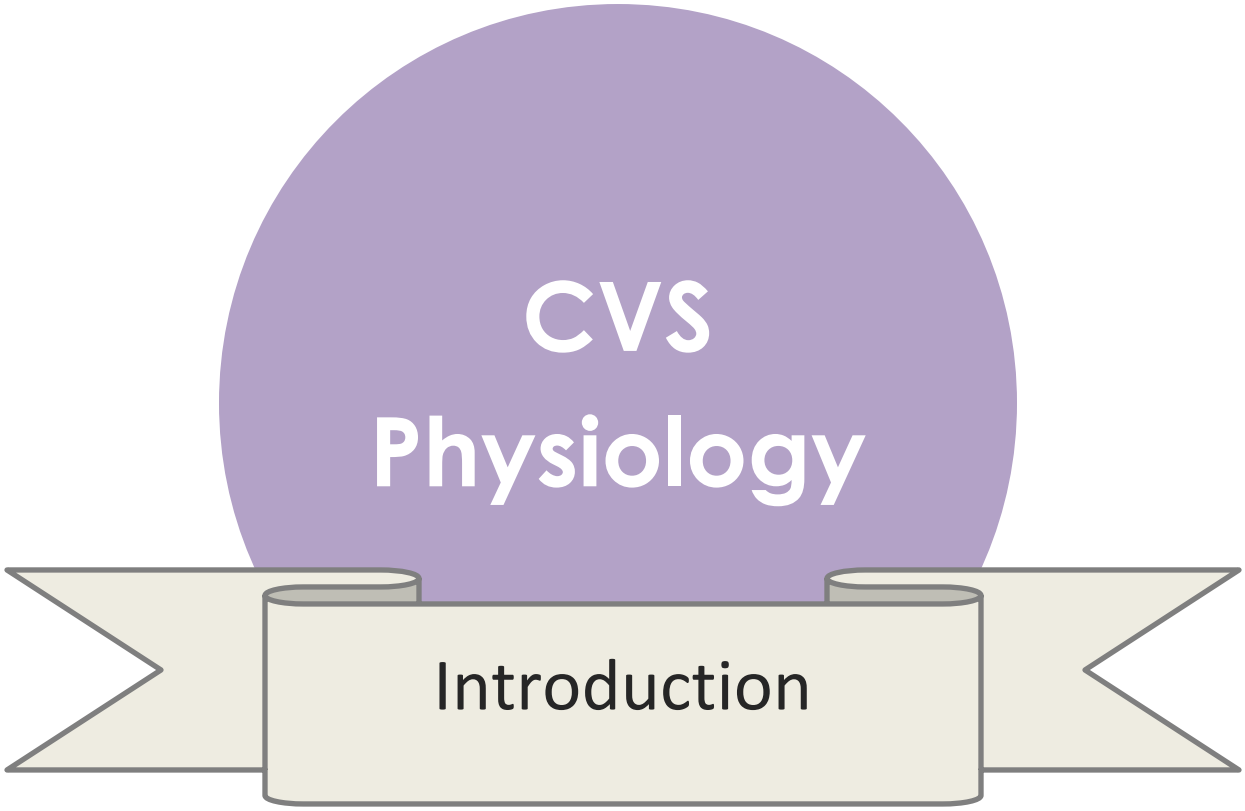

CVS
Physiology
Introduction

Before we start:

- ✓ Physiology of the cardiovascular system is one of the most interesting subjects. So try to enjoy our 18 lectures with Dr. Faisal Mohammad.
- ✓ Our reference book is "textbook of medical physiology by Guyton & Hall" [11th edition, 12th edition or the latest 2016, 13th edition]. You can find the pages needed in the first two slides. Dr. Faisal encouraged us to read from the book, because not all the details are included in the slides and we may be asked about them.
- ✓ The cardiovascular system is composed of two parts:
    - Cardiac --> Heart.
    - Vascular --> Blood vessels.

-We will start by studying the cardiac part in the first 10 lectures,

then we'll continue with the vascular part. But keep in mind that

nothing works alone in our body, it's all connected!

- ✓ In our first year's physiology course we've studied the cardiac muscle action potential, these lectures will be revised but not in details, you should refer to them when needed.
- ✓ This lecture will be an introduction and it'll be one of the easiest lectures you've ever encountered.
- ✓ Why do we need basic sciences like physiology, pharmacology and microbiology as doctors?

>>Simply to solve problems for our patients. Let's have a look on a

clinical problem to show us how:

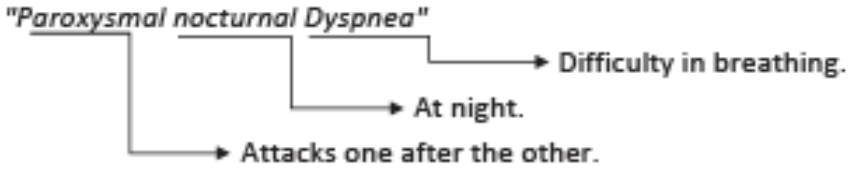
A 54 years old man seen in the cardiology clinic complaining of severe weakness, fatigue, dry cough, weight gain and difficulty in breathing. He feels severe shortness of breath while walking up stairs of his second floor apartment. He still complains of lesser severity of symptoms at rest. He states he often awakens at night feeling like he was suffocating. He is now sleeping with three pillows under his head. Lately he has taken to fall asleep while he is sitting watching T.V. He also complains of having to urinate 3-4 times per night. He was hospitalized with heart problem two months ago and was told that the efficiency of his heart is less than 30% and he needs ?? and has to wait until??. On examination his weight is 95Kg, height is 165 cm, blood pressure was 140/85 mmHg, his heart rate 90 beats/min and regular, his resp. rate is 28/min and labored.

Auscultation of the heart reveals abnormal heart sounds

**Let's discuss every single symptom:

- ✓ **[Severe weakness]**: The cardiovascular system is what deliver oxygen to the tissues, so lack of oxygen --> no energy --> weakness.
- ✓ **[Fatigue]**: Unable to move especially when walking up stairs and during other heavy activities, because it needs extra energy to be done.
- ✓ **[Dry cough]**: Because of the fluid in the lung (Edema) will irritate the lung resulting in coughing and It's dry because no inflammation took place.
- ✓ **[Weight gain]**: Because of fluid retention.
- ✓ **[Difficulty in breathing]**: Because the fluid in the alveoli broadens its membrane making the diffusion of gases much harder (If the membrane is thinner the diffusion is faster). Plus, the fluid makes it easier for CO2 to pass, because it's 20 times more soluble than O2.
- ✓ **[Severe shortness of breath while walking up stairs and less symptoms at rest]**: Because the severity of symptoms depends on the amount of energy and, as a result, oxygen needed.
- ✓ **[Awakens at night feeling like he was suffocating]:** While sleeping the fluid accumulates in the lungs causing the feeling of

suffocation, the patient wakes up, goes to the window to breathe some air, he feels better and think that the fresh air did that, go back to sleep a d it all happens again, it's not the fresh air which made him feel better its simply the **gravity** pulling the fluid downward when he stands up making him feel better.
The patient's episodes have the medical name:



✓ **[He's sleeping with 3 pillows under his head]:** He found out that it's much more comfortable and that's because he's avoiding "orthopnea" which is dyspnea when lying flat. [Sleeping with three pillows will, to a lesser extent, prevent pleural edema that is causing this difficulty in breathing]

✓ **[Sleeping while watching TV]:** Decreased amount of oxygen that carries out metabolic actions, & because of increased CO2 content. (High CO2 & Low O2).

✓ **[Urinate 3-4 times per night]:** Some doctors might quickly decide that this patient has a renal failure or urinary tract infection! But NO, too much fluid in his body, increases fluid filtration in the kidneys, filling his bladder, therefor too much urine excreted.
So when a patient comes to you with excessive urination, take Heart failure into consideration, not only renal failure. Here you can see the interrelation between different body systems [Cardiac/Respiratory/Urogenital]

✓ **[His heart efficiency is less than 30%]:**
The efficiency is the percentage of blood pumped out of the ventricle over the total amount of blood in the ventricle.
A normal person will have a heart efficiency of about 50-75%
The patient here has only 30% which is very low.
We will find out what does that mean in more details later on during this physiology course.

✓ **[He was told that he need a heart transplant and he need to wait for someone *young* to die]:** Before a heart transplant decision is

made, we need to try to solve any cardiac problem by fixing the patients diet[nutrition], drugs, and a continuous therapy. If all of these don't work then we decide to make a transplant. It's not an easy process, first we need to find a healthy heart, it's usually found when someone young die usually from a car accident. And next we have to avoid rejection by matching antigens, especially HLA antigens (MHC) and using immunosuppressant drugs like cephalosporins.

Note: The transplanted heart can be:
[1] Natural Heart – A young dead human being or even an animal [mammal].
[2] Mechanical Heart – This heart is being made in medical laboratories, it's easier that waiting for a young healthy person to die.
But the main problem with the mechanical heart is that, its transplant will lead to blood clot and therefor the doctors will give the patient anticoagulants, leading to excessive bleeding →Death.
So most of the times the mechanical heart transplant will lead to the death by excessive bleeding not because another heart failure.

- ✓ **[His weight= 95 KG, blood pressure= 140/85, respiratory rate= 28]:**

His weight is high due to fluid retention [edema].
His blood pressure is slightly high.
His respiratory rate is high. {Normal respiratory rate is 12-20 breaths/min}

- ✓ **[Auscultation of the heart reveals abnormal heart sounds]:**

Listening to the heart sound using stethoscope revealed an abnormality.{Using stethoscope we can hear two heart sound; S1 and S2 as a result of closing the valves}
From this case you should have realized that you need to understand the *physiology* in order to *analyze* the symptoms, need pharmacology to determine the drugs needed to be taken, and you need *microbiology* to figure out what *microorganisms* may have caused a particular disease.
Basic sciences are much more important than you think.

الأشياء التي ستذكر في هذا القسم غير مهمة

Objectives of this lecture:

1. Introduction to the CVS physiology and a brief history of cardiac transplant.
2. Review the anatomy of the CVS (Just basic anatomy is needed to understand physiology).
3. List the function of the CVS (carry oxygen & hormones from area to another and carry carbon dioxide back to the heart).
4. Comprehend the pump nature of the heart (may be repaired, replaced, made mechanically).

History of cardiac Transplant:

As we said, the heart is a pump and it can be replaced.

- ✓ In 1967, Cape Town, South Africa

The first human heart which was transplanted, was taken from a **25 year** old woman who had **died** from a **car accident** and placed in a 55 year old man dying of heart damage by Dr. Barnard.
18 days later, the recipient **died because of rejection**.
Immunosuppressants (cyclosporins) were not known back then.

- ✓ In 1984, Columbia

The first pediatric heart transplant on four year old boy, he received a second transplant in 1989 and lived a productive life till 2006, he died from non-cardiologic problem. It is thought that the transplant was more successful in pediatrics because of their less differentiated immune system.

- ✓ In 1984, California

Baboon heart was transplanted into a 12 day old girl, she survived for twenty days and **died because of rejection**.

- ✓ In 1982, Utah

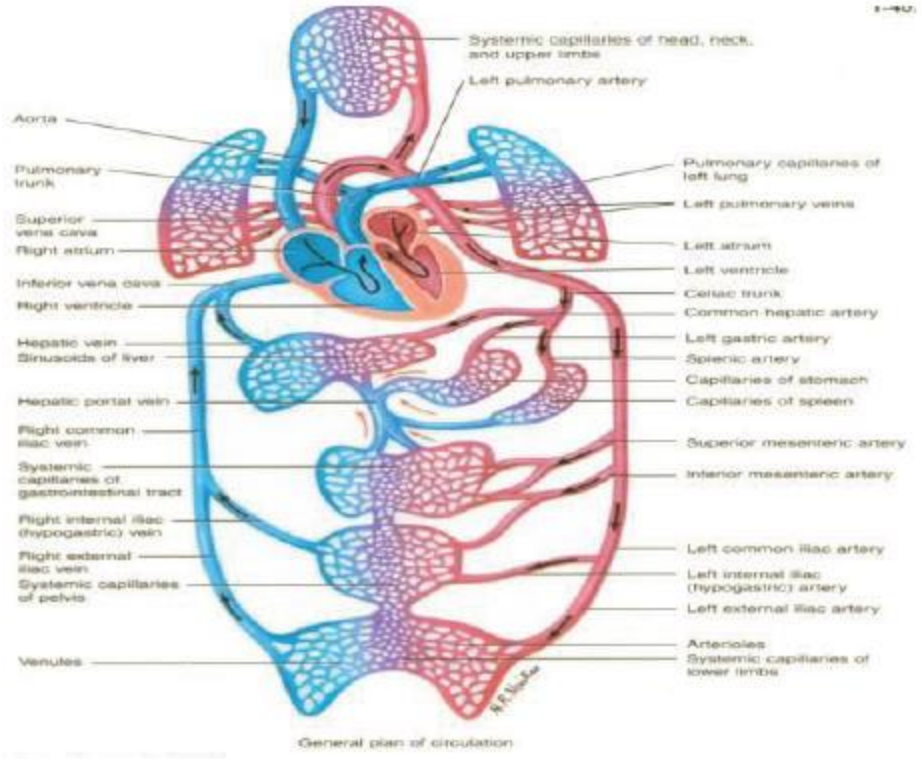
The first artificial *[mechanical]* heart was implanted in a dentist named Barney Clarck, he **died** after 112 days because of **bleeding**.
Why? Because as mentioned earlier when blood is exposed to foreign bodies it clots, to avoid this we give anticoagulants, and because it's hard to regulate the anticoagulant dose, he died from bleeding.

✓ The experiments didn't stop there. Ventricular support by muscles like the pectoralis muscle has been tested.

إذا كنت قد درست الأناتومي فلا حاجة إلى دراسة هذا القسم

Introduction to the anatomy of CVS:

<u>Anatomy of the Vascular part:</u>



General plan of circulation

-We have two types of blood vessels:

Artery = **A**way from the heart.

Vein = towards the heart.

-Regardless of the oxygenation:

The main blood vessel is the aorta and it has an arch going from anterior to posterior, and it gives three branches:

On the right side: brachiocephalic artery which divides into right common carotid and right subclavian.

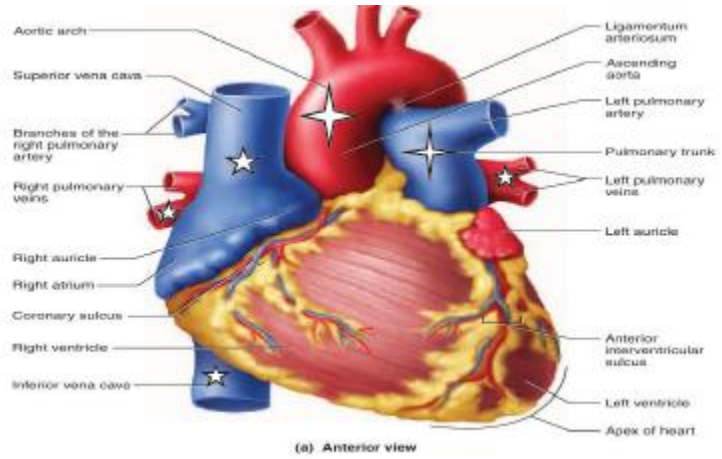
On the left side: common carotid artery (to the head and neck) and subclavian artery (to the upper limb).

Then the arch descends downward forming the thoracic aorta.

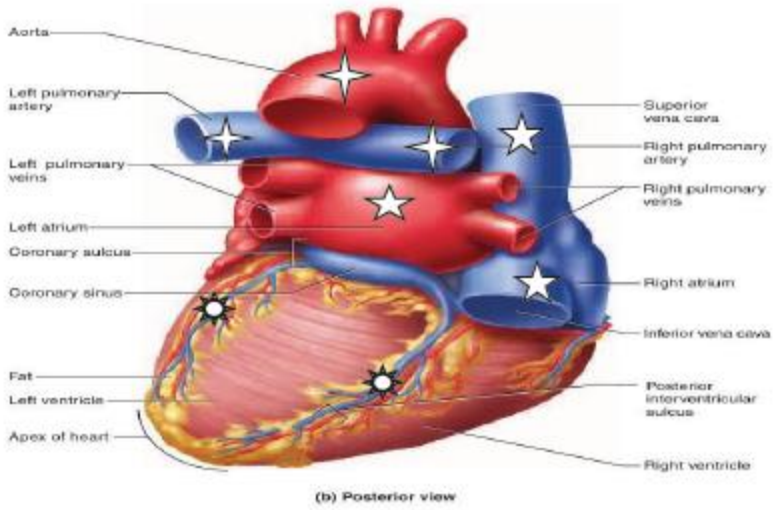
After piercing the diaphragm it's named the abdominal aorta

which gives a lot of branches (superior and inferior mesenteric arteries, renal arteries, etc...) and end up in forming two common iliac arteries.
So the aorta distributes blood to all parts of the body.
-The major arteries divide into big arteries and end up in forming arterioles then capillaries (arterial side of the circulation). Capillaries collect into venules that end up in forming large veins that forms at the very end, Superior and inferior vena cava that brings blood to the heart again (venous side of the circulation).
-We have two types of circulation: **systemic circulation** (greater circulation) and **pulmonary circulation** (lesser circulation, pulmonary arteries and veins).
-These circulations are more important than the heart. Why? Because we can fix the heart by drugs or transplantation but not the microcirculation (where filtration and reabsorption and sometimes edema take place).

<u>Anatomy of the cardiac part:</u>
-The heart is located in the mediastinum (middle of the chest).
- The figure below shows an anterior view of the heart:

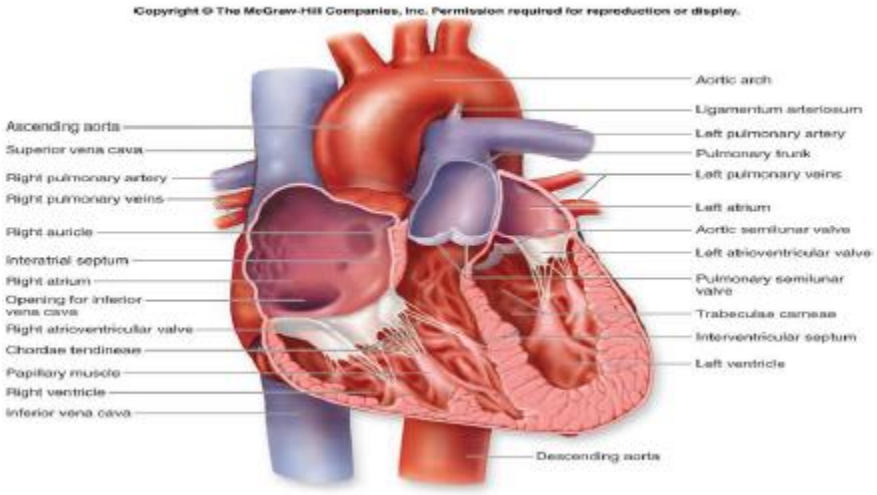


**Notice the marked blood vessels that we've talked about.
** The pulmonary arteries carry deoxygenated blood but still called arteries.
- The figure below shows a posterior view of the heart



(b) Posterior view

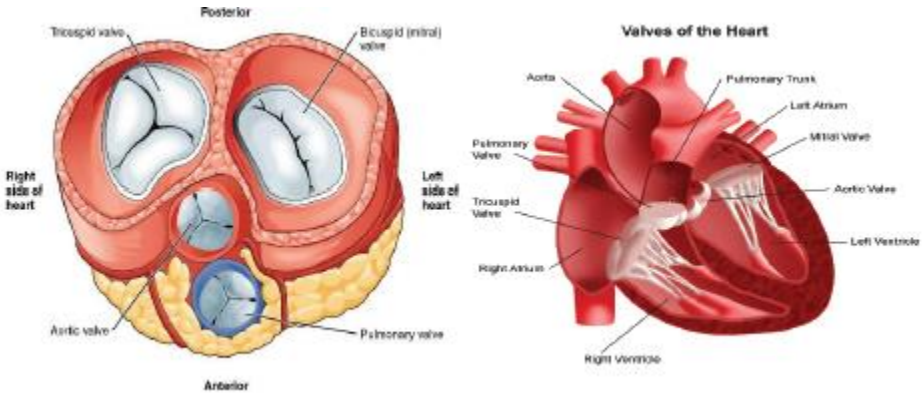
-Notice the arteries that supply the heart (coronary arteries {  }) run superficially (unlike arteries of other systems) and that has a huge advantage, if they get blocked we can make a bypass [replace the damaged artery] from other vessel (saphenous vein) or we can use a string or a balloon to release the blockage.
-The heart is composed of **4 champers** (two atria and two ventricles), see the next figure and notice the following:



** Each one of the atria and ventricles is separated from each other by atrioventricular septum (fibrous tissue), so the atria and ventricles are not continued muscularly.
** The atria are continuous muscularly and the ventricles are

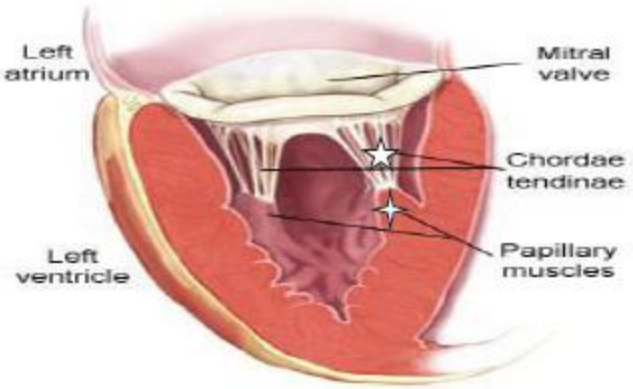
continuous too. So any stimulus that goes for one of the atria it goes for both atria at the same time. And any stimulus that goes for one of the ventricles it goes for both ventricles at the same time. This is called syncytium (one unit), so we have two syncytia; atrial syncytium and ventricular syncytium.

Cardiac valves are shown in the figure below:



** Each atrium is separated from its corresponding ventricle by a valve; so we have:
One the right side= atrioventricular valve (AV valve) = **Tricuspid valve**.
One the left side= atrioventricular valve (AV valve) = **Bicuspid valve**= Mitral valve.
** We also have two other valves:
Aortic valve and **pulmonary valve**:
-Prevent the backflow of blood from the aorta to the left ventricle. And from the pulmonary trunk to the right ventricle respectively.
-They are called semilunar valves because each of those valves has leaflets that are shaped like half-moons.
** These valves open or close passively; according to pressure gradient.

** The edges of AV valves are attached to a tendinous structure called Chorda Tendineae (☆) they're inserted in a muscle called papillary muscle (✧). Notice the figure next page:



[Papillary muscle is part of the ventricular muscle, so when the ventricles contracts the papillary muscle does too and when the ventricle relaxes, it relaxes too. Chordae tendineae prevent regurgitation (prolapse) which is the movement of blood from the ventricle to the atrium. When the ventricle contracts to empty its content, the AV valves close and the papillary muscle contracts pulling the edges of the valve limiting its movement. So papillary muscle neither closes nor opens the valve, it regulates its movement.**]**

- **We conclude the importance of the heart valves:**

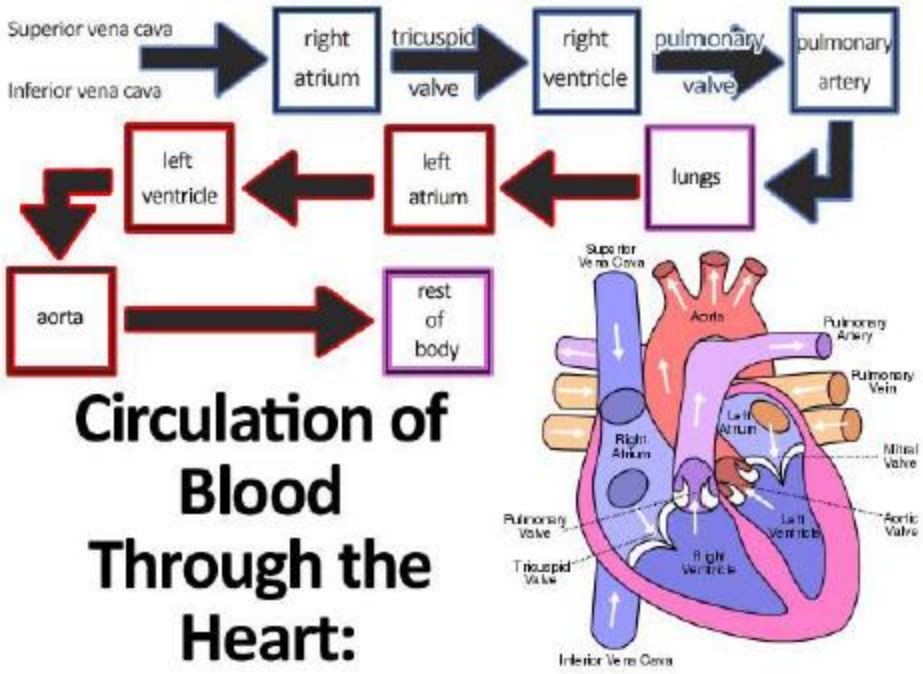
o Atrioventricular Valves:

- ✓ Prevent backflow to the atria
- ✓ Prolapse is prevented by the chorda tendineae.
- ✓ Tensioned by the papillary muscle.

o Semilunar valves:

- ✓ Prevent backflow into the ventricles.

Movement of blood in the heart:



** Follow the flow of the blood in the heart and make sure you know it well.

** Notice that the arterial system (of the systemic circulation) supplies the lung through bronchial arteries but bronchial veins do not empty in the venous system (of the systematic circulation) they drain through pulmonary veins to the left side of the heart.

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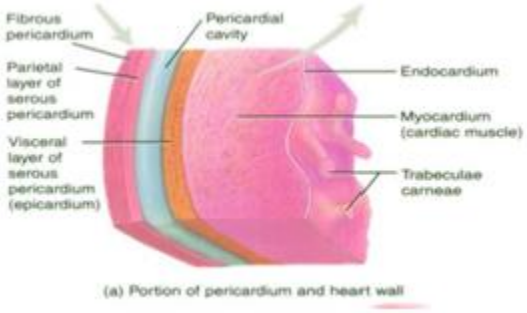
* The main function of the heart is to contract, the heart pumps the blood upon contraction, and this pumping activity results in the ejection of blood out of the heart, which is cardiac output.

<u>Layers of the heart (from inside to outside):</u>

1) The endocardium :

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 skeletal muscle cells and cardiac muscle cells

in terms of histological appearance:

- ✓ Skeletal muscle cells are cylindrical (spindle) in shape, whereas cardiac muscle cells are rectangular in shape.
- ✓ Each skeletal muscle cell is separate from other cells, whereas cardiac muscle cells are interconnected (Interdigitating) through intercalated discs.

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 voltage in a certain cell. Moreover ,they are sometimes called electrical couplers 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 hexagonal 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

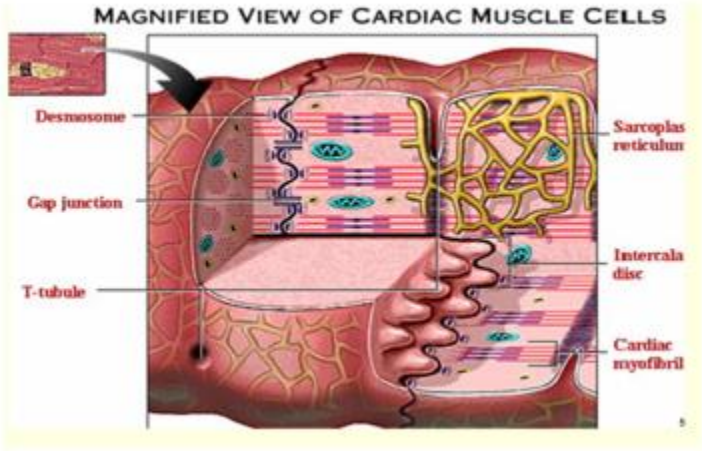
(They work as if they are one cell)

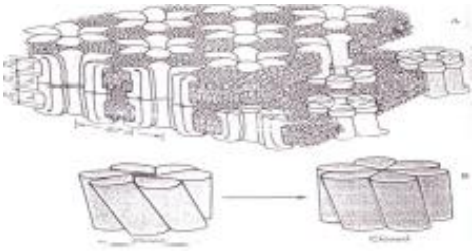
-There are two syncytia in the heart:

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: مش مهم

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.

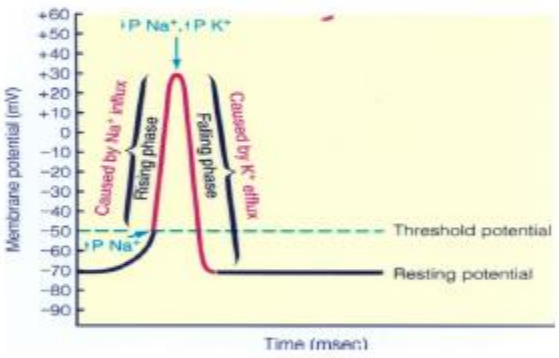
Action potential -Important

- **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:



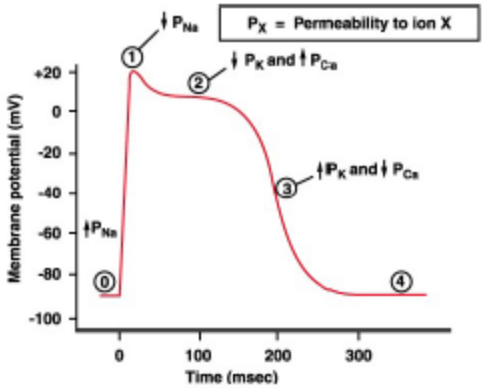
1. Resting membrane potential of skeletal muscle cell is low (-70).
2. There are only two phases:
   - Depolarization phase (rising phase).
   - Repolarization phase (falling phase).

- 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)

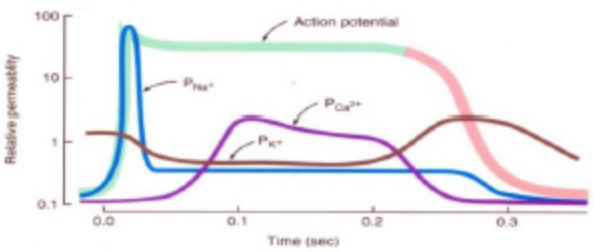
3- Phase (2) → plateau: due to opening of slow voltage-gated calcium channels (only in cardiac muscle).

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.



**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).

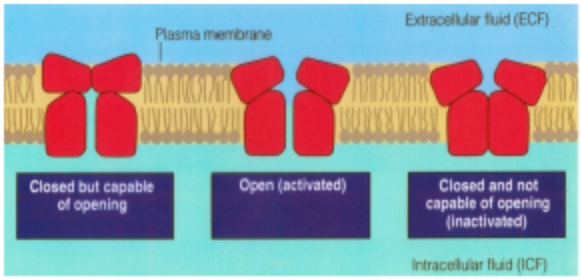
NOTE: the membrane potential is actually a result of a balance between all ions mentioned, not only one. For example, for the plateau to be accomplished we need to achieve a decrease in Na^+ influx, K^+ efflux and an increase in the Ca^{++} influx. If one of them is disrupted we won't get the plateau. 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.

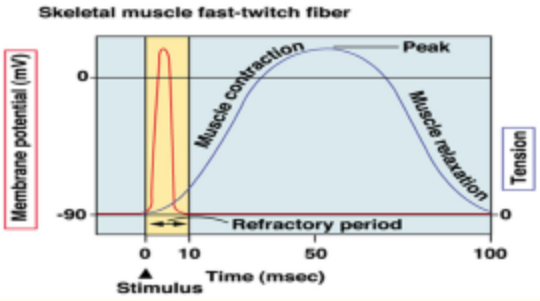
Absolute refractory periods and tetanisation

- 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.

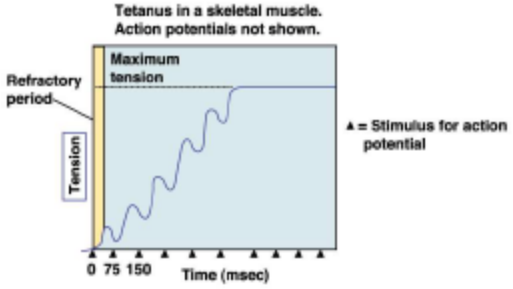
- This is very crucial to life since this will protect cardiac muscle from tetanisation which may occur in skeletal muscle when stimulated repeatedly.

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

➔ The whole skeletal muscle action potential occurs in the <u>latent period</u> 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.

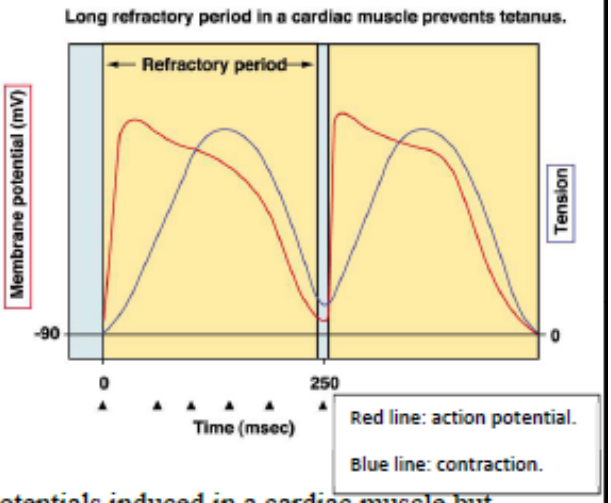


This mean that If there's another action potentials in the latent period, this will induce repeated contractions without giving a chance for the muscle to relax



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.



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.

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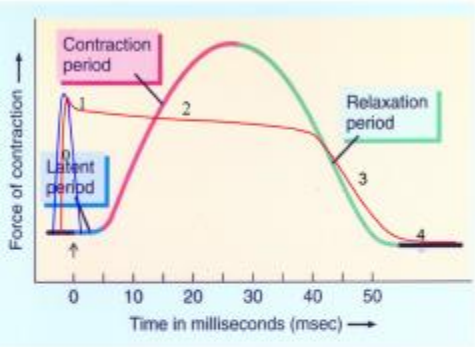
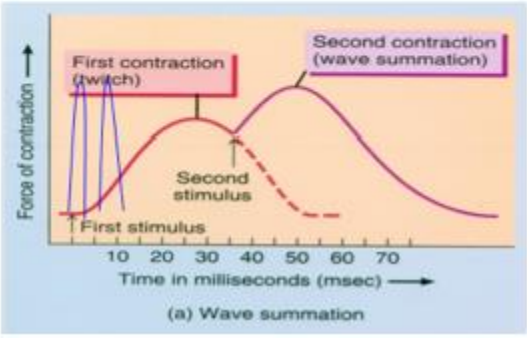
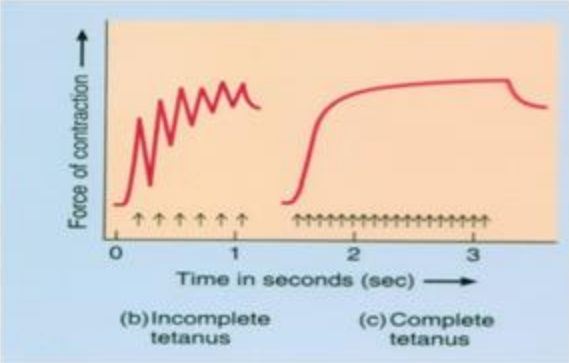


As you can see in the figure, the absolute refractory period overlaps with the relaxation phase of cardiac muscle.

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.



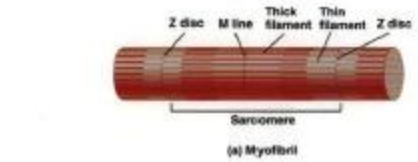


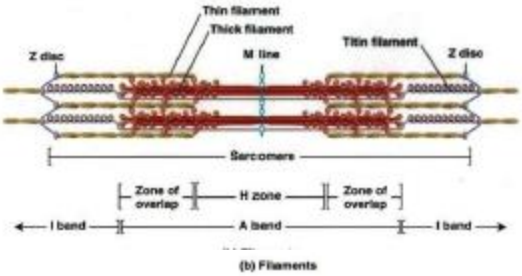
❖ In case (B) there's incomplete tetanus. i,e, there's some relaxation.

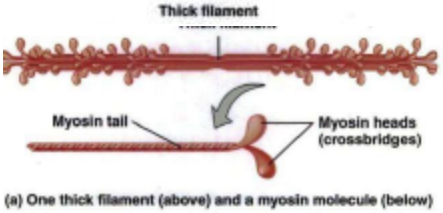
❖ In case (C) there's complete tetanus results in <u>fatigue</u> due to the high frequency of successive stimulations unlike case (B).

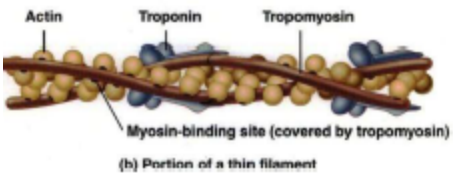
❖ <u>The structure of sarcomere:</u>

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.

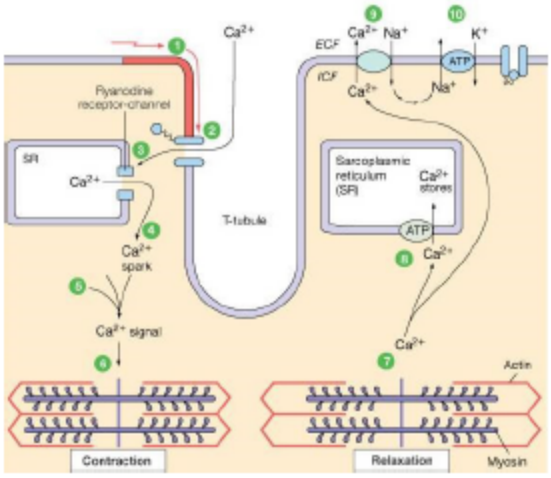
b) Portion of a thin filament appears as a double helix and composed actin, tropomyosin and troponin C which covers the myosin-binding sites "on the actin".

Mechanism of cardiac muscle excitation, contraction and relaxation:

FIRST: Excitability

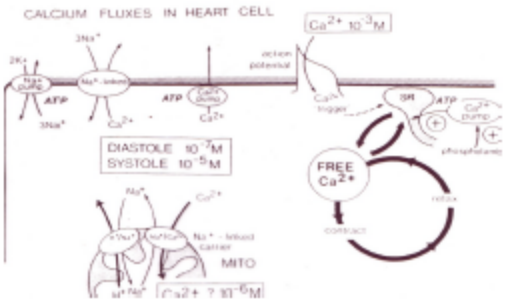
In systole, As the action potential reaches the cell this will triggers an increase in Ca^{++} influx with its concentration gradient due to the activation of slow voltage-gated Ca^{++} channels in the sarcolemma during phase (2), (hence, [Ca++] extracellularly is 10^{-3} while intracellularly is 10^{-7} 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.

Inotropic:

Modifying the force or speed of contraction of muscles.

"*Google translate*".

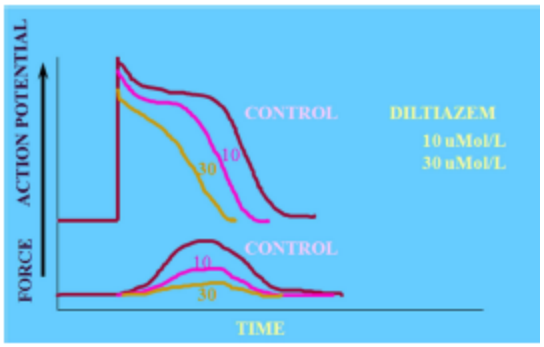
3- Ca^{++} pumps in the sarcolemma.

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.

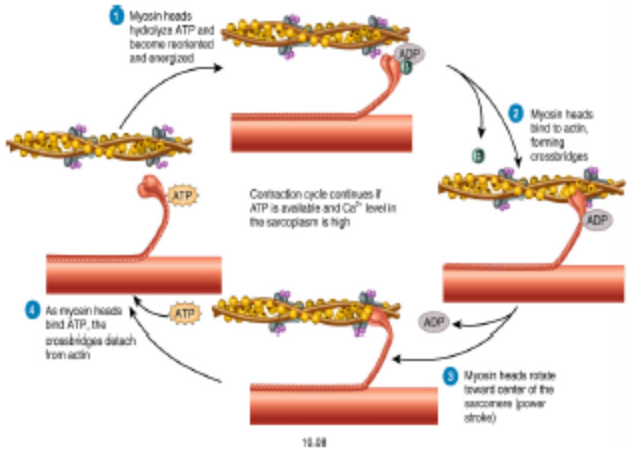


Let's take a look at pharmacodynamics of this drug more extensively; this drug will block the slow voltage-gated Ca++ channels. And as we said earlier, the importance of these channels rises in the maintenance of plateau. So, if we block these channels we are letting the K+ currents (efflux) to have 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.

Frank-starling law and the conduction system

Introduction

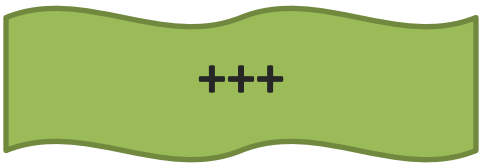
- Let's suppose that a muscle fiber (whether cardiac or skeletal) is a rubber band .

The length of this band is at rest = 4mm.

Force (passive)

- suppose that a force is applied on the band increasing its length (stretched) , this will create a tension which we refer to as **passive tension** .

active tension



- if this band, is contractile like the muscle :p, the force that will shorten the length will create a tension we refer to as active tension.
- A total tension in the band will be formed, equal to the resultant of both tensions .
- The more the passive tension we have, the more the total tension will be .

The relation between the length of the muscle and the force of contraction (tension):

- This relation is almost the same for both skeletal and cardiac muscle.
- This relation is stated by a law called **frank-starling** law of the muscle .
- Frank-starling law : "Within physiological limits, an increase in the resting length of the muscle , or an increase in the passive tension (resting tension) causes an increase in total tension and active tension until we reach a limit at which this active tension is maximum, when you exceed this limit the active tension decreases ".
- So, we have 3 forces (tensions):

  1.passive tension 2.active tension 3.total tension

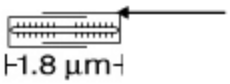
  Passive tension : the tension that is found in a muscle before it contracts and required to extend a resting muscle (stretching outside).
  When the muscle is stimulated, the muscle first overcomes the passive tension then muscle contracts by **active tension** thus the **total tension** required in contraction is the summation of active and passive tensions.

  We can not measure active tension directly but we can measure the other two tensions hence**, active tension = total tension – passive tension.**

Because the volume of the blood in ventricles is proportional to the length of cardiac muscle fibers (resting length creating passive tension); as the volume increases, the resting length increases. So, when the ventricles are filled with blood in end of diastole (**End diastolic volume EDV**) the length of muscle fibers increases **within the physiological limits** then the ventricle will contract pumping the blood and the amount of the blood pumped in each beat is called **stroke volume (SV)** and the amount that still remained in ventricles in end of systole is called **End systolic volume (ESV).** As the volume increases **exceeding the physiological** limits the resting (passive) tension increases but the active tension **decreases** , as a result the stroke volume decreases and ESV increases consequently more blood will be accumulated in ventricles and finally we end with **heart failure.**

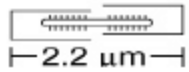
❖ The length of the muscle will be either : (follow each part on the full diagram below)

1. **Short , When the muscle is not stretched:**



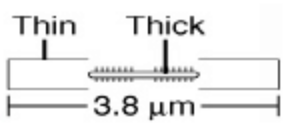
- The length of the fiber is short.
- The number of the actin filament binding sites (pointed with arrow) facing the myosin heads is low due to overlapping between the actin filaments in one half of sarcomere and the other half of the same sarcomere.
- This result in a lower force of contraction, low tension.

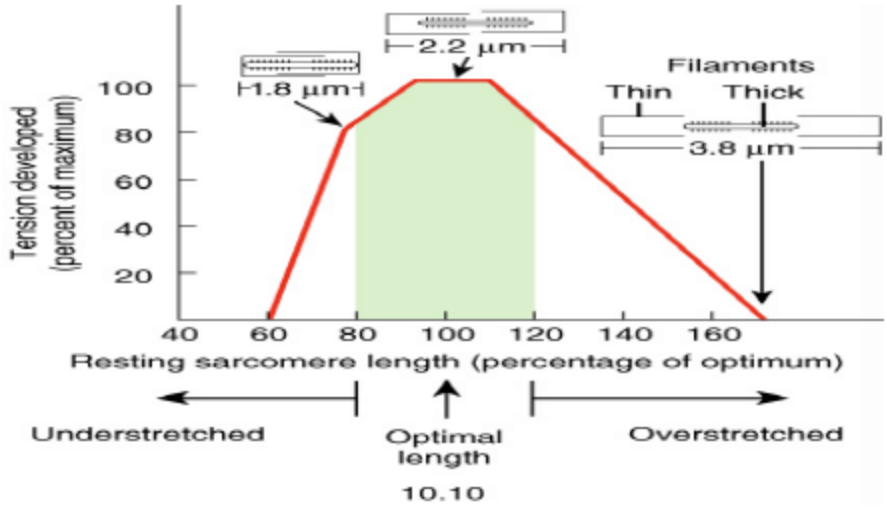
2. **The optimal length** :



- The number of the actin sites interacting with myosin is high (the highest).
- The force of contraction is high (look at the diagram)
- This is the length our muscles normally have.
- This corresponds to an optimal length 2.2 micrometer (optimal length of the sarcomere).

3. **Over stretched** :
   - When you stretch it more, the number of the active sites interacting decreases again and the force become less , until no more actin sites are opposite to myosin head, then the muscle no longer contracts .

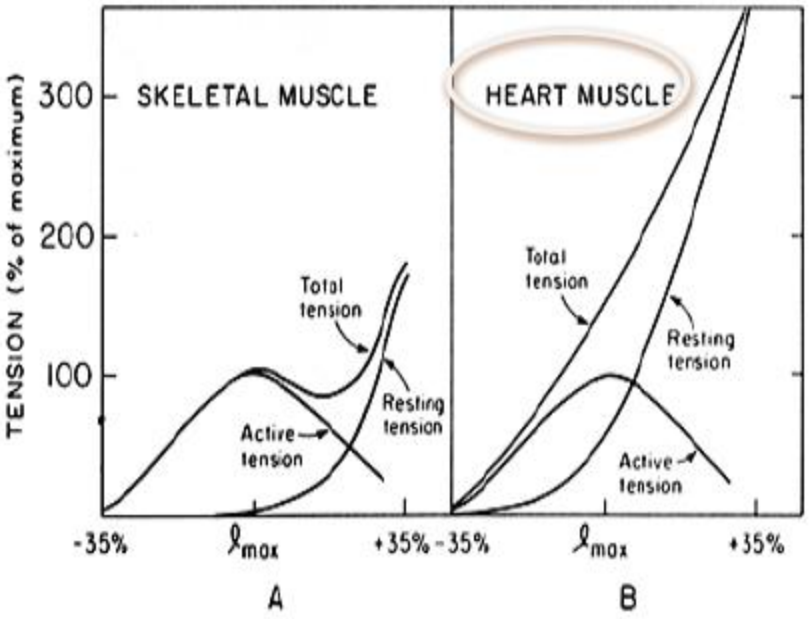




10.10

❖ According to the previous graph :

1. When the length is very short, the tension is very low and increases as the length increases.
2. The maximum tension (y axis) is reached when the length is within our optimal length.
3. As the length increases beyond this optimal limit, the tension starts to decrease again until the muscle can no longer contract.

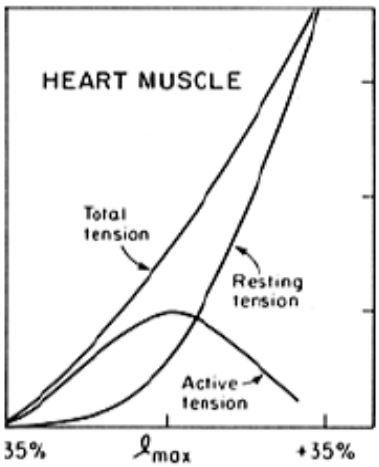


Y-axis represents tension while X-axis represents the length.

Cardiac Vs skeletal muscle :

1. **Cardiac muscle :**
   - The cardiac cells are arranged in the heart spirally , not straight, **so how do we know the length of the muscle??**
   - The length of the cardiac muscle in the heart is proportional to the volume of the blood before the muscle contracts .
   - The more the volume, the more is the length .
   - The volume before the muscle contracts is called (**end diastolic volume**) : The more the end diastolic volume, the more is the length, the more is the force of contraction, the more the amount of blood pumped .

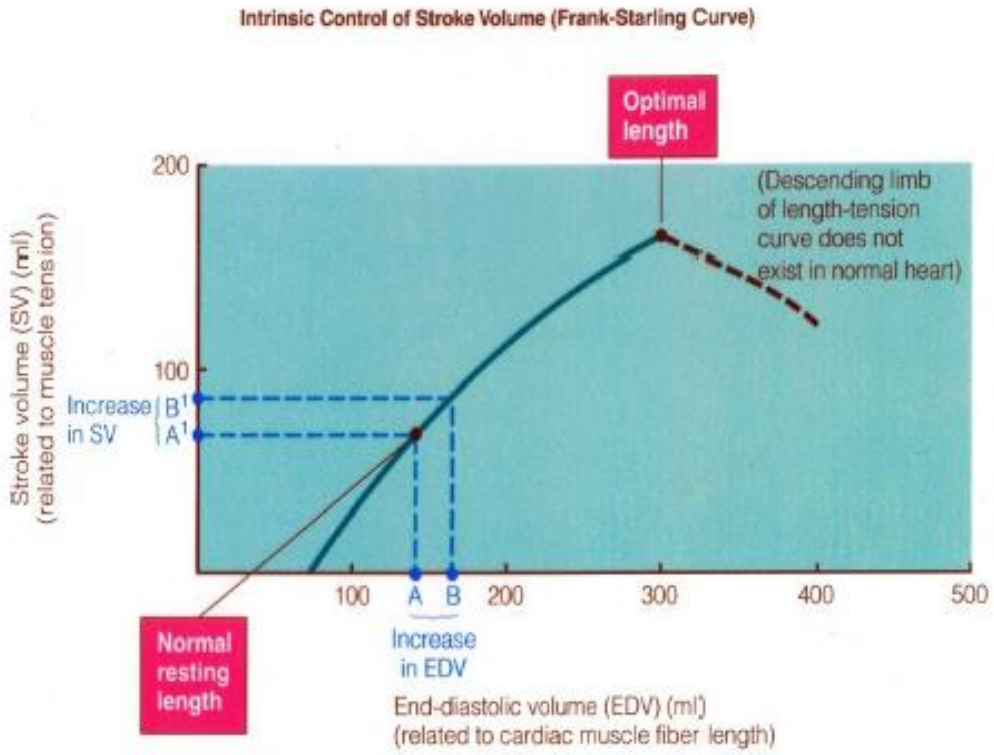
- **Stroke volume** : amount of blood pumped per one beat , equals the difference between the end-diastolic volume and the end-systolic volume , normally = 70 ml .



B

- Whenever you increase the length, the total tension increases.
- **Active tension** : the difference between the total and the passive.
- An outside force stretching the muscle will create a passive tension.
- contraction (active tension) happens within the muscle : for this contraction to occur it must overcome the **force outside** (passive tension) then it will show effect.
- Total tension is the sum of the active and the passive.
- We can't measure the active tension , we measure the total and the passive and the difference between them is the active tension.
- The cardiac muscle works at much less than its optimal length , this makes the heart capable of increasing its total volume when needed, the muscles can be stretched and remain within safe range for contraction, skeletal

muscles are already working within their maximum optimal length so they can no longer be stretched .



According to previous diagram:

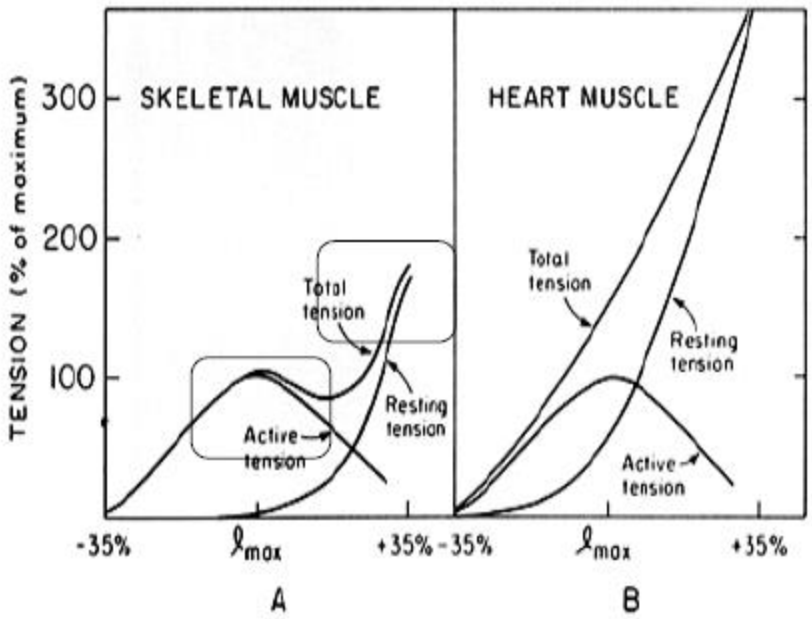
- When you exceed the volume(the volume that corresponds to the optimal length) ,we reach heart failure since the stroke volume starts to decrease.
- **Heart failure :** means that the heart can't pump the same amount that receives.
- **End diastolic volume** : 125 ml in ventricle(same in both right and left).
- **Stroke volume** : 70 go out, 70 return .
- **End systolic volume** : 55 ml

2. Skeletal muscle:

- Works normally at its optimal length.
- The skeletal muscle is already at its optimal length so if you stretch it more the force of contraction will become less.
- The active tension increases as we increase the length (within optimal range).

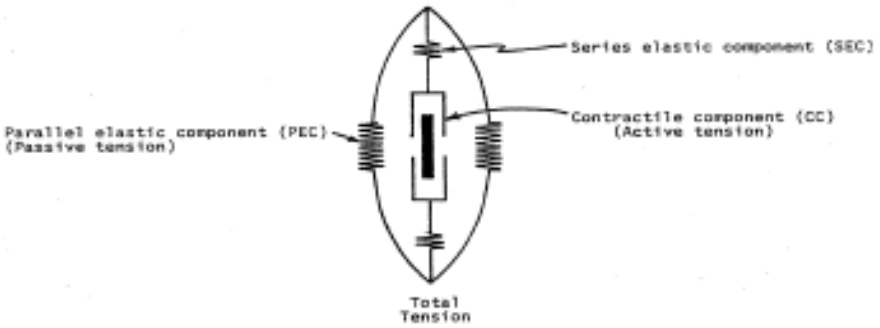
Regarding starling law, there are some differences between skeletal muscle and the cardiac muscle:

Skeletal has two peaks (in squares) :



But why there are two peaks for the maximal tension for skeletal muscle ??

- Because of the series elastic elements , that holds the thin filaments (these elastic fibers are not contractile proteins)



Series : تَوالي

Parallel : تَوازى

- By looking to the two figures in previous page, suppose that isometric contraction will occur then sarcomere will shorten stretching these elastic fibers (become tensed) until you reach the limit, after this limit these fibers will not tolerate more stretching, so notice that at the first peak; the active tension starts to decrease creating a hump in total tension and after a while it begins to rise up because the increase in passive tension will overcome the active tension until you reach another peak.

  Note: isometric contraction means that the length of muscle itself will not change during contraction but the length of sarcomere shortens stretching the elastic fibers(in skeletal muscles) creating a tension.

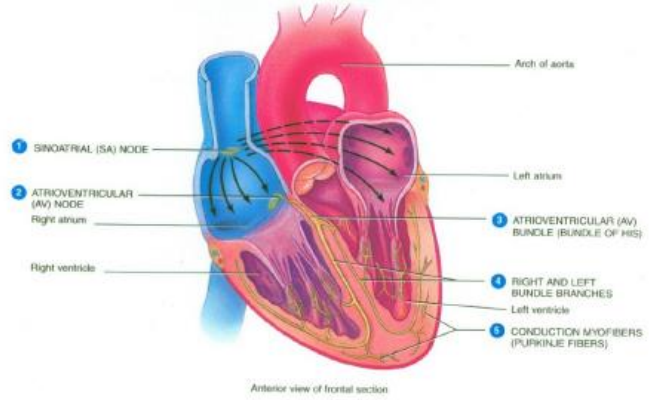
- In cardiac muscle cells are interdigitating we don't have these elastic fibers, so one peak will be present .
- Total and passive tension differ in cardiac and skeletal muscles (remember we have two peaks within skeletal).

The conduction system of the heart :

- The heart contract without the aid of any external nerve impulses, if you remove the heart from the body , the heart will keep pumping, only if you put it in a solution contains calcium.
- But **for any muscle to contract** there **must be a action potential**, this comes from ***an intrinsic source*** within the heart itself . (This is called the conduction system of the heart).

- **Components of the conduction system :**

1. SA node.
2. AV node.
3. AV bundle (bundle of his).
4. Bundle branches (right and left).
5. Purkinji fibers.



- Some believe that there are internodal bundles between the AV node and the SA node (The doctor doesn't believe that).

- The conduction (physiologically) :

    1. The ***SA node*** generate the first impulse due to its intrinsic activity (it is the normal pace maker of the heart) pace means speed , anything else is considered ectopic.
    2. The impulse is conducted through the muscles of the atria .
    3. The ***AV node*** receives impulse from the SA node through muscle fibers within both atria.
    4. The impulse is then conducted through the bundles (bundle of his and bundle branches) till reaching the ***Purkinji fibers*** .

- All of these cells are called autorythmic cells : they can depolarize and repolarize independent from an external innervations.

- These are modified cardiac muscle cells , and these modifications are:
    1. Modification in terms of **anatomy** include : rounded instead of rectangular, lack myofibrils (contractile proteins; actin and myosin) they are unable to contract, they form around 1% of total cells.
    2. Modification in terms of **physiology**: these cells are leaky to sodium by special channels called ***leaky channels*** which means that resting membrane potential is less negative (-60 to – 65 mV) instead of (-85 to -90 mV)

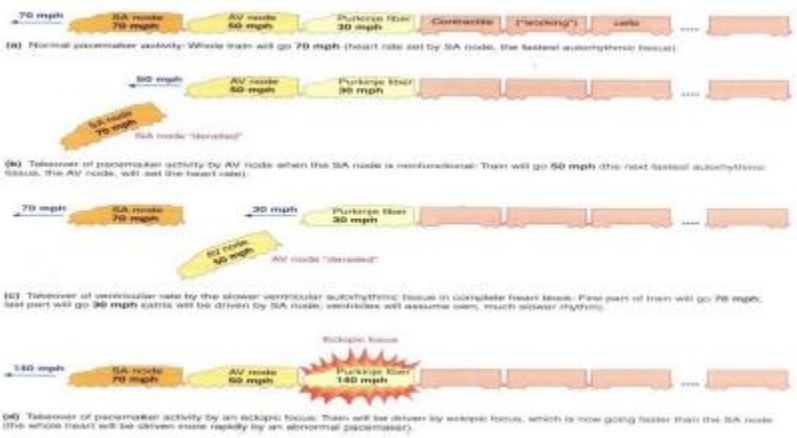
        - There are differences between them in:
        1. Their Intrinsic rate:

Intrinsic rate : The number of impulses generated per minute .

- Sa node : 70-80/min.
- Av node : 40-60/min.
- Purkinji fibers : 15-40/min.

- Think of them as carts of a train, the higher cart lead ;)
- normally the ventricle contract within a rate that is 70-80 (pace maker) ,this means that the Purkinji is also working within a rate that is 70-80 , the intrinsic rate here is said to be suppressed , this is called **over drive suppression** ,the same is for the AV node .
- So, the heart beats by a rate equals the highest intrinsic rate (how many action potentials per minute), normally SA node has that the highest rate once SA node is nonfunctional , AV node will set the heart rate (ectopic pacemaker), it needs from 30-60 seconds to shift to new rate.

- If the AV node is destroyed (even if the SA node is intact) the ventricle will not receive signal, since there is no connection between the atria and the ventricles).
- We have septa (fibrous tissue) ,separate the atria from the ventricles and doesn't conduct impulses .
- A damage in the AV node is called AV block, the impulse will not reach the ventricles so they will follow the Purkinji rate, this needs 15-30 seconds to begin.
- People who have AV block have a heart rate(rate of ventricles) that's 15-40(purkinji rate).
- They also have other rate for of the atria (SA node will set the rate of atria).



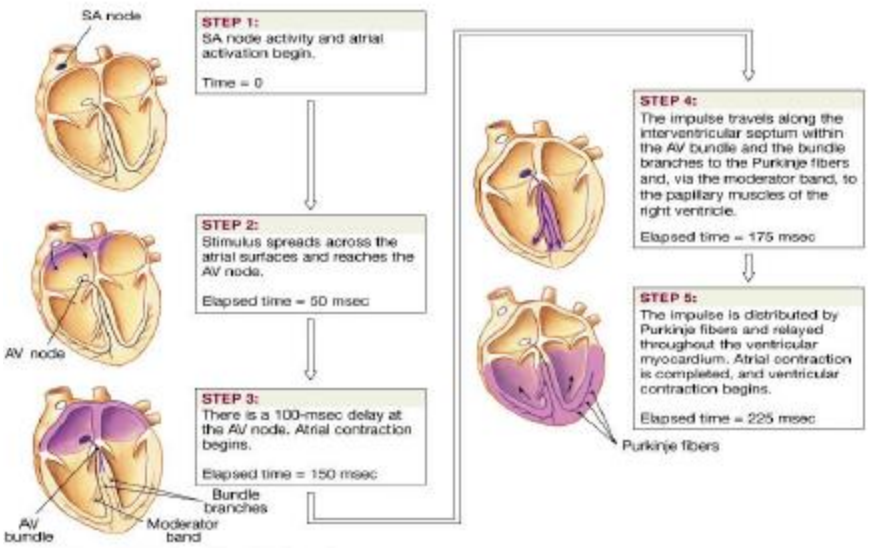
2. Conduction rate :

    - The conduction rate is **fastest** in the Purkinji, 4m /sec, due to higher number of gap junctions to make sure that ventricles will receive the impulse at the same time and contract at the same time, otherwise , each ventricular fiber contracts dependant from the others, this is called ***ventricular fibrillation*** , it's lethal and the physician should interfere to relief the condition.

    - The conduction rate is **slowest** in AV node, why?
      To assure that the atria and ventricles will not contract at the same time; atria contracts and finish its contraction then ventricles are able to contract and this mediated through AV node which delays the impulse.

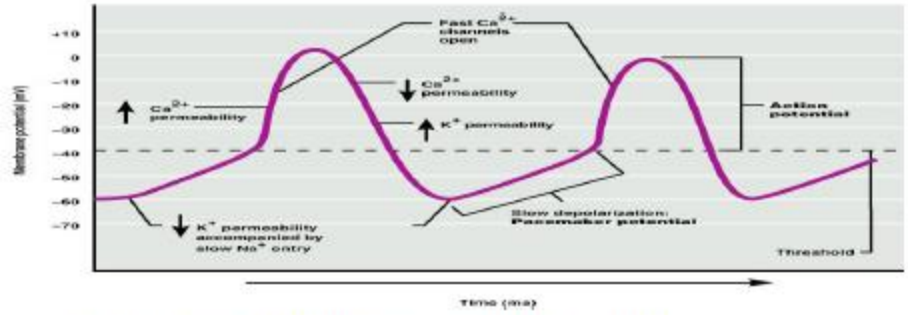
    - The conduction Is by definition unidirectional, this is due to refractory period (anything behind the impulse will not be polarized again for a while so the wave can't go back).

- Conduction Speed (conduction rate):
    - **SA node**: slow speed of conduction.
    - Ventricular and Atrial muscle : Moderate speed
    - **AV node**: slowest speed of conduction.
    - **Purkinje fibers**: Fastest speed of conduction.



❖ **Why do these cells have intrinsic activity?**

- These cells have slow response potential called **pace maker potential**.
- In terms of physiology the cells are modified : they are leaky to sodium , sodium will follow its electrochemical gradient ,move toward intracellular compartment(inside cells) and cause slow depolarization to reach the threshold.
- The resting potential will be less negative reaching -60 never -90 .



The diagram represents the action potential of pacemaker.

By looking to previous diagram in previous page, you can notice that:

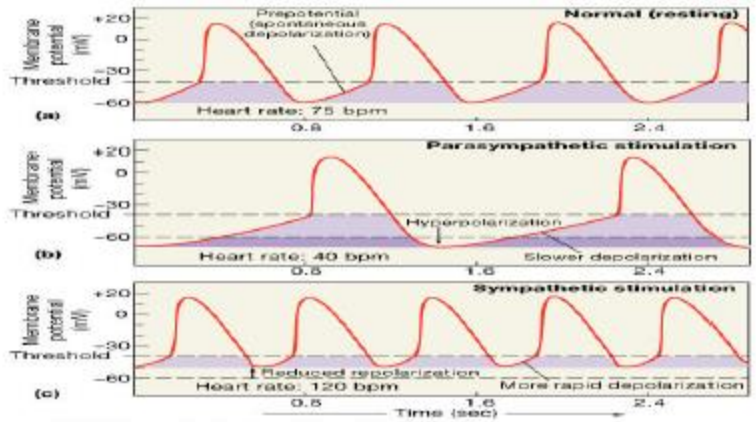
- in **phase 4** (from -60 to threshold) we have **slow** diastolic **depolarization** ,We reach the threshold slowly.
- Thus the inactivation gate of sodium channel (H gate) will close before the M gate opens thus , **Na ions do not enter through fast channels.**
- **phase zero** (depolarization) is due to **slow voltage calcium channels** , and this depolarization is slower than the depolarization of action potential for contractile cardiac fibers which is fast depolarization.
- There is no phase1 (partial repolarization) nor phase 2 (plateau)
- There is **phase 3** which represents the repolarization by increasing the permeability for K ions.

Autonomic innervations of the heart :

- The heart intrinsically can pump blood and generate action potentials.
- But if the heart can intrinsically pump, then why we have the autonomic nerves then?

We have both sympathetic and parasympathetic innervations :

1. ***Sympathetic*** from ***cardiac plexus*** supplies all the heart (ventricles and atria).
2. ***Parasympathetic*** from **vagus nerve** , supply only the atria (SA node and AV node) , don't affect the ventricles.



The diagram represents the effect of autonomic innervations on heart rate.

- **The sympathetic stimulation(giving epinephrine/ norepinephrine) :**

1. increase permeability to sodium and calcium.
2. the resting membrane potential become less negative , the slow depolarization occurs faster(increasing the slope of phase 4), the rate increases and the strength of contraction also **increases due to higher calcium entering.**
3. The increase in the rate is referred to **as positive chronotropic effect .**
4. The increase in the strength of contraction is referred to **as positive inotropic effect.**
5. The sympathetic also have **positive dromotropic effect** "higher rate of conduction" .

- **Parasympathetic stimulation(giving acetylcholine) :**

1. **Affect only the atria including SA node and AV node.**
2. Increase permeability to potassium.
3. Decrease permeability to Na+ and Ca++.
4. The resting membrane potential become more negative.
5. Slow depolarization occurs slower (decreasing the slope of phase4), so the heart rate decreases thus **negative chronotropic effect.**

In both types of stimulation the peak **doesn't change** ; because action potential follows "the all or none principle".