CVS
PHYSIOLOGY

Modified NO: 3

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Cardiovascular Physiology

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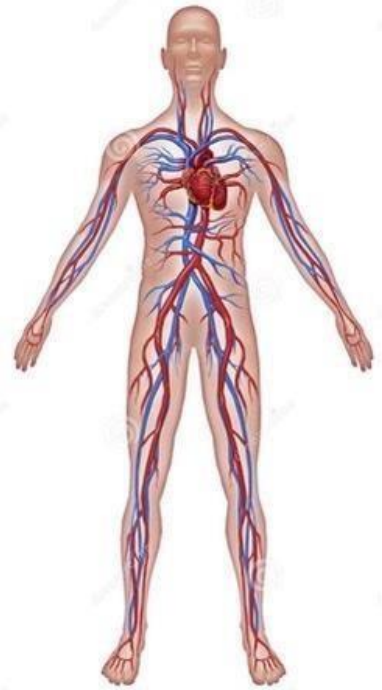

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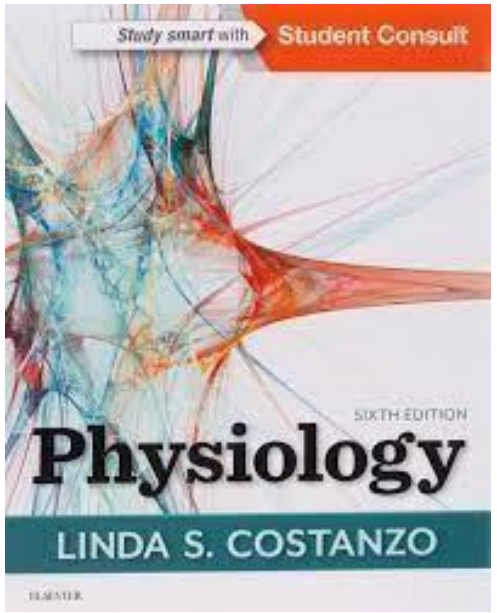
References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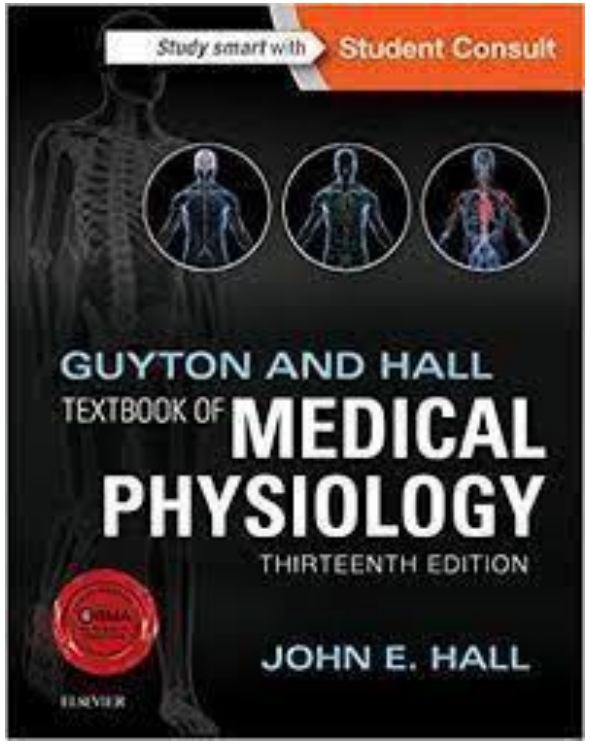
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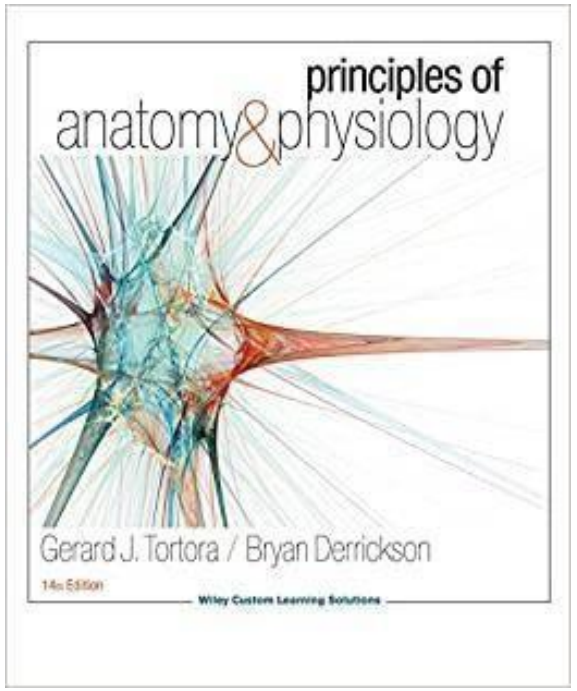
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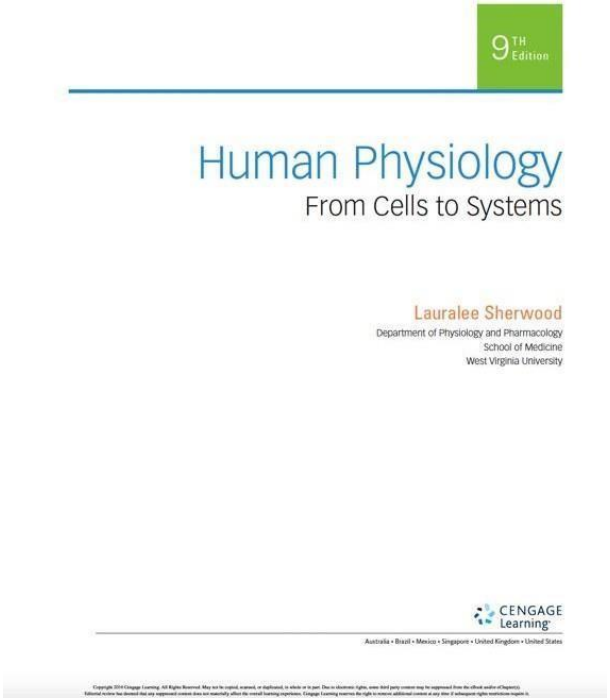
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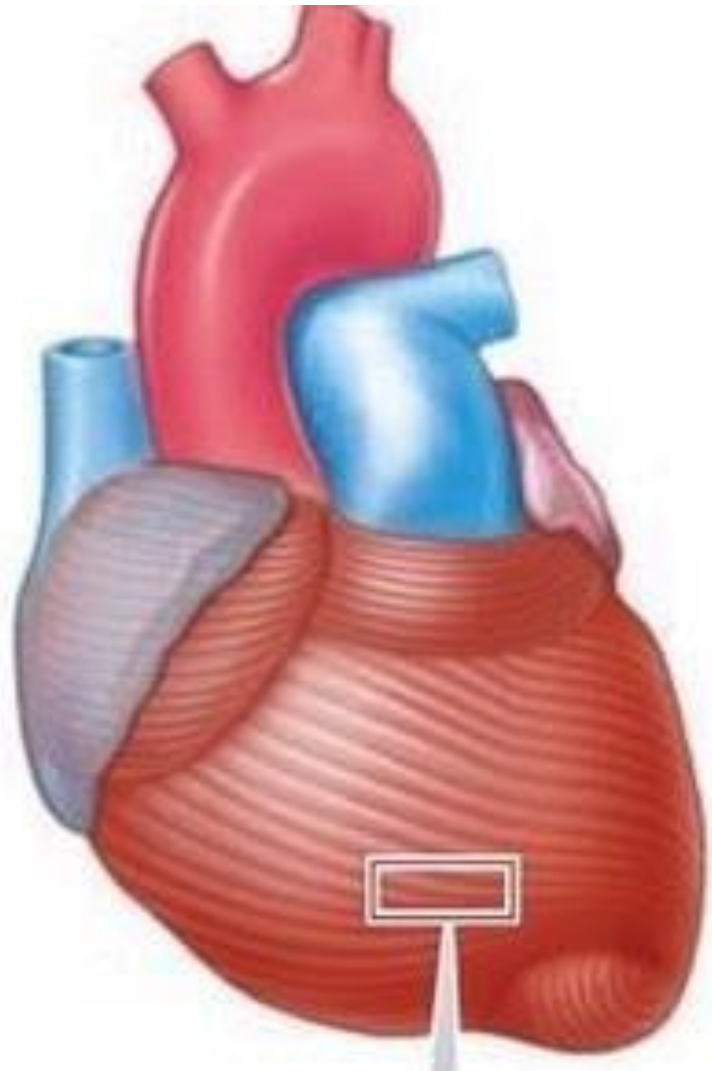
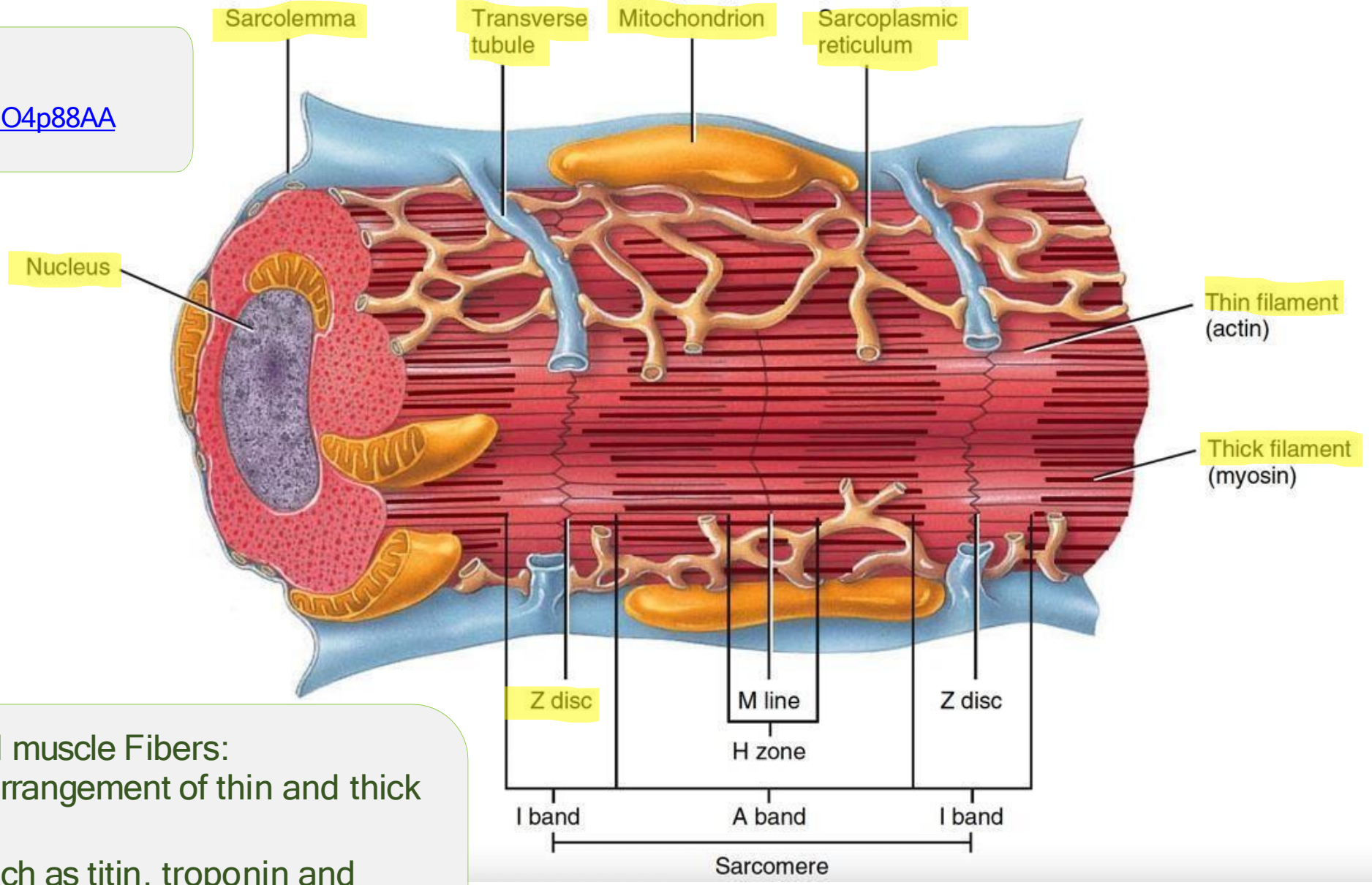
Cardiac muscle

last lecture we talked about special cardiac cells that self-generate actual potential, in this lecture we will talk about the other type of cells in the heart which is contractile cardiac muscle cells divided into: ventricular and atrial cells



Revision video from the doctor:
https://www.youtube.com/watch?v=BVcgO4p88AA



- Some similarity with skeletal muscle Fibers:
- striated due to the unique arrangement of thin and thick filament (actin and myosin)
- Same regulatory proteins such as titin, troponin and tropomyosin
- Same Z and M lines
- Same I and A bands

T-tubules

- The transverse tubules of cardiac muscle are wider but less abundant than those of skeletal muscle; the one transverse tubule per sarcomere is located at the Z disc.

- Transverse tubule : invagination of the sarcolemma and they contain the extracellular fluid; which is very important to transmit actual potential to the deeper structure within the muscle fiber.
- The Transverse tubule are in close connection to the sarcoplasmic reticulum, and this is very important for their function because the actual potential transmitted by T-tubules are supposed to release the calcium stored in the sarcoplasmic reticulum.

SR

- The sarcoplasmic reticulum of cardiac muscle fibers is less well developed than the SR of skeletal muscle fibers.
- As a result, cardiac muscle has a smaller intracellular reserve of Ca+.

Mitochondria

- Mitochondria are larger and more numerous in cardiac muscle fibers than in skeletal muscle fibers.
- This is very important because the cardiac muscle as you know they contract all the time throughout the life, so we need lots of energy production
- Cardiomyocyte (cardiac muscle cells) depend on aerobic respiration mainly and they get abundant of oxygen from coronary circulation and from the myoglobin

ATP Production

- In contrast to skeletal muscle, cardiac muscle produces little of the ATP it needs by anaerobic cellular respiration.
- Instead, it relies almost exclusively on aerobic cellular respiration in its numerous mitochondria.
- The needed oxygen diffuses from blood in the coronary circulation and is released from myoglobin inside cardiac muscle fibers.

ATP Production

- Cardiac muscle fibers use several fuels to power mitochondrial ATP production.
- In a person at rest, the heart's ATP comes mainly from oxidation of fatty acids (60%) and glucose (35%), with smaller contributions from lactic acid, amino acids, and ketone bodies.
- During exercise, the heart's use of lactic acid, produced by actively contracting skeletal muscles, rises.
- Like skeletal muscle, cardiac muscle also produces some ATP from creatine phosphate.

Clinical correlation (question from the doctor in the video)

1. Lactic Acid as an Alternative Fuel

•Exercise and Acute Metabolic Demand: During intense exercise, skeletal muscles produce lactic acid as a byproduct of anaerobic metabolism when oxygen supply is insufficient for complete aerobic respiration. This lactic acid enters the bloodstream, where cardiac muscle can efficiently use it as an energy source, especially under oxygen-limited conditions.

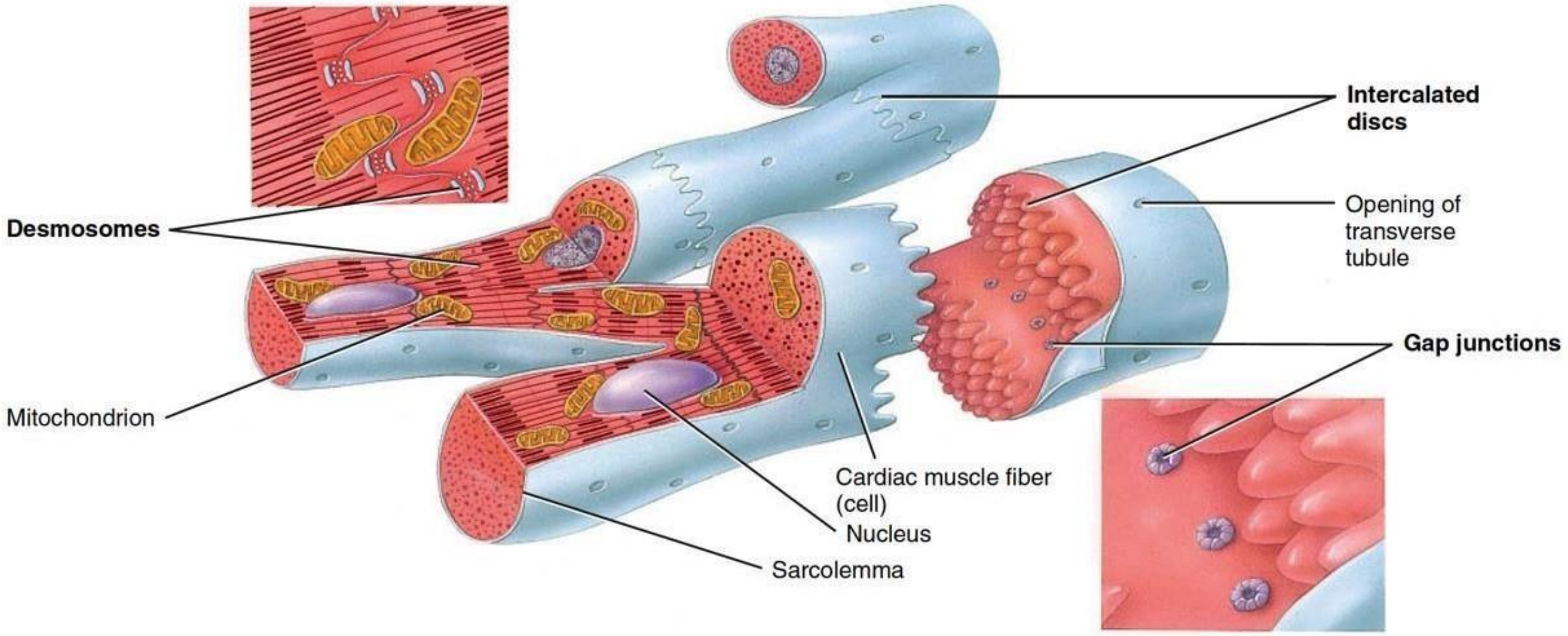
•Clinical Relevance in Ischemia and Heart Failure: During ischemic episodes (reduced blood flow to the heart, such as in coronary artery disease or heart failure), the oxygen supply to the heart muscle is compromised. In these conditions, the heart may increasingly rely on lactic acid and other alternative fuels to sustain ATP production. The heart's ability to switch to lactic acid metabolism may thus support continued function even when oxygen levels are low.

2. Creatine Phosphate as a Rapid ATP Source

•Role in High-Energy Demand: Both cardiac and skeletal muscles use creatine phosphate as a quick reserve for ATP, allowing the heart to respond to sudden increases in workload, such as during exercise or stress. Creatine kinase, the enzyme responsible for transferring a phosphate group from creatine phosphate to ADP, generates ATP rapidly to meet the increased demands.

•Clinical Relevance in Heart Failure and Ischemic Conditions: In heart failure, the capacity to produce ATP is often reduced. Patients with heart failure have shown lower levels of creatine phosphate and creatine kinase activity, which impairs the heart's ability to maintain sufficient ATP during demand spikes. Similarly, during ischemia, limited ATP availability from oxidative metabolism can be partially offset by using creatine phosphate, but only for a short time. Diminished creatine phosphate reserves are associated with worsened outcomes in these patients, highlighting the importance of this pathway for maintaining cardiac function during stress.

Cardiomyocyte are shorter and more branched than skeletal muscles, they are also connected by the intercalated discs
Intercalated → (specialized type of connection between cells)



(a) Cardiac muscle fibers

Intercalated disc

- The discs contain two types of special structures:
  1.desmosomes and 2.gap junctions.

- Desmosomes are specialized adhesive protein complexes that localize to intercellular junctions and are responsible for maintaining the mechanical integrity of tissues.
  - because the heart is under high mechanical stress so you need to connect these cells together in order to contract and relax all the time

- At each intercalated disc, the cell membranes fuse with one another to form permeable communicating junctions (gap junctions) that allow rapid diffusion of ions.
  - Allow the formation of a low-resistant pathway for the flow of ions from one cell to another that will guarantee a rapid conduction velocity so they can contract as one unit

Syncytium

- The cardiomyocyte that are connected together by intercalated discs they form together one functional unit, we call it syncytium
- The heart actually is composed of two syncytia; the atrial syncytium and the ventricular syncytium.

- The atria are separated from the ventricles by fibrous tissue that surrounds the A-V valvular openings between the atria and ventricles.
  - No direct connection between atria and ventricle except the AV bundle because of the fibrous tissue surrounding the AV valve which act as insulator to prevent any actual potential transmit between atria and ventricle except through the AV bundle.

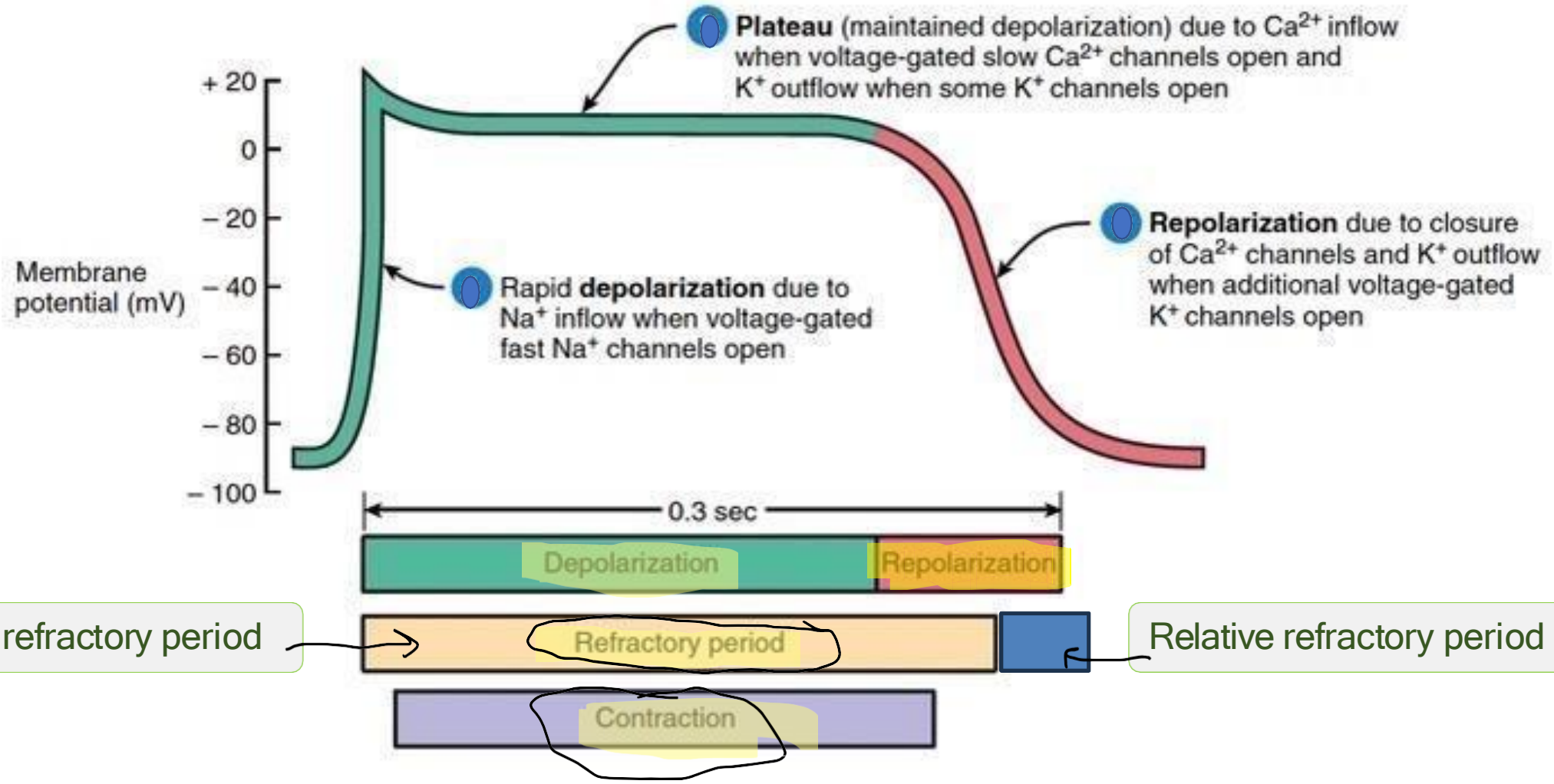
- Normally, potentials are not conducted from the atrial syncytium into the ventricular syncytium directly through this fibrous tissue. Instead, they are only conducted by the A-V bundle.

Syncytium

- This division of the muscle of the heart into two functional syncytia allows the atria to contract a short time ahead of ventricular contraction, which is important for the effectiveness of heart pumping.

- No gap junctions between atria and ventricles.

Action potential



Absolute refractory period

Relative refractory period

Duration of contraction

- Cardiac muscle begins to contract a few milliseconds after the action potential begins and continues to contract until a few milliseconds after the action potential ends.

- Therefore, the duration of contraction of cardiac muscle is mainly a function of the duration of the action potential, including the plateau, which depend on calcium concentration.

Refractory period

- The period during which a normal cardiac impulse cannot re- excite an already excited area of cardiac muscle.
- The normal refractory period of the ventricle is 0.25 to 0.30 second, which is about the duration of the prolonged plateau action potential.
- The refractory period of atrial muscle is much shorter; about 0.15 second.

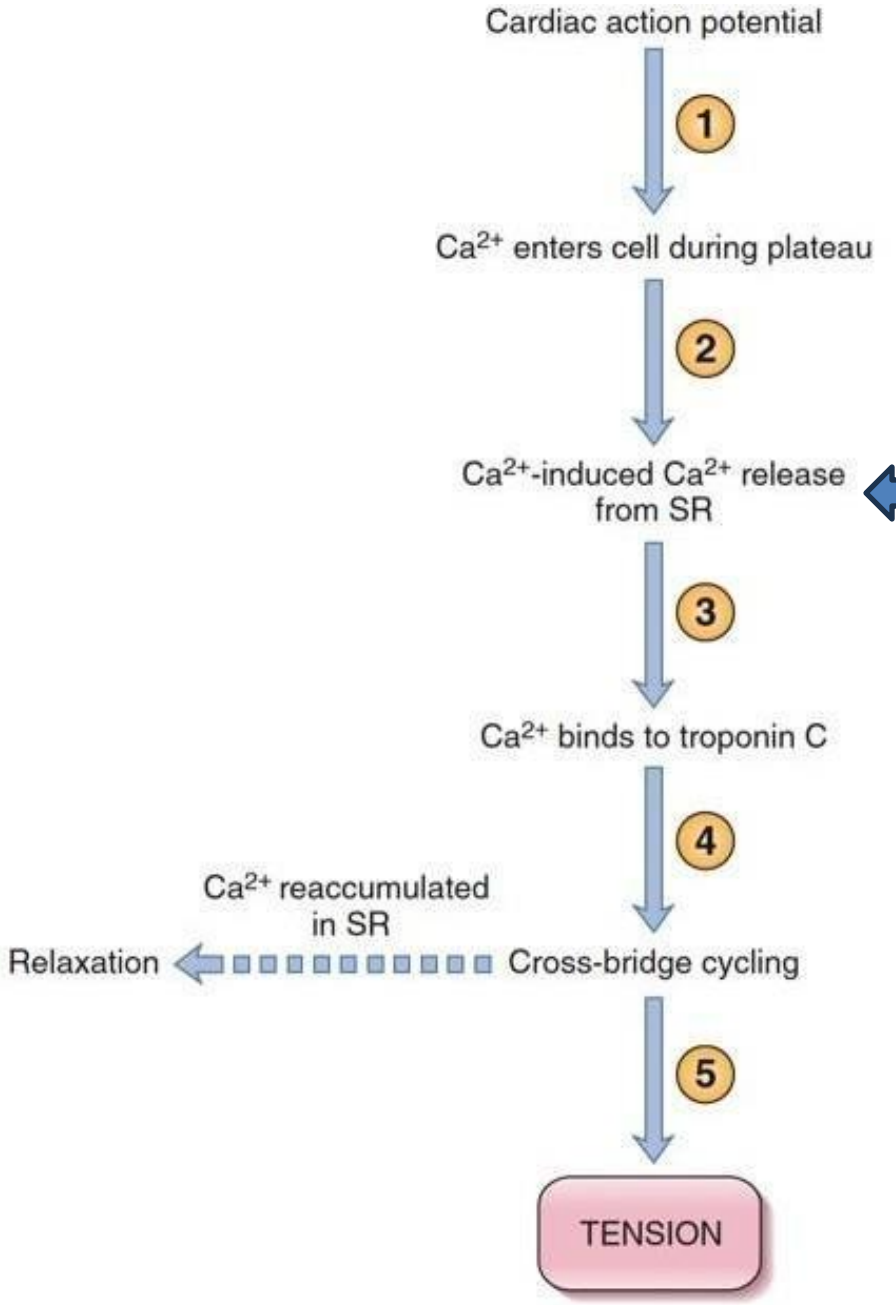
- **Absolute refractory period** : absolutely no stimulus can stimulate the cardiomyocyte at this time (end just before the end of the repolarization)
- There is an additional **relative refractory period** of about 0.05 second during which the muscle is more difficult to excite than normal but can be excited by a very strong excitatory signal (early premature contraction).

Excitation-contraction coupling

- In addition to the calcium ions that are released into the sarcoplasm from the sarcoplasmic reticulum, calcium ions also diffuse into the sarcoplasm from the T tubules at the time of the action potential, which opens voltage-dependent calcium channels in the membrane of the T tubule.

- Calcium entering the cell then activates calcium release channels (ryanodine receptor channels) in the SR membrane, triggering the release of calcium into the sarcoplasm.

- Excitation-contraction coupling is all the series of events that happens from arrival of the action potential to the cardiac muscle cell until the sliding of the actin and the myosin.
- It is similar to the skeletal muscle, when action potential come especially through the t tubules, calcium will pass through voltage gated calcium channels and enter the sarcoplasm, then it will activate a calcium release channels in the sarcoplasmic reticulum.
- the sarcoplasmic concentration of the calcium will increase enough so it can bind to the troponin, then the confirmational changes of the troponin and tropomyosin structure will lead to binding of the actin and myosin and start sliding.



This term is impotent

CICR

C: cilium

I: induced

R: release

Calcium

- Without the Ca+ from ECF, the strength of cardiac muscle contraction would be reduced considerably because the SR of cardiac muscle is less well developed than that of skeletal muscle and does not store enough calcium to provide full contraction.

T tubules have a high concentration of L-type calcium channels, they are also wide in diameter so they can enter more cilium.

Calcium

- The T tubules of cardiac muscle have a diameter five times as great as that of the skeletal muscle tubules.

- Also, inside the T tubules is a large quantity of mucopolysaccharides that are electronegatively charged and bind an abundant store of calcium ions, keeping them available for diffusion to the interior of the cardiac muscle fiber when a T tubule action potential appears.

Relaxation

- At the end of the plateau of the cardiac action potential, the influx of calcium ions to the interior of the muscle fiber is suddenly cut off, and calcium ions in the sarcoplasm are rapidly pumped back out of the muscle fibers into the sarcoplasmic reticulum and T tubule–extracellular fluid space.

Relaxation

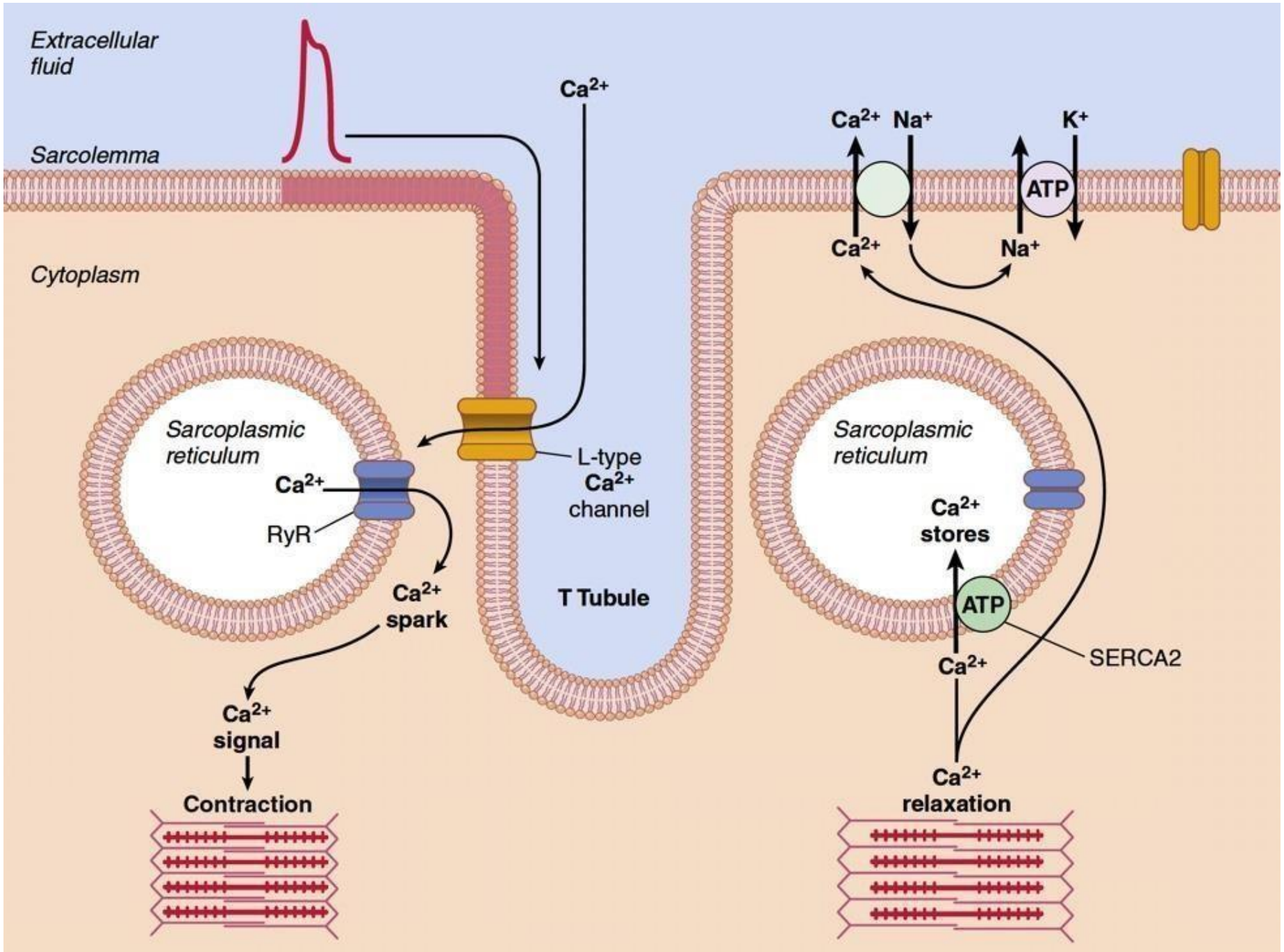
- Note that SERCA2 pump use ATP

- Transport of calcium back into SR is achieved with the help of a calcium pump (SERCA2).
- Calcium ions are also removed from the cell by a Na-Ca exchanger.
- Na that enters the cell during this exchange is then transported out of the cell by Na-K ATPase pump.
- As a result, the contraction ceases until a new action potential comes along.

Relaxation

- these sarcolemmal transporters pump Ca+ out of the cell against its electrochemical gradient, with the Ca+ ATPase using ATP directly and the Ca2+-Na+ exchanger using energy from the inward Na+ gradient.

- As a result of these transport processes, the intracellular Ca+ concentration falls to resting levels, Ca+ dissociates from troponin C, actin-myosin interaction is blocked, and relaxation occurs.


Extracellular fluid
Sarcolemma
Cytoplasm
Ca2+
Ca2+ Na+
K+
ATP
Ca2+
Na+
Sarcoplasmic reticulum
Ca2+
RyR
L-type Ca2+ channel
T Tubule
Ca2+ spark
Ca2+ signal
Contraction
Sarcoplasmic reticulum
Ca2+ stores
ATP
SERCA2
Ca2+
Ca2+ relaxation

Contractility

- Contractility, or inotropism, is the intrinsic ability of myocardial cells to develop force at a given muscle cell length.

- Agents that produce an increase in contractility have positive inotropic effects.
- Positive inotropic agents increase both the rate of tension development and the peak tension.

- Agents that produce a decrease in contractility have negative inotropic effects.
- Negative inotropic agents decrease both the rate of tension development and the peak tension.

Contractility

- Contractility correlates directly with the intracellular Ca+ concentration, which in turn depends on the amount of Ca+ released from sarcoplasmic reticulum stores during excitation-contraction coupling.

- The amount of Ca+ released from the SR depends on two factors:
- The size of the inward Ca+ current during the plateau of the myocardial action potential.
- The amount of Ca+ previously stored in the SR for release.

- Therefore the larger the inward Ca+ current and the larger the intracellular stores, the greater the increase in intracellular Ca+ concentration and the greater the contractility.

Contractility

- The magnitude of the tension developed by myocardial cells is proportional to the intracellular Ca2+ concentration.

- Therefore, hormones, neurotransmitters, and drugs that alter the inward Ca2+ current during the action potential plateau or that alter SR Ca2+ stores would be expected to change the amount of tension produced by myocardial cells.

What do you think about Digitalis?

Digitalis refers to a group of medications derived from the leaves of the Digitalis plant. The primary active component, digoxin, has been widely used in medicine for its effects on the heart, particularly in treating heart failure and certain types of irregular heartbeats, like atrial fibrillation.

Mechanism of Action:

1. Inhibition of Na^+/K^+-ATPase: Digoxin inhibits the Na^+/K^+-ATPase pump in cardiac cell membranes. This inhibition increases intracellular sodium levels, which indirectly raises intracellular calcium levels through the sodium-calcium exchanger.
2. Increased Contractility (Positive Inotropic Effect): Higher calcium levels inside heart cells lead to more robust cardiac muscle contractions. This effect is beneficial in heart failure, where the heart struggles to pump blood effectively.
3. Reduced Heart Rate (Negative Chronotropic Effect): Digoxin increases vagal (parasympathetic) tone, which slows down the heart rate. This effect is useful in treating conditions like atrial fibrillation, where heart rate control is essential.

It may seem contradictory at first that digitalis (e.g., digoxin) increases heart muscle contraction while also decreasing the heart rate, but these effects actually complement each other in terms of therapeutic benefit. Let's break down why this isn't a contradiction:

1. Increased Muscle Contraction (Positive Inotropy)

•In heart failure, the heart's pumping ability is weakened, making it difficult to circulate blood effectively. Digitalis helps by increasing the force of each contraction, so the heart pumps more blood per beat. This effect is essential for improving cardiac output and helping alleviate symptoms of heart failure.

2. Decreased Heart Rate (Negative Chronotropy)

•A slower heart rate can be beneficial because it allows the heart more time to fill with blood between beats. By slowing the rate, digoxin helps ensure that each beat is more efficient, pushing more blood out with each contraction.

•The slowing effect is particularly useful in cases of rapid or irregular heartbeats, like atrial fibrillation, where excessive heart rates reduce filling time and efficiency.

Why This Isn't a Contradiction:

•Efficiency: By increasing contractility, digoxin allows the heart to pump more effectively without having to increase its rate. This is a more efficient way to improve cardiac output than simply speeding up the heart rate.

•Reduced Workload: Slowing the heart rate decreases the workload on the heart, reducing the amount of oxygen it requires. This effect is crucial for patients with compromised heart function, as it helps prevent further damage or stress to the heart muscle.

•Synergistic Benefits: In heart failure and certain arrhythmias, the combination of stronger contractions and a controlled heart rate works synergistically, as it maximizes the amount of blood ejected with each beat while minimizing unnecessary energy expenditure.

So, rather than being contradictory, these effects are complementary. By improving contraction strength and optimizing heart rate, digoxin helps the heart function more effectively under compromised conditions, like heart failure or atrial fibrillation.

Thank you

Additional sources

دع أثر للكاتب (اية،حديث،عظة)

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	Slide 6 Slide 12 Slide 32 & 33		Additional video from the doctor Clinical correlation Digitalis
V2→V3	Change the some of the text in blue to green(required)		

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!