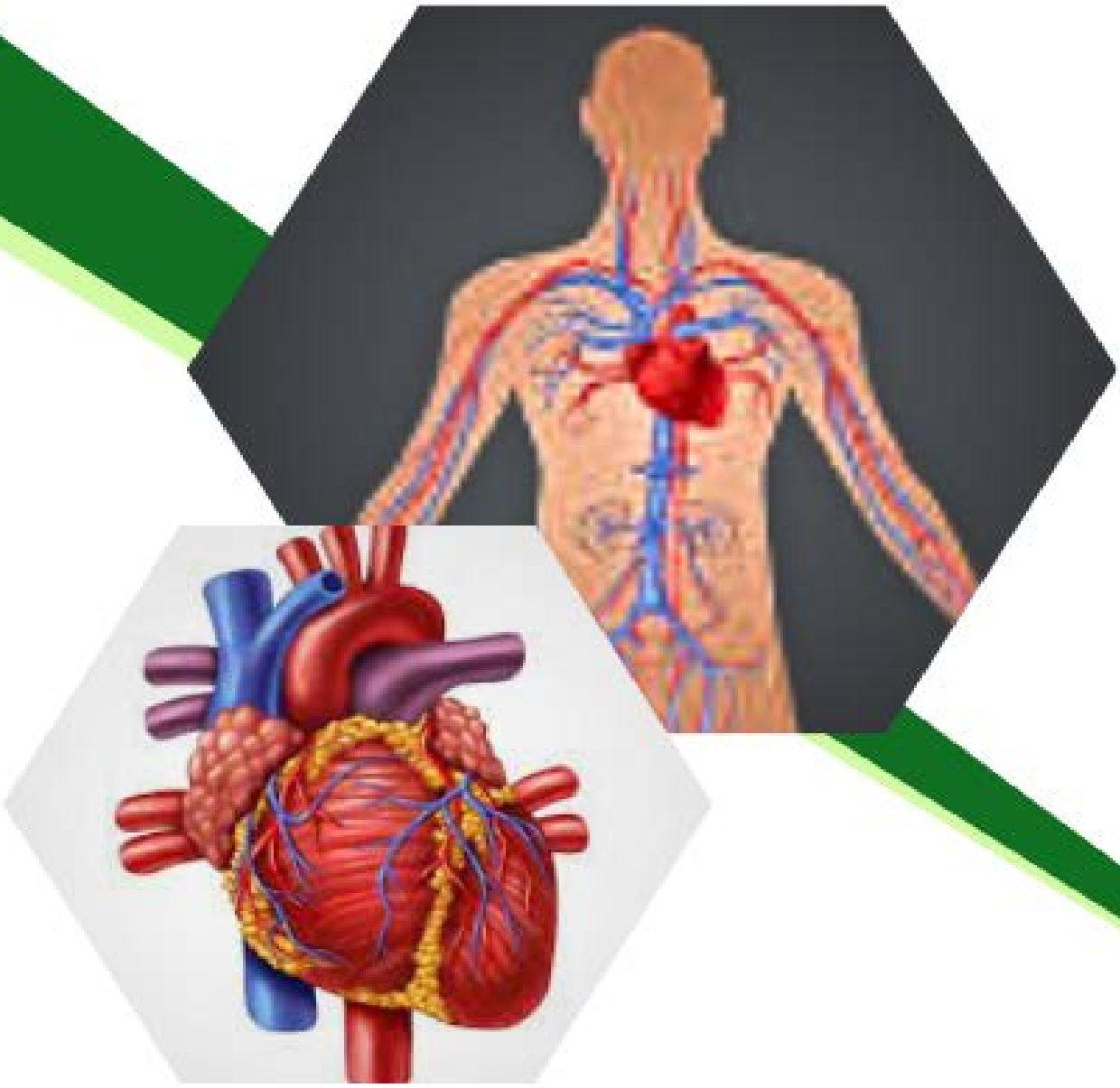
Doctor.021

no. 4

CVS

PHYSIOLOGY



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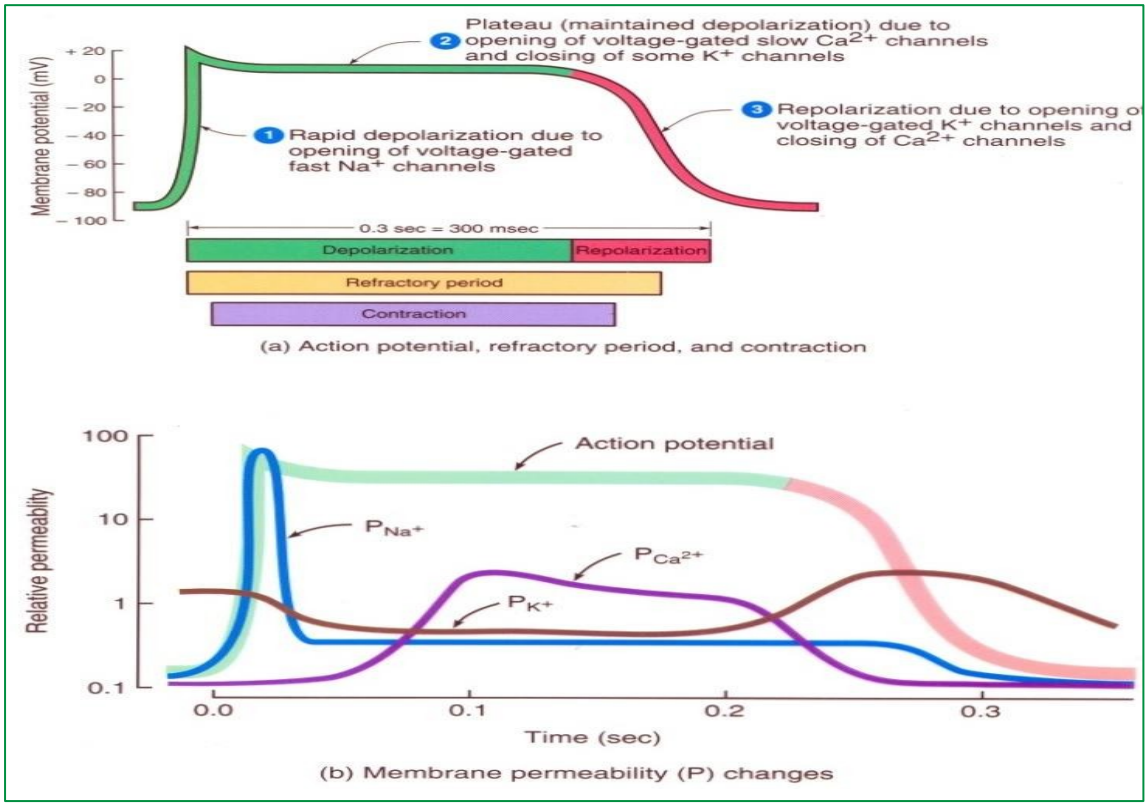
- Let's continue our talk on cardiac muscle physiology:

Action Potentials and Contraction



- Concerning the diagram:
  - We have 5 phases of cardiac muscle action potential (0-4).

1. Depolarization – contractile fibers (ventricular) have stable resting membrane potential. They cannot reach threshold by themselves (not autorhythmic).
   - Voltage-gated fast Na^+ channels open →Na^+ flows in; very high sodium conductance; almost 100 times higher relative to the conductance at rest.
   - Then deactivate and Na^+ inflow decreases
2. Plateau – period of maintained depolarization
   - Due in part to opening of voltage-gated slow Ca^{2+} channels – Ca^{2+} moves from interstitial fluid into cytosol
   - Ultimately triggers contraction
   - Depolarization sustained due to voltage-gated K^+ channels balancing Ca^{2+} inflow with K^+ outflow
   - L-type calcium channels (long-lasting channels) are open and some potassium channels are now close. There's 1:1

movement of calcium to potassium (balance, no generation of new currents).

-Permeability is interchangeable with conductivity.

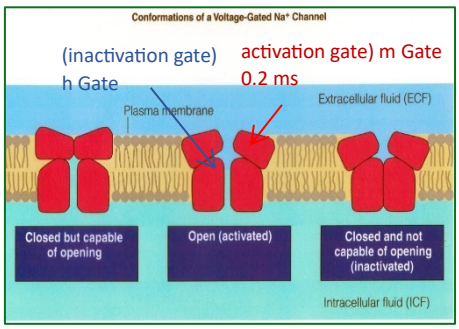
-Interstitial calcium is important for cardiac muscle contraction unlike skeletal muscle which depends on SR calcium stores.

-Interstitial calcium after entering the cardiac myocytes, it either binds troponin or it binds to certain receptors on SR membrane inducing calcium release (AKA calcium induced calcium release).

- Remember: plateau is maintained for 250-300 msecs to allow mechanical response; contraction and relaxation (no summation should occur).

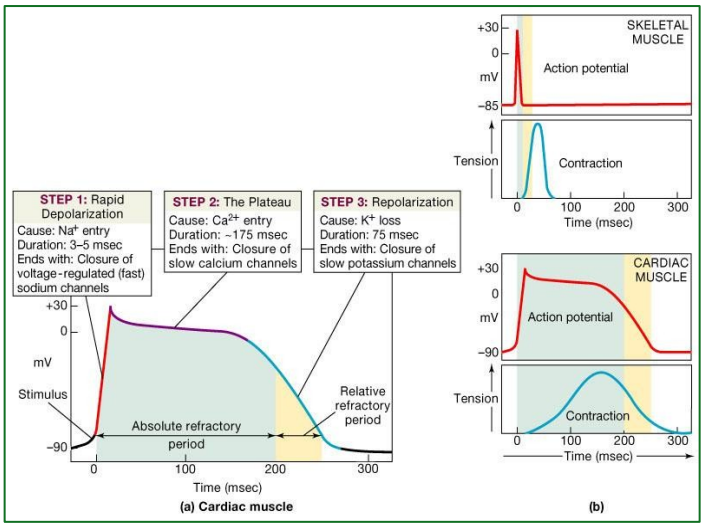
3. Repolarization – recovery of resting membrane potential
   - Resembles that in other excitable cells
   - Additional voltage-gated K^+ channels open
   - Outflow K^+ of restores negative resting membrane potential
   - Calcium channels closing

➢ Refractory period – time interval during which second contraction cannot be triggered



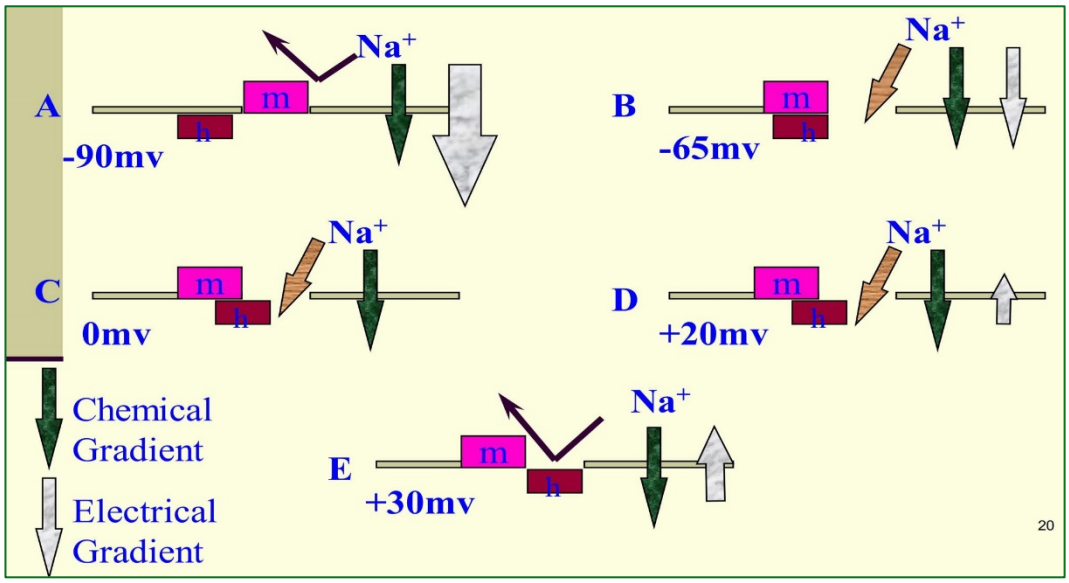
- Refractory period can be divided into relative and absolute; in vivo we only refer to it as *refractory period*.
- We can define it as; the phase at which fast sodium channels are closed and inactivated, in relative refractory period, stronger stimulus will activate them.
- Lasts longer than contraction itself.
- Tetanus (maintained contraction) cannot occur in ventricles.

- In skeletal muscles, depolarization occurs in 2-3 msec.
- Muscle twitch (contraction) happens in about 70 msec, other contractions may be stimulated and summation occurs.



- In cardiac muscles, no summation occurs as relaxation is reached simultaneously with the end of refractory period.

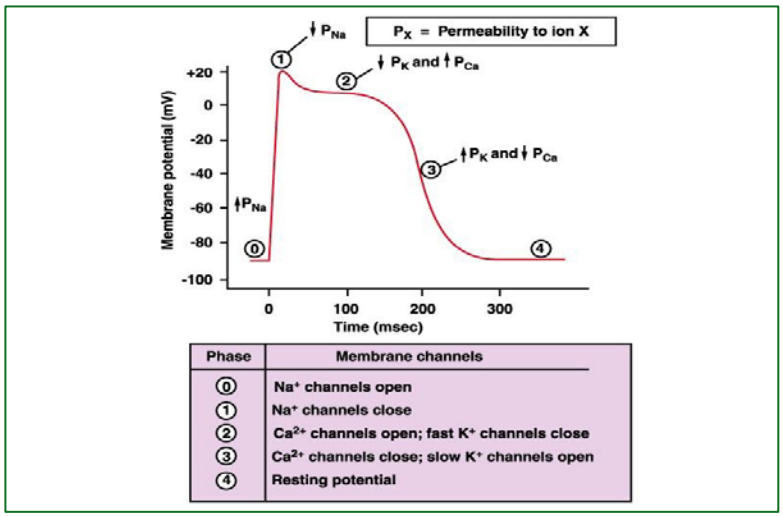
PHASE 0 OF THE FAST FIBER ACTION POTENTIAL



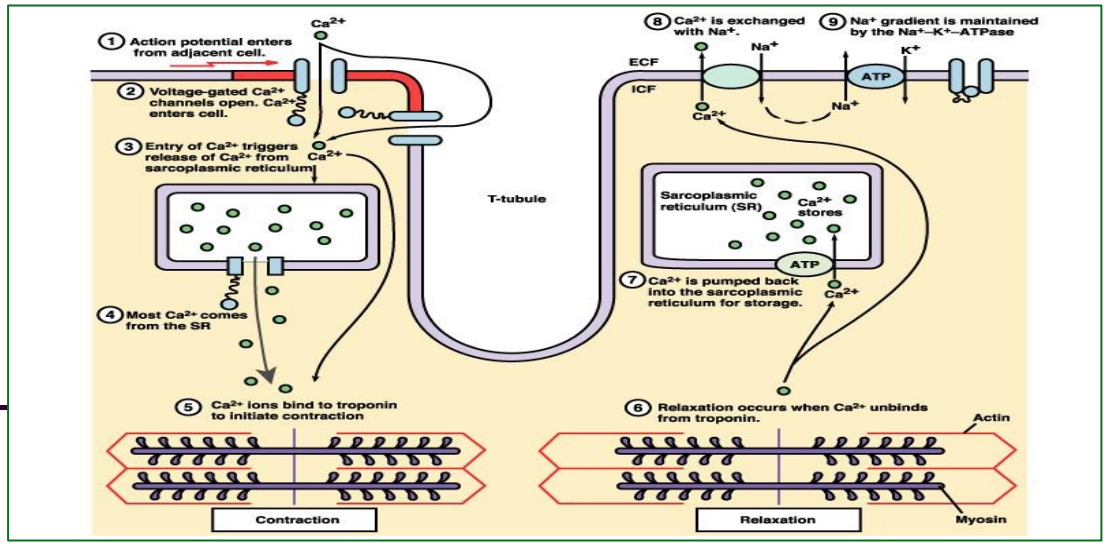
- A: M channel is close, and the H gate is far away from it.
- B: stimulus caused M channel (fast gate, 0.2 msec) movement towards H gate allowing sodium to enter in large amounts causing more stimulation (+ve feedback).
- C: H gate is trying to re-close (relatively slow; needs 1 msec).
- D: H gate has not fully closed yet.
- E: now H gate is closed at +30mV.

Take a look at all voltage values.

- Again, same concepts repeated.
- Those channels are voltage-gated.
- In the heart, there are at least 8 potassium channel variants counterbalance calcium entry.



Phase	Membrane channels
0	Na^+ channels open
1	Na^+ channels close
2	Ca^{2+} channels open; fast K^+ channels close
3	Ca^{2+} channels close; slow K^+ channels open
4	Resting potential



- In the heart:

1. Gap junctions aid conduction of action potential in adjacent cells.
2. Calcium enters through the now open voltage-gated channels (calcium concentration outside the cell 10,000 times more than inside).
   - Calcium has two fates:
3. Binds to certain receptors on SR membrane leading to step 4.

5. Or it directly binds to troponin C.

After calcium has done its function we need to get it back to SR and interstitial fluid to prevent further contractions through:

7. Calcium pump on SR membrane (pump=ATPase; utilizes ATP)

8. Calcium pump on sarcolemma.

Calcium conc.: 10^{-7} in cytosol, 10^{-3} extracellular and $2*10^{-5}$ in SR.

9. Calcium-sodium exchange (secondary active transport; sodium enters the cell driven by chemical gradient, while calcium is countertransported)→ 3 Na for 1 Ca.

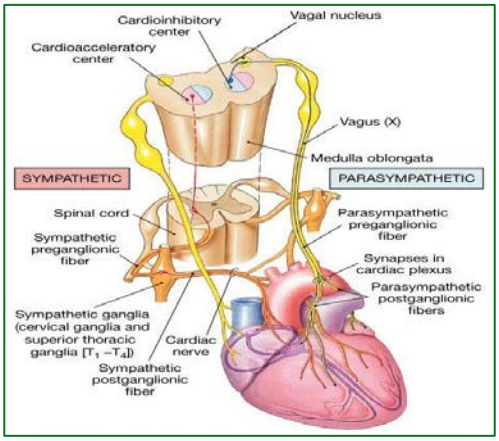
The 3 sodium ions are pumped out by sodium potassium pump and 2 potassium ions are pumped in, therefore, no net change in charge.

Consequently, sodium-potassium pump is needed for the function of secondary active calcium transporter (a drug target).

For ex; Digoxin targets sodium-potassium-ATPase and prevents it from functioning, then, sodium accumulates inside the cell and its gradient is disrupted (no more secondary calcium transportation)→ calcium accumulates inside the cell and contractility is increased.

Now let's move onto Conduction System of the Heart

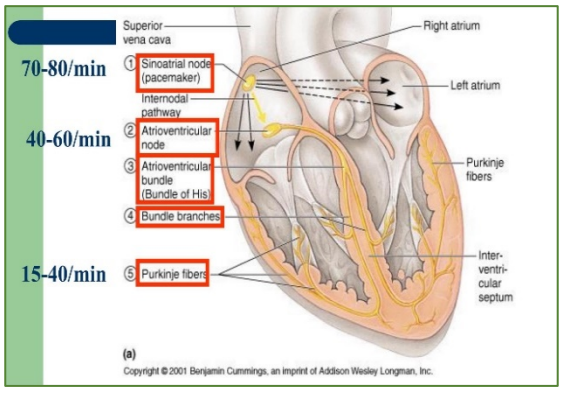
➢ Autonomic Innervation of the Heart



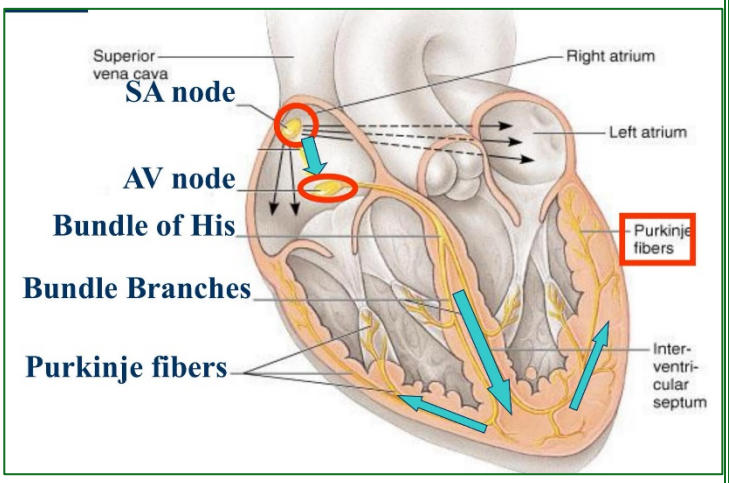
- Parasympathetic innervation through vagus nerve (from medulla oblangata) reaches SA node and AV node and not the ventricles.
- Meanwhile, sympathetic innervation reaches SA and AV nodes and ventricles.

➢ Intrinsic Cardiac Conduction System

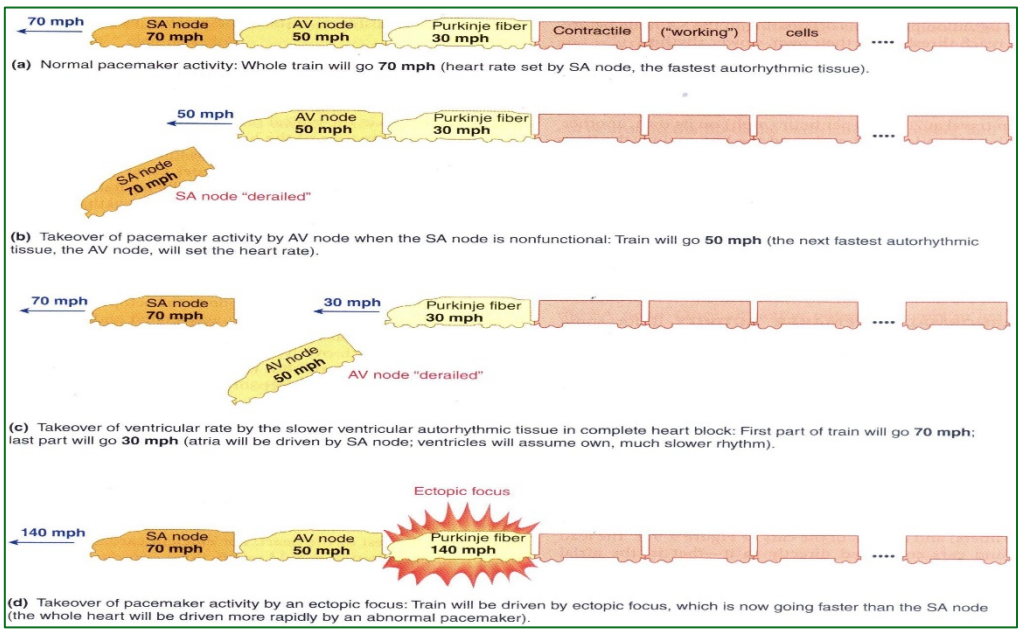
- **Approximately 1% of cardiac muscle cells are autorhythmic rather than contractile.**
- Remember the difference in T-tubules between cardiac and skeletal muscle cells, if we remove T-tubules, excitation and contraction are uncoupled in skeletal cells, the importance of T-tubules in cardiac cells is questionable.



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



- We need to consider the velocity of conduction; being the slowest in AV node (0.5 m/s), 1 m/s in atrial internodal pathways and the highest in Purkinje fibers (4 m/s).
- Same concepts that we already mentioned in lec1: follow the timeline; SA node 0.00→ AV node 0.04→ bundle of His 0.16→ Purkinje fibers 0.22 (we needed 0.06 msec to travel through left and right ventricle which is relatively fast).
- This can be explained by the rapid depolarization in phase 0 (the slope is almost infinity), once you depolarize one cell it's transmitted to other cells in no time, in addition to the conduction velocity in Purkinje fibers.
- Contraction in ventricular cells occurs simultaneously; very efficient contraction.
- In AV nodes; small cells (resulting in high resistance), fewer gap junctions and a more negative resting membrane potential; making it harder to reach threshold.



- It's the same concept as a train with the first node leading it.

- Normally, the physiologic pacemaker is SA node, driven at a velocity of 70 mph.
- In the case of SSS (sick sinus syndrome; SA node isn't functioning), AV node leads the train with a velocity of 50 mph.
- In complete AV block, Purkinje fibers lead the train with a velocity of 30 mph.
- In another case in which ectopic focus takes over pacemaker activity, the train will be driven faster than the SA node.
- An ectopic focus could be in the ventricles, leading to ventricular fibrillation (V-fib), which could be fatal, or in the atrium, leading to atrial fibrillation (A-fib), non-fatal.

Recheck those info from the slides:

- Conduction system parts are modified cardiac muscle cells consist of:
  - SA (sinoatrial) node (**Pacemaker**)
  - AV (atrioventricular) node
  - A-V (atrioventricular) bundle
  - Bundle branches (right and left bundle branches)
  - Purkinje fibers
- **Pathway of Heartbeat:**
  - Begins in the sinoatrial (S-A) node.
  - Internodal pathway to atrioventricular (A-V) node??
  - Impulse delayed in A-V node (allows atria to contract before ventricles).
  - A-V bundle takes impulse into ventricles.
  - Left and right bundles of Purkinje fibers take impulses to all parts of ventricles.
- **Sinus node**
  - Specialized cardiac muscle connected to atrial muscle.
  - Acts as pacemaker because membrane leaks Na^+ and membrane potential is -60mV.
  - When membrane potential reaches -45 mV, slow Ca^{++} channels open causing action potential.
  - After less than 100 msec Ca^{++} channels close and K^+ channels open more thus returning membrane potential to -60mV.

-The action potential in slow response takes a total of 150 msec.

➢ Internodal Pathways

Their speed is approximately (1m/s).

- Transmits cardiac impulse throughout atria.
- Anterior, middle, and posterior internodal pathways.
- Anterior interatrial band carries impulses to left atrium.

➢ A-V Node

- Delays cardiac impulse.
- Most delay is in A-V node.
- Delay AV node---0.09 sec.
- Delay AV bundle--0.04 sec.
- AV node can be subdivided into 3 regions:
  - AN region (atrio-nodal).
  - N region (nodal).
  - NH region (nodal-his).

Total delay is 0.13.

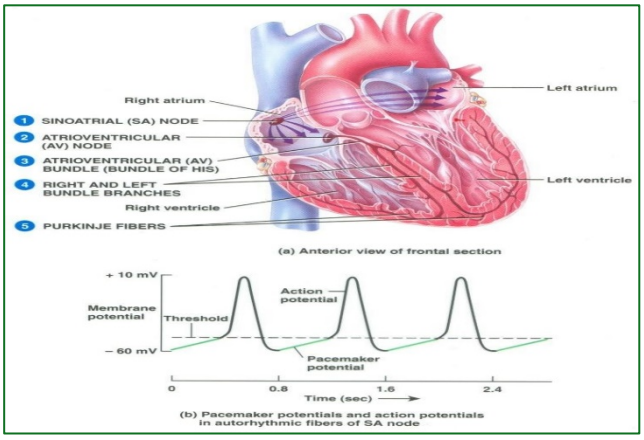
➢ Purkinje System

- Fibers lead from A-V node through A-V bundle into Ventricles.
- Fast conduction (1-4 m/s); many gap junctions at intercalated disks and large Purkinje cells (70 µm), they lack T-tubules.

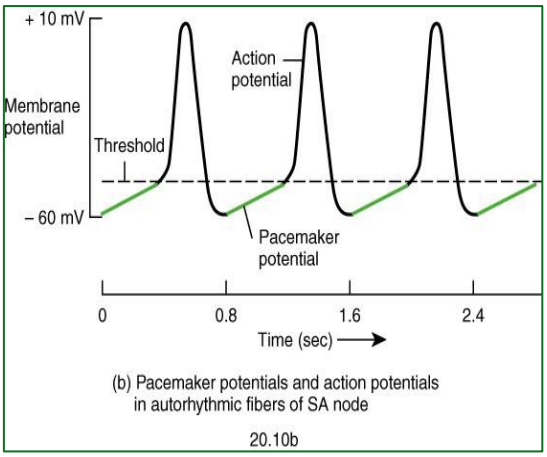
➢ A-V Bundles

- Normally one-way conduction through the bundles.
- Only conducting path between atria and ventricles is A-V node-A-V bundle.
- Divides into left and right bundles.
- Transmission time between A-V bundles and last of ventricular fibers is 0.06 second (QRS time in the ECG).

➢ Sympathetic innervation increases phase 4 slope, while parasympathetic decreases it.



- What makes SA node the pacemaker of the heart?
  - It is the most leaky to sodium; reaches threshold faster.
  - There's overdriven suppression by SA node (masking AV node).
  - If SA node is not functional, AV node expresses itself by a slower rate.



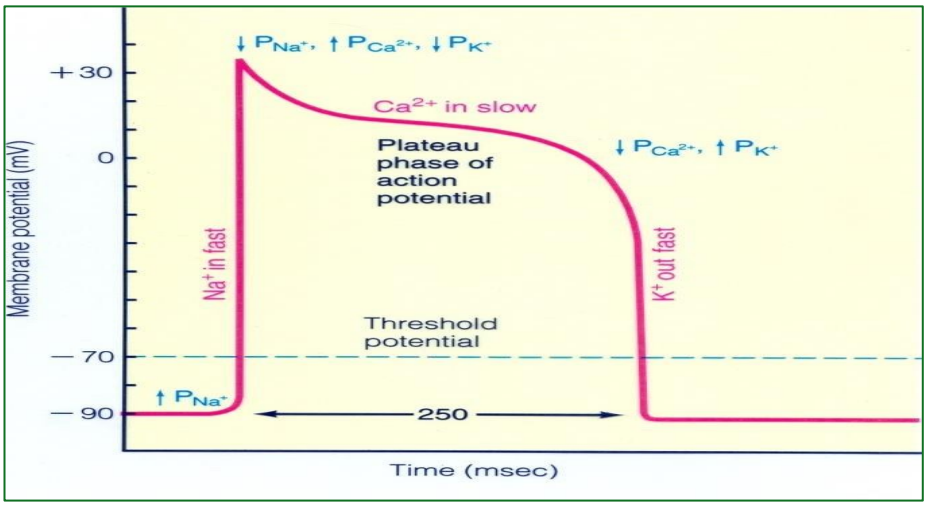
(b) Pacemaker potentials and action potentials in autorhythmic fibers of SA node

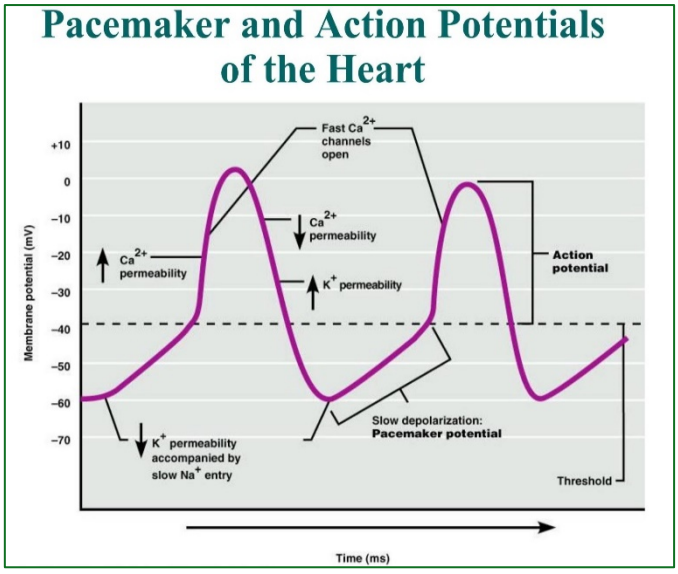
20.10b

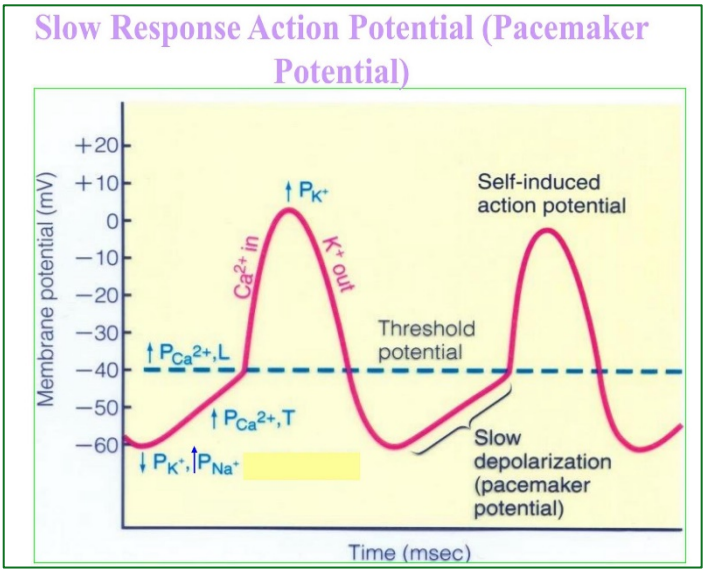
Fast Response Action Potential of Contractile Cardiac Muscle Cell

Again and again and again..

Make a recap :)







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 (latent pacemaker)
- Purkinje 15-40 action potential /min (latent pacemaker)
  Conduction Speed
- SA node: slow speed of conduction (it's not its function to conduct).
- Ventricular and Atrial muscle: Moderate speed
- AV node: slowest speed of conduction
- Purkinje fibers: Fastest speed of conduction
- ***Ectopic Pacemaker- Abnormal site of pacemaker***

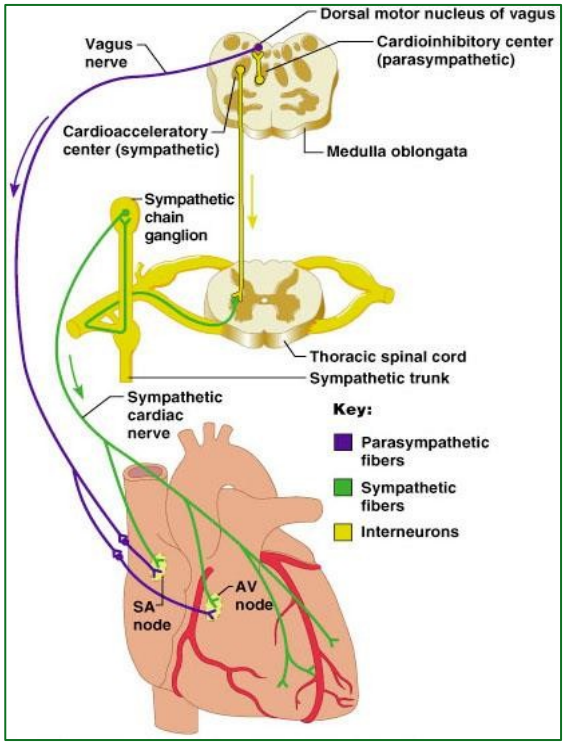
➢ **Conduction Velocity**

- In myelinated fibers, velocity is μ r (up to 100 m/sec), and in unmyelinated μ √r, (up to 0.5 m/sec)
- Atrial Muscle 0.3-0.5 m/sec.
- Interatrial band 1 m/sec.
- Purkinje 1.5-4 m/sec.
- Skeletal muscle fiber 5 m/sec.

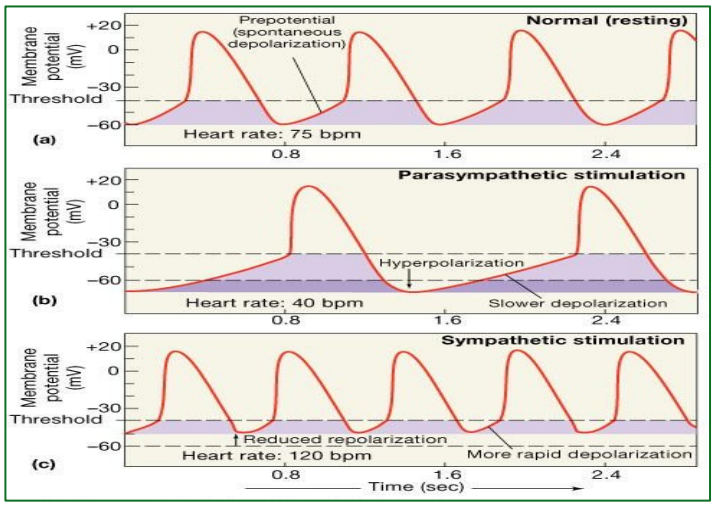
➢ **Extrinsic Innervation of the Heart**

- **Vital centers of medulla**

  1- Cardiac Center
  - *Cardioaccelerator center*; activates sympathetic neurons that increase HR.
  - *Cardioinhibitory center*; activates parasympathetic neurons that decrease HR.
- Cardiac center receives input from higher centers (hypotha- lamus), monitoring blood pressure and dissolved gas concentrations.



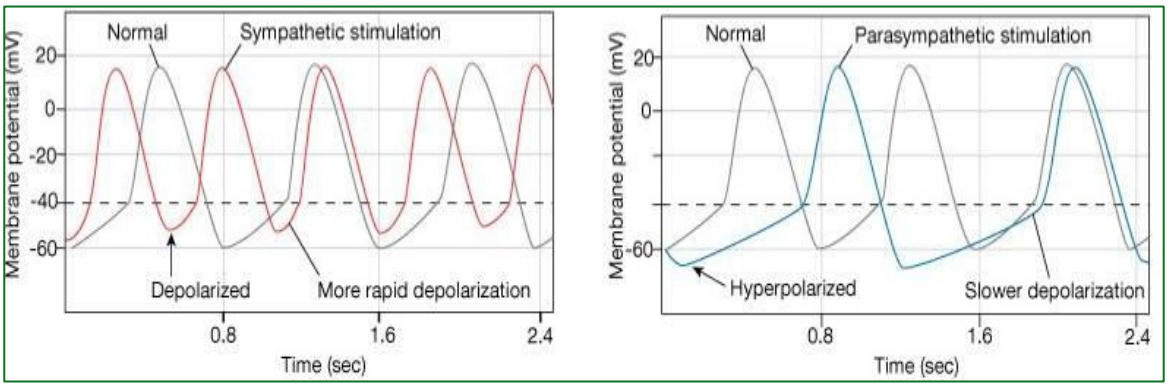
Pacemaker Function



Autonomic neurotransmitters affect ion flow to change rate

- **Sympathetic** – increases heart rate by Ca^{+2} & I_f Na^{+}) flow
  - Increases the slope of depolarization phase, hence, increases the heart rate.
- **Parasympathetic** – decreases rate by K^{+} efflux & $^{-}$ Ca^{+2} influx

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



Effect of autonomic nerve activity on the heart		
Region affected	Sympathetic Nerve	Parasympathetic Nerve
SA node	Increased rate of diastolic depolarization ; increased cardiac rate	Decreased rate of diastolic depolarization ; Decreased cardiac rate
AV node	Increase conduction rate	Decreased conduction rate
Atrial muscle	Increase strength of contraction	Decreased strength of contraction
Ventricular muscle	Increased strength of contraction	No significant effect

اللهُمَّ إنا نستودعك غزة وأهلها وأمنها وأمانها وليلها ونهارها وأرضها وسماءها وشبابها وأطفالها ونساءها، فاحفظها بعينك التي لا تنام يا الله.

V2

- Remember: plateau is maintained for 250-300 msecs to allow mechanical response; contraction and relaxation (no summation should occur).