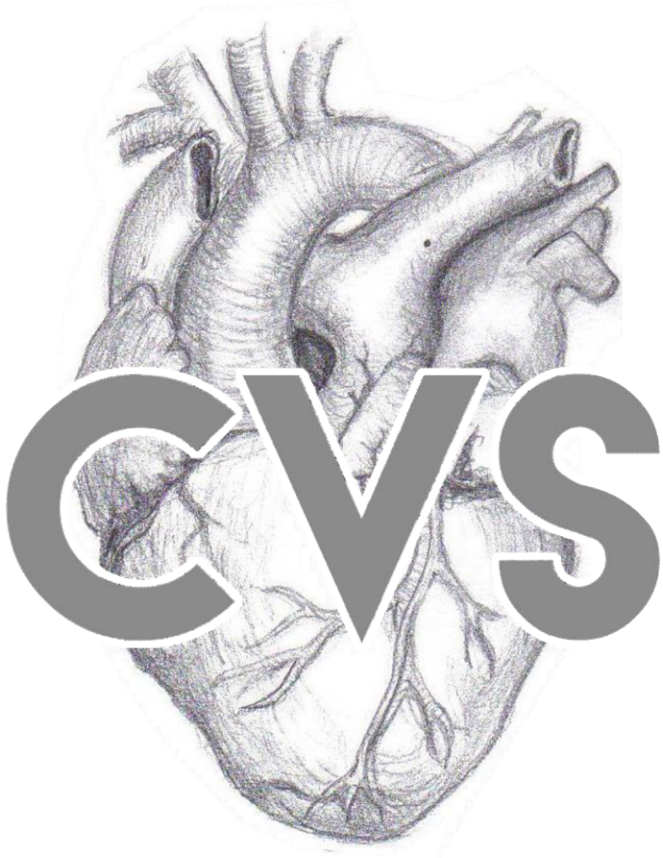

CVS

PHYSIOLOGY

☑ Sheet ○ Slide ○ Handout

Number

2

Subject

Cardiac Muscle Physiology

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Date: 19/10/2016

Price:

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***This sheet was written according to the recording of section 2.**

***Most of the points discussed during this lecture have already been mentioned in the first year physiology course.**

The anatomy of the heart:

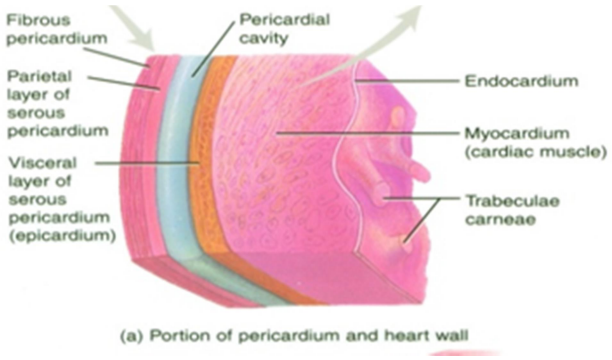
*** Cardiovascular system consists of two main parts:**

- Cardiac part → the heart.
- Vascular part → the circulations.

*** The main function of the heart** is to contract, the heart pumps the blood upon contraction, and this pumping activity results in the ejection of blood out of the heart, which is cardiac output.

- **Layers of the heart (from inside to outside):**

1) The endocardium :



(a) Portion of pericardium and heart wall

It's the epithelial layer of the heart. This layer is of great importance as it secretes hormones which are chemical substances that are important for regulation of blood flow. These hormones include:

- Endothelin: a local vasoconstrictor.
- Nitric oxide (NO) Or endothelium-derived relaxing factor: a local relaxing factor (a local vasodilator).

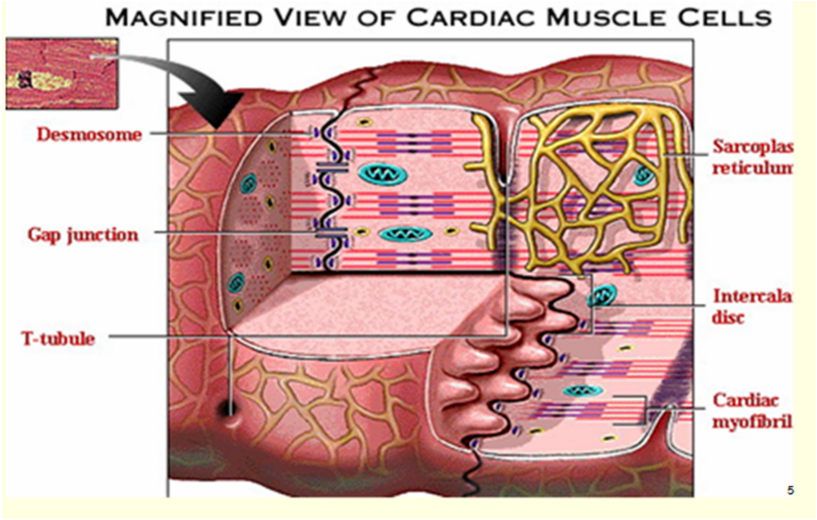
2) Myocardium:

Is the main layer and the most important layer in the heart, and consists of cardiac muscle cells.

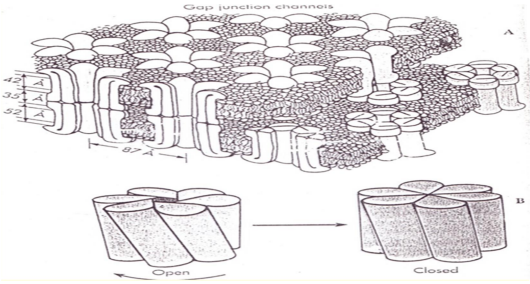
- **A comparison between <u>skeletal muscle cells</u> and <u>cardiac muscle cells</u> in terms of histological appearance:**

  I. Skeletal muscle cells are cylindrical (<u>spindle</u>) in shape, whereas cardiac muscle cells are <u>rectangular</u> in shape.
  II. Each skeletal muscle cell is separate from other cells, whereas cardiac muscle cells are interconnected (Interdigitating) through <u>*intercalated discs*</u>.

➢ Components of intercalated discs:
1. Macula adherence (desmosomes).
2. Zonula adherence.



3. Gap junctions: (couplers: they connect cells together) areas of low electrical resistance, they also described as *voltage-gated channels-like structures* as they open and close in response to changes in <u>voltage</u> in a certain cell. Moreover, they are sometimes called <u>electrical couplers</u> as they couple one cell to another by transmitting the action potential from one cell to another.



If there is a change in the membrane electrical potential of one cell, it will be transmitted to the adjacent cells through these gap junctions.
As shown in the figure, here are the gap junctions, they are <u>hexagonal</u> protein structures. They have two conformations (open & closed).

They open and close according to the change in voltage. Thus, they are voltage-gated channel-like structures.
➔ This results in functional syncytium in the heart
(They work as if they are one cell)
➔There are two syncytia in the heart:

1- Atrial syncytium.
2- Ventricular syncytium.

Note: There are other differences in the microstructure of skeletal and cardiac muscle cells and these will be mentioned later.

3) **Pericardium:**
The outermost layer of the heart and it consists of two layers and a space between them:
1. An outer parietal layer.
2. An inner visceral layer.
3. The pericardial space (cavity): this space resides between the parietal and visceral pericardial layers. This space usually consists of about 50ml of proteinaceous fluid. The role of this fluid is shock absorbance and protection of the heart from external damage like an accident for example.

- In a pathological condition called cardiac tamponade, the amount of fluid increases causing pericardial effusion. This pericardial effusion may limit the ventricular filling. Improperly filled ventricles won't be able to properly eject blood, in this case the oxygen supply will be reduced which leads to ischemia and hypoxia (infarctions…) in the peripheral tissues.
- If you diagnose cardiac tamponade, you have to quickly relieve the excess fluid using any tool you have. In hospitals, it's easy to use sterile syringes to evacuate the fluid, and if you are outside, you can use any sharp object to burst the chest wall and reach the pericardium to relief the pressure, because patients with cardiac tamponade are in a very bad situation, they suffocate and strive for air. Thus, we don't care about infections, but rather the life of the patient. Once relieved, the patient will be able to breathe easily.

Microstructure of the cardiac muscle cell:

The cardiac muscle cells contain the following structures:

1- Plasma membrane: plasma membrane of muscle cells including cardiac muscle cells is called the sarcolemma. This sarcolemma runs into transverse invaginations called T-tubules. These T- tubules are:

- ❖ Wider and shorter in cardiac muscle cells and they are located at the (Z) line.
- ❖ Longer, more cylindrical and thinner in skeletal muscle cells and they are located between the Z-lines.

- Note: The distance between two Z-lines is called Sarcomere. So, in the cardiac muscles we have only one T-tubule per sarcomere on the other hand in skeletal muscles we have two T-tubules per sarcomere.

2-Sarcoplasmic reticulum: (synonymous to Endoplasmic Reticulum)
This sarcoplasmic reticulum functions to store calcium necessary for contraction, and it is:
- Well-developed in skeletal muscle cells → which means that the calcium stored in the SR of skeletal muscle is enough to initiate contraction.
- Not well developed in cardiac muscle cells (Its storage of calcium is not enough to initiate contraction) → which means that we need extracellular calcium in addition to the calcium stored inside the SR to initiate contraction.

- **NOTE** that it was accidentally discovered by scientists that the heart requires extracellular calcium to contract when they were trying to figure out what is the perfect solution to maintain a functional heart during heart transplantation surgery.
- **Historical note:**
  Christiaan Neethling Barnard: he performed the world's first successful human-to-human heart transplant (1967).
  And it was only in the 1980s when they discovered the slow voltage-gated calcium channels on the sarcolemma of the heart. Calcium enters through these

voltage-gated calcium channels and induces calcium release from the SR in a process called calcium-induced calcium release. “Will be discussed later”.

3- Other differences in the microstructure of cardiac and skeletal muscle cells is in the number of mitochondria: Their number in cardiac muscle cells is much higher than their number skeletal muscle cells, and this makes sense as cardiac muscle is all the time contracting and requires high amount of ATP which is mainly generated in the mitochondria through oxidative phosphorylation.

4- The number of nuclei → the skeletal muscle nuclei are much more numerous and peripherally located, whereas those of the cardiac muscle cells are much less numerous (one nucleus per cell) and they are centrally located.

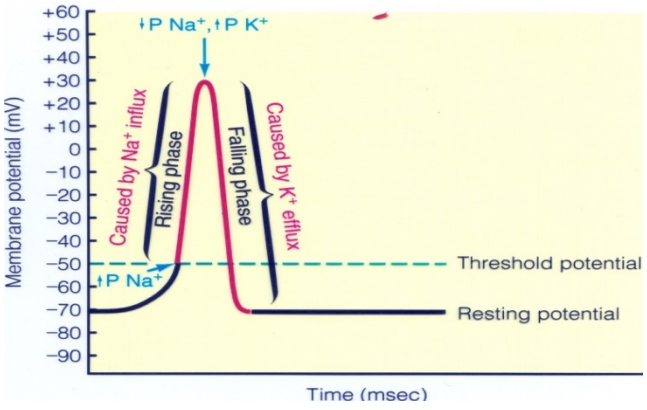
❖ Action potential

Understanding the action potential is important to understand the ECG (electrocardiogram) as it stems from the action potential.

I. Permeability changes and ionic fluxes during an action potential (skeletal muscle)

From an action potential of a skeletal muscle cell, you can notice the following:

1. Resting membrane potential of skeletal muscle cell is low (-70).
2. There are only two phases:
   - Depolarization phase (rising phase).
   - Repolarization phase (falling phase).

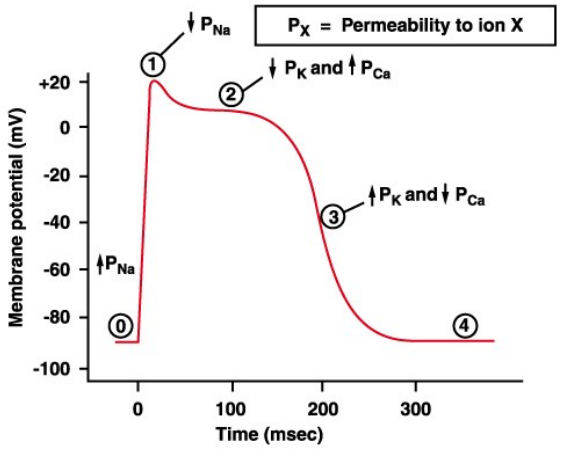


- Depolarization occurs as a result of the opening of fast voltage gated sodium channels.

- Repolarization occurs as a result of opening of fast voltage gated potassium channels.

3. The duration of an action potential is very short, much less than 10ms → sometimes reaches 0.1ms. (ms: milliseconds)

II. Action potential of cardiac muscle has 5 phases:



1- Phase (0) → fast depolarization phase (common in skeletal and cardiac muscles)

2- Phase (1) → partial repolarization: due to transient opening of K^+ or Cl^- channels (in cardiac muscle only)

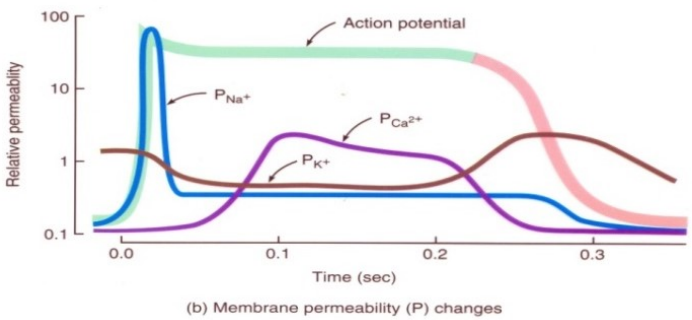
3- Phase (2) → plateau: due to opening of slow voltage-gated calcium channels (only in cardiac muscle).

The importance of this phase is to increase the duration of action potential "prolonging depolarization" of cardiac muscle → protects against tetanisation.

4- Phase (3) => repolarization phase.
5- Phase (4) => resting phase.

❖ Changes in permeability of ions during these 5 phases :

* During phase (0) there's an increase in the permeability (conductance) of the cell membrane to Na+ and this's convenient since this ion is responsible for the firing action in this phase.



(b) Membrane permeability (P) changes

**Also, there's a decreased permeability of k+ in phase (0) and early phase (1) and this's very important in the maintenance of the plateau in the next phase.
Then, K+ permeability starts to increase in phase (3).

***The peak conductance of Ca^{++} is during phase (2).

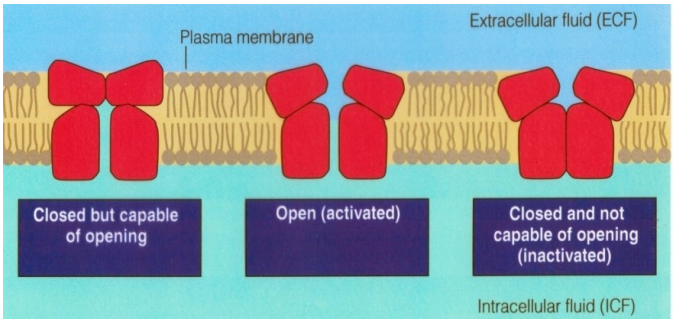
NOTE: the membrane potential is actually a result of a balance between all ions mentioned, not only one. For example, for the plateau to be accomplished we need to achieve a decrease in Na^{+} influx, K^{+} efflux and an increase in the Ca^{++} influx. If one of them is disrupted we won't get the plateau. For example if the decrease in K^{+} efflux wasn't accomplished "wasn't lowered in Phase (2)", this will over-balance the Ca^{++} influx and make the intracellular compartment more negative, and this will deteriorate the plateau "make it very short if it wasn't gone completely" by decreasing membrane potential.

So to sum up the differences in action potentials between skeletal and cardiac muscle:

1- Resting membrane potential of skeletal muscle is -70 mV, whereas it's about 85-90 mV in cardiac muscle. (More negative in cardiac muscles).
2- The duration of action potential in cardiac muscle is about 200-300ms (it may reach up to 400ms) whereas in skeletal muscle it's about 10ms as mentioned earlier.
3- In cardiac muscle action potential there's a plateau that is absent in skeletal muscle action potential.

Now regarding fast voltage-gated Na+ channels:

They have a special feature that enables them to function properly during action potential:
each one has 2 gates; M gate (activation gate) and H gate (inactivation gate)
During resting state, M gate is closed and H gate is opened. However, as long as one gate is closed Na+ won't enter the cell. (Even there is electrochemical gradient for sodium).



During depolarization, when membrane potential becomes less negative => M gate (Activation gate) opens very fast and consequently H gate (Inactivation)starts to close at a lower speed. This difference in timing gives Na+ ions a small window of time to escape down their electrochemical gradient (influx of Na^+). So, we will have depolarization until we reach the overshot and by that time the H gate will be closed and no more Na^+ influx occurs.

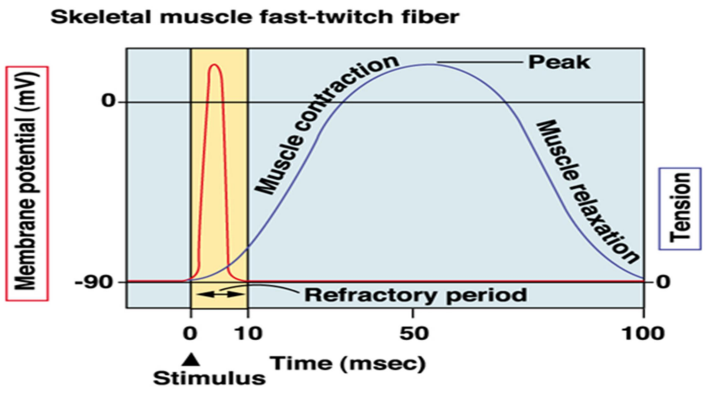
Absolute refractory periods and tetanisation

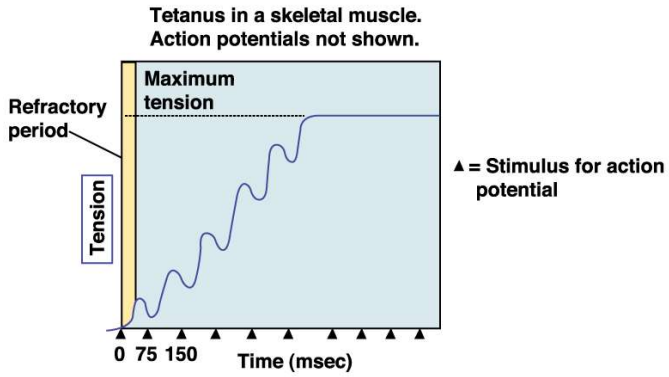
- Another difference between cardiac muscle action potential and skeletal muscle action potential is the absolute refractory periods which is much longer in cardiac muscle and extends from the beginning of the action potential till half-way of repolarization leaving the cardiac muscle membrane (sarcolemma) unresponsive to any stimulus.

- This is very crucial to life since this will protect cardiac muscle from tetanisation which may occur in skeletal muscle when stimulated repeatedly.

- The action potential is followed by contraction and relaxation of the muscles.

➔ The whole skeletal muscle action potential occurs in the latent period before the contraction starts. Thus, you can induce another and another action potentials before the relaxation of the muscle (and even before the contraction of it) which results in repeated contractions of the skeletal muscle to an extent when the high frequency of action potentials will result in complete contraction with no relaxation.

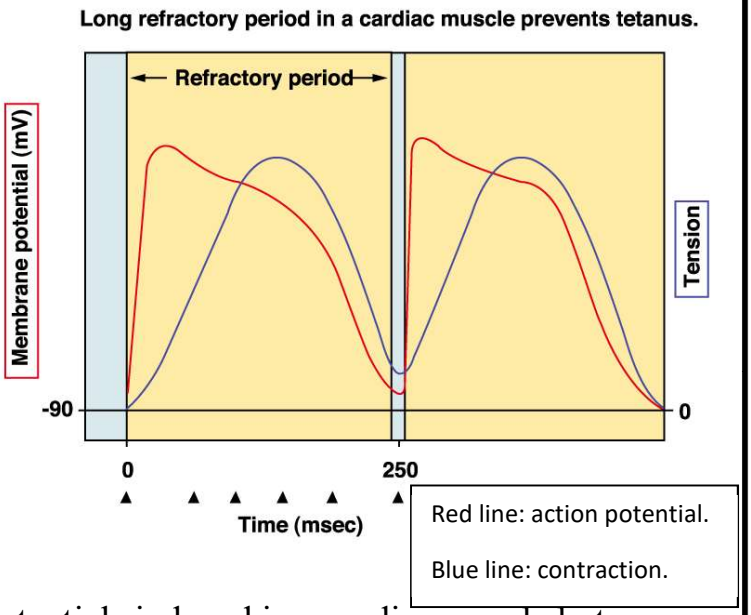




This mean that If there's another action potentials in the latent period, this will induce repeated contractions without giving a chance for the muscle to relax

which results in the summation of mechanical contractions and you might reach a stage when the muscle stays contracted and tetanisation occurs.

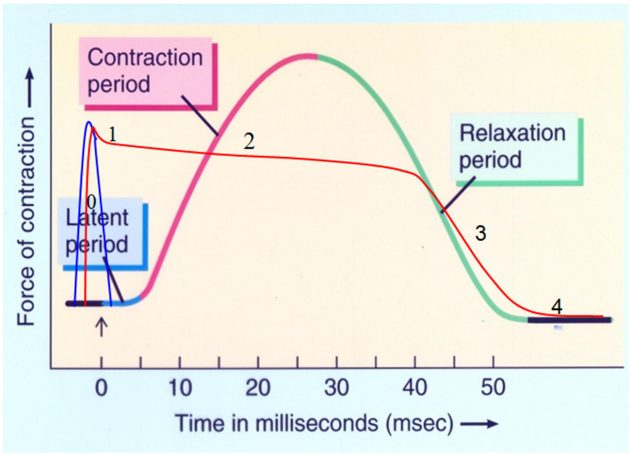
➔ While in cardiac muscle, thankfully, the long absolute refractory period in which the sarcolemma is unresponsive to any stimuli gives the muscle the enough time to relax before responding to another stimulus and contract again. So tetanisation won't occur.
We will never have summation during contraction only during relaxation, so the cardiac again won't tetanize.



Red line: action potential.

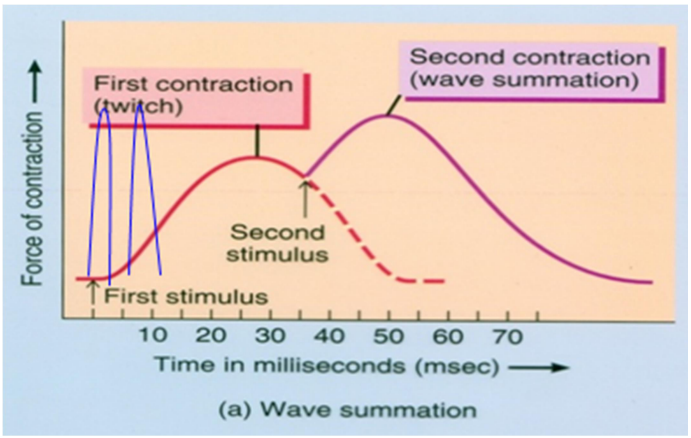
Blue line: contraction.

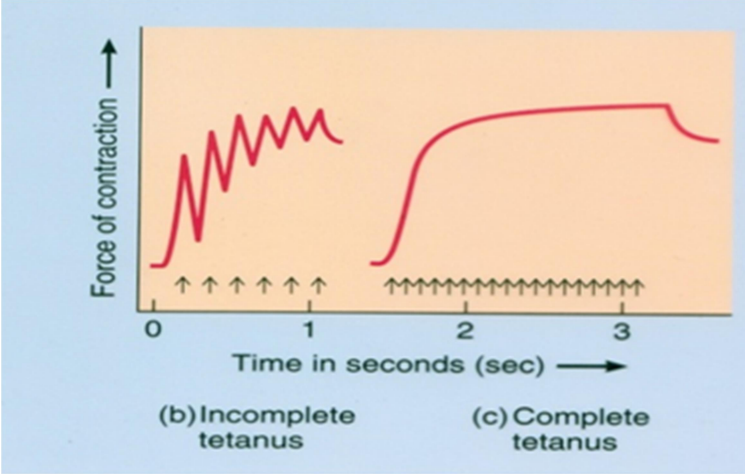
In the figure above, we have two action potentials induced in a cardiac muscle but actually when you induce the later action potential, the cardiac muscle is already relaxed and ready to contract again. Thus, there's no tetanus in cardiac muscle.



As you can see in the figure, the absolute refractory period overlaps with the relaxation phase of cardiac muscle.

Here is a skeletal muscle stimulated twice but with a small period of time between the two successive stimulations permitting some relaxation in the muscle.



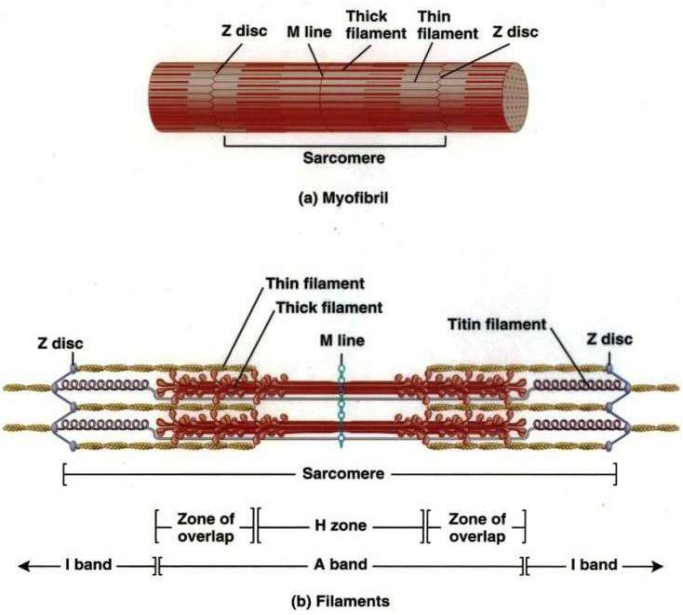


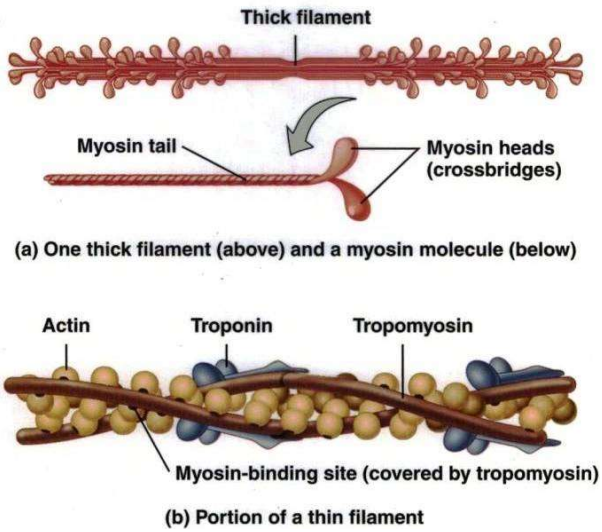
❖ In case (B) there's incomplete tetanus. i,e, there's some relaxation.

❖ In case (C) there's complete tetanus results in fatigue due to the high frequency of successive stimulations unlike case (B).

❖ The structure of sarcomere:

The area between the two z lines is the sarcomere (the functional unit of a muscle filament) and inside each sarcomere are the thick filaments and the thin filaments overlapping each other to produce muscle contraction, in addition to the elastic filament (titin) that is not part of the contractile proteins and exists in both skeletal and cardiac muscles (striated muscles).





a) Here is a thick filament that is composed of myosin. The myosin heads can bind actin when it's charged (charged means that it's bound to ADP + Pi). These heads bind at myosin-binding site as soon as these binding sites are uncovered by tropnin C-Ca++ complex.

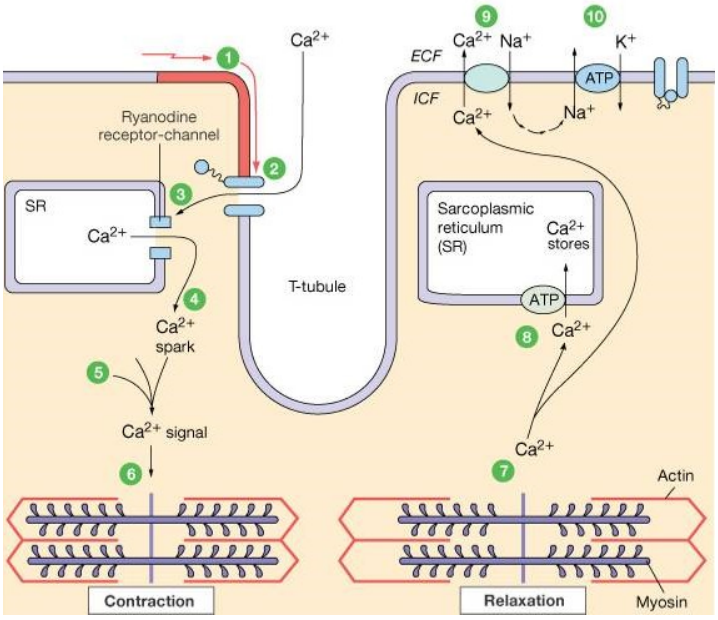
b) Portion of a thin filament appears as a double helix and composed actin, tropomyosin and troponin C which covers the myosin-binding sites "on the actin".

Mechanism of cardiac muscle excitation, contraction and relaxation:

FIRST: Excitability

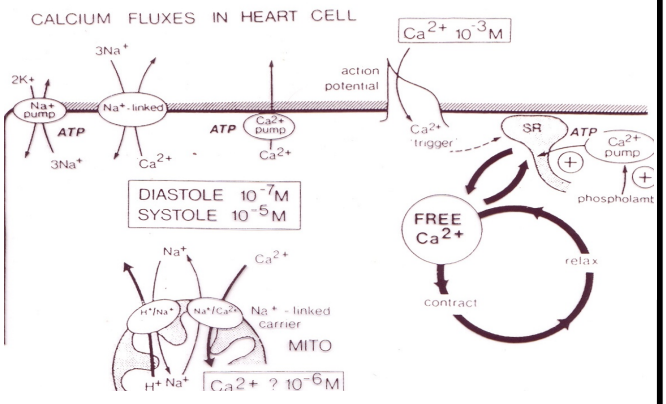
In systole, As the action potential reaches the cell this will triggers an increase in Ca^{++} influx with its concentration gradient due to the activation of slow voltage-gated Ca^{++} channels in the sarcolemma during phase (2), (hence, [Ca++] extracellularly is 10^{-3} while intracellularly is 10^{-7} and during systole "cardiac muscle contraction") the intracellular concentration of Ca^{++} will increase to reach 10^{-5}. (We care here about the ionic calcium not the bound).

Consequently, calcium ions which entered to the cell will activate a ryanodine receptor-channel in the membrane of the sarcoplasmic reticulum so as to permits the exit of further Ca^{++} from intracellular storages (Sarcoplasmic reticulum). This is called **"calcium-induced calcium release"** which means that Ca^{++} ions which came from outside the cell trigger further release of intracellular Ca^{++} in order to accomplish the Ca^{++} spark needed. After that Ca^{++} ions bind to troponin and muscle contraction occurs. "Will be discussed later".



Now, in diastole (relaxation) ➔ Ca++ intracellularly has to be decreased again through:

1- Ca++ pump on the sarcoplasmic reticulum (not the sarcolemma) (Ca++_ATPase) and this pump is exclusively regulated by a protein called phospholamban (sarcoplasmic reticulum membrane protein) that once phosphorylated by ATP it will activate this pump and enhances its efficiency in reuptaking Ca++ to SR.



A very important note:

The protein is an inhibitor of cardiac muscle sarcoplasmic reticulum Ca^{++}-ATPase (SERCA) in the unphosphorylated state, but inhibition is relieved upon phosphorylation of the protein.

"Wikipedia"

2- Na^{+}_Ca^{++} exchanger which exchanges one Ca^{++} ions go outside for each three Na^{+} ions enter the cell (electrogenic pump leads to the accumulation of charges across the plasma membrane "sarcolemma") this is where certain drugs act. "Not the calcium channel blockers since they block the slow Ca^{++} channels".

- Inotropic agents: Can block the Na^{+}- Ca^{++} exchanger. So, they can induce inotropic action.

3- Ca^{++} pumps in the sarcolemma.

Inotropic:

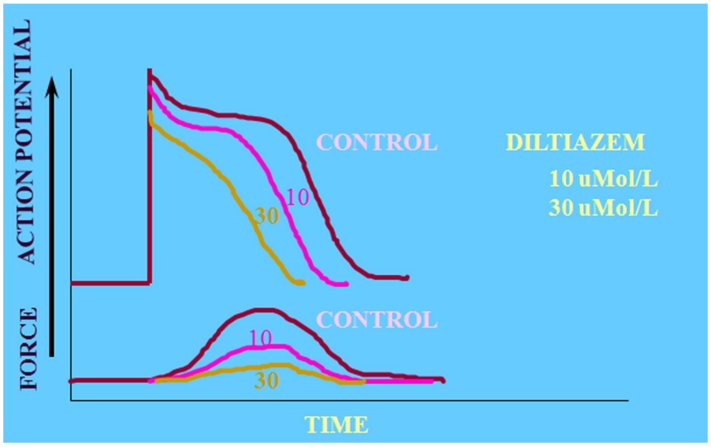
Modifying the force or speed of contraction of muscles.

"*Google translate*".

REMEMBER: Ca^{++} pumps in the sarcolemma have a high affinity and low capacity. i,e, capable of working at low concentrations of calcium but does not transport too much Ca^{++}. On the other hand, Na^{+}- Ca^{++} exchanger in the sarcolemma have low affinity and high capacity.

NOTE: All of the previous mechanisms utilized to normalize Ca++ concentration intracellularly after systole (i,e, the two pumps and the exchanger) work under physiological conditions. In some instances, when the intracellular concentrations of calcium rises (pathological state) beyond the capacity of these mechanisms, Na+ - Ca++ exchanger in the membrane of the mitochondria take part of the job and start functioning.

❖ **Effects of slow Ca++ channel blockers and the cardiac cell action potential:**



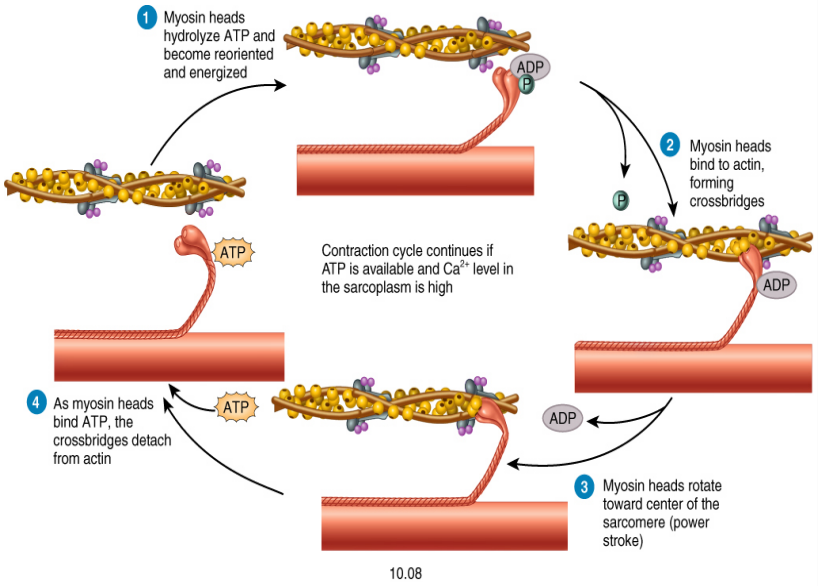
The figure shows the effects of two different doses of the drug **DILTIAZEM** (10 & 30) which works as a Ca++ channel blocker. This drug will affect both the action potential and the force of contraction. And if we, theoretically, use high doses of this drug, we will convert the action potential of the cardiac muscle into an action potential of skeletal muscle due to the complete block of Ca++ channels.

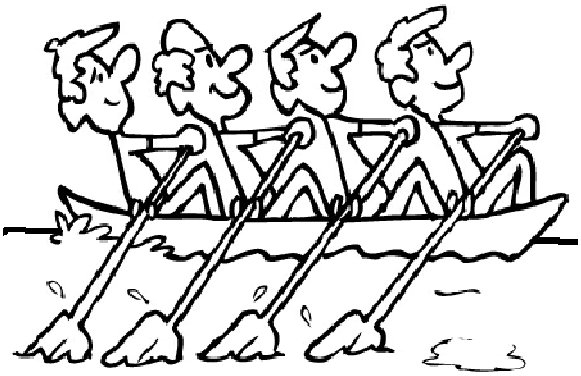
Let's take a look at pharmacodynamics of this drug more extensively; this drug will block the slow voltage-gated Ca++ channels. And as we said earlier, the importance of these channels rises in the maintenance of plateau. So, if we block these channels we are letting the K+ currents (efflux) to have the upper hand in determining the polarization of the membrane so that the repolarization in phase 3 will come earlier and the plateau will end soon making the action potential shorter in duration.

#NOTE again, what we care about here in determining the membrane potential is the ionic Calcium (Ca++)

SECOND: Contraction

When calcium concentration increases in the sarcoplasm, two Ca^{++} ions will bind to troponin C on the actin filaments. This complex troponin C-Ca++ causes the tropomyosin to slide over actin filament and unblock the Myosin-binding sites. This will induce a hydrolysis in the ATP on the myosin heads (power strokes) and the utilization of this energy to rotate the heads toward their binding sites on actin and pull the thin filament toward the centre of sarcomere causing a shortening in it. The myosin heads will remain attached to the actin filament until another ATP molecule comes and detach them. (1 Power stroke … 1 ATP).





And then the myosin will come to another actin bind it, moves inside and so on…

We call it **Rowing**.

- rigor mortis: stiffening of the joints and muscles of a body a few hours after death, because of lacking ATP that's needed to detach myosin from actin >>> permanent contraction.

Sources of ATP for muscle contraction:

1- ATP from creatine phosphate (enough for only 10 seconds).
2- ATP from anaerobic respiration “glycolysis”. (Not good source of energy “1 glucose gives only 2 ATP”).
3- ATP from aerobic cellular respiration “oxidative phosphorylation” (the best source).

So for example,

*100 meters runners use creatine phosphate as a source of energy.

* 400 meters runners use anaerobic glycolysis and creatine phosphate at the end.

* But for marathons’ runners, the main source of energy is oxidative phosphorylation.

The end

كُن بسيطًا وَ مسالمًا إلَّا بأحلامك، انتزعها من يد الحياة بقوَّة.