Subject | Physiology
Done by | Tala Saleh
Corrected by | Rand Abu Anzeh
Doctor | Faisal

Layers of The Heart

1- Pericardium:

The heart is enclosed within the pericardium fixing it in the mediastinum. It is a double-walled sac containing the heart and the roots of the great vessels. The pericardial sac has **two** layers:

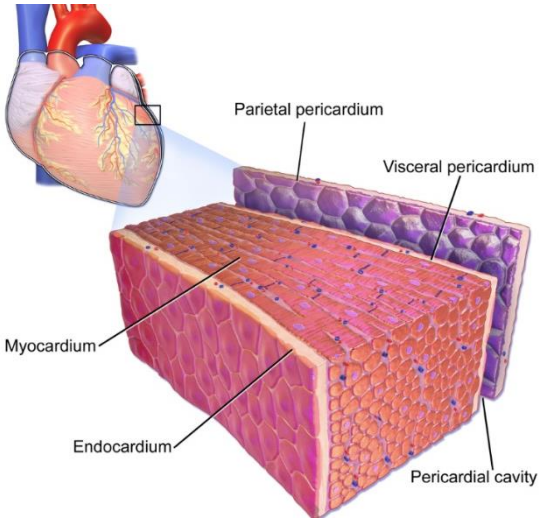
1- **The fibrous layer:** the most superficial layer which acts to protect the heart and anchors it.
2- **The serous layer:** functions in lubricating the heart to prevent friction during heart activity. It is divided into two layers:
   - **a- Parietal layer**, which is fused to the fibrous layer.
   - **b- Visceral layer** (epicardium), which is in contact with the myocardium.

⇨ In between the parietal and visceral layers, there is a potential space called the **pericardial cavity**, which contains the **pericardial fluid** which acts as a **shock absorber**.

Abnormal accumulation of fluid in the pericardial cavity is a pathological case called '**pericardium effusion**'. A pericardial effusion with enough pressure to adversely affect heart function is called **cardiac tamponade**. In this case, the fluid is drained through a needle to restore normal conditions temporarily until treating the underlying cause.

2- Myocardium:

It is the **middle** layer of the heart wall. It is composed of cardiac **muscle fibers**, which enable heart **contractions**. The myocardium is the **thickest** layer of the heart wall.



3- Endocardium:

It is the **thin** inner layer of the heart wall. This layer lines the inner heart chambers, covers heart valves, and is continuous with the endothelium of large blood vessels.

It is made up of endothelial cells that produce substances **regulating** the myocardial function affecting contractility and blood flow. For example, Nitric Oxide (NO) is an endothelium-derived relaxing factor.

Cardiac Muscle: Myocardium

The myocardium is an **involuntary**, striated muscle, and located between the epicardium (visceral pericardium) and endocardium.

It **differs** from the skeletal muscles in:

1- The skeletal cells are **spindle** in shape, while the myocardial cells are **rectangular** in shape.

2- Myocardium has a **syncytium** structure 'discussed later'.

3- Skeletal muscles do not have any cell-cell junctions, whereas cardiac muscle cells contain **gap junctions** and desmosomes at the intercalated discs.

➔ Desmosomes stop separation during contraction, while gap junctions transmit action potentials.

4- In contrast to skeletal muscle, the myocardium cells are **rich** in mitochondria but **low** in nuclei. In the cardiac muscle, there is a lot of oxidative phosphorylation needed to provide energy which explains the large amounts of mitochondria.

5- Poorly developed sarcoplasmic reticulum in the cardiac muscle compared to the skeletal muscle indicates that skeletal muscle stores enough calcium, while in cardiac muscle it is not enough and accordingly it takes calcium from the extracellular fluid.

6- Cardiac muscle contains **one** T-tubule per sarcomere at the **Z-line**. Skeletal muscles contain 2 T-tubules.

7- **T-tubules** in the cardiac muscle are **wider** and **shorter** compared to them in the skeletal muscle.

8- There is **no tetany** in the cardiac muscle 'discussed later'.

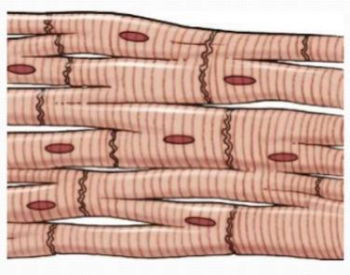
9- **Fatty acids** are the main source of energy for contraction in the myocardium.

Gap Junctions

- Gap junctions are hexagonal proteins that are **voltage-sensitive**. They allow action potentials to spread between cardiac cells by permitting the passage of ions between cells.
- They are called **'electrical couplers'** as they provide low electrical resistance areas between the myocardium cells, thereby increasing their electrical coupling to adjacent cells allowing **coordinated** contractility.
- The **loss** of the coordinated contraction of the ventricular myocardium causes **Ventricular Fibrillation**, which requires defibrillation through a DC shock *(direct-current shock)*.

Cardiac Syncytium

- It is a network of cardiac cells connected to each other by **intercalated discs** that enable the rapid transmission of electrical impulses, enabling the syncytium to act in a **coordinated** contraction of the myocardium as **a single unit**.
- The heart contains 2 syncytia: **Atrial** and **Ventricular** Syncytium.



Action Potential in The Cardiac Muscle

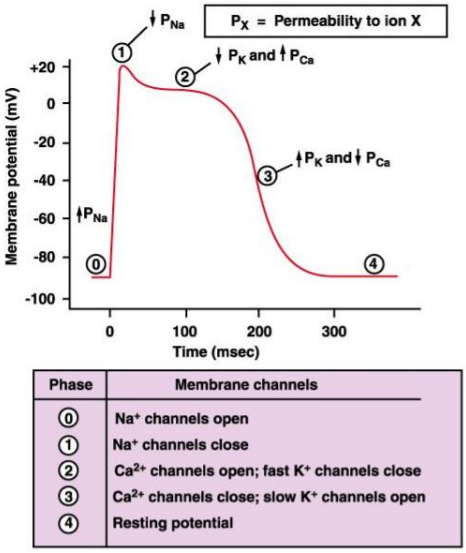
- As we took before, in skeletal muscle the resting membrane potential is -70 mV. **Depolarization** takes place caused by **Na^+ influx**, followed by **repolarization** caused by **K^+ efflux**.

  As for cardiac muscle, the resting membrane potential is **more negative**, around **-90 mV**. The action potential has 5 phases:

Phase 0 (depolarization): *fast Na^+ channels open*

When the cardiac cell is **stimulated**, voltage-gated sodium channels *(fast sodium channels)* **open** and permit sodium to rapidly flow into the cell depolarizing it.

⇨ High conductance of Na+ with decreased permeability of K^+.



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

Phase 1 (initial repolarization): *fast Na^+ channels close*

Na^+ channels **close**, the cell begins to repolarize, and **K^+** leave the cells through **open** K^+ channels.

Phase 2 (plateau): *Ca^{+2} channels open and K^+ channels close:*

After the brief initial repolarization, **decreased K^+** permeability *(decreased efflux)* and **increased Ca^{+2}** permeability *(increased influx)* causes the action potential to **plateau**.

Note: **Ca^{+2}** ions are important for the plateau.

Phase 3 (rapid repolarization): *Ca^{+2} channels close and K^+ channels open*

The **closure** of **Ca^{+2}** channels and **increased K^+** permeability, permitting K^+ to rapidly exit the cell, **end** the plateau and returns the cell membrane potential to its **resting** level.

Phase 4 (resting membrane potential): averages about -90 mV.

Ion gates conformational changes during action potential:

- The 3 typical voltage-gated channels in an action potential are:

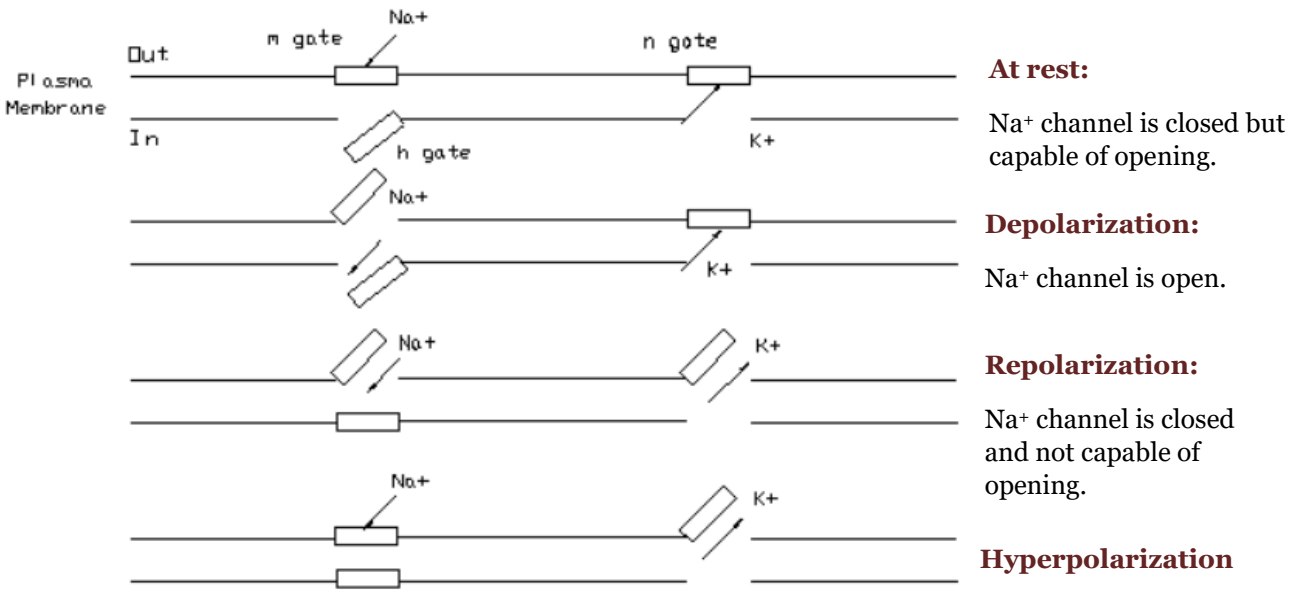
  1- M gate (activation gate): controls Na+ channel opening (extracellular gate).

  2- H gate (inactivation gate): controls Na+ channel closing (intracellular gate).

  3- N gate: controls K+ channel opening.

- The **M gate** acts **very fast** while the **H gate** is **slow**. As the membrane potential becomes **less negative**, the M gate opens and the H gate closes **after** a while; since its slower.

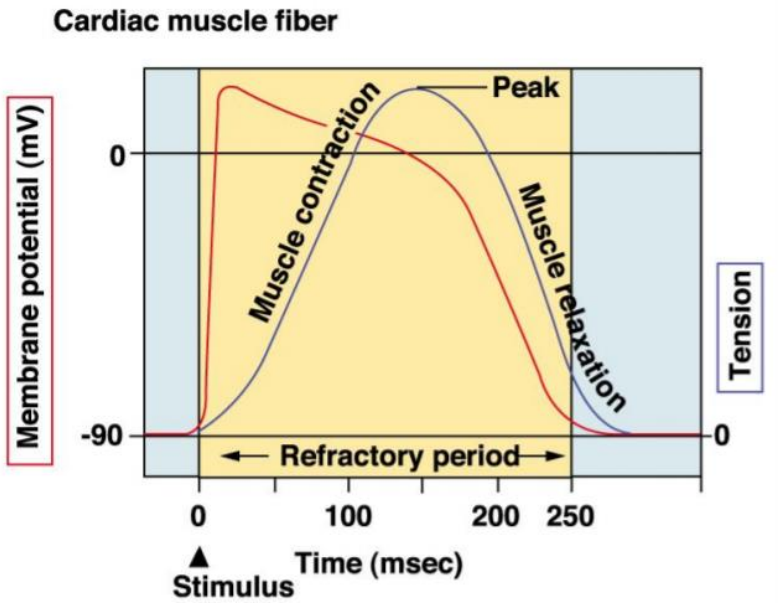
- This image is a simple presentation of the ion channels during 4 stages of action potential:



The refractory period in cardiac muscle:

The cardiac muscle has a **long refractory period** given the presence of a **plateau**. During this period, the membrane is refractory (resistant) to further stimulation until the contraction is over.

Notice the length of the refractory period in the picture and how it ends near complete relaxation:



In skeletal muscles, the refractory period ends earlier permitting 'Tetanus'. The refractory period in the cardiac muscle is **longer** than in the skeletal muscle **preventing** tetanus. This is important to:

1- Give time to the heart to relax after each contraction preventing fatigue.

2- Allow the heart chambers to fill during diastole before the next contraction.

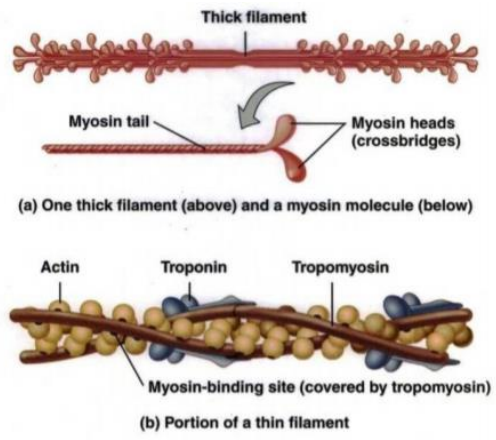
Mechanism of Cardiac Muscle Contraction

- The mechanism by which calcium concentrations within the cytosol rise differ between skeletal and cardiac muscle.
- In cardiac muscle, the action potential comprises an inward flow of both Na^{+} and Ca^{+2} ions. The flow of Na^{+} is **rapid** but very **short-lived**, while the flow of Ca^{+2} is **sustained** and gives the **plateau** phase of cardiac muscle action potentials.
- The small flow of **extracellular** Ca^{+2} triggers a larger release of Ca^{+2} from the **sarcoplasmic reticulum** in a phenomenon known as 'calcium-induced calcium release'.
- In contrast, in skeletal muscle, minimal Ca^{+2} flows from the endoplasmic reticulum **only**. This difference can be attributed to the fact that cardiac muscle fibers require high concentrations of Ca^{+2} in order to contract, while skeletal muscle fibers will contract without extracellular Ca^{+2}.

During Contraction:

- During contraction of a cardiac muscle cell, the protein myofilaments bind forming **crossbridges** to slide over each other allowing contraction. There are thick 'myosin' and thin 'actin' myofilaments:

a- **Troponin** is a complex attached to the protein **tropomyosin** which are both components of the **thin** actin filament. In a relaxed muscle, tropomyosin **blocks** the attachment site for myosin blocking crossbridges formation, thus **preventing** contraction.



b- When the muscle cell is **stimulated** by an action potential to contract, Ca^{+2} channels open in the sarcoplasmic membrane and release Ca^{+2} into the sarcoplasm. Calcium ions attach to **troponin** which moves tropomyosin **away** from the myosin-binding sites on actin exposing them. Myosin then binds to actin pulling it towards the M-line using ATP through "power strokes", shortening the sarcomere where then contraction of the muscle begins.

During Relaxation:

- Relaxation occurs when calcium is **pumped back** to its storage site by three mechanisms:

1- Ca+2 ATPases (Ca^{+2} pumps on the sarcoplasmic reticulum membrane):

They are **intracellular** pumps located in the sarcoplasmic or endoplasmic reticula of muscle cells. They **translocate** Ca^{+2} from the **cytosol** to the **sarcoplasmic** reticulum lumen, sequestrating calcium ions. They are regulated by a protein called **phospholamban** *(located on the sarcoplasmic reticulum membrane).*

a- Phospholamban in the **dephosphorylated** state is an **inhibitor** of Ca^{+2} ATPases.

b- Phospholamban in the **phosphorylated** state **activates** Ca^{+2} ATPase and enhances its efficiency in moving Ca^{+2} to SR inducing relaxation.

Phospholamban can get phosphorylated through:

- Protein Kinase A: **cAMP** dependent protein kinase.
- Protein Kinase B: **Ca^{+2} - Calmodulin** dependent protein kinase.
- Protein Kinase C: **Ca^{+2}- phospholipid** dependent protein kinase.

⇨ The overall effect of **phospholamban** is to **sequester** calcium ions into the SR by **activating** Ca^{+2} ATPase; this **increases** the rate of **relaxation** (increasing heart rate). Also, sequestering the calcium ions **increases** their concentration for **subsequent** beats; thus, increasing the **inotropic effect** (force of contraction).

2- Na+ / Ca+2 exchanger (on the sarcolemma):

It exchanges **one Ca^{+2}** ion for **three Na^{+}** ions **reducing** intracellular Ca^{+2} concentration. It is an electrogenic pump which means that it leads to the accumulation of charges across the plasma membrane "sarcolemma".

Some drugs **block** Na^{+} / Ca^{+2} exchanger, producing an **inotropic effect**, they are called **positive inotropic drugs**; which are agents that **increase** the strength of muscular contraction.

Note: Na^{+} / Ca^{+2} exchangers can work in both ways; either sodium in-calcium out, or calcium in-sodium out.

3- <u>ATP-dependent Ca^{+2} pumps</u> (on the sarcolemma):

These pumps act to maintain a **low concentration** of free cytosolic Ca2+.

Remember:

a- *Affinity is related to Km; it is the binding strength between the substrate and the enzyme.*

b- *Capacity is how many molecules can the enzyme act on in a certain amount of time.*

Ca^{+2} pumps in the sarcolemma have **high affinity** and **low capacity**. Thus, they are capable of working at **low** concentrations of calcium but does not transport too much Ca^{+2}. On the other hand, **Na^{+} / Ca^{+2} exchangers** in the sarcolemma have **low affinity** and **high capacity**.

<u>Note:</u> if the three mechanisms are not enough to reduce Ca^{+2} concentration in the cardiac muscle and cause relaxation, which is a **pathological condition**, **Na^{+} / Ca^{+2} exchanger** in the membrane of the **mitochondria** will start functioning to reduce Ca^{+2} concentration.

Good Luck