CVS

Physiology

Writer: Yamama al lemon

corrected by: Jana zaidan

Doctor: Faisal ahmad

Red: what doctor said in our lecture

Blue and brown : 019 sheet. Black : from the slides

In this lecture , we will review cardiac muscle physiology

Objectives:

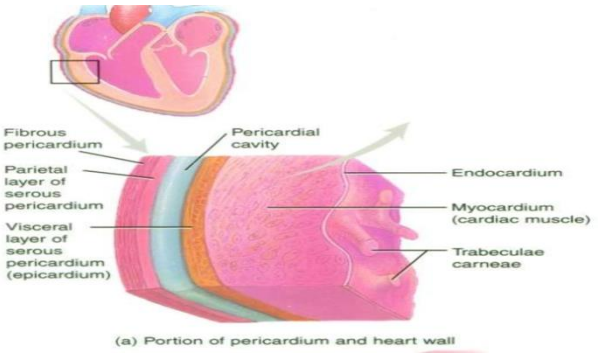
By The end of this lecture students should be able to:

- Distinguish the cardiac muscle cell microstructure
- Describe cardiac muscle action potential , its important for ECG .
- Point out the functional importance of the action Potential .
- Follow the cardiac muscle mechanism of contraction its same to skeletal muscle , the sliding filaments hypothesis.
- Delineate cardiac muscle energy sources , the main source of energy is fatty acids (for brain: glucose)
- Outline the intracellular calcium homeostasis , the extracellular calcium is very important to cardiac muscle in contract to skeletal muscle
- Explain the relationship between muscle length and tension of cardiac muscle (Frank-Starling law of the heart) , we will focus on it

Layers of The Heart, here

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.



(a) Portion of pericardium and heart wall

3. Pericardium; which has 2 parts:

A. Visceral layer: close to the cardiac muscle

B. Parietal layer : the outermost layer

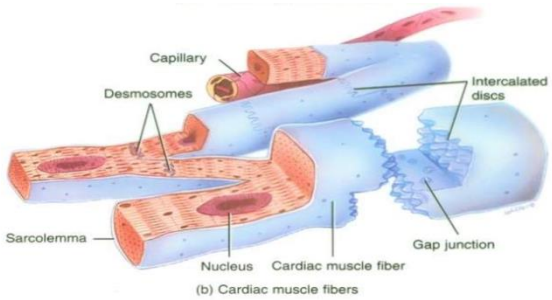
**in between they form the pericardial cavity , its filled with fluid almost 50-100ml or sometimes until 150ml , this cavity contains protein substances and it might increases for certain reason maybe infection or accidents which causes hemorrhage so we have pericardial effusion which might limit the 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 , its an emergency case (could be caused by bacteria like TB) 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

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

1. The skeletal cells are spindle in shape that runs between origin and insertion ,it might be as long as millimeters and some times meters , while the myocardial cells are rectangular in shape,

Between these rectangular cells we have intercalated discs, these discs connect the cardiac muscle cells together, inside these intercalated discs we have gap junction which is a low resistance area .



(b) Cardiac muscle fibers

The cells are electrically coupled , if there is change of one cell, this potential will spread to all the cells in the same time through the gap junctions and it's important for heart , if there is depolarization of one cell so it will spread to all ventricles cells as well as to all atrium cell at the same time (the spread between atria and ventricles is through the conduction system ; S.A node ,A.V node and so on , because there is fibrous septa between them, we are going to talk it later)

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 at the extent if a depolarization spread between cells it happens at the same time of all ventricular cells then they contract as one unit(because we should always remember

that electrical changes precede mechanical change) then act as one unit , they will develop pressure in the middle of ventricle , this pressure will control the valves , 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 so Ventricular fibrillation it happen at ventricles ; as each fiber contacts for itself it means there is no pressure develop on the ventricles so no pump ,,,,then death

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

So this is the dangerous of MI, sometimes they develop Ventricular fibrillation so we should immediately talk them to hospital .

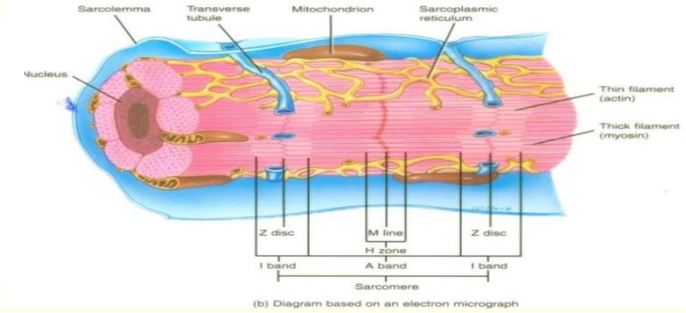
2. Cardiac muscle has poorly developed endoplasmic reticulum called sarcoplasmic reticulum. compared to the skeletal muscle that stores enough calcium, cardiac muscle capability for calcium storage is less, and accordingly it takes calcium from the extracellular fluid to accomplish proper contraction.

3. 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.

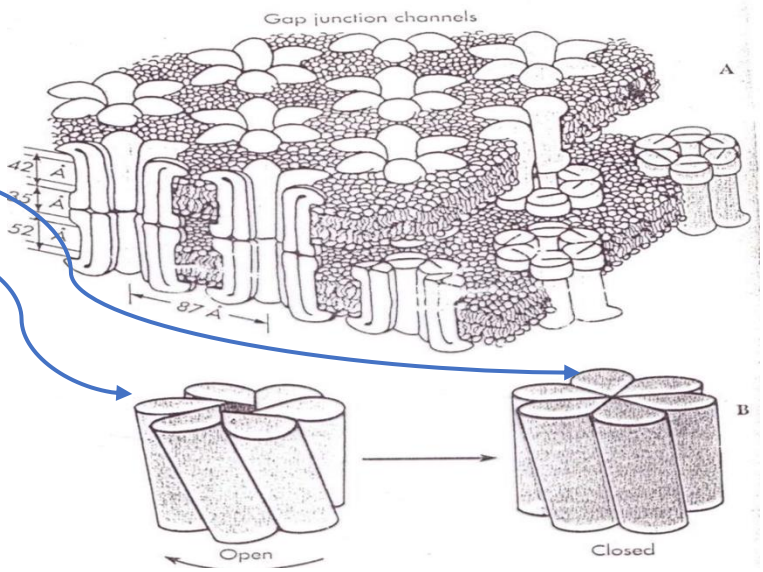
4. Superiorly to skeletal muscles, the myocardium cells are rich in mitochondria since these cardiac muscles never stop contracting and they need energy which they get from aerobic respiration. *Cardiac muscle cells have only one nucleus. In contract to skeletal muscle doesn't have that much mitochondria but it's multinucleate.



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)



At skeletal muscle there is no gap junctions, each cell contract by itself, there is motor unit which is the neuron and the muscle fibers is supplying , and these fibers work as a unit (not the whole muscle) but at cardiac muscle we find the all ventricle cells contract as a one unit , so we have two syncytial ; atrial and ventricle.

Action Potential in The skeletal muscles

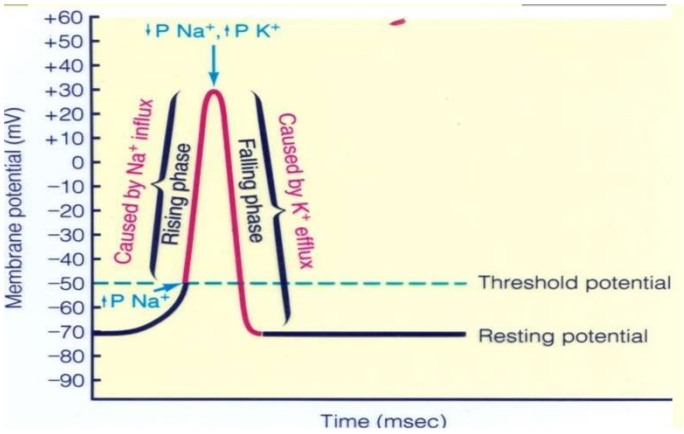
Let's revise the action potential of skeletal muscles

: 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 EeqNa+= +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 EeqK+= -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),

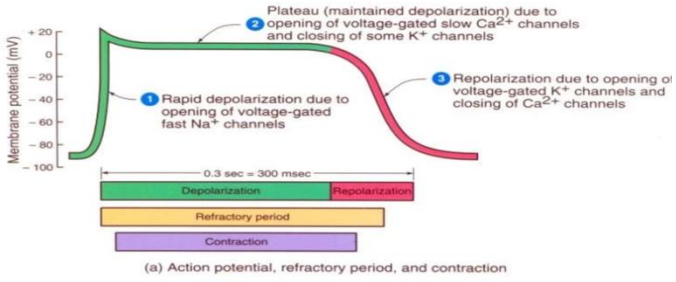


Remember skeletal muscles might get tetanus after prolonged contraction.

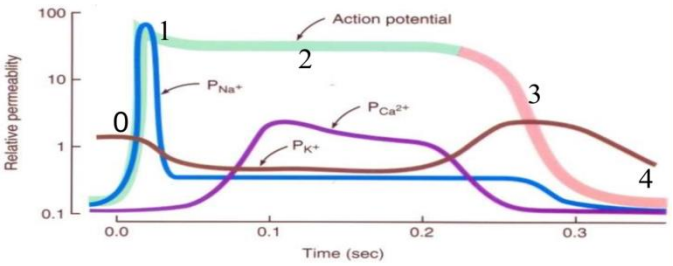
Action Potential in The Cardiac Muscles

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

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



(a) Action potential, refractory period, and contraction



Phase 1 (initial repolarization): cell begins to repolarize, due to K+ leaving cells through open K+ channels (transient) & 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.

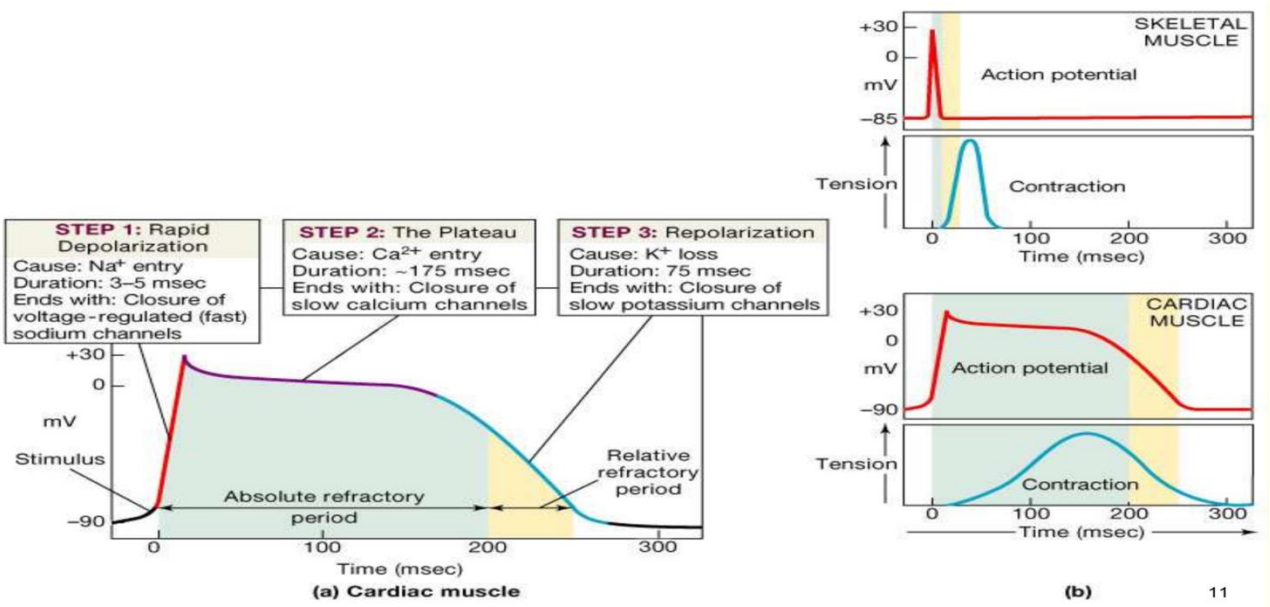
Remember in the plateau there's maintained depolarization due to the influx of calcium.

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 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 ,

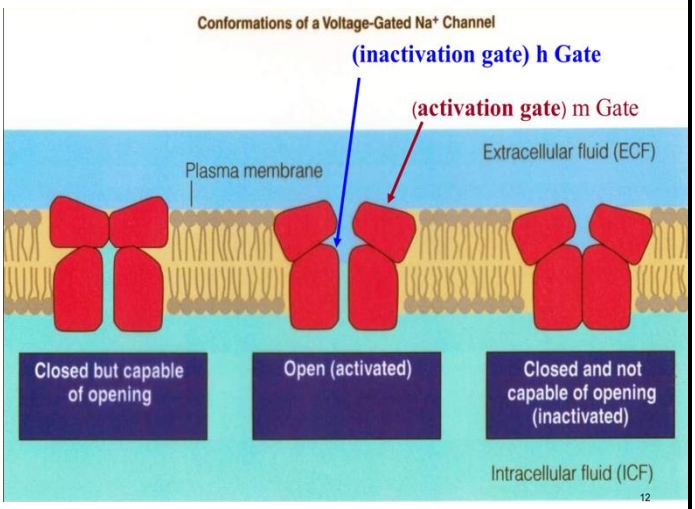
what is the tetanus ; is maintained contractions , at heart it can't happen even we give an electrical shock to patient , but the patient will die of tetanized diaphragm; no respiration.

Conformations of voltage gated Na+ channels

Sodium channels have 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:

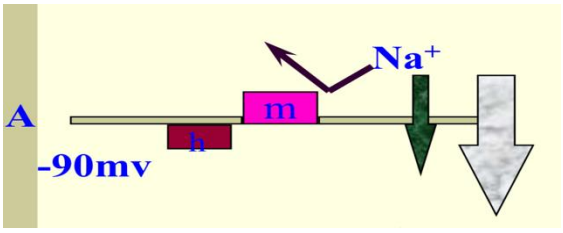
Time constant: the activation gate is fast and the inactivation gate is slow in movement and Voltage constant: threshold for opening of the activation gate and closing of inactivation gate is the same

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:

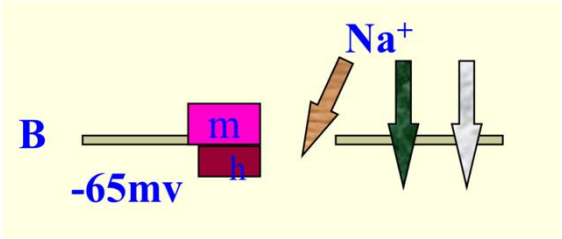
A. RESTING membrane potential (-90 mV):

The Fast M gate is closed while the slow H gate is open, so there is no influx of Na+.



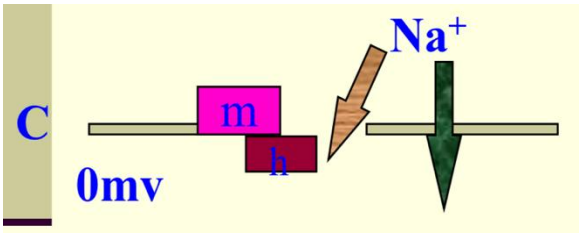
B. LESS NEGATIVE membrane potential (nearly -65mV):

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!



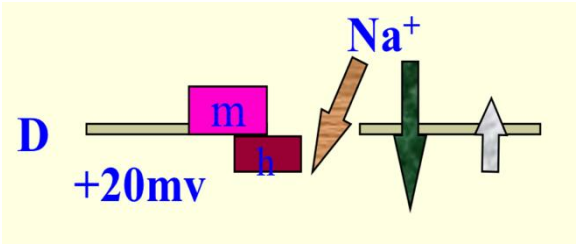
C. Lesser negative membrane (about 0 mV):

the slow H gate closes a little, the fast one is still open, so sodium influx is still happening.

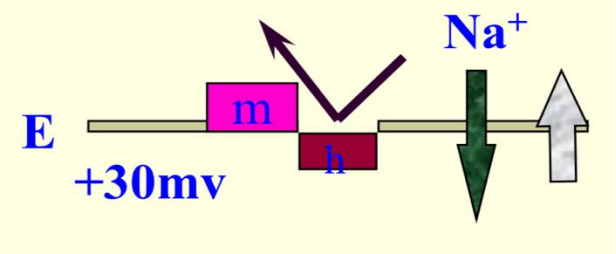


D. +20 mV:

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



5 calcium stores in sarcoplasmic reticulum are released in a different manner ,its another different thing between skeletal and cardiac muscle , at cardiac , "calcium induced/triggered calcium release" takes place; calcium influx in phase 2 cause more release of calcium from sarcoplasmic reticulum by activating ryanodine receptor channels (RyR) in the SR

Released calcium will bind to troponin c , 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

The binding between troponin c and calcium is a reversible process, more calcium so will bind to troponin , less calcium then let troponin and relaxation

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.

How does the muscle relax?

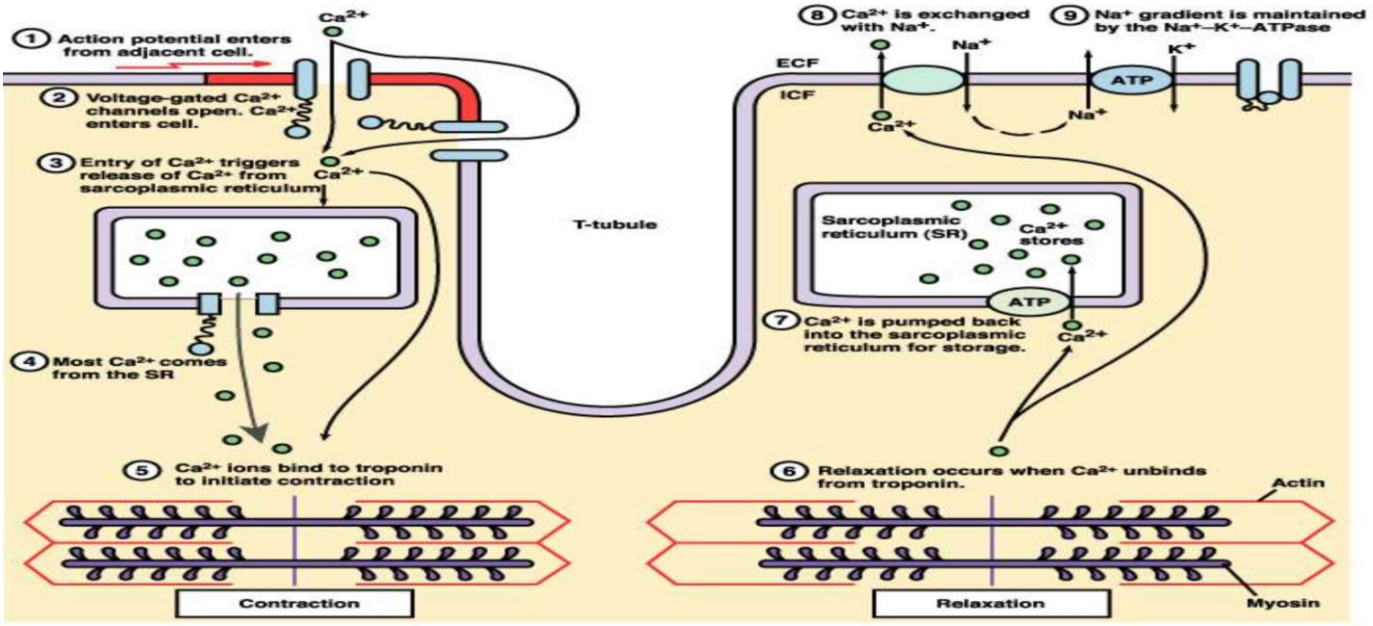
by lowering the Ca2+ concentration inside (10-5 to 10-7) and dissociating it from troponin.

how does that happen?

1. First, Ca2+ uptake into the sarcoplasmic reticulum by Ca2+ ATPase (pump, its active transport) on the SR [this is the only mechanism used in the skeletal muscles , its exactly like it]
2. Second, by the Ca2+ /Na+ exchanger, which starts working upon sensing the increase in Ca2+ concentration and kicks out 1 Ca ion for 3 Na ions getting in , It uses secondary active transport , it's called electrogenic exchanger (differs in charges) .
   The sodium that gets in gets out again through the Na+/K+ ATPase to maintain its gradient , This exchanger is superrrr , 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]

3. Third, there are Ca++pumps on the sarcolemma sending the calcium out, against concentration gradient.

4. Fourth, this mechanism works in pathological states, the mitochondrial Ca2+/Na+ exchanger, it differs from the other exchanger in that it enters 1 Ca2+ per 2 Na+ ,, sodium that's lost from the mitochondria is then gained back through the exchange with hydrogen (Na+ in, H+ out)



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+ /Ca2+ exchanger in the other way, to pump Na+ outside by getting Ca+2 inside, causing increased Ca+2 and thus increased contractility at heart failure patients.

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

In the heart we don't say contraction and relaxation , we say systole and diastole where systole means contraction and diastole relaxation

Cardiac Muscle action potential Vs. Skeletal Muscle

Phase 0 –Depolarization phase (Na+ influx) it's the same
Phase 1 partial repolarization (Not in skeletal)
Phase 2 Plateau (depolarization not in skeletal) slow calcium channels
Phase 3 fast repolarization phase (K+ efflux) it's the same
Phase 4 resting membrane potential

Cardiac Muscle contraction Vs. Skeletal Muscle

Sliding filament hypothesis
No tetany (Long refractory period because of plateau)
Fatty acids main source of energy unlike
Skeletal muscle (Anaerobic and Aerobic)
Attachment and detachment cycle and ATP dependence is the same

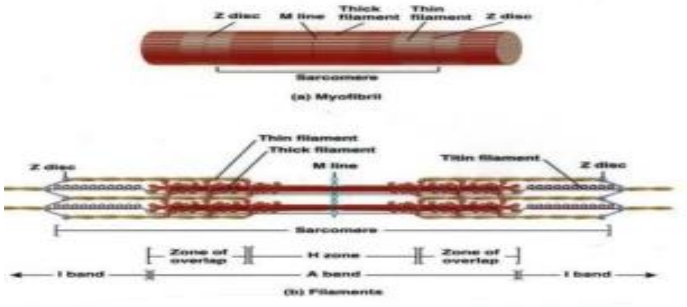
Mechanism of contraction in cardiac and skeletal muscles

☐ The mechanism of contraction is similar in cardiac and skeletal muscle, except that cardiac muscle is an involuntary muscle and it's supplied by the autonomic nervous system (sympathetic and parasympathetic), whereas skeletal muscle is voluntary and is supplied by motor spinal nerves.
☐ Although cardiac muscle is supplied by the ANS, it doesn't initiate contraction of the cardiac muscle. Rather, the contraction is initiated by a special system called the conduction system of the heart, which we will discuss later.
☐ The sympathetic and parasympathetic nervous systems regulate the heart response by either increasing or decreasing the heart rate or the contractility

Mechanism of contraction

As we know, there is an increase in calcium influx in phase 2 through slow calcium channels which triggers the release of more calcium from the sarcoplasmic reticulum.
Calcium binds to troponin on actin filaments. Tropomyosin then moves, exposing the binding sites for myosin.
Myosin heads bind to actin, generating power strokes. Each power stroke consumes 1 ATP.
Actin filaments are pulled toward the center of sarcomere, resulting in shortening of the sarcomere (sliding filament theory).
Ca+2 release channels in SR close and Ca+2 active transport pumps use ATP to get back to the state of low Ca+2 levels in sarcoplasm (Ca+2 moves back from cytoplasm to SR).
This in addition to other mechanisms , contribute for lowering Ca+2 concentration in cytoplasm from 10-5 to 10-7

When Ca+2 concentration decreases in the cytoplasm, Troponin-tropomyosin complex slides back into position where it blocks the myosin binding sites on actin, resulting in muscle relaxation.



Remember

o The sarcomere is located between two Z lines.

o The M line is at the center of the sarcomere.

o Titin filaments connect Z lines to each other, and they are called elastic elements of the muscle.

o The I band contains thin filaments only

o The A band is the whole length of thick filaments (including areas that overlap with thin filaments).

o The H zone contains only thick filaments.

o The H zone and I band shorten with contraction of the sarcomere, and they completely disappear in maximal contraction. The A band stays the same.

o Myosin filaments are composed of heavy and light chains. These light chains are phosphorylated by MLCK in smooth muscles, but NOT in cardiac or skeletal muscles.

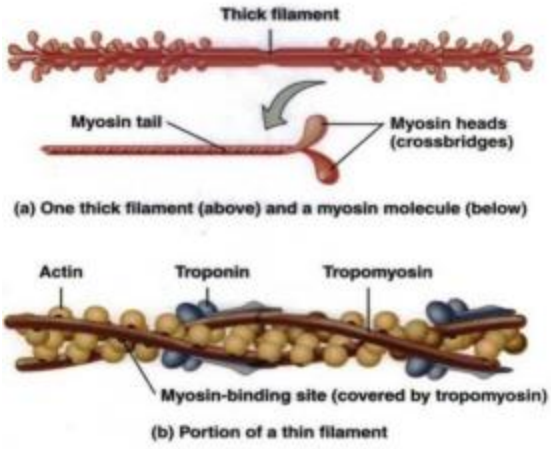
o Thin filaments are composed of actin, tropomyosin and troponin.

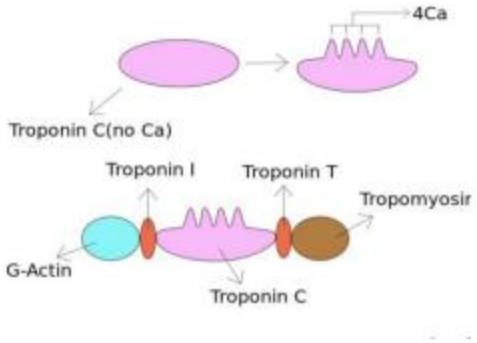
Troponin consists of three subunits:

-Troponin I (inhibitory),

-Troponin C (binds calcium),

-Troponin T (binds tropomyosin).





Cardiac muscle vs. skeletal muscle contraction

” Sliding filament hypothesis is The same

” No tetany in cardiac muscle (long refractory period because of plateau).

” Fatty acids are the main source of energy in cardiac muscle, unlike skeletal muscle which depends on aerobic and anaerobic glycolysis. However, cardiac muscle canalso use anaerobic glycolysis. {extra: Anaerobic metabolism in heart muscle plays a role in maintenance of myocardial preservation only during ischemia or hypoxia}.

” Attachment and detachment cycles and ATP dependency is The same

Contraction-relaxation cycle

The binding between myosin heads and actin occurs only when myosin heads are charged, meaning that they are bound to ADP+Pi after the hydrolysis of ATP. There also needs to be enough Ca+2 to bind to troponin C.

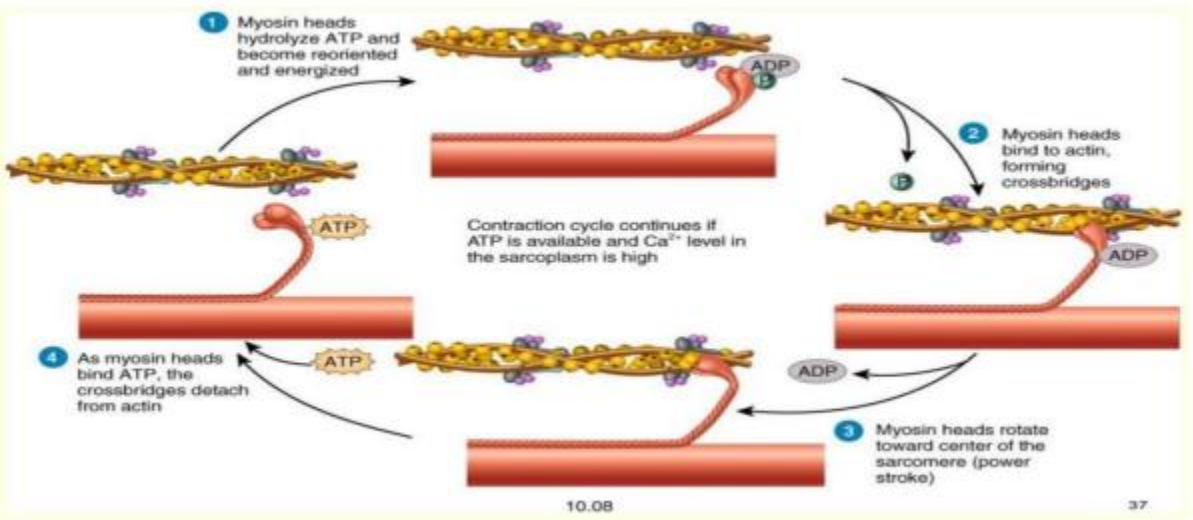
After the binding occurs, the ADP will be released, then the sliding of myosin heads generates a power stroke.

The myosin heads then detach, which also requires ATP.

The myosin heads are free again to bind another actin after hydrolysis of ATP, and a new cycle begin.

So, both contraction and relaxation require ATP.

After death, ATP is unavailable and the cross bridges cannot be broken, so the muscles remain contracted resulting in what is called rigor mortis.



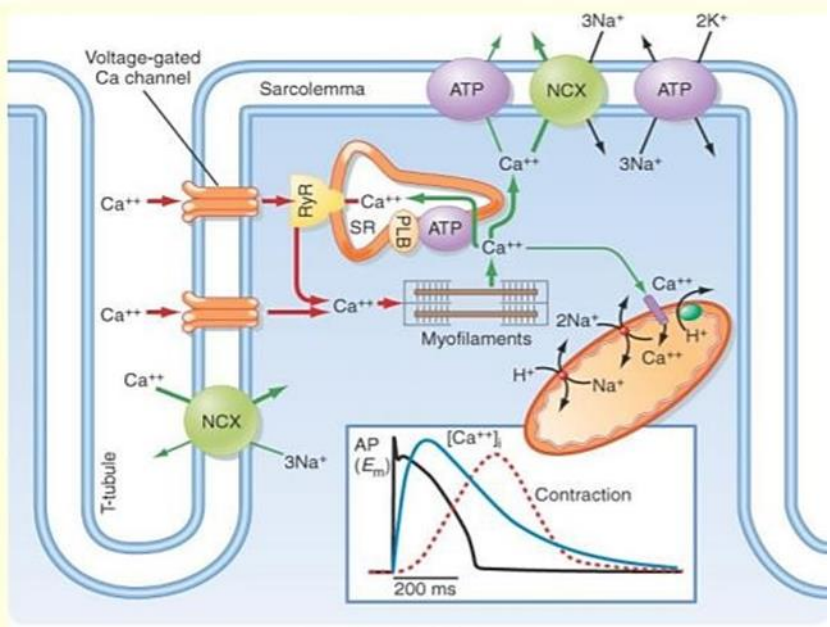
ATP stores that are found in the muscles are enough to supply energy for just three seconds. If creatine phosphate is used as a source of phosphate to convert ADP back to ATP by the enzyme creatine phosphokinase (CPK), enough energy will be provided for 10-15 seconds.

Sources of ATP:

1) Aerobic phosphorylation/respiration uses fatty acids (main source), amino acids from protein breakdown, and pyruvic acid from glycolysis (1 glucose = 36 ATP).

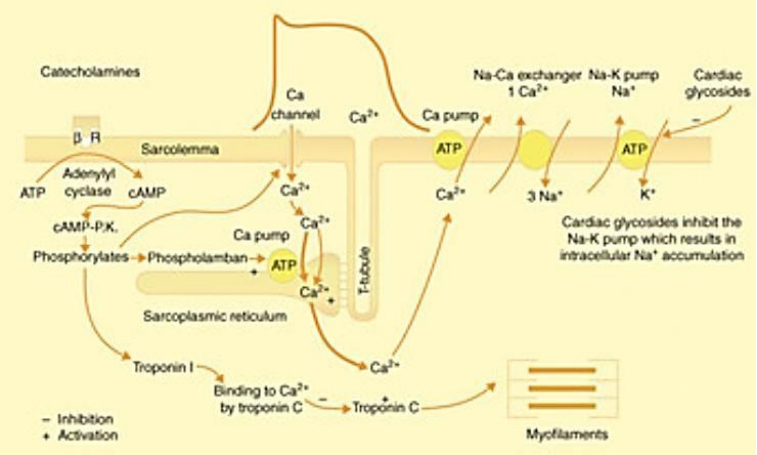
***75% of energy is released as heat.

2) Anaerobic glycolysis (1 glucose = 2 ATP).



This picture summarizes all the steps of 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 startswith 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*

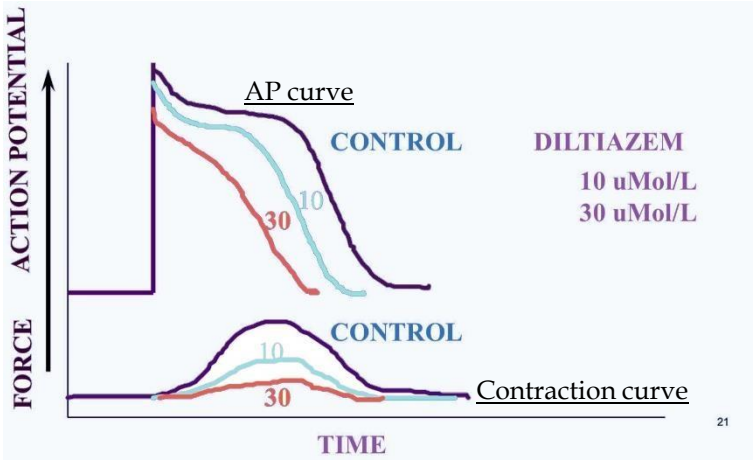
Regarding this subject:

***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

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

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



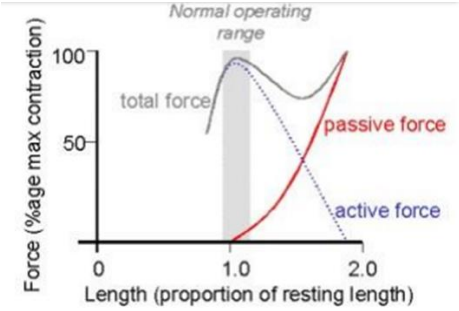
- DILTIAZEM it block at different concentrations
- 10 uMol/L
- 30 uMol/L
- giving them causes shortening ofthe plateau phase, and force of contraction decreases.

Length-Tension Relation for Skeletal Muscle ,,

This explanation is exactly from 19 sheet

The length-tension relationship in muscles refers to the effect of muscle fiber length on the amount of tension the fiber can develop.
X-axis: Muscle length in proportion of resting length (1 = 100% of resting length, 2 = 200% of resting length).
Y-axis: The tension that is produced during isometric contraction

This relationship is controlled by the Frank-Starling law, which states that, within physiological limits, an increase in the length of the muscle increases the tension (think of the tension produced in a rubber band as it is progressively stretched to longer lengths).



When the muscle is stimulated, the muscle will contract and shorten. But in order for this shortening to occur, the muscle should overcome the stretching force (the force that is pulling the muscle outwards).

The stretching force is called passive tension (or resting tension), and this tension ispresent during rest.
The tension developed when a muscle is stimulated to contract is called total tension.
The difference between the total tension and passive tension is called active tension (or developed tension),, It represents the active force developed during cross-bridge cycling.
Now, there are two peaks where we can get maximum total tension (notice the graph).
The first peak is when the muscle is at optimum length (resting length), which is at a sarcomere length of about 2.2 um. At this point, maximal overlap of thick and thin filaments and maximal possible cross-bridges are formed.

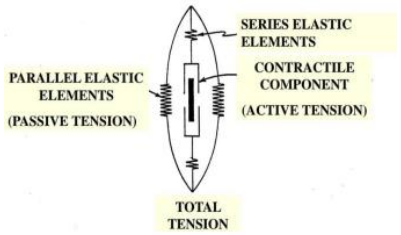
If the muscle is stretched beyond its resting length, the tension decreases. Why? Remember the titin filaments that we called elastic elements? When the muscle is stretched too much, these filaments will be relaxed (think of it as a spring), and the number of possible cross-bridges is reduced, so the active tension is reduced.

The second peak is when the muscle is stretched too much beyond its optimum length, so that the total tension becomes equal to the passive tension, and the active tension becomes zero (the rubber will eventually tear and will not be able to contract).

Notice that the active tension decreases linearly with increasing length.
Active tension cannot be measured directly. What can be measured is the passive tension and the total tension. Then we can find the active tension by subtracting passive tension from total tension (AT= TT - PT).

The figure aside shows the elastic elements (titin filaments)

- o When the muscle is stretched (beyond the optimal length), the series elastic elements and the parallel elastic elements become lax, so the active tension that can be generated is low.
- o Parallel elastic elements are responsible for the passive tension.
- o The contractile component is responsible for the active tension (when it contracts, the possible cross bridges that can be formed increases)



The figure below shows the active tension of the muscle. Notice that the number of cross bridges formed between myosin and actin increases with increasing muscle length until it reaches the optimal length, where the maximum number of possible cross bridges are formed (the max. active tension). When the muscle length exceeds the optimal length, the overlap between actin and myosin filaments decreases, so the number of cross bridges decreases and the active tension decreases