Introduction

The sheet isn't that long, just many repeated information and unfortunately we had to include much of this information as it is mentioned in this lecture.

The ordering of information isn't exactly like in the lecture, but hopefully everything mentioned is covered.

The diagrams and figures contain information so do read them.

Some information aren't mentioned in the lecture but are added to this sheet for explanation purposes, these are typed in red font. (Just check the slides electronically)

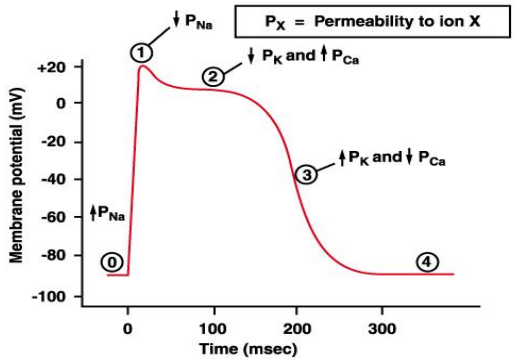
"*" sign indicates an elaboration is to come about this point

Good luck, hope it is clear and forgive us for any mistakes.

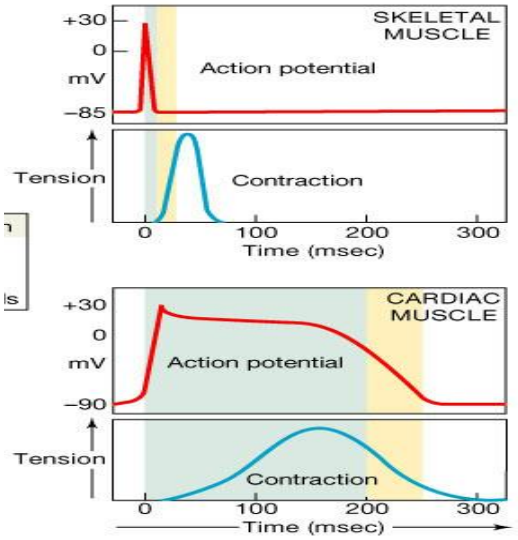
Cardiac Muscle Physiology

Quick Review:

Remember from previous lectures that the cardiac muscle action potential has 5 phases: 0,1,2,3,4 as shown by the diagram below, and recall the mechanical response that follows and its comparison with the skeletal muscle.



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



Note: phase 1 is due to the opening of transient Potassium and/or Chloride Channels.

Note that the cardiac muscle contraction and relaxation is almost entirely in the refractory period of AP, so no tetany.

Cardiac muscle contraction:

The action potential reaches the sacrolemma (SL) and causes the influx of Calcium ions through the slow gated Ca^{2+} during phase 2. 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 toxin.

Calcium ion concentrations:

During contraction (**Systole**, since we consider the ventricles' contraction as reference): 10^{-5} in cytoplasm

During relaxation (**Diastole**) : reaches 10^{-7} in cytoplasm

Extracellular: 10^{-3} calcium in skeletal

Discovery of need of Calcium for heart contraction

The discovery was accidental which helped heart transplant progress.

The heart shortly stops contracting if placed in a solution without calcium ions.

The solution containing calcium ions needed for maintained heart beating is called **Ringer solution**. (In reference to the one who discovered it)

Application: Ca++ channel blockers e.g. **Diltiazem (**shortens phase 2 and so, it increases heart rate). Dilzem is its commercial name.

This drug increases heart rate and decreases contractility (force) (as shown by

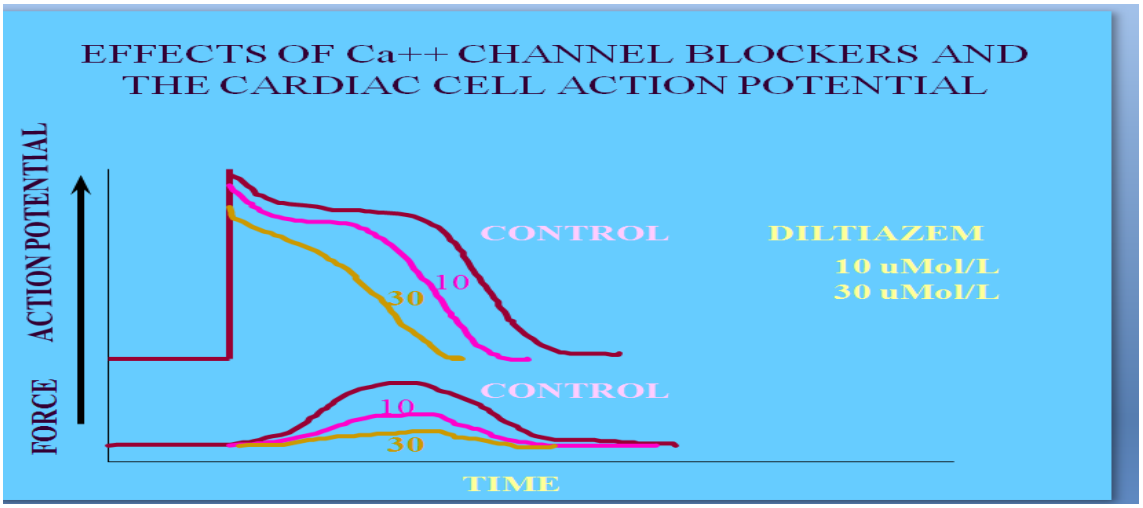


diagram below)* and is given to MI or hypertensive patients to reduce oxygen consumption of the cardiac muscle by decreasing the force of contraction because in MI there is a coronary block and not enough oxygen is reaching the heart so we decrease the consumption of oxygen.

*The bottom curves represent force of contraction while upper curves show the action potential. The control is a normal cardiac muscle. Check slide 19, the slide notes, there are extra information the dr. didn't explain but they seem to be unimportant (hopefully).

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:

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. Ca^{2+}/Na^{+}exchange transport on the SL (**active countertransport**) in which 3 Na^{+}enter the cytosol and 1 Ca^{2+} 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.*

Remember:

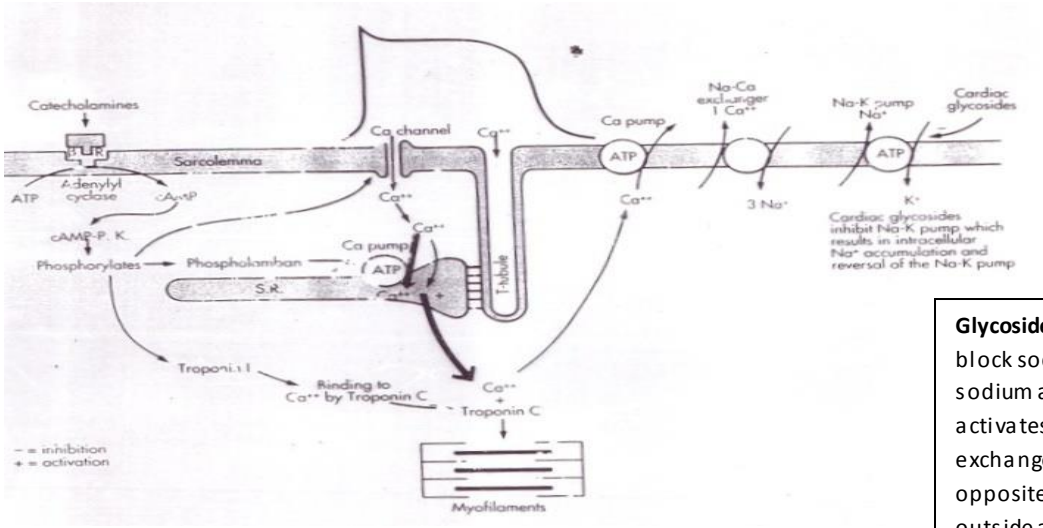
PK-A: is cAMP dependent

PK-B: is Calcium- calmodulin dependent

PK-C: is calcium - phospholipid or DAG (diacylglycerol) dependent

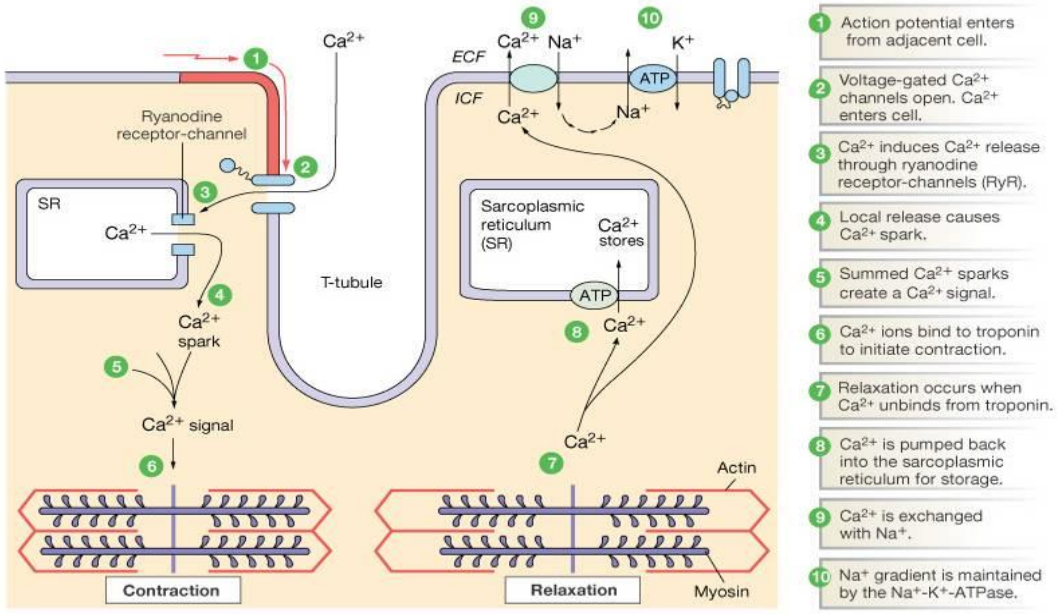
Remember:
***Km** can be defined as the substrate concentration at which the velocity is half Vmax, and is a measure of affinity.*
***Vmax**: is maximum speed of transportation is a measure of capacity.*

**** 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. Extra note: according to the internet phospholamban is actually an inhibitor of the calcium pump and upon phosphorylation the phospholamban is inactivated allowing the Ca pump to work more effeiciently, check the following diagram***



An illustration of the cardiac contraction and relaxation process:

Glycosides (Digioxin or Digitalis): block sodium potassium pump, sodium accumulate inside and activates sodium calcium exchanger which works in opposite direction to pump Na+ outside and Ca++ inside, and this increases force of contraction. (positive ionotropic)



Pathological condition: Myocardial Infarction (MI)

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.

A comparison between cardiac muscle (CM) and skeletal muscle (SM)

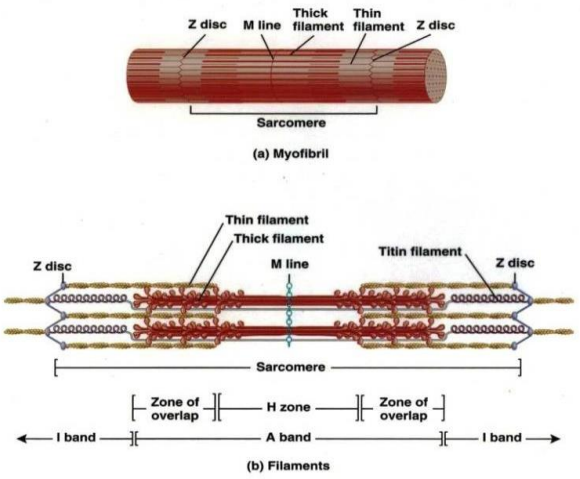
Cardiac Muscle	**Skeletal muscle**
Phase 0,1,2,3,4	Phase 1 and 2 not present
Long refractory period (no tetany, complete relaxation before the succeeding contraction)*	AP directly followed by mechanical action (short refractory period); leads to summation and tetany if **frequency** of stimulation increased
No neuromuscular junction (only T-tubule invagination)	Neuromuscular Junction
Ca++ pump in SR and SL	Ca++ in SR only
Na+/ Ca++ exchanger	**No Na+/Ca++ exchanger**
Phospholamban	**No Phospholamban**
Calcium induced release of calcium from SR (influx of calcium across SL is what induces further release of calcium fro SR)	**Electrostatic transfer of action potential from SL to foot of SR which causes release of calcium from SR (no slow calcium channel)**
T-tubule over Z -line (1 per sarcomere)	T- tubule over I-band (2 per sarcomere)

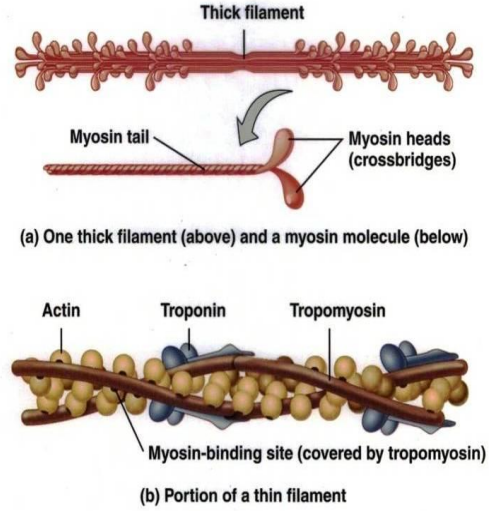
Note: this is just a short comparison that the dr. mentioned in this lecture, there are much more differences and similarities than mentioned above (probably mentioned in previous lectures)

*In case of non physiological prolonged increase of Ca^{2+}concentration in the cytosol of the cardiac muscle, tetany can occur however it will **not** be because of action potential but the large amount of calcium accumulated inside will keep binding to troponin facilitation contraction. Example: calcium injection, or MI

Sliding Filament Theory

Revision: sarcomere



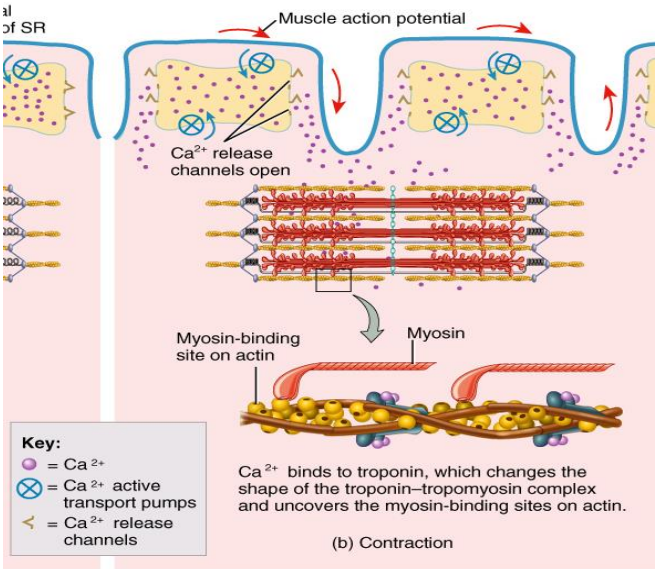


- I - bands : light bands (only thin filaments)
- A - bands : region containing thick and thin filaments
- H zone : thick filaments only (myosin)
- Z - disc (sarcomere is the distance between 2 Z lines)
- Titin: elastic material between Z-disc and myosin that allows stretch

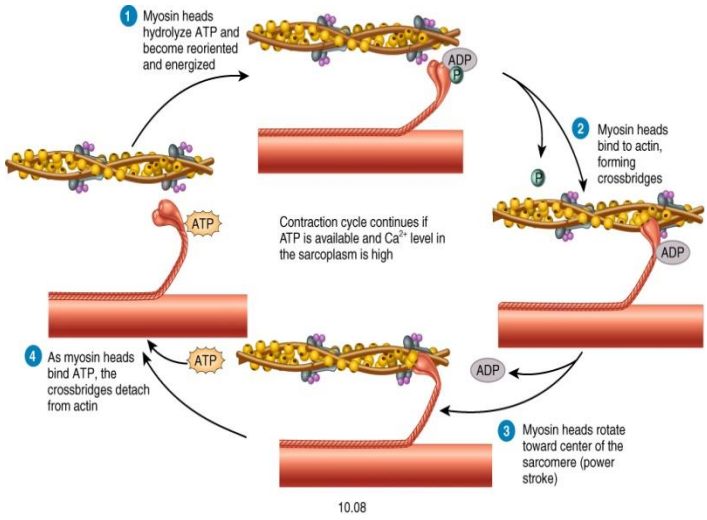
A -band size doesn't change during sliding, only I - band shortens. (I - band can completely disappear at maximum contraction)

The process: same for both skeletal and cardiac

- Troponin C 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 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 P_i and is now called charged myosin head
- This charged myosin head can bind the active site on actin now, releasing P_i 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.

Energy sources: comparison between cardiac and skeletal muscle

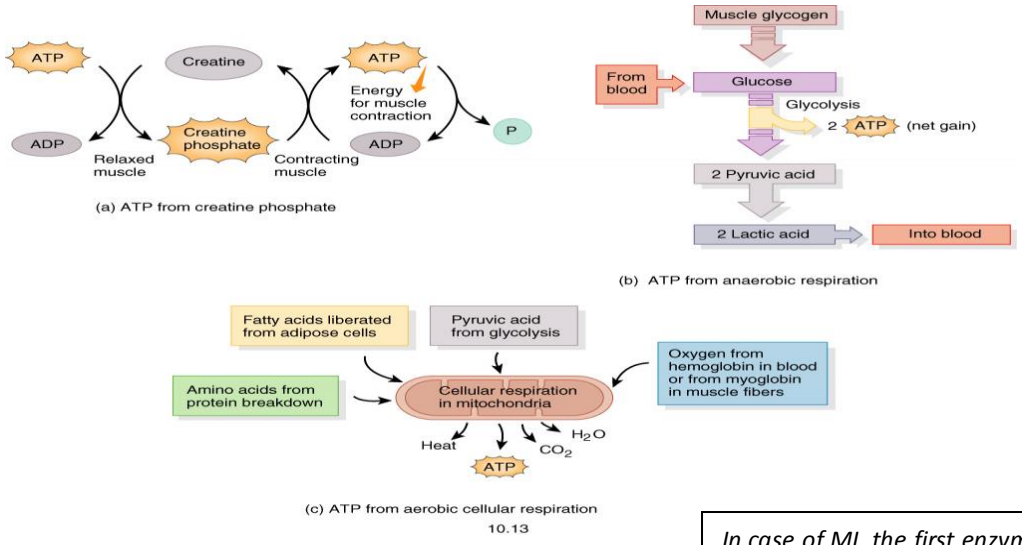
The energy sources for muscles in general can be through:

- **Creatine phosphate pathway:**
  Fastest energy store which can be accessed, almost instant, however fastest depleted, lasting only for about 10 seconds in skeletal muscle (most depended on for example in 100 m races). Creatine phosphate charges ADP into ATP and becomes creatine.
- **Anaerobic respiration (glycolysis):** (mainly for skeletal muscle)
  2 ATP per glucose molecule (poor source of energy), 2-3 mins lasting, example: 400 m race
- **cytochrome system in mitochondria:** aerobic, best source of energy ,used by cardiac muscle mainly through **beta oxidation** of fatty acids to

keep creatine phosphorylated through ATP and hence keeps an instant supply of energy through creatine phosphate

In skeletal muscles: 36 ATP molecules per glucose molecule, marathon races

Check the following diagrams:



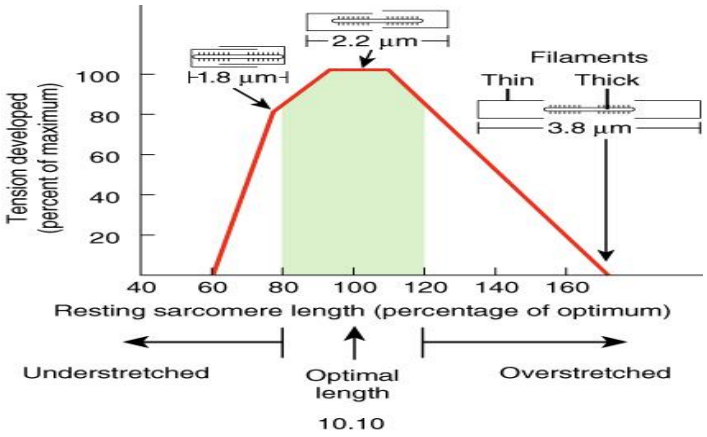
In case of MI, the first enzyme to appear in blood stream that can be detected is ***Creatine PhosphoKinase (CPK),*** *followed by* ***troponin****, then* ***Lactate DeHydrogenase (LDH)***

Length - Tension Relationship

Frank-Starling law of the Heart: within physiological limits, an increase in the resting length of the heart muscle increases tension / force of contraction.

In case of overstretch (pathological condition), the tension will decrease and this can lead to heart failure (the amount of blood pumped by the heart is less than the amount received leading to the accumulation of the blood in the heart). According to the law, more blood in means more blood out until we reach the optimal length because after that more in means less out.

To explain this phenomenon, first observe the following graph below of an isometric contraction:



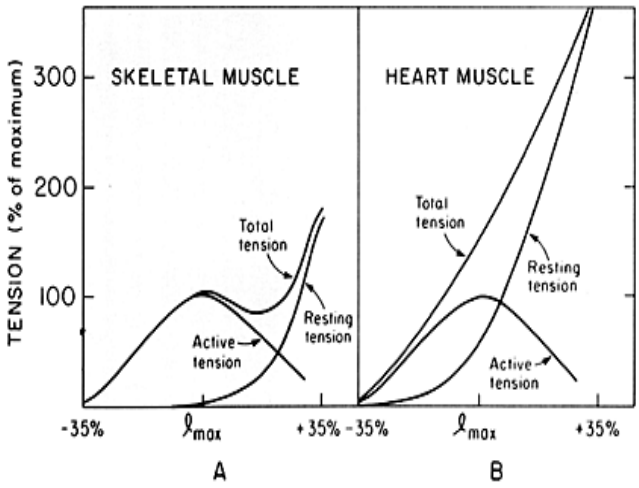
For either the skeletal or cardiac muscle this same general principle applies in which that at a certain range of length of the sarcomere the muscle can contract at maximum **active tension**, this length is called the **optimal length**. Stretching the muscle fiber above or below this optimal length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

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.

Total tension, Passive tension, Active tension

Observe the following diagram below (also isometric contraction):



Let's define the terms

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.

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 experiment procedure: we stretch the muscle, then fix its length and now record the tension: this is the passive tension. Then we apply a stimulus (electric current) to the muscle to stimulate contraction and hence active tension, and now record the new tension: this is the total tension (passive + active).

So as you can notice, the passive and the total tension are **measurable** while the active tension is only **calculated**.

Note: at the muscle's normal length, the passive tension is **zero** either if it's skeletal or cardiac

The graph

As you can see, stretching the muscle away from the optimal length reduces the **active**

tension (due to the decrease in the opposition between actin and myosin). Stretching the muscle above its normal length (resting length) increases the **passive tension** alot, that's why the total tension is increasing.

Notice that the small decrease in the total tension of the skeletal muscle that is not present in the cardiac muscle. This is due to the elastic elements in the skeletal muscle being regularly arranged in **series** causing them to be overstretched (broken) at one point however in the cardiac muscle they are arranged in many different directions.

So, during the filling of cardiac muscle both active and passive tensions will increase, which makes the contraction stronger and the cardiac output higher.

Since it is difficult to measure the length of the heart muscle fibers, we measure the volume of the chambers which is proportional to the length

"Believe you can, and you are half way there"

Good luck