PHYSIOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 2

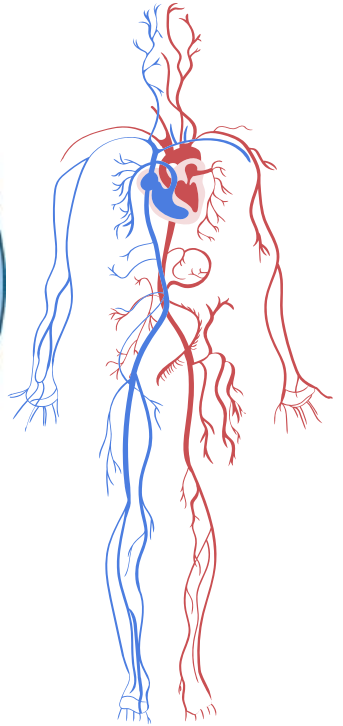
Cardiac Muscle Physiology

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

Written by: Dana Al Oudat, Raya Al Weshah

Reviewed by: Sara Masadeh



Cardiac Muscle Physiology

Faisal Mohammed, MD, PhD

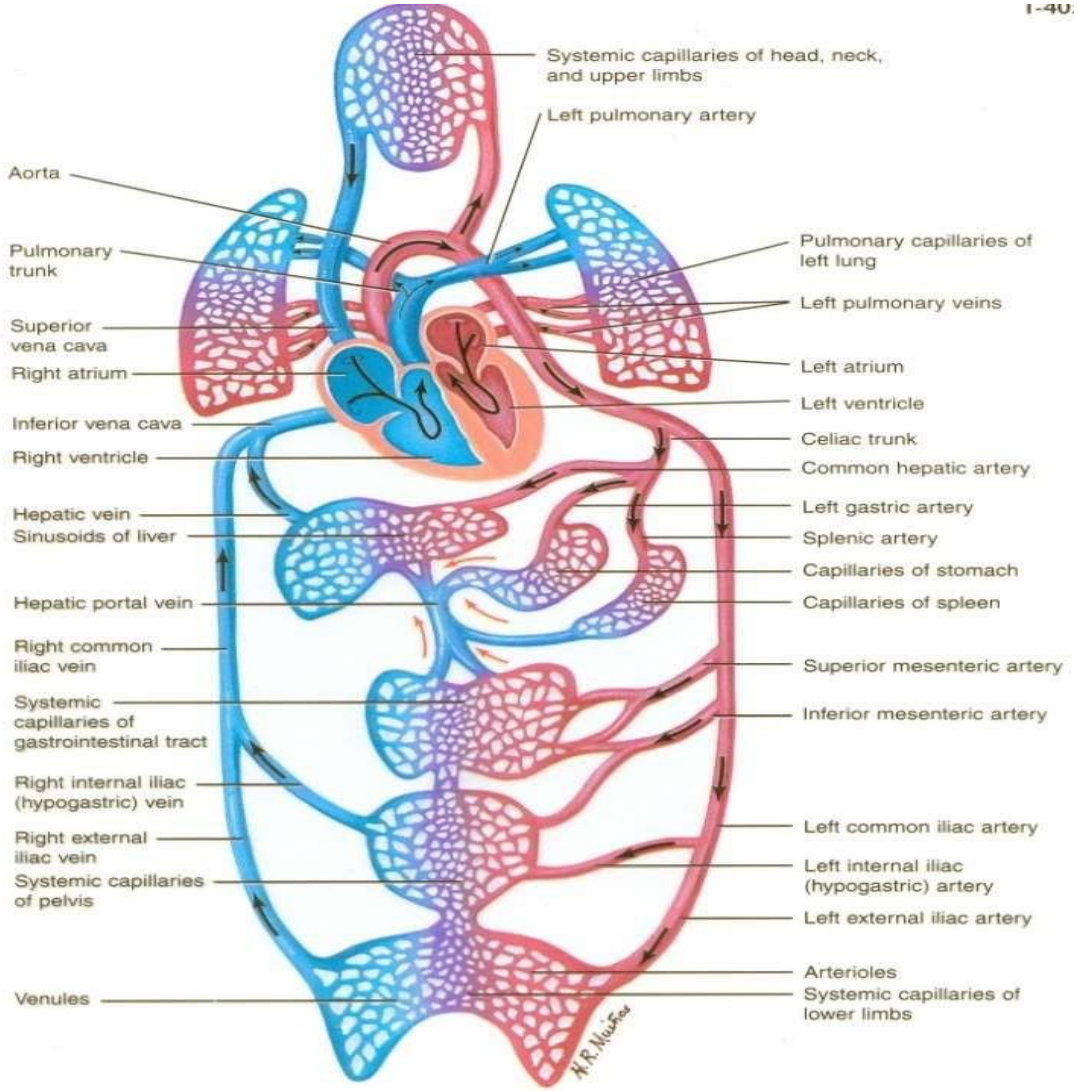
على الرغم من طول الملف، بس نصه معلومات احنا اخذناها قبل، او صور .
سموا بالله و ابدؤوا (:

Objectives:

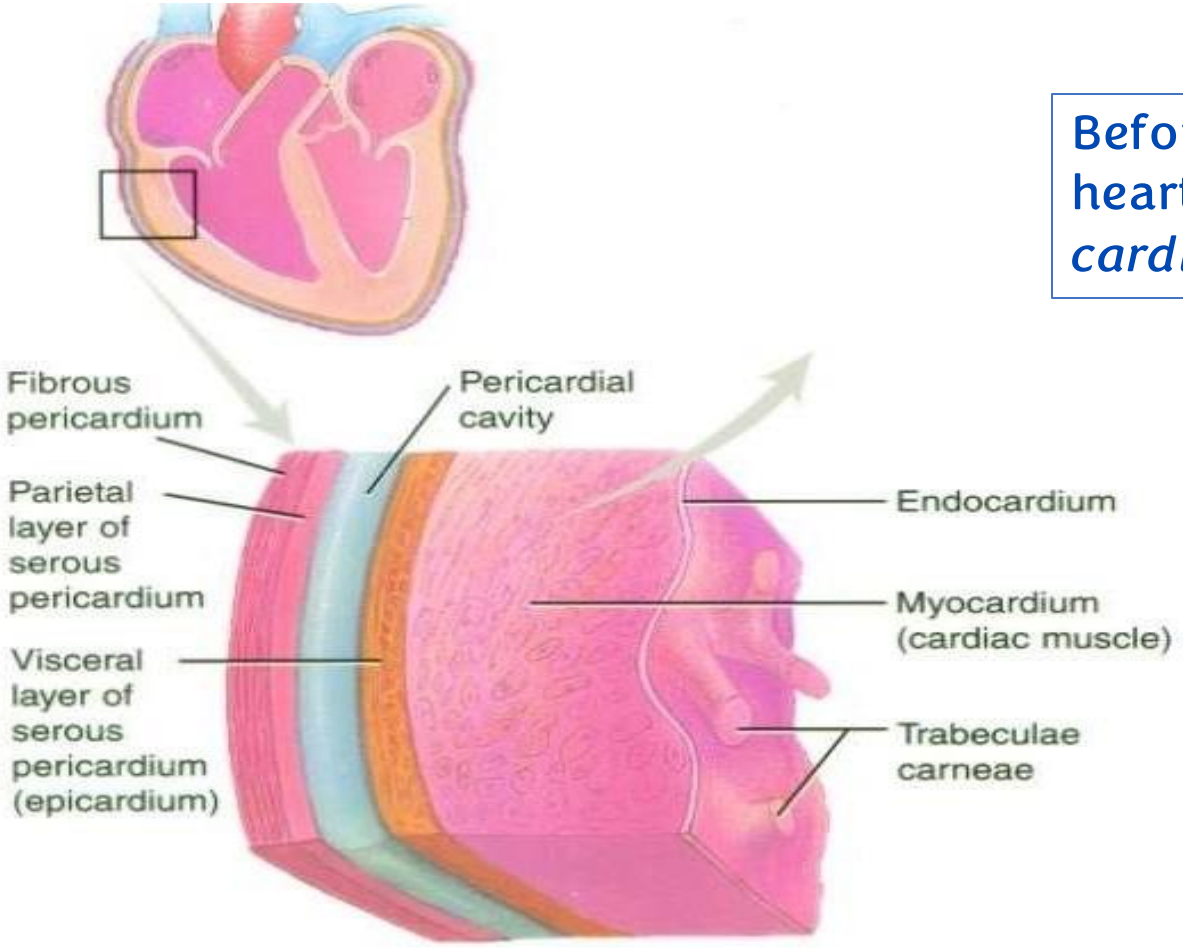
By The end of this lecture students should be able to:

- Distinguish the cardiac muscle cell microstructure.
- Describe cardiac muscle action potential.
- Point out the functional importance of the action potential.
- Follow the cardiac muscle mechanism of contraction.
- Delineate cardiac muscle energy sources.
- Outline the intracellular calcium homeostasis.
- Explain the relationship between muscle length and tension of cardiac muscle (Frank-Starling law of the heart).

Overview of the greater and lesser circulations



Layers of the heart



(a) Portion of pericardium and heart wall

Before we start, please note that term related to the heart is described using the prefix ***"cardiac"*** (e.g., *cardiac drugs*, *cardiovascular system*, *cardioversion*).

When examining a section of the heart wall, it is found to consist of **three main layers:**

1. **Endocardium.**
2. **Myocardium.**
3. **Pericardium.**

For a detailed explanation, see the next slides.

Layers of the heart

- **Endocardium:**
  The innermost layer of the heart is called the *endocardium*.
  Unlike typical epithelial tissue, the endocardium not only provides protection but also has **secretory functions**. It releases important **substances and hormones** that regulate blood flow within the heart, including **endothelin** (which causes vasoconstriction) and **nitric oxide** (which promotes vasodilation).

- **Myocardium:**
  The middle layer, also considered the main layer of the heart, known as the *myocardium*, is composed of specialized cardiac muscle fibers. It is responsible for the **contraction and relaxation** of the heart, which enables the pumping of blood throughout the body.

- **Pericardium:**
  The outermost covering of the heart is called the *pericardium*, which has two layers:
  - The **visceral pericardium** (also called the *epicardium*) is directly attached to the heart muscle.
  - The **parietal pericardium** forms the outer fibrous sac.

•Between these two layers lies the **pericardial cavity**, which normally contains about 50–100 mL of protein-rich fluid. This viscous fluid acts as a **lubricant and shock absorber**, preventing friction or injury to the heart during movement or contraction.

Layers of the heart – clinical application

- If the amount of pericardial fluid increases abnormally, the condition is known as **pericardial effusion**. Excessive accumulation of this fluid can **compress the heart**, restricting its filling during relaxation (diastole) and thereby reducing **cardiac output**. In severe cases, this leads to **ischemia** (insufficient blood flow to body tissues), **dyspnea** (difficulty breathing), and a sensation of **suffocation**.

- You might encounter this condition in a hospital setting or after an accident where bleeding occurs into the pericardial cavity, causing rapid fluid accumulation. As the pericardium fills with blood, the heart becomes unable to expand properly, and the patient experiences severe respiratory distress.

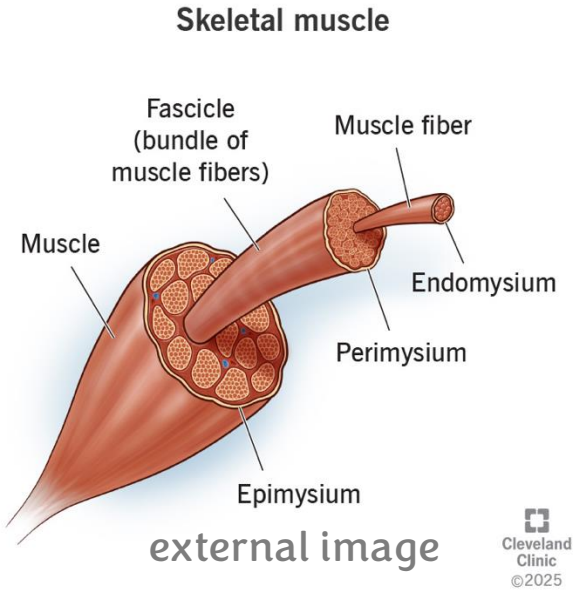
- If pericardial effusion is diagnosed, the immediate treatment is pericardiocentesis – a procedure to remove the excess fluid using a syringe and needle. If a syringe is not available in an emergency situation, any object capable of creating a small opening to allow drainage can be used temporarily to relieve the pressure.

- This condition, pericardial effusion, also known as **cardiac tamponade** when severe, refers to the accumulation of fluid within the pericardial cavity, which compresses the heart and interferes with its normal pumping function.

Cardiac muscles VS Skeletal Muscles

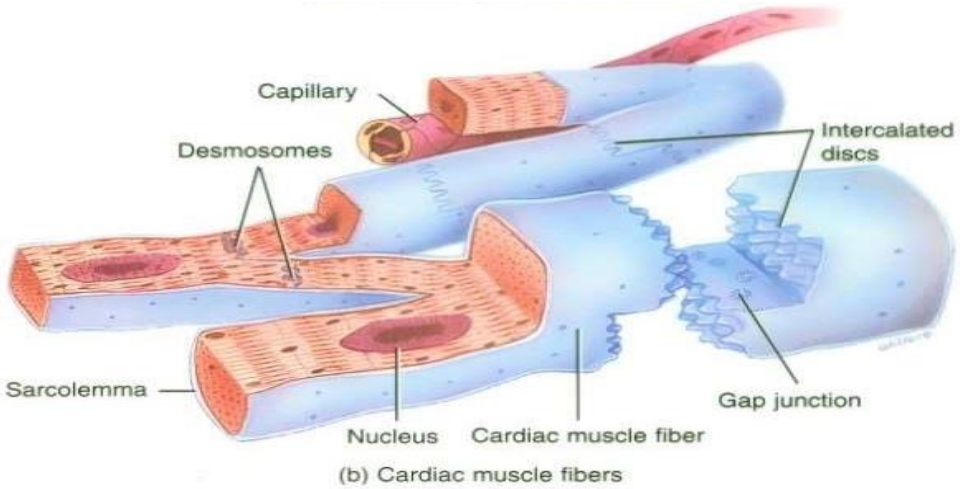
Skeletal muscle fibers are **spindle-shaped** and can range in length from a few millimeters up to about a meter, such as in the case of the *sartorius muscle* (عضلة الخياط), which may reach nearly one meter in length.

In contrast, cardiac muscle cells are **rectangular or cylindrical** in shape and are much shorter—only a few millimeters long. They are interconnected with one another by specialized structures called **intercalated discs**. Between these cells are **gap junctions**, which are low-resistance pathways that allow ions to move freely from one cell to another.

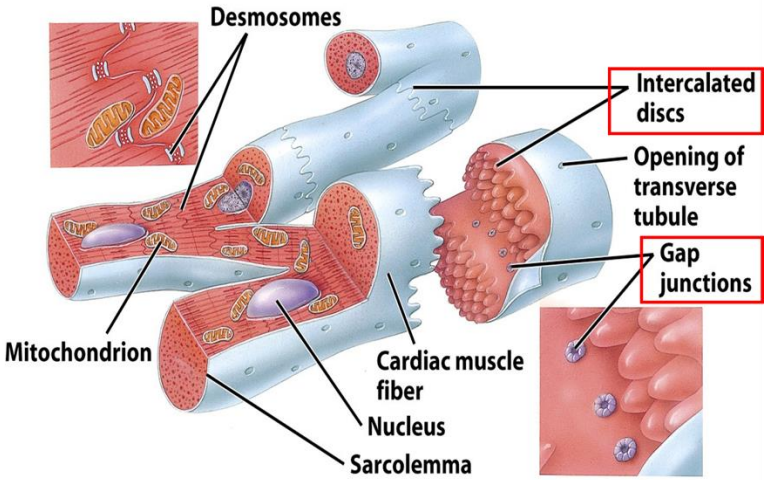


external image

Cleveland Clinic ©2025



(b) Cardiac muscle fibers



Cardiac muscle fibers

Figure 20-9a Principles of Anatomy and Physiology, 11/e
© 2006 John Wiley & Sons

external image

Cardiac muscle syncytium- clinical application

- When an electrical change (depolarization) occurs in one cardiac cell, it rapidly spreads to all neighboring cells through the gap junctions. This coordinated activity allows the entire heart chamber to contract as a single functional unit.
- In the atria, these interconnected cells are called the **atrial syncytium**, and in the ventricles, they form the **ventricular syncytium**. Thus, the heart functions as two syncytia – one atrial and one ventricular

- If, however, each cell were to contract independently, the result would be **ventricular fibrillation** – a state of chaotic, uncoordinated contraction that leads to an **immediate loss of cardiac output and death** unless treated urgently with **direct current (DC) shock (defibrillation)**.

- If you suspect **myocardial infarction (heart attack)** in any patient, send them **immediately to the hospital**, because one of the serious complications of MI is **ventricular fibrillation**.

- There is also **atrial fibrillation (AF)**, but unlike ventricular fibrillation, it is **compatible with life**, although it causes an irregular heartbeat and reduces the efficiency of cardiac output. **Ventricular fibrillation (VF)**, however, is **fatal** if not treated immediately.

Remember from MSS physiology

- Skeletal (or striated) muscle is **voluntary muscle**, meaning it contracts under conscious control.

- It depends completely on its nerve supply – if the nerve that innervates a skeletal muscle is cut, the muscle will undergo **atrophy**. Atrophy means that the muscle loses its **actin and myosin filaments**, becomes weak, and decreases in size.

- When skeletal muscle is trained or used more frequently, it undergoes **hypertrophy**, which means an increase in the size of each muscle fiber due to an increase in actin and myosin content – not an increase in the number of muscle cells.

- The term **hyperplasia** means an **increase in the number of muscle fibers**, but this **does not occur** in skeletal or cardiac muscles under normal physiological conditions. So, skeletal muscle adapts mainly through hypertrophy, not hyperplasia.

Remember from general histology

The **sarcomere** is the **functional** unit of striated muscle. It **extends** from **one Z line to the next Z line.**

Z line (Z disc):

- Marks the boundary between two sarcomeres.
- Anchors actin (thin) filaments.

I band:

- Light band containing only thin (actin) filaments.
- Spans two adjacent sarcomeres (on either side of the Z line).

A band:

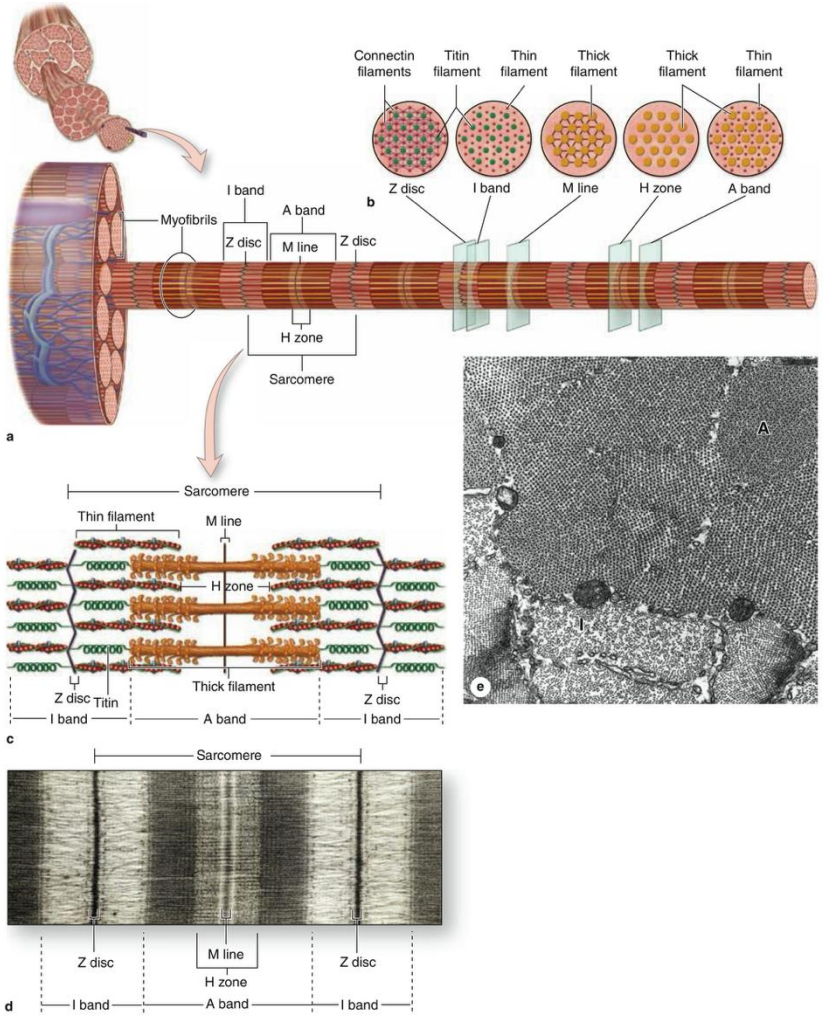
- Dark band corresponding to the entire length of thick (myosin) filaments.
- Contains regions of overlap between actin and myosin.

H zone:

- The lighter central area of the A band.
- Contains only thick (myosin) filaments, no overlap.

M line:

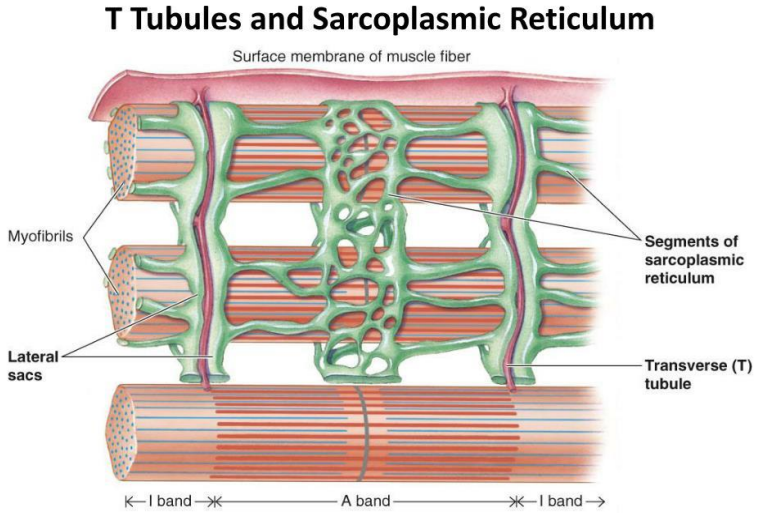
- Found at the center of the H zone.
- Holds myosin filaments together and stabilizes their alignment.



Remember from MSS physiology

T-Tubules

- To trigger Ca2+ release from sarcoplasmic reticulum (ER of the muscle cells) throughout the muscle fiber simultaneously and produce uniform contraction of all myofibrils, the sarcolemma has tubular infoldings called transverse or T-tubules.
- These long fingerlike invaginations of the cell membrane penetrate deeply into the sarcoplasm and encircle each myofibril near the aligned A- and I-band boundaries of sarcomeres.



External image of a skeletal muscle sarcomere

- In **skeletal muscle**, the **T-tubules** are long, narrow, and cylindrical. They are located in the **I band region**, at the junction between the A and I bands, and each **sarcomere** contains **two T-tubules**.
- The **sarcoplasmic reticulum (SR)** in skeletal muscle is well developed and serves as the main storage site for calcium ions (Ca^{2+}).
- Because of this large internal calcium reserve, skeletal muscle contraction depends primarily on calcium released from the SR.

Cardiac muscles, again

- **Cardiac muscle cells**, like **skeletal muscle cells**, are **striated**.
- However, **cardiac muscle** is **involuntary** – it contracts automatically without conscious control.
- It is regulated by the **autonomic nervous system**, which includes both the **sympathetic** and **parasympathetic** divisions.

- Despite this regulation, the **initiation of cardiac impulses** does not depend on nerve supply. Even if both the sympathetic and parasympathetic nerves are cut, the heart will **continue to beat**, because the electrical impulses originate **intrinsically** -primarily from the sinoatrial (SA) node, the heart's natural pacemaker.
- This concept is clearly demonstrated in **heart transplantation**.
  When a donor heart is transplanted into a recipient, it is **not reconnected** to the sympathetic or parasympathetic nerves, yet it continues to **beat and pump normally**, as long as it receives adequate blood supply and calcium.

- Therefore, the role of the **autonomic nervous system** is **not to start the heartbeat**, but to **regulate it**:
  - The **sympathetic** system **increases** the heart rate and the force of contraction.
  - The **parasympathetic** system **decreases** the heart rate and contraction strength.

- So, the **cardiac muscle** is both **excitable** and **intrinsically active.**

The Structures Within Cardiac Muscle Cells

The cardiac muscle has T-tubules just like skeletal muscle, but there are important differences between them.

In **cardiac muscle**, the T-tubules are **shorter and wider**, which allows a greater exchange of fluid and ions with the extracellular space. This is because extracellular calcium (Ca^{2+}) plays a major role in cardiac muscle contraction, and therefore there is more surrounding fluid in this area to facilitate calcium movement.

In contrast, **skeletal muscle** has **longer and narrower T-tubules**, and it does not rely on extracellular calcium, since it stores sufficient Ca^{2+} inside its sarcoplasmic reticulum (SR).

The **position** of the T-tubules also differs:

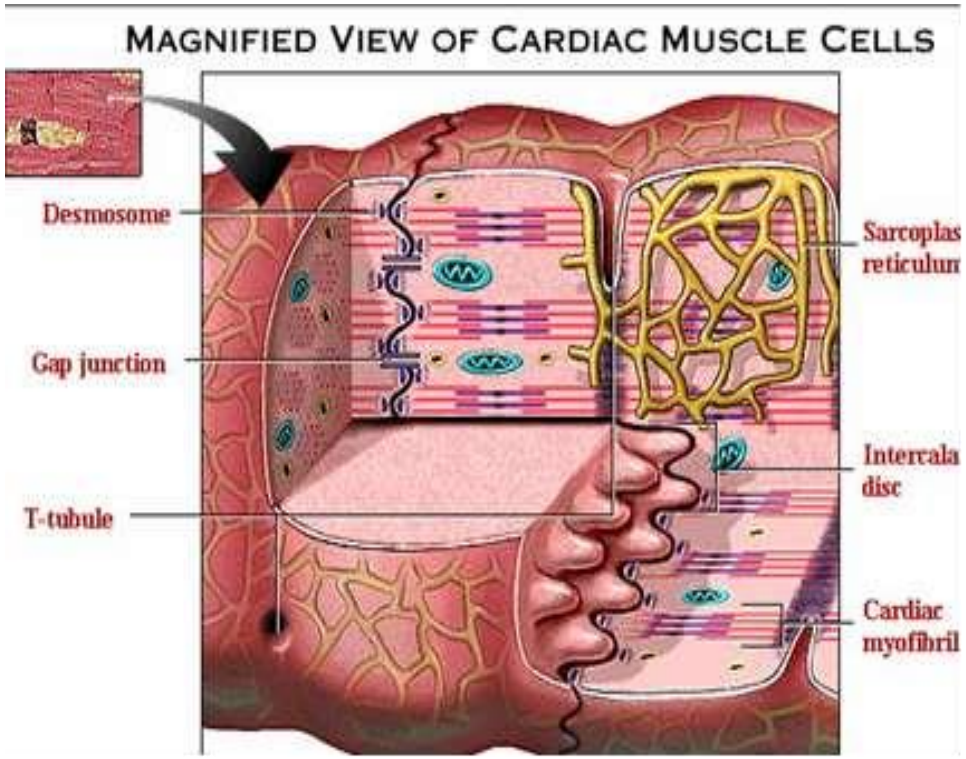
- In **cardiac muscle**, the T-tubule is located at the **Z line**.
- In **skeletal muscle**, the T-tubule is located at the junction of the A and I bands **(in the I band region)**.

Each **sarcomere** in cardiac muscle has **one T-tubule**, while in skeletal muscle there are **two per sarcomere**.

The Structures Within Cardiac Muscle Cells

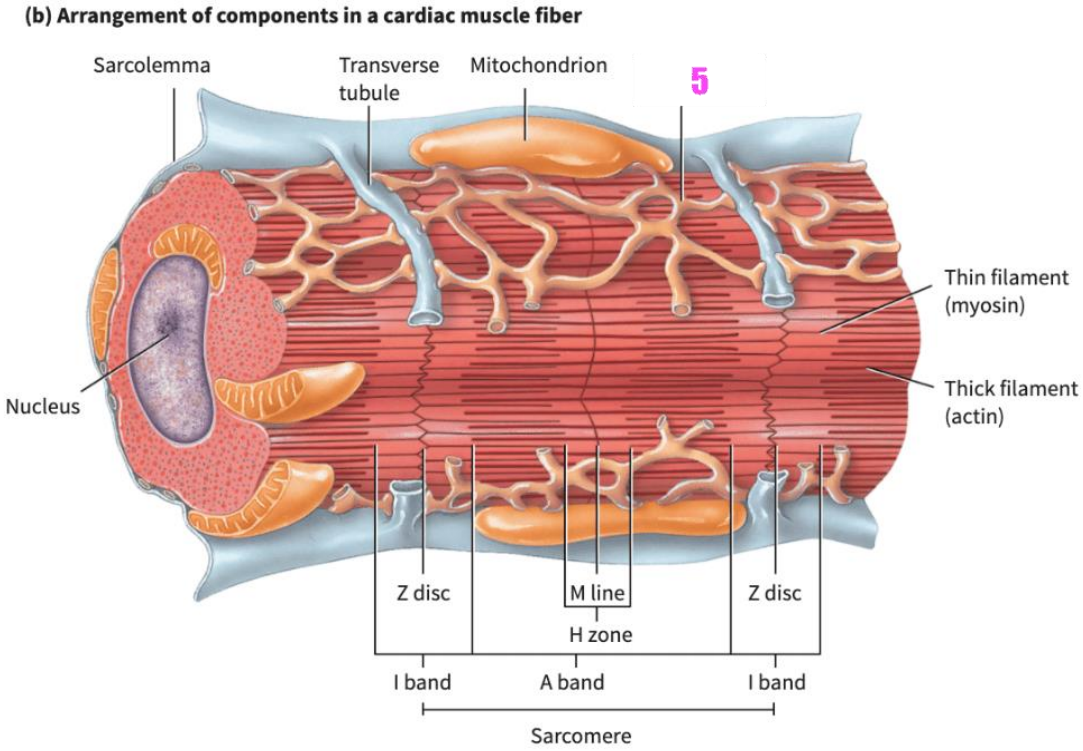
The **sarcoplasmic reticulum (SR)** in cardiac muscle is **less developed** and stores **much less calcium** than the SR of skeletal muscle. Because of this limited storage capacity, cardiac muscle requires an additional source of calcium from the extracellular fluid (ECF) to initiate and maintain contraction.

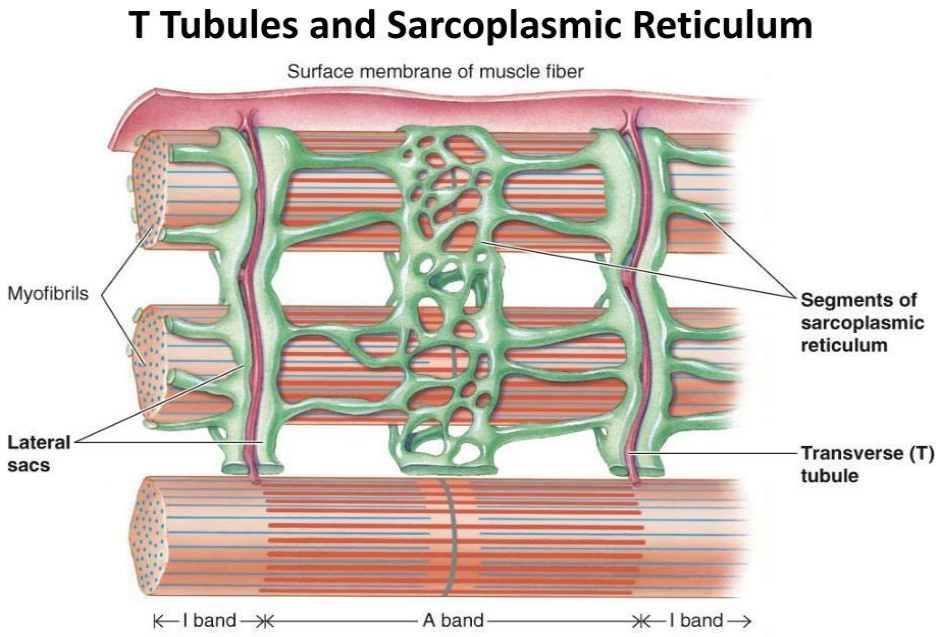
Thus, the entry of extracellular Ca^{2+} during each action potential is essential for cardiac muscle contraction and helps trigger further calcium release from the SR – a mechanism known as calcium-induced calcium release (CICR).



سبحان الله، والحمد لله، ولا إله إلا الله، والله أكبر

T-tubules in the cardiac vs skeletal muscle



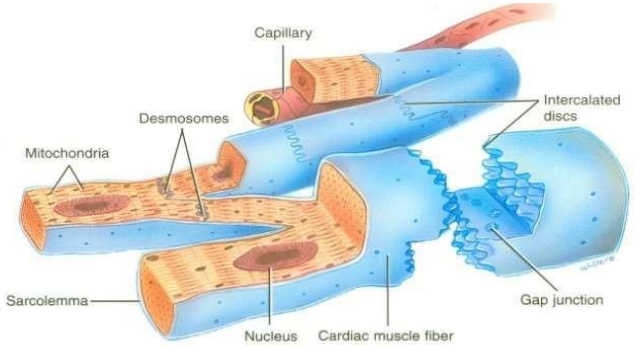


In this image, you can see that the transverse (T) tubules of cardiac muscle are located on the Z line, with one T-tubule corresponding to each sarcomere.

While in this image, you can see that there are two T-tubules in each skeletal muscle sarcomere, located in the I band region.

The Structures Within Cardiac Muscle Cells

The **cardiac muscles** are **always contracting**; if they stop, it means death, which shows that they require a continuous supply of energy. The powerhouses that produce ATP are the **mitochondria**, and that's why cardiac muscle cells contain a large number of mitochondria. They have much fewer nuclei compared to skeletal muscle cells.

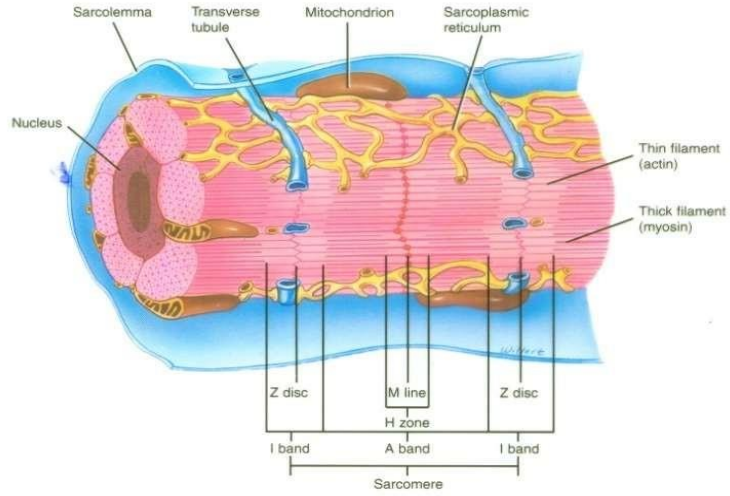


(a) Cardiac muscle fibers

Again, Cardiac muscle cells also contain **gap junctions**, which are very important. These gap junctions are low-resistance areas, allowing ions to move freely from one cell to another.

So, if there is a change in the membrane potential of any single cell, this change spreads rapidly to all other cells, causing them to depolarize and contract together.

The cells of the **atria** are connected together, and the cells of the **ventricles** are connected together, forming what is called a **syncytium** (its plural is **syncytia**).



(b) Diagram based on an electron micrograph

Thus, we have **two syncytia** in the heart: an **atrial syncytium** and a **ventricular syncytium**, separated by the **atrioventricular septum**, which acts as a structural barrier.

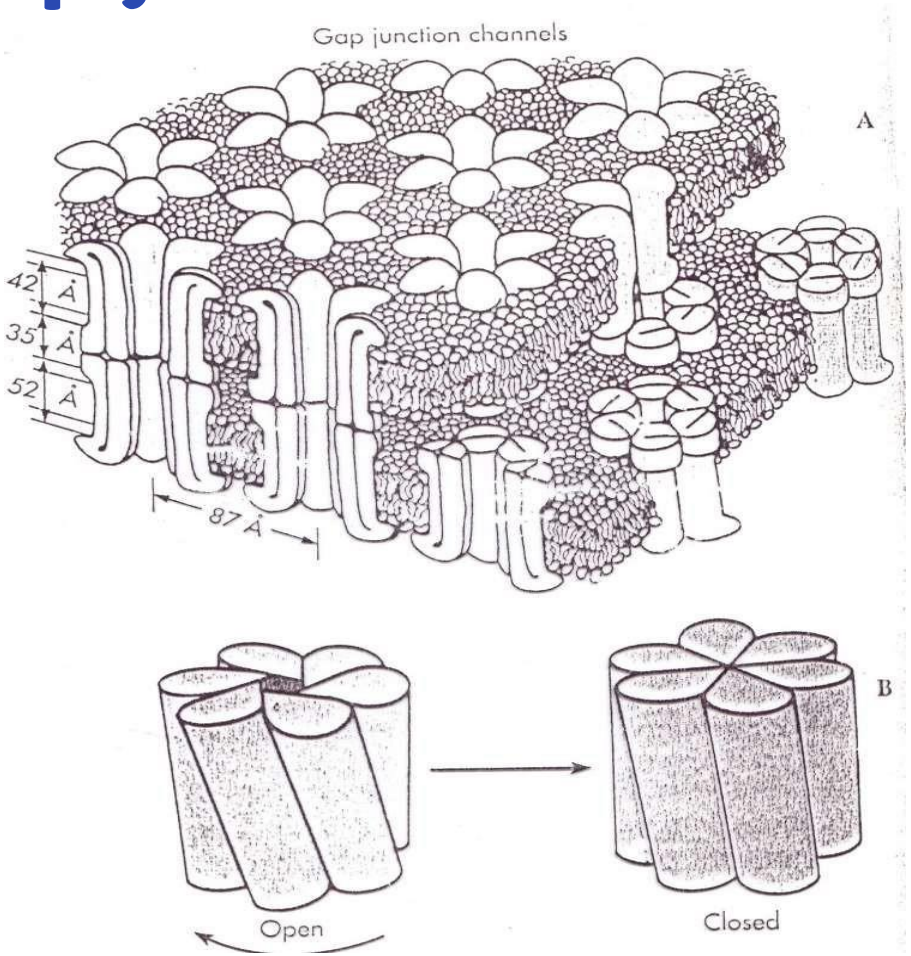
Cardiac Muscle Cells-Gap junctions

The **gap junction** is formed by **hexamers** – six groups of proteins – that can open or close in response to changes in membrane voltage.

When they open, ions can move freely from one cell to another in both directions (bidirectional movement).

This allows electrical impulses to spread quickly between cells, so that all the cardiac muscle cells depolarize together. As a result, the ventricles contract as one unit, and the atria contract as one unit.

Any **defect** in the **electrical connection** between the cardiac cells, which causes them to contract independently, is known as atrial / ventricular **fibrillation**, for further information, check slide 9.



لا إله إلا الله

Cardiac Muscle Vs Skeletal Muscle

- Syncytium structure.
- Gap Junction (electrical coupling) low resistance area.
- Poorly developed Sarcoplasmic reticulum (SR), **that's why the cardiac muscle requires extracellular calcium (Ca^{2+}).**
- Transverse (T)Tubule on Z-line (i.e.One T-tubule per sarcomere).
- Rich in mitochondria.
- Low in nuclei.

Remember from general physiology

·How do we calculate the **driving force** for ions ?
It can be determined using the **Nernst equation**.

·The **statement of the Nernst equation** is:
·The **electromotive force (E)** or **equilibrium potential** =
± (depending on the charge of the ion: use **–** for positive ions and **+** for negative ions) ×
(RT / zF) × ln([ion inside] / [ion outside])
·Where:
R = gas constant
T = absolute temperature (in Kelvin)
z = valency (charge) of the ion (for example, +1 for Na^+ and K^+, +2 for Ca^{2+}, –1 for Cl^-)
F = Faraday constant

·Since **R**, **T**, and **F** are constants — and **T** in the human body is approximately **37°C (310 K)** — these values remain almost constant.
·The variable **z** changes depending on the ion under consideration.
·After converting the natural logarithm (**ln**) to logarithm base 10 (**log10**) and substituting physiological constants, the equation becomes approximately:
· **E = –(61 / z) × log([ion inside] / [ion outside])**

Remember from general physiology

Calculating the **equilibrium potential** for **sodium**:

The concentration of Na^+ inside the cell = 14 mmol/L.
The concentration of sodium outside = 140 mmol/L.

Using the Nernst equation:
$E_{na} = -61 \times \log(14 / 140)$
$E_{na} = -61 \times \log(1 / 10)$
$E_{na} = -61 \times (-1) = +61$ mV
If the Na^+ channel opens, sodium ions will move into the cell, trying to bring the membrane potential toward their equilibrium potential of **+61 mV**. However, the membrane potential will never actually reach +61 mV because other ions also influence it.

The **Nernst equation** calculates the equilibrium potential for only one ion at a time.

For **K^+ (potassium)**:
- Inside the cell = 120 mmol/L
- Outside the cell = 5 mmol/L
  → The equilibrium potential (E_k) is approximately **-90 mV**.

For **Cl^- (chloride)**, the equilibrium potential (ECl) is approximately **-70 mV**.

For **Ca^{2+} (calcium)**:
- Valency (z) = 2 → 61 / 2 = 30
- Outside concentration = 10^{-3} mol/L
- Inside concentration = 10^{-7} mol/L

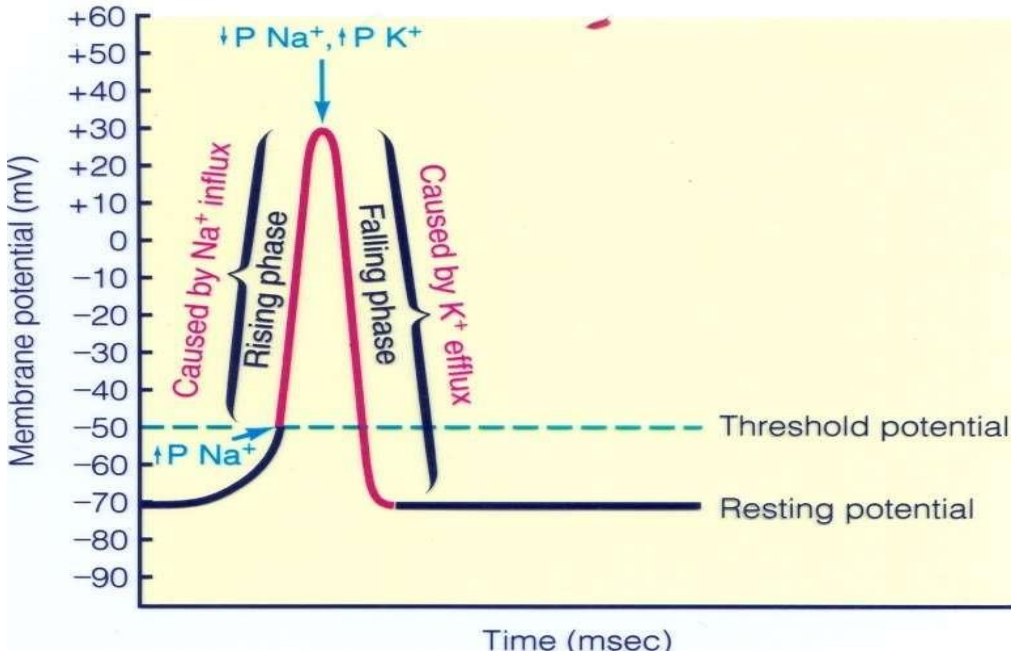
$\log(10^{-7} / 10^{-3}) = \log(10^{-4}) = -4$
Eca = $-30 \times (-4) =$ **+120 mV**

Thus, the equilibrium potential for calcium is very high. If calcium channels open, Ca^{2+} will flow **into the cell rapidly** due to the large electrochemical gradient.

Remember from MSS physiology

Skeletal Muscle Action Potential

- The **resting membrane potential** of skeletal muscle is about **-70 mV, that's due to:**
- ➢ The **difference in membrane permeability** to **potassium (K^+)** and **sodium (Na^+)** ions. The cell membrane is almost **100 times more permeable to K^+ than to Na^+**, allowing more positive charge to leave the cell than to enter, which makes the inside more negative.
- When the membrane potential **reaches the threshold**, **voltage-gated Na^+ channels open**, causing **rapid depolarization** as sodium ions rush into the cell.



Permeability Changes and Ionic Fluxes During an Action Potential (skeletal Muscle)

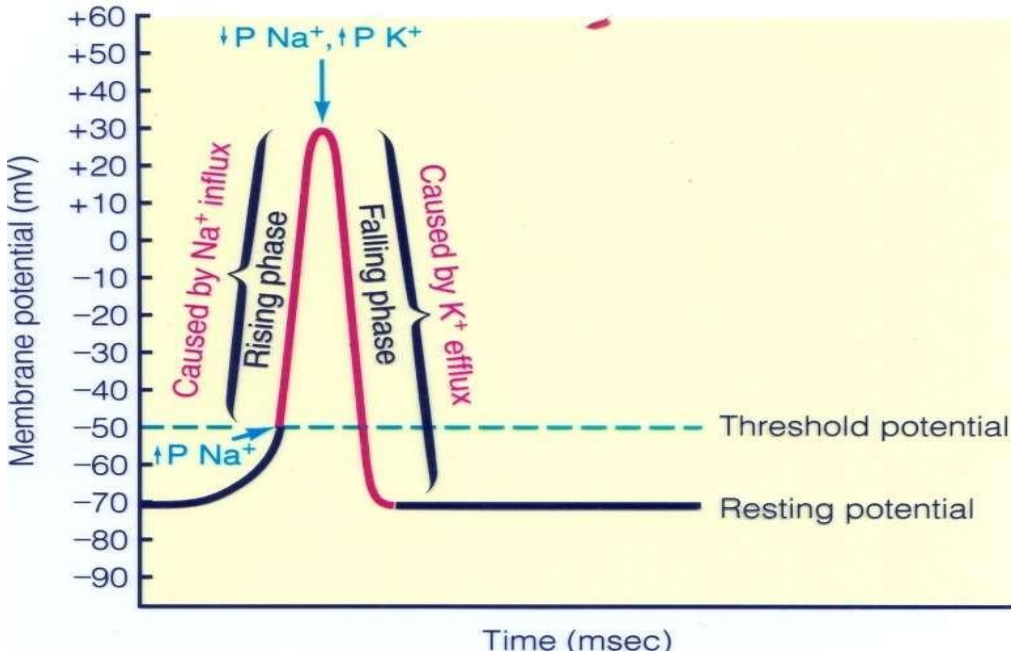
- Immediately after, **voltage-gated K^+ channels open**, allowing potassium ions to leave the cell, leading to **repolarization**.
- This whole process happens very quickly – lasting only **1-2 milliseconds**.

Remember from MSS physiology

Skeletal Muscle Action Potential

- From the beginning of depolarization until part of repolarization, the membrane is in the **absolute refractory period**, during which **no new action potential** can be initiated, no matter how strong the stimulus.

- However, this **absolute refractory period** is **very short (less than 1 ms)**, which allows **skeletal muscle fibers to generate frequent action potentials** in rapid succession and ultimately reach tetanus – a sustained, continuous contraction that occurs when the muscle has no time to relax between successive stimuli.



Permeability Changes and Ionic Fluxes During an Action Potential (skeletal Muscle)

Cardiac Muscle Action Potential

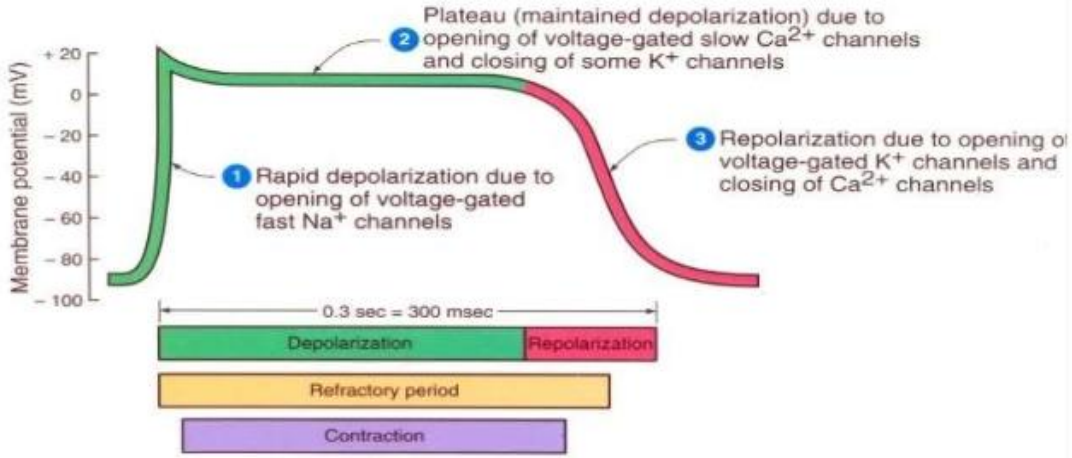
·The **cardiac muscle action potential** is **different from that of skeletal muscle.**
·The **resting membrane potential** is about **–90 mV.**

Phase 0

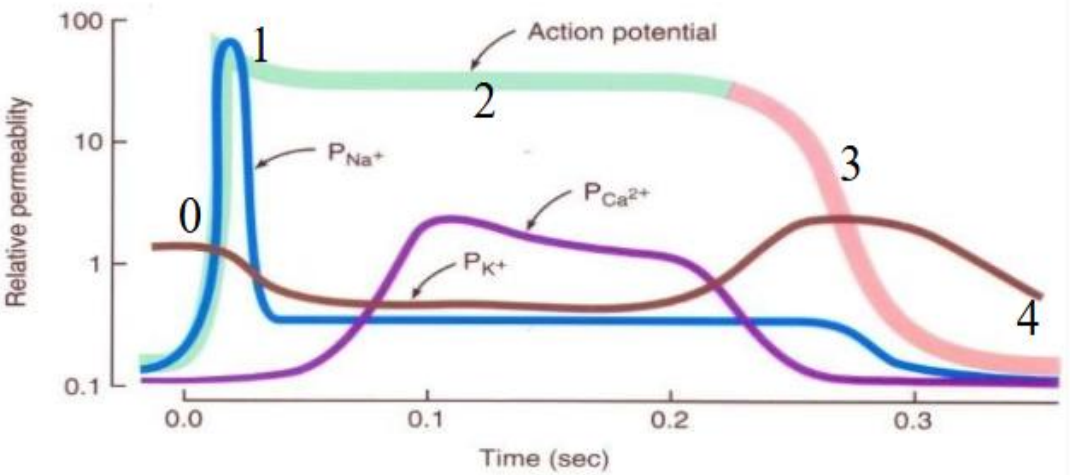
·There is a **depolarization phase** called **Phase 0**, which is the **rapid depolarization phase**. It occurs due to the **influx of sodium ions (Na^+)** through **voltage-gated sodium channels,** there is also an **increase** in the sodium permeability **(sodium conductance)** .
·Sodium enters the cell because of the **driving force** acting on it. (Recall slide 21)

Phase 1

This is followed by **Phase 1**, a **partial (initial) repolarization** due to the opening of **transient K^+ channels** (there are several types of K^+ channels).



(a) Action potential, refractory period, and contraction



(b) Membrane permeability (P) changes

Cardiac Muscle Action Potential

Phase 2

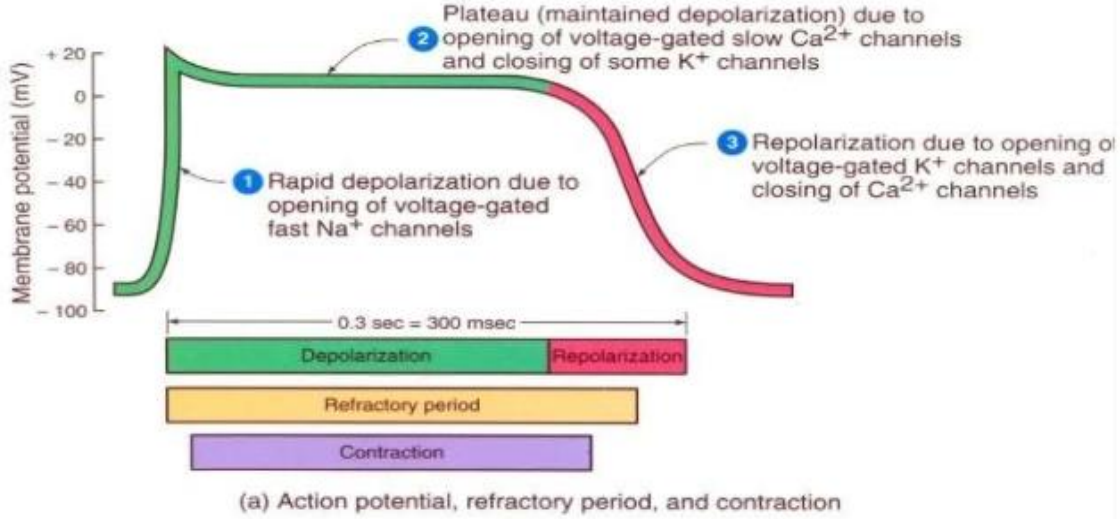
In **Phase 2**, **slow voltage-gated Ca^{2+} channels (L-type)** open, allowing calcium to enter the cell, producing the **plateau phase**.

Phase 3

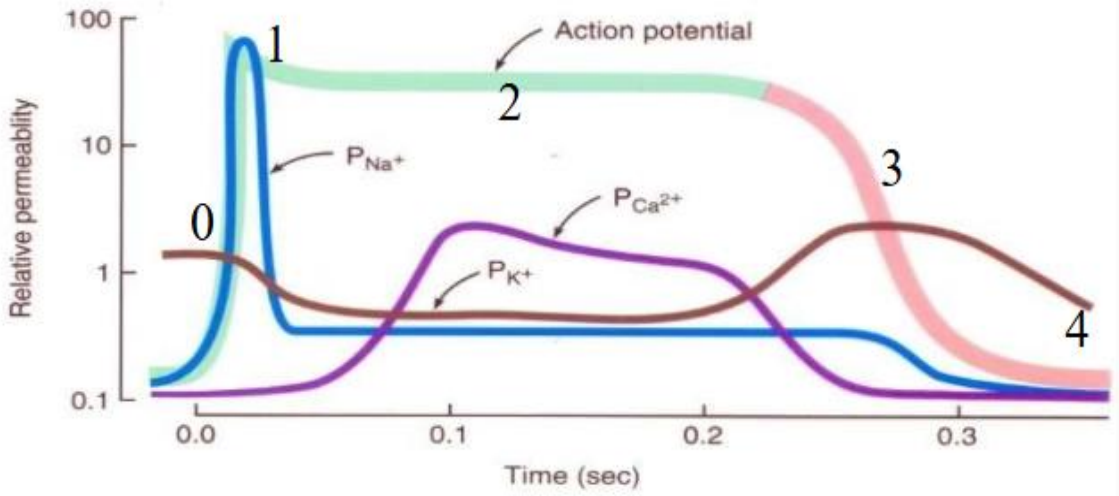
Then comes **Phase 3**, where **voltage-gated K^+ channels** open, leading to **repolarization**.

Phase 4

Finally, **Phase 4** represents the **return to the resting membrane potential**, which is approximately **-90 mV**.



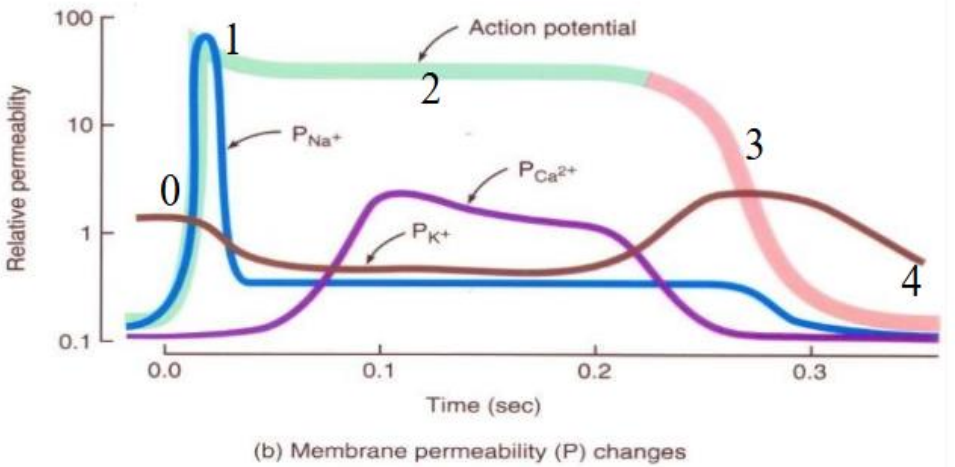
(a) Action potential, refractory period, and contraction



(b) Membrane permeability (P) changes

Cardiac Muscle Action Potential

- During **phase 0** they is an increase in **sodium conductance.**
- During **Phase 1 (towards its end)**, there is a **decrease in K^+ conductance**– this phenomenon is known as **potassium rectification**. It is very important because, in **Phase 2**, **Ca^{2+} enters the cell** through slow voltage-gated calcium channels.(This brief efflux of K^+ slightly repolarizes the membrane while still allowing the membrane potential to remain near the plateau level, so that Ca^{2+} can enter the cell via slow voltage-gated calcium channels during Phase 2 (the plateau phase).
- If potassium permeability were high during this time, the strong efflux of K^+ would **counteract (outbalance)** the calcium influx, and the **plateau phase** would not occur.

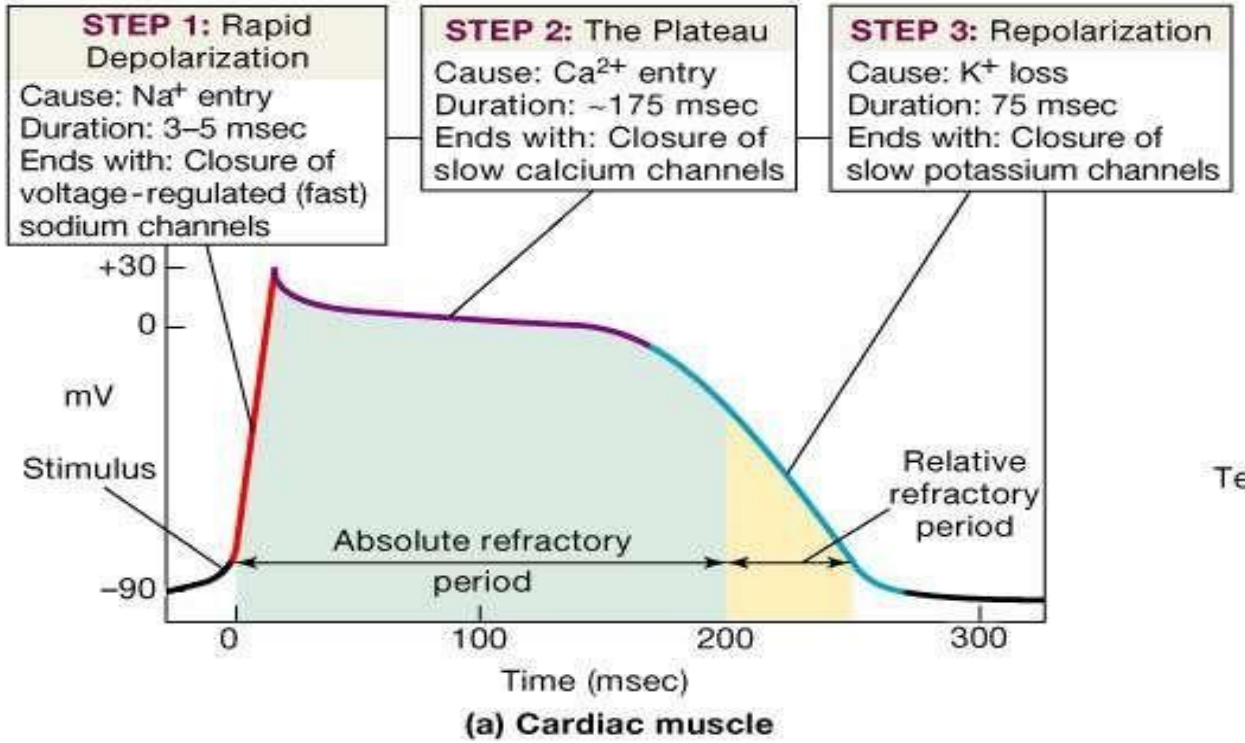


(b) Membrane permeability (P) changes

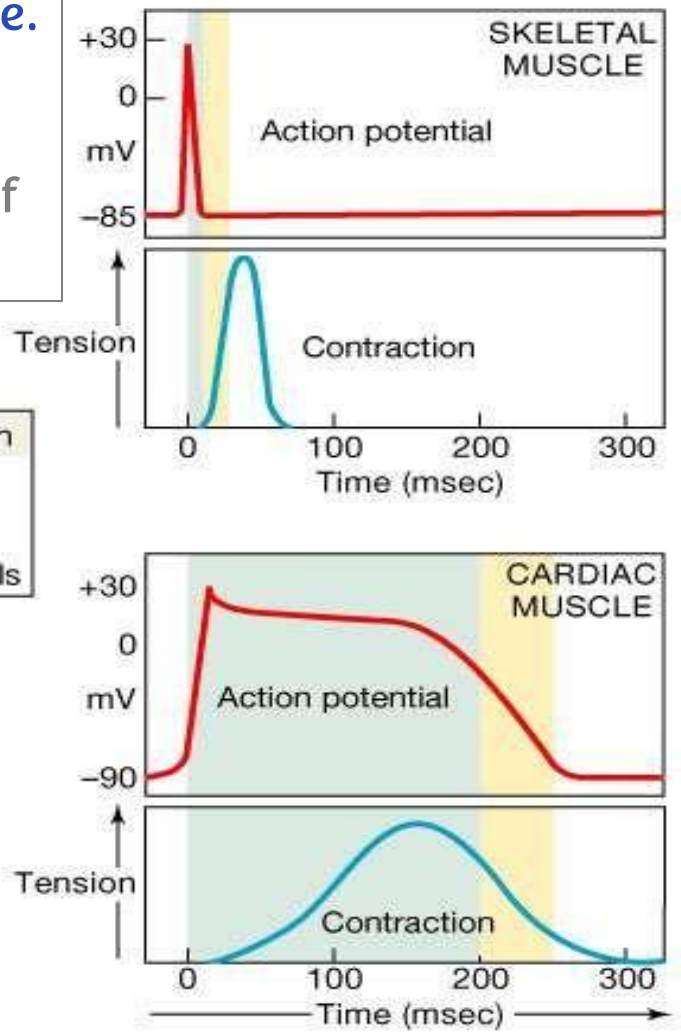
- Therefore, the **decrease in K^+ conductance during Phases 0, 1, and 2** is essential to **maintain the plateau.**
- In **Phase 3**, **K^+ permeability increases again**, allowing repolarization.
- Thus, **K^+ permeability during Phases 0 and 1 is lower than at rest**, while **Ca^{2+} permeability during Phase 2 is very high** to sustain the plateau and support contraction.

The Action Potential in Skeletal and Cardiac Muscle

- Any electrical change should be followed by mechanical change.
- The short absolute refractory period in skeletal muscle fibers allows repeated stimulation, which can lead to tetanus.
- The latent period is the short interval between the application of a stimulus to a muscle and the beginning of contraction.



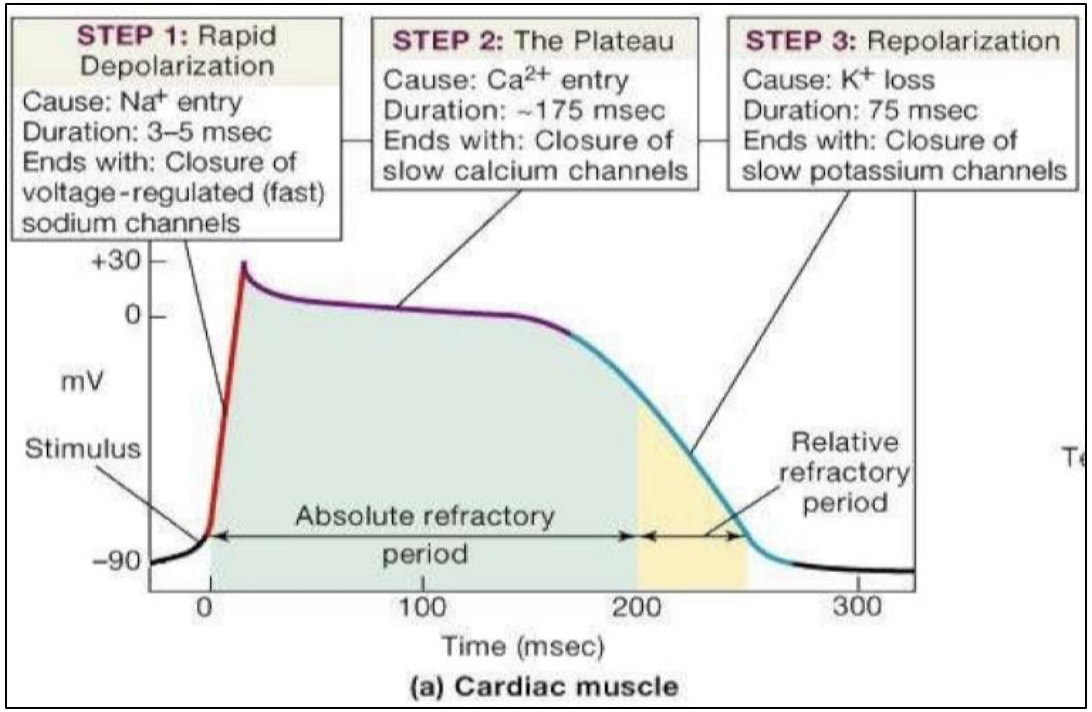
(a) Cardiac muscle



(b)

Cardiac Muscle Action Potential

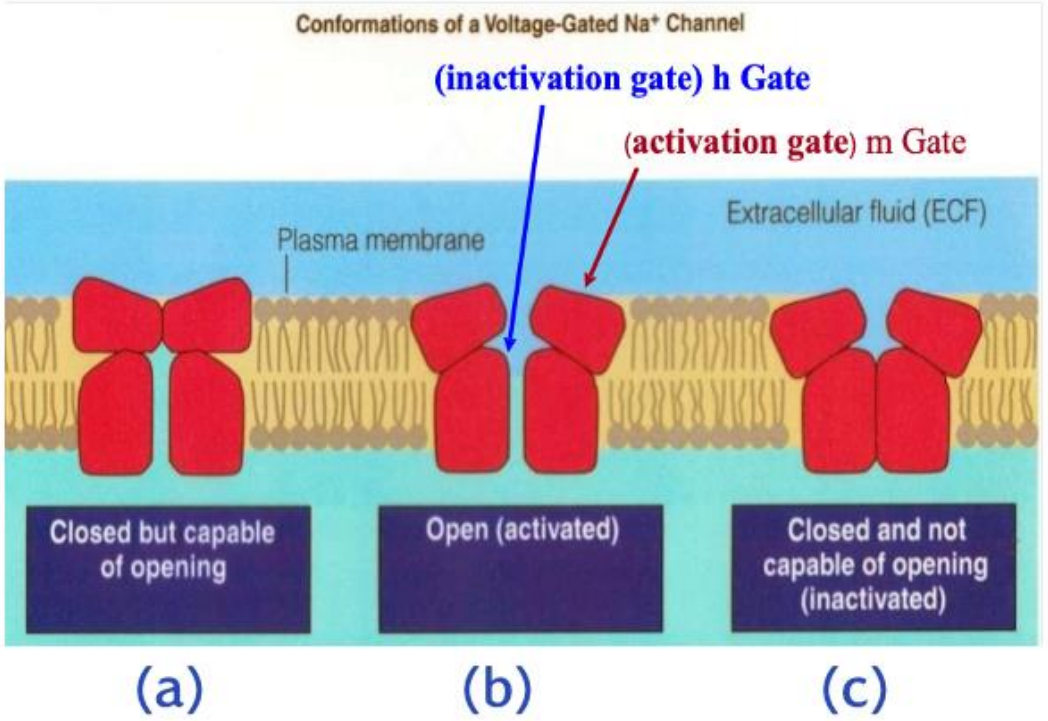
Action potential in cardiac muscles ranges from **200-300 msec** (in comparison to 1-5 msec in skeletal muscle). The **absolute refractory period** (the green area under the curve) is long, therefore, if another action potential were to re-stimulate the muscle, it would have to be in the **relative refractory period** (yellow area under the curve) where the muscle is already relaxed. These long absolute refractory periods ensure that **tetany** does **not** occur in the cardiac muscle .



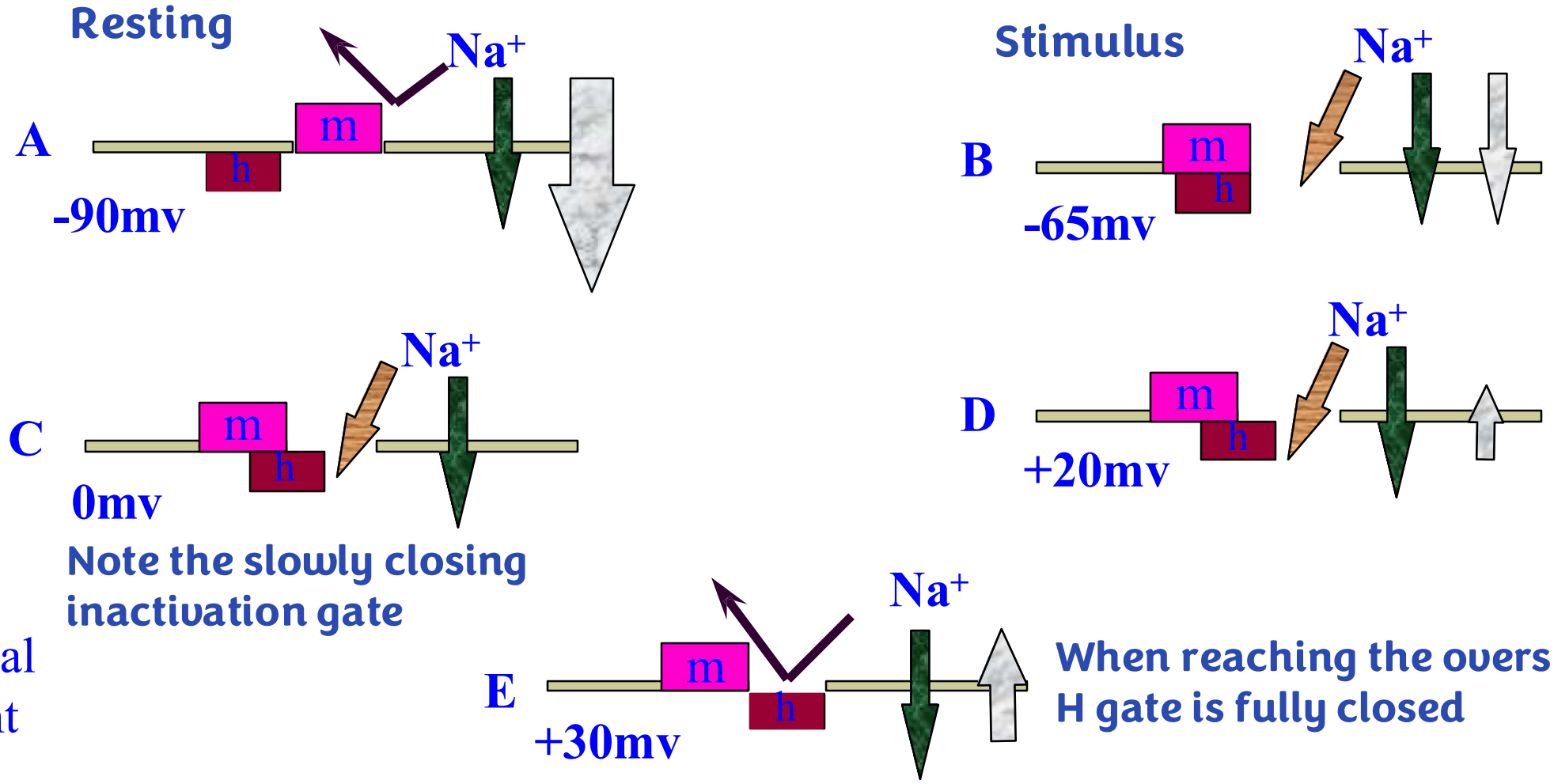
لا إله إلا الله، وحده لا شريك له، له الملك، وله الحمد، وهو على كل شيء قدير

Cardiac Muscle Action Potential

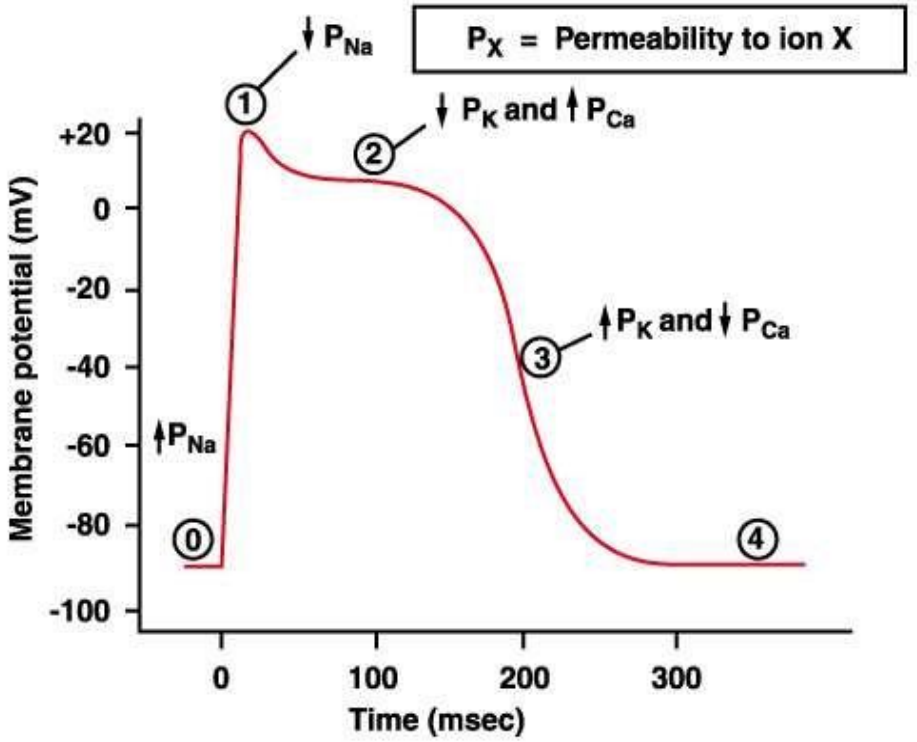
In the sarcolemma, voltage-gated **sodium** channels have **two gates:** the **m gate**, or the **extracellular/activation gate** which is a **rapidly-acting gate**, and the **h gate**, which is the **intracellular/inactivation gate** that is also **slowly-responding**. (a) The **m gate,** is **closed** when the **cell is at rest**, while the **h gate** is **open.** The sodium is thus unable to flow into the cell. (b) When the membrane potential is **depolarized** (less negative) the h gate **closes** and the m gate **opens**. However, due to its slow nature, the h gate will allow for the passage of sodium ions as it closes. Imagine someone slipping in the elevator as its doors close (c) Once the h gate closes, no more sodium ions will be allowed through, even if the m gate is open.



PHASE 0 OF THE FAST FIBER ACTION POTENTIAL



Cardiac Muscle Action Potential-Summary



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

1) transient opening of potassium channels.
2) Calcium channels slowly open.

[] = concentration.

Ca^{2+} in Skeletal Muscle

Action potential occurs in the sarcolemma and then spreads to the t-tubule. Proximal to the t-tubule is the **sarcoplasm reticulum**. The electric transfer, or the **electrostatic transfer**, from the action potential to the sarcoplasm reticulum will open the **calcium, ryanodine receptor (RyR) channels**, which are named so because they are **blocked by ryanodine.** The [Ca^{2+}] in the SR is 10^{-4} or 10^{-5} mmol, while in intracellular plasma it's 10^{-7} mmol, so it effluxes out of the SR. The released Ca^{2+} will bind troponin and cause **contraction**. Consequently, **relaxation** of the muscle occurs when Ca^{2+} returns into the SR via Ca^{2+}-pump which requires ATP as Ca^{2+} is moving against its [gradient] through primary transport.

[] = concentration.

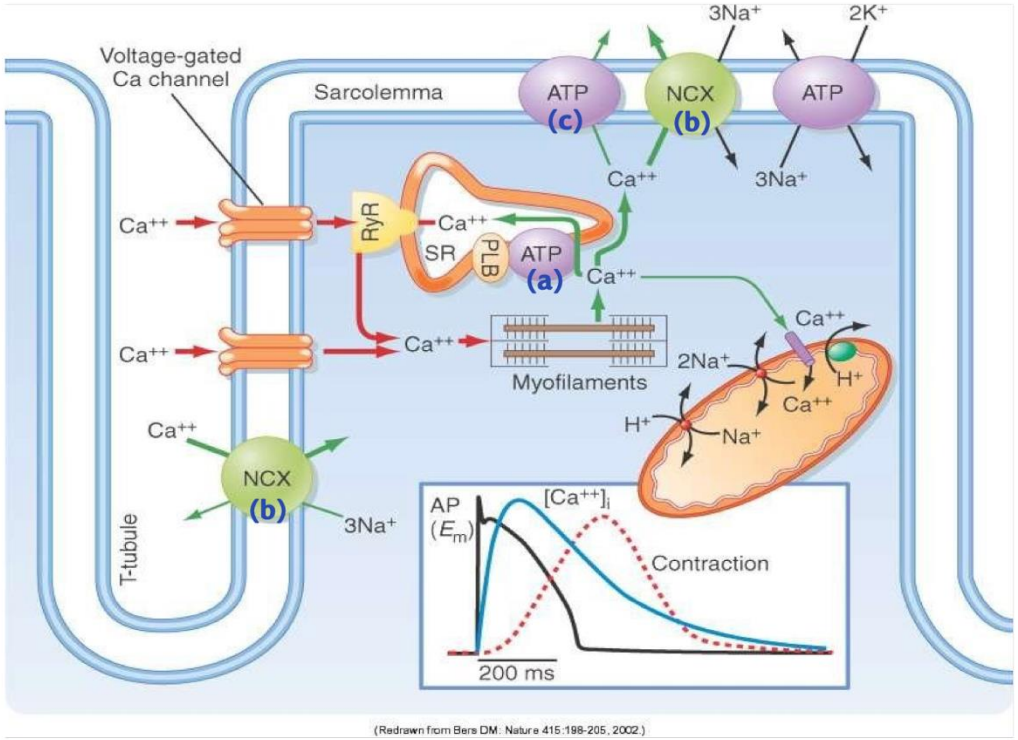
Ca^{2+} in Cardiac Muscle

[Calcium] in the cardiac muscles' SR are much lower than those of the skeletal muscles'. The calcium that enters through the slow Ca^{2+} channel triggers Ca^{2+} release from the SR in a process called **calcium-induced calcium release (CICR)**, which causes contraction. Relaxation in the cardiac muscle is achieved through **three mechanisms:**

A. Through the **calcium pump** in the **SR**, just like skeletal muscle.

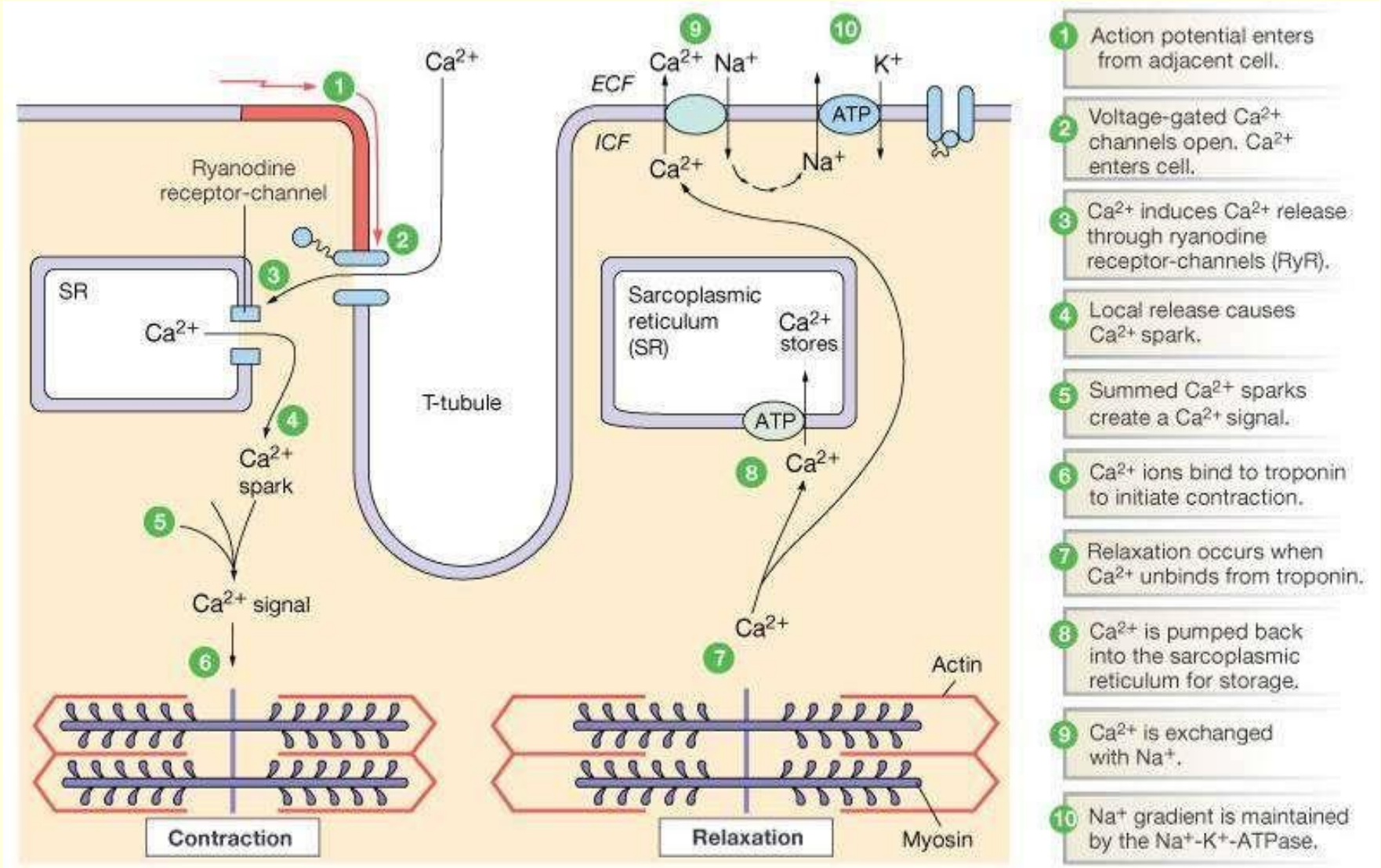
B. The **sodium-calcium exchanger** (NCX), which is a **secondary** active transporter and an **electrogenic** pump, meaning it generates a difference in electrical charge across the membrane. It operates by allowing three Na^+ ions to enter the cell in exchange for the exit of one Ca^{2+} ion.

C. A **calcium pump** present in the **sarcolemma**. The calcium pump in the sarcolemma (SL) has a **high affinity (low K_m), but low capacity (low V_{max}/T_{max})** for calcium, while the sodium-calcium exchanger has a **low affinity (high K_m)** and **a high capacity (high V_{max}/T_{max})** – meaning that a higher intracellular [Ca^{2+}] is required to activate the exchanger. If radioactive calcium was administered, it'd be hard to track individual calcium ions because of their rapid movement and widespread distribution in the cell.



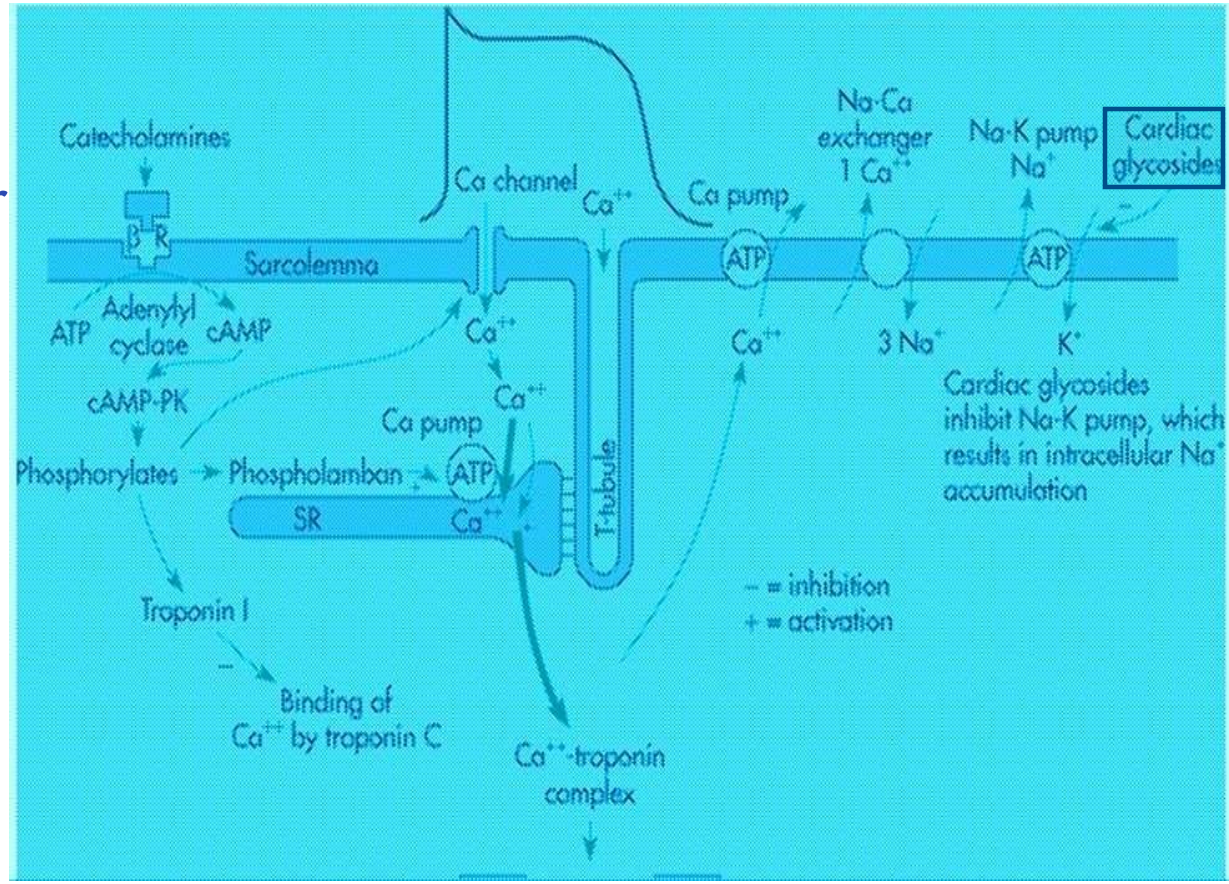
(Redrawn from Bers DM: Nature 415:198-205, 2002.)

Mechanism of Cardiac Muscle Excitation, Contraction & Relaxation



Intracellular Calcium Homeostasis…1

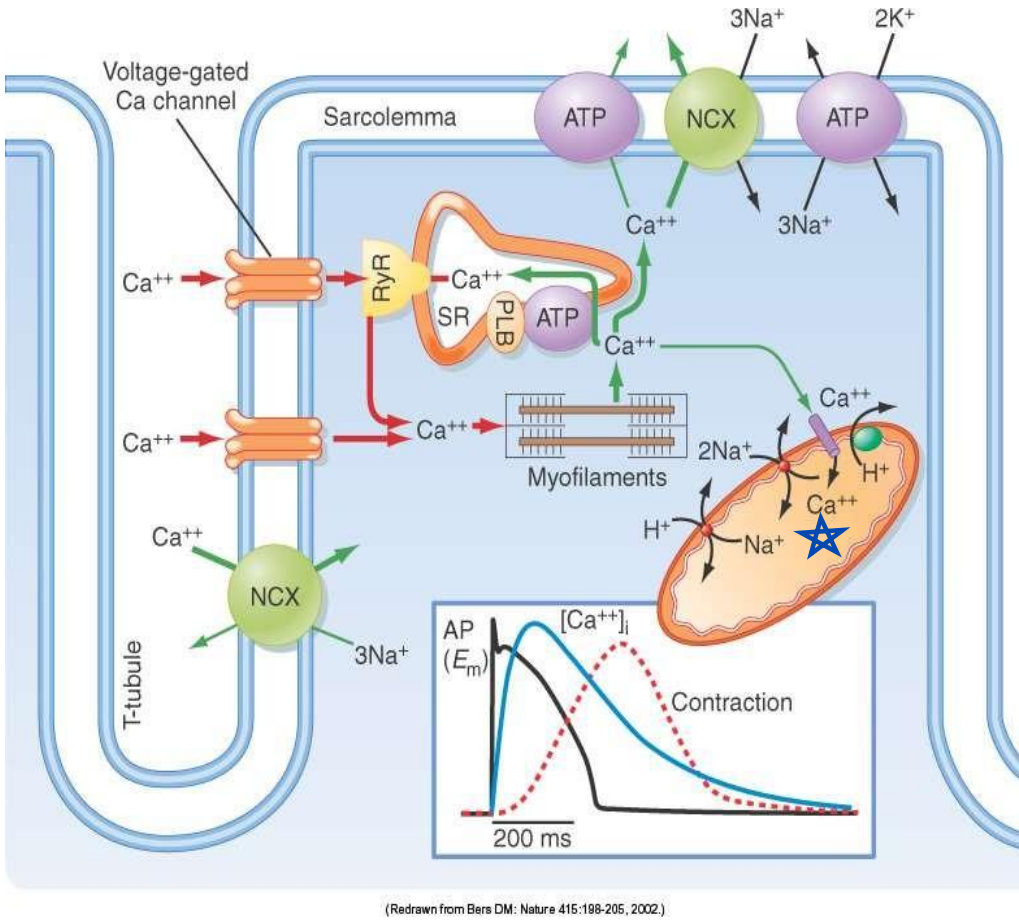
Digoxin (a cardiac glycoside) is a drug administered in very low doses (~0.125 mg or less). It **inhibits the Na^+/K^+-ATPase** which pumps **out** 3 Na^+ in exchange for 2 K^+ using ATP, thereby increasing the intracellular [Na^+]. The NCX is concentration-dependent and relies on the Na+ gradient across the sarcolemma. Normally, NCX extrudes Ca^{2+} from the cell in exchange for Na^+ influx. However, when intracellular [Na^+] increase, the gradient is reduced and the activity of NCX is reversed, allowing Ca^{2+} to enter the cell. The resulting surge in intracellular [Ca2+] enhances its uptake into the SR, so that with each heartbeat, more Ca^{2+} is released during excitation-contraction coupling. leading to stronger cardiac contractions -more calcium → more binding to troponin → more cross-bridges → stronger contractions (+ inotropic effect).



Myocardial Infarction

In **pathological** states, the **mitochondrial** Na^+/Ca^{2+} exchanger (NCX) is activated, but why?

- MI causes increased membrane permeability to calcium due to faulty ion pumps, ATP depletion, and membrane damage. The sarcolemma's sodium/calcium exchanger cannot handle the excess cytosolic [calcium]; consequently, calcium enters the mitochondria through the **mitochondrial calcium uniporter (MCU)**. To prevent mitochondrial calcium overload, the mitochondrial **sodium/calcium exchanger (mitoNCX)** pumps out calcium ions in exchange for sodium. Mitochondrial NCX differs from the sarcolemma's as it is **electroneutral (not electrogenic)**– 1 Ca^{2+} out in exchange for 2 Na^+ in (*no* charge difference), concluding from this, the **Km** of this transport is **very high**.



(Redrawn from Bers DM: Nature 415:198-205, 2002.)

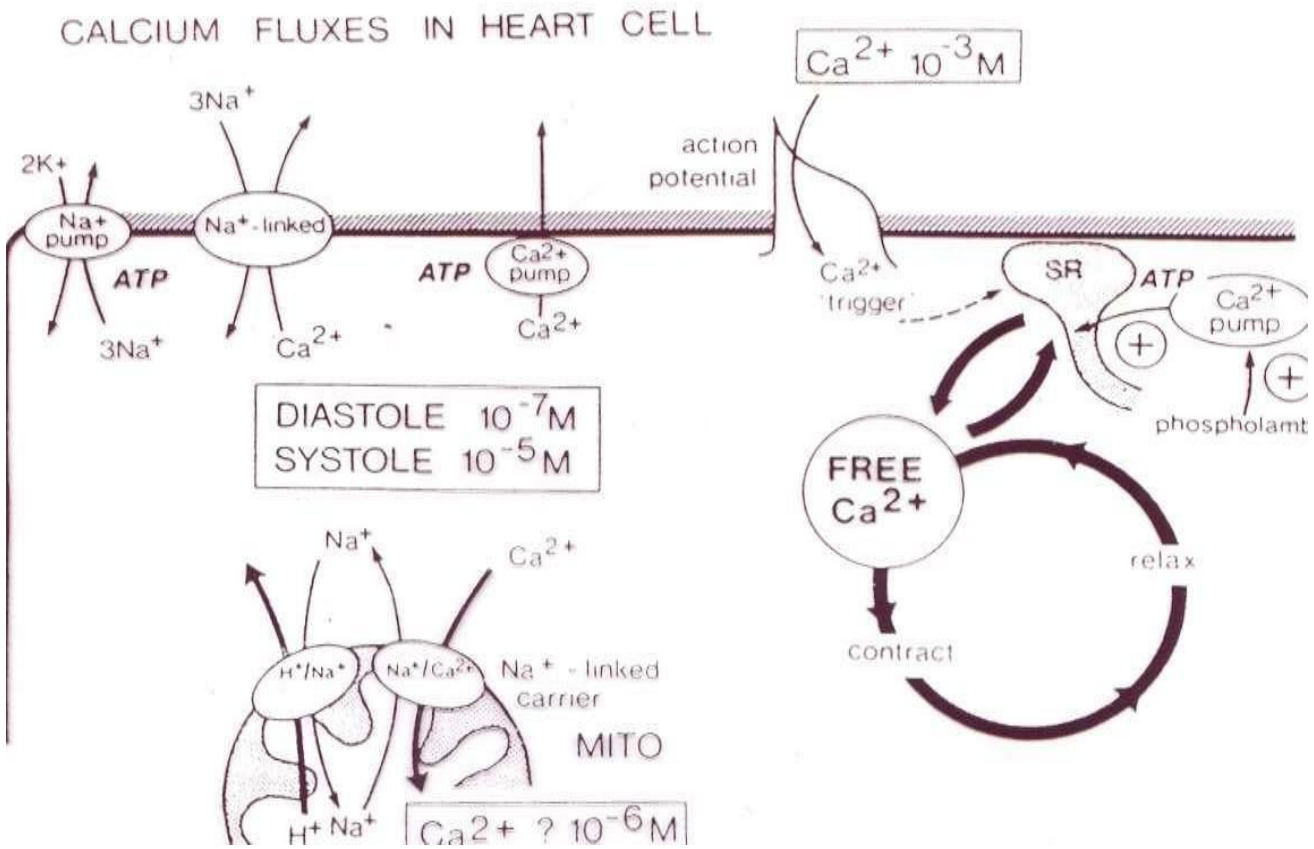
•MCU (inward transporter): low Km → activated at normal Ca^{2+}.
•mitoNCX (outward transporter): high Km → activated only in overload.
This prevents mitochondria from losing Ca^{2+} needed to activate metabolic enzymes and prevents mitochondrial calcium overload.

Intracellular Calcium Homeostasis…2

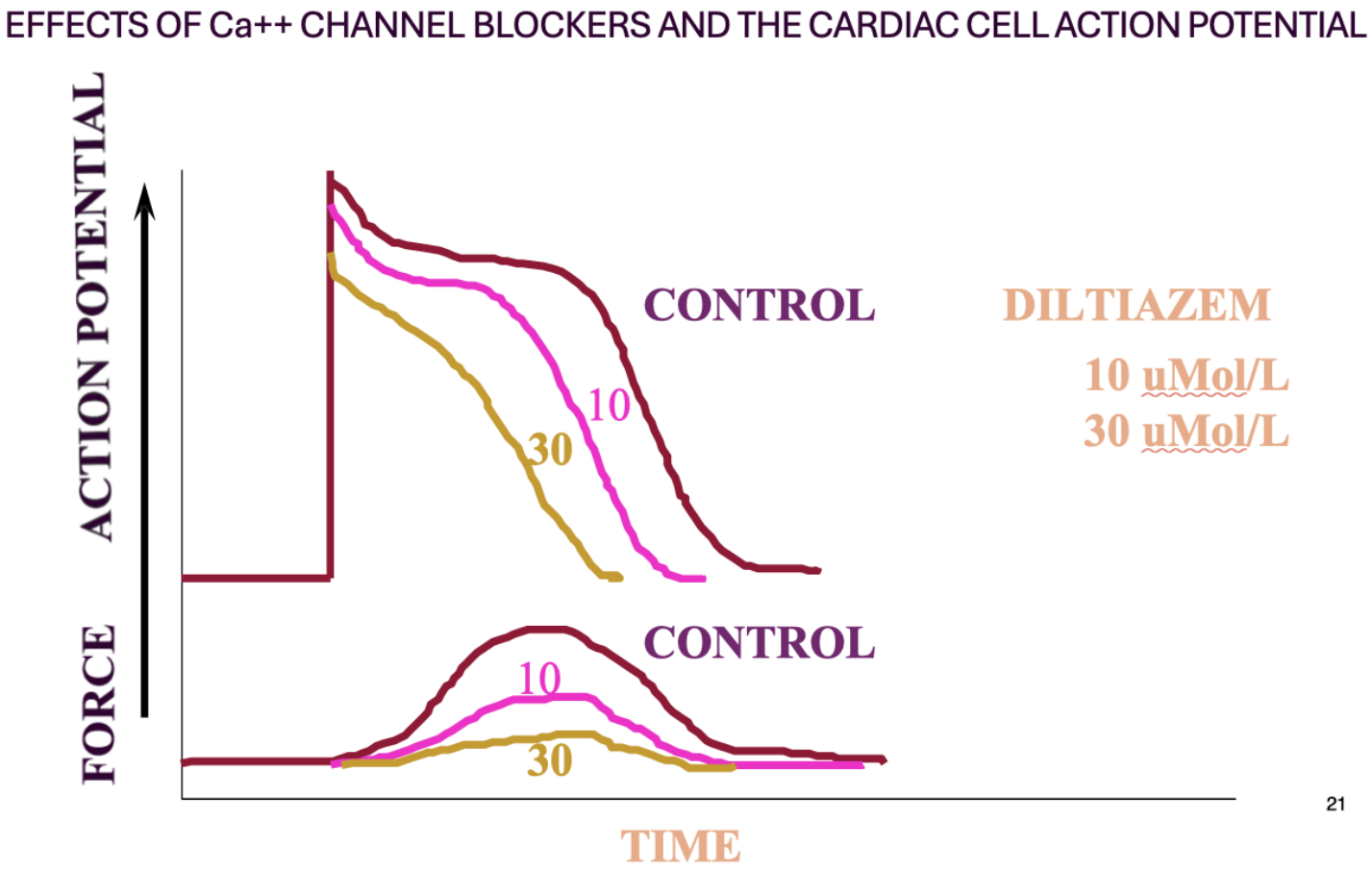
Regarding the heart, the terms contraction and relaxation are replaced by **systole** and **diastole**, respectively.

Intracellular [calcium] during diastole is 10^{-7}, rises to $10^{-4 \text{ or } -5}$ during systole and is 10^{-3} mMol extracellularly.

The **total [calcium]** in plasma is ~2.5 mMol (100 mg/L * 1 mol/40g). 50% of calcium in our body is bound, while the other 50% is free (or **ionized**), this is the fraction that we care about.



Calcium Channel Blockers

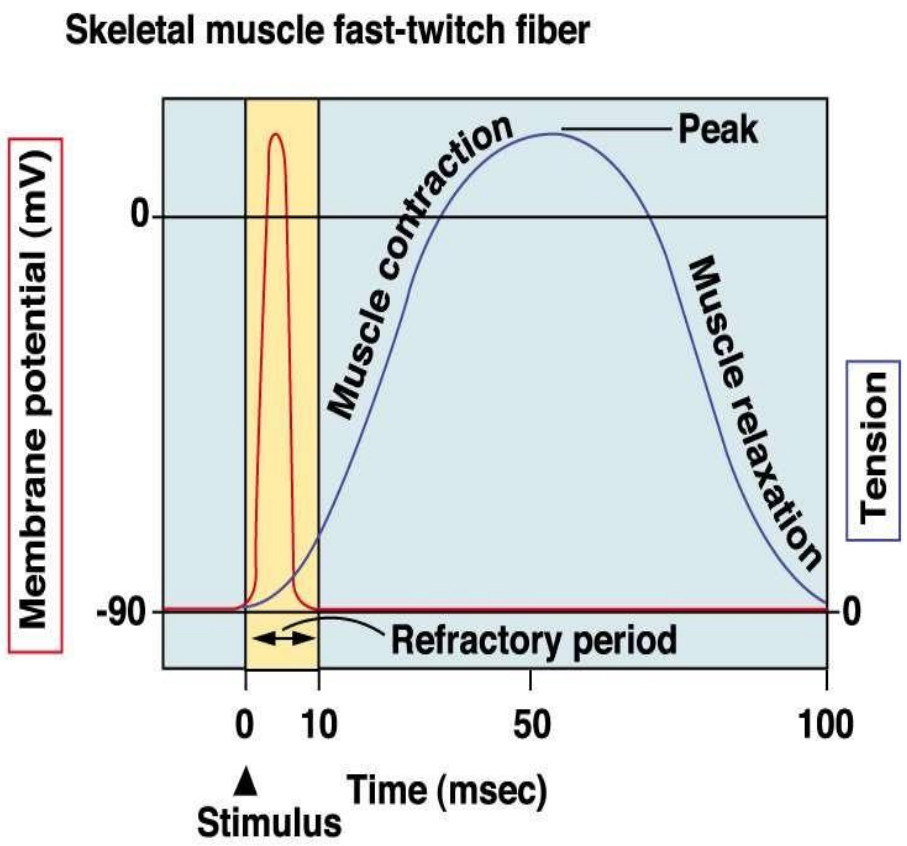


The pink curve represents the 10 µMol concentration, while the gold one represents the 30 µMol/L. You can see that as the dose increases, the APs as well as the force of contraction decrease (dose-dependent effect).

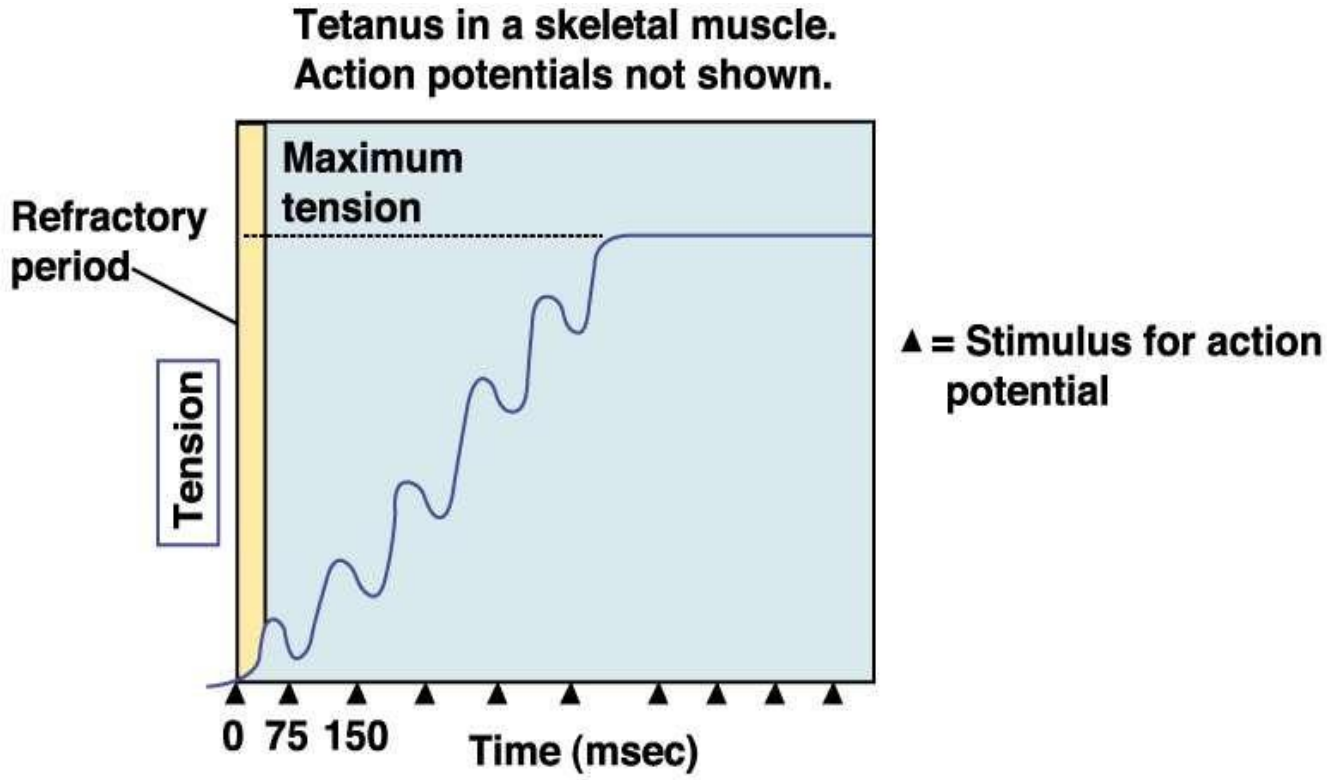
Cardiac Muscle action potential Vs. Skeletal Muscle

- Phase 0 –Depolarization phase (Na^+ influx)
- Phase 1 **partial repolarization** (**Not in skeletal**)
- Phase 2 **Plateau** (depolarization **not in skeletal**) slow calcium channels.
- Phase 3 fast repolarization phase (K^+ efflux)
- Phase 4 resting membrane potential

Skeletal Muscle Action Potential

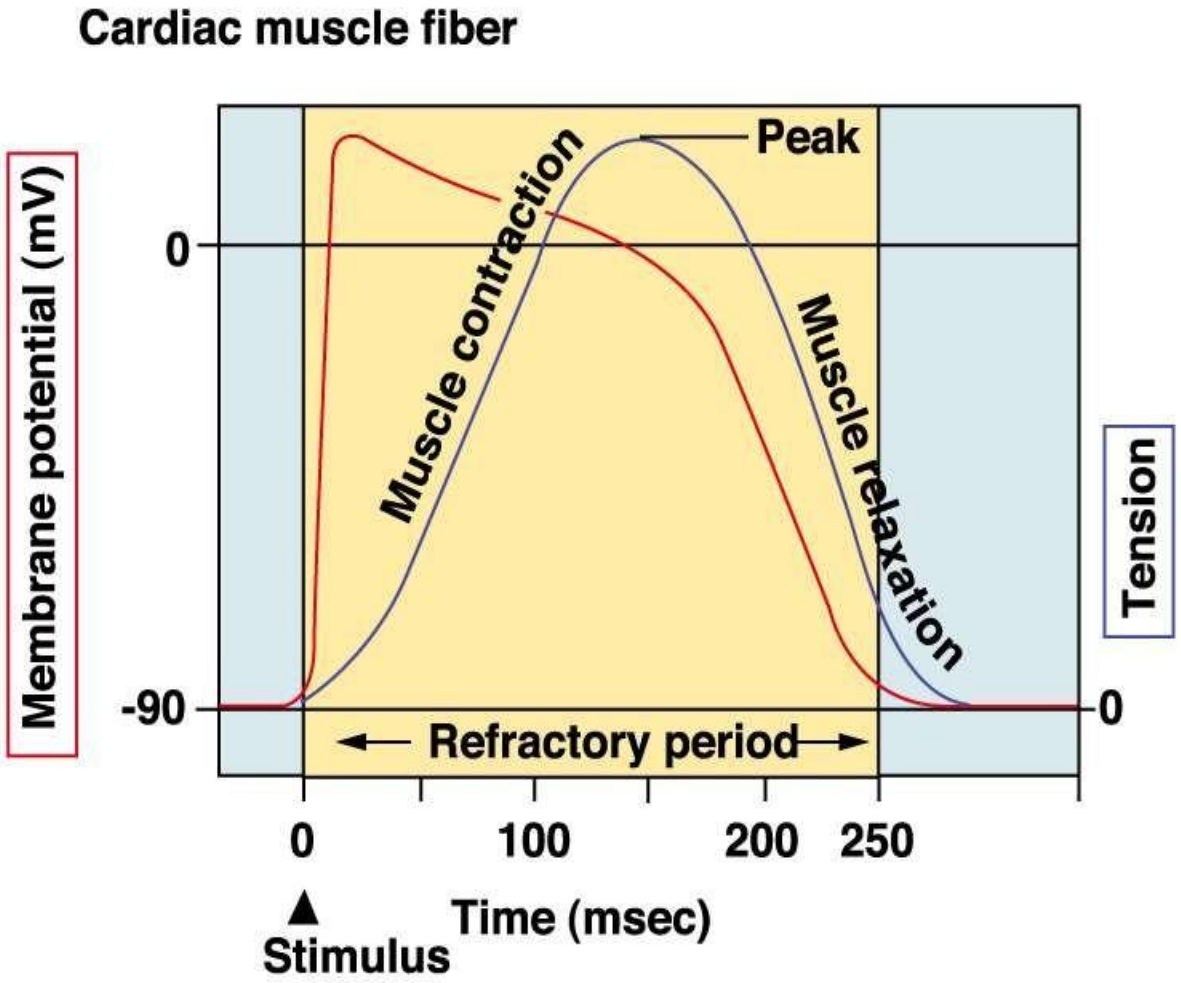


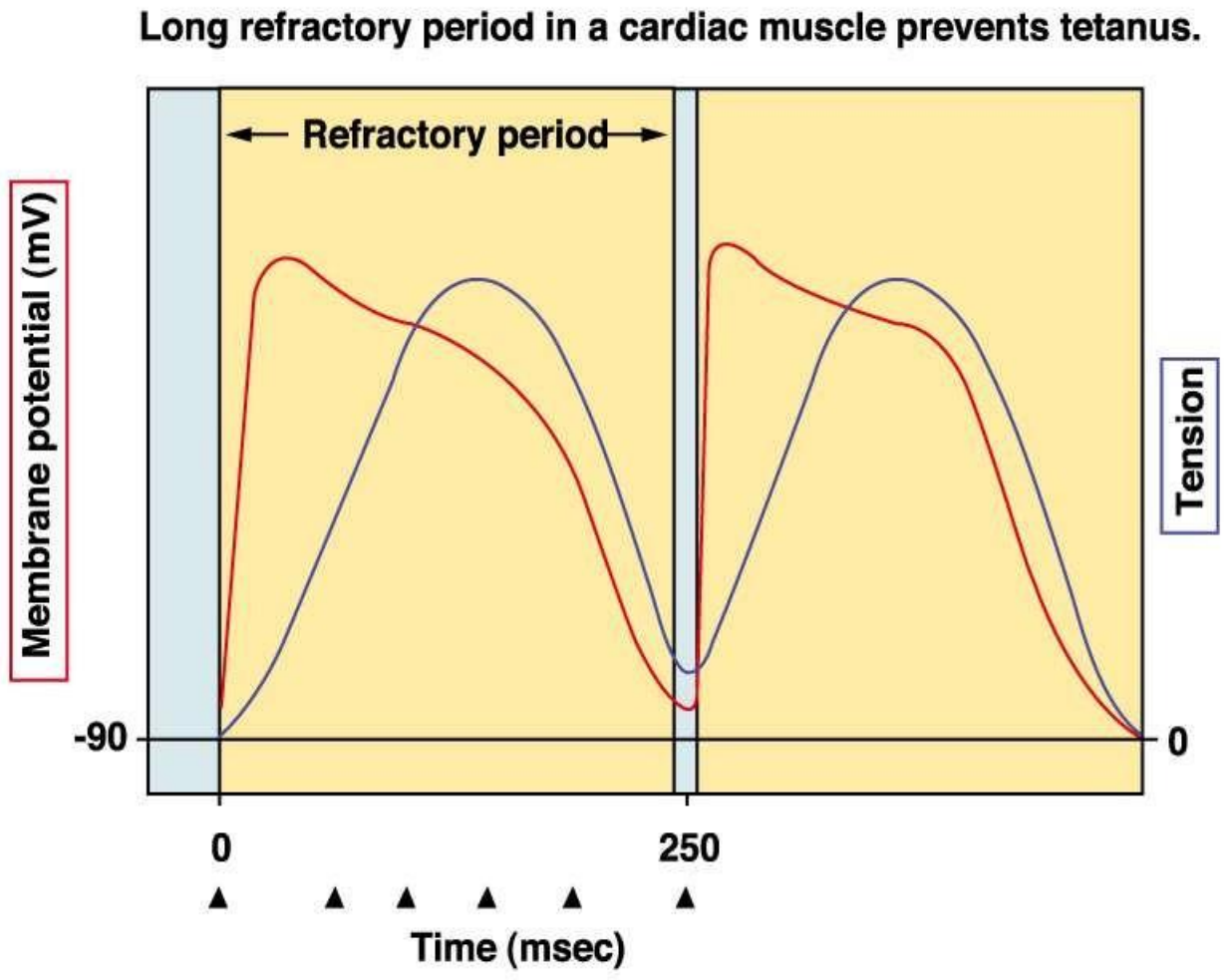
The AP occurs during the latent period. Note the short refractory period.



Multiple closely spaced stimuli → summation → incomplete tetanus → complete tetanus (sustained contraction).

Cardiac Muscle Action Potential





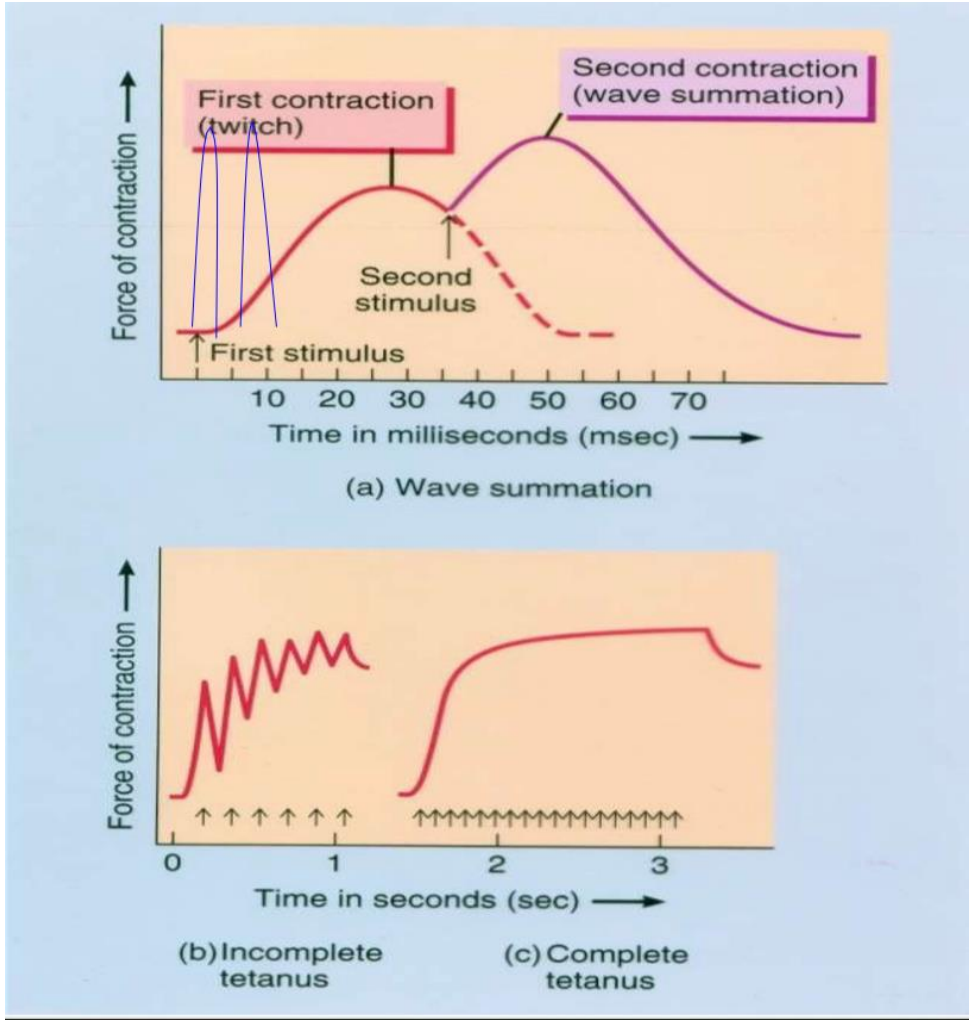
To give a second stimulus after the first one, you should wait until the refractory period ends, by that time, the msucle will be relaxed due to the **long refractory period** of the cardiac muscles.

This is crucial to prevent tetanus is cardiac muscle.

Action Potential

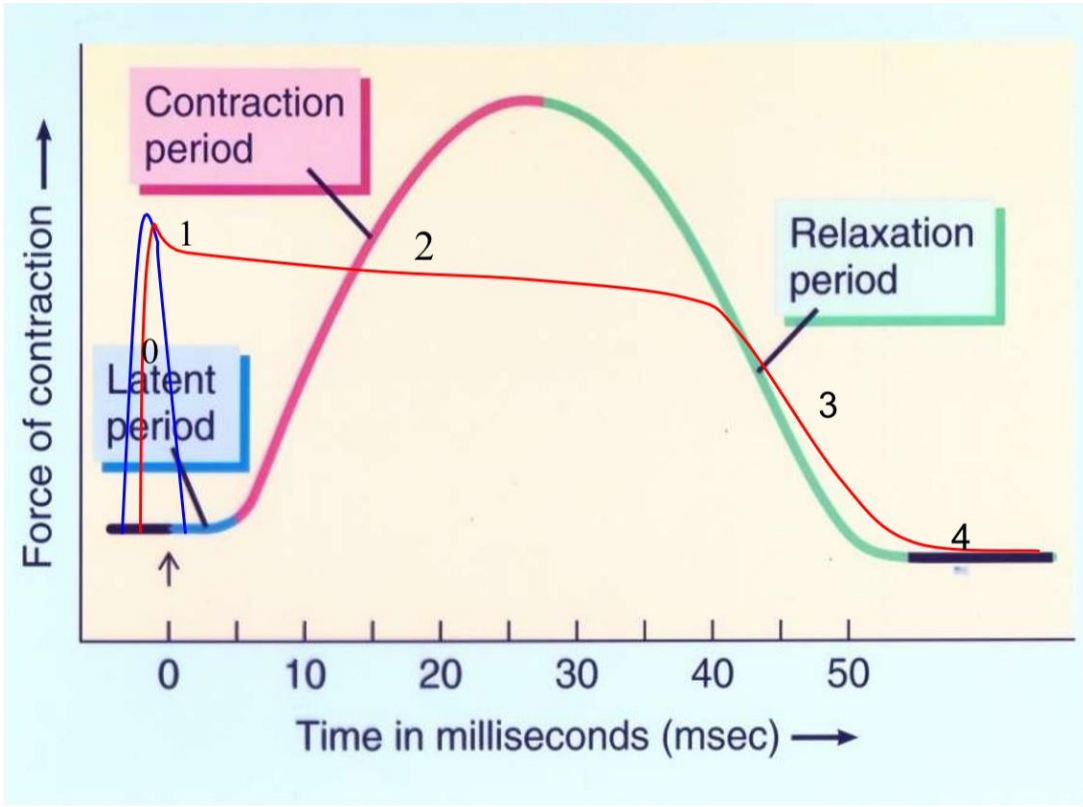
Skeletal Muscle

Multiple stimuli → summation → incomplete tetanus → complete tetanus



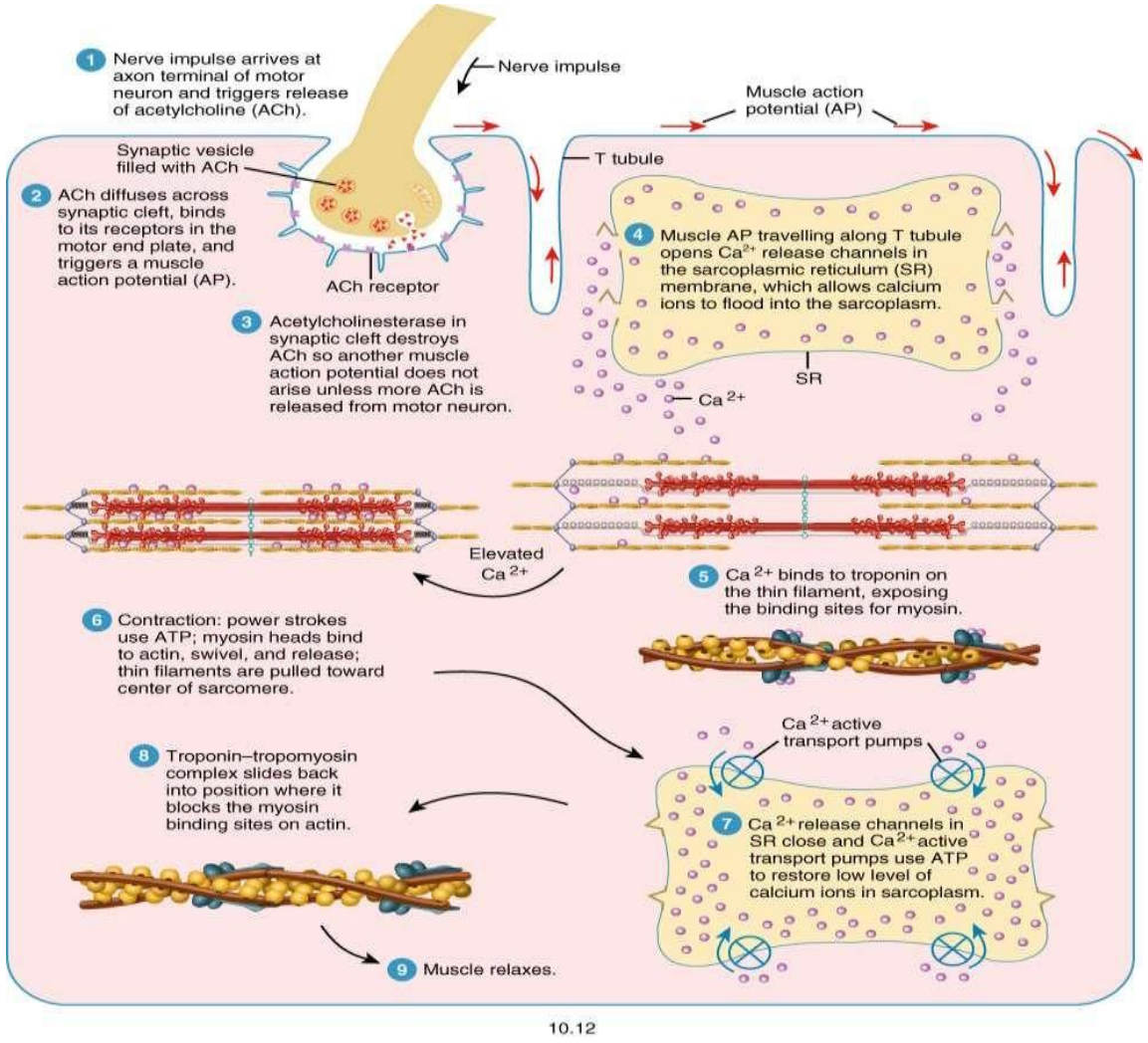
Cardiac Muscle

No summation, no tetanus

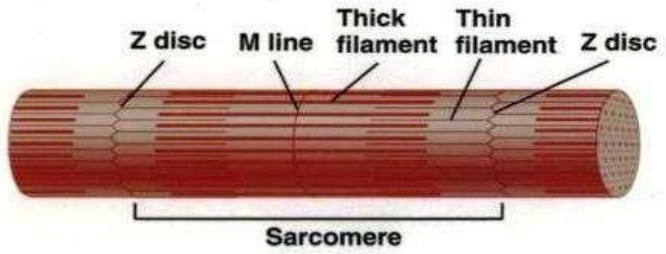


AP in Skeletal Muscle

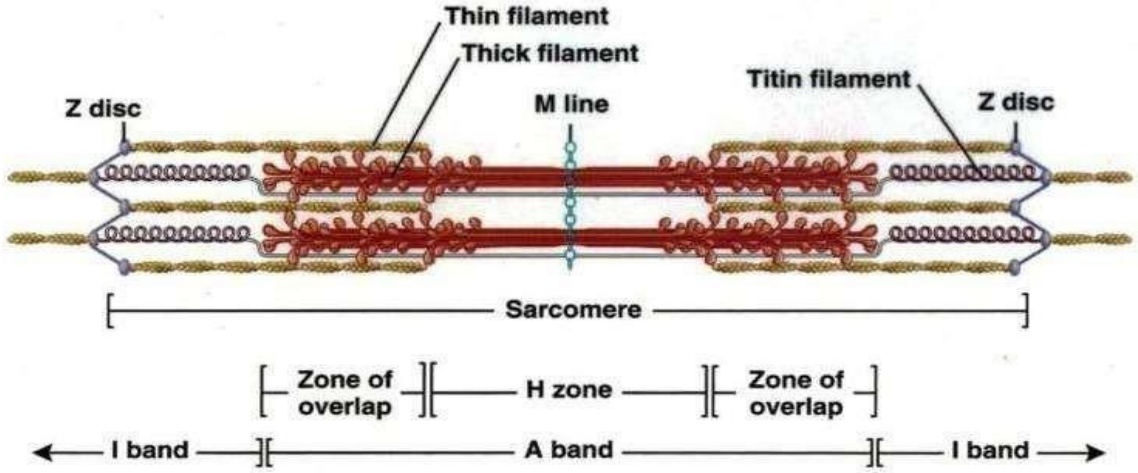
Skeletal muscle requires neural input through a neuromuscular junction for its supply. Thus, if the nerve supply was cut from the skeletal muscles, they will atrophy. This characteristic is absent in cardiac muscle as the heart is intrinsically activated and will contract as long as calcium is present. Calcium will then induce calcium-induced calcium release (CICR).



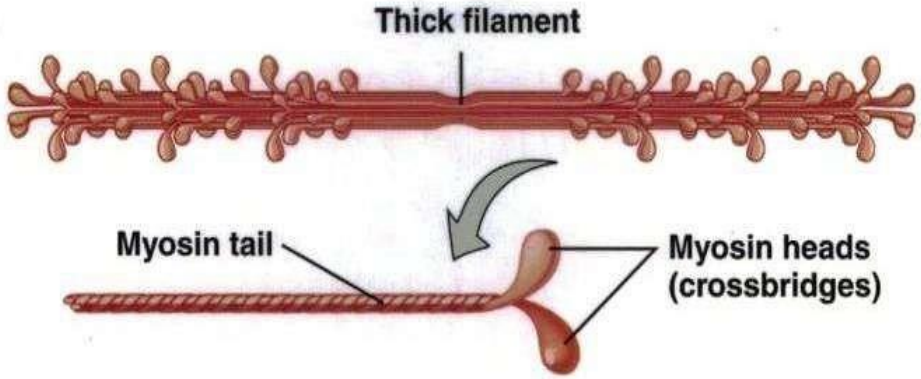
Sarcomere, closely observed



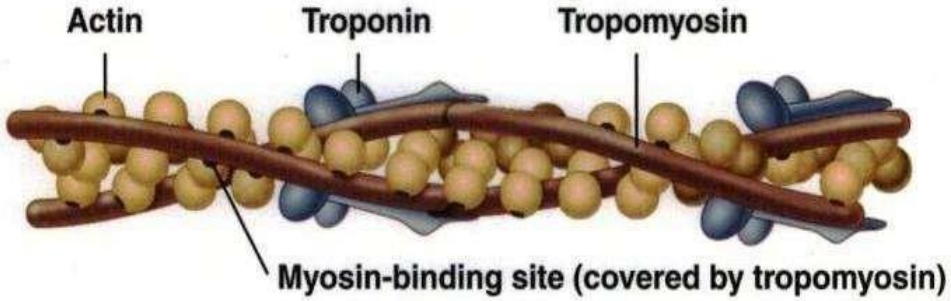
(a) Myofibril



(b) Filaments



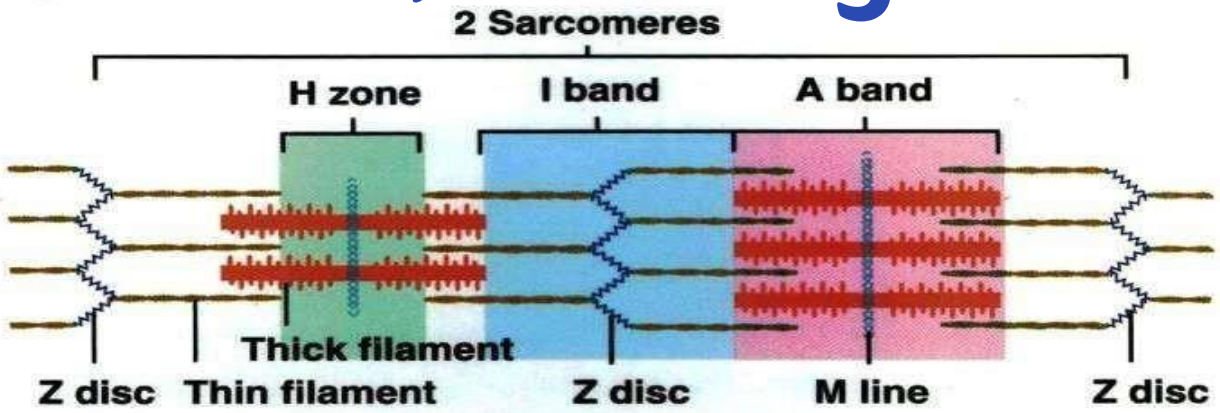
(a) One thick filament (above) and a myosin molecule (below)



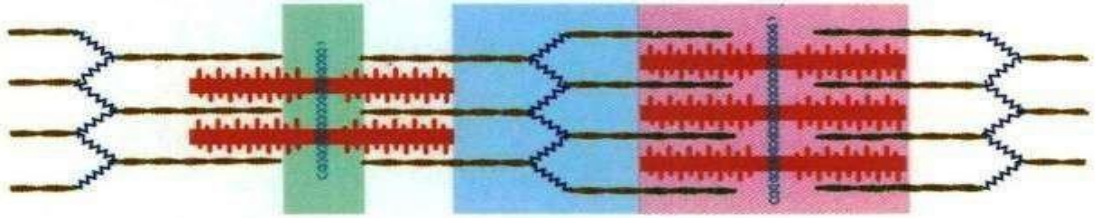
(b) Portion of a thin filament

Notice the spring-like proteins, the **titins**, the are considered "**series elastic elements**".
They are important in the skeletal muscles, unlike the cardiac ones.
It will be better discussed in the coming lectures.

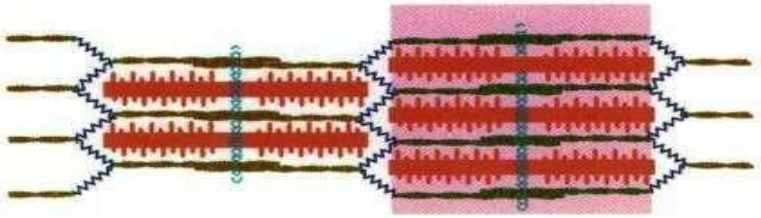
Sarcomere, closely observed



(a) Relaxed muscle

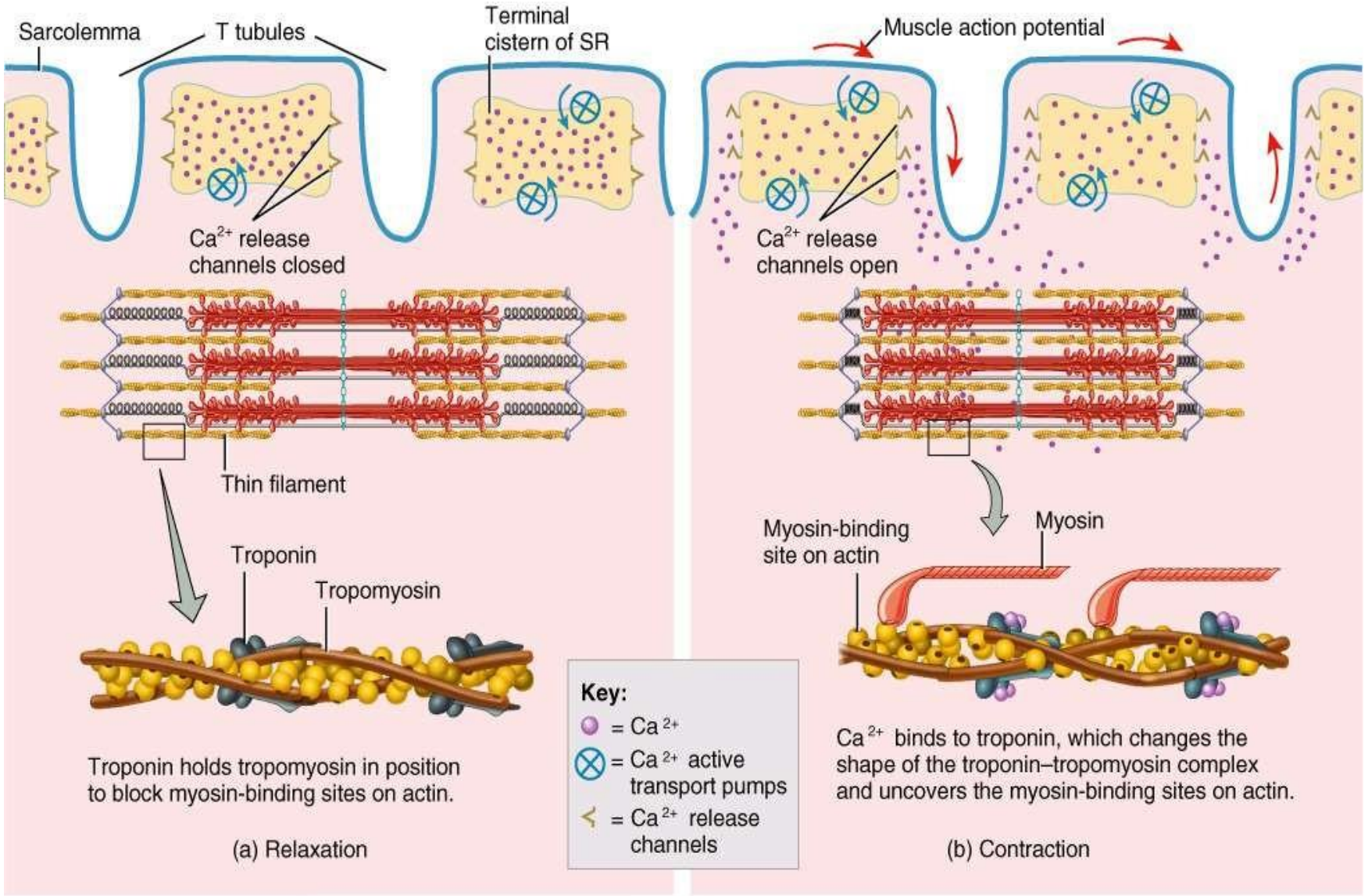


(b) Partially contracted muscle



(c) Maximally contracted muscle

Sarcomere, closely observed



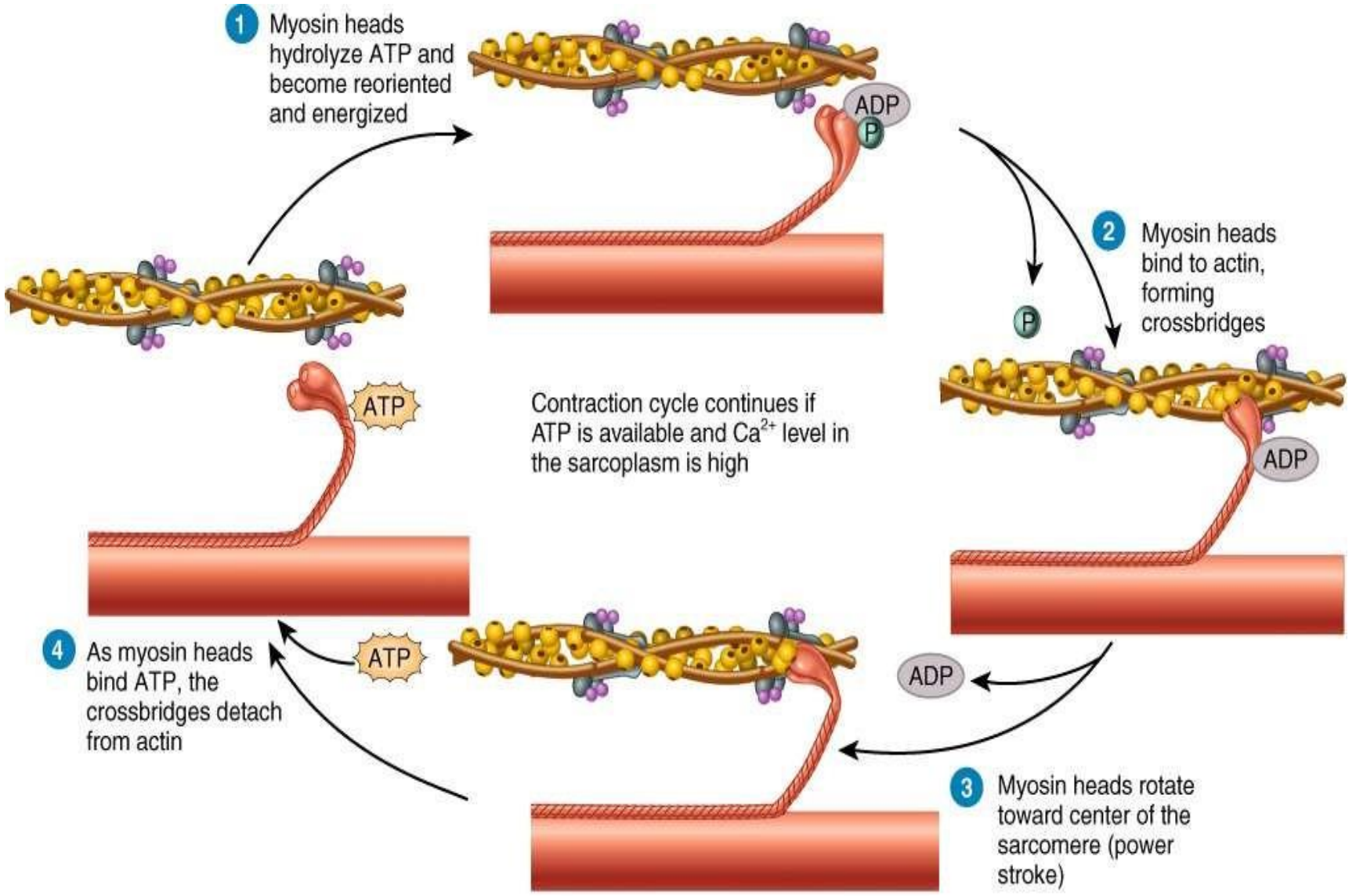
10.09

Cardiac Muscle contraction Vs. Skeletal Muscle

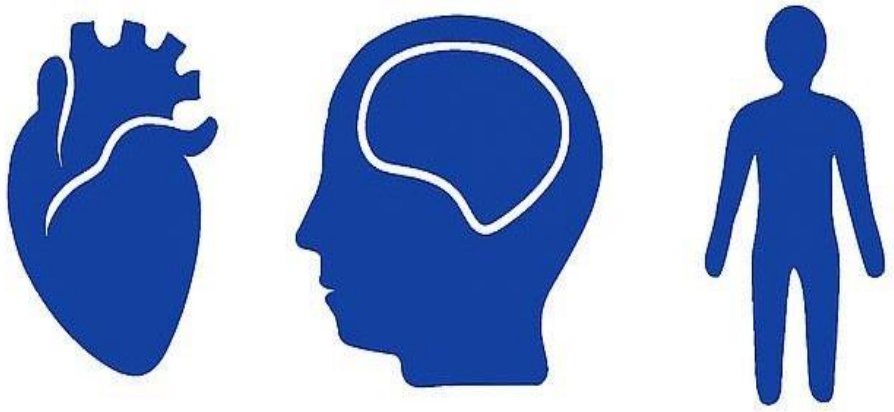
- Sliding filament hypothesis
- No tetany (Long refractory period because of plateau)
- Fatty acids main source of energy unlike skeletal muscle (Anaerobic and Aerobic)
- Attachment and detachment cycle and ATP dependence is the same

Will be better discussed in the next lectures

Notice the muscle's requirement for **ATP** to both attach and detach myosin heads during contraction; this importance is clearly demonstrated in **rigor mortis**, when the absence of ATP after death prevents detachment, causing sustained muscle stiffness.



10.08



PHYSIOLOGY QUIZ LECTURE 2

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	20, last line 31 36, line 7 36, the last line 36 Quiz	The nernst equation doesn't include a "–" sign, the gray note indicates which sign should be used. 1) Transient… calcium Cystolic [calcium] Km is very low Not done yet	The "–" has been added and the gray note had been removed to avoid confusion. 1) Transient… potassium Cytosolic [calcium] Km is very high Extra note is added in grey Done.
V1 → V2			