Cardio-Vascular System

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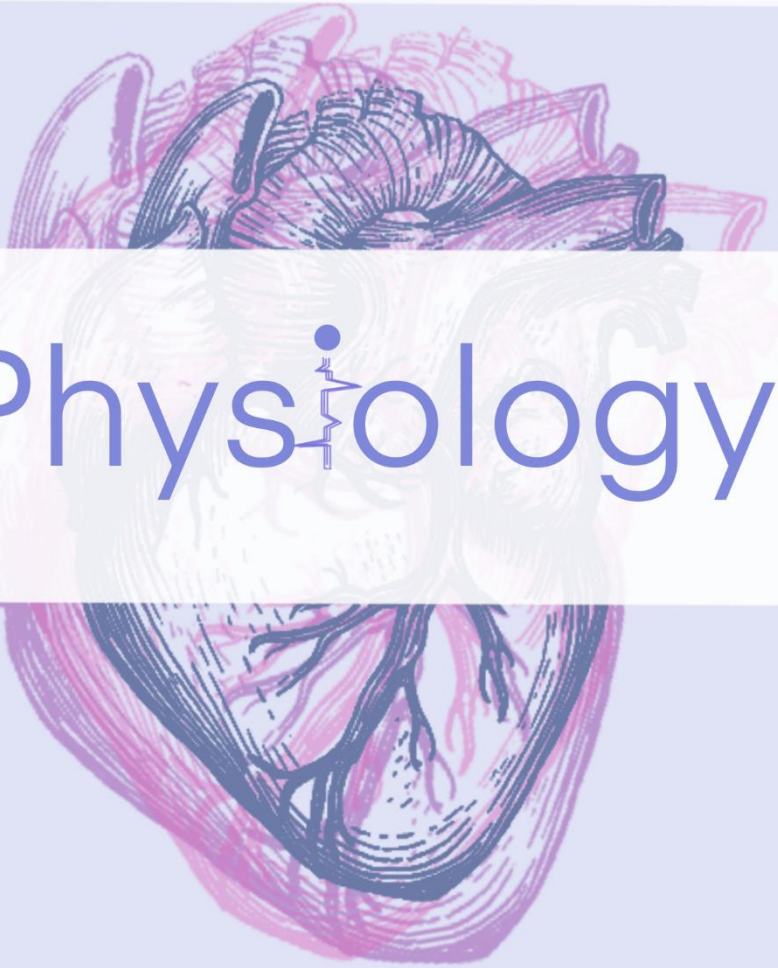

Physiology

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Topics of this lecture:

- *Mechanism of contraction in skeletal and cardiac muscles*
- *Contraction- relaxation cycle*
- *Length-tension relationship in skeletal muscles*
- *Length- tension relationship in cardiac muscles*

Let's begin 😊

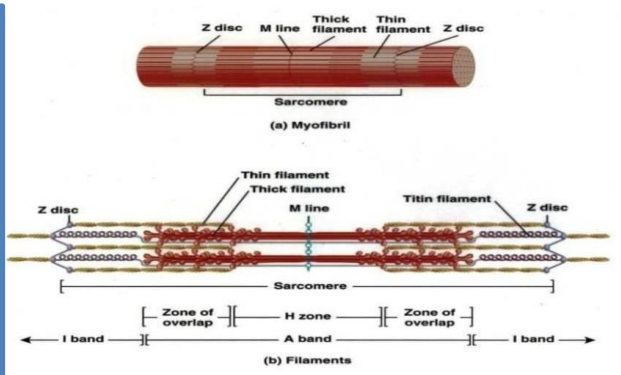
- The mechanism of contraction is similar in cardiac and skeletal muscle, except that cardiac muscle is an **involuntary** muscle and it's supplied by the autonomic nervous system (sympathetic and parasympathetic), whereas skeletal muscle is **voluntary** and is supplied by motor spinal nerves.
- Although 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

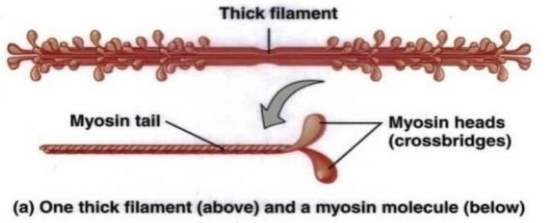
- ✓ As we know, there is an increase in calcium influx in phase 2 through slow calcium channels which triggers the release of more calcium from the sarcoplasmic reticulum.
- ✓ Calcium binds to troponin on actin filaments. Tropomyosin then moves, exposing the binding sites for myosin.
- ✓ Myosin heads 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 (discussed in the last lecture), 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

- The sarcomere is located between two Z lines.
- The M line is at the center of the sarcomere.
- Titin filaments connect Z lines to each other, and they are called elastic elements of the muscle.
- The I band contains thin filaments only.

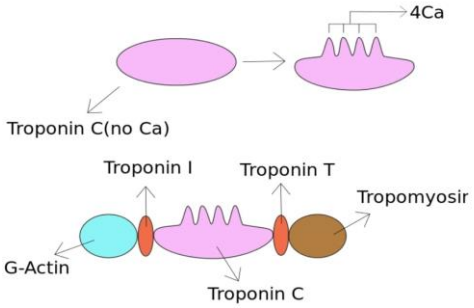


- The A band is the whole length of thick filaments (including areas that overlap with thin filaments).
- The H zone contains only thick filaments.
- The H zone and I band shorten with contraction of the sarcomere, and they completely disappear in maximal contraction. The A band stays the same.
- Myosin 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.
- Thin filaments are composed of <u>actin</u>, <u>tropomyosin</u> and <u>troponin</u>.
  Troponin consists of three subunits:
  -Troponin I (inhibitory),
  -Troponin C (binds calcium),
  -Troponin T (binds tropomyosin).



(a) One thick filament (above) and a myosin molecule (below)

(b) Portion of a thin filament



Cardiac muscle vs. skeletal muscle contraction

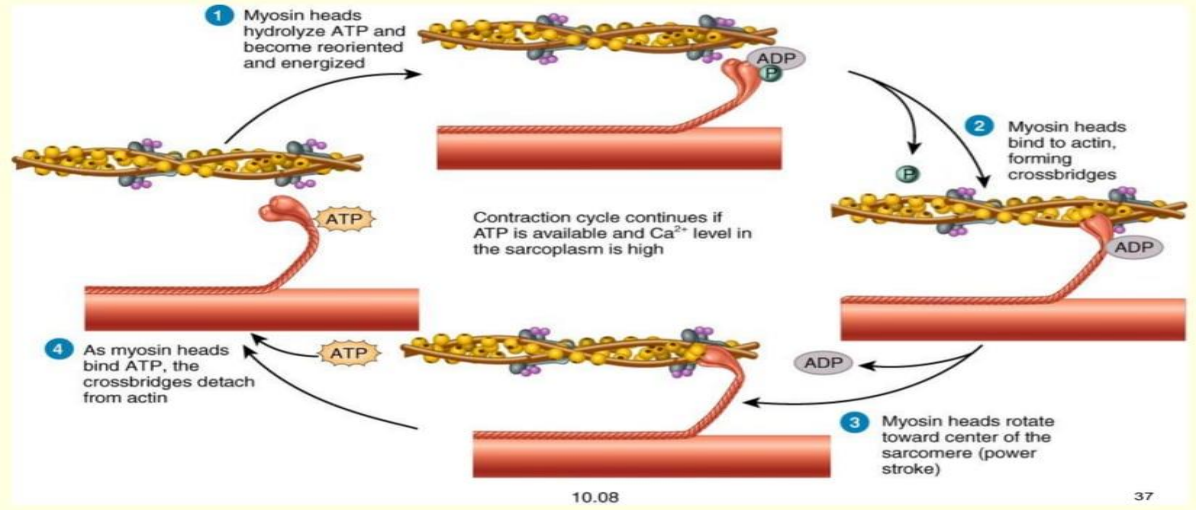
- Sliding filament hypothesis → The same
- No tetany in cardiac muscle (long refractory period because of plateau).
- <u>Fatty acids</u> are the main source of energy in cardiac muscle, unlike skeletal muscle which depends on aerobic and anaerobic <u>glycolysis</u>. However, cardiac muscle can also use 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 → The same

Contraction-relaxation cycle

- ✓ The binding between myosin heads and actin occurs only when <u>myosin heads are charged</u>, meaning that they are bound to ADP+P_i after the hydrolysis of ATP. There also needs to be <u>enough Ca^{+2}</u> 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, <u>both contraction and relaxation require ATP</u>.

After death, ATP is unavailable and the crossbridges cannot be broken, so the muscles remain contracted resulting in what is called **<u>rigor mortis</u>**.



- 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:

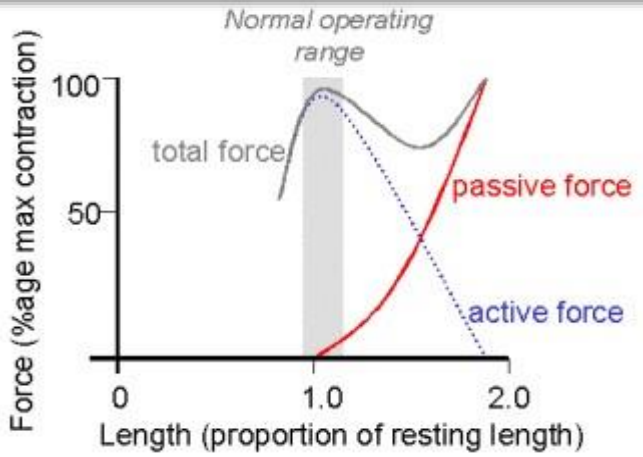
1) **Aerobic phosphorylation/respiration** uses fatty acids (main source), amino acids from protein breakdown, and pyruvic acid from glycolysis (1 glucose = 36 ATP).
   - ✓ 75% of energy is released as heat.
2) **Anaerobic glycolysis** (1 glucose = 2 ATP).

The length-tension relationship in skeletal muscle

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 is present 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.

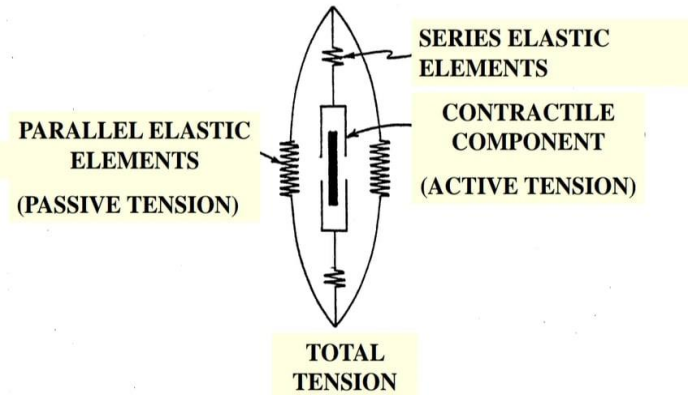
Now, there are two peaks where we can get **maximum total tension** (notice the graph).

- 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).

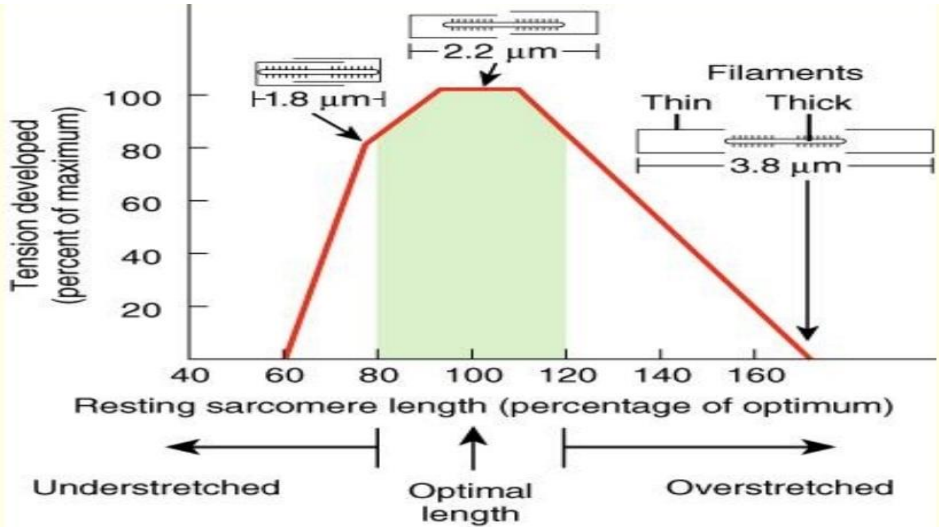
✓ Notice that the active tension decreases linearly with increasing length.
✓ Active tension cannot be measured directly. What can be measured is the passive tension and the total tension. Then we can find the active tension by subtracting passive tension from total tension (AT= TT - PT).

The figure aside shows the **elastic elements (titin filaments)**

- 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.
- Parallel elastic elements are responsible for the passive tension.
- The contractile component is responsible for the active tension (when it contracts, the possible cross bridges that can be formed increases).



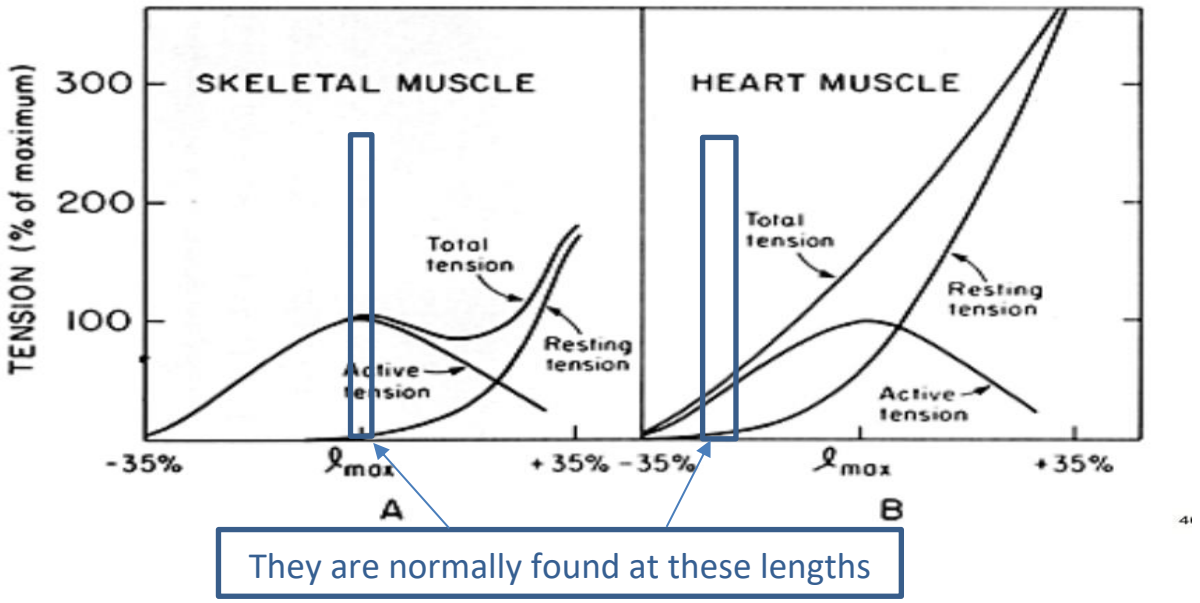
The figure below shows the **active tension of the muscle**. Notice that the number of cross bridges formed between myosin and actin increases with increasing muscle length until it reaches the **optimal length,** where the **maximum number of possible cross bridges** are formed (the max. active tension).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



The length-tension relationship in cardiac muscle

Notice in the figure below that cardiac muscle only has one peak unlike skeletal muscle. This is because skeletal muscle cells are spindle in shape, so when they are stretched too much, the titin filaments will relax as we discussed, decreasing the tension. Whereas cardiac muscle cells are rectangular in shape, so when they are stretched too much the titin filaments will not relax, and the tension will not decrease.

{extra: the greater stiffness of cardiac muscle normally prevents its sarcomeres from being stretched beyond 2.2 microns.}



- ✓ When the muscle is stretched beyond optimum length, the **passive tension** increases, the **active tension** decreases and the **total tension** increases.
- ✓ At the end, when the **passive tension** is too high, the **total tension** will be equal to **passive tension**, and the **active tension** will reach zero.

- ◆ Skeletal muscles are usually found at their **optimal length**, while cardiac muscles are found in our body at a **length much less than their optimal length. (Check the previous figure).** So, increasing the cardiac muscle's length will lead to an increase in the active tension until it reaches the optimum length.

But wait.. How can we measure the length of cardiac muscle???

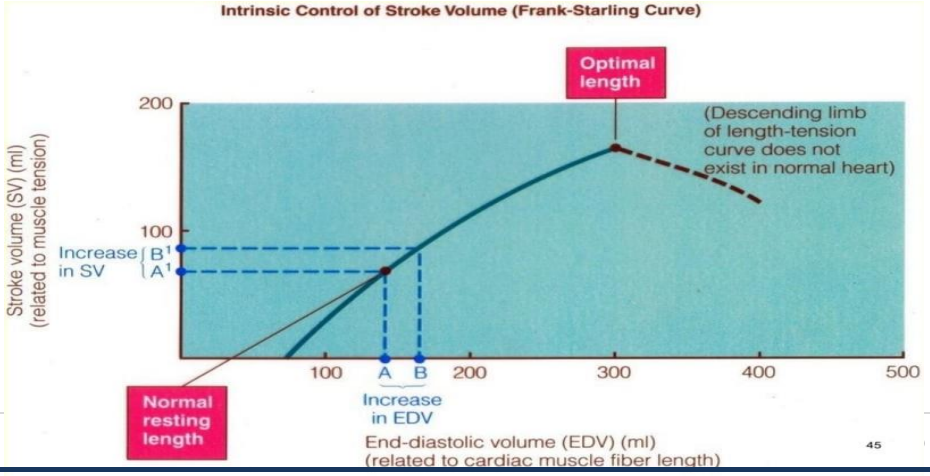
The length of cardiac muscle is measured by the increase or decrease in the **volume of the ventricle**. When the volume increases, the muscle is stretched and the length increases.

Now, the volume of the ventricle before it contracts is called the **end-diastolic volume (EDV)**. This volume is **high** because at the end of diastole the heart is filled with blood.

High EDV → increases the length of the cardiac muscle → increases the force of contraction (active tension) → high amount of blood is ejected from ventricles (high stroke volume).

- ✓ **Stroke volume (SV)**: Amount of blood that is ejected from the ventricles per one beat.
- ✓ **SV** and **EDV** in the right ventricle are always equal to the **SV** and **EDV** in the left ventricle, respectively.
- ◆ The figure below shows the **relationship between EDV and the power stroke.** Notice that the **stroke volume** increases with an increase in **EDV** and it reaches its maximum level when the length of the muscle reaches its optimum (300 ml). However, if the length exceeds the optimum, the **stroke volume** will decrease even with an increase in **EDV** (because of less force of contraction), so the heart will not be able to eject the whole amount of blood. Therefore, blood will remain in the ventricle and we call this heart failure.

⇒ **Passive tension** is proportional to **EDV**, and **active tension** is proportional to **stroke volume**.



Good Luck!!