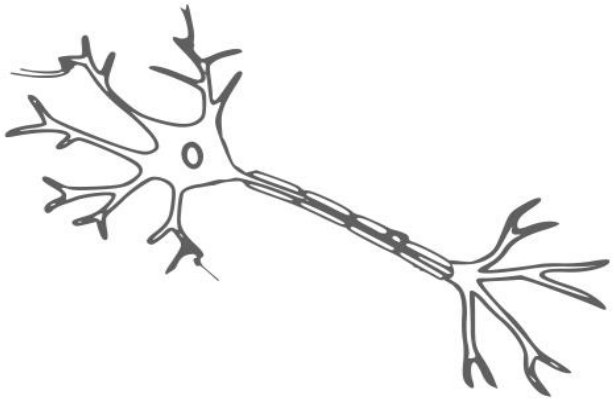
Sheet no. 18

Physiology



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Doctor: Yanal Shafagoj

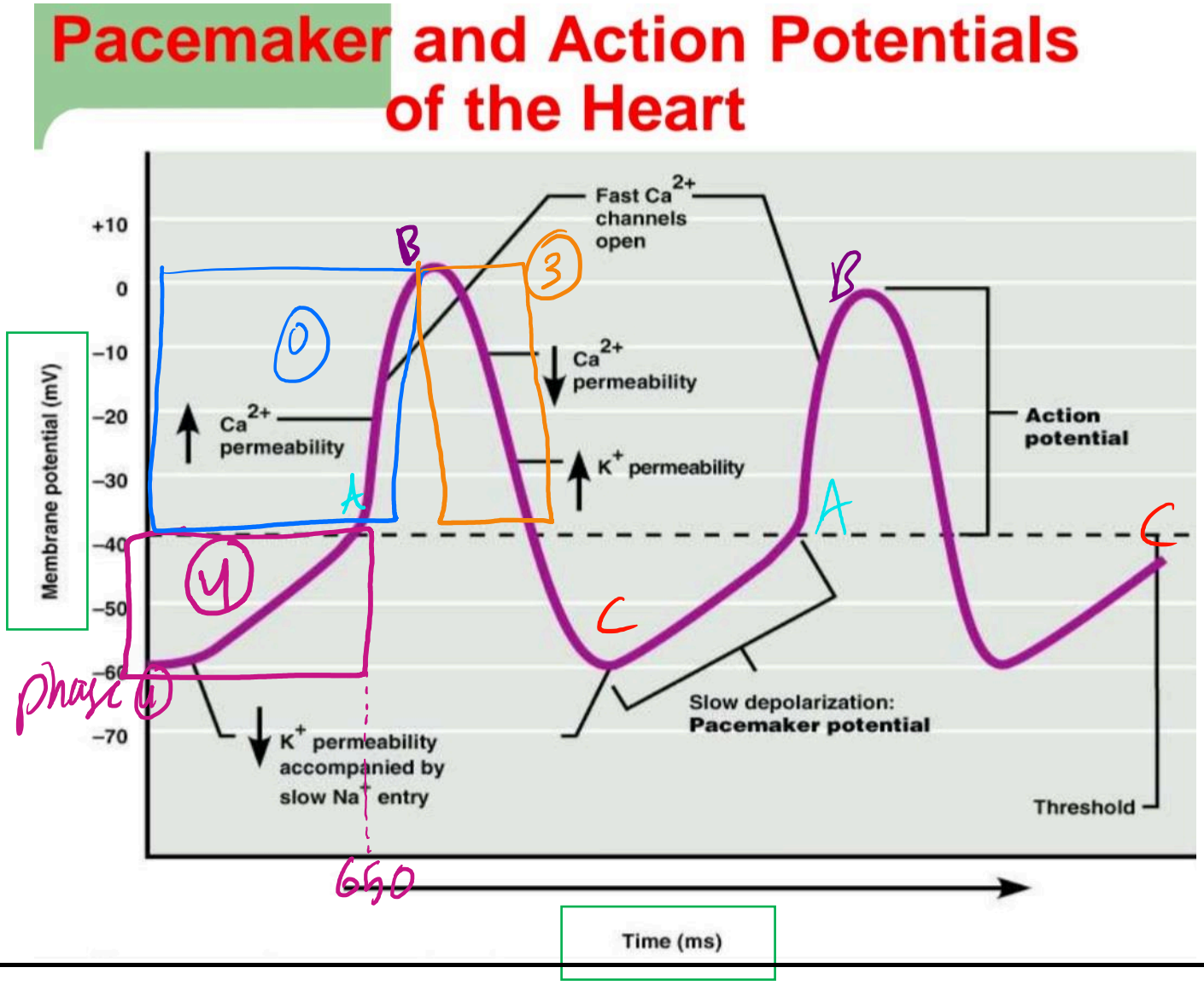
Instructions:

What the doctor said in the lecture → Black

So we are still talking about the electrical behaviour of the heart , for example , in the SA node (the following diagram) there are three phases :

1-Resting phase 2-Depolarizing 3- Repolarizing

1-resting phase: also called phase 4, it is unstable with respect to time (there is a change in voltage per time), the slope is ascending.



In this phase Na^+ enters the cell (because of Na^+ channels which open only in the first half of this phase So we call them funny channels), and at the end of this phase Ca^{2+} enters, until we reach the thresholds ,then Ca^{2+} permeability increases leading to depolarizing (the next phase, phase 0)

this phase takes about 650 ms (to reach threshold) and it takes another 150 ms for the action potential to occur so the summation of both is 800 ms=0,8 s, and this is what we call the cardiac cycle duration.

so eventually the heart rate = 60/0.8 = 75 BPM.

if we had sympathetic stimulation this will increase Na^+ entry, so we will reach threshold faster, the duration between two action potential become Shorter (shrinks), and this will lead to increase the heart rate.

in the following diagram, note that:

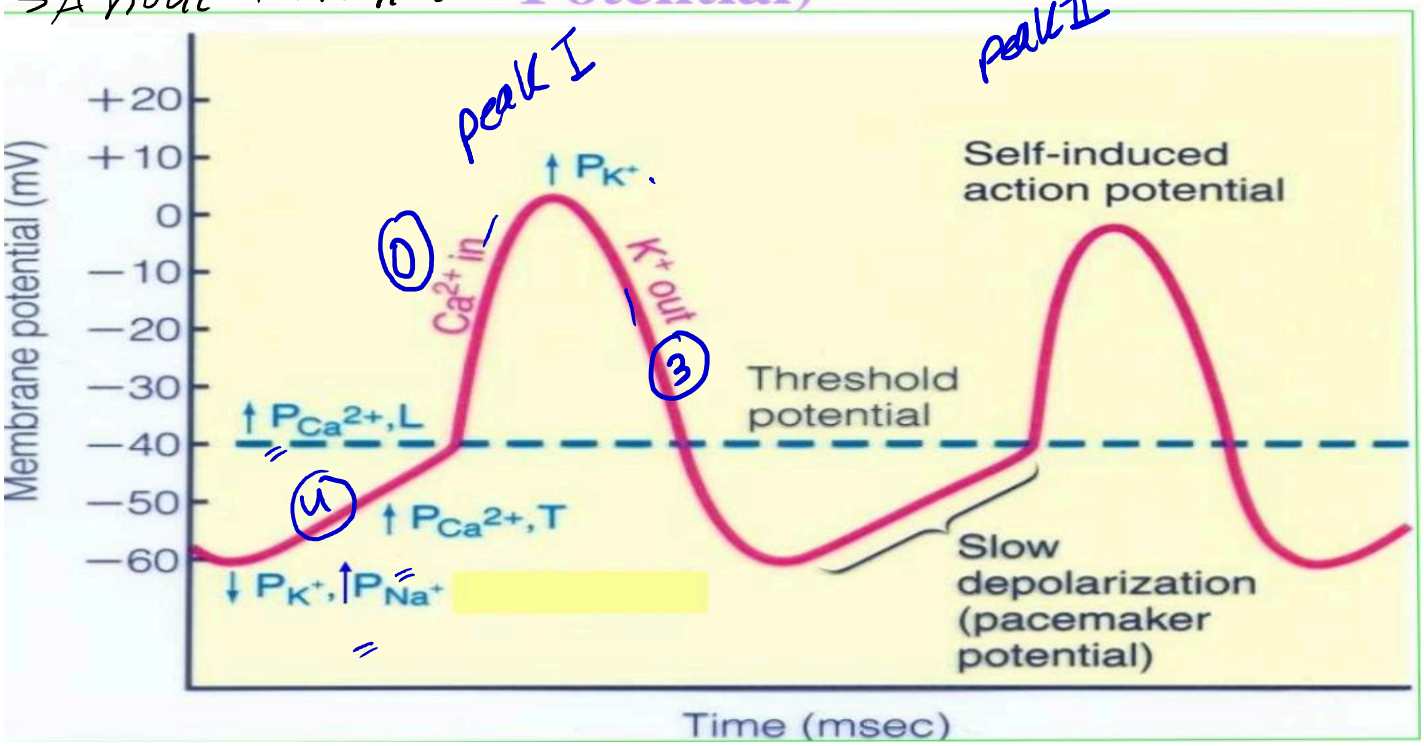
1) at the resting phase (-60mv) there is low(decreasing) K^+ permeability (conductance),high (increasing) Na^+ conductance (there is Sodium leakage at rest),and at the end of this phase Ca^{2+} conductance increases and continue increasing in the depolarizing phase (phase 0) .
2) at phase 3 ,K^+ starts to diffuse out of the cell (out flux) bringing the cell back to phase 4(resting phase).

3) we can calculate the cardiac cycle duration between two peaks or between any two similar points of two action potential as illustrated on the diagrams.

When the potential reaches a threshold voltage of about -40 millivolts, the L-type calcium channels become "activated" thus causing the action potential.

Slow Response Action Potential (Pacemaker Potential)

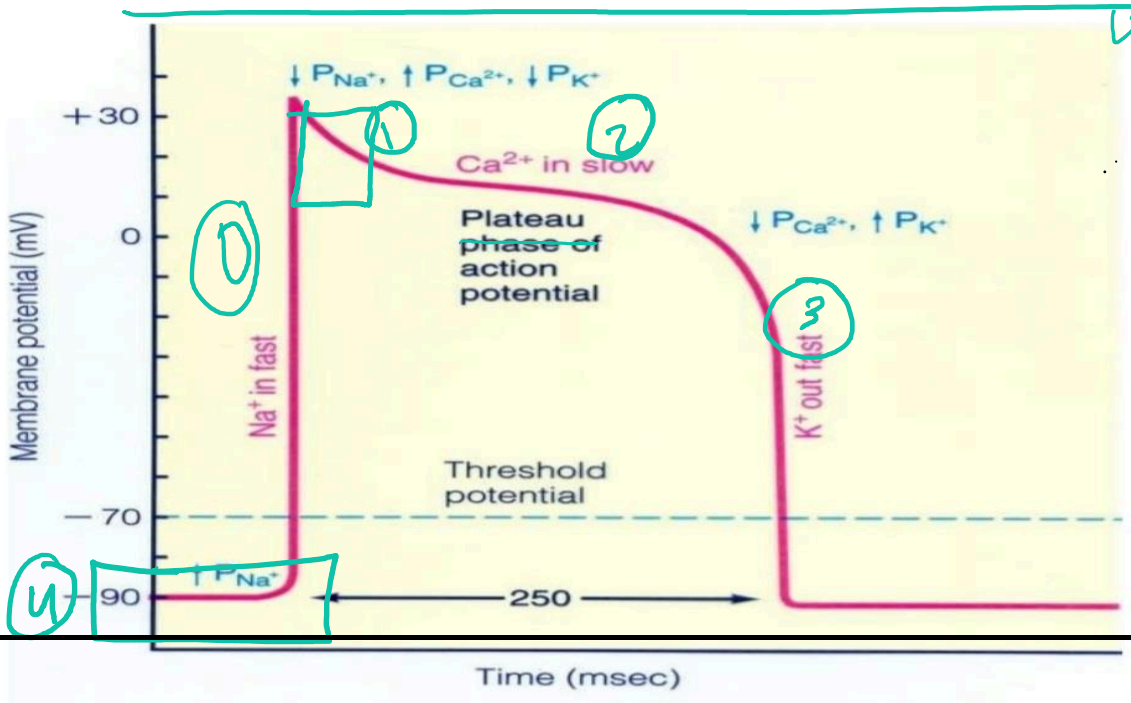
SA node + AV node



However , the following diagram represent the action potential in the ventricles:

Fast Response Action Potential of Contractile Cardiac Muscle Cell

ventricles



Note that:

The cause of this difference in negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium and calcium ions.

there is 5 phases

resting phase (4),phase0, phase 1, phase 2 (plateau) and phase 3

*Phase 4 is the resting membrane potential, and it differs from the RMP of the SA NODE ,here it is -90 mv and the threshold is -70 mv .

*in phase 0,due to Na^+ entry (by fast Na^+ channels) the action potential changes from -90mv to +30mv in no time .

they are voltage gated Na^+ Channels

Initial repolarization phase

*in phase 1, we have what we call transient out (TO) current ,which is a current that result from K^+ moving out of the cell and this will cause Less negative membrane potential until the next phase.(from the diagram: the conductance for Na^+ and K^+ decrease, and it increases for Ca^{2+}).

*phase 2 (the plateau):at this phase the entering positive currents Ca^{2+}= the exiting positive currents K^+, so the membrane potential will remain stable with respect to time ,

(plateau is a French word means Straight line)

note that there are two K^+ ions exiting the cell for each Ca^{2+} ion entering because of the different charges ,at the end of this phase, Ca^{2+} current will be turned off (Ca^{2+} won't be entering anymore), k^+ current will increase and this will bring the cell back to the resting membrane potential-90 (phase 3)

then phase 4 starts again

*Note that phase 4 in ventricles is stable because the entering of positive charges (Na^+) = exiting of positive charges (K^+),whereas in the SA node it wasn't stable ,it was ascending, because of the leaky Na^+ Channels

So what Cause the movement of these ions at this phase??

Firstly ,let's examine Ohm's law

$I_x = (Em - E_x)x\, g_x$

I_x :the current of a specific ion

Em :resting membrane potential

E_x: ion's equilibrium potential

G_x:ion conductance

$(Em-E_x)$:the driving force

Na^+ is entering due to the electrochemical gradient(the driving force) →- 90 - +61 = -151 (high driving force), however ,Na^+ has very low conductance(almost 0,01 of potassium conductance) so eventually only small amount of Na^+ will enter the cell

*what about k^+?

the driving force for K^+ is almost zero (very little) even though it conductance is high , and this makes small amount of K^+exit from the cell.

If Na^+ current= K^+ current, then the RMP remain stable.

Now, let's talk about the heart , what really manner for us (electrically) are 3 things: 1-SA node 2- AV node 3- the ventricles(AV bundle, both branches and Purkinje cells ,but what matter is the muscle itself)

Here is an exam question , what is so special about the SA node (which allow it to produce action potential)?

because it is the **most** leaky to Sodium, so it reach the threshold faster than any other cell .Although the AV node is leaky to Na^+, it is less leaky than the SA node ,so when both of them try to generate action potential ,the SA node will be faster, while the AV node will need more time.

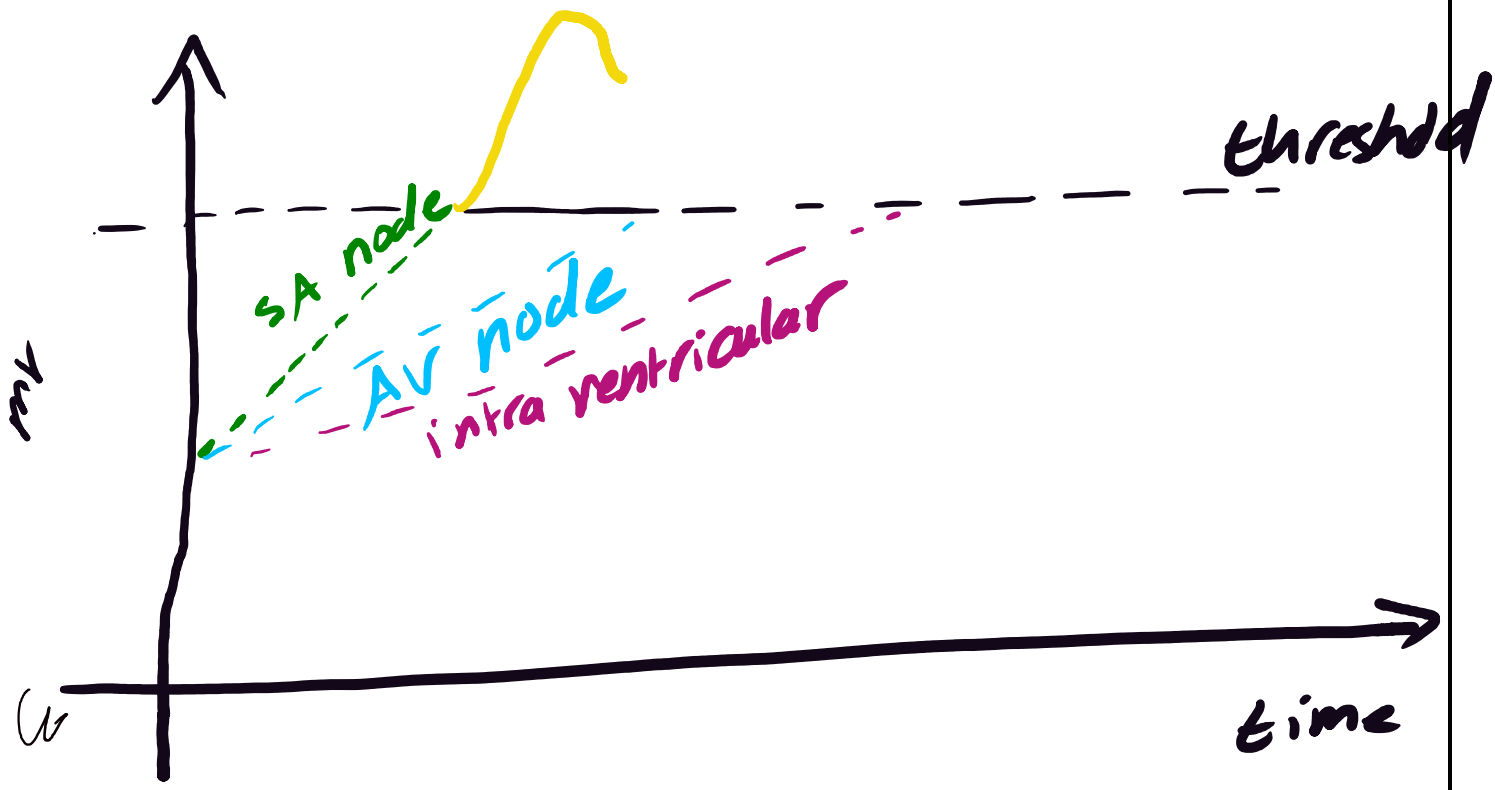
Because the SA node is faster than the AV node, SA node will act as an external stimulus on the AV node, so the AV node will stop being auto-rhythmic (produce it own potential) because it is unable to express itself (bring the action potential to the threshold) and it will follow the SA node.

So, the AV node is suppressed (تم قمعها)and driven by the SA node.

*Note that intra ventricular cells are leaky to Na^+ but they are less leaky than the SA node or the AV node ,this is called overdrive suppression .

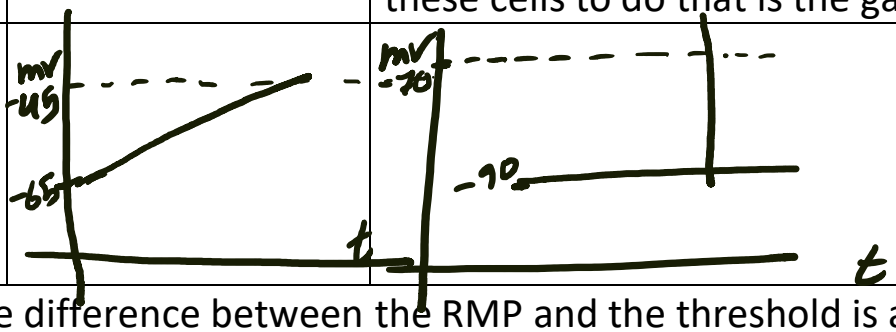
(the doctor mentioned an example about overdrive suppression: when the heart stops or the SA node produces a lot of action potentials at a high rate we can make a DC Shock , which generates action potential at a very high rate, higher than the SA node itself, this will stops the SA node for a short time ,because it was suppressed by higher rhythm (DC shock) but the doctor said we are not talking about DC Shock now)

Note that SA node are non contractile cells, they lack of actin and myosin, they are in the right atrium of the heart, they are the smallest cells in our body, their diameters is 3um ,(ventricular 15- 20 um, Purkinje 70 um) .



So, if we want to compare between action potential in SA node and in ventricles,

firstly, in phase 4:

	SA node	ventricle
RMP	-65mv	-90mv
Relationship with EK^+	Close but not very much	very close to K^+ potential equilibrium
Driving force of Na^+	lower	higher
Threshold	-45mV (almost)	- 70 mv
D V / Dt (الميل)	>0 (not stable) does not need a stimulation	= 0 (Stable) needs a stimulation
Fast Na^+ channels	closed and inactive→so depolarizing will be slower	closed and ready to open→so when we reach the threshold they will open by positive feedback → will Cause depolarizing in a very short time (phase 0),this is very important because cardiac muscle cells must work as one unit(syncytium),and what really enable؛ these cells to do that is the gab Junctions
The diagram		

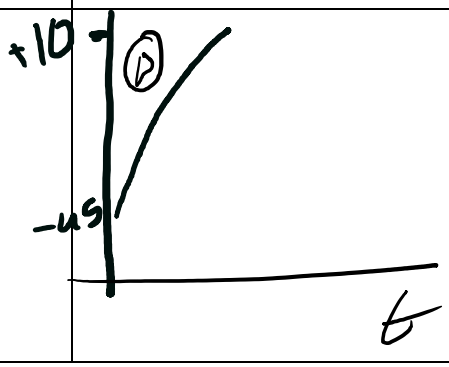
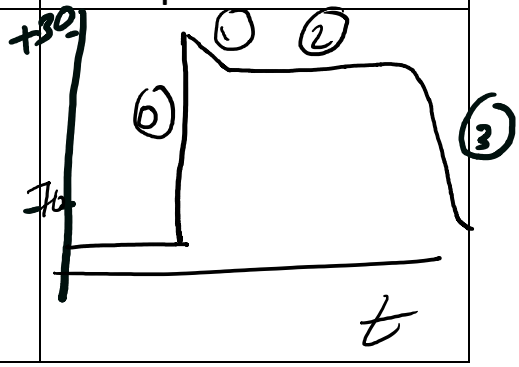
explanation from the book

Note that the difference between the RMP and the threshold is almost the same in both, so exiting them is almost the same.

* If the ventricles for some reason become the pacemaker we call it ectopic pacemaker, this leads to ventricular fibrillations (no enough time to fill ,cycle duration very short),which lead؛to death

At the level of -55 mv, the fast Na+ channels mainly have already become inactivated.is that any time the membrane potential remains less negative than about -55 millivolts for more than a few milliseconds, the inactivation gates on the inside of the cell membrane that close the fast sodium channels become closed and remain so. Therefore, only the slow sodium- calcium channels can open (i.e., can become "activated") and thereby cause the action potential.

*Now phase 0:

	SA node	ventricle
Dv/Dt (the slope)	lower	very high(almost ∞)
The extend	+10 mv	+30mv(more Na_+ and Ca^{2+} channels are open)
The difference between the Peak and the RMP	-75mv	-120m v
Phase1 (initial repolarizing)	no phase 1	there is phase 1 after phase 0
phase 2 (Plateau)	No plateau	there is a plateau after phase 1
The diagram		

*Advantages of the plateau:

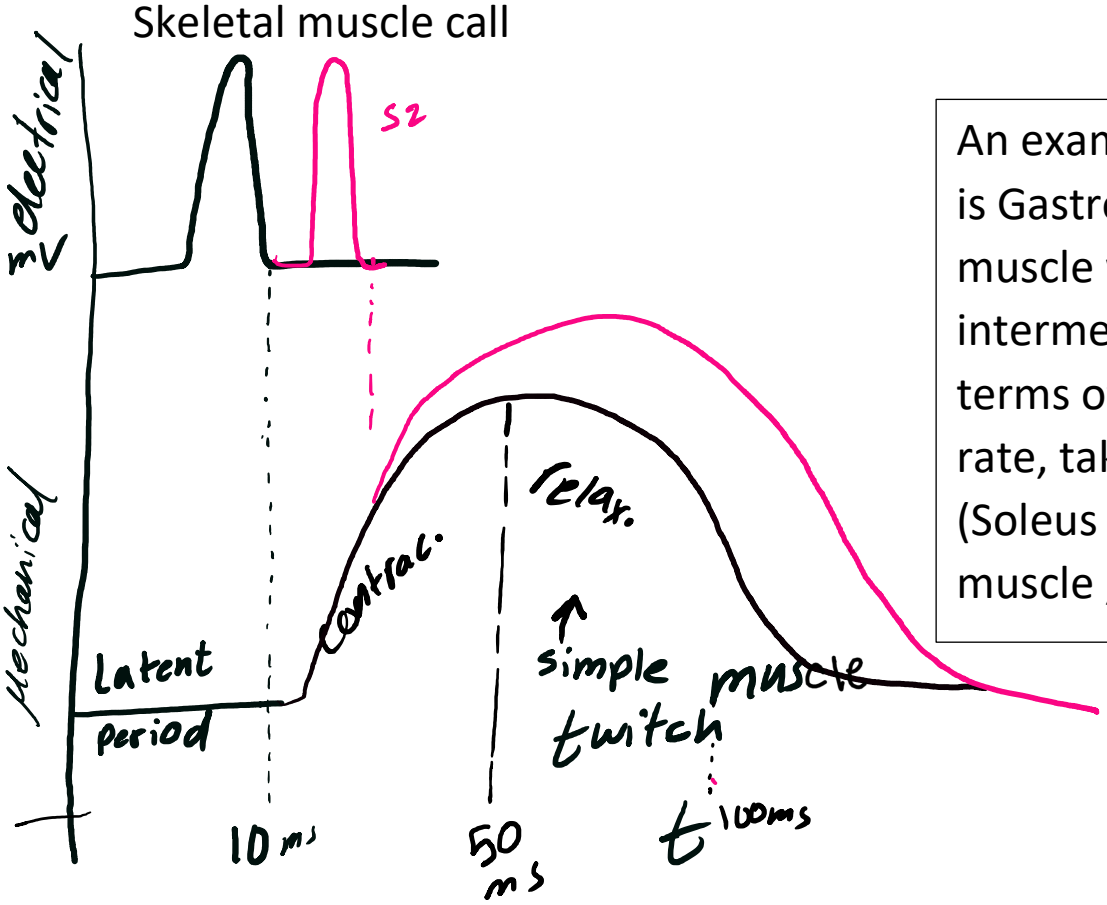
1-increase the duration of the action potential (Skeletal AP lasts for 2 ms whereas the plateau lasts for 250ms)

2-the cell can't be stimulated unless it is completely repolarized (at the end of phase 3)((prevent tetanus))

***A comparison between Skeletal muscle cells and cardiac muscle cells:**

The following diagrams show what is going on in muscle cells electrically and mechanically (excitation contraction coupling) :

Skeletal muscle call



An example of a muscle is Gastrocnemius muscle which is an intermediate muscle in terms of contraction rate, takes 100 ms (Soleus muscle is slow muscle , takes 300 ms)

Explanation for skeletal muscle cell diagram:

the upper part represent the electrical part (excitation of the cell),while the lower part represent simple muscle twitch (mechanical or contraction of the cell)

latent period: is the period between excitation and contraction (how much time it took the contraction to start)

then contraction start ,followed by relaxation

However, since the first stimulus is over, another be stimulus can be produced (the pink one) after 2 ms ,as the second stimulus is produced, the first contraction is still proceeding, and this will result in the summation of the two contractions. If we kept stimulating the muscle (with 3rd , 4th... simulations),all of those contractions will be combined together and this will cause sustained contraction without relaxation, this is called tetanus.

So why muscle cells can develop tetanisation while cardiac cells can't ?

The short action potential of skeletal muscle cells, it enable us to re-stimulate the muscle before it relax completely, so we can add contraction to a previous one.

*What is the function of the ventricles of the heart?

Ejection (pump blood), in order to eject ,we need to fill them with blood and in order to fill we need to relax the ventricles,

Note :relaxation (filling the heart with blood) is more important than contraction(emptying the heart) , it takes about 0, 5 s while contraction takes 0, 3 s.

Contraction→systole →0,3 s

Relaxation→diastole→0, 5 s

systole + diastole→0, 8 s=the cardiac cycle

If the heart was tetanised (hypothetically) ,it will only contract, no relaxation, no filling with blood, no ejection of blood, this will lead to death !

So what actually happen ?

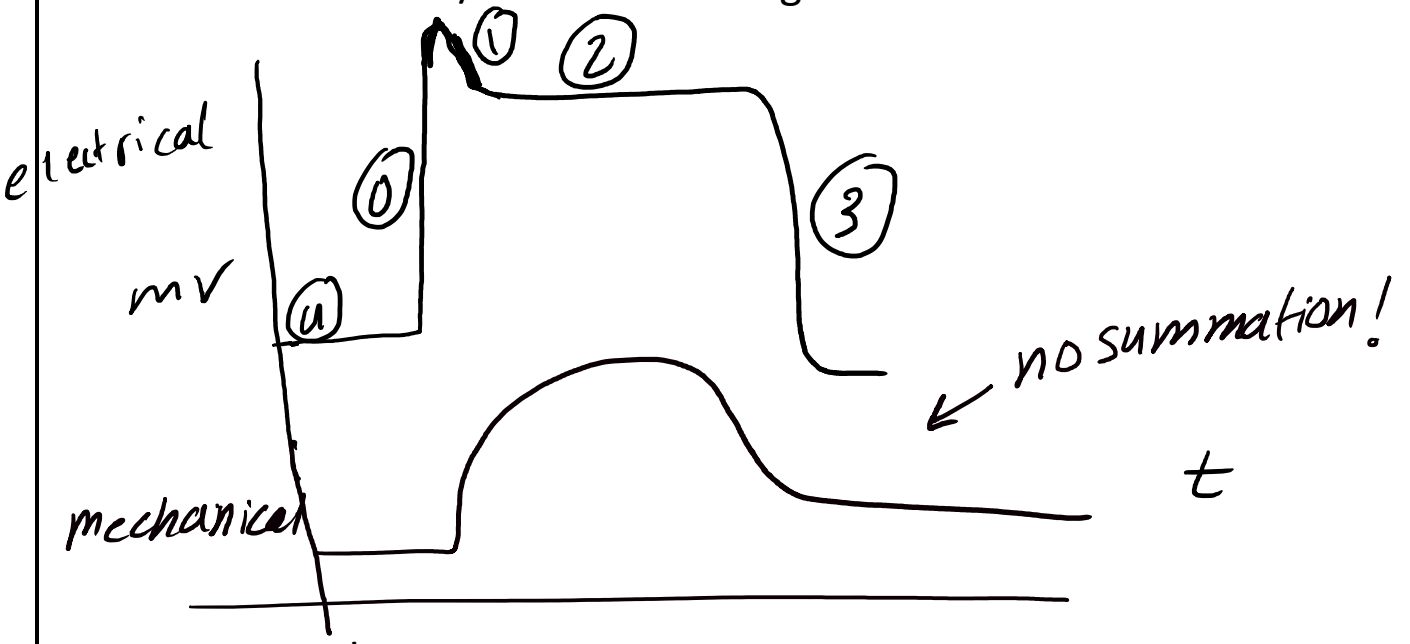
due to the presence of the plateau, the action potential of the cardiac muscle is very prolonged ,which means that in order to re- excite the ventricles we need at least 250 ms (plateau duration) ,and that's why we call it refractory period (Phase 1+2).

in conclusion, what makes tetanisation impossible in ventricular cells ? phase 2 ,or entry of Calcium (there is no entry of calcium in skeletal muscle cells, because Ca^{2+} in skeletal Cells comes from inside the cell while in cardiac cells, it comes from outside).

T- tubules

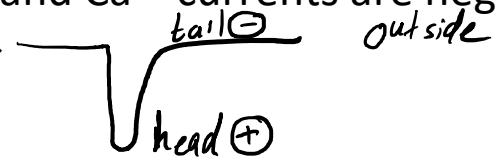
Actually Ca2+ has three benefits, One of them that it prolongs the action duration by prolonging the refractory period, So we can't stimulate the muscle unless it reaches complete repolarizing.

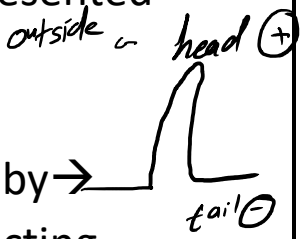
The electrical/mechanical diagram of the cardiac muscle cell:



Remember:

1- Sympathetic Stimulation :increases Na^{+} and Ca^{2+} current and decreases K^{+} (increase the heart rate),while parasympathetic do the opposite.

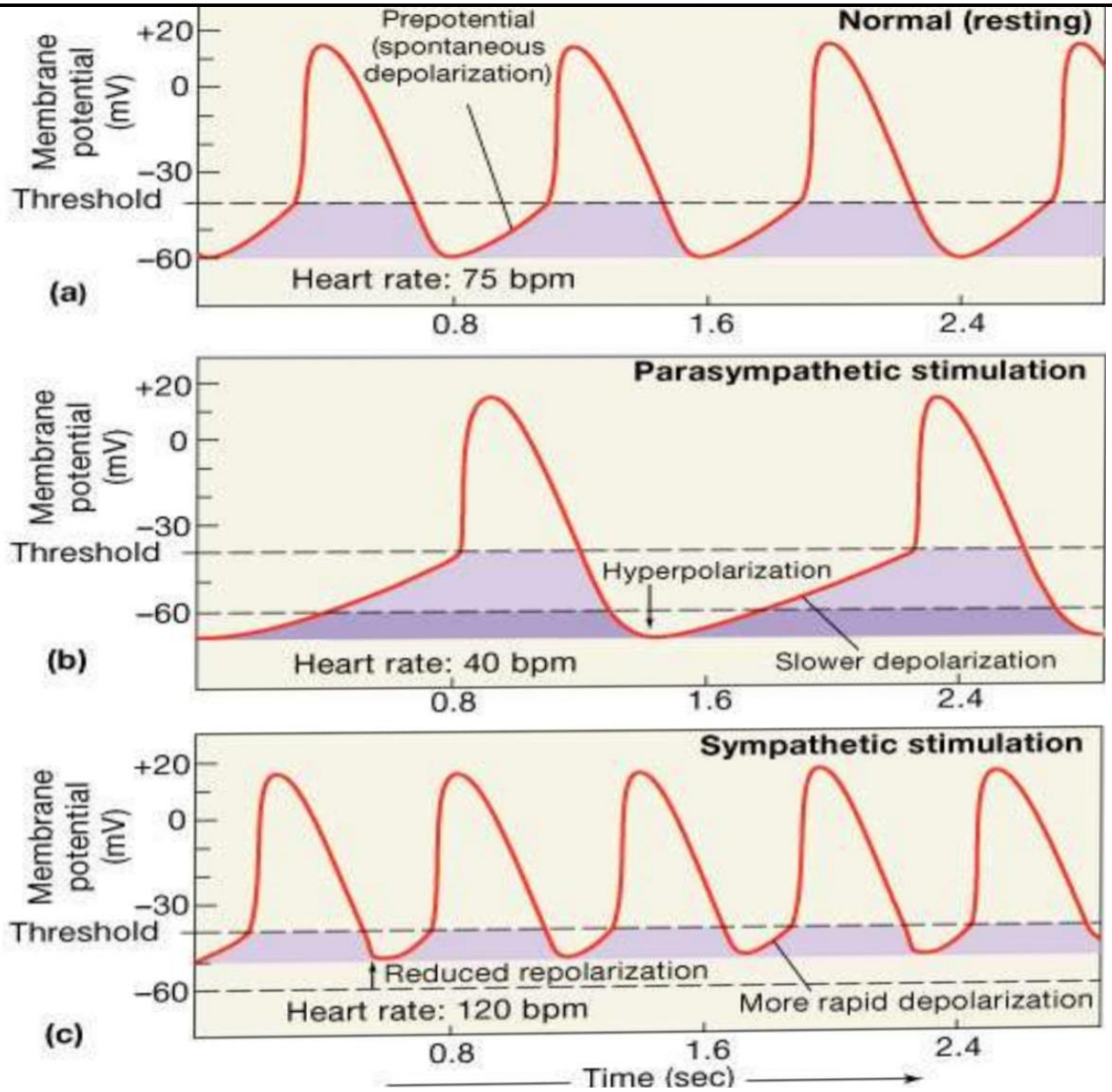
2- Na^{+} and Ca^{2+} currents are negative currents represented by→ 



while K + current is positive current represented by→ because we record from outside , so outside directing current Is positive like K+, while inside directing current is Negative.

3- The following diagram represent the difference between normal, sympathetic and parasympathetic stimulations , note that in sympathetic there is more AP generated than in normal at the same period of time.

4- Under severe parasympathetic stimulations (vagal stimulations) ,cardiac arrest can develop (complete stop)



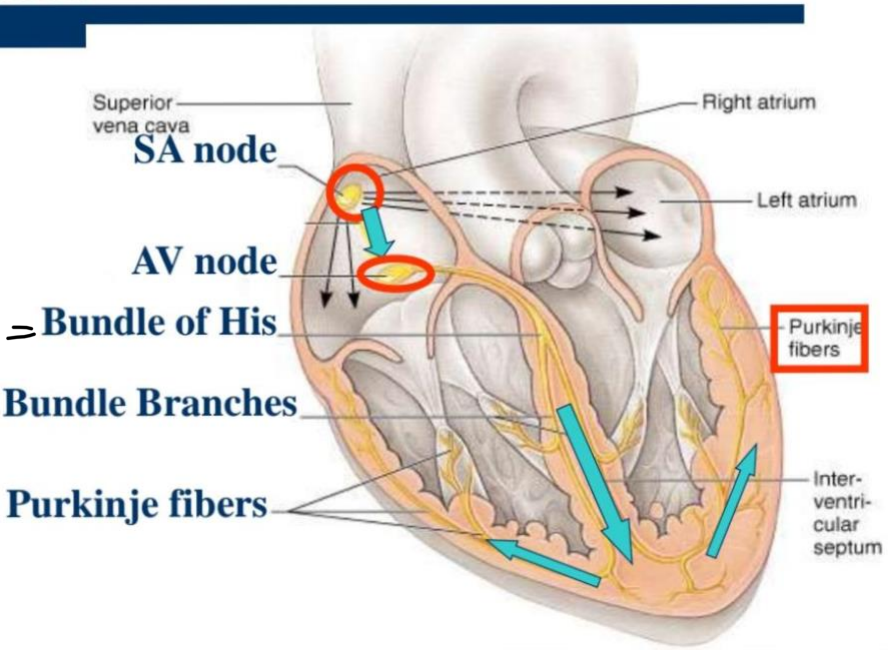
5- AV node function :A- deliver the stimulation from the SA node to the ventricles ,B- AV Delay: Capture the stimulus for a short time then deliver it (to increase diastole phase),and deliver it after the cardiac muscle relax.

6- **Just for further emphasizing,** phase 0 can proceed quickly (almost in no time) in ventricles due to the presence of the fast Na^+ channels, which Cause fast depolarizing of the membrane ,another important factor is the presence of gap junctions between ventricles, these two factors cause fast stimulation for ventricular cells which allow them to work as a one unit ,and contract at the same time (Syncytium).

The following pictures are the doctor 's slides, he didn't mentioned some of what is written inside them in the lectures ,so please pay attention.

Intrinsic Conduction System

Function: initiate & distribute impulses so heart depolarizes & contracts in orderly manner from atria to ventricles.



AV Bundle = Bundle of His

6

Sinus Node

- Specialized cardiac muscle connected to atrial muscle.
- Acts as pacemaker because membrane leaks Na^+ and membrane potential is -55 to -60mV
- When membrane potential reaches -40 mV, slow Ca^{++} channels open causing action potential.
- After 100-150 msec Ca^{++} channels close and K^+channels open more thus returning membrane potential to -55mV.

Intrinsic rate and speed of conduction of the components of the system

- SA node 60-80 action potential /min (***Pacemaker***)
- AV node 40-60 action potential /min
- Purkinje 15-40 action potential /min

Conduction Speed

- SA node: slow speed of conduction
- Ventricular and Atrial muscle: Moderate speed
- AV node: slowest speed of conduction
- Purkinje fibers: Fastest speed of conduction
- ***Ectopic Pacemaker- Abnormal site of pacemaker***

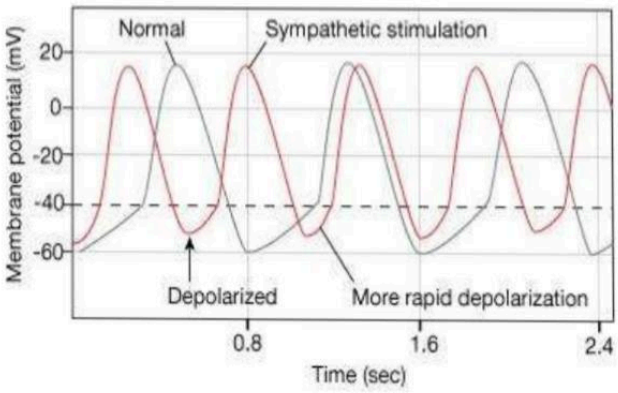
3

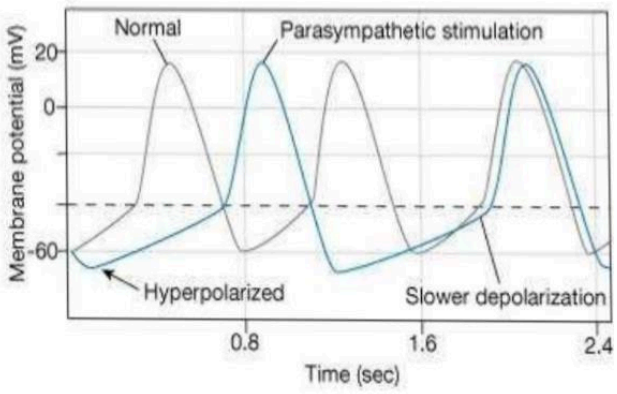
The rapid transmission of action potentials by Purkinje fibers is believed to be caused by a very high level of permeability of the gap junctions at the intercalated discs between the successive cells that make up the Purkinje fibers.

Autonomic neurotransmitters affect ion flow to change rate

- **Sympathetic** – increases heart rate by ↑ Ca^{+2} & I_f channel (net Na^+) flow
- **Parasympathetic** – decreases rate by ↑ K^+ efflux & ↓ Ca^{+2} influx

What part of the graph is <u>not</u> changed by autonomic influences?





Regulation of the heart beat

- Sympathetic from the cardiac plexus supplies all parts of the heart (atria, ventricle and all parts of the conduction system)
- Parasympathetic from Vagus nerves supply mainly the atria, SA and AV nodes, very little supply to ventricles
- Sympathetic: increase the permeability of the cardiac cells to Na^+ and Ca^{++} i.e Positive Chronotropic and positive Inotropic action
- Parasympathetic: Increase the permeability of the cardiac cells to K^+ and decrease its permeability to Na^+ and Ca^{++}

Sinus Node is Cardiac Pacemaker

- Normal rate of discharge in sinus node is 70-80/min.; A-V node - 40-60/min.; Purkinje fibers - 15-40/min.
- Sinus node is pacemaker because of its faster discharge rate
- Intrinsic rate of subsequent parts is suppressed by "Overdrive suppression"

Ectopic Pacemaker

- This is a portion of the heart with a more rapid discharge than the sinus node.
- Also occurs when transmission from sinus node to A-V node is blocked (A-V block).

Parasympathetic Effects on Heart Rate

- Parasympathetic (vagal) nerves, which release acetylcholine at their endings, innervate S-A node and A-V junctional fibers proximal to A-V node.
- Causes hyperpolarization because of increased K^+ permeability in response to acetylcholine.
- This causes decreased transmission of impulses maybe temporarily stopping heart rate.

1

Sympathetic Effects on Heart Rate

- Releases norepinephrine at sympathetic ending
- Causes increased sinus node discharge (***Chronotropic effect***)
- Increases rate of conduction of impulse (***Dromotropic effect***)
- Increases force of contraction in atria and ventricles (***Inotropic effect***)

2

from google : **Inotropic drugs affect the force of cardiac contraction. Chronotropic drugs affect the heart rate. Dromotropic drugs affect conduction velocity through the conducting tissues of the heart.**

79. At phase (2) of an action potential in a ventricular muscle cell which of the following is true?

A) The chemical gradient for Ca++ tends to move this ion inside
B) The electrochemical gradient for K+ tends to move this ion inside
C) Na+ permeability greatly increases
D) This phase is responsible for the short refractory period of cardiac action potential
E) The chemical gradient for K+ tends to move this ion inside

ANSWER A

85. The sinoatrial (SA) node and atrioventricular (AV) are autorhythmic because:

A) Their cells are rounded instead of rectangular
B) Their cells are more permeable to Na+ at rest
C) Their cells have a lot of voltage-gated slow Ca++ channels
D) Their cells are non-contractile
E) Their cells are leaky to anions

ANSWER B

87. The cardiac tissue with the slowed auto-rhythmicity is the:

A) Atrioventricular bundle cells
B) Sino-atrial node
C) Purkinje fibers
D) Bundle branches cell
E) Atrioventricular node

ANSWER C

***Note :Conduction differs from Auto-rhythmicity!!!**

80. Which of the following structures will have the slowest rate of conduction of the cardiac action potential?

A) Atrial muscle
B) Ventricular muscle
C) Purkinje fibers
D) Atrioventricular node
E) Sinoatrial node

ANSWER D

82. Slow response action potential (pacemaker potential) is characterized by?

A) During phase 4 the transmembrane potential is closer to Ca++ equilibrium
B) potential rather than to Na+ equilibrium potential
C) It has longer plateau phase than fast response potential of ventricular cells
D) dV/dT (change in voltage per unit change in time)of phase 0 is much slower than ventricular cell potential phase 0
E) Ca++ ions is responsible for phase 2
F) It has more negative resting membrane potential than ventricular cell potential

ANSWER D

83. Which of the following is NOT caused by Sympathetic stimulation:

A) Increase in the heart rate
B) Decrease of the permeability of the sinoatrial node to K+
C) Positive inotropic effect
D) Decrease of the slope of the slow depolarization phase pf the pacemaker potential
E) Increase of the conduction of the atrioventricular phase

ANSWER D

84. Parasympathetic stimulation of the heart leads to:

A) Negative chronotropic but almost no inotropic action
B) Negative chronotropic and negative inotropic effect
C) Negative chronotropic and positive inotropic effect
D) Positive chronotropic but negative inotropic effect
E) Positive chronotropic and positive inotropic effect

ANSWER A

Note: parasympathetic stimulation decreases the heart rate(Negative chronotropic),also it doesn't supply the ventricles so there is no effect on the heart contraction(inotropic).