Cardiovascular Physiology

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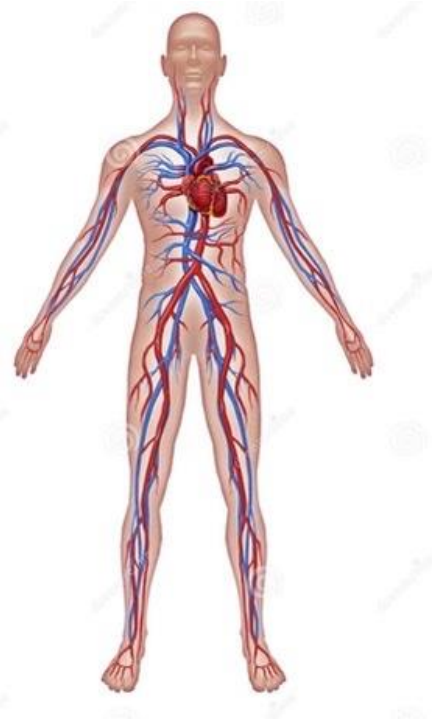

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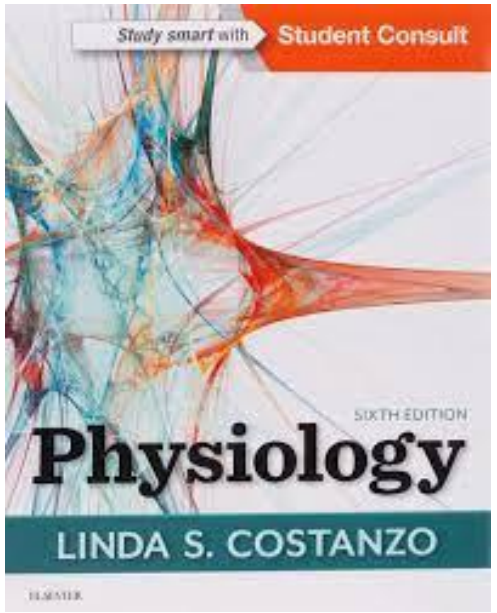
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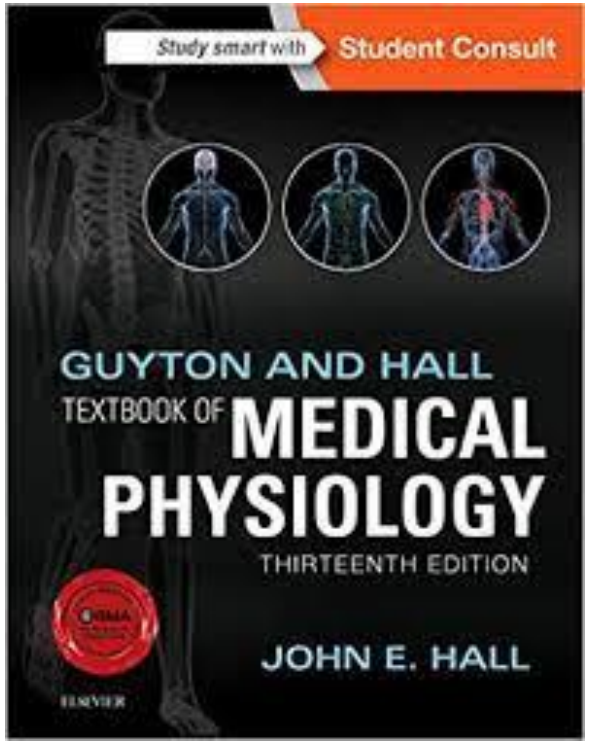
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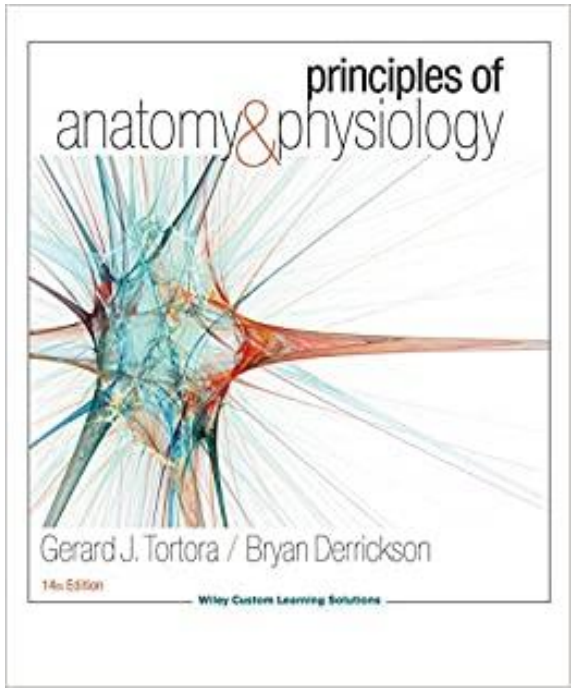
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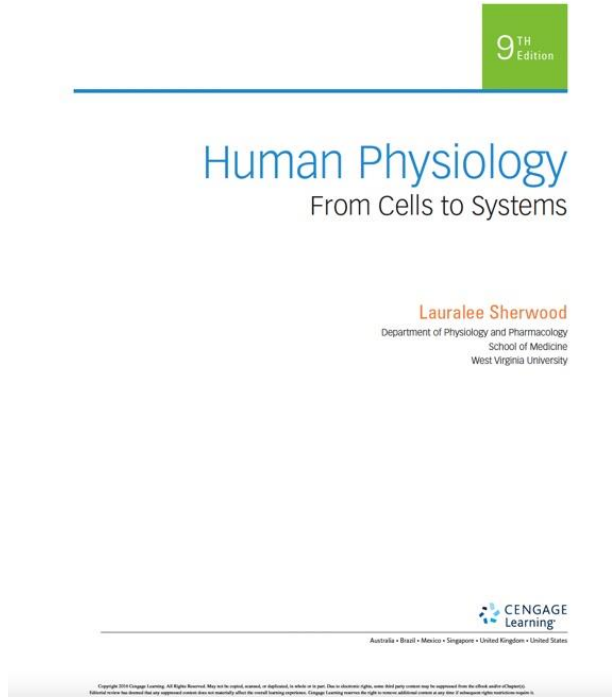
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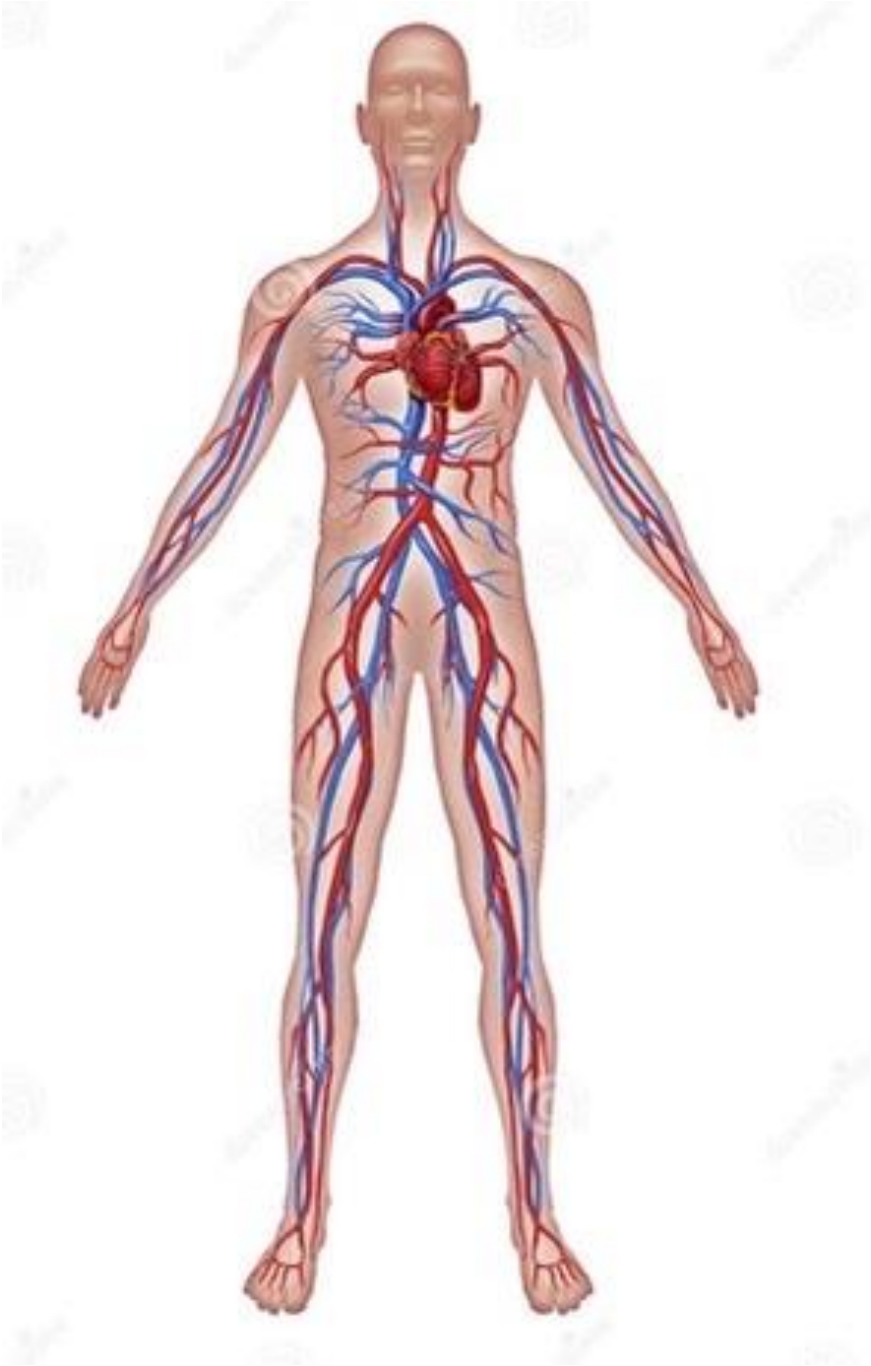
Overview of the cardiovascular system (CVS)

- 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.



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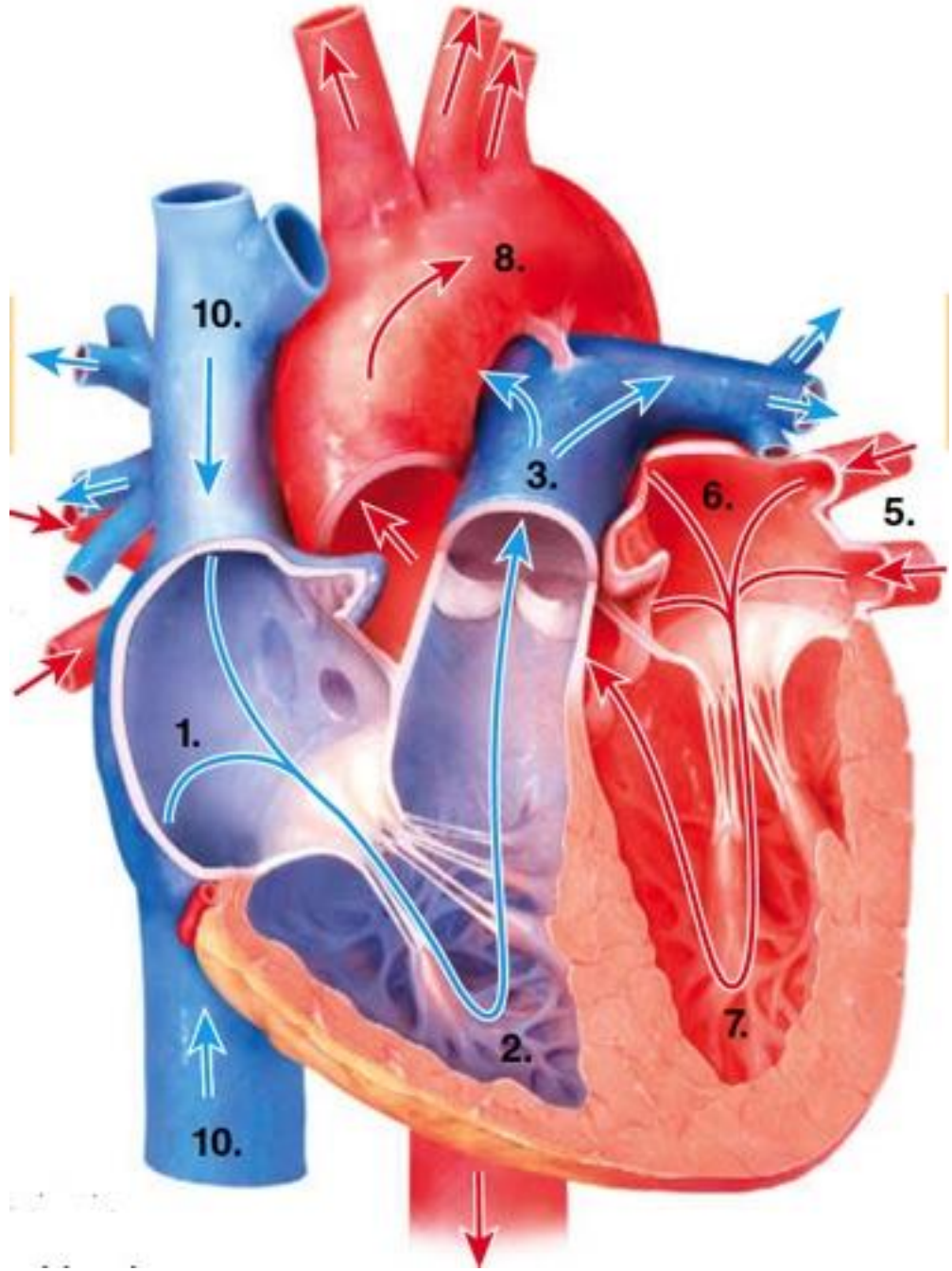
Parts of the CVS

- 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.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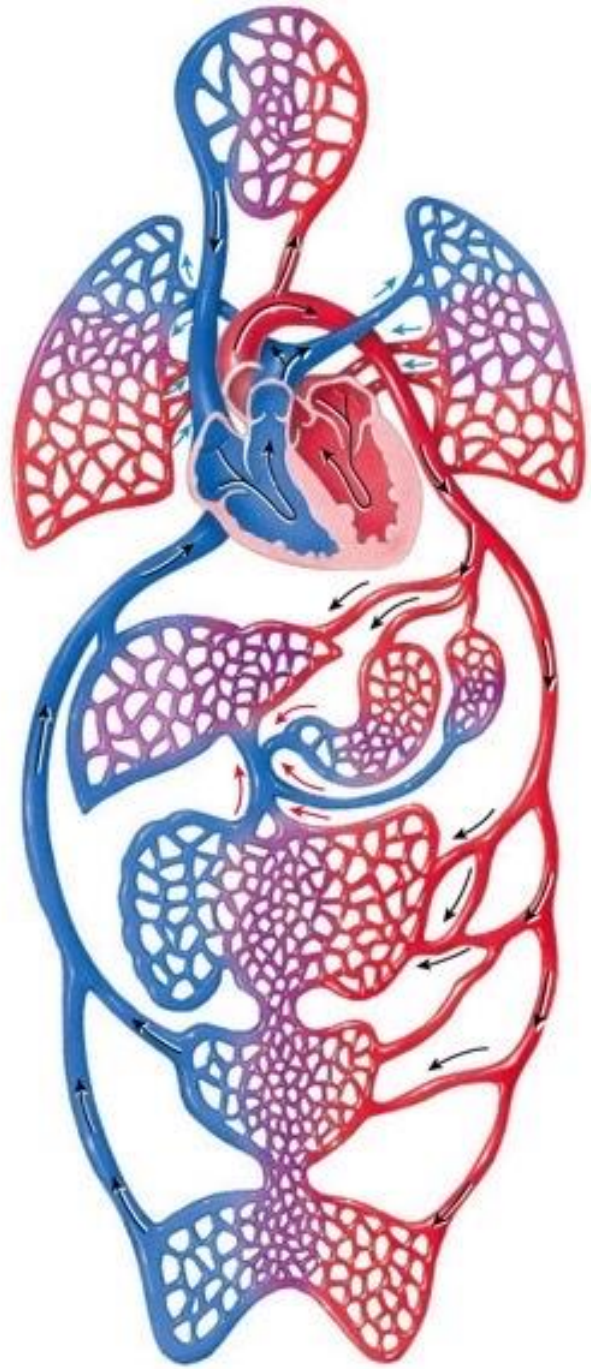
Valves

- 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

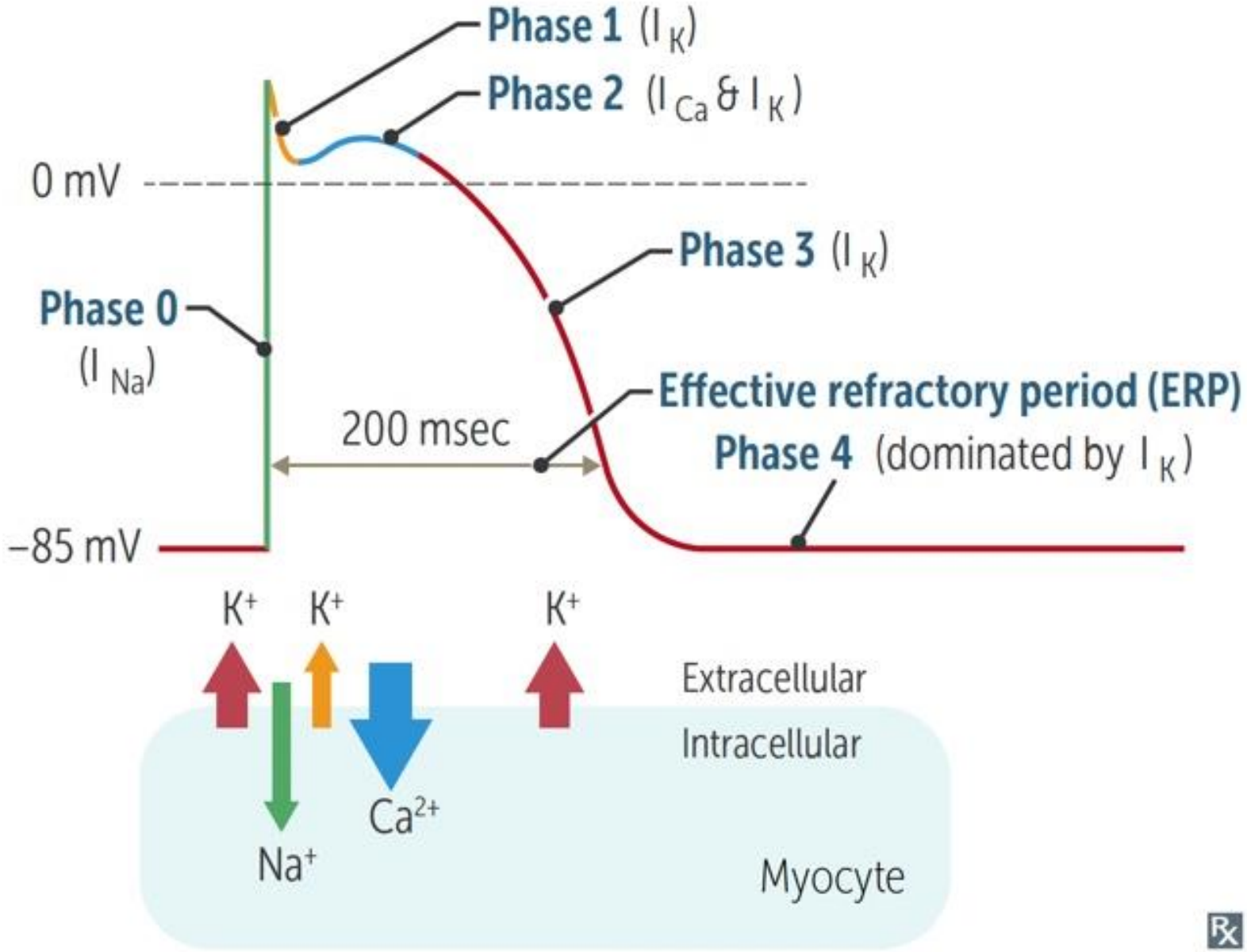
- Both sides of the heart simultaneously pump equal amounts of blood.
- The pulmonary circulation is a low-pressure, low resistance system, whereas the systemic circulation is a high pressure, high-resistance system.
- Even though the right and left sides of the heart pump the same amount of blood, the 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

Phases of action potential in cardiac cells

- 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.


Phase 1 (I_K)
Phase 2 (I_{Ca} & I_K)
0 mV
Phase 3 (I_K)
Phase 0
(I_{Na})
Effective refractory period (ERP)
200 msec
Phase 4 (dominated by I_K)
−85 mV
K^+
K^+
K^+
Extracellular
Intracellular
Ca^{2+}
Na^+
Myocyte

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.

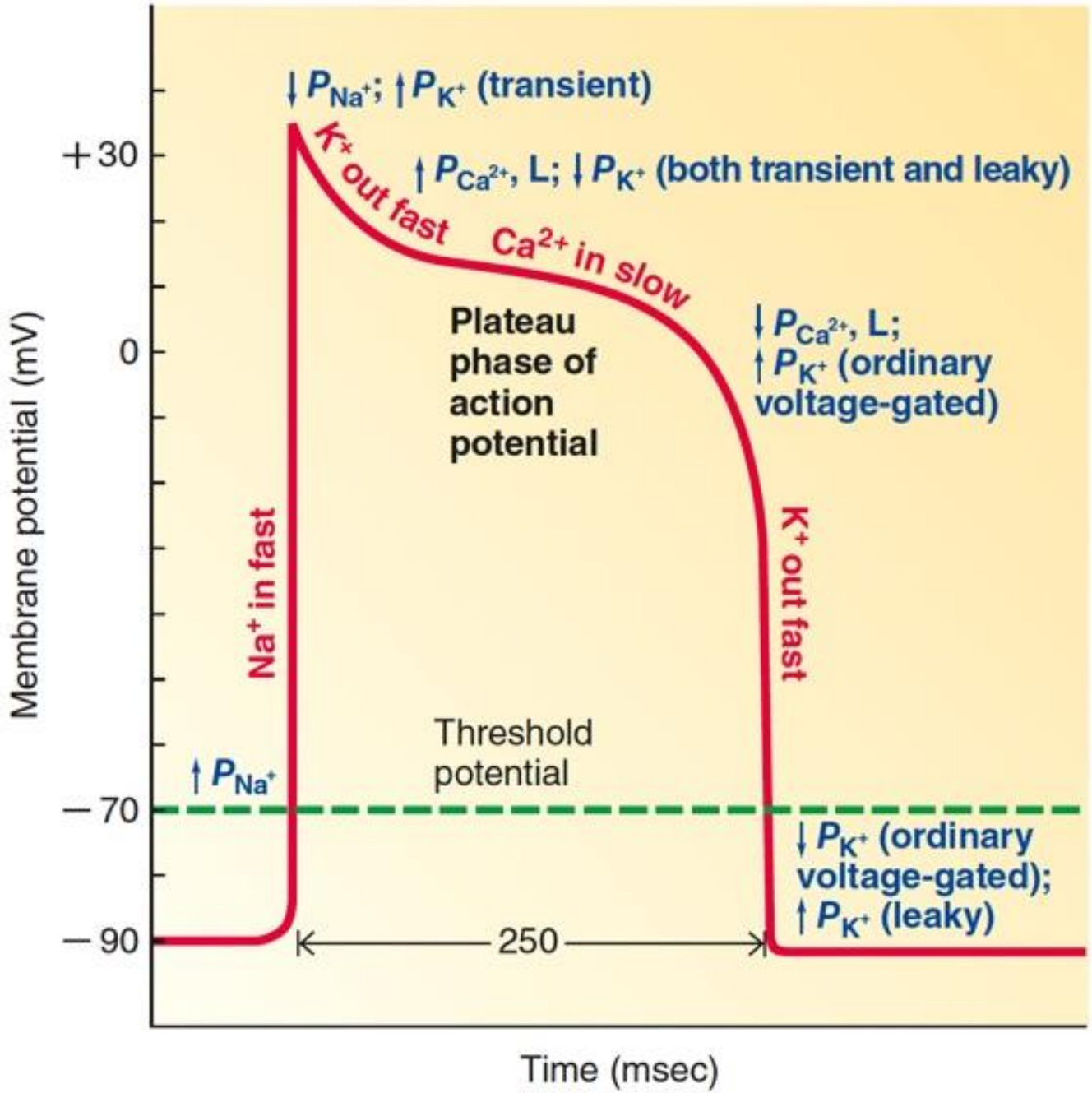
- This rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.

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.

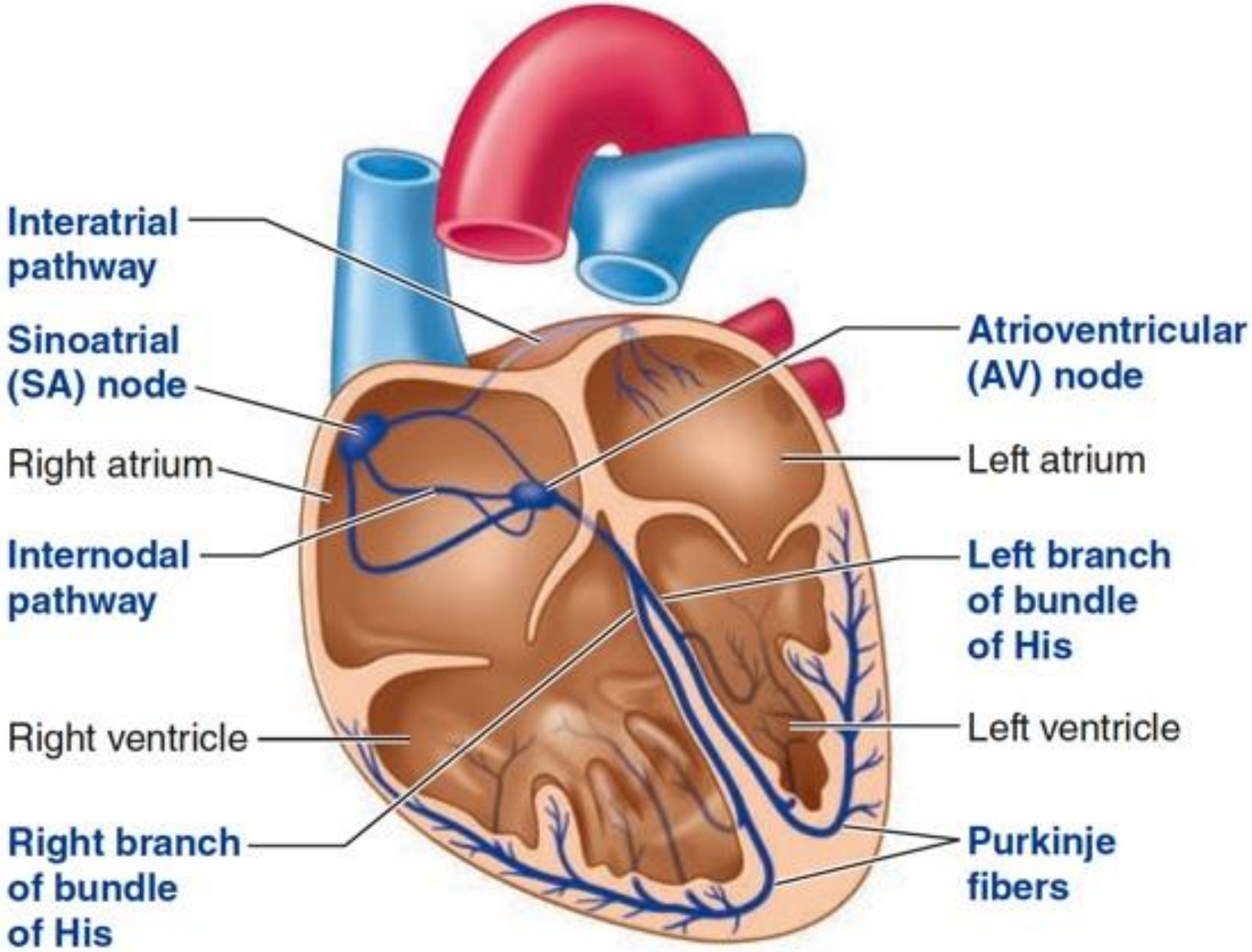
- Phase 4 (Resting Membrane Potential):
- This averages about−80 to −90 millivolts.


↓ P_{Na^+}; ↑ P_{K^+} (transient)
↑ $P_{Ca^{2+}}$, L; ↓ P_{K^+} (both transient and leaky)
K^+ out fast
Ca^{2+} in slow
Plateau phase of action potential
↓ $P_{Ca^{2+}}$, L; ↑ P_{K^+} (ordinary voltage-gated)
Na^+ in fast
K^+ out fast
↑ P_{Na^+}
Threshold potential
↓ P_{K^+} (ordinary voltage-gated); ↑ P_{K^+} (leaky)
250
+30
0
−70
−90
Membrane potential (mV)
Time (msec)

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.

- They are a network of specialized cardiac muscle fibers called autorhythmic fibers, that repeatedly generate action potentials that trigger heart contractions.

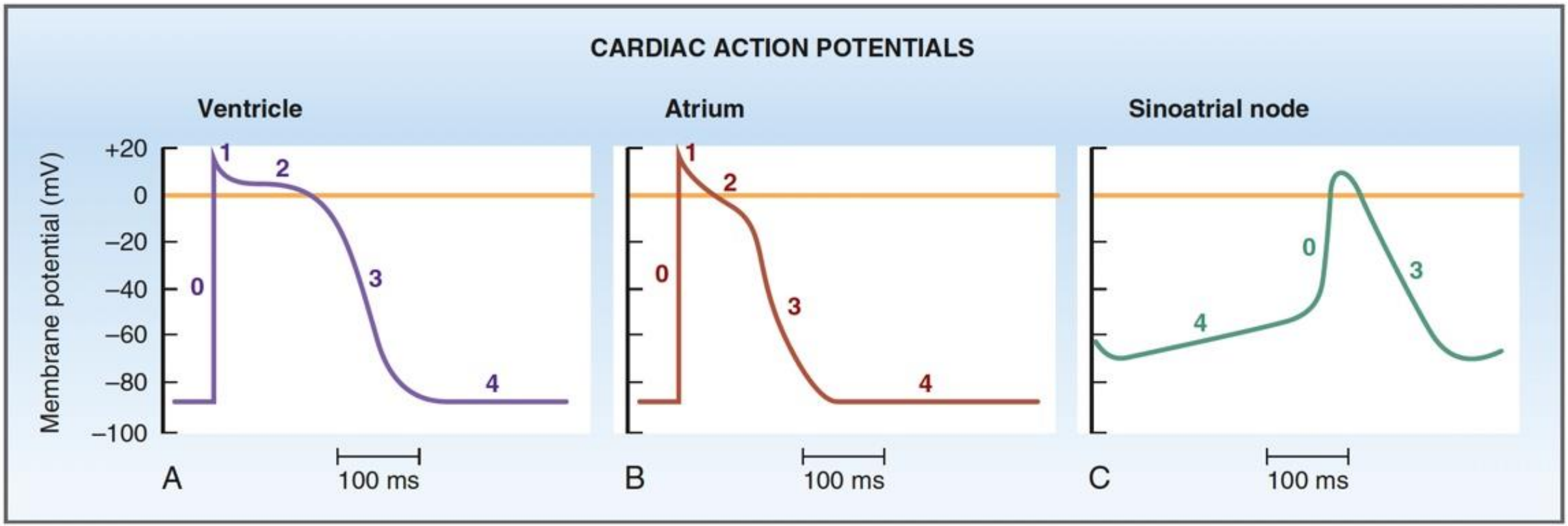


(a) Specialized conduction system of the heart

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.


CARDIAC ACTION POTENTIALS
Ventricle
Atrium
Sinoatrial node
Membrane potential (mV)
+20
0
−20
−40
−60
−80
−100
0
1
2
3
4
A
100 ms
B
100 ms
C
100 ms

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.

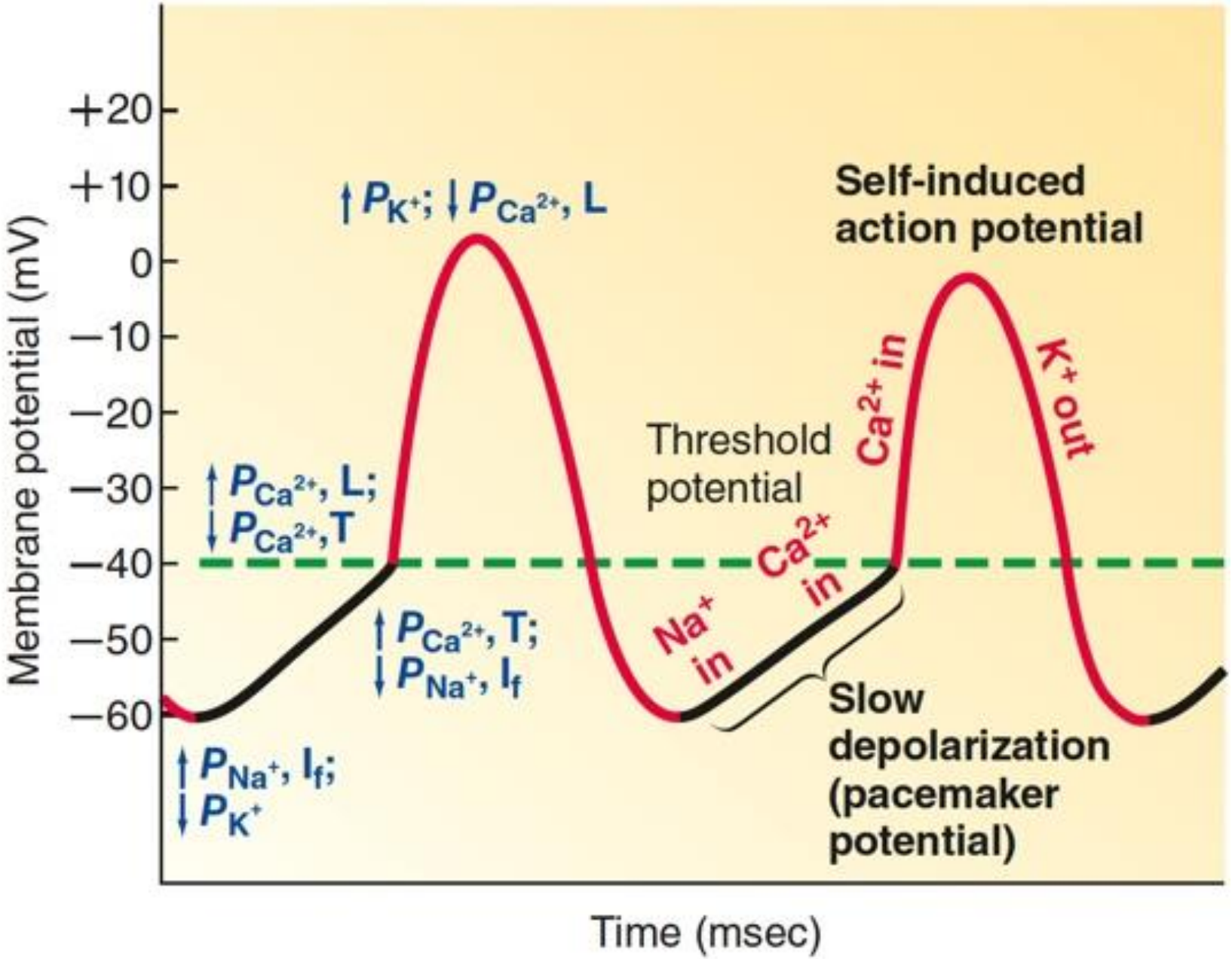
- They are (1) fast sodium channels, (2) calcium channels (particularly L-type or “slow” calcium channels), and (3) potassium channels.

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.


+20
+10
0
−10
−20
−30
−40
−50
−60
Membrane potential (mV)
↑ P_{K^+}; ↓ $P_{Ca^{2+}}$, L
↑ $P_{Ca^{2+}}$, L;
↓ $P_{Ca^{2+}}$, T
↑ $P_{Ca^{2+}}$, T;
↓ P_{Na^+}, I_f
↑ P_{Na^+}, I_f;
↓ P_{K^+}
Threshold potential
Na^+ in
Ca^{2+} in
Self-induced action potential
Ca^{2+} in
K^+ out
Slow depolarization (pacemaker potential)
Time (msec)

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.

Thank you