
◉ Sheet ○ Slides

Number

24

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Before we discuss Cardiac physiology let's have an overview of excitable tissues. In order to understand what governs the conductance of ions as it relates to the function of excitable tissues (nerves and muscles) it is important to understand the following ***5 key principles***:

1. **Membrane potential :**

There is a separation of charge across the membrane of excitability tissue at rest .This separation of charge means there is the ***potential to do work*** and is measured by volts .Thus, Em represents the measured value.

2. **Electrochemical gradient:**

Ions diffuse based upon chemical (concentration) gradients (high to low) and electrical gradients (like charges repel each other, opposites attract).Electrochemical gradient indicates the combination of these 2 forces.

3. **Equilibrium potential:**

This is the membrane potential that puts an ion in electrochemical equilibrium, i.e., the membrane potential that results in no NET diffusion of an ion. If reached, the tendency for an ion to diffuse in one direction based upon the chemical gradient is countered by the electrical force in the opposite direction.

4. **Conductance (g) :**

Conductance refers to the flow of an ion across the cell membrane. Ions move across the membrane via channels. Open/closed states of channels determine the relative permeability of the membrane to a given ion and thus the conductance.

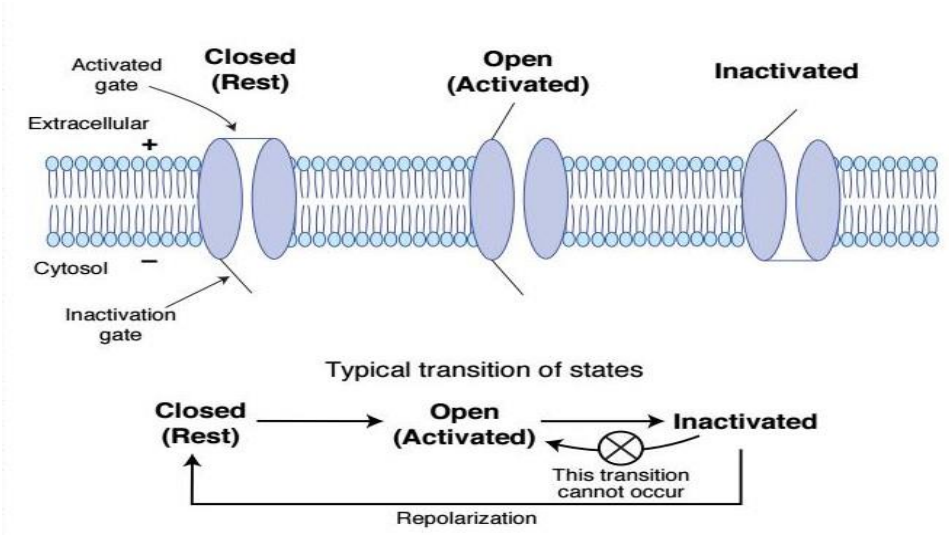
Open states create high permeability and conductance, while closed states result in low permeability and conductance. (Conductance is the reciprocal of resistance) and is measured by Mho (1/Ohm).

**5.Net force (driving force):**

This indicates the relative "force" driving the diffusion of an ion. It is estimated by subtracting the ions equilibrium potential from the cell's membrane potential. In short, it quantitates how far a given ion is from equilibrium at any membrane potential.

## ➢ ***Sodium Voltage gated channels (Fast Na+ channels):***

The opening of these channels is responsible for the rapid depolarization phase (upstroke) of the action potential . It has two gates and 3 conformational states:




**Closed**: in this state, The activation gate the (m-gate) is closed and the inactivation gate (h gate) is open. Because the activation gate is closed, Na+ conductance is low, but the driving force is high.

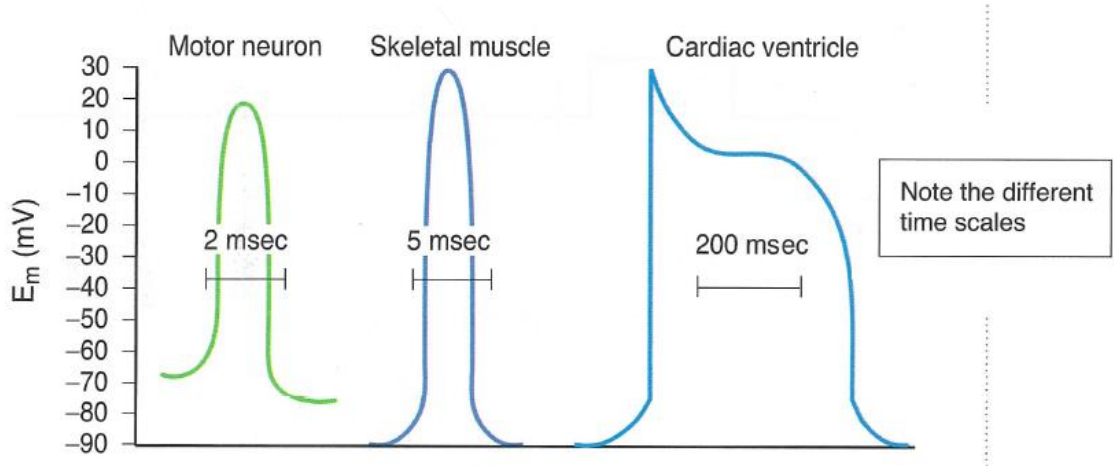
**Open:** Depolarization causes the channel to transition to the open state, in which both gates are open and thus Na+ G increases. The elevated G causes further depolarization, which in turn opens more N+ channels, causing further depolarization. In short, a positive feedback cycle can be initiated.

**Inactivated**: After opening, the fast Na+ channel typically transitions to the inactivated state. In this state, the activation gate is open and inactivation gated (h gate) is closed. Under normal circumstances, this occurs when membrane potential becomes positive as a result of action potential.

Once the cell repolarizes, the fast Na+ channel transitions back to closed state, and is thus ready to reopen to cause another action potential.

KEY point: Once Na+ channel inactivates. It cannot go back to the open state until transitions to the closed state (see the figure). The transition to the closed state typically occurs when the cell repolarizes.

The figure below shows the action potential from 3 types of excitable cells. Even though there are many similarities , there are differences between cell types, Most notably the duration of the action potential .Action potential in muscle and nerve cells is very similar (virtually the same). But cardiac action potential has several differences, will be discussed in this sheet.




**The previous pages were an overview that might help in understanding cardiac action potential, you don't have to memorize any of them.**

***Heart*** *serves as the pump that imparts pressure to the blood to establish the pressure gradient needed for blood to flow to the tissues, like all liquids blood flow down a pressure gradient from area of higher pressure to an area of lower pressure.*

## *The heart is a dual pump:*

*Even though anatomically the heart is a single organ, the right and left sides of the heart function as two separate pumps. (We can have Left or Right heart failure), the heart is divided into Right and Left halves and has four chambers, an upper and lower chamber with each half. The upper chambers, the* ***Atria*** *(singular,* ***atrium****), receive blood returning to the heart and transfer it to the lower chambers, the* ***Ventricles****, which pump blood from the heart.*

*The two halves of the heart are separated by the* ***Septum*** *, (a continuous muscular partition that prevents mixture of blood from the two sides of the heart > extra info ) . This separation is extremely important, because the right side of the heart is receiving and pumping O2-poor blood (deoxygenated), whereas the left side of the heart receives and pumps O2-rich blood (oxygenated).*

- *The heart is* ***separated mechanically*** *by the septum.*
- *It is also* ***separated electrically****: Atria and ventricles are structurally connected by electrically nonconductive fibrous tissue (The AV node is the only point of electrical contact between the atria and ventricles) depolarization can't shift between compartments without passing through the AV node (it is like a border) .*
- *Below is the normal conduction pathway for the heart. (Dr.Yanal mentioned it once to clarify the pathway direction)*


## ***Pressure-operated*** *heart valves ensure that blood flows in the right direction through the heart:*

*Blood flows through the heart in ONE FIXED direction from veins to atria to ventricles to arteries. The presence of four* ***One-way*** *heart valves ensures this Unidirectional flow of blood. The valves are positioned so that they open and close Passively because of pressure differences, similar to one way door.*

- ***A forward pressure gradient (that is a greater pressure behind the valve forces the valve to open)*** *, much as you open a door by pushing on one side of it, whereas a* ***backward pressure gradient (that is a greater pressure in front of the valve)forces the valve to close*** *, just as you apply pressure to the opposite side of the door to close it . NOTE that a backward gradient can force the valve closed but CANNOT force it to swing open in the opposite direction, that is, heart valves are not like swinging , saloon-type doors.*

## AV valves between the atria and ventricles:

- Two of the heart valves, The ***right*** and ***left atrioventricular (AV) valves*** are positioned between the atrium and the ventricles on the right and left sides, respectively.
- These valves let blood flow from the atria into the ventricles during ventricular filling (when atrial pressure exceeds ventricular pressure 8 Vs 0 respectively) but prevent the backflow of blood from the ventricles into the atria during ventricular emptying (when ventricular greatly exceeds atrial pressure about 120) .

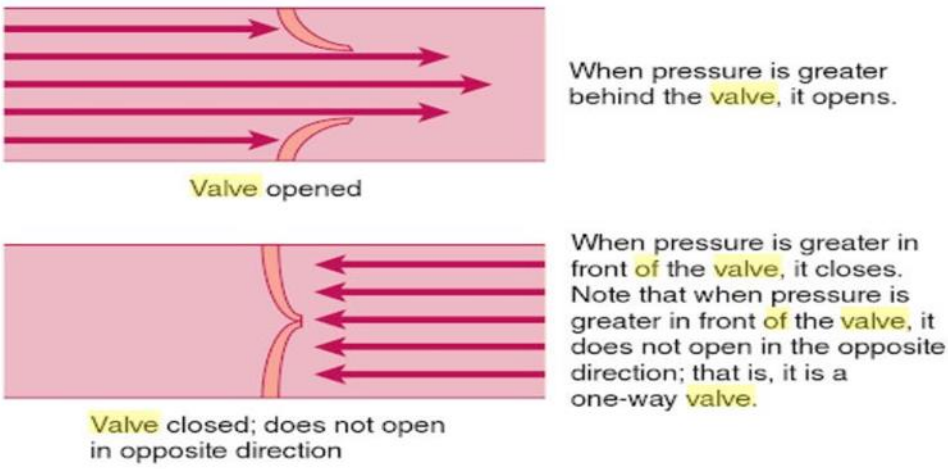
***NOTE: The pressures stated as relative to surrounding atmospheric, which is the typical "0" reference pressure used in medicine.)***

***For example: 0= atm =760mmHg( reference level)***

***+5=765 mmHg***

***-5=755mmHg***

- ***For clarification*** see the figure below: If the rising ventricular pressure did not force the AV valves to close as the ventricles contracted to empty , much of the blood would inefficiently be forced back into the atria and veins (back to lungs ) instead of being pumped into arteries.



- The cardiac cycle is the sequence of events that occurs when the heart beats; there are two phases of the cardiac cycle. In the ***diastole*** phase, the heart ventricles are ***relaxed and the heart fills with blood***. In the ***systole*** phase, the ***ventricles contract and pump blood out of the heart and to arteries***. ***One cardiac cycle is completed when the heart chambers fill with blood and blood is then pumped out of the heart.***

- (All you need to know is that the heart cycle is ***One to One*** cycle ⟶ ***Diastole to systole*** )
  ***Diastole*** ⟶ ***relaxation*** ⟶ ***0.5s***
  ***Systole*** ⟶ ***contraction*** ⟶ ***0.3s***
  ***One Cardiac cycle duration*** ⟶ ***0.8s***
  ***Heart rate = 60s/0.8s=75 beat/min***
  ↓
  ***1 min***

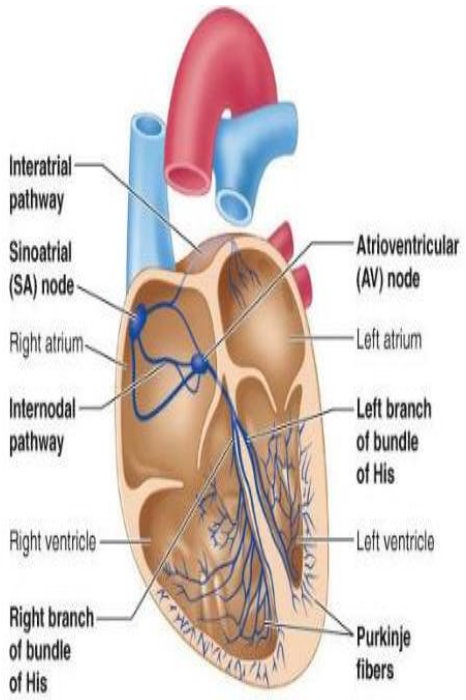
- ***Cardiac muscle fibers form functional syncytia:***
  The individual cardiac muscle cells are interconnected with each other via Gap junctions ,which are areas of low electrical resistance that allow action potentials to spread from one cardiac cell to adjacent cells, some cardiac cells can generate action potentials without any nervous stimulation, when one of the cardiac cells spontaneously undergoes an action potential ,the electrical impulse spreads to all other cells that are joined by gap junctions ,so they become excited and contract as a single functional syncytium .

**EXTRA INFO:** no gap junctions join the atrial and ventricular contractile cells, and furthermore, the atria and ventricles are separated by the electrically nonconductive fibrous skeleton that surrounds and supports the valves, However, an important, specialized conduction system facilitates and coordinates transmission of electrical excitation from the atria to the ventricles to ensure synchronization between atrial and ventricular pumping.

- Because of both the syncytial nature of cardiac muscle and the conduction system between the atria and ventricles, an impulse spontaneously generated in one part of the heart spreads throughout the entire heart ,therefore either all the cardiac muscle fibers contract or none do . A "***Halfhearted" contraction is NOT possible***.
- Cardiac contraction is graded by ***varying the strength of contraction of all the cardiac muscle cells.***

- ***Electrical activity of the heart:***
  ***Contraction of cardiac muscle cells to eject blood (the ultimate function of the heart is to eject blood) is triggered by action potentials sweeping across the muscle cell membranes.***
  The heart contracts or beat, rhythmically as a result of action potential that is generates by itself ,a property called ***Autorythmicity*** .

- There are two specialized types of cardiac cells:
  1. ***Contractile cells***, which are 99%of the cardiac muscle cells ,do the mechanical work of pumping. These working cells normally do **NOT** initiate their own action potentials.
  2. In contrast, The small but extremely important remainder of the cardiac cells, the ***Autorhythmic*** cells,do not contract but instead are ***specialized for initiating and conducting the action potentials responsible for contraction of the working cells.***
- The specialized noncontractile cardiac cells capable of autorhythmicity are the following:
  1. The ***Sinoatrial node(SA node)*** :specialized cardiac cells connected to atrial muscle (in the right atrial wall).The ***SA node acts as pacemaker*** of the heart because the membrane ***leaks Na+*** and its membrane potential is -55 to -60 mV
  2. ***Atrioventricular node (AV node)*** a small bundle of specialized cardiac muscle cells located at the base of the right atrium near the septum, just above the junction of the atria and ventricles.
  3. ***Bundle of His (AV bundle***) ,a tract of specialized cells that originate at the AV node and enters the interventricular septum ,here it divides to form the RIGHT and LEFT bundle branches .
  4. ***Purkinje fibers.***



(a) Specialized conduction system of the heart

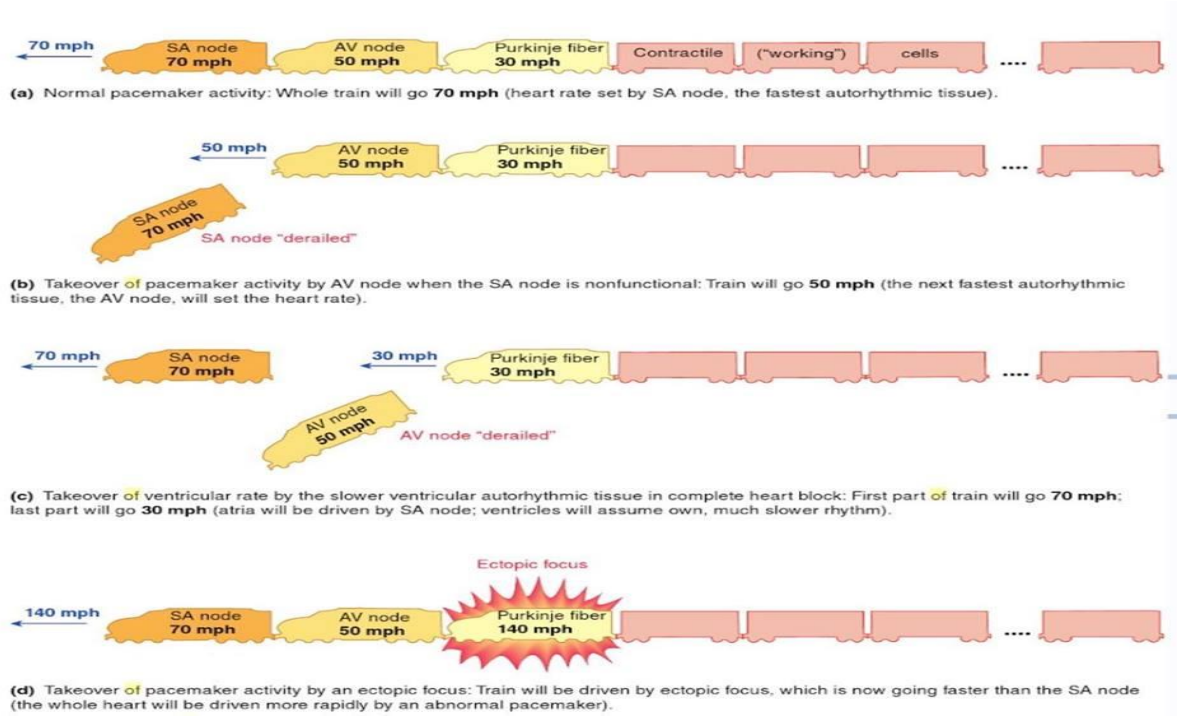
***(***The previous details were mentioned briefly in the lecture).

- ***Normal pacemaker activity:*** Because these various autorhythmic tissues have different rates of slow depolarization to threshold, the rates at which they are normally capable of generation action potentials also differ.

| TISSUE | Action Potential /min |
|---|---|
| ***SA node (normal pacemaker)*** | 60-80 Action potential/min |
| **AV node** | 40-60 Action potential/min |
| **Purkinje fibers and bundle of his** | 15-40 Action potential/min |

- The heart cells with the fastest rate of action potential initiation are localized in the ***SA node*** .Once an action potential occurs in any cardiac muscle cells it is propagated throughout the rest of the myocardium via gap junctions and the specialized conduction system .Therefore the SA node , ***which normally has the fastest rate of autorhythmicity drives the rest of the heart at this rate and thus known as the Pacemaker of the heart*** ,That is the entire heart becomes excited, triggering the contractile cells to contract and the heart to beat at the pace or rate set by SA node
- The other autorhythmic tissues **cannot** assume their own naturally slower rates, because they are activated by action potentials originating in the SA node before they can reach threshold at their own ,slower rhythm.

- The following analogy shows how the SA node drives the rest of the heart at its own pace. Suppose a train has 100 cars ,3 of which are engines capable of moving in their own , the other 97 cars must be pulled .One engine (SA node) can travel at 75 m/s on its own, another engine (the AV node) at 40m/s ,and the last engine (the Purkinje fibers) at 20 m/s .If all these cars are joined, the engine that can travel 75m/s will pull the rest of the cars at that speed. The engines that can travel at lower speeds on their own will be pulled at a faster speed by the fastest engine and therefore cannot assume their own slower rate as long as they are being driven by a faster engine .The other 97 cars (nonautorhythmic ,contractile cells), being unable to move on their own, will likewise travel at whatever speed the fastest engine pulls them.




***Abnormal pacemaker activity :*** If for some reason the fastest engine breaks down (SA node damage) ,the next fastest engine the (AV node) takes over and the entire train travels at its own rate ,that is if the SA node becomes nonfunctional ,the AV node assumes pacemaker activity .

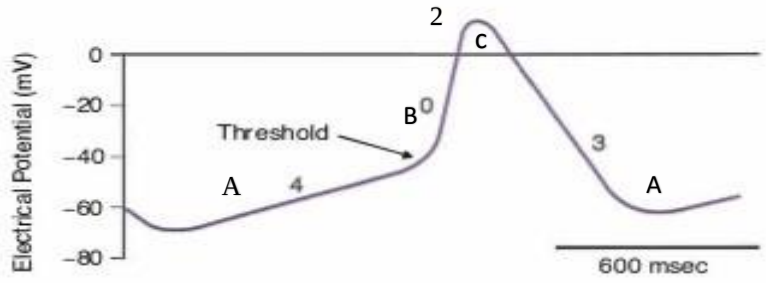
- The non SA-nodal autorhythmic tissues are ***Latent pacemakers*** that can take over, although at a lower rate, if the normal pacemaker fails.
- ***Ectopic pacemaker-abnormal site of pacemaker***
  1. This is a portion of the heart with a more rapid discharge then the SA node (like for example occasionally Purkinje fiber becomes overly excited and depolarizes more rapidly than the SA node ).
  2. Also occurs when transmission from the SA node to AV node is blocked (***AV block)*** **.**
- If we cut the AV node by mistake let's say ,the conduction becomes blocked between the atria end ventricles resulting in ***complete heart block*** (conducting tissue between the atria and ventricles is damaged, as for example during a heart attack) .
- When a person that has abnormally low heart rate, as in SA node failure or heart block, an ***Artificial pacemaker*** can be used, such device rhythmically generates impulses at the typical heart rate 75 beats/min.

***Action potential in nodal cells:***

***Nodal tissue (SA and AV) lacks Na+ fast channels. Thus the upstroke (overshot) of action potential is mediated by Ca+2 current rather than Na+ current.Nodal cells have a less negative membrane potential (-65mV) so (Fast Na+ channels are closed inactive)***

- ***Phase 4 (RMP ):*** the membrane of these cells leaks Na+ ,given this specialized behavior ,these cells show spontaneous depolarization at rest . This pacemaker potential results from:
  1. ***Slow depolarization wave due to Na+ entry.***
  2. ***Later on this phase Ca+2 enters too,the resultant brief influx further depolarizes the membrane ,bringing it to threshold..***
  - The inward Na+ current is referred to as the "Funny" current (If).
  - ***Extra info:*** there is another ionic mechanism that helps in producing the pacemaker potential (a progressive reduction in the passive outward flux of K+ ).
- ***Phase 0***: upstroke of action potential
  1. At the end of the previous phase (4) ,when RMP reaches threshold ***Ca+2 enters and leads to upstroke*** .(Na+ enters too during this phase, but the large influx of Ca+2 makes it the major player in this phase)
  2. The ***Ca+2-induced rising phase of a cardiac pacemaker*** cell differs from that in nerve and skeletal muscle cells, where Na+ influx rather than Ca+2 influx swings the potential in the positive direction.
- ***Phase 2***: is Due to Ca+2 mainly and to less extent Na (short duration of this phase compared to contractile cardiac muscle cells ,to be discussed later).
- ***Phase 3***: ***repolarization phase.***

  Falling phase is the result ,as usual, of the K+ efflux that occurs when K+ permeability increases on activation of voltage gated K+ channels ***gk+*** ↑
  - After the action potential is over ,slow closure of these K+ channels contributes to the next slow depolarization to threshold.



- ***Phase A duration (slow depolarization)*** ⟶ ***600milliSec***
- ***Action potential duration*** ⟶ ***150milliSec***
- ***Heart cycle duration*** ⟶ ***800milliSec / 0.8 sec***
- ***From A to A /B to B / C to C*** ⟶ ***One heart cycle*** ⟶ ***0.8 sec***

- ***The spread of cardiac excitation is coordinated to ensure efficient pumping , Once initiated in the SA node, an action potential spreads throughout the rest of the heart .For efficient function, the spread of excitation should satisfy the following criteria:***
  ***Atrial excitation and contraction should be complete before the onset of ventricular contraction.***
  ***Why? (Extra info for clarification:*** if the atria and ventricles were to contract simultaneously , the AV valves would close immediately because ventricular pressures would greatly exceed atrial pressures (ventricles have much thicker walls and accordingly can generate more pressure), atrial contraction would be unproductive because the atria could not squeeze blood into the ventricles through closed valves ,therefore to ensure complete filling of the ventricles during atrial contraction, the atria must become excited and contract before ventricular excitation and contraction).

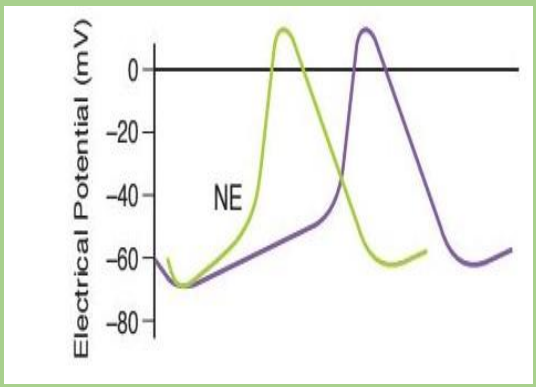
  ***How is this maintained?***
- ***The action potential is conducted relatively slow through the AV node .This slowness is due to: more –ve RMP and less gap junctions.***
- This slowness is advantageous because it allows time for complete ventricular filling. The impulse is delayed ***(AV nodal delay),*** which enables the atria to become completely polarized and to contract, emptying their contents into the ventricles, before ventricular depolarization and contraction occur.
- ***Autonomic control of SA node activity and heart rate :***
  ***As a typical of the autonomic nervous system, sympathetic and parasympathetic effects on heart rate are antagonistic (opposite to each other). (The following table summarizes the differences)***

## ***Sympathetic effects on SA nodal cells:***

- *Norepinephrine released from postganglionic sympathetic nerve terminals ⟶ greater inward movement of Na+ and Ca+2 (If ↑& Ca+2↑) ⟶ Increased slope of pacemaker potential(reaches threshold faster).*
- *Shrinking the cardiac cycle duration ⟶ 0.5s rather than 0.8s*
- *Rate : 60/0.5=120 beat/min*

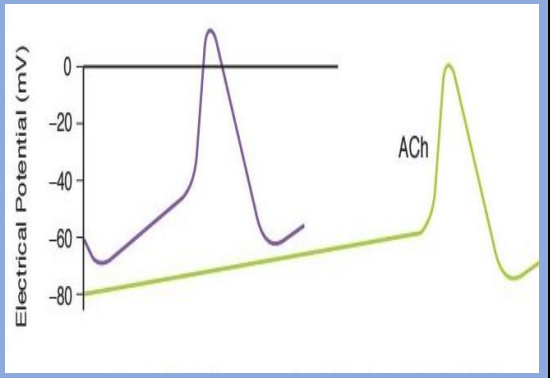
*120>75 ⟶ Heart rate is increased*

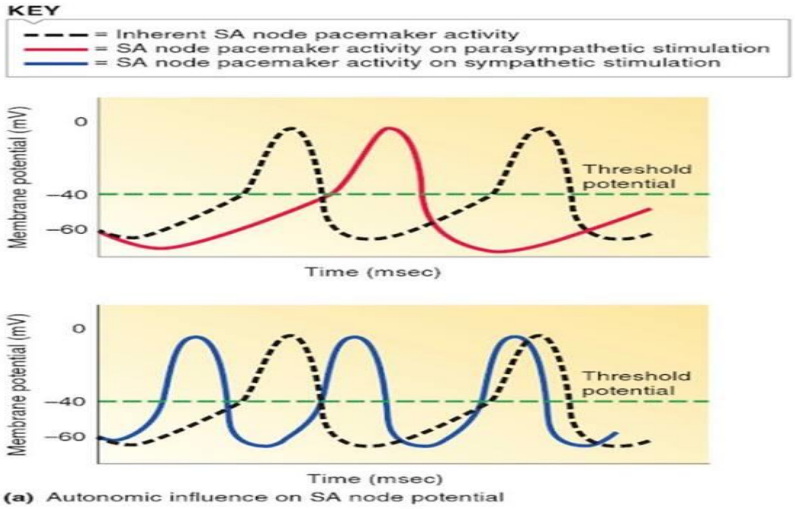
*(Sympathetic nervous system also makes RMP less –ve (gk+↓).*



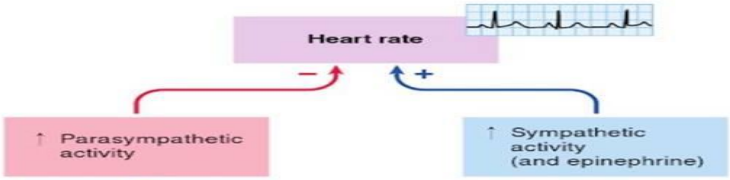

## ***Parasympathetic effects on SA nodal cells:***

- *Ach released from postganglionic fibers.*
- *(gk+↑& If↓ & I Ca+2↓) ⟶ makes RMP more –ve (hyperpolarizes) ⟶ reduced slope of pacemaker potential .*
- *Duration of cardiac cycle is increased to 1.5s*
- *Rate = 60/1.5=40 beat/min*
- *40<75 ⟶ Heart rate is decreased.*




(a) Autonomic influence on SA node potential




- ***Parasympathetic stimulation*** *decreases the rate of SA nodal depolarization so that the membrane reaches threshold more slowly, and has fewer action potentials.*
- ***Sympathetic stimulation*** *increases the rate of depolarization so that the membrane reaches threshold more rapidly and has more frequent action potentials.*

- ***Action potential of cardiac contractile cells.***
  ***Ventricular muscle fiber action potential :***

➢ ***Phase 4 (RMP) :*** RMP = -90mV , Em constant (straight line ) why??
***1.RMP is stable with respect to time*** ⟶ *Inward (Na&Ca) current = outward (K) current*

- *gk+ is high but driving force is so small (EM-Ek=-90-(-94))= (+4mv)*
- *gNa+ is low but driving force is high (Em-ENa=-90-61=-151mv as an inward force).*
- ***2. FAST NA+ channels are closed but available (capable of opening)***

➢ ***Phase 0:*** *overshot potential is the positive portion .*

➢ *Because of the activation of gNa, and since driving force is great, Na+ runs inside the cell causing further depolarization ( INa ... rapid regenerative depolarization occurs (self-sustained) and Em approaches ENa. Late phase (O) INa decreases because: 1. Driving force decreases 2. Depolarization causes inactivation of gNa.*

➢ *Similar to nerve and skeletal muscles, mediated by opening of voltage gated* ***,FAST Na+ channels .***

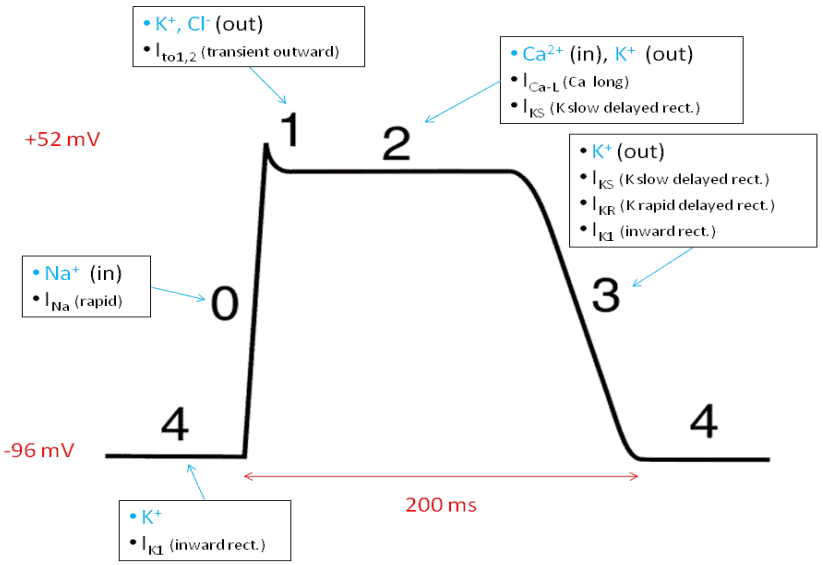
➢ ***Phase 1 :*** *(This phase is ABSENT in nodal cells)*

- *Early repolarization. Outward current > inward current*
- *INa↓because of depolarization. gK↓ because of depolarization but driving force now is great (20-(-100))= +120 as an outward driving force.(brings about a brief ,small repolarization as the membrane becomes slightly less +ve).*

➢ ***Phase 2 (Plateau )*** *note that phase 2 in nodal cells is different (which have no plateau)*
*Inward = outward*

- *Unique to these cardiac muscle cells ,the membrane potential is maintained at their near peak positive level for 250 milliseconds .In contrast, the short action potential of neurons and skeletal muscles lasts 1 to 2 msec.*
- *This plateau is maintained by slow inward of Ca+2 .*
- *This continued influx of positively charged Ca+2 prolongs the positivity inside the cell and is primarily responsible for the plateau portion of the action potential.*

- ***Phase 3 :***
- *Final repolarization( Iout > Iin) (gK↑ gCa↓ )*
- *The rapid falling phase results from inactivation of Ca+2 channels and delayed activation of the "ordinary" K+ voltage gated channels ,as in other excitable cells, the cells returns to resting as K+ leaves the cell .*
- *At resting potential, the ordinary voltage gated K+ channels close and the leaky K+ channels open.*

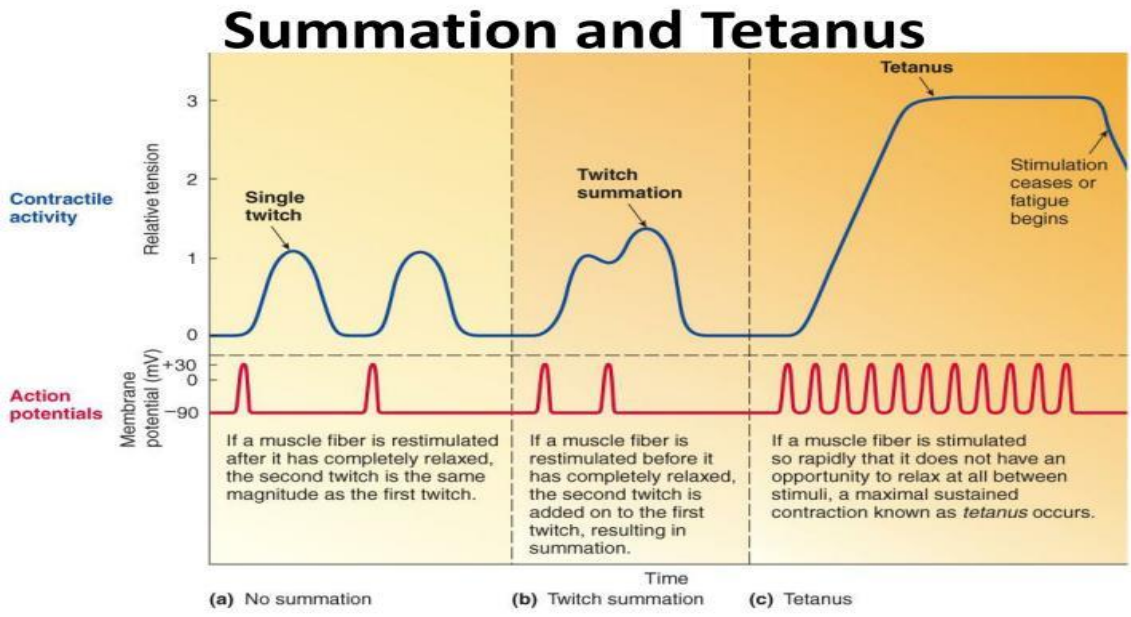



- ***What is the physiological significance of the plateau phase in cardiac muscle cells?***

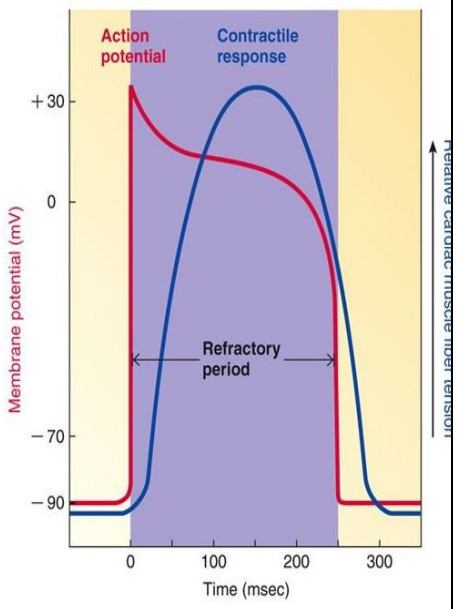
  ***A long refractory period prevents tetanus of cardiac muscle.***

  ***The idea will be described just to clarify the significance of this phase, you don't have to memorize the following explanation!!***

  *Like other excitable tissues ,cardiac muscle has a refractory period .During the refractory period , a second action potential cannot be triggered until an excitable membrane has recovered from the preceding action potential . In skeletal muscles, the refractory period is very short compared with the duration of the resulting contraction, so the fiber can be restimulated before the first contraction is complete to produce summation of contraction ,Rapidly repetitive stimulation that does not let the muscle fiber to relax between stimulations results in a sustained maximal contraction known as* ***TETANUS*** *. (See the figure below).*




- *In contrast , cardiac muscle has a long refractory period the lasts about 250msec because of the prolonged plateau phase of the action potential. This is almost as long as the period of contraction initiated by action potential,a cardiac muscle fiber contraction averages about 300msec .Consequently ,cardiac muscle* ***CANNOT*** *be restimulated until contraction is almost over, preventing summation of contractions and tetanus of cardiac muscle .A valuable protective mechanism, because the pumping of blood requires alternate periods of contraction (emptying) and relaxation (filling). A prolonged tetanic contraction would prove fatal, the heart chambers could not be filled (relaxed) and emptied again.*
- ***The chief factor responsible for the long refractory period is inactivation (during the plateau phase ) of the FAST Na+ channels that were activated during the initial Na+ influx of the rising phase,that is , the channels is in its closed but NOT capable of opening state*** *,Not until the membrane recovers from this inactivation state (when the membrane has already repolarized to resting) , can Na+ channels be activated once again to begin another action potential. (The figure shows the relationship of an action*



*potential and the refractory period to the duration of the contractile response in cardiac muscle).*

- ***Too sum up : Due to the long action potential ,cardiac muscle cannot be tetanized.***

# Short quiz

***1. It is impossible to tetanize a heart because:***

a) There is a long mechanical refractory period

b) The refractory period and the mechanical contractile response are of almost equivalent duration.

c) The heart muscles do not contain Ca+2 .

d) The mechanical contractile event is usually shorter than the duration of the electrical depolarization.

***2. Regarding the S-A node*** :

a) Cells within the S-A node act as heart pace maker because their membrane depolarize to threshold and initiate an action potential with the highest rate .

b) Acetyl choline increases the slope of the pace - maker potential .

c) Sympathetic stimulation decreases the slope of the pace - maker potential .

d) The pace - maker cells within the S-A node are neurons rather than myocytes

**3.What area of the heart is responsible for the delay of conduction between the artria and ventricles?**

a)SA node

b)AV node

c)Bundle of His

d)Perkinje fiber.

***4.Which of the following statements is wrong regarding effects of the autonomic nervous system?***

a) Parasympathetic nervous system increases the AV delay.
b) Sympathetic nervous system increases the AV delay.
c) Parasympathetic nervous system decreases the rate of depolarization to threshold.
d) Sympathetic nervous system increases the rate of depolarization to threshold.

***5.which of the following receptors is responsible for decreasing the heart rate (bradycardia)?***

a) β2 (beta2) adrenergic receptor.

b) alpha-2 (α2) adrenergic receptor.

c) Muscarinic receptor M2.

d) Muscarinic receptor M1.

ANSWERS:

1) B

2) A

3) B

4) B

5) C

I tried to explain some concepts so you can get the whole idea but none of these explanations are for memorizing.

The figures are as similar as possible to Dr's Yanal drawings during the lectures; I hope these figures would make it easier for you to understand the concepts.

Please do not hesitate about asking me.

***When some space has uneven beats, Humans need to pace and bring peace.***

Good luck Doctors, and take care of your hearts ♥