The Cardio-VASCULAR System

- ○ Anatomy
- ○ Histology
- ○ Pathology
- ○ Pharmacology
- ● Physiology
- ○ Microbiology

Lec #: 2

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Done By: أسامة أبو شاور

- ○ Handout
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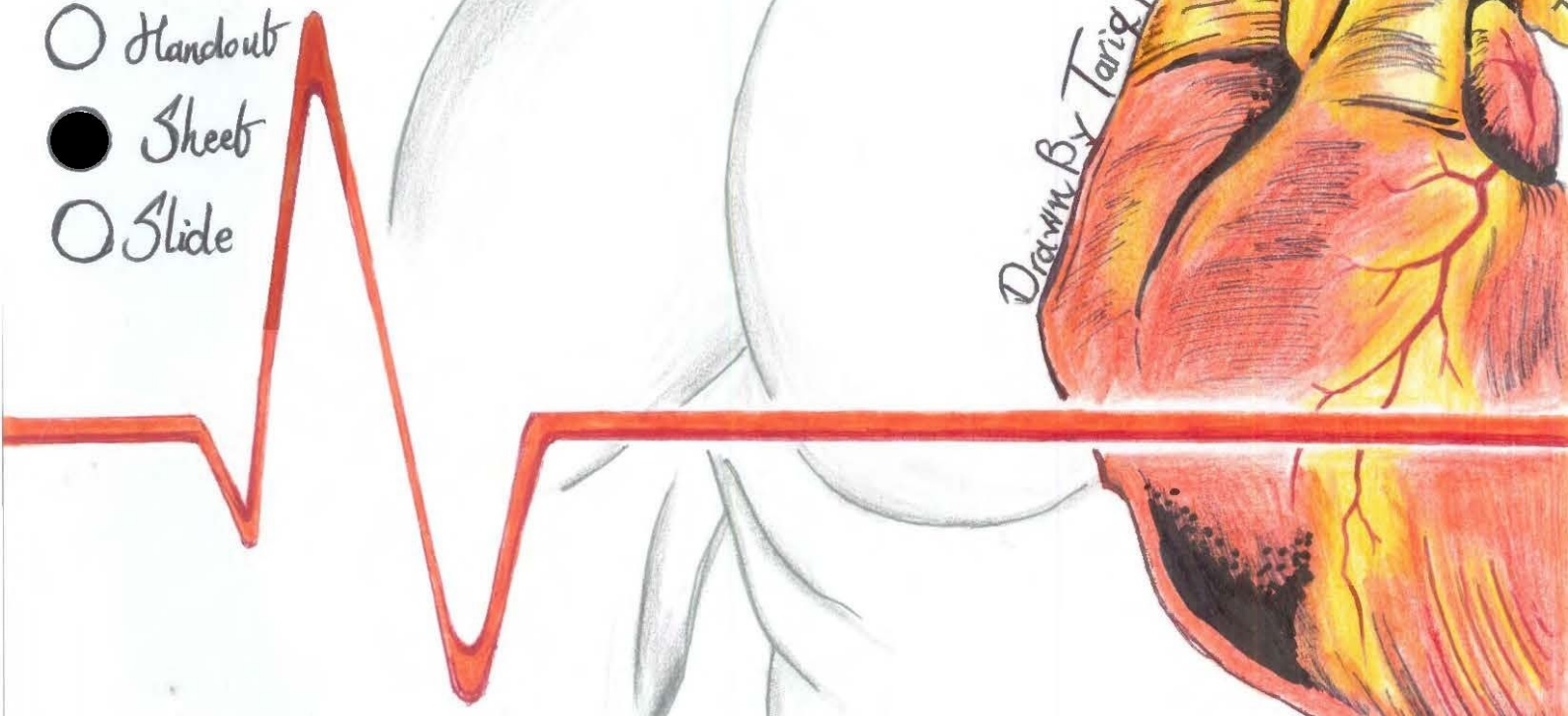


بسم الله الرحمن الرحيم

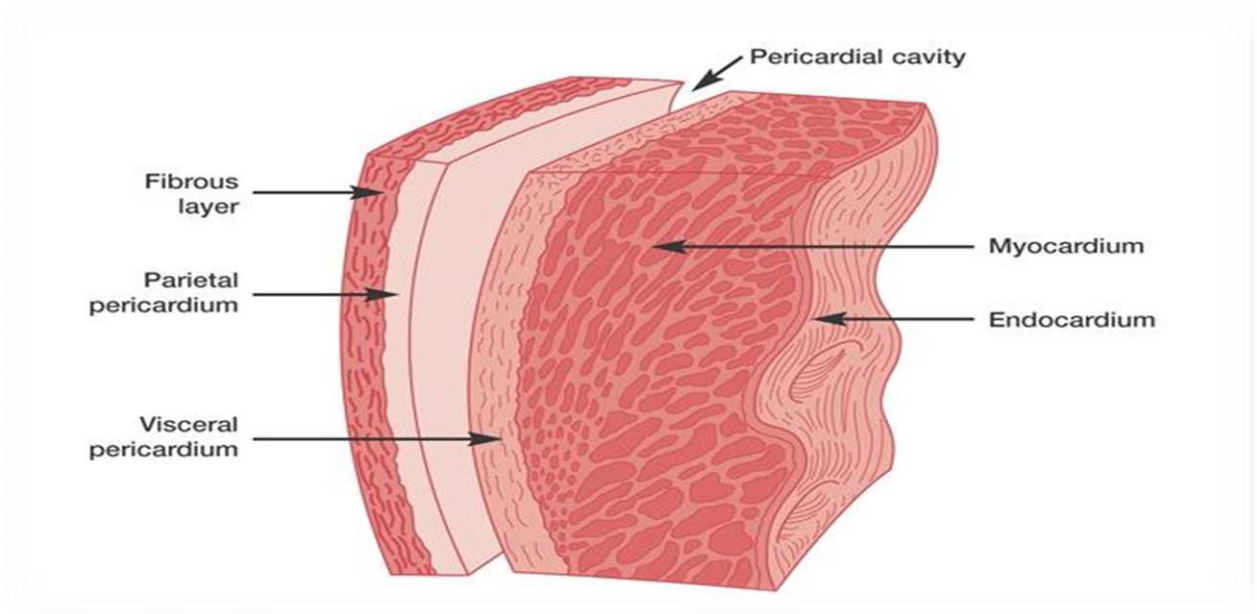
Cardiac muscle physiology

Introduction:

The heart is the center and the pump of the cardiovascular system by the action of its muscle layers; it pumps blood to the circulations.

We have two circulations: The greater circulation that distributes the blood to all over the body and is also called systemic because it distributes the blood to all systems except the lungs that receive blood through the lesser (or pulmonary) circulation.

The wall of heart has three layers: (from inside to outside)



1. Endocardium (innermost layer, epithelium)
(Note: the epithelial layer of the vessels is called endothelium). Endocardium is very important and has many functions: control blood flow, protection. It secretes certain substances that control blood flow to the heart and to the tissue ex: nitric oxide (vasodilation) or Endothelin that causes local vasoconstriction.

2. Myocardium (major layer, Muscle) >> later.

3. Pericardium (outermost layer), two layers: Visceral (close to the heart), and Parietal with the pericardial space between them which contains a fluid for protection. This pericardial fluid is very important, since it acts as a shock absorber and it protects the heart from the injuries that might occur because of certain movements.

Written by Osama Abu-Shawer

This condition where the pericardial fluid has increased too much to the extent that it limits the filling too much is called Cardiac tamponade. The pericardium space limits the filling so if we put too much fluid in the space there will be a limit to the filling >> the filling might reach zero >>so the cardiac output will equal zero >> which leads to death!!

A comparison between Skeletal and Cardiac Muscle:

(very important)

- Skeletal muscles are spindle in shape and start from the origin to the insertion so they are long, while the cardiac muscle cells are rectangular in shape and smaller.
- Both are striated due to the presence of sarcomeres that contain contractile muscle fibers (proteins). There are four types of contractile proteins: **Myosin** forming the thick filaments and the thin filaments are three types: **Tropomyosin** forming the double helical line to which **actin** "beads" are connected and we have **Troponin**.

- Skeletal muscle cells are not connected to each other, and motor nerves supply a number of fibers to cause their contraction (a motor unit). While cardiac muscle cells are connected with each other by intercalated discs with gap junctions between them. The gap junctions conduct electricity from one cell to another; so they form low resistance areas, and they open or close as response to a change in voltage (voltage-gated channels). When they open the ions move from one cell to another fast, and thus cardiac muscles are electrically coupled. Any change (action potential) in one cell spreads into all cells (in the same syncytium) at the same time through gap junction.

Notice the desmosomes between intercalated discs that serve to bind cardiac muscle cells firmly together to prevent their pulling apart in contraction.

This electrical change (action potential) is followed by a mechanical change (the contraction), and since the cells receive the action potential at the same time they contract at the same time as one unit and the heart will work as a pump. Pathologically, if each cardiac muscle cell contracts by itself (Atrial or Ventricular fibrillation) the heart will not function and ventricular fibrillation will cause death. Gap junctions are hexagonal proteins with an open and a close conformation.

- Skeletal muscles are voluntary; it cannot contract unless it is innervated. While cardiac muscles are involuntary; supplied by the autonomic nervous system (sympathetic and parasympathetic). This innervation of the cardiac muscle is not important for the initiation of cardiac muscle contraction (during cardiac transplants the autonomic supply is cut but the heart is still running).

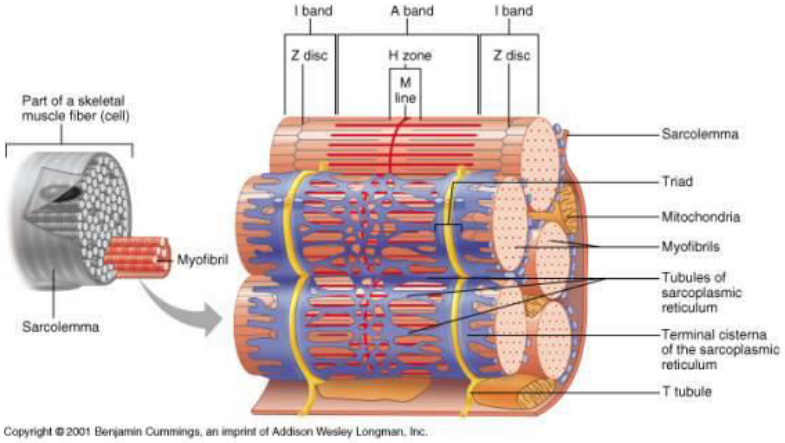
- Skeletal Vs Cardiac muscle:

The plasma membrane: sarcolemma SL

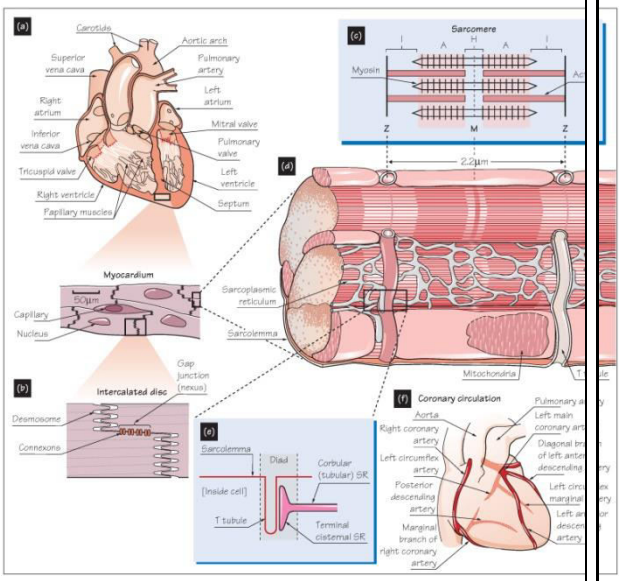
The endoplasmic reticulum: sarcoplasmic reticulum (smooth not rough) SR.

The cytoplasm: sarcoplasm.

- The sarcolemma of cardiac and skeletal muscles has deep invaginations called the T-tubules or transverse tubules. The T-tubules of skeletal muscles is slender, longer and occurs in the I band so each sarcomere has two T-tubules, while in the cardiac muscle they are wider and shorter and occur at the Z line (disk) so each sarcomere has one T-tubule. The sarcomere is the distance between two Z lines.



Skeltal muscle, two T-tubules per sarcomere

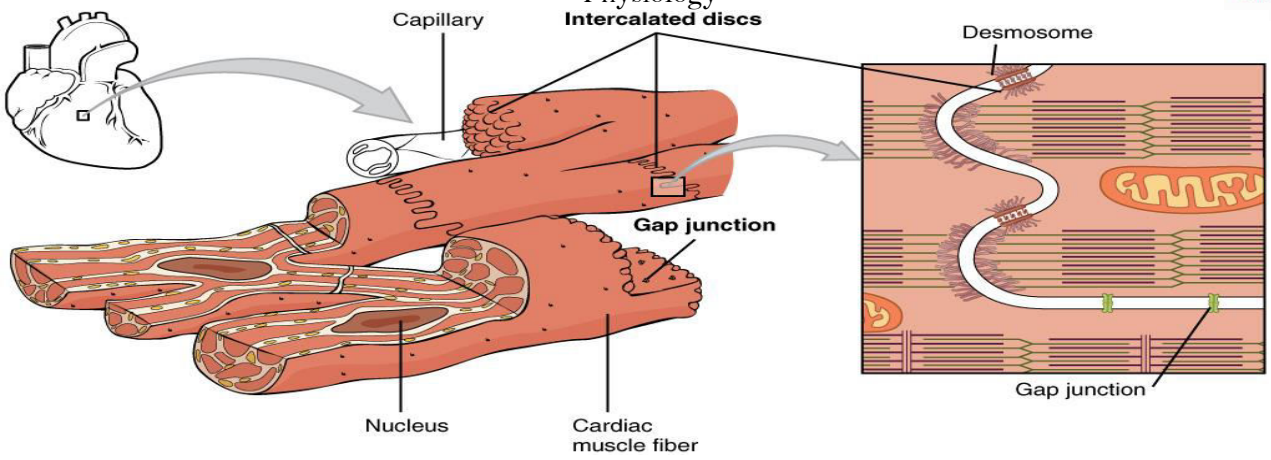


Cardiac muscle, one T-tubule per sarcomere at Z line

- The sarcoplasmic reticulum (which stores Ca++) in the skeletal muscle is well-developed, while it is less developed in the cardiac muscle so the cell doesn't store enough Ca++ for its contraction and needs an extra source of Ca+ from outside (extracellular fluid around cells – interstitial fluid). That's why during heart transplant, the heart is put into a solution with Calcium.

- Cardiac muscle is contracted all the time which requires more energy, that's why it has lots of mitochondria to provide ATP compared to skeletal muscles that, on the other hand, have much more nuclei.

Written by Osama Abu-Shawer



-The gap junctions are low electrical resistance areas, which means that if there's any potential change in one of the cells, this potential change spreads to the other cells very fast to the extent that if there's an action potential in one of the cells, the action potential will spread to ALL cells that are connected with these gap junctions at the same time. And this is very important, if these cells depolarizes at the same time it means that they will contract simultaneously (at the same time)… and this is very important for the heart to have a simultaneous contraction because if a part of the heart was contracted and another part was relaxed the force that's formed by the contraction is going to be relieved by the relaxation and thus no force will emerge!

For example if the left ventricle contracted and the right ventricle relaxed, the force coming from the left side contraction will go to the right side and no blood comes out of the ventricles! But if both ventricles contracted at the same time the blood has no other option but to get out of the ventricles, so this is very important that the ventricles contract at the same time. This is what we call an Effective pump.

Sometimes the gap junction is called the electrical synapse, since it's a synapse (connection) between cells but it's also electrical synapse not chemical synapse.

Now, the muscles of the atria are separated from the ventricular muscles by the atrioventricular septum. The atrial muscles themselves are connected to each other. The ventricular muscles are also connected to each other. So we have two syncytia, atrial syncytium and ventricular syncytium. We have two pumps, atrial pump and ventricular pump. Thus both atria contract simultaneously, and both ventricles do as well. Normally, potentials are not conducted from the atrial syncytium into the ventricular syncytium directly. Instead, they are conducted only by way of a specialized conductive system called A-V bundle, we'll discuss it next lecture.

Recap (Cardiac muscle characteristics):

- Cardiac muscles show Syncytium structure because cells are connected to each other by gap junctions. They function as one unit.
- Gap junctions are electric couplers, which mean that they connect one cell to the other. And they're of low resistance.
- Poorly developed SR in contrast to the skeletal muscles that contain well developed SR.
- Transverse (T)Tubules are located on the Z-line (i.e.One T-tubule per sarcomere)
- Rich in mitochondria
- Low in nuclei

'Learning medicine without understanding can be a torture, but with clear concepts it becomes fun and pleasure'..... Dr. Najeeb

BTW, his lectures on cardiac physiology are highly recommended for us, try them with a cup of green tea as our kind-hearted friends (Mamoun & Saeed) do.
So the golden way for studying Cardiac physiology (and the decision for you):
Dr. Najeeb >> BRS Ch3 >> Slides + PPQ >> Exam

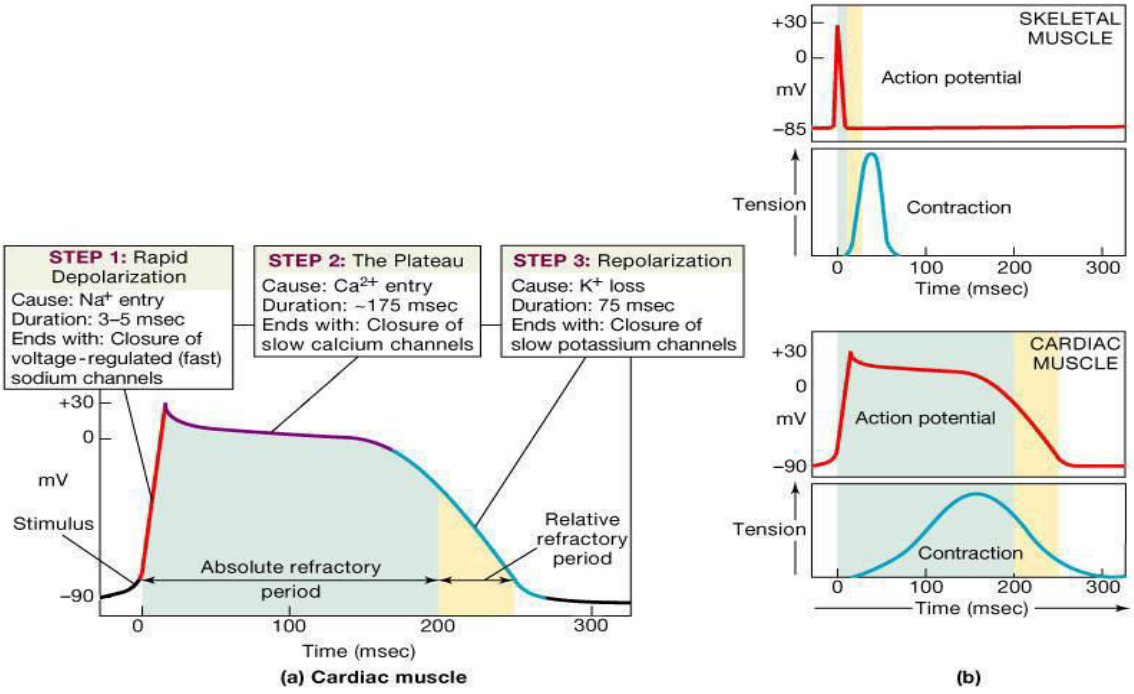
Action potential of skeletal muscle

- Resting stage due to K+ diffusion starts at -70 (negative intracellular related to extracellular).
- Slow depolarization till it reaches the threshold.
- Fast depolarization (firing stage) due to the fast open Na+ voltage gated channels.
(Trying to reach the equilibrium potential for Na+ {+61} but it doesn't get there because other ions are involved).
- Repolarization (falling stage) due to opening of K+ channels.
- Very short (between 1 msec to 10 msec maximum)

Action potential of cardiac muscle

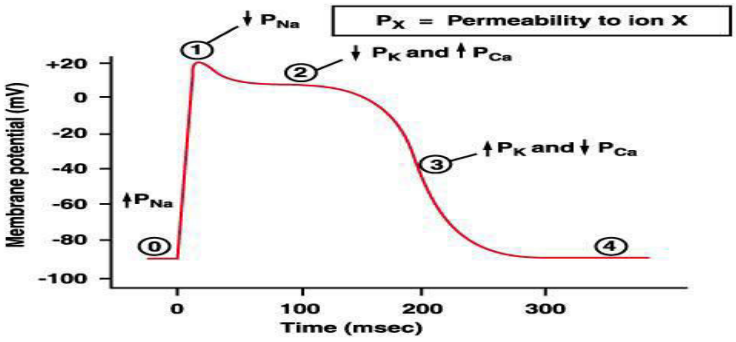
- The resting membrane potential is -90mV (more negative than in the skeletal muscle). Phase 4.
- Fast depolarization is due to the opening of Na+ voltage gated channels. Phase 0.
(There's an increment in the permeability of Na+ and decrease in the permeability of K+ >>during resting stage K permeability 100 times more than Na permeability).
- Partial repolarization is due to the opening of transient K+ and Cl- specialized channels. Phase 1.
- Plateau (maintaining depolarization) is due to slow opening of Ca+ channels, Ca++ influx . Phase 2.
(This induces releasing Ca+ from SR and this process plays the main role in contraction and this process called "Ca induced Ca release").
- Repolarization is due to the opening of very fast K+ voltage gated channels. Phase 3.
- Return to resting stage by Na diffusion, K diffusion and Na-K pump for the rearrangement of ions. Phase 4.
- Longer, occurs in about 200 – 400 (normally 300 msec) thanks to the long refractory period (an absolute refractory period from the beginning to half of the repolarization stage where the muscle cannot contract)

https://www.youtube.com/watch?v=rIVCuC-Etc0



The changes in ions permeability during the cardiac action potential:

- Phase zero: we have very high conductance for Sodium (through voltage gated channels) and goes down during phase 1.
- At the end of phase 1 there's a decrease in potassium permeability, and this doesn't occur in skeletal muscle.
- At the same time there's an increase in the permeability of the cell to calcium. Note: if there wasn't a decrease in the cell permeability to potassium, there will be no maintenance for the depolarization because Ca+2 that comes in will be neutralized by the Potassium that gets out, so it is important to maintain the plateau.
- Then during phase 3 the potassium permeability increases (through voltage gated potassium channels)



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

Summation and tetany:

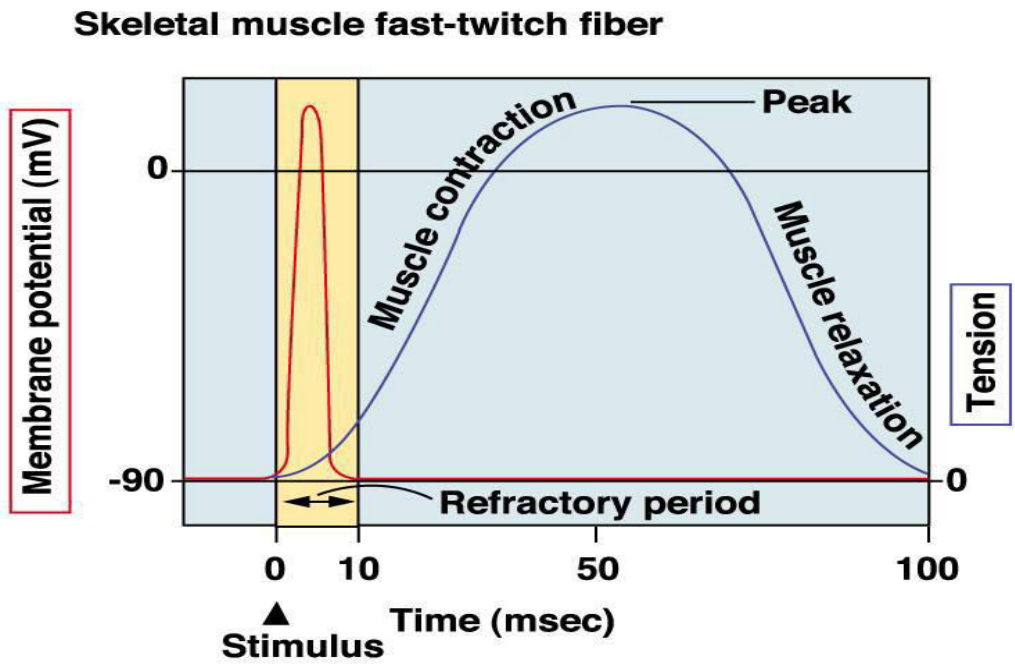
Always, in action potential, the electrical change is followed by mechanical change, which means that after the action potential we get the contraction and relaxation (mechanical change). After depolarization: contraction while after re-polarization : relaxation.

Now, if we get back to the skeletal muscle, the action potential is very short, around 1 millisecond to 10 milliseconds maximum. so we can give/fire another action potential in the skeletal muscle before the muscle relaxes so the first contraction was followed by a second

contraction which leads to their summation to the extent that if the frequency of the action potential of the skeletal muscle is very high, the muscle will not relax and this is called Tetany.

So the skeletal muscle might get tetanized, why?

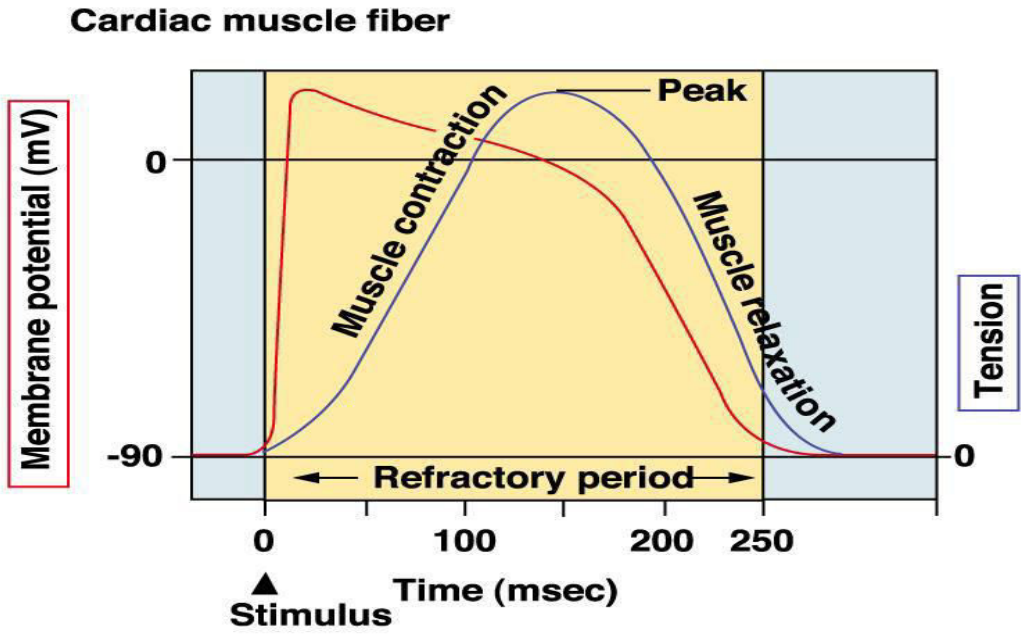
1. Because it's action potential is very short.
2. You can get too many action potentials.
3. The refractory period is too short.



Now look at the cardiac muscle, its action potential is very long, at least 200 milliseconds… Also, as soon as the refractory period ends, the muscle would be already relaxed, so when another action potential starts; a new contraction occurs that isn't affected by the previous contraction because it was already relaxed. So no summation >> no tetanization.

So, the cardiac muscle never gets tetanized, why?

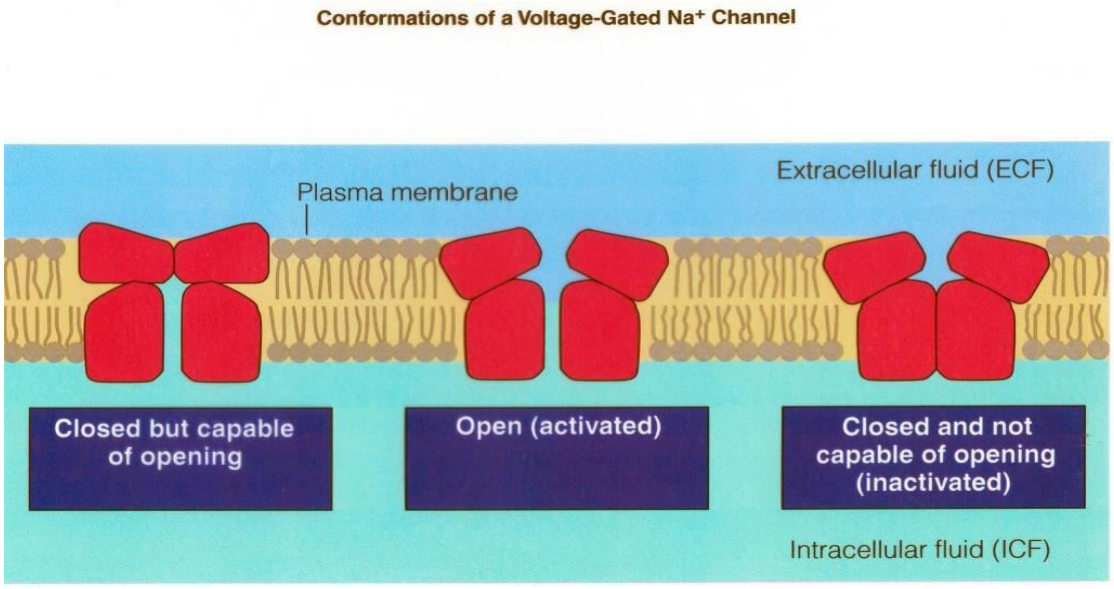
Because of the long refractory period of its action potential.



Na+ voltage-gated channels:

Sodium channels have two gates:

1. Activation gate (m gate), extracellularly.
2. Inactivation gate (h gate), intracellularly.



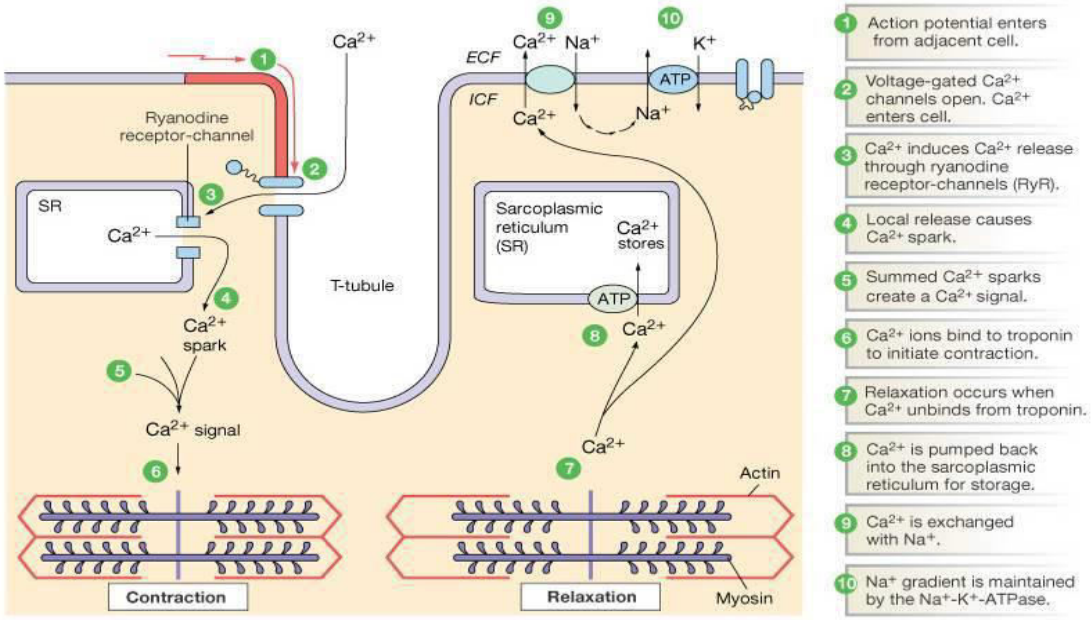
-The activation gate during rest is closed and the inactivation gate is open. The activation gate opens when the membrane potential gets less negative. And the inactivation gate closes when the membrane potential

gets less negative.

Note: since one gate opens and the other one closes, logically we didn't benefit anything, but actually we do because of the difference in timing. The activation gate is very fast while the inactivation gate is very slow. So when the membrane potential gets less negative, the activation gate opens, sodium will move according to its electrochemical gradient, after a while the inactivation gate closes (slow)

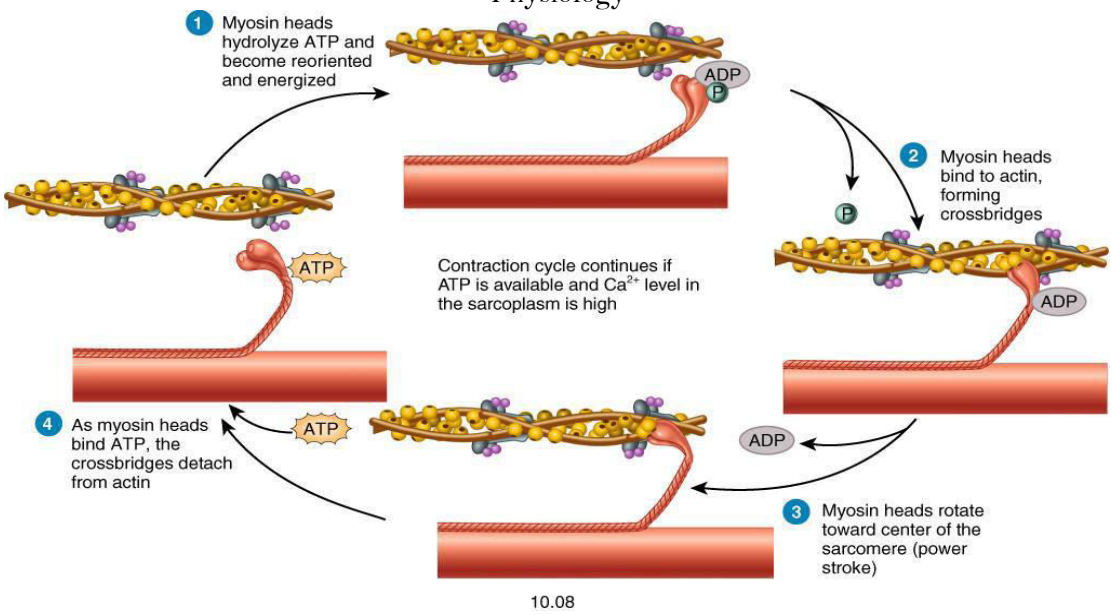
So the difference is in the TIME CONSTANT while the VOLTAGE CONSTANT is the same.

Cardiac muscle contraction:



- The action potential reaches the sarcolemma (SL) and causes the influx of Calcium ions through the slow gated $Ca2+$ channels during phase2.

- The influxed calcium ions causes further release of calcium ions from the sarcoplasmic reticulum (SR) through calcium channels called Ryanodine Receptor which accounts for the major source of calcium ions accumulation in the cytoplasm but isn't enough on its own; it accumulates along with calcium entering through the SL which binds to troponin C and causes the cardiac muscle cell to contract through the sliding filament theory (to be explained in a bit). Ryanodine receptor is a calcium channel that is blocked by ryanodine drugs.



10.08

• Troponin C normally binds to tropomyosin forming a complex that blocks the sites on the actin filaments that can bind myosin heads

• Increase of Ca++ concentration in cytosol leads to Ca++ binding with troponin C

• This induces a conformational change in the troponin-tropomyosin complex that reveals the myosin binding sites on actin

• Myosin head ,initially bound to ATP, have ATPase activity and now hydrolyses ATP and becomes bound to the products of this process: ADP and Pi and is now called charged myosin head

• This charged myosin head can bind the active site on actin now, releasing Pi in the process

• Then the myosin head moves the actin filament inwards (shortening), releasing the bound ADP almost at the same time as this movement which is called power stroke. The angle between the myosin head and its body (which was almost perpendicular) becomes acute in this movement.

• For the myosin head to unbind the actin, an ATP molecule must bind to it, hence this cycle consumes only one ATP per cycle. The cycle continues as long as there are enough concentrations of calcium and ATP

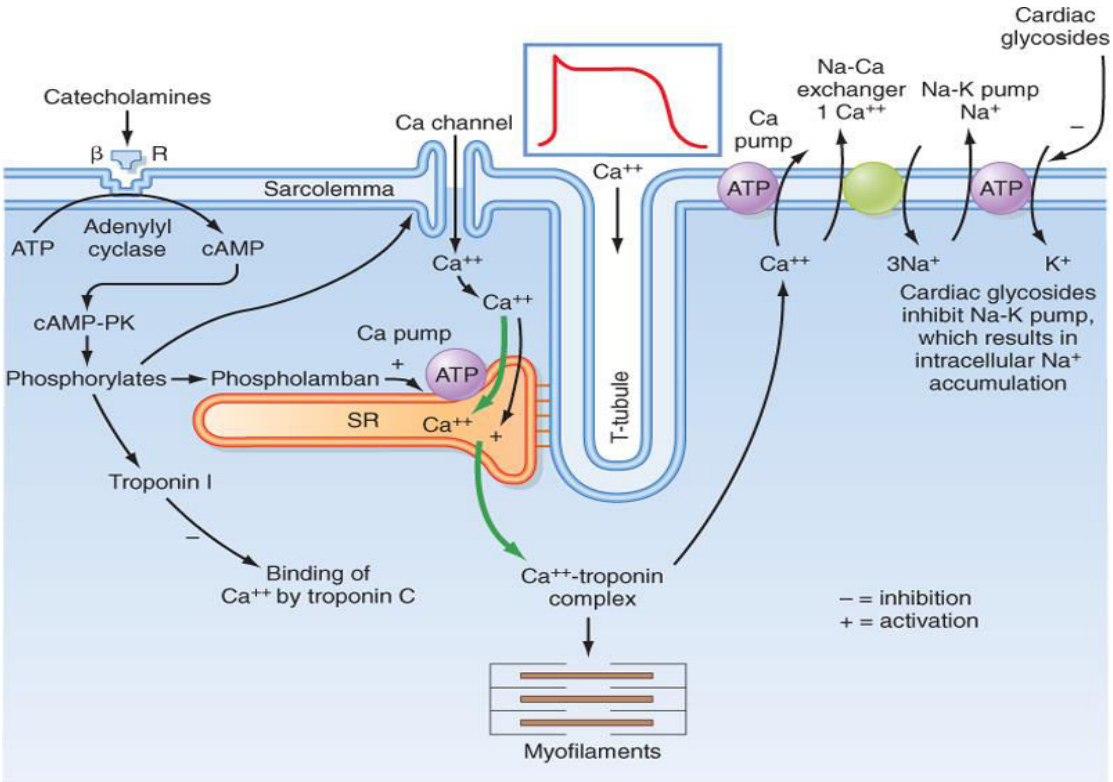
• So, The ATP that is used to charge myosin is the same one used in the power stroke.

Recap: https://www.youtube.com/watch?v=Ct8AbZn_A8A

Calcium ion concentrations:
During contraction (Systole): 10^-5 molar in cytoplasm.
During relaxation (Diastole): 10 ^-7 molar in cytoplasm.

Cardiac muscle relaxation

For the cardiac muscle to relax, the accumulated calcium ions in the cytoplasm must be pumped back to its stores (outside the SL and to the SR), and this is done by the following:



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

1. ***Ca*2+pump in the SR** pumps the calcium ions actively (has ATPase activity) against their concentration gradient back into the SR from the cytosol. - **The pump has a high affinity** (low Km, works even at low Ca++ concentrations) but **low capacity** (need considerable time to move Ca++

so it pumps small amount of calcium)

2. $Ca2+/Na+$**exchanger** on the SL of cardiac muscle only. (active counter transport) in which 3 $Na+$enter the cytosol and 1 $Ca2+$ is pumped outside the cell. -It is an electrogenic pump meaning that it affects the electrochemical gradient across the SL due to unequal charge transport. - The exchanger can work in both directions. Example: if the Na+ inside the cell is actually high like during phase 0, then the Na+ can be moved from inside to outside and the Ca++ is moved inside the cell across the SL. This increases intracellular calcium to initiate contraction and induces calcium release from SR. - **The pump has a low affinity** (high Km, works at large concentrations of Ca++ only) but has **a high capacity** (can pump large amounts of Ca++ in a short time).

3. **Ca++ pump in the SL**, similar affinity and capacity to the one in the SR Phospholamban: (an SR protein) Influxed calcium binds calmodulin and the activated calmodulin activates calcium-calmodulin dependent protein kinase (protein kinase B). The protein kinase B (PK-B) then phosphorylates the protein phospholamban hence activating it. Phospholambdan activates the Ca++ pumps on SR, so it shortens the relaxation (diastole) and so increases heart rate.

DO YOU BELIEVE THAT THE HEART IS ONLY A GREAT PUMP??

HTTPS://WWW.YOUTUBE.COM/WATCH?V=TKJNU7FQSEY

The phospholamban can be phosphorylated by PK-A (cAMP dependent that activates phospholamban). During sympathetic stimulation, epinephrine and norepinephrine (catechol amines) stimulate β receptor and activate adenylate cyclase which increases cAMP activating PK-A

which will increase the heart rate through phospholamban . It can also be phosphorylated by PK-C.

In MI, the SL becomes more permeable to Ca++ which leads to greater accumulation of cytosolic Ca++. This causes Na+/Ca++ exchanger in the membrane of mitochondria to be activated and to pump the excess Ca++ from the cytoplasm to the mitochondria to help relaxation. This pump works only pathologically.

DILTIAZEM: Ca channel blocker used for reducing cystolic Ca level. Less Ca >> less contraction.

Cardiac muscle contraction VS Skeletal muscle

Sliding filament hypothesis

No tetany in cardiac (Long refractory period because of plateau)

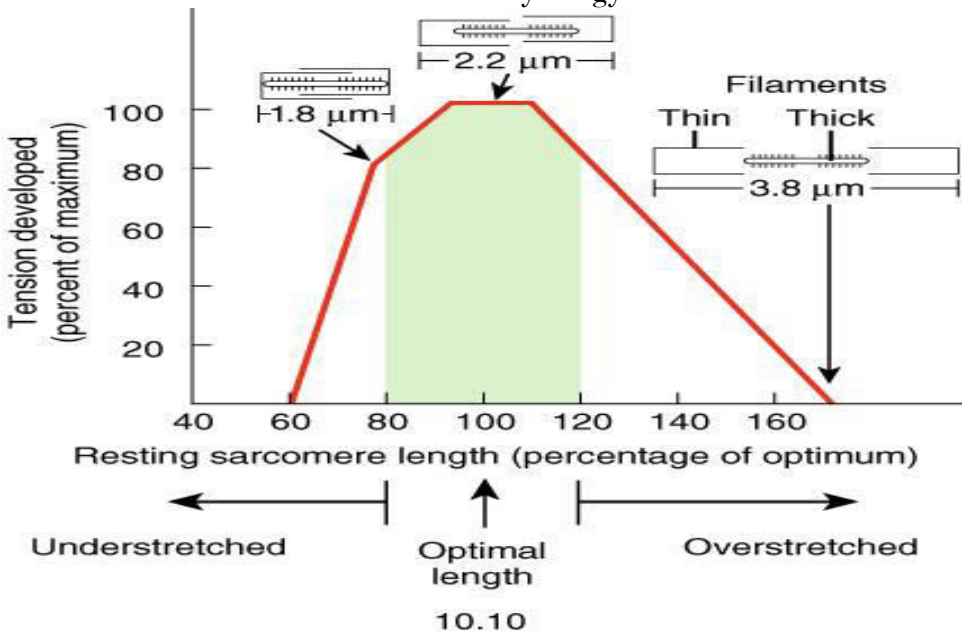
Fatty acids main source of energy (oxidative phosphorylation) unlike skeletal muscle (Anaerobic and Aerobic)

Attachment and detachment cycle and ATP dependence is the same

Length - Tension Relationship (Frank-Starling law):

'Within physiological limits, an increase in the resting length of the heart muscle increases tension / force of contraction'

For either the skeletal or cardiac muscle this same general principle applies in which that at a certain range of length of the sarcomere the muscle can contract at maximum active tension, this length is called the optimal length. Stretching the muscle fiber above or below this optimal length will reduce the active tension a muscle can develop and hence reduce the force of contraction.



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In the skeletal muscles, the sarcomeres are already at their optimal length so already reaching their maximum force of contraction; if stretched any further the force of contraction will decrease.

In cardiac muscles, the sarcomeres are at a length much below their optimal length, so stretching the muscle will cause the length to approach the optimal length and hence stronger contraction, which explains the Frank-Starling Law of the Heart.

https://www.youtube.com/watch?v=5SO58NndlPI

اذا كان بحوزتك ثلاثة أسلاك مطاطية "المغيط" وقمت بشد الأول قليلا "شورت لينغث" والثاني بشدة متوسطه "أوبتمال لينغث" والثالث بشدة مطلقة "أكثر من الاوبتمال لينغث" فماذا سيحدث؟ سيرجع السلك الأول الى حالته الطبيعية بقوة بسيطه بينما سيرجع الثاني بقوة عاليه في حين أن الثالث قد يتلف وينقطع.

Active tension: this is the tension in the muscle due to the sliding filament theory in which a stimulus causes the myosin to pull upon the actin (contraction of muscle)

Passive tension or resting tension: this is the tension in the muscle due to the elasticity of its components. It is a physical property that any material has like a spring not a chemical process.

Total tension: It is the total tension in the muscle due to the sum of the passive and active tensions. The doctor said that he will complete this topic later.

قال تعالى:"أَفَلَمْ يَسِيرُوا فِي الْأَرْضِ فَتَكُونَ لَهُمْ قُلُوبٌ يَعْقِلُونَ بِهَا أَوْ آذَانٌ يَسْمَعُونَ بِهَا فَإِنَّهَا لَا تَعْمَى الْأَبْصَارُ وَلَٰكِنْ تَعْمَى الْقُلُوبُ الَّتِي فِي الصُّدُور".

Past paper questions:

1. All of the following regarding Ca2+ regulation in cardiac muscles during both physiological and pathological conditions is correct EXCEPT:

(a)SR Ca-ATPase pump
(b) Sarcolemma Ca-Na exchanger
(c) Passive diffusion of calcium to the outside of the cell
(d) Ca-Na exchanger Ca-ATPase pump
(e) Mitochondrial Ca-Na exchanger

2. All of the following regarding skeletal and cardiac muscles is correct EXCEPT:

(a)Skeletal muscles has more developed sarcoplasmic reticulum
(b) Gap junctions are only found in cardiac muscle
(c) Cardiac muscles are more rich in mitochondria
(d) Nuclei are much more in skeletal muscles than in cardiac muscles
(e) There are larger and shorter T-tubules in skeletal muscles than in cardiac muscles

3. Cardiac muscle cell differ from skeletal cell:
a- poor in mitochondria
b- have more t tubules per sarcomere
c- cardiac rest length is less than its optimal

Answers:

1	C
2	E (slender and longer)
3	C