CVS

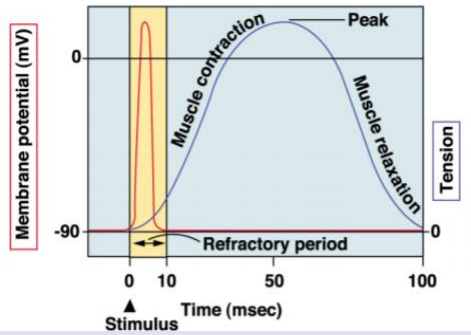
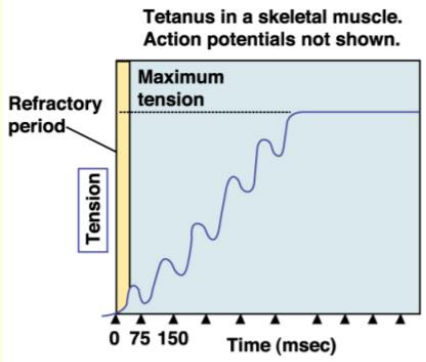
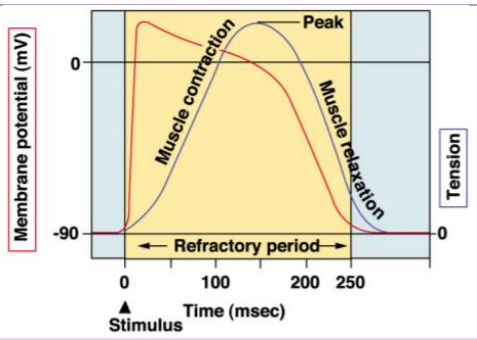
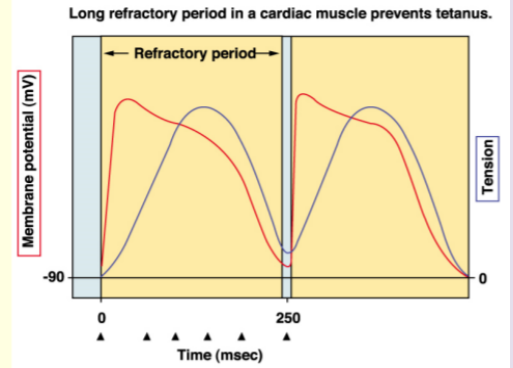
PHYSIOLOGY

WRITER: 018 sheet

CORRECTOR: 019 sheets team

DOCTOR: Faisal Mohammad

Difference between cardiac and skeletal muscle AP and contraction:

criteria	Skeletal muscle	Cardiac muscle
Phase 0 Depolarization phase (Na+ influx)	Present	present
Phase 1 partial repolarization	**Not present**	Present
Phase 2 Plateau (slow Ca++)	**Not present**	Present
Phase 3 fast repolarization phase (K+ efflux)	present	Present
Phase 4 resting membrane potential	Present	Present
diagrams	 Notice how the AP ends then the contraction follows  Absolute refractory period is tiny, so successive APs can take place causing summation of contraction and resulting tetanus. Tetanus can be complete and incomplete	 Notice how the contraction happens simultaneously with the AP, the long absolute refractory period gives time for the muscle to relax, so that when the next AP hits, the muscle would already be relaxed.  No summation during contraction, summation occurs during relaxation.

***There are extra repeated diagrams in slides: 14,16, 20, 27, 29 if you want to view them.**

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 😊

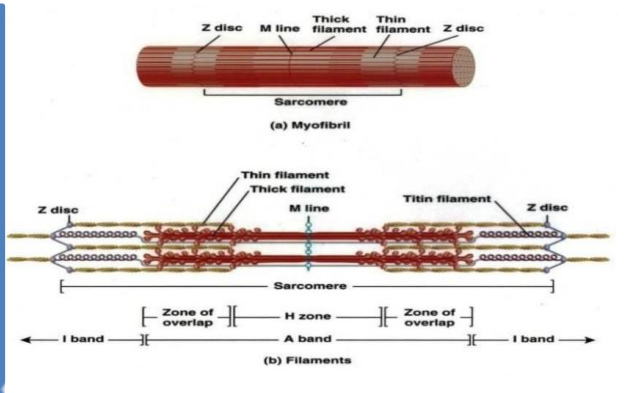
- The mechanism of contraction is similar in cardiac and skeletal muscle, except that cardiac muscle is an **involuntary** muscle and it's supplied by the autonomic nervous system (sympathetic and parasympathetic), whereas skeletal muscle is **voluntary** and is supplied by motor spinal nerves.
- Although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

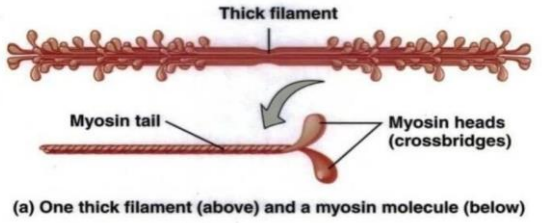
- ✓ As we know, there is an increase in calcium influx in phase 2 through slow calcium channels which triggers the release of more calcium from the sarcoplasmic reticulum.
- ✓ Calcium binds to troponin on actin filaments. Tropomyosin then moves, exposing the binding sites for myosin.
- ✓ Myosin heads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

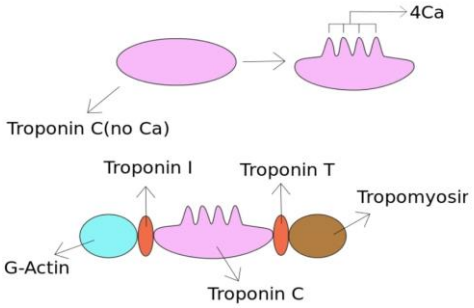


- The A band is the whole length of thick filaments (including areas that overlap with thin filaments).
- The H zone contains only thick filaments.
- The H zone and I band shorten with contraction of the sarcomere, and they completely disappear in maximal contraction. The A band stays the same.
- Myosin 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

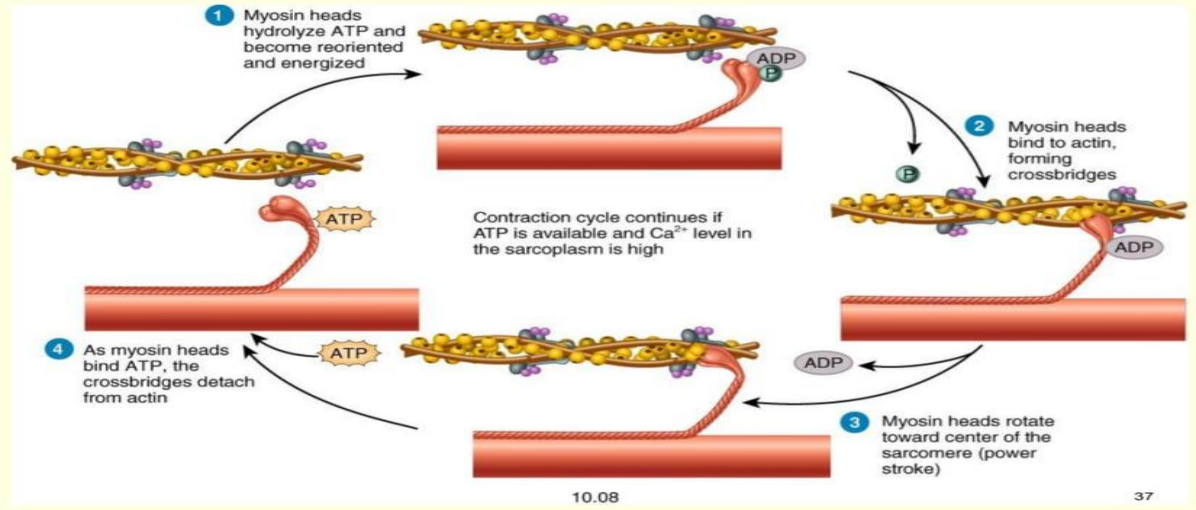
- Sliding filament hypothesis → The same
- No tetany in cardiac muscle (long refractory period because of plateau).
- <u>Fatty acids</u> are the main source of energy in cardiac muscle, unlike skeletal muscle which depends on aerobic and anaerobic <u>glycolysis</u>. However, cardiac muscle can also use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

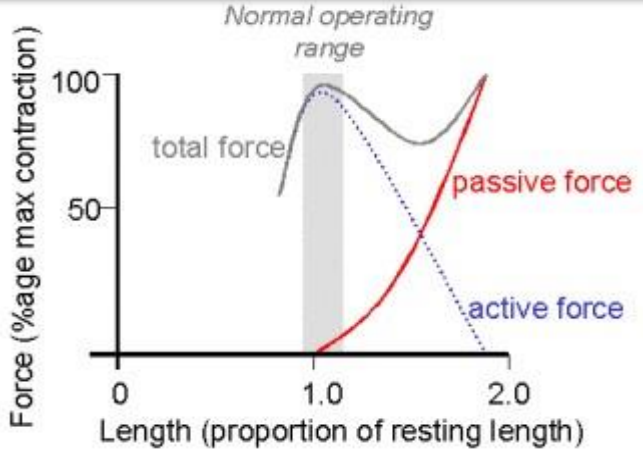
1) **Aerobic phosphorylation/respiration** uses fatty acids (main source), amino acids from protein breakdown, and pyruvic acid from glycolysis (1 glucose = 36 ATP).
   - ✓ 75% of energy is released as heat.
2) **Anaerobic glycolysis** (1 glucose = 2 ATP).

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.

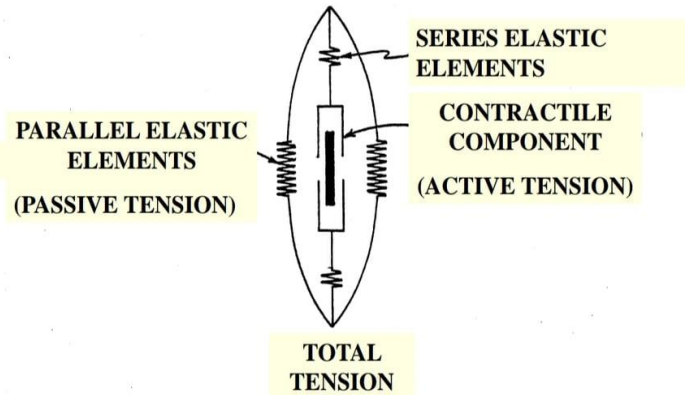
Now, there are two peaks where we can get **maximum total tension** (notice the graph).

- 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).

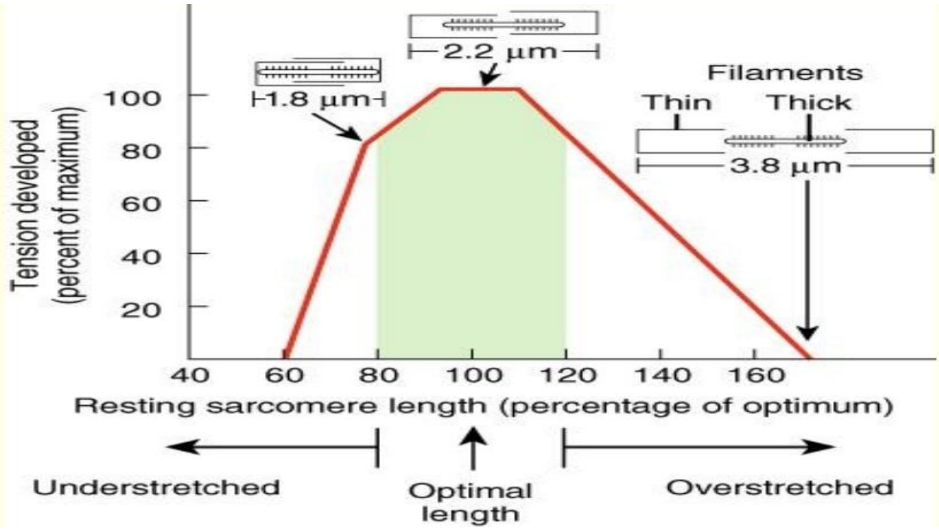
✓ Notice that the active tension decreases linearly with increasing length.
✓ Active tension cannot be measured directly. What can be measured is the passive tension and the total tension. Then we can find the active tension by subtracting passive tension from total tension (AT= TT - PT).

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).



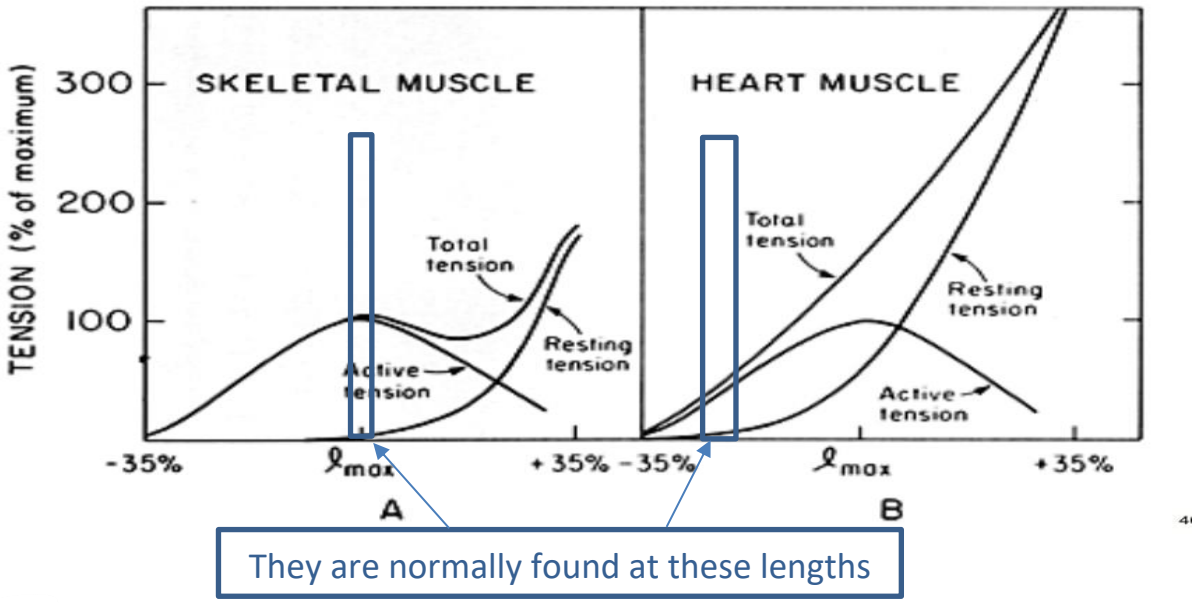
The figure below shows the **active tension of the muscle**. Notice that the number of cross bridges formed between myosin and actin increases with increasing muscle length until it reaches the **optimal length,** where the **maximum number of possible cross bridges** are formed (the max. active tension).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

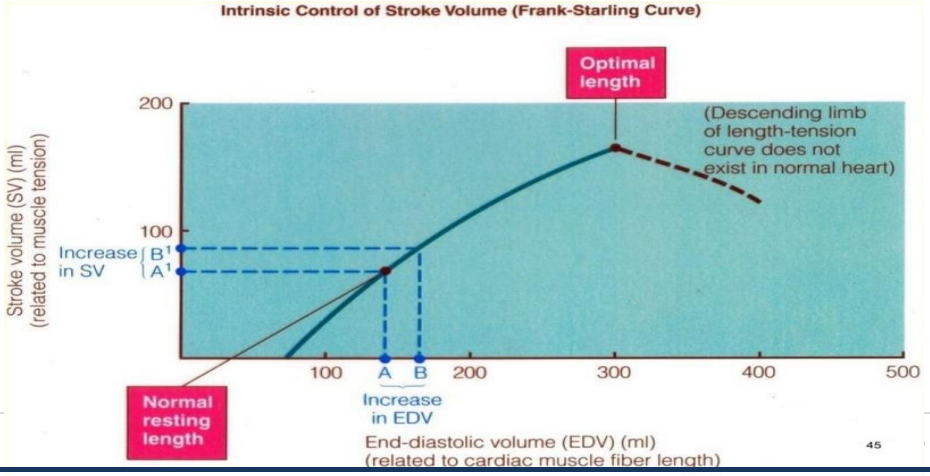
The length of cardiac muscle is measured by the increase or decrease in the **volume of the ventricle**. When the volume increases, the muscle is stretched and the length increases.

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!!

This is lecture 3 of CVS physiology with the title The Conduction System of the heart.

At first, you should know that the cardiac muscles are involuntary, which means they are innervated by ANS (sympathetic, parasympathetic) not the Somatic Nervous system. However, even if the ANS innervations were cut, the heart would still be working normally because the effect of the ANS is not to initiate the impulse, but to REGULATE it.

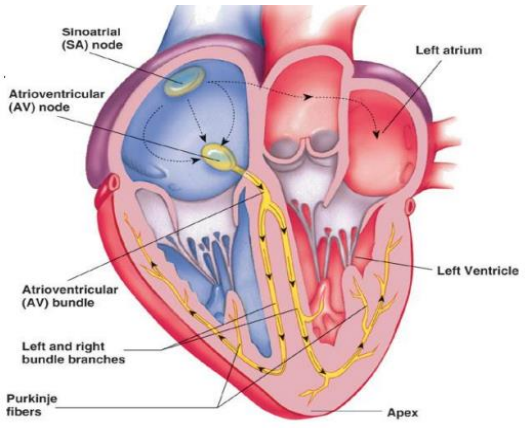
To make things clear, let's mention this example: ☺

When transplanting a heart to a faraway patient, the transport medium must contain calcium (Ca^{2+}), WHY? so that the heart keeps on contracting and stays functional. HOW? The calcium ions enter muscle cells through slow calcium channels, this in turn induces more calcium influx and calcium release from ER, thus overall increasing intracellular calcium concentration causing the contraction cycle (explained in previous lectures).

But wait a minute, we know that there is no mechanical response without electrical response, so there must be a source for this electrical response (cardiac action potential) and it can't be the ANS because we already said it only regulates the impulse and doesn't initiate it. This source is the sheet's main subject: The Conduction System of the heart. This system is a specialized system found in the heart; specialized as in it has a special structure and function. It's composed of modified (specialized) cardiac muscle cells that give intrinsic impulses to the heart, followed by contraction and relaxation cycles.

STRUCTURES OF THE CONDUCTION SYSTEM

1- **Sinoatrial Node (SA):** in the posterior wall of the right atrium just below the entrance of the superior vena cava. (sinus-like structure)
2- **Atrioventricular Node (AV):** found in the right atrium just at the junction between the right atrium and the right ventricle.
3- **Atrioventricular Bundle (Bundle of His):** from the AV the fibers continue forming this bundle that runs in the interventricular septum.



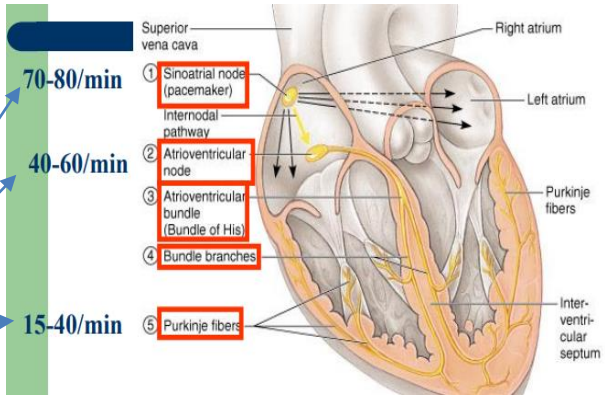
* Since the atrium and ventricle are not connected to each other muscularly (the septum between the atrial and ventricular tissue is a FIBROUS tissue), impulses from the atrial muscle won't reach ventricular muscle unless there's a way to transmit impulses between them. This way is through the AV node, then from AV node to a wire-like connection called the AV bundle (bundle of his).

4+5- The AV bundle bifurcates into **right and left bundle branches**, both of which run in the sub endocardium. They are normally one-way conduction. The only conducting path between atria and ventricles are AV node & bundles. The branches finally divide into the last division of this conduction system **the Purkinje Fibers.** Purkinje fibers have fast conduction due to the presence of many gap junctions at intercalated disks.

* It is said that there are additional internodal fibers between SA and AV nodes (ant, post and middle internodal fibers), the doctor however believes that atrial muscle cells conduct the signal from SA to AV node and there is no need to internodal fibers. Also, anterior interatrial band carries impulses to left atrium.

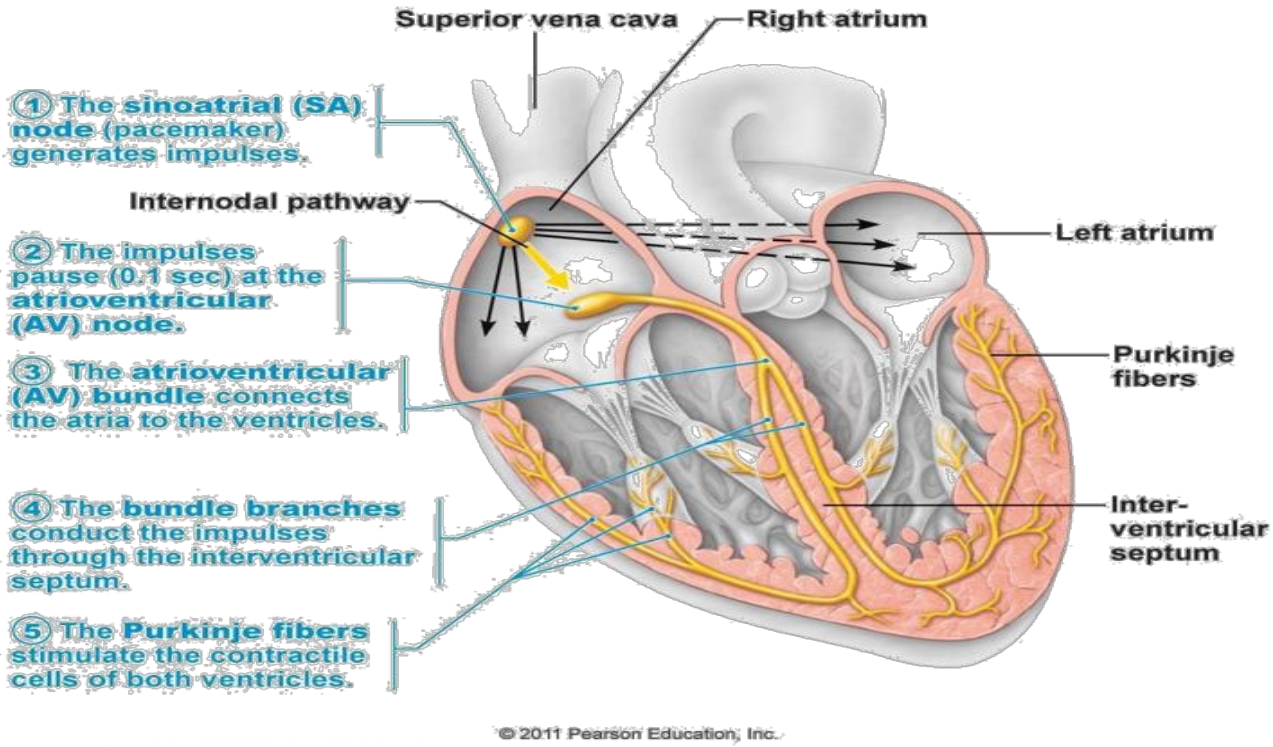
INTRINSIC CONDUCTION SYSTEM & ITS COMPONENTS

The intrinsic conduction system is composed of these 5 parts, they are also called (autorhythmic cardiac muscles cells) because they produce regular action potential rather than contractile. They approximately represent 1% of cardiac muscles cells. These conductive cells are able to produce intrinsic impulses but with different **RATES**.



Function of the conduction system: initiate & distribute impulses so the heart depolarizes & contracts in an orderly manner from atria to ventricles.

Pathway of the heartbeat:



Before we talk about the pathway, let's mention some notes about the components of the conduction system:

- -**Intrinsic rates** (the number of impulses -action potentials- generated per minute) as follows: SA node 70-80/min, AV node 40-60/min and Purkinje fibers 15-40/min.
- -All these components have the ability to generate their own intrinsic impulses. However, since SA node has the fastest intrinsic rate, its rate will be the one conducted through to AV→AV bundle →Purkinje fibers→ contractile muscles of the heart, setting the pace (speed) of the heart, thus the SA node is called **PACEMAKER**.
- -At this point, you just have to be familiar with the terms Systole and Diastole since they're going to be discussed later. You must know that Systole means contraction, Diastole means relaxation.

The pathway begins in the SA node, then there are 2 possible ways to AV node: either by the internodal pathway or the atria muscle cells. Then, it reaches the AV node and there the impulse is **delayed**. Then, the AV bundle (Bundle of His) takes impulse through left and right bundle of Purkinje fibers to all parts of ventricles.

WHY IS IT DELAYED? so the atria contract and finish their contraction (systole of the atria) before the ventricles contract (systole of the ventricles), otherwise the contraction of the atria and the ventricles will overlap and this causes an abnormal function of the heart.

→we said that SA node is the pacemaker since it has the fastest intrinsic rate, and the conductor that has the fastest intrinsic rate suppresses other conductors of subsequent parts, this is called **OVERDRIVE SUPRESSION.** But, what will happen if the SA node is not functional anymore??

-Think of this system as a train having multiple carts, and of course the cart with the highest rate leads, thus heart rate measures (that of atrial and ventricular contraction) will be that of SA intrinsic rate =70-80 beats/min. If the SA rate is absent, the leading cart (conductor) will be the 2nd fastest rate which is the AV, so the heartbeat will be 40-60 beats. However, the AV node is an abnormal site for the pacemaker, thus is called Ectopic pacemaker. (any pacemaker other than the SA is an ectopic pacemaker).

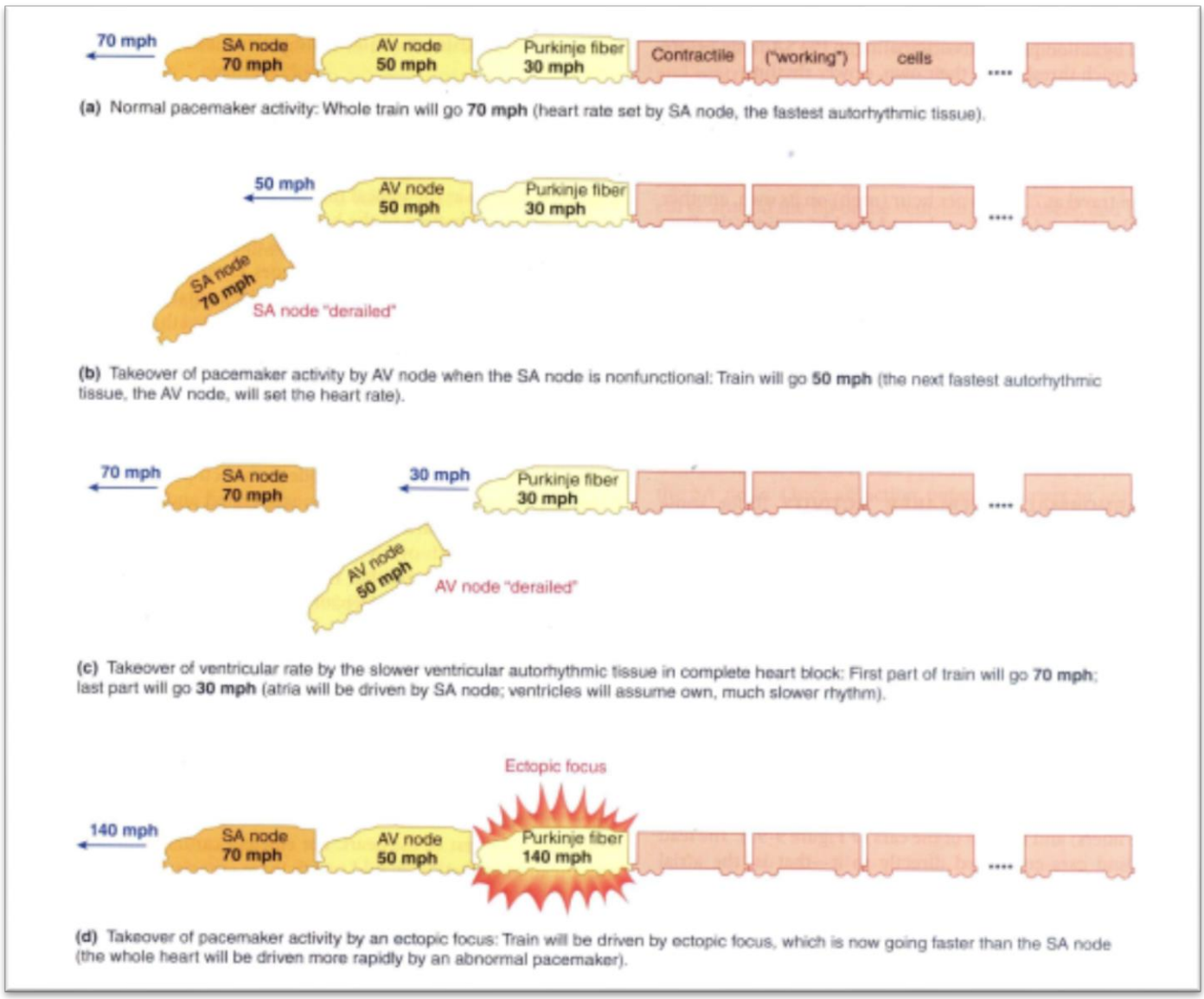
-If both SA & AV rates are absent, the heart rate will equal that of Purkinje fibers' rate =15-40 beats/min, this is called AV block (heart block).

-Ectopic pacemaker can result in **BOTH** higher and lower heart rates, not necessarily lower.

-Absence of AV node rate could either be due to a dysfunctional AV node or dysfunctional AV bundle→ the point is: impulses don't reach Purkinje.

-What if only AV node is dysfunctional but SA node and Purkinje are still working? there will be two rates in the heart, atrial rate (70-80) and ventricular rate (15-40).

Please study the following scenarios especially (d):

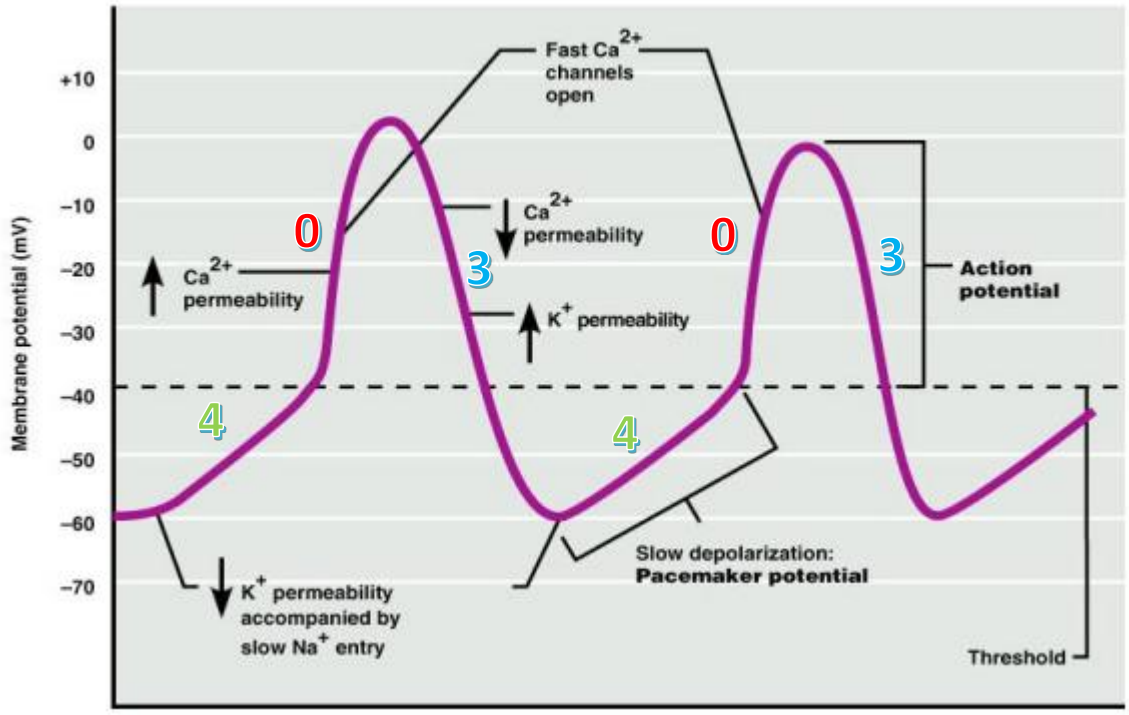


MECHANISM OF THE INTRINSIC CONDUCTION SYSTEM

→The conduction system cells are specialized differentiated cells. They are small and rounded in contrast to normal cardiac cells, which are quadrant in shape. Also, they lack contractile fibers, so they are unable to contract; and they have less intercalated discs & less gap junctions. These points were in terms of structural specialization. In terms of functional specialization, these cells are leaky to Na^+. (by leaky we mean "slow leakage").

The conduction system has a different action potential than the contractile cardiac muscle action potential. First, we will simplify the SA node action potential and compare it with the contractile action potential, then we will mention the differences between SA node and other conductors.

➢ THE SINOATRIAL (SA) NODE POTENTIAL:



I. Phase 4:

- Is slow depolarization.
- Accounts for the pacemaker activity of the SA node (automaticity).
- Is caused by an increase in Na^+ conductance, which results in an inward Na^+ current.

II. Phase 0:

- Is the upstroke of the action potential.
- Is caused by an increase in Ca^{2+} conductance. This increase causes an inward Ca^{2+} current that drives the membrane potential toward the Ca^{2+} equilibrium potential.

III. Phase 3:

- Is repolarization.
- Is caused by an increase in K^+ conductance, which results in an outward K^+ current that causes repolarization of the membrane potential.

Some notes:

- The resting membrane potential will never reach -90mV due to the leakage of Na^+ in phase 4.
- Since they leak Na^+ in a slow manner, the membrane potential will slowly reach the threshold due to slow depolarization. So when reaching the threshold, the inactivation gate of Na^+ channels had enough time to close and no Na^+ can enter the cell, luckily there are Ca^{2+} slow gated channels (slower than Na^+ channels) which allow the Ca^{2+} influx.

	SA node	Contractile cardiac AP
Names	Slow response action potential, pacemaker action potential, self-induced action potential, autorhythmic.	Fast response action potential, Non-pacemaker action potential.
Phase 0	Due to Ca^{2+} influx.	Due to Na^{+} influx. (rapid)
Phase 1+2	Not present in SA node action potential.	Phase 1: initial repolarization by K^{+} efflux. Phase 2: transient increase in Ca^{2+} influx.
Phase 3	Due to K^{+} efflux.	Due to K^{+} efflux and decrease in Ca^{2+} influx.
Phase 4	Due to Na^{+} influx. (leaky)	Due to equal efflux and influx currents.
Plateau	No presence of plateau.	Presence of plateau in Phase 2.
Resting membrane potential	The cells of the conduction system have no actual resting potential as the membrane potential does not stay the same due to leaky sodium channels. We also call it pacemaker potential and it equals -60mV.	The resting membrane potential equals -90mV.
Na^{+} channel gates status at the threshold	The activation gate is open, but the inactivation gate is closed because the membrane potential reached the threshold slowly.	The activation & inactivation gates are open.

➢ THE DIFFERENCES BETWEEN (SA) NODE AND OTHER CONDUCTING SYSTEM COMPONENTS: (3 differences)

- ✓ **Resting membrane potential:** slow depolarization is slower in the AV node and much slower in Purkinje fibers *(in fact the Purkinje action potential looks similar to contractile muscle fiber)*.
  Although the resting membrane potential of AV node is more negative than SA node membrane potential, it will never reach -90mV because there is still some leakage of Na^{+}.
- ✓ **Intrinsic rate:** the number of impulses- action potentials- generated per minute are as follows: SA node 70-80/min, AV node 40-60/min and Purkinje fibers 15-40/min.
  The slope of AV is lower than SA because the Na^{+} leakage in AV is lesser than Na^{+} leakage in SA.

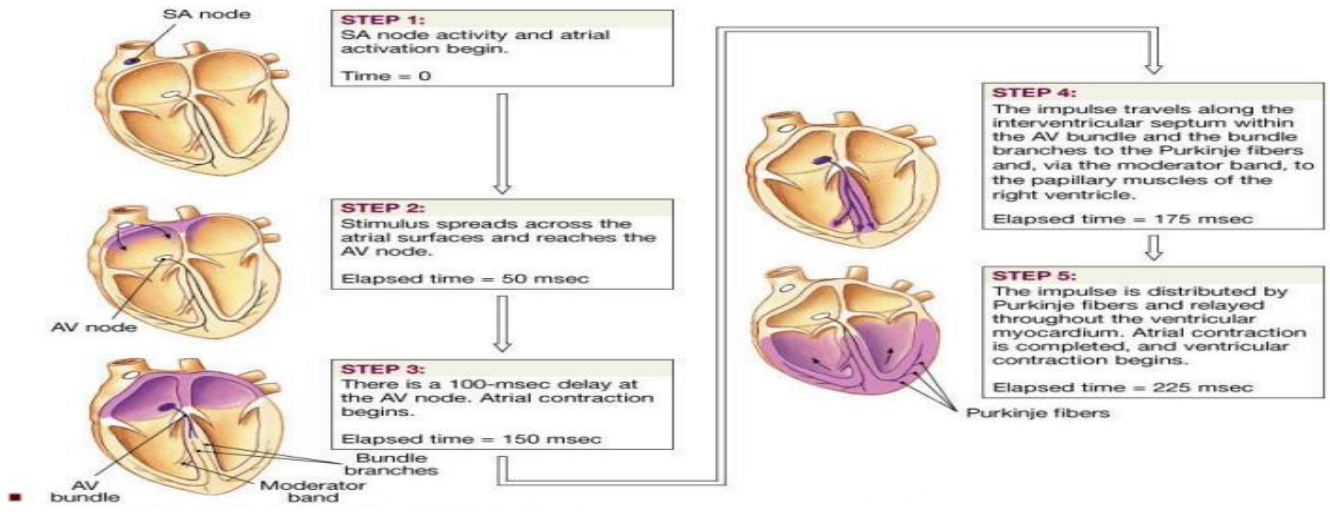
This rate depends on:

1- **The slope of the Phase 4** (-60 to the -40, threshold). Higher slope means less time to reach the threshold, thus a higher rate.
2- **The extent of negativity of the membrane potential**, the less negative it is, the shorter the time needed to reach the threshold. →Steepness of the slope and membrane potential depends on the permeability of the membrane to sodium, potassium, and calcium. Finally, this is what creates the difference in the rhythmic rates between SA, AV nodes and Purkinje. It is due to the difference in their sodium permeability (sodium leakage), and AV node being less permeable to sodium than SA, so the membrane potential is more negative, more time is needed to reach the threshold, intrinsic rate is less than that of SA node.

✓ **The conduction rate:** (It is the speed at which an impulse propagates, how fast they conduct an action potential)
-SA node: slow speed of conduction.
-Ventricular and Atrial muscle: Moderate speed of conduction.
-**AV node:** slowest speed of conduction.
-Purkinje fibers: Fastest speed of conduction, slowest intrinsic rate as noted earlier.

Reminder → **why the conduction rate in the AV node is the slowest?** To ensure that the atria and ventricles do not contract at the same time; atria systole finishes, followed by ventricular systole, this is mediated through AV node which delays the impulse. This delay is called **AV delay.**

- The conduction rate is the fastest in the Purkinje, 4m /sec, due to high number of gap junctions, large diameter and low resistance. All of which to make sure that ventricular muscle cells receive the impulse at the same time and contract at the same time as one unit (one pump), within milli seconds the entire ventricle will have contracted. Otherwise, each ventricular fiber contracts independent from the others, which is called ventricular fibrillation; it is lethal, and the physician should interfere to relief the condition by defibrillation (either defibrillation shock or drug).



Tissue	Conduction rate (m/s)
Atrial muscle	0.3
Atrial pathways	1
AV node	0.05
Bundle of His	1
Purkinje system	4
Ventricular muscle	0.3-0.5