CVS
PHYSIOLOGY

Modified NO: 1

كتابة: عمر الصمادي و زينة أبوذياب

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Cardiovascular Physiology

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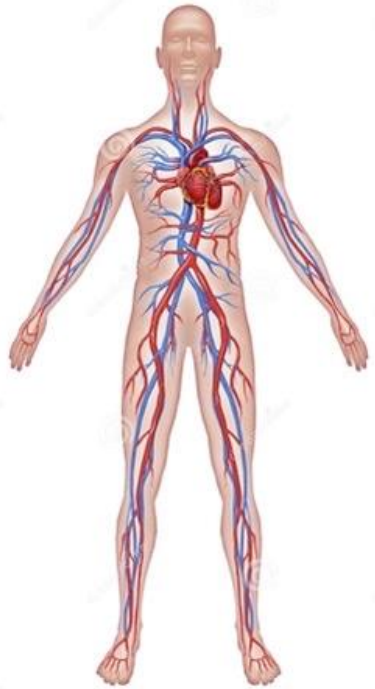

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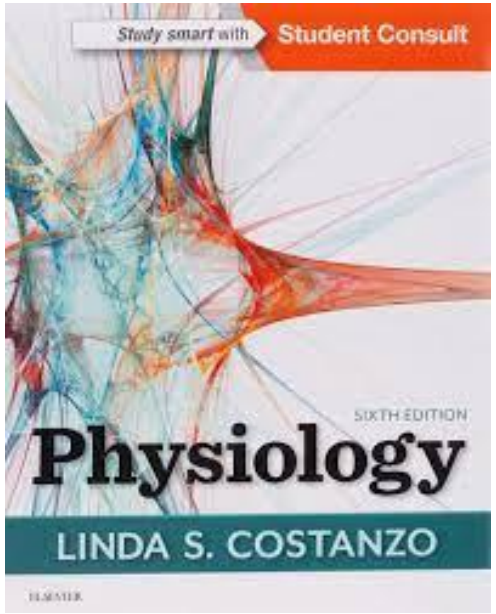
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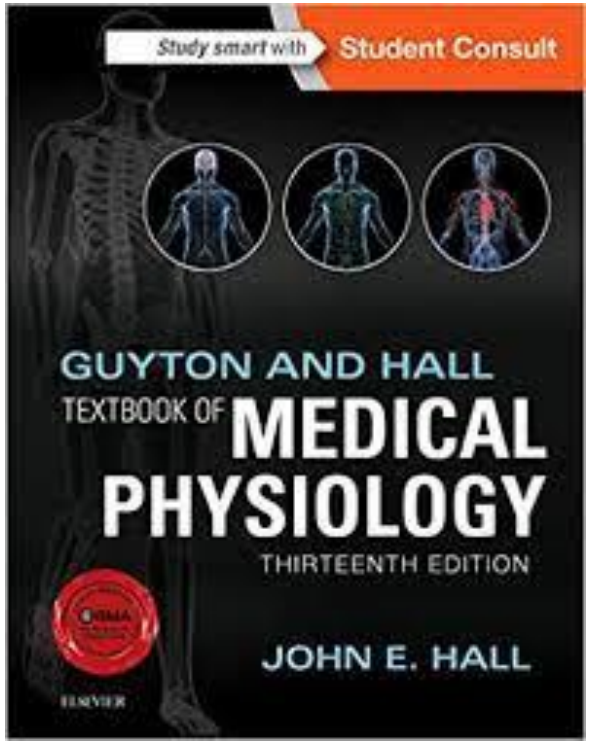
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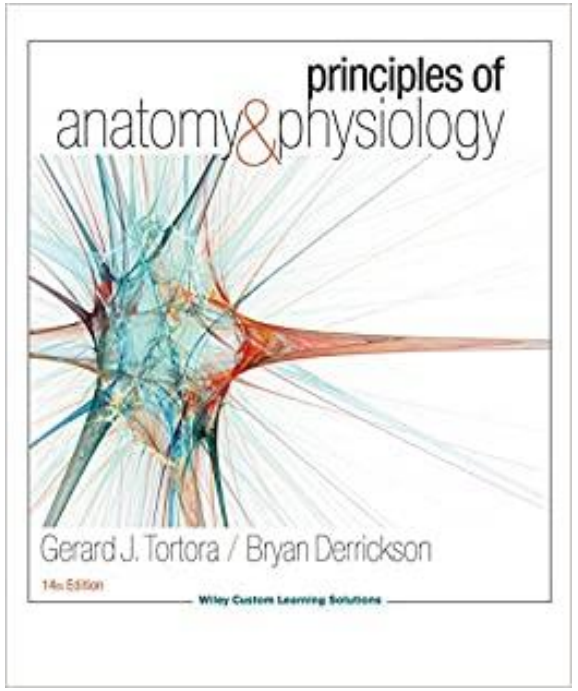
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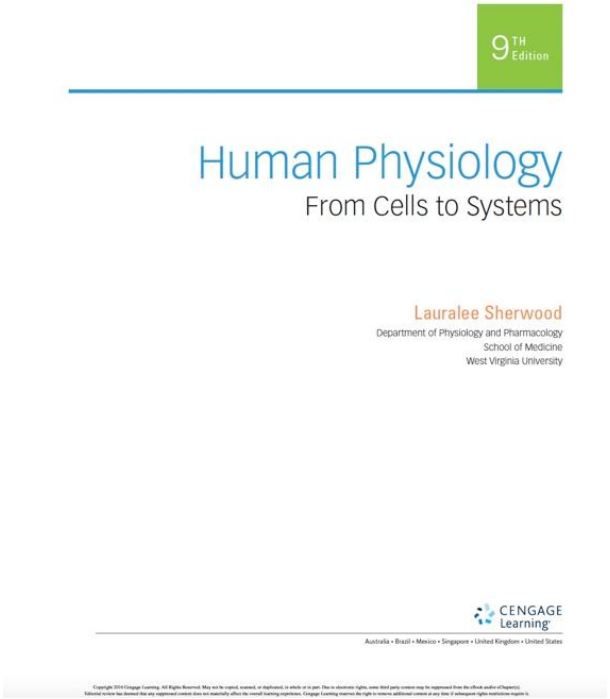
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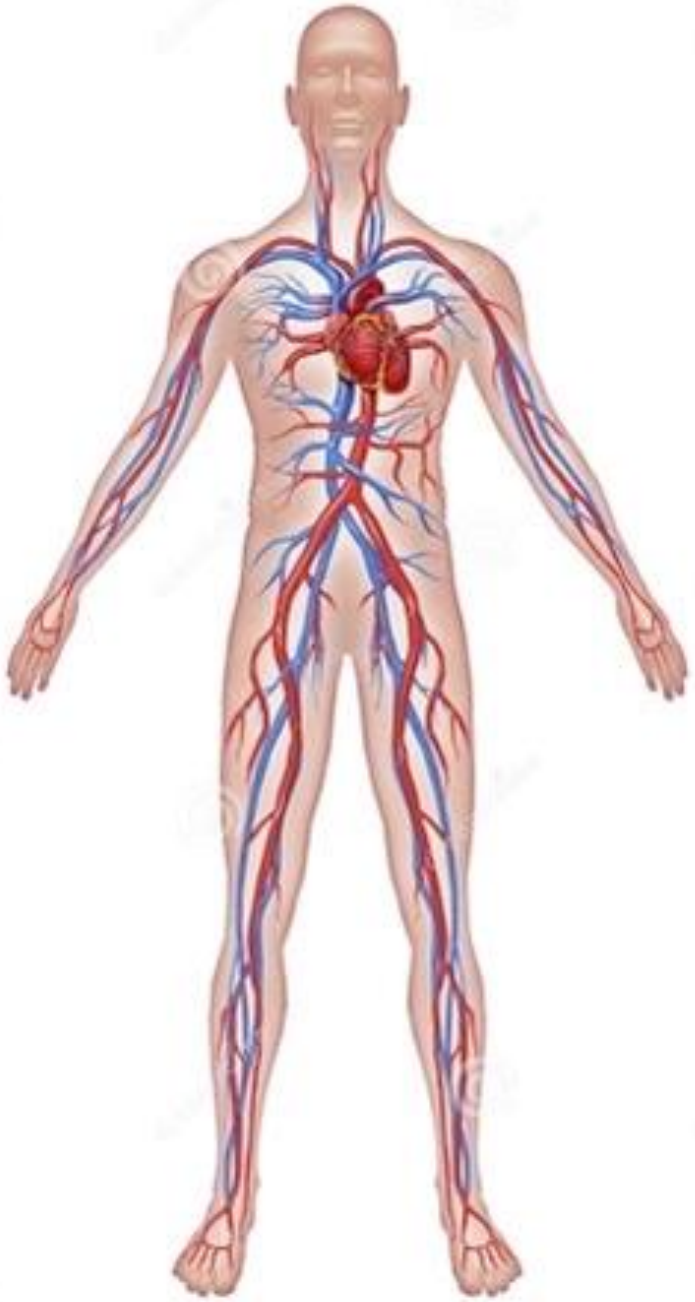
Overview of the cardiovascular system (CVS)

- The primary function of the CVS is to deliver blood to the tissues, which provides essential nutrients to the cells for metabolism and removes waste products from the cells.

- The CVS also is involved in several homeostatic functions, such as the regulation of body temperature, blood pressure, hormones, as well as making adjustments to altered physiological states such as exercise and hemorrhage.

- The vessel part of the CVS consists of arteries, veins and capillaries.
- For the blood to flow through the vessels it needs different pressure at different points.
- This pressure is made by the pumping movement of the heart, which makes a pressure gradient.
- The highest pressure is the nearest to the heart and the lowest pressure is the furthest away from the heart, that maintains the one-way direction of the blood flow, it will go from area of high pressure to an area with lower pressure.
- We have two circulations, the systemic and the pulmonary.
- The systemic delivers oxygenated blood to the tissues, while the pulmonary delivers deoxygenated blood to the lungs to be oxygenated ..

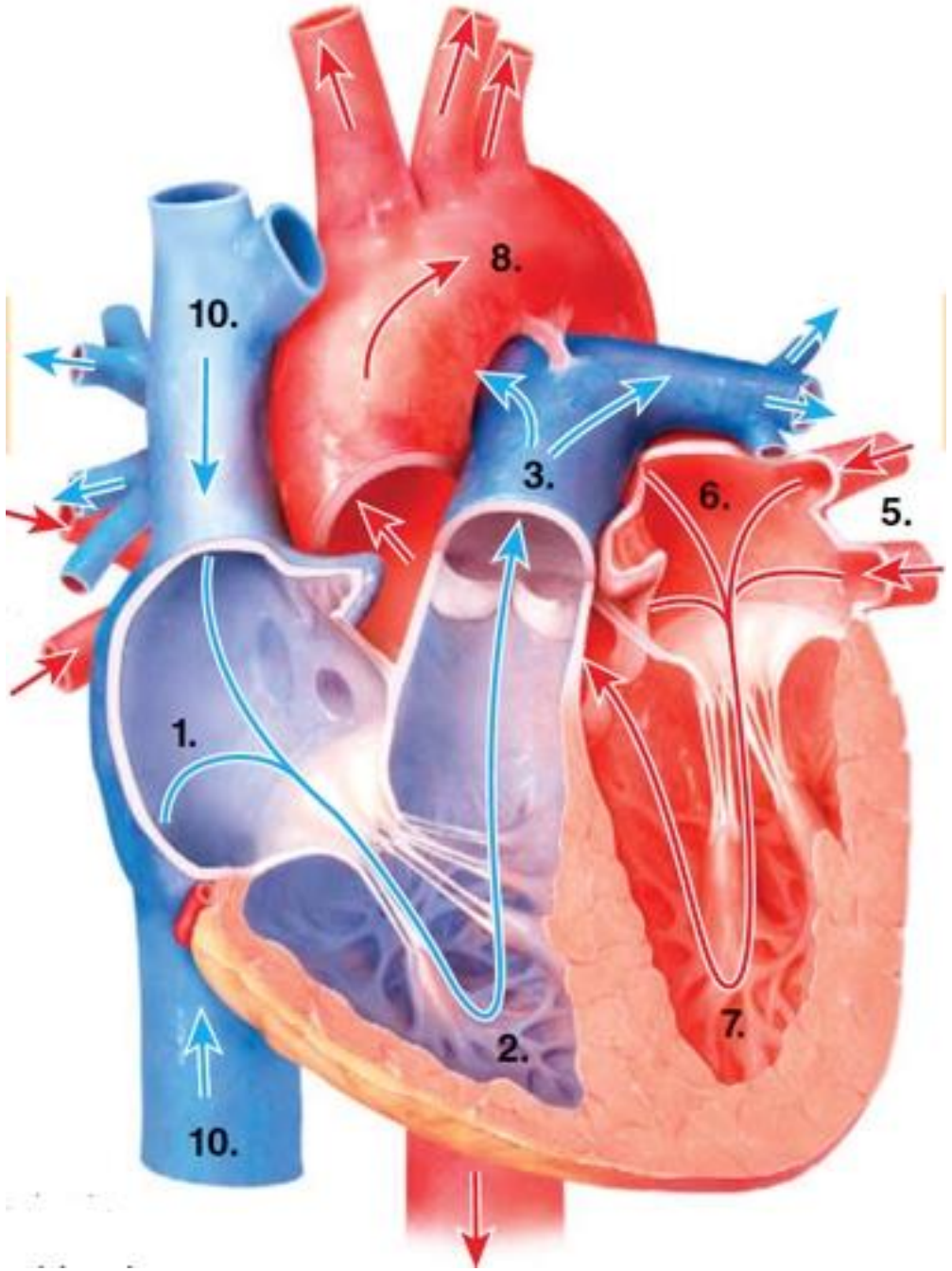


- When some organs require more blood flow, their demand will be met by dilation of arteries and an increase in the cardiac output , which results in more blood flow .
- This extra blood is stored in the venous system, because veins have the characteristic of capacitance in which they act as a reservoir for blood until needed, in addition to other mechanisms we will discuss later in the vascular system

Parts of the CVS

- The heart serves as the pump, which, by contracting, generates the pressure to drive blood through a series of blood vessels.
- The vessels that carry blood from the heart to the tissues are the arteries, which are under high pressure and contain a relatively small percentage of the blood volume.
- The veins, which carry blood from the tissues back to the heart, are under low pressure and contain the largest percentage of the blood volume.
- Within the tissues, thin-walled blood vessels, called capillaries, helps in the exchange of substances.

- The pumping force is generated by the heart which has two sides : left and right.
- Each side has an atrium and a ventricle separated by a valve, on the right we have the tricuspid valve and on the left we have the bicuspid or mitral valve.
- We also have two other valves : the aortic (on the opening of the aorta) and the pulmonary (on the opening of the pulmonary artery), which eventually adds up to 4 valves in the heart.
- The blood will always flow from the atrium to the ventricle.
- The main pumping function is performed by the ventricles.
- Notice that the left ventricle muscle is thicker than the right ventricle muscle, which means that the left side works harder to pump blood, because it works at a higher pressure higher resistance circulation (the systemic circulation) , whereas the right side works at low-pressure low resistance circulation (pulmonary circulation) .
- But the cardiac output (the amount of blood) that is pumped from both ventricles is the same.



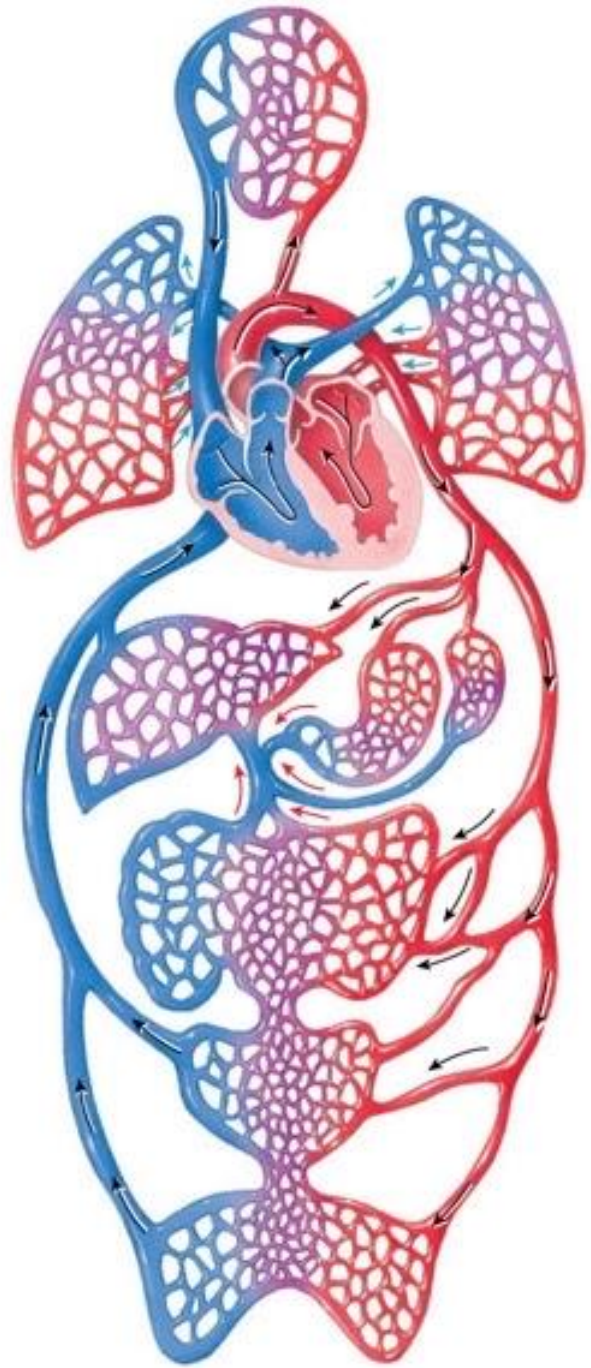
Valves

- 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.

- Although anatomically the heart is a single organ, the right and left sides of the heart function as two separate pumps.

- The heart is divided into right and left halves and has four chambers, an upper and a lower chamber within each half.

- The upper chambers, the atria, receive blood returning to the heart and transfer it to the lower chambers, the ventricles.



Sytemic vs pulmonary circulation

- Blood travels continuously through the circulatory system to and from the heart through two separate vascular loops, both originating and terminating at the heart.

- The pulmonary circulation consists of a closed loop of vessels carrying blood between the heart and the lungs.

- The systemic circulation is a circuit of vessels carrying blood between the heart and all body systems (except for the air sacs of the lungs, which are supplied by the pulmonary circulation).

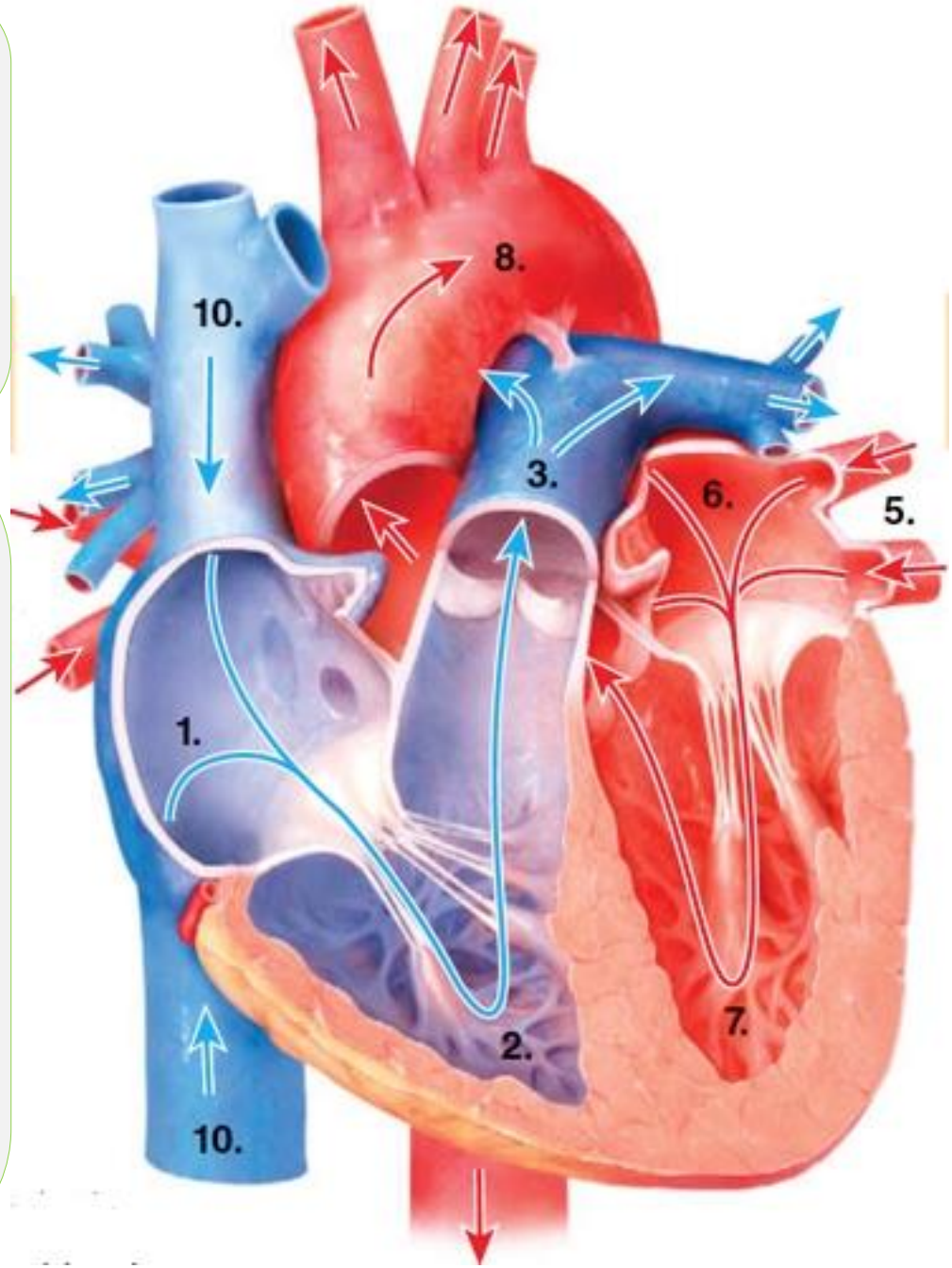
Systemic vs pulmonary circulation

- Both sides of the heart simultaneously pump equal amounts of blood.
- The pulmonary circulation is a low-pressure, low resistance system, whereas the systemic circulation is a high pressure, high-resistance system.
- Even though the right and left sides of the heart pump the same amount of blood, the left side works harder because it pumps an equal volume of blood at a higher pressure into a higher resistance and longer system.
- Accordingly, the heart muscle on the left side is thicker than the muscle on the right side, making the left side a stronger pump.

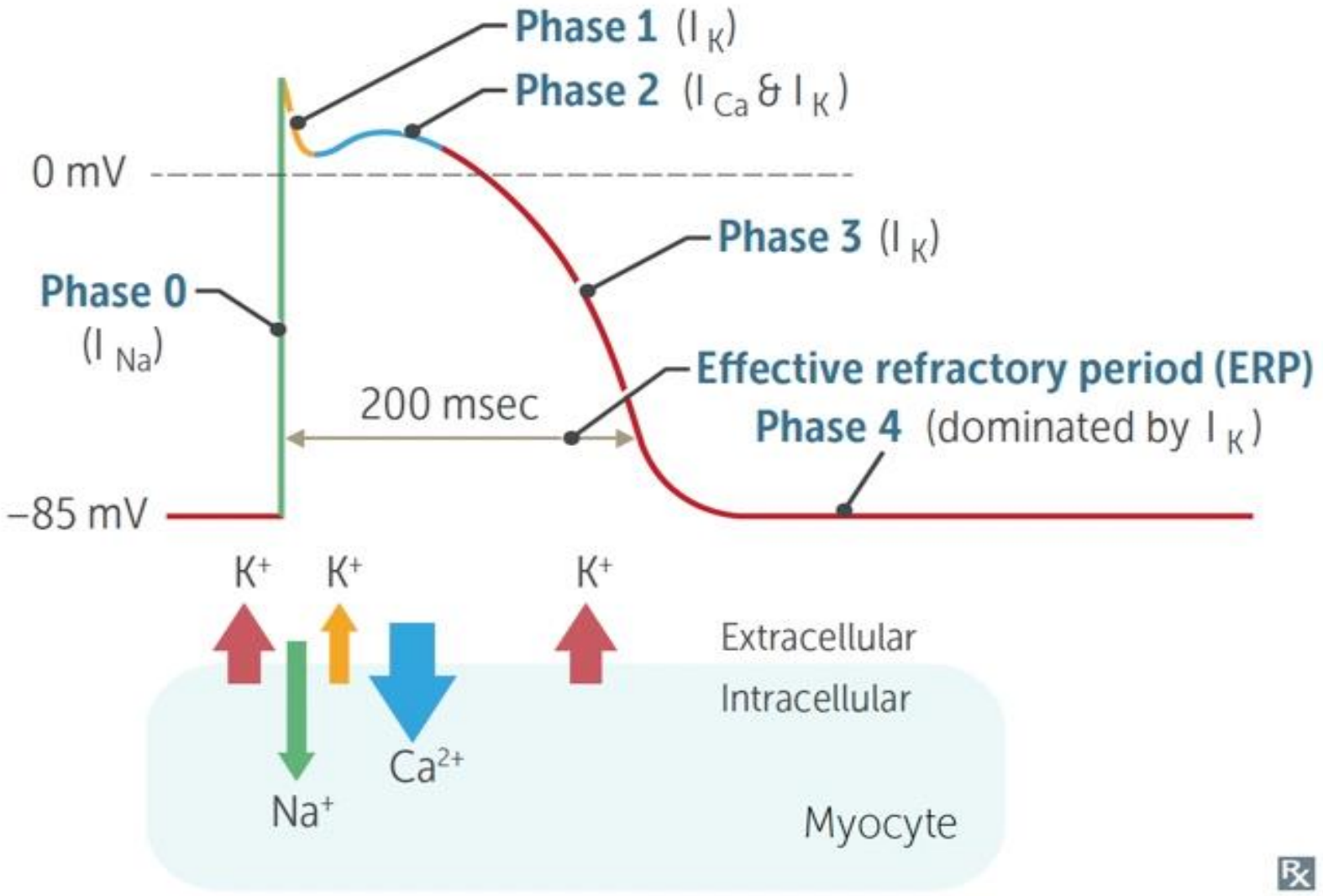
Cardiac muscle action potential

- While skeletal muscles need nervous stimulation to contract, cardiac muscles contract on their own.
- Cardiac muscles consist of three types of muscles : atrial, ventricular, and conductive system.
- Conductive muscles have no contractile function, but their role is to generate action potential.

- As we remember, tissues have a membrane potential made by the difference in concentrations of ions mainly calcium Ca+2 and sodium Na+ (extracellular) and potassium K+ (intracellular).
- The flow of ions inside and outside the cell membrane will cause a change in the membrane potential.
- The flow of sodium Na+ inside will strongly increase the membrane potential while calcium Ca+2 flow inside will make a slow increase in membrane potential and make it more positive (depolarization).
- On the other hand, potassium K+ flow outside the cell will strongly decrease the membrane potential and will make it more negative (repolarization).



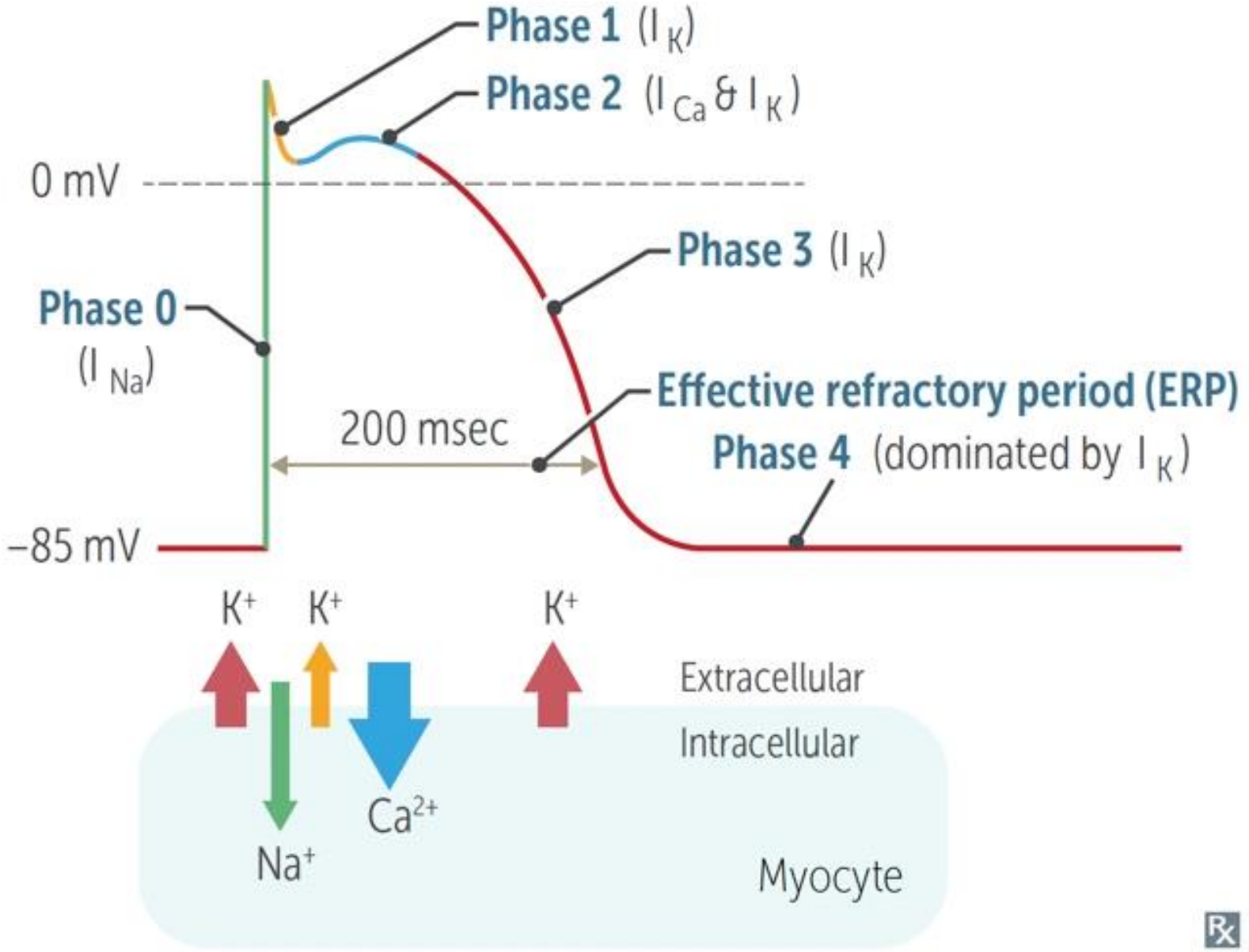
- Na+ channels open fast and close fast , making a **steep** line in the graph like in phase 0.
- Ca+2 channels are slow and make a weak depolarization resulting in a **plateau**, shown in phase 2, and causing the repolarization in phase 3 to be gentle as well.
- K+ channels cause repolarization as shown in phase 1 and phase 3.



- Let's start with the atrial and ventricular action potential
- We will discuss this graph in details now

Before starting the story , keep in mind that :

- Sodium ions cause depolarization
- Calcium ions cause depolarization
- Potassium ions cause repolarization



We start with the RESTING membrane potential, which is about -80/-90 in the ventricles , then we have a RAPID depolarization (phase 0) , fast, upward and steep depolarization => So it is Sodium channels !

- **In phase 0** , Fast Na channels are opened , until a certain level (+20 for example) , it will be inactivated.
- **Now phase 1** , we will have a BRIEF repolarization , which ion is responsible to cause it ? It is Potassium "anything down = potassium "

The potassium thinks he can cause repolarization easily as in skeletal muscles , but not this time potassium :) Another channel will open and causes a plateau, Who do you think is behind this slow repolarization? It's Calcium

- **Here in phase 2**, calcium channels are responsible for the plateau, specifically the L- type calcium channels (L for long lasting , طولت لفتحت وطولت لسكرت and give us long duration through plateau) , actually it knew that there is an action potential since phase 0, but it had started to work in phase 2 !

Don't forget that potassium has started to make repolarization (in phase 1) , but when calcium channels have opened , the permeability of potassium is decreased . As a normal result the calcium will try to make depolarization, and we already have potassium which makes repolarization, that's why we have a plateau (phase 2) ! , so phase 2's main ion is calcium with little potassium

- **Now phase 3** , we have a REAL repolarization phase , which is the responsibility of potassium, it will continue the repolarization until we reach the membrane potential (**phase 4)**
- Phase 4 = membrane potential

Phases of action potential in cardiac cells

All these slides are about what we have talked about in the previous slide , read it and make sure you understand everything :)

- Phase 0 (Depolarization):

- Fast Sodium Channels Open.
- When the cardiac cell is stimulated and depolarizes, the membrane potential becomes more positive.
- Voltage-gated sodium channels (fast sodium channels) open and permit sodium to rapidly flow into the cell and depolarize it.
- The membrane potential reaches about +20 millivolts before the sodium channels close.

Phases of action potential in cardiac cells

- Phase 1 (Initial Repolarization):

- Fast Sodium Channels Close.
- The sodium channels close, the cell begins to repolarize, and potassium ions leave the cell through open potassium channels.

Phases of action potential in cardiac cells

- Phase 2 (Plateau):

- Calcium Channels Open and Fast Potassium Channels Close.
- A brief initial repolarization occurs and the action potential then plateaus as a result of increased calcium ion permeability and decreased potassium ion permeability.
- The voltage-gated calcium ion channels open slowly during phases 1 and 0, and calcium enters the cell.
- Potassium channels then close, and the combination of decreased potassium ion efflux and increased calcium ion influx causes the action potential to plateau.

Plateau in cardiac action potential

- The major differences between the membrane properties of cardiac and skeletal muscle account for the prolonged action potential and the plateau in cardiac muscle.

- First, the action potential of skeletal muscle is caused almost entirely by the sudden opening of large numbers of fast sodium channels that allow tremendous numbers of sodium ions to enter the skeletal muscle fiber from the extracellular fluid.
- These channels are called fast channels because they remain open for only a few thousandths of a second and then abruptly close.

Plateau in cardiac action potential

- In cardiac muscle, the action potential is caused by opening of two types of channels:

- (1) the same voltage-activated fast sodium channels as those in skeletal muscle.
- (2) L-type calcium channels (slow calcium channels).
- These channels differ from the fast sodium channels in that they are slower to open and, even more importantly, remain open for several tenths of a second.

Plateau in cardiac action potential

- During this time, a large quantity of calcium ions flows through these channels to the interior of the cardiac muscle fiber, and this activity maintains a prolonged period of depolarization, causing the plateau in the action potential.

- Furthermore, the calcium ions that enter during this plateau phase activate the muscle contractile process, whereas the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum.

- The second major functional difference between cardiac muscle and skeletal muscle that helps account for both the prolonged action potential and its plateau is that immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions decreases about fivefold, an effect that does not occur in skeletal muscle.

- This decreased potassium permeability may result from the excess calcium influx through the calcium channels.

- Regardless of the cause, the decreased potassium permeability greatly decreases the efflux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level.

- When the slow calcium channels do close at the end of 0.2 to 0.3 second, and the influx of calcium ions ceases, the membrane permeability for potassium ions also increases rapidly.

- This rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.

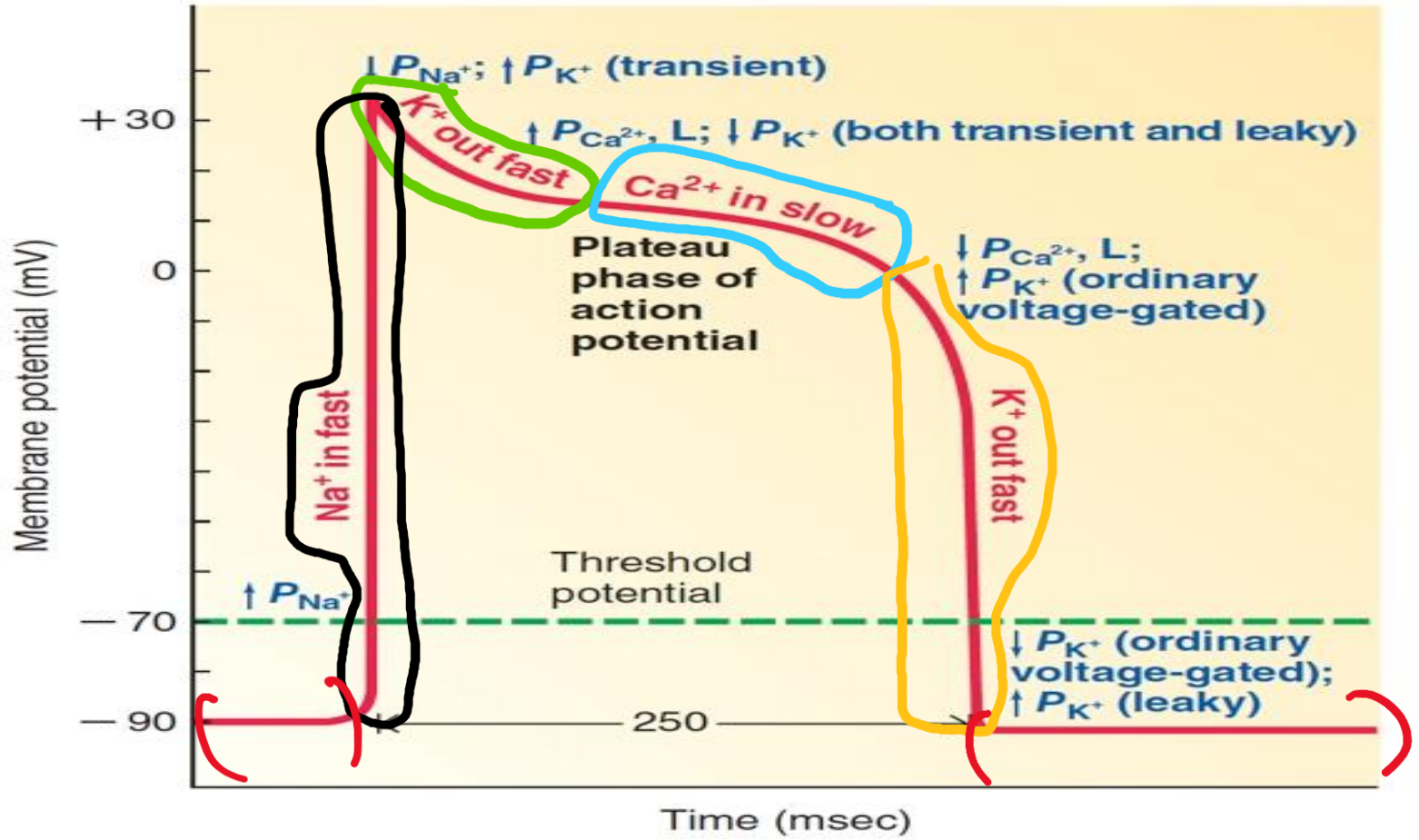
Phases of action potential in cardiac cells

- Phase 3 (Rapid Repolarization):

- Calcium Channels Close and Slow Potassium Channels Open.
- The closure of calcium ion channels and increased potassium ion permeability, permitting potassium ions to exit the cell rapidly, ends the plateau and returns the cell membrane potential to its resting level.

- Phase 4 (Resting Membrane Potential):
- This averages about−80 to −90 millivolts.

Again it is a picture of the action potential in a ventricle .
So what do we have in black ? It is phase 0 , depolarization, sodium channels
What about the phase in green ? It is phase 1, brief repolarization, potassium channels
What about the phase in blue ? It is phase 2 , plateau, L type – calcium channels and little potassium channels
What about the phase in yellow ? It is phase 3 , repolarization, potassium channels
What about the phase in red ? It is the resting membrane potential



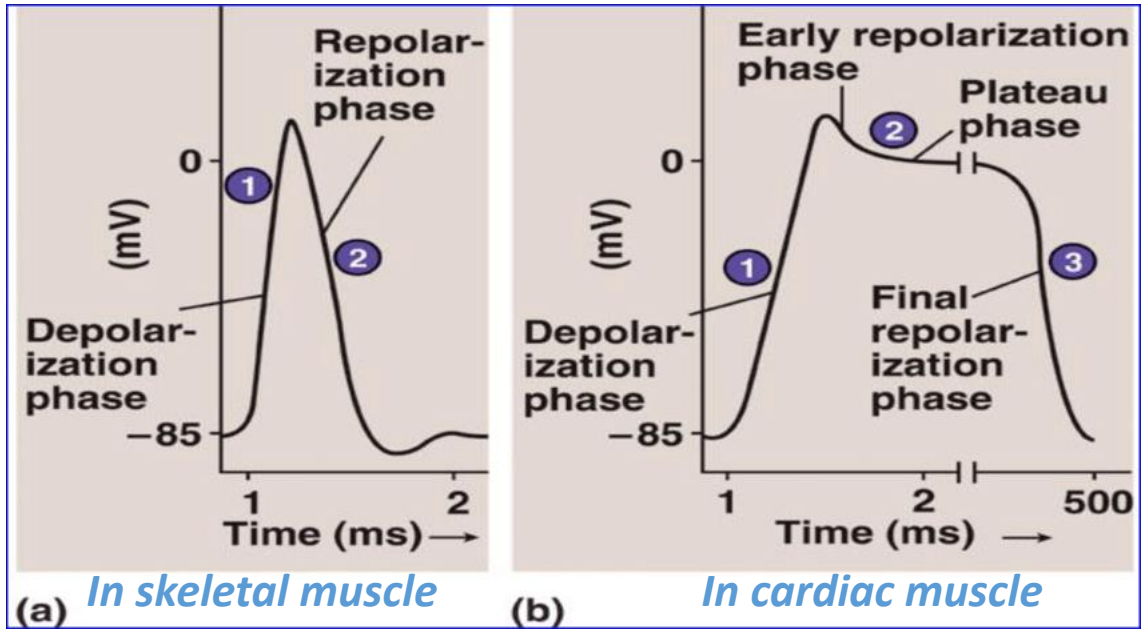
The difference between action potential in skeletal muscles and cardiac (ventricular) muscle is the PLATEAU

so what is the purpose or the function of the plateau ?

⇒ To prolong the action potential , so by default the refractory period will be prolonged!

⇒ The prolongation of refractory period is important to prevent tetanization (so there is no overlap in muscle contraction) , we will wait until the refractory period ends to start another contraction in the ventricle

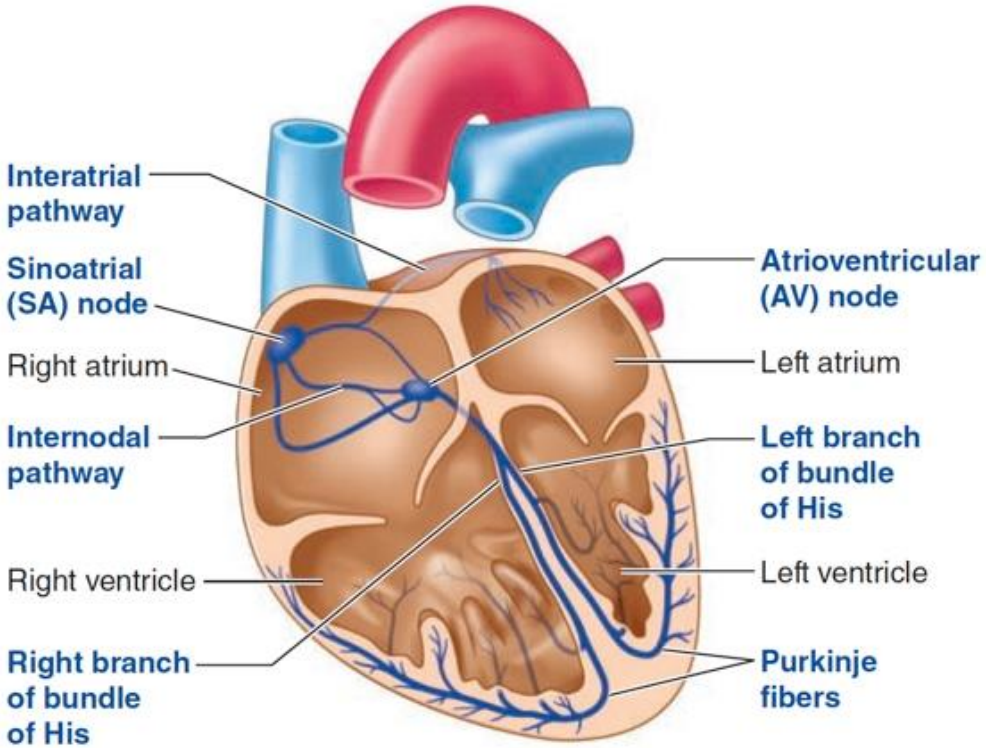
Extra picture



Heart autorhythmicity

- The human heart has a special system for rhythmic self-excitation and repetitive contraction approximately 100,000 times each day or 3 billion times in the average human lifetime , it is too much for the heart to wait for orders from CNS or motor neurons to contract each time ! So we have self excitation characteristic . This is the function of the pacemakers in the heart or the conduction system => our primary one is the Sinoatrial node
- They are a network of specialized cardiac muscle fibers called autorhythmic fibers, that repeatedly generate action potentials that trigger heart contractions.

- Our main pacemaker is the SA node , then we have the AV node and other parts that are connected to the ventricular and atrial muscle fibers
- Their main function isn't to contract , however, it is to generate action potential and provide autorhythmicity , so the heart by itself can produce action potential
- (strong independent heart 😎 💪🏻)

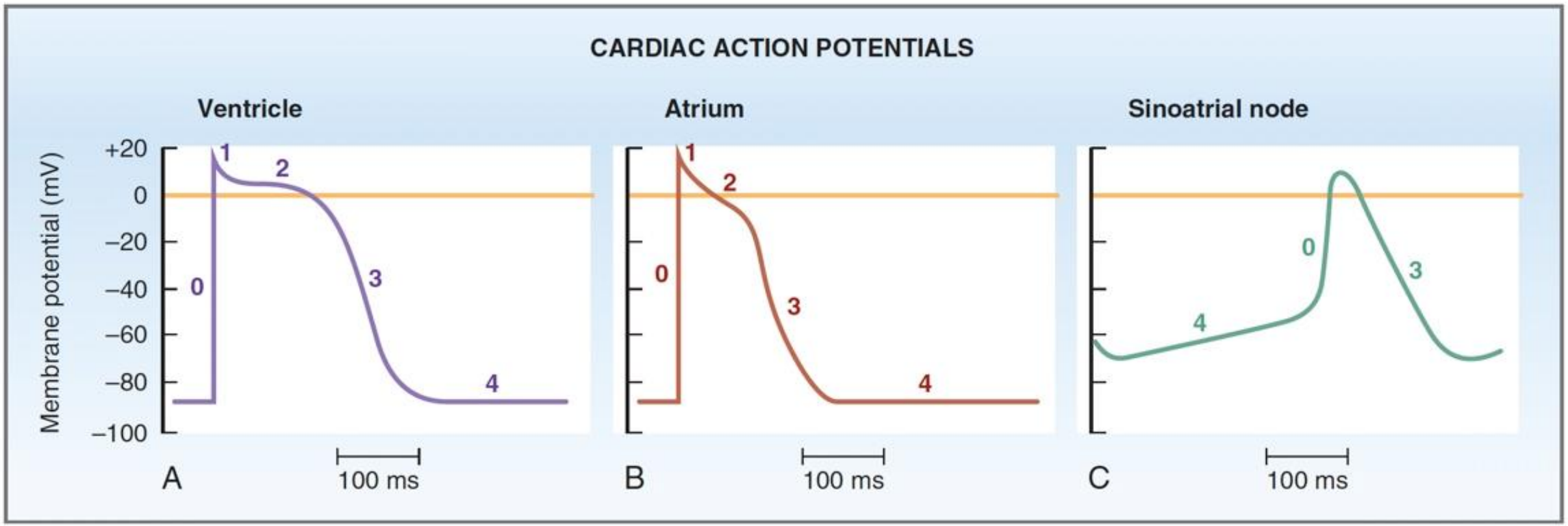


(a) Specialized conduction system of the heart

SA node

- The fibers of this node have almost no contractile muscle filaments and are each only 3 to 5 micrometers (μm) in diameter, in contrast to a diameter of 10 to 15 μm for the surrounding atrial muscle fibers.

- However, the sinus nodal fibers connect directly with the atrial muscle fibers, so that any action potential that begins in the sinus node spreads immediately into the atrial muscle wall.



More explanation =>

- What kind of differences do you see between the SA node and ventricular action potential?

- There is no plateau in the SA node , remember why do we need the plateau? To prevent tetanization in the contraction but we don't have contractile fibers in the SA nodes , so no need to the plateau, and there is no phase 1 , 2 . We have phases 4,0, 3 only .
- There is no steep depolarization, it seems like the fast sodium channels aren't working here!
- Now in phase 4 , The resting membrane potential is also different, in the ventricle it's about -85/-90 and the same in the atrium , but in the SA nodes it's about -55/-65 => less negative (higher membrane potential) so it's easier to reach threshold .
- The resting membrane potential in the ventricle is a straight line , but in the SA nodes it's not rested (not straight) , it's kind of inclined towards depolarization phase , SO there's NO resting membrane potential in the pacemaker cells , instead of calling phase4 resting membrane potential we call it Pacemaker potential :) as simple as this .
- So it is always in partial depolarization phase , but why? As we mentioned, there is no fast sodium channels , we have special type of ion channels that only exist in pacemaker cells => funny sodium channels (IF sodium channels) 😁 ,they are called funny because they open in the repolarization phase while usually voltage gated channels are opened in the depolarization phase .
- There is also no L type calcium channels in phase 4, we have T type calcium channels (T for transient) , it will open for a short period then it will close .
- The third factor for the partial depolarization or a drift towards the action potential (drift in the depolarization phase) is that the pacemaker cells are less leaky to potassium , other cells are more leaky to potassium which will maintain their resting membrane potential .
- In phase 0 , When it reaches the threshold , L type calcium channels are the leaders , the responsible for depolarization in pacemaker cells, so it's a slow depolarization because the leaders are calcium channels :)
- **Phase 3 i**s repolarization, potassium channels will open .

To organize your ideas , check this table 🌟
A summary for the channels in SA nodes and ventricles

“Extra table”

Phase	SA node channels	Ventricular channels
Phase 4 (Resting/Prepotential)	Funny sodium channels (If) gradually open, causing a slow depolarization. T-type calcium channels open briefly near the end of Phase 4 to bring the membrane potential closer to threshold.	No active channels; membrane potential is stable.
Phase 0 (Depolarization)	L-type calcium channels open, allowing calcium influx for a slow depolarization.	Fast sodium channels open, causing a rapid influx of sodium and a fast depolarization
Phase 1 (Initial Repolarization)	Not present in SA node cells.	Potassium channels open briefly, causing an initial repolarization
Phase 2 (Plateau)	Not present in SA node cells.	L-type calcium channels open, balancing potassium efflux and creating a plateau phase.
Phase 3 (Repolarization)	Potassium channels open, allowing potassium efflux and repolarizing the cell.	Potassium channels (mainly delayed rectifier potassium channels) open, allowing potassium to exit and repolarize the cell.

Mechanism of sinus nodal rhythmicity

- the resting membrane potential of the sinus nodal fiber between discharges is about –55 to –60 millivolts, in comparison with –85 to –90 millivolts for the ventricular muscle fiber.
- The cause of this lower negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium and calcium ions, and positive charges of the entering sodium and calcium ions neutralize some of the intracellular negativity.

Pacemaker potential

- In contrast to nerve and skeletal muscle cells, in which the membrane remains at constant resting potential unless the cell is stimulated, the cardiac autorhythmic cells do not have a resting potential.
- Instead, they display pacemaker activity—that is, their membrane potential slowly depolarizes, or drifts, between action potentials until threshold is reached, at which time the membrane fires or has an action potential.
- An autorhythmic cell membrane’s slow drift to threshold is called the pacemaker potential.
- Through repeated cycles of drift and fire, these autorhythmic cells cyclically initiate action potentials, which then spread throughout the heart to trigger rhythmic beating without any nervous stimulation.

- cardiac muscle has three main types of membrane ion channels that play important roles in causing the voltage changes of the action potential.

- They are (1) fast sodium channels, (2) calcium channels (particularly L-type or “slow” calcium channels), and (3) potassium channels.

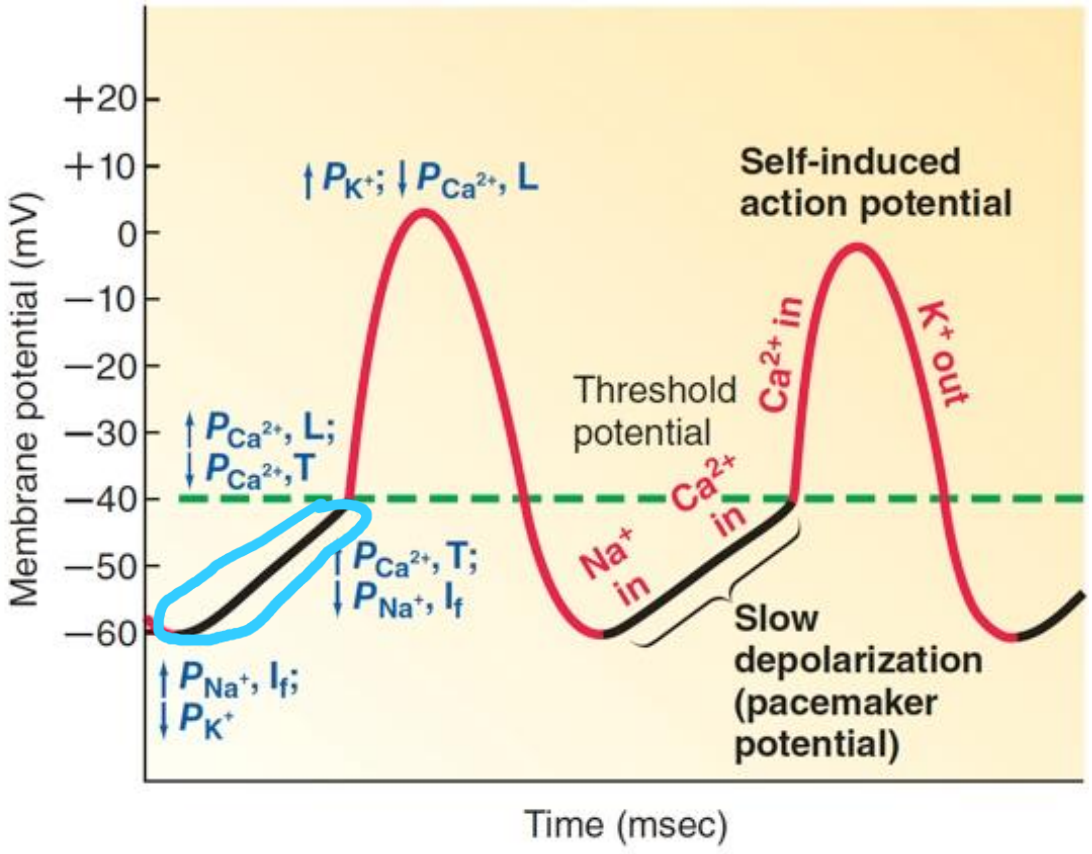
Pacemaker potential

- However, there is a difference in the function of these channels in the sinus nodal fiber because the resting potential is much less negative—only –55 millivolts in the nodal fiber instead of the –90 millivolts in the ventricular muscle fiber.

- At this level of –55 millivolts, the fast sodium channels mainly have already become inactivated, or blocked.
- This is because 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 calcium channels can open (i.e., can become activated) and thereby cause the action potential.

- What do we call this change in the membrane potential (in blue) ? Pacemaker potential , partial depolarization (drifting towards depolarization), funny sodium channels and T type calcium channels and less leakage of potassium
- Now we reached the threshold , who will open? L type calcium channels
- In the repolarization , who will open ? Potassium channels (will try to drive the cell down until reaching the equilibrium level) but the funny sodium channels and T type calcium channels will prevent this



So the three factors of the partial depolarization or pacemaker potential are:

1) Funny sodium channels
2) T type calcium channels
3) Low leakage for potassium

- We need to know the type of calcium channels because in pharmacological treatment when we know that a specific drug is a calcium channel blocker ,we should know if it will work on L or T types

Pacemaker action potential

- Why is this new state of hyperpolarization not maintained forever?

- The reason is that during the next few tenths of a second after the action potential is over, progressively more and more potassium channels close.
- The inward-leaking sodium (“funny” current) and calcium ions once again overbalance the outward flux of potassium ions, which causes the resting potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about –40 millivolts.
- Then, the entire process begins again: self-excitation to cause the action potential, recovery from the action potential, hyperpolarization after the action potential is over, drift of the resting potential to threshold, and finally re-excitation to elicit another cycle. This process continues throughout a person’s life.

Action potential in pacemaker cells

- Once threshold is reached, the rising phase of the action potential occurs in response to activation of a long-lasting, voltage-gated Ca channel (L-type Ca channel) and a subsequently large influx of Ca.
- The Ca-induced rising phase of a cardiac pacemaker cell differs from that in nerve and skeletal muscle cells, where Na influx rather than Ca influx swings the potential in the positive direction.
- The falling phase is the result, as usual, of the K efflux that occurs when K permeability increases on activation of voltage-gated K channels, coupled with closure of the L-type Ca channels.
- After the action potential is over, slow closure of these K channels contributes to the next slow depolarization to threshold.

Funny Na channels

- The initial phase of the slow depolarization to threshold is caused by net Na entry through a type of voltage-gated channel found only in cardiac pacemaker cells.
- Typically, voltage gated channels open when the membrane becomes less negative (depolarizes), but these unique channels open when the potential becomes more negative (hyperpolarizes) at the end of repolarization from the previous action potential.
- Because of their unusual behavior, they are called funny, or If, channels.
- When one action potential ends and the If channels open, the resultant depolarizing net inward Na current through these open channels starts immediately moving the pacemaker cell’s membrane potential toward threshold once again.

Self excitation

- Because of the high sodium ion concentration in the extracellular fluid outside the nodal fiber, as well as a moderate number of already open sodium channels, positive sodium ions from outside the fibers normally tend to leak to the inside through inward, “funny” currents.
- Therefore, between heartbeats, the influx of positively charged sodium ions causes a slow rise in the resting membrane potential in the positive direction.
- Thus the resting potential gradually rises and becomes less negative between each two heartbeats.
- When the potential reaches a threshold voltage of about –40 millivolts, the L-type calcium channels become activated, thus causing the action potential.
- Therefore, basically, the inherent leakiness of the sinus nodal fibers to sodium and calcium ions causes their self-excitation.

K channels

- The second mechanism contributing to this pacemaker potential is a progressive reduction in the passive outward flux of K.
- In cardiac autorhythmic cells, permeability to K does not remain constant between action potentials as it does in nerve and skeletal muscle cells.
- The K channels that opened during the falling phase of the preceding action potential slowly close at negative potentials.
- This slow closure gradually diminishes the outflow of K down its concentration gradient.
- The resultant slow decline in the rate of K efflux occurring simultaneous with the slow inward leak of Na through the open If channels further contributes to the early drift toward threshold.

Ca channels

- The third ionic contribution to pacemaker potential is increased Ca entry.
- In the second half of the pacemaker potential, the If channels close and transient Ca channels (T-type Ca channels), one of two types of voltage-gated Ca channels, open before the membrane reaches threshold.
- The resultant brief influx of Ca further depolarizes the membrane, bringing it to threshold, at which time the transient Ca channels close.

Test your self

1) In which phase of the ventricular muscle action potential is the potassium permeability the highest?

A) 0

B) 1

C) 2

D) 3

E) 4

D) During phase 3 of the ventricular muscle action potential, the potassium permeability of ventricular muscle greatly increases, which causes a more negative membrane potential.

2) In which phase of the ventricular muscle action potential is the sodium permeability the highest?

A) 0

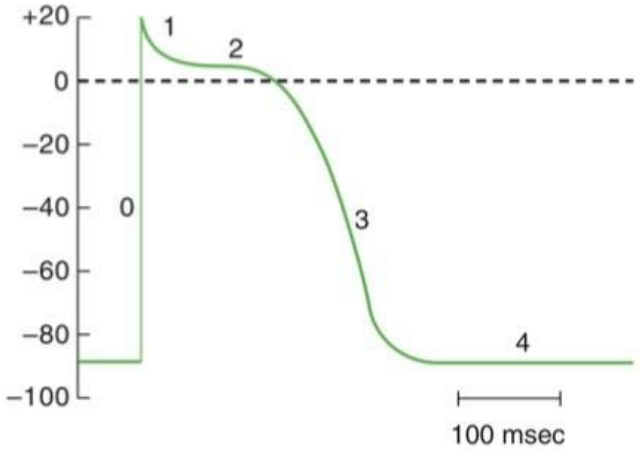
B) 1

C) 2

D) 3

E) 4

A) The normal resting membrane potential of the S-A node is −55 millivolts. As the sodium leaks into the membrane, an upward drift of the membrane potential occurs until it reaches −40 millivolts. This is the threshold level that initiates the action potential at the S-A node.



3) **During which phase of the ventricular action potential is the membrane potential closest to the K+ equilibrium potential?**

A. Phase 0
B. Phase 1
C. Phase 2
D. Phase 3
E. Phase 4

Answer : **E**

4) **During which phase of the ventricular action potential is the conductance to Ca2+ highest?**

A. Phase 0
B. Phase 1
C. Phase 2
D. Phase 3
E. Phase 4

Answer : **C**

Additional sources

1. Pacemaker’s action potential
2. Cardiac Action potential animation

النُّور في قلبي وبينَ جوانحي فَعَلامَ أخشى السَّيرَ في الظلماءِ

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!