no.

CVS
PHYSIOLOGY

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Objectives:

By The end of this lecture students should be able to:

- Distinguish the cardiac muscle cell microstructure
- Describe cardiac muscle action potential
- Point out the functional importance of the action potential
- Follow the cardiac muscle mechanism of contraction
- Delineate cardiac muscle energy sources
- Outline the intracellular calcium homeostasis
- Explain the relationship between muscle length and tension of cardiac muscle (Frank-Starling law of the heart)

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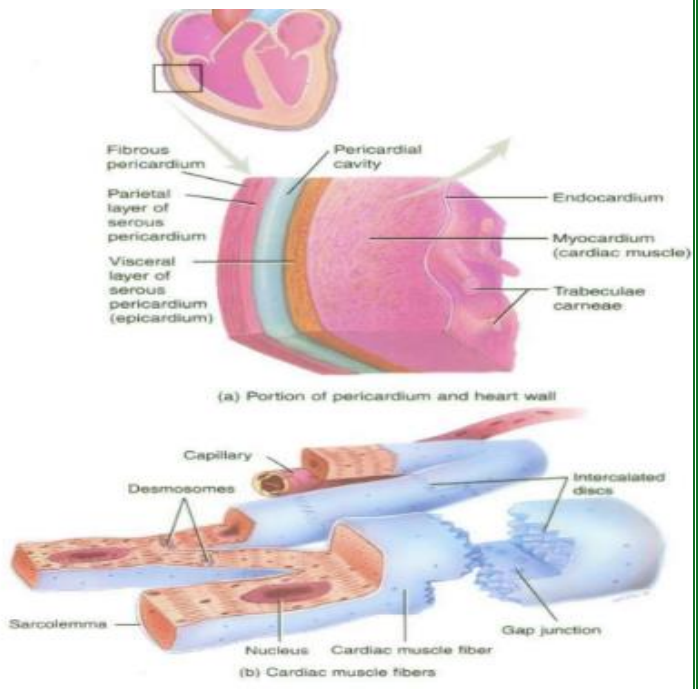


Cardiac Muscle Physiology

The wall of the heart separates into the inner **Endocardium** and intermediate **myocardium**, and outer **Epicardium**.

The epicardium represents the visceral part of the inner layer of a surrounding sheath called **pericardium**.

The innermost fibers are called endocardial fibers and outermost fibers are called epicardial cells.

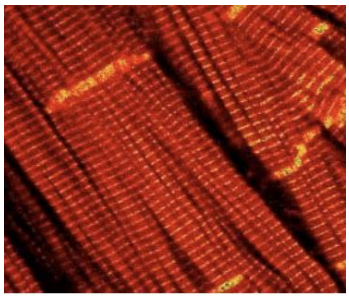
The Pericardium is divided into:

1. The outer **non-elastic, non-stretchable** tough fibrous layer connects the heart to the great vessels and sternum, and the diaphragm.
This layer prevents overstretch ability of the heart.
2. The inner layer has two Layers
A. The visceral layer (adhered to the heart) also known as **epicardium** which folds on itself to form the second layer.
B. the parietal layer.
Between these two layers is the 30-50 ml of serous fluid

Endocardium→myocardium→ Epicardium→Pericardium

Cardiac Muscle Tissue and the Cardiac Conduction System

we concern the central motor contractile layer, that ranges in thickness between 10-15 mm, the myocardium, it consists of cardiac myocytes, each of which is characterised as:



- Shorter and less circular than skeletal muscle fibers
-**cellular length** of 50-100 um compared to that of 10-20 in skeletal muscles.

-**Uni-nucleated**, or generally low in nuclei, usually, one centrally located nucleus.

-**Rich mitochondrial content** -which indicates its continuous aerobic respiratory activity and ATP production, such fibres are called RED fibres, mitochondria are larger and more numerous than skeletal muscle , cardiac myocytes depend on free fatty acids for more the 65% of ATP production.

-**Limited amounts of Sarcoplasmic reticulum**

-**Cellular diameter** of 10-20 um.

$$A = \pi r^2$$

A: surface area
r: radius

Resistance to Ionic current across the plasma membrane is inversely proportional to cellular diameter and surface area: the narrower the diameter is, the weaker in permeability and slower in velocity the ionic conduction is!

$$R \propto \frac{\eta L}{r^4}$$

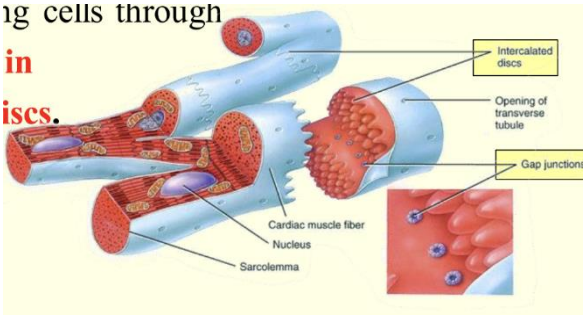
R: resistance
r: radius

$$R = \rho \frac{l}{A^2}$$

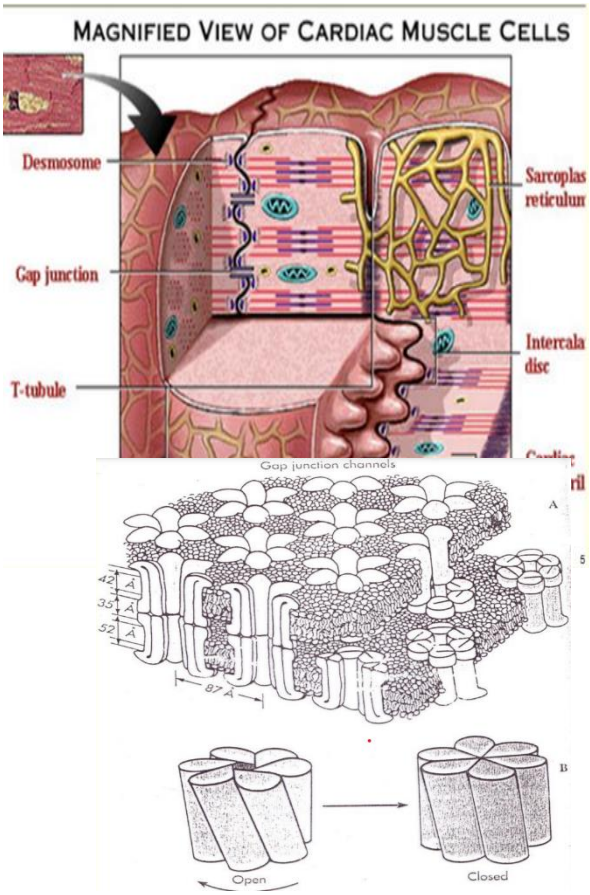
R: resistance
A: surface area

- **Intercellular adherence**: Ends of fibers are connected by end-end fashion intercalated discs (longitudinally) which attach adjacent branched myocytes by means of desmosomes and Gap-junctions, desmosomes are to preserve the durability and prevent detachments of cardiac tissue during contraction.

Discs contain desmosomes (hold fibers together) and gap junctions (allow action potential conduction from one fiber to the next) → syncytium (cells together)



-**Intercellular communication** Cardiac muscle cells connect to and communicate with neighbouring cells through gap junctions in intercalated discs.–these are special channels where the resistance of sarcolemma against cationic diffusion is 1 /400 that in the remaining points of the membrane -, thereby, Na^{+}, Ca^{2+} cations and several other critical particles for contraction are spread over to neighbourhoods whenever the electrical membrane potential changes take place in one myocyte and consequently, excitation-contraction coupling occurs in the whole myocytes specific to a certain cardiac atrial or



ventricular chamber, independently, simultaneously altogether as one unit in the appropriate stage of cardiac cycle, such phenomenon is referred to as ventricular and atrial Syncytium , it occurs in no time nearly , because of well-interconnected myocytes due to the huge abundance of gap junctions .
Obviously, the more numerous gap junctions are there, the larger and faster intercellular cationic conductance is!

Remember that atrial contraction serves in the last 20% of blood squeezing and assembly in ventricles (this is active squeezing), atrial blood squeezing is considered by its first 80% as a passive procedure , (no need for energy-dependent contraction)

While ventricular contraction serves in ejection.

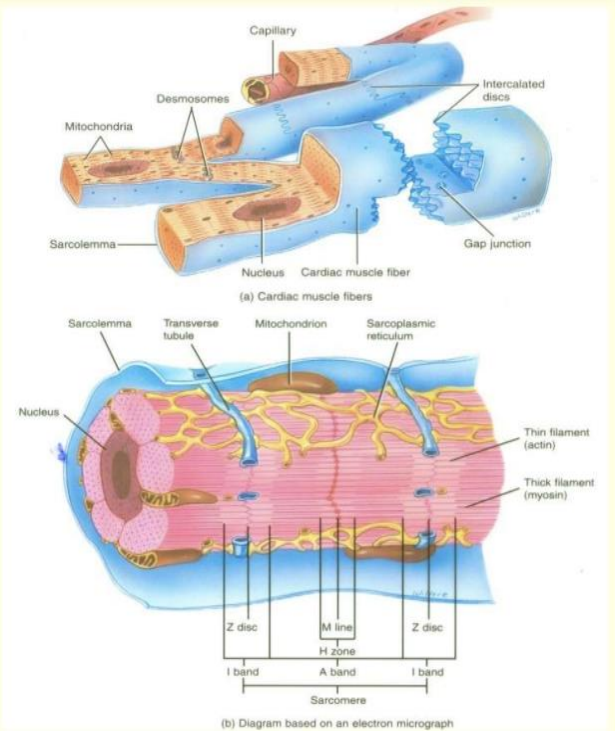
There is no compartmentalization or insulation of cardiac myocytes (Gap junctions) into motor units -in contrast to skeletal motor units- therefore, skeletal myofibers don't exhibit syncytium in their overall pattern of contraction.

please remember the absence of Gab junctions in between skeletal muscles as they originally fuse during embryonic development to give rise to skeletal multinucleated myofibers.

Skeletal muscles are insulated (no inter cellular communication) from each other!

- **Shorter and broader T-tubules (TT),** They have 5 times more diameter, this results in a 25 fold increase in volume.
It makes sense to have more ECF volume with more Ca++ in it.

remember, T-tubule is an inward invagination of the sarcolemma at the Z-line (cardiac one TT for each sarcomere).
In skeletal muscle, TT tubules extend longitudinally at both ends of the myosin: the border of A-I bands (two TT for each sarcomere).
TT Contain Ca++ binding sialic acid.



TTs correspond to delivery of electrical impulses towards calcium stores in the two adjacent terminal cisternae of sarcoplasmic reticulum. -please refer to adjacent photo to get it cleared- the resultant structural pattern of T-tubule separating in between two cisternae is called the SR-T-SR triad-, this electrical propagation initiates the contractile cycle by calcium release, and therefore, these tubules give cells the property of Excitation-contraction coupling (response mechanically to an electrical impulse)

In the skeletal muscle, long T-tubules correspond effectively and essentially in their function of electric propagation, thus, osmotic-shock-mediated de-tubulation (TT removal) uncouples excitation from contraction (no mechanical response to the electrical impulse)and is severely harmful, however short, and broad cardiac T-tubules importance in excitation-contraction coupling is questionable in the degree of benefit they provide as they poorly reach calcium stores.

For example, In frog and birds, their ventricles contain no TT. In mammals, atria contain no TT

-**poorly developed , less abundant sarcoplasmic reticulum** , the main source of calcium required for contractility is ensured by the extracellular environment , on contrast , well-developed sarcoplasmic reticula and calcium stores in skeletal muscles satisfy their need from within, therefore , in -vitro experiments of cardiac myocytes require appropriate extracellular preparation and calcium supplements beside the electrical impulses ,otherwise, they weakly contract, whereas skeletal in-vitro contraction DOESN'T necessities such care even in free calcium isotonic environment .

Over the numerous previous skeletal-cardiac muscle differences

- They share the feature of **depolarization-dependant contraction** and **possess common contractile filaments and factors** Same arrangement of actin and myosin, troponin, tropomyosin, which collaborate in the same context of **sliding-filament theory**, where the muscle contraction is referred to the overlap-sliding of contractile filament upon each other, resulting in the shortness of the whole sarcomere, but pay attention **No LITERAL contraction or length change occurs in the filament itself.**
Cardiac muscle, like skeletal muscle, is striated.

Cardiac Muscle Vs Skeletal Muscle

However, the table below highlights further differences between skeletal and cardiac contraction:

Cardiac and Skeletal Muscles

Differences

Skeletal muscle	Cardiac Muscle
• Neurogenic (motor neuron-end plate-acetylcholine)	• Myogenic (action potential originates within the muscle)
• Insulated from each other	• Gap-junctions
• Short action potential	• Action potential is longer

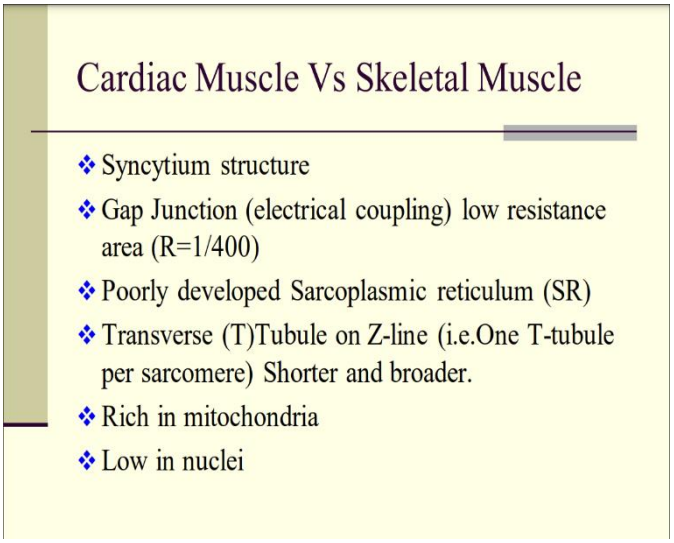
-**Skeletal muscles are neurogenic**, relying on motor neurons to provide the external electrical stimulus, **whereas cardiac myocytes are myogenic**, they possess the intrinsic ability to auto-excite and initiate their own current independently from outer nervous system or hormonal help, major physiological controllers.

Thus, cardiac myocytes are described as AUTO-RHYTHMIC.

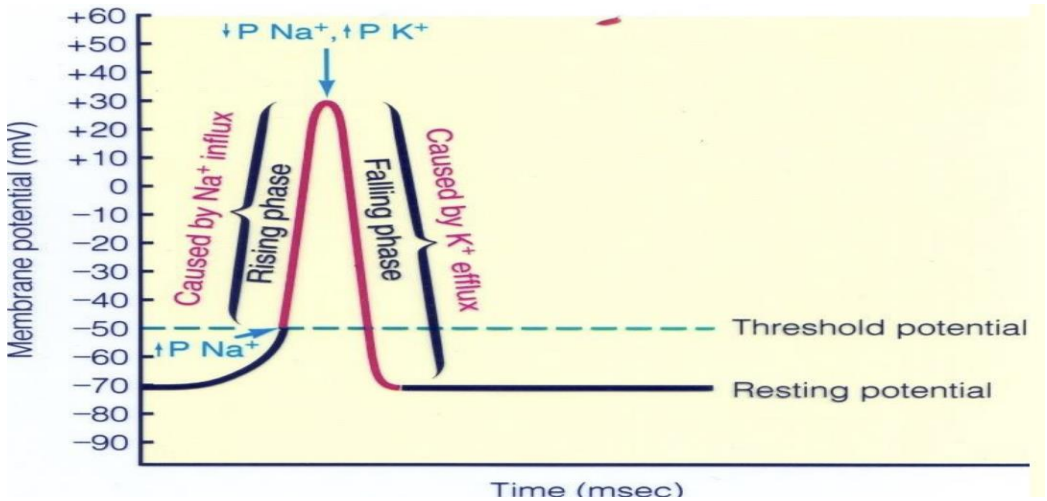
-In skeletal muscles, action potential **consumes about 2-3 millisecond**, whereas cardiac potential lasts for about **250-300 milliseconds.**

- Unlike skeletal muscle, fibers of cardiac tissue are shorter, they branch, and they have only one (usually centrally located) nucleus.

-Conclude with this quick recap 😊



Permeability Changes and Ionic Fluxes During an Action Potential (skeletal Muscle)



The electrical behaviours of the heart:

Auto rhythmicity of the heart is referred to 1% non-contractile, de-tubuled cardiac cellular population (pace makers)with absent excitation-contraction coupling, compartmentalized as the following:

-first, Sinoatrial node (SA node):
Characterized by:

-**located nearly at the junction with the SVC.**

-**small diameter** of 3-5 um ,may be the smallest cells in our body, even smaller than RBCs which are known by7-9 um diameter!

-**lack actin and myosin contractile filaments**.

-**They auto-excite their cellular membrane** without the external neural or hormonal stimuli (help), they are auto rhythmic and self-by generate action potential by an intrinsic ability in the rate of 1 per 0.8 second (pacemakers), each impulse corresponds for 1 heartbeat.

Collectively, in one minute (60 seconds), this brings the physiologic heart rate of 75 beats per minute.

-**The SA impulse represents the normal electrical behavior of the heart, considering its initiation time as "time zero", it propagates via inter atrial nodal pathway by a velocity of 1 m/s and reaches the last point in the** right and left atrial myocardium by the 0.09 second post SA impulse generation ,thereby , atrial contraction occurs , it **is also directed to the subsequent further autorhythmic noncontractile** cardiac cellular compartments, that serve as the only conductive system to deliver impulses towards ventricle

It seems like this pathway (fibrous ring) serves an electrical insulate between atria and ventricles , abnormalities in these pathways are fatal as the following:

1)by 0.03-0.04 second post its generation, the SA impulse reaches **AV node** at the floor of the right atrium, remains captured within, and delayed for 0.12 seconds, before leaving by the 0.16 second post SA impulse generation.

The delayed electrical conductance could be explained by the poor intercellular gap- junction in between AV nodal cells, as well as the extremely tiny diameter (remember the diameter is inversely proportional to resistance against flow), and finally the slightly more negative resting membrane displaces its potential away from threshold further than normal.

This 0.12 second delay is to allow atrial contraction to squeeze sufficient blood inside relaxed ventricles in adequate time before excitation-contraction coupling begins in the ventricular myocardium and resultant ejection takes place.

Without such delay, simultaneous atrial-ventricular contraction gonna cause closure of the mitral bicuspid valve and prevent blood flow, this is mainly because the contraction-accompanied increase in

the intra-ventricular pressure of (0 up to 120 mmHg), exceeds the contraction-accompanied increase in the intra-atrial pressure of (5 up to 8 mmHg).

Upon this closure, blood rejects strongly back through pulmonary vein, resulting in abnormal pulsating veins.

Back to the conductive system ….

2) impulse reaches **AV bundle** (Bundle of His).

3) **left and right bundle branches** (at the ventricular apices) by the 0.19 second post SA node impulse generation.

4) **Purkinje fibers** through which impulses ascend back to bases in the highest cardiac conductive velocity (1-4m/s) by the 0.22 second post SA impulse generation! so that on the outer surface of the bases, the right and left ventricular contraction breaks out altogether, as one cell in the one-unit syncytium pattern discussed before.

Notice that the conductive pathway from AV bundle until outer surface of base consumes only about 0.06 seconds, half the time of delay in the AV node!

Again, the rapid Purkinje conductance is referred to the abundant gap junction, larger diameter of 70 um and fewer resistance.

Alternative electrical behaviors of the heart.

Such behaviors are achieved by subsequent (LATENT) autorhythmic cardiac centers, whose rates of auto rhythmicity are slower, therefore, originally in the conditions of normal SA node these

behaviors are **override-suppressed by the rapid SA impulses** that predominate over any other electrical pattern.

Thus, SA node is the physiologic Pacemaker!

In SA nodal defect, latent autorhythmic centers become pacemakers in the following priority order:

-**AV node**: electrical auto rhythmicity predominates bringing heart rate of 40-60 (50 on average) beats per minute, however, if defect,

-**AV branches** and Purkinje fibers electrical auto rhythmicity predominates bringing heart rate of 15-40(30 on average) beats per minute, if defect ...

SA nodal action potential:

Before previewing the SA nodal action potential let's revise primary principles regarding electrochemical gradient-based ionic currents across permeable plasma membranes generally.

-please refer to downwards cellular concentrations of electrolytes, Electrochemical gradient drives Na^+ and Ca^{2+} conductance **through channels** by **simple diffusion** towards intracellularly, and K^+ conductance towards extracellularly

-**If left without external barriers, flow continues until reaching a state of electrochemical equilibrium** in which No net movement takes place, this occurs when electrical gradient counterbalances (is equal to) and opposes the chemical (concentration) gradient, but equilibrium is not reached because of lack of membrane permeability.

For example, initial higher extracellular concentrations of Na^+ forces its inward diffusion (influx)through channels, this accumulates positive charges on the inner-cytoplasmic side of the membrane, which gradually repulses, impedes the opposite positive ionic

currents, until certain positive membrane potential when no more net movement could be recognized.

-**This equilibrium is determined by a specific potential across the plasma membrane**, which can be calculated by reference to the intra and extra cellular concentrations in the context **of Nearnest equation as the following:**

Ion	Intracellular concentration (mM)	Extracellular concentration (mM)	
Na^+	14	140	10 folds difference
K^+	150	4	35 folds difference
Cl^-	5	120	
Ca^{2+}	10^{-7}	10^{-3}	10^4 folds difference
Mg^{2+}	1	0.5	
HCO_3^-	8	27	
Nonpenetrating anions	155	0	

$$V_m = \frac{61}{z} \times \log_{10} \frac{[C]_0}{[C]_i}$$

you can use the reciprocal of the logerethmic concentration ratio : C_i/C_o , but the mathematical procudure necissates the multiplication of the equation by -1 .

We conclude by these equillibrium membrane potentials :

$E_{k+=}$ -92 mV E_{Na+}=+61 mV E_{ca2+}=122mV

-Electochemical Ionic current is basically measured by :

$I_x=(E_m-E_x)*g$

I_x : Ionic conductance E_m: existing membrane potential

E_x:Electrochemical equillibrium potential of the ion (meausered by nearnest equation) g: conductance.

-Determinants of Ionic flow are :

1) Driving force (electro chemical gradient) : driving force of ionic conductance is referred to as the difference between existing membrane potential and ionic specific equilibrium potential.

2)membrane conductance-resistance (ohm-mho):

-Resistance is opposite to permeability, they both vague expressions telling how much difficult or easy the procedure is.

It is simply how open and active channels responsible for the flow are.

For example: having cardiac myocyte -90 mV resting membrane potential, is most probably achieved by profuse K^+ efflux ionic flow, because E_{k+}=-92 –
remember that Ex is the target of any ionic diffusion (each ionic flow -if left freely- tries to bring the membrane potential towards its electrochemical potential)
Which means that resting potential is determined by the special conductance provided by active open channels in resting conditions.

During then, although membrane permeability towards K+ is the greatest, driving force (electrochemical gradient) of the other cationic Na+ and Ca2+ diffusions is higher because of the poor permeability the membrane exhibits towards , which gets Ex further and further from Em.

MEMBRANE RESISTANCE TOWARDS IONIC FLOW IS DIRECTLY PROPORTIONAL TO DRIVING FORCE OF THE ARRESTED CURRENT.

*SA nodal -60 resting membrane potential is consequent to major K^+ and minor Na^+ diffusions targeting E_{k+}=-91 and $E_{Na+=}$=+61.
*Smooth muscle resting potential is -30 mv, RBCs = -7 mv skeletal muscle=-70 mV.

Note : refer to Nearnest equasion, ia case of Hypercalemua (Increased extracellular concentrations of K^+) E_{k+} becomes less negative , bearing in mind that $E_M = E_{K+}$ because resting conditions provide highest permeability for K^+ , collectively this will give cardio myocytes less negative (closer-to-threshold) new resting E_M.

Yalla lets start with the SA nodal action potential.

SA nodal cells have normal resting membrane potential of -60 mv.

The special auto rhythmicity of SA nodes -and further pacemakers- is referred to the Auto ability to reach the less negative threshold potential spontaneously (-45 mv), by means.
of:
1- **Na^+ leakage** through **partially opened** funny channels down its EC gradient : funny current I_F .
This corresponds by +**10 voltage depolarization**, (-60 to -50) mV.
Please make sure in this point, it's only sodium flow, neither Ca^{2+} nor K^+ channels are permeable, they are closed.

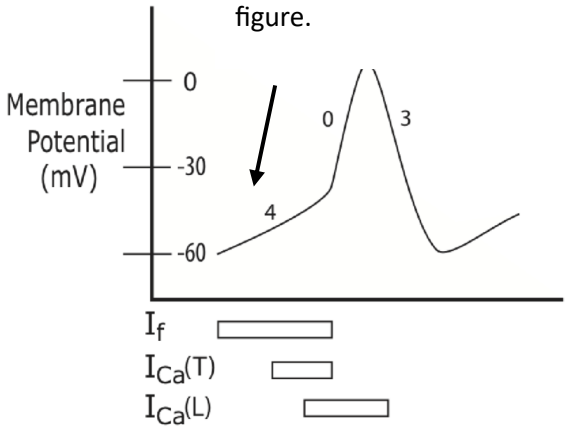
2-**Transient Ca^{2+} influx** through T-type Ca^{2+} voltage gated channels.
This corresponds to **+5 voltage depolarization**, (-50 to -45) mv.
By this, threshold is auto generated.
Remember Threshold potential is the membrane voltage value after which action potential fires.

The initial depolarization in the actual SA nodal action potential is carried out by the long-lasting Ca^{2+} influx through L-type Ca^{2+} voltage gated channels.
This corresponds to **+55 voltage depolarization**, (-45 to +10) mv.

Maximal depolarizing point in SA action potential is +10

Hyperpolarization occurs by K^+ efflux through voltage gated channels.

This is the pre-threshold depolarization phase figure.



Notice, the appropriate rapidity in Threshold achievement and AP generation, with regard to sodium I_F , calcium I_T and I_L.

This rapidity is indicated in terms of the slope of the pre-threshold depolarization phase figure 😊

Mathematically, the slope is measured as the tan of the angle the curve makes with the x-axis.

﴿ الله نور السماوات والأرض ﴾

V2

All added notes are highlighted by yellow.