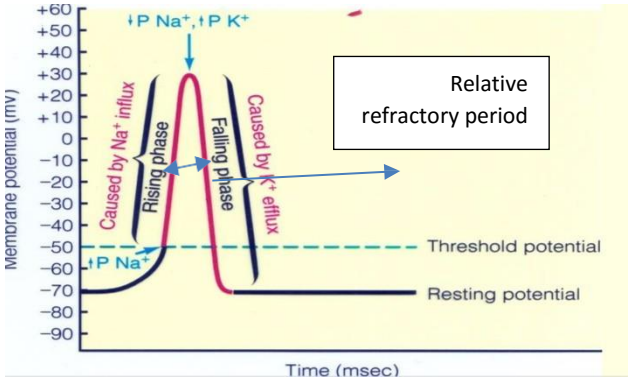
The gap junctions change their conformation through the change in voltage so in this conformation it is closed while in this conformation it is opened. When they open they allow the movement of ions in both directions (same as electrical synapses in nerves, they are bidirectional)

Action Potential in The skeletal muscles 💪

Let's revise the action potential of skeletal muscles:

Resting membrane potential is **-70 mV**, when we reach the threshold, **very rapid Depolarization** takes place caused by Na+ influx due to opening of the fast voltage gated sodium- channels so the sodium moves according to its electrochemical gradient as

$E_{eq}Na+ =$ **+61 mvolt** (outside to inside)



This rapid depolarization is called **rising phase** and by the time it reached the maximum, the k channels has opened so k efflux occurs according to its electrochemical gradient as

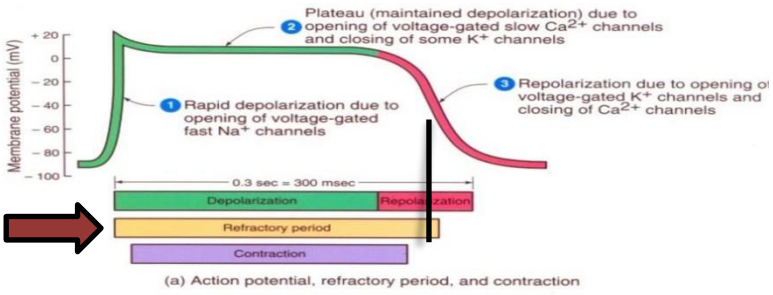
***E*eqK+ = -94 mvolt** (inside to outside)

As you can see the skeletal muscles' action-potential is very short, it takes (0.5-2) msec and it might reach a maximum of 10 msec , and the absolute refractory (when you cannot have another action-potential) period is about half of the repolarization period, and the relative refractory period (when a second action – potential can be initiated if the stimulus is stronger than the threshold) as well.

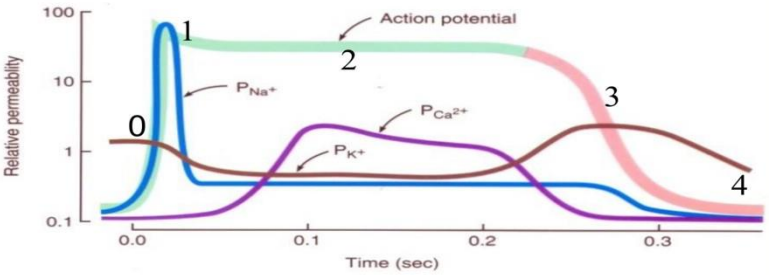
Because the skeletal muscles' action potential is short, each electrical change has to be followed by a **mechanical change** (they have to be followed by contraction and relaxation), Remember skeletal muscles might get tetanus after prolonged contraction.

Action Potential in The Cardiac Muscles ❤️

As for cardiac muscle, the resting membrane potential is more negative, around **-90 mV**. The action potential has 5 phases:



(a) Action potential, refractory period, and contraction



Phase 0 (depolarization): fast Na+ channels open. When the cardiac muscle cell is stimulated, voltage-gated sodium channels (fast sodium channels) open and permit sodium to rapidly flow into the cell depolarizing it.

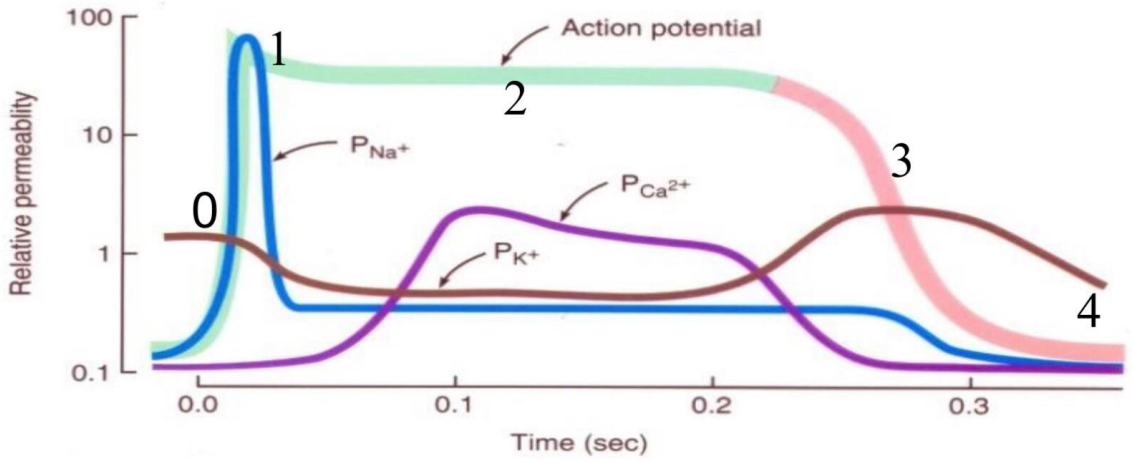
Phase 1 (initial repolarization): cell begins to repolarize, due to K+ leaving cells through open K+ channels & maybe the action of some chloride channels.

Phase 2 (plateau): slow voltage gated Ca+2 channels open so the calcium moves according to its electrochemical gradient from outside to inside (extracellular fluid calcium $=10^{-3}$ M, while intracellular fluid calcium = 10^{-7} M) [this calcium is very important for contraction] and some K+ channels close (decreased permeability).

Phase 3 (rapid repolarization): voltage gated Ca+2 channels close and K+ channels open and K+ goes out of the cell

Phase 4 (resting membrane potential): averages about -90 mV (and here we're back to the resting state).

The length of this action potential is around 300msec. **The absolute refractory extends through the AP to around-half of the repolarization**, that time gives space for the muscle to contract AND relax [by repolarization] so, when the next AP comes the muscle would be relaxed and ready to contract again in a way that will never produce tetanus [the muscle doesn't receive signals to contract again, while it's already contracting, rather when it is relaxed]. i.e. the cardiac muscle won't be tetanized because of this long absolute refractory period unlike skeletal muscles.



- **The permeability/conductance changes in the cardiac muscle action-potential:**

Phase zero: It has high permeability of Na^+ and the change in voltage over time during this phase is very high (high dv/dt), at the end of phase zero the permeability of Na+ decreases due to closure of Na^+ channels.

Phase one: Increased permeability of a special kind of K+ and/or Cl- and some decrease in the permeability of Na+ (partial repolarization)

phase two; very high permeability of Ca+2 and decreased K+ permeability

****another difference in the action potential between cardiac and skeletal muscles is that at the end of phase 0 and through phases 1&2 there is a decrease in the permeability of k+ by the closing of fast K+ channels until the efflux plateaus at phase 2, as we know the resting state permeability of k+ is much higher than that of Na+ , it is about 100 times more. This K^+ permeability during phase 0 decreases and stays low until the end of phase 2 then it starts to increase before phase 3, this is very important as it maintains the plateau phase.

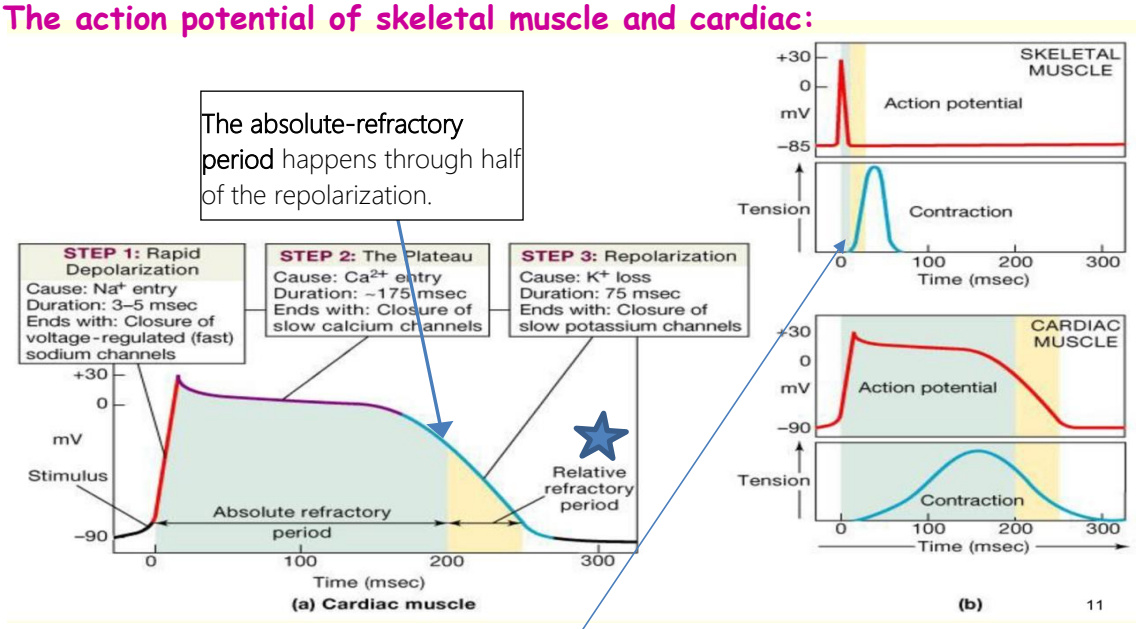
→ Remember in the plateau there's maintained depolarization due to the influx of calcium.

→If the permeability of k^+ didn't somewhat decrease, this means that K^+ will go outside as the Ca^{+2} enters. Meaning, the high permeability of K^+ will overcome the influx of Ca^{+2} and the membrane potential will be repolarized and remain more negative, (i.e. no plateau will be established) but because the K+ permeability decreases enough to have an equilibrium with Ca2+ influx during phase 2 the depolarization of the cardiac muscle will be prolonged → keeping the plateau → thus preventing tetanus.

→I know everything is clashing, but it's all relative, in phase 1 the permeability of K+ increases compared to Na+, but it decreases compared to its normal state.

Phase 4: recovery of the ions and coming back to the resting state

- **The action potential of skeletal muscle and cardiac:**



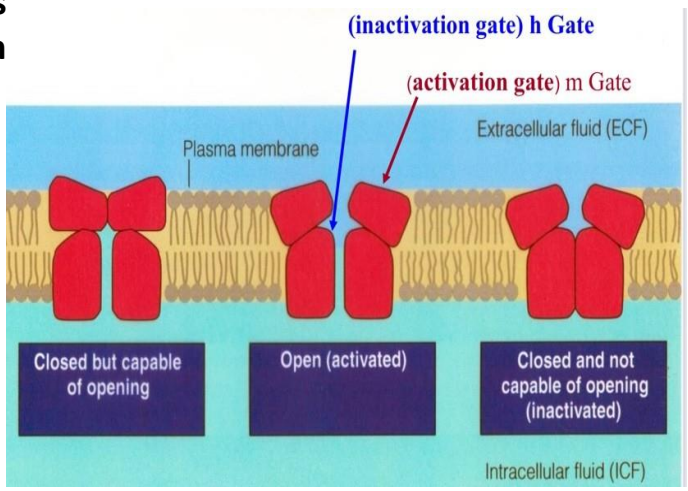
Notice that the action potential of skeletal muscles is very short and all this action potential occurs during the **latent period [before the muscle contracts]** this means, you can have a lot of AP adding up until this muscle can be tetanized.

Conformations of voltage gated Na+ channels

Sodium channels are amazing! With two gates playing a role in sodium channel activation and sodium ions movement.

1- The **M gate** (activation gate): the extracellular gate [during rest it is **closed]**

2- The **H gate** (inactivation gate): the intracellular gate [normally during rest it is **opened]**



NOW, when the membrane potential becomes less negative (it's moving towards the threshold), the activation gate opens and the inactivation gate closes!! And this sounds crazy as sodium will never pass in this way!! so how is this solved?!

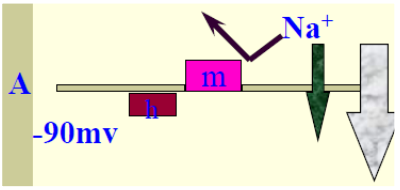
Here comes what's interesting: the inactivation gate is a **slow gate** and the activation gate is **fast** so when the membrane potential is becoming less negative the activation gate opens **before** the inactivation gate gets fully closed, meanwhile Na+ influx is very fast to the inside of the cell according to its electrochemical gradient i.e. if we reached the threshold FASTLY, the activation gate will open while the inactivation gate is still open and moving slowly towards closure, and Na^+ would take that chance to rush in.

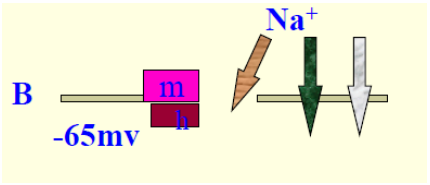
However, if we reached the threshold slowly, Sodium won't be able to enter.

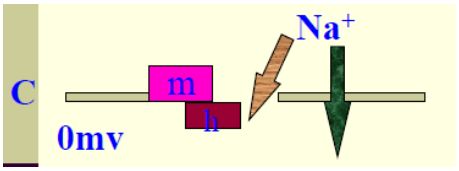
So, there are two things affecting these gates:

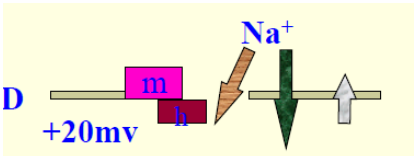
Time constant: the activation gate is ***fast*** and the inactivation gate is ***slow*** in movement
and Voltage constant: threshold for ***opening*** of the activation gate and ***closing*** of inactivation gate is the **same**

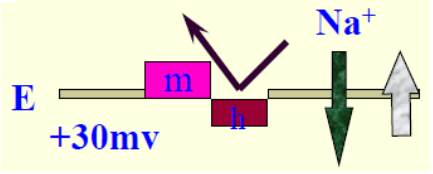
Let's demonstrate with pictures (green arrow represents the chemical gradient tendency to move and white arrow represents the electrical one):
Note: try to connect voltages here with what you already know about action potential phases and ion channels' activity:





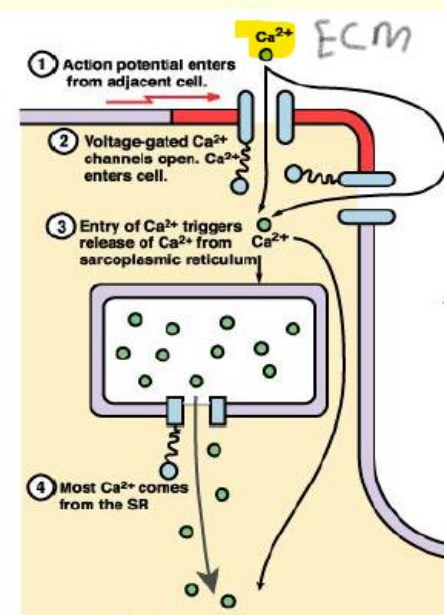






A. RESTING membrane potential (-90 mV):
   - ↳ The Fast M gate is closed while the slow H gate is open, so there is no influx of Na+.
B. LESS NEGATIVE membrane potential (nearly -65mV):
   - ↳ the M gate opens very fast while the slow H gate is stimulated to close but is still open, sodium influx is taking place according to its electrochemical gradient!
C. Lesser negative membrane (about 0 mV): the slow H gate closes a little, the fast one is still open, so sodium influx is still happening.
D. +20 mV: More closure of the inactivation slow H gate and still, there is sodium influx.
E. About +30 mV: now the slow (H) gate is fully closed and sodium influx is **stopped**.

Now, what happens when action potential takes place, at the MOLECULAR level?



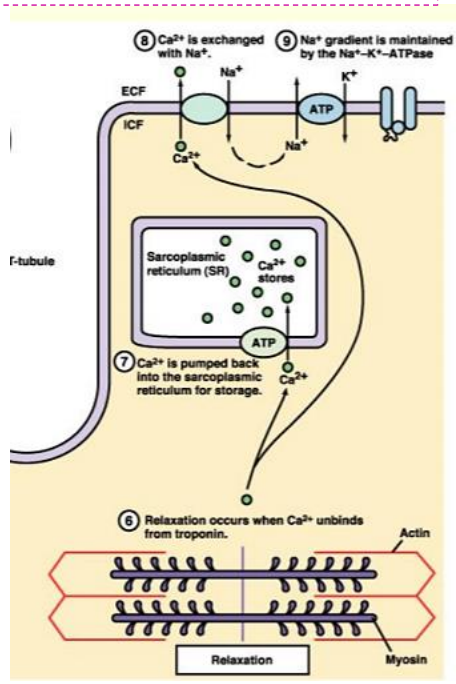
→ The story here is different than what happens in skeletal muscles, as *calcium stores in sarcoplasmic reticulum are released in a different manner.*
In skeletal muscles: when action potential fires, a wave of depolarization passes down the T-tubule which lies next to the sarcoplasmic reticulum cisternae, causing the calcium to get out of its stores.
In cardiac muscle: "calcium induced/triggered calcium release" takes place, that is: during the plateau phase (phase 2) **extracellular** Calcium ions start to influx through **slow calcium voltage gated channels**, this entering calcium causes **release of calcium** from its stores in the **sarcoplasmic reticulum** by activating ryanodine receptor channels (RyR) in the SR

- **Released calcium** will bind to **troponin**, moving the tropomyosin and exposing the myosin binding sites on actin, and then when myosin is charged (by forming myosin-ADP.Pi) it will bind to actin resulting in sliding (power stroke) and muscle contraction

Normal Ca concentration: 10^{-7} M
Ca concentration during contraction: 10^{-5} M

◆ How does the muscle relax?

- We should ask ourselves how it got tensed, in order for it to relax we have to reverse the contraction conditions, and that is by lowering the Ca^{2+} concentration inside (10^{-5} → 10^{-7}) and dissociating it from troponin.



how does that happen?

i. **First**, Ca^{2+} uptake into the sarcoplasmic reticulum by **Ca^{2+} ATPase (pump)** on the SR [this is the only mechanism used in the skeletal muscles]

ii. **Second**, by the **Ca^{2+} /Na^{+} exchanger**, which starts working upon sensing the increase in Ca^{2+} concentration and kicks out 1 Ca ion for 3 Na ions getting in.

- It uses secondary active transport.
- The sodium that gets in gets out again through the **Na+/K+ ATPase** to maintain its gradient.
- This exchanger is super, it can actually work *both ways*, if there's too much Na^{+} inside, it would start kicking IT out instead [this might happen during phase 0]

iii. **Third**, there are **Ca^{++}pumps on the sarcolemma** sending the calcium out.

iv. **Fourth**, this mechanism works in **pathological states**, the **mitochondrial Ca2+/Na+ exchanger**, it differs from the other exchanger in that it enters **1 Ca^{2+}** per **2 Na^{+}**

- sodium that's lost from the mitochondria is then gained back through the exchange with hydrogen (Na^{+} in, H^{+} out)

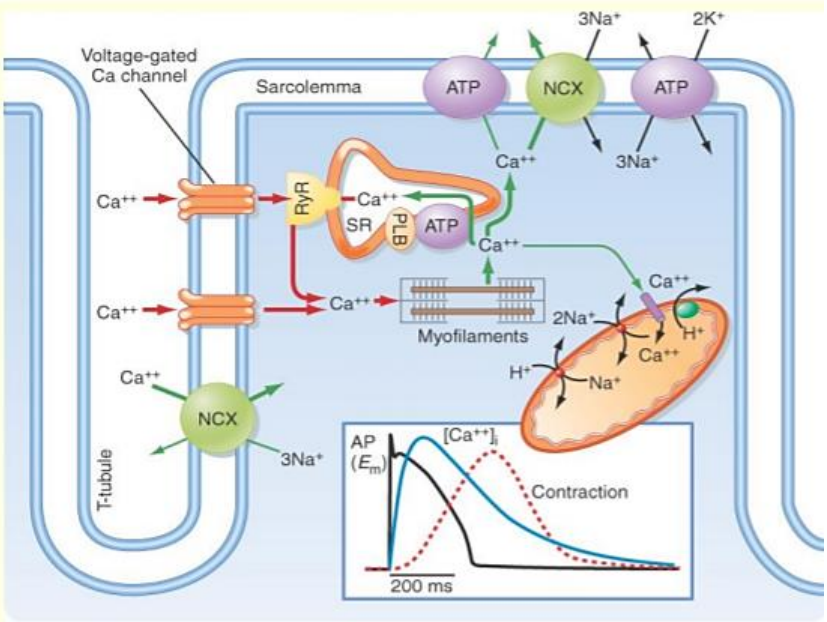
here's a comparison between the pump and the exchanger:

	Affinity	**Capacity**	Ca2+ concentration it needs to work
Ca^{2+} pump	High	Low (can't bind many ions)	Small
Na+/Ca2+ exchanger	Low	High	High

Pharmacology visitor:

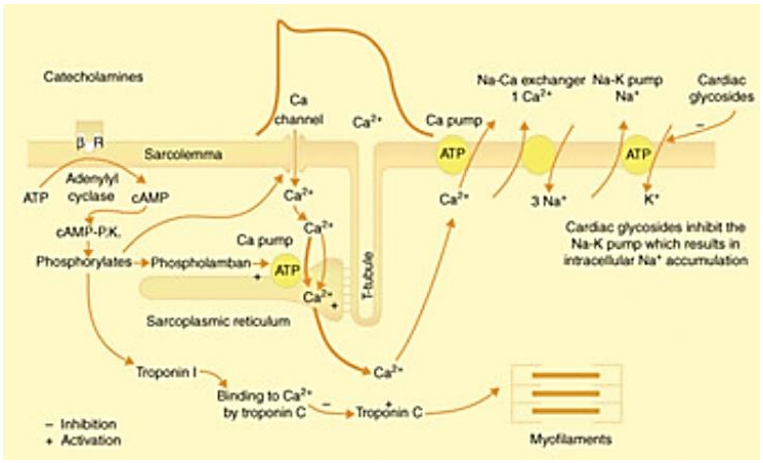
There are drugs called cardiac glycosides like **digoxin,** which cause increased contractility of the heart by blocking the Na^{+}/K^{+} ATPase, which means sodium will accumulate inside, this activates the Na^{+}/Ca^{2+} exchanger in the *other way*, to pump Na+ outside by getting Ca^{+2} inside, causing increased Ca^{+2} and thus increased contractility.

This picture summarizes all the steps to contraction and the mechanisms of relaxation:



◆ How does epinephrine increase heart rate?

catecholamines [epinephrine] would stimulate beta receptors on the sarcolemma of the heart muscle cells, stimulating a G protein system that starts with the dissociation of alpha subunit, that activates adenylyl cyclase, which converts ATP into cAMP, which activates cAMP dependent protein kinase (PKA) which in turn phosphorylates the phospholamban which is a SR protein that activates SR calcium pumps calcium gets inside the SR, thus shortening the relaxation time and increasing the rate. *doctor's explanation*

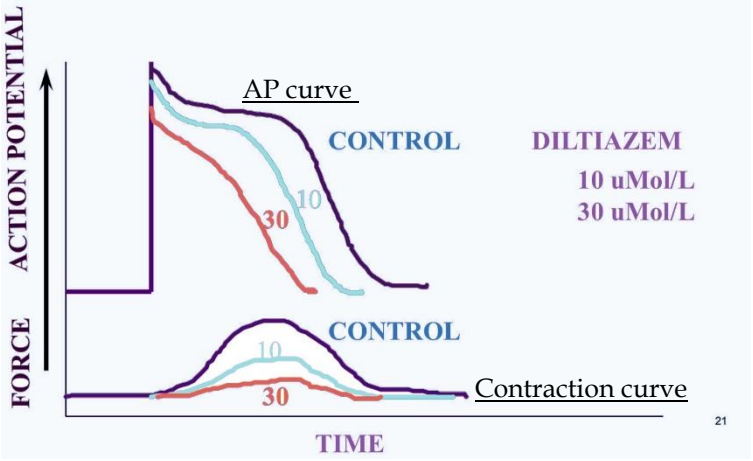


New terms:
Diastole is Relaxation of the heart
Systole is contraction of the heart

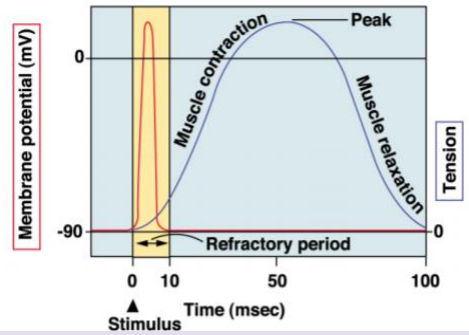
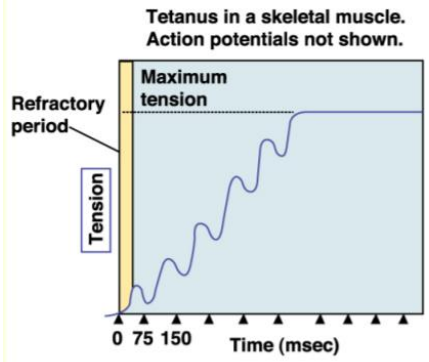
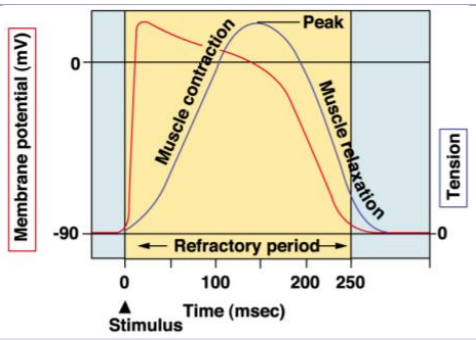
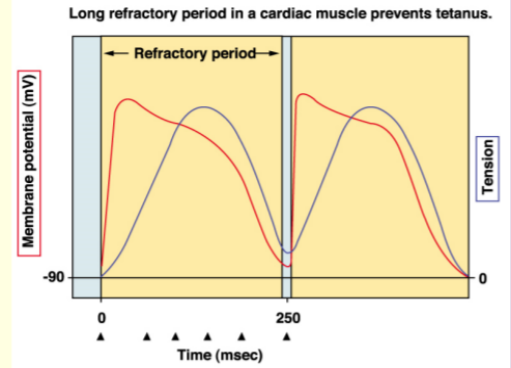
Regarding this subject:
Scientifically, the accurate explanation is:
Unphosphorylated Phospholamban basically acts as an **inhibitor of SR Ca^{+2} pumps**, when it gets phosphorylated by PKA, it **loses this power and the inhibition is stopped**, thus the **Ca+2 pumps work more efficiently** at pumping Ca+2 and give the mentioned effect.

Effects of Ca channel blockers, and the cardiac cell action potential.

- giving them causes shortening of the plateau phase, and force of contraction decreases.



Difference between cardiac and skeletal muscle AP and contraction:

criteria	Skeletal muscle	Cardiac muscle
Phase 0 Depolarization phase (Na+ influx)	Present	present
Phase 1 partial repolarization	**Not present**	Present
Phase 2 Plateau (slow Ca++)	**Not present**	Present
Phase 3 fast repolarization phase (K+ efflux)	present	Present
Phase 4 resting membrane potential	Present	Present
diagrams	 Notice how the AP ends then the contraction follows  Absolute refractory period is tiny, so successive APs can take place causing summation of contraction and resulting tetanus. Tetanus can be complete and incomplete	 Notice how the contraction happens simultaneously with the AP, the long absolute refractory period gives time for the muscle to relax, so that when the next AP hits, the muscle would already be relaxed.  No summation during contraction, summation occurs during relaxation.

***There are extra repeated diagrams in slides: 14,16, 20, 27, 29 if you want to view them.**