MEDICINE
KING SAUD UNIVERSITY

Physiology Team 436

Revised by
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Contractile Mechanisms in Cardiac Muscle

CVS BLOCK

Red: very important.
Green: Doctor's notes.
Pink: formulas.
Yellow: numbers.
Gray: notes and explanation.

Physiology Team 436 – Cardiovascular Block Lecture 1

Lecture: If work is intended for initial studying.
Review: If work is intended for revision.

Objectives

Study Smart: focus on mutual topics.

From the guide:

- Define cardiac muscle contractility
- Describe the mechanism of excitation contraction coupling
- Understand the mechanism of isovolumetric and isometric contraction
- Factors affecting cardiac contractility

From slides:

- Describe the general features and overall design of the cardiovascular system.
- Explain how the heart accomplishes its function as the central pump of the cardiovascular system.
- Understand the phases of cardiac action potential and the ionic bases
- Describe the structure of a typical myocyte.
- Explain sliding-filament mechanism of contraction.
- Summarize the effects of sympathetic and parasympathetic stimulation on cardiac contractility.
- Discuss the role of calcium ions in the regulation of cardiac muscle function

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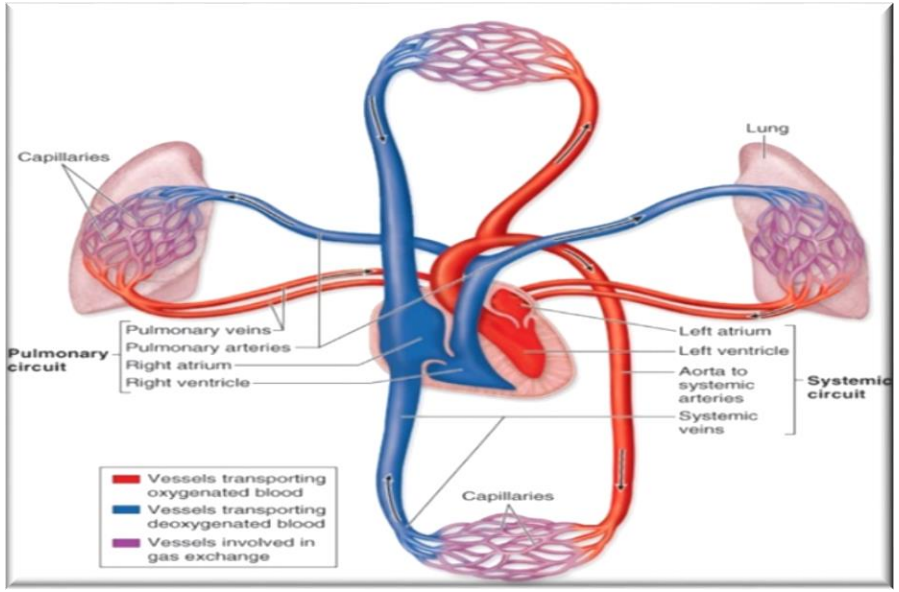
Components and Functions of Cardiovascular System

Components of CVS:

- CVS consists of the heart and blood vessels.
- It is a closed system in which blood circulates. Therefore, we call it circulatory system.



Main functions of CVS:

- Delivery of O2, glucose and other nutrients to active tissues.
- Removal of CO2, Lactate and other waste products (by-products of metabolism) from active tissues.
- Participate in homeostatic mechanisms.
- Adjustment of oxygen and nutrient supply in different physiologic states.
- Transport of metabolites and other substances to and from storage sites.
- Transport of hormones, antibodies and other substances to site of action.
- Defense.
- Thermoregulation.

(Mainly transport functions)

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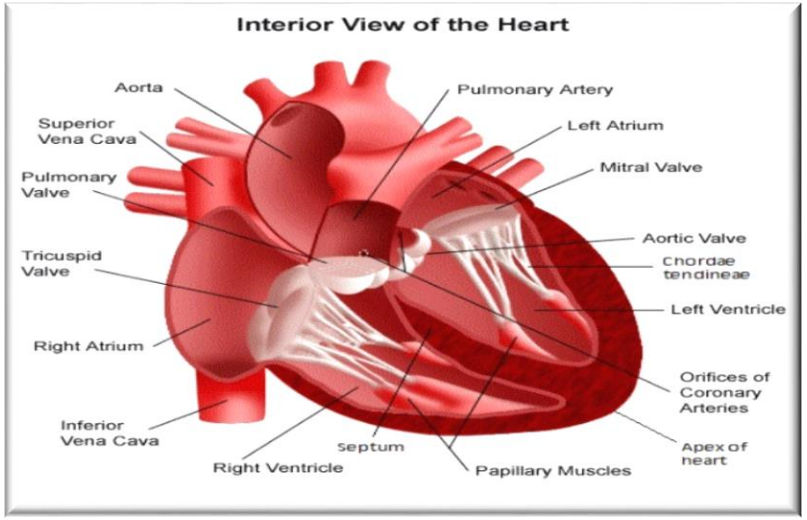
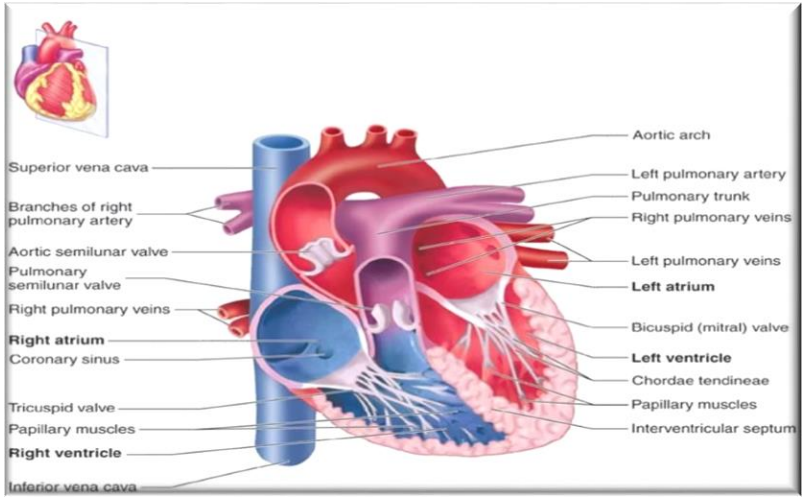
The Heart as a Central Pump

The right and left atria	The right and left ventricles
▸ Thin-walled, low pressure chambers. ▸ They function as blood reservoirs for their respective ventricles. ▸ Under normal conditions, the atria are not important as pumps.	▸ Are the principle pumps of the cardiovascular system. They are capable of generating flow with pressure. ▸ The right ventricle is considerably thinner than the left ventricle. ▸ The thickness of the ventricular wall is related to pressure generated. LV has higher pressure and a thicker wall than RV The flow in left and right ventricle is the same; however, pressure is higher in the left ventricle.





- Systole (contraction phase) + Diastole (relaxation phase) = Heart beat (cardiac cycle).

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The Heart as a Central Pump

Cardiac valves:

- The atrio-ventricular valves (AV valves)

1. Tricuspid valve (between RA & RV)
2. Mitral valve(bicuspid valve). (between LA & LV)

- The semilunar valves are:

1. Aortic valve (between LV & aorta)
2. Pulmonary valve (between RV & pulmonary trunk)

- The edges of the AV valves are attached to ventricular papillary muscle by the chordae tendineae. (why) In order to prevent eversion* of valves during ventricular systole (contraction phase).

- For effective pumping, the heart must be functioning properly in five basic respects:

1. The contractions of individual cardiac muscle cells (myocytes) must occur at regular intervals and be synchronized (not arrhythmic).
2. The valves must open fully (not stenotic**).
3. The valves must not leak (not insufficient or regurgitant).
4. The ventricular contractions must be forceful (not failing).
5. The ventricles must fill adequately during diastole.

*تنقلب للخارج **متضيق

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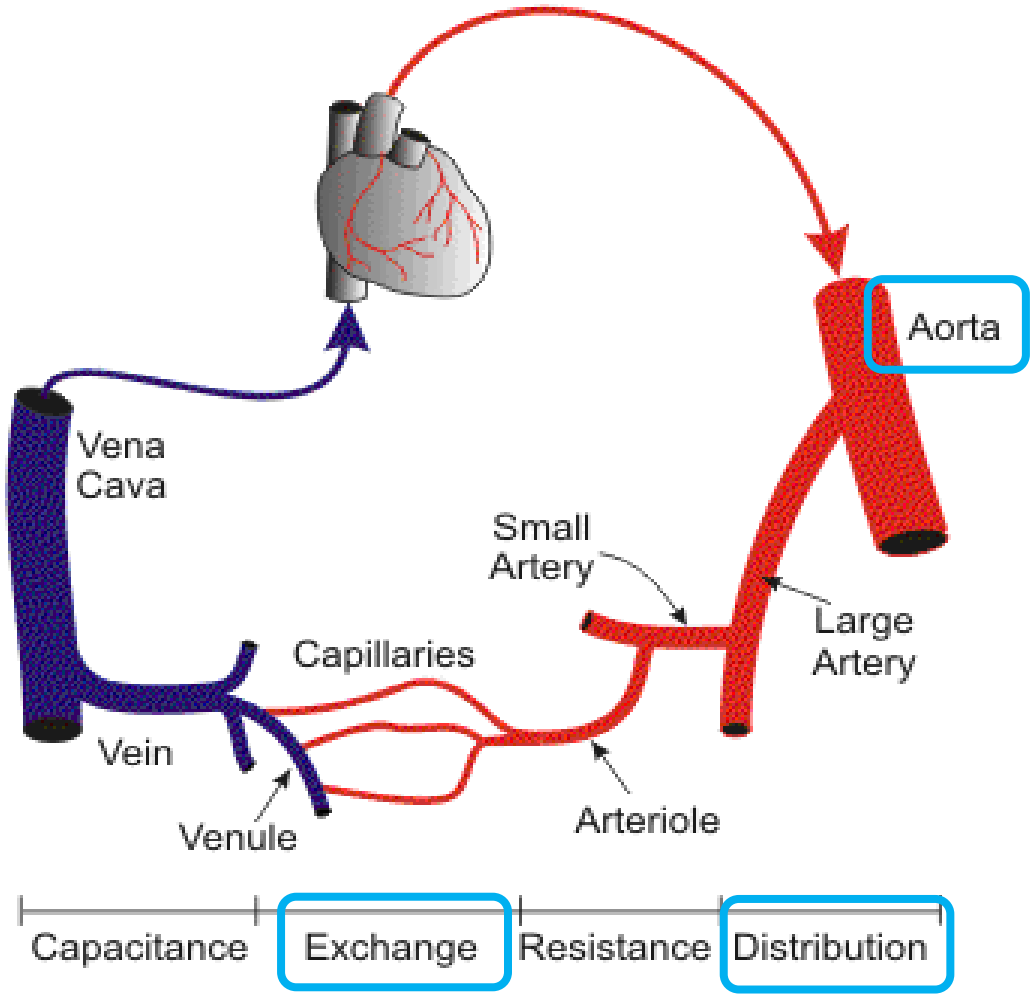
Blood Vessels (Explanation)



Heart → aorta → large artery → small artery → arterioles

Vena Cava ← Vein ← Venule ← Capillary ← Arteriole

Aorta and large arteries have high pressures so their function is DISTRIBUTION.
Small arteries and arterioles have low pressure so their function is RESISTANCE.
(Arterioles have the highest resistance in circulation → significant drop in pressure in order to decrease the pressure of the blood going to capillaries)

لو كان الدم الي جاي للكابيلاريز ضغطه عالي بتتفجر الكابيليريز

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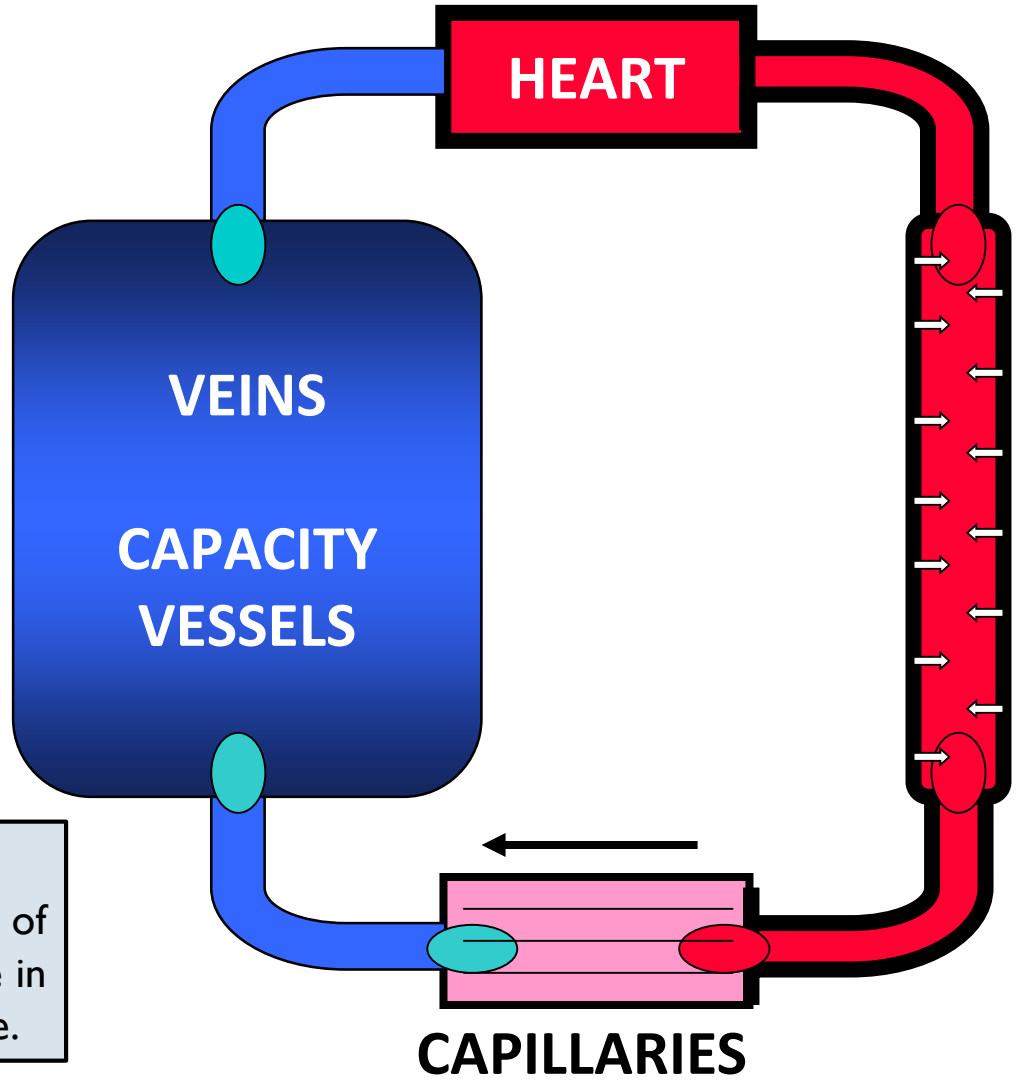
Blood Vessels

VEINS
Are also called (Volume reservoirs)

(HIGH COMPLIANCE)
(LOW PRESSURE)
MORE BLOOD VOLUME



ARTERIES
Are also called (Pressure reservoirs)

(LOW COMPLIANCE)
(HIGH PRESSURE)
LESS BLOOD VOLUME

Recall

COMPLIANCE: is the property of undergoing elastic deformation , as change in volume when subjected to an applied force.

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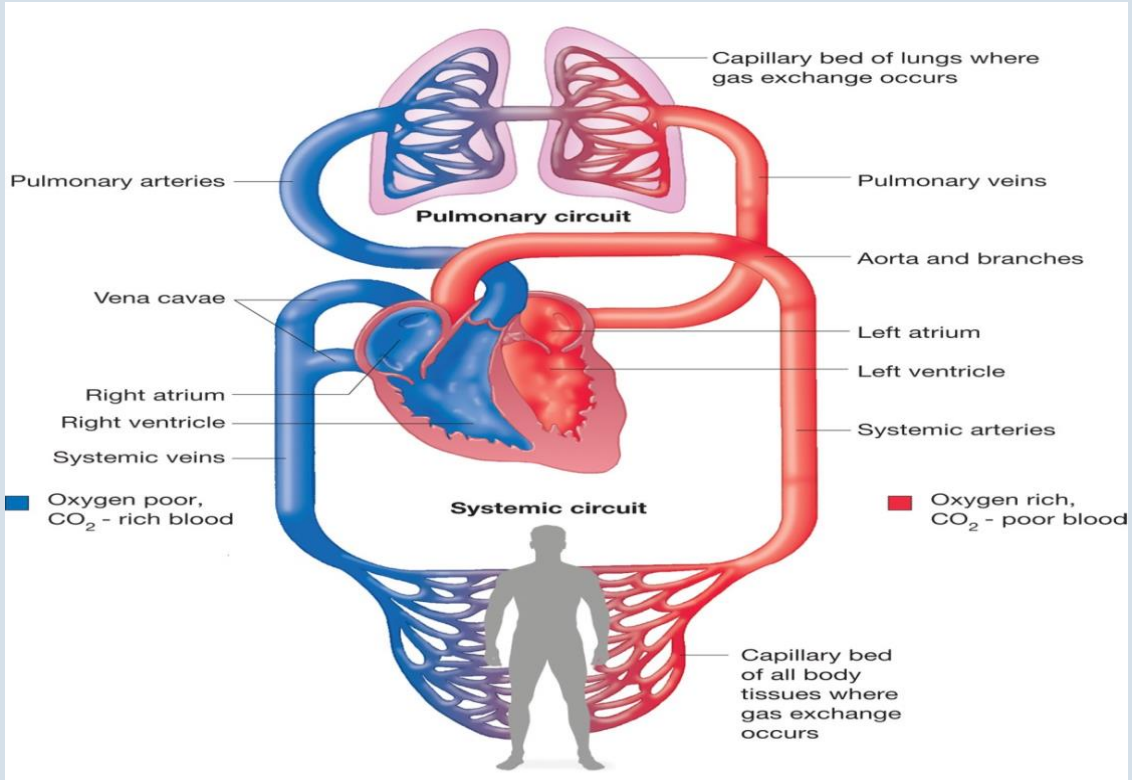
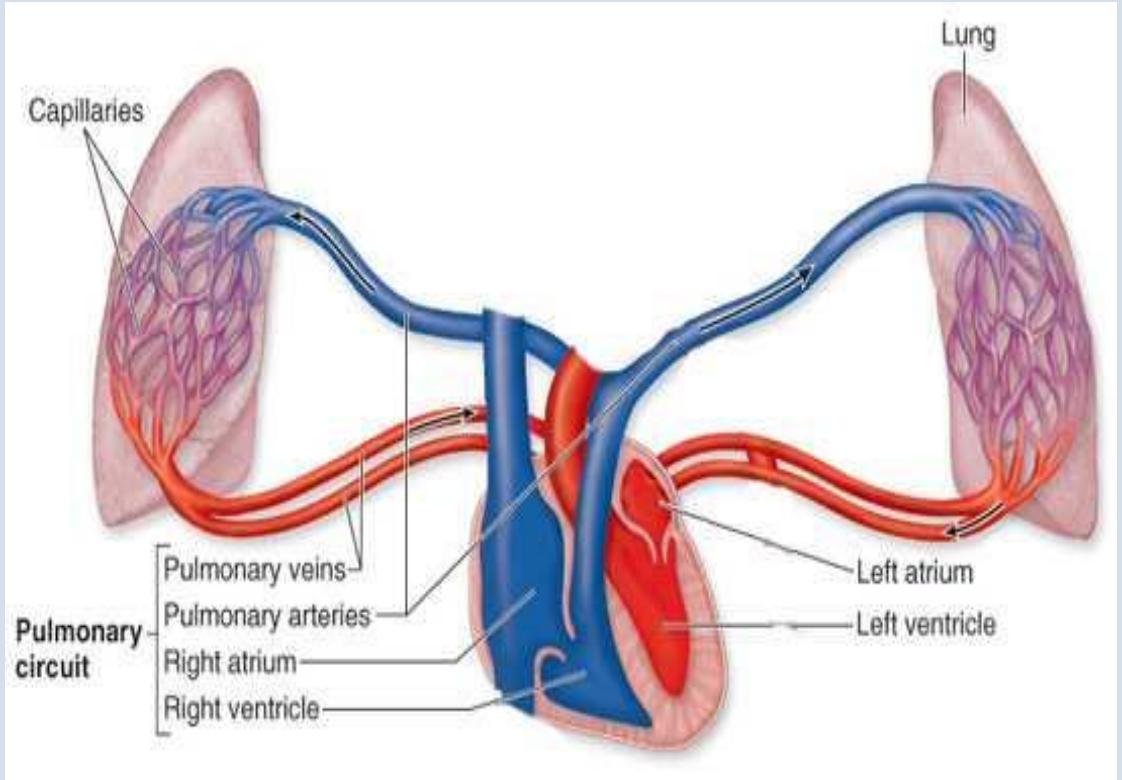
Systemic and Pulmonary Circulations

Systemic Circulation:



Starts at LEFT VENTRICLE and ends at RIGHT ATRIUM

Pulmonary Circulation:



Starts at RIGHT VENTRICLE and ends at LEFT ATRIUM

These 2 circulation are connected in **series.**

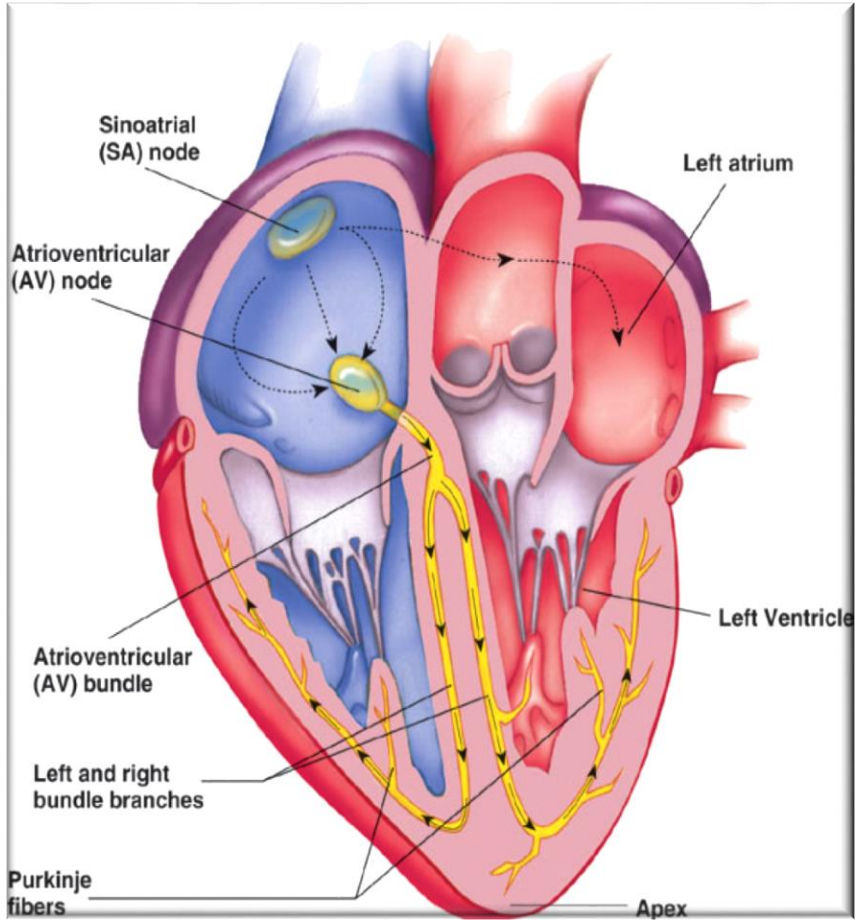
How the Heart Performs its Function as the Central Pump of the CVS

The heart has four basic properties which are essential for its functioning as the central pump of the CVS. These are:

- Autorhythmicity
- Conductivity
- Excitability
- Contractility

There are 2 main types of cells in the heart:

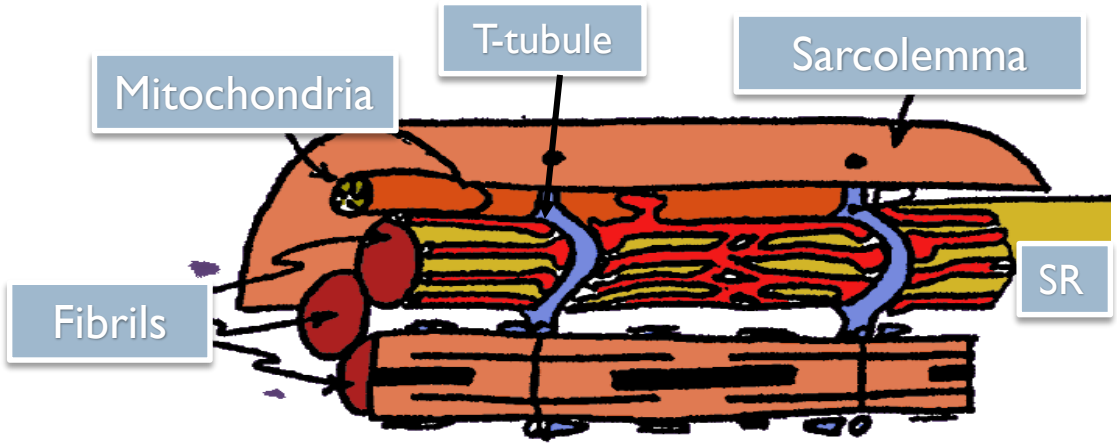
- Cells of the specialized conduction system. (SA node, AV node, AV bundle, Left & Right Bundle Branch, Purkinje fibers)
- Contractile cells (myocytes; working cells). (wall of atria & inter-arterial septa and wall of ventricle & inter-ventricular septa)



Ultrastructure of myocyte (the contractile, working cell)

- The cardiac muscle cells (fibers; myocytes) branch and interdigitate, but each is a complete unit surrounded by a cell (plasma) membrane (sarcolemma).
- Where the end of one muscle fiber abuts (adjoin) on another, the membranes of both fibers parallel each other through an extensive series of folds. These areas are called intercalated disks (intercalated discs: cell membranes, separate individual cardiac muscle cells from one another).

- Thus, each fiber is separated from its neighboring fibers by its sarcolemma (laterally) and by the intercalated disks (end-to-end).
- Cardiac muscle cell contains large amounts of mitochondria to provide continuous ATP for the cell.
- Cardiac muscle has a rich capillary supply: about 1 capillary per fiber.



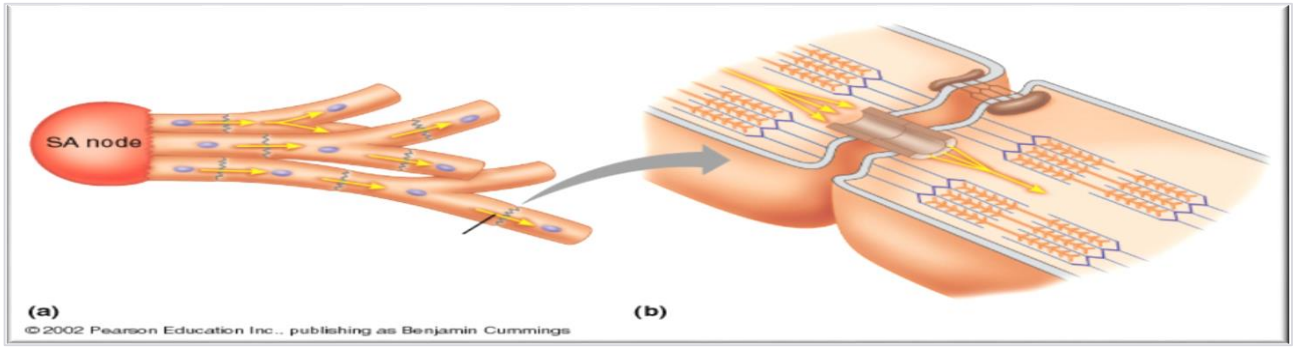
 NOTE: unlike Skeletal muscles , the cardiac muscle fiber DOES NOT mean muscle cell , the cardiac fiber consists of several cardiac muscle cells

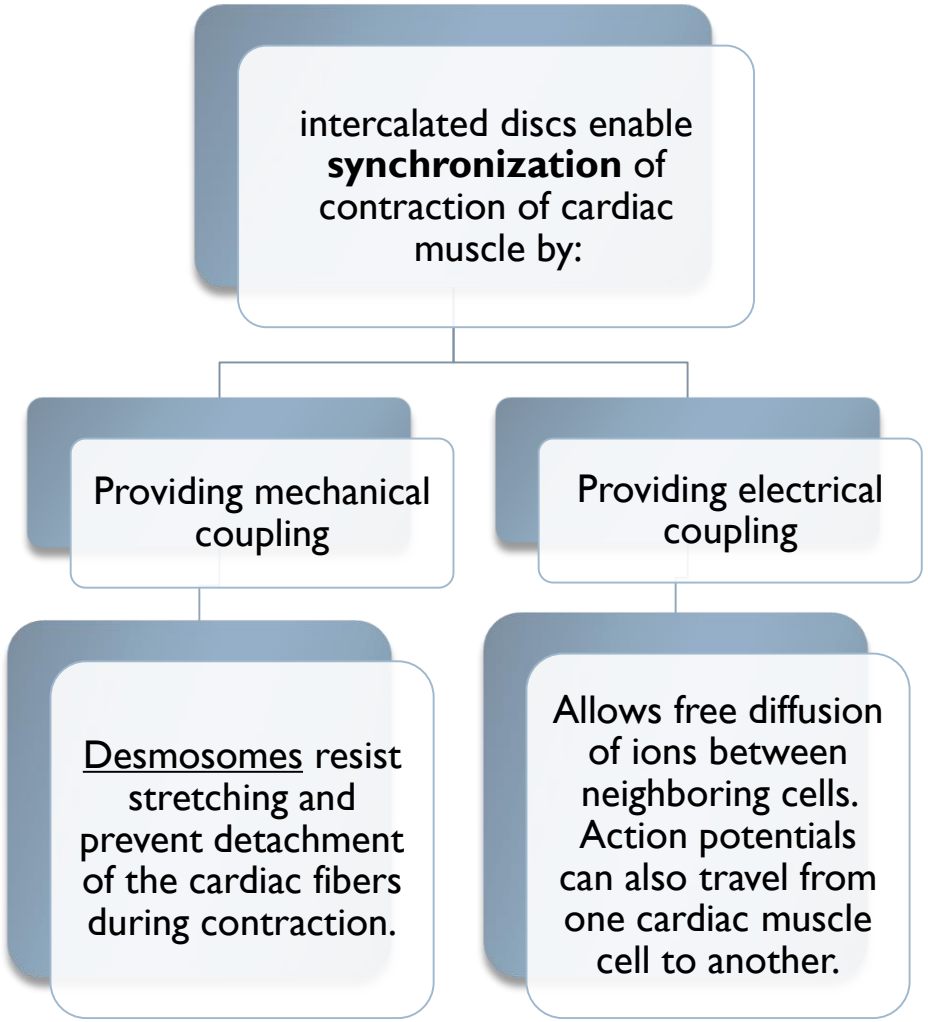
Mechanical Coupling and Electrical Coupling

Gap junctions: are trans-membrane channel proteins, connecting the cytoplasm of the neighboring cardiac muscle cells.

- They allow free diffusion of ions between neighboring cells.
- Action potentials can also travel from one cardiac muscle cell to another.

So intercalated discs allow passage of current through cells, this mechanism ensures electrical coupling of the cells.





Cardiac Muscle is a Syncytium

- Cardiac muscle functions as a syncytium* as each muscle cell is electrically connected to its neighboring cells through the gap junctions.
- Thus, stimulation of a single myocyte:
  - → the action potential spreads from cell to cell through the gap junctions.
  - → synchronous** contraction of all the myocytes.
- The atrial syncytium is separated from the ventricular syncytium by the fibrous tissue surrounding the valvular openings (fibrous skeleton of the heart).

Differences between cardiac and skeletal muscles	
Cardiac Muscle	Skeletal Muscle
T system in cardiac muscle is located at the Z lines of the sarcomeres	T system in skeletal muscle is located at the A–I junction
The sarcoplasmic reticulum makes complexes with the transverse tubular membrane at dyad junction	The sarcoplasmic reticulum makes complexes with the transverse tubular membrane at triad junctions.

- Cardiac muscle cells (myocytes) typically resemble skeletal muscle in also having:

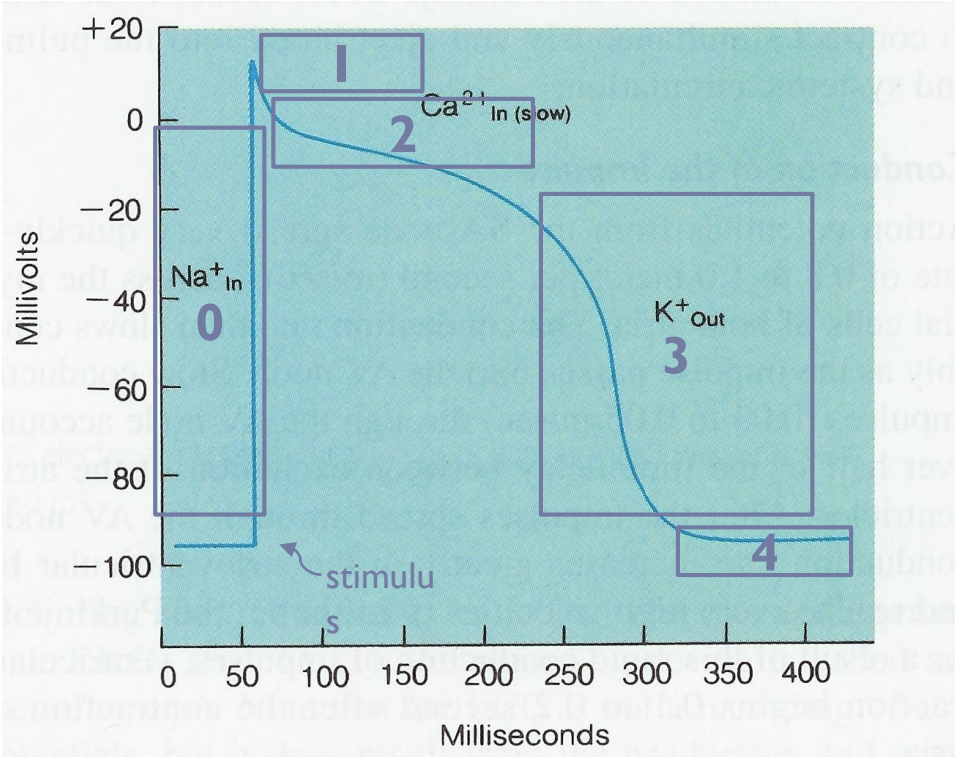
(a) Myofibrils packed in the cytoplasm (sarcoplasm), (b) specialized transverse tubular and sarcoplasmic reticular membrane systems.

- Syncytium*: a group of cells in which the cytoplasm of one cell is continuous with that of adjoining cells.
- Synchronous**: existing or occurring at the same time.

Action Potential in Cardiac Muscle

- Resting membrane potential -90 mV (it is more negative inside the cell comparing to the ECF)
- Duration of cardiac action potential is 0.4 seconds

Phases of cardiac Action Potential	Ionic changes
0- Rapid depolarization (+20 mV)	Fast sodium channels opens → Na^+ influx
1- Partial repolarization (5-10mV)	Opening of K^+ channels → K^+ out
2- Action potential plateau (0 mV) In this phase the membrane potential will stay steady	Slow calcium channels opens → Ca^{2+} influx وقناة البوتاسيوم لاتزال مفتوحة لكن تقل النفاذية
3- Repolarization (back to RMP)	K^+ out



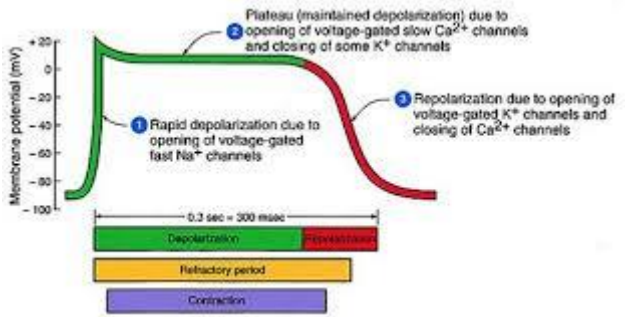
Action Potential in Cardiac Muscle

What causes the Plateau in the Action Potential?

1. **The main cause is slow calcium channels:** slow to open & remain open for several tenths of a second → Large quantity of calcium ions flow into the interior of the cardiac muscle fiber → maintains prolonged period of depolarization → causing the plateau in the action potential.

2. **Another factor** to maintain the plateau phase is the **decreased permeability** of the cardiac muscle membrane for potassium ions → decrease outflux of potassium ions during the action potential plateau.

When the slow calcium channels close at the end of the plateau, the membrane permeability for potassium ions increases rapidly, and this returns the membrane potential to its resting level, thus ending the action potential.



الكالسيوم شحنته موجبة أكثر من البوتاسيم . فيكون هو يدخل والبوتاسيوم يطلع في نفس الوقت فيكون ما في تغير في الشحنة داخل وخارج الخلية = تظل متساوية وفي الرسم تكون عند الصفر

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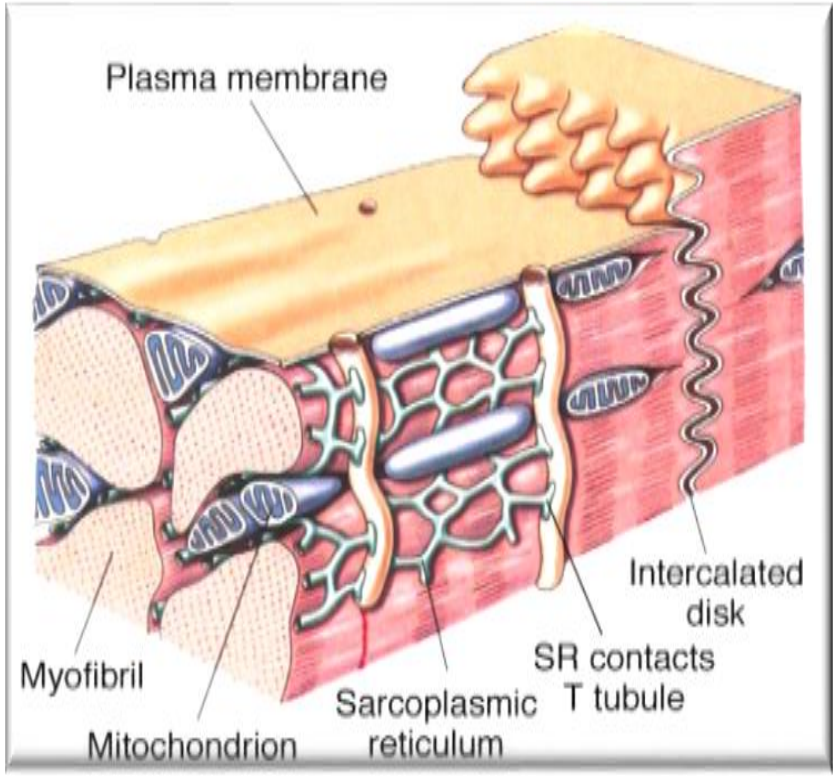
Calcium-induced Calcium Release through the Ryanodine Receptors (RyR) at the Sarcoplasmic Reticulum

- In the myocytes, a significant Ca^{2+} influx comes from extracellular space during the plateau phase of the action potential.
- The role of Ca^{2+} in excitation–contraction coupling in myocytes is similar to its role in skeletal muscle; (the term "excitation-contraction coupling" refers to the mechanism by which the action potential causes the myofibrils of the muscle cell to contract).
- *However*, it is the influx of extracellular Ca^{2+} through the voltage-sensitive Dihydropyridine receptors (DHPR) in the T system (L-type calcium channels), which triggers calcium-induced calcium release through the ryanodine receptors (RyR) at the sarcoplasmic reticulum*.
- Cardiac ryanodine receptors are different from the skeletal muscle ryanodine receptors.



Mechanism of Calcium-induced Calcium Release through the Ryanodine Receptors (RyR) at the Sarcoplasmic Reticulum

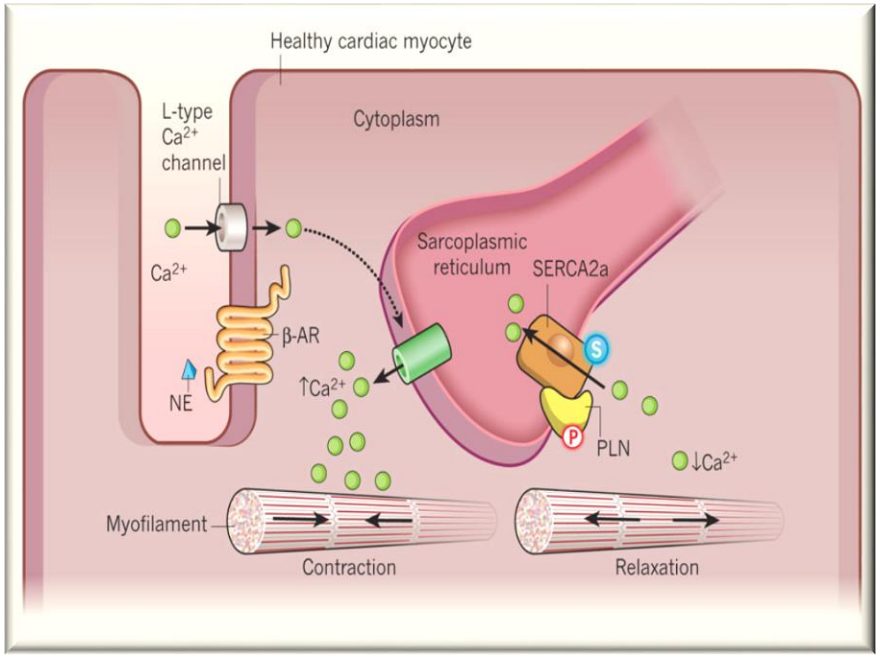
1. When the myocytes are excited, the action potential spreads through sarcolemma and travels down to the transvers tubules.

2. The action potential will open Voltage-gated L-type calcium channels (dihydropyridine receptors DHPR), then Ca^{2+} ions move inside the cell (from extracellular fluid).

3. Ca^{2+} ions bind to the ryanodine receptor of the sarcoplasmic reticulum to trigger releasing the stored Ca^{2+} in the sarcoplasmic reticulum.

4. The ryanodine receptors are now opened, the stored Ca^{2+} are released.

5. The increased intracellular Ca^{2+} level will cause contraction of the myocytes.

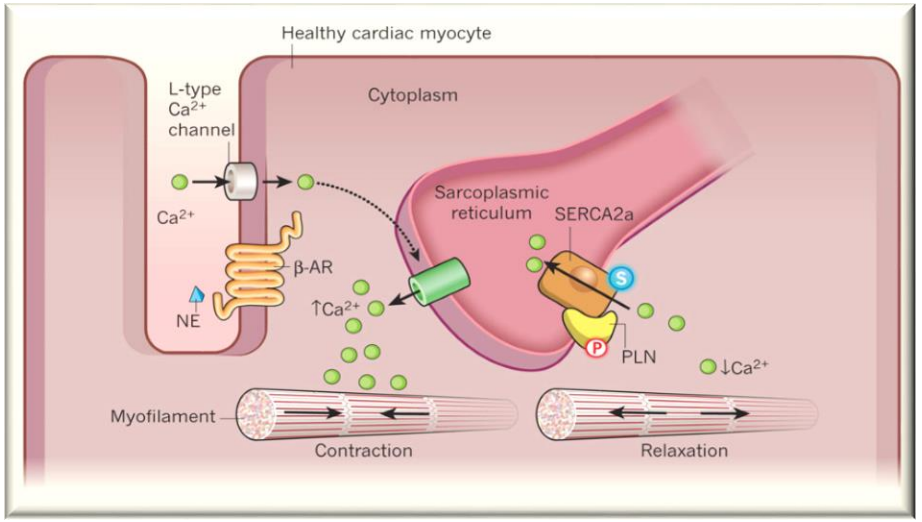


شرح:

١. لما يكون فيه excitation , ال action potential راح ينشر في sarcolemma & T-tubules الى ما يوصل لل DHPR , راح يفتحها و الكالسيوم راح يدخل جوا الخلية.

٢. لما يدخل الكالسيوم راح يرتبط في ryanodine receptor و راح يحفز ال Ca^{2+} releasing , هذا الكالسيوم راح يسبب انقباض عضلات القلب.

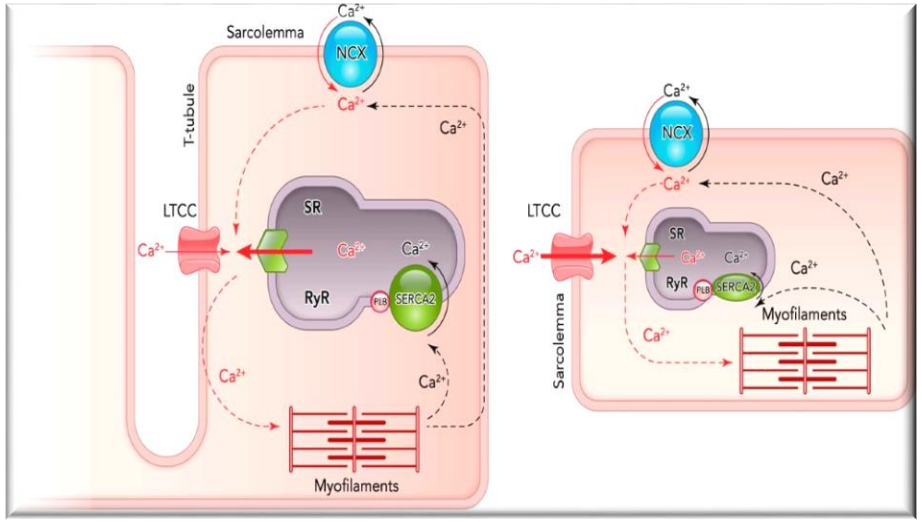
Cont.



- External Ca^{2+} (Ca^{2+} influx) is required for the excitation-contraction coupling in the heart, but is not sufficient to produce contraction by itself. It is used as a trigger for Ca^{2+} release from the sarcoplasmic reticulum.

الكالسيوم اللي يدخل للخلية غير كافي لحاله انه يسبب انقباض عضلات القلب, عشان كذا راح نحتاج ال sarcoplasmic reticulum لأنها راح تفرز كمية كالسيوم اكبر كافية انها تسبب انقباض عضلات القلب .

- This calcium-induced calcium release is pH sensitive, showing strong inhibition at pH 6.5 and maximal release at pH 7.4.



- Voltage-gated L-type calcium channels are present on the sarcolemma as well as the T-tubules.

- The Voltage-gated calcium channels are usually very **near** to the ryanodine receptors, so that Ca^{2+} influx will induce high local levels of Ca^{2+}.

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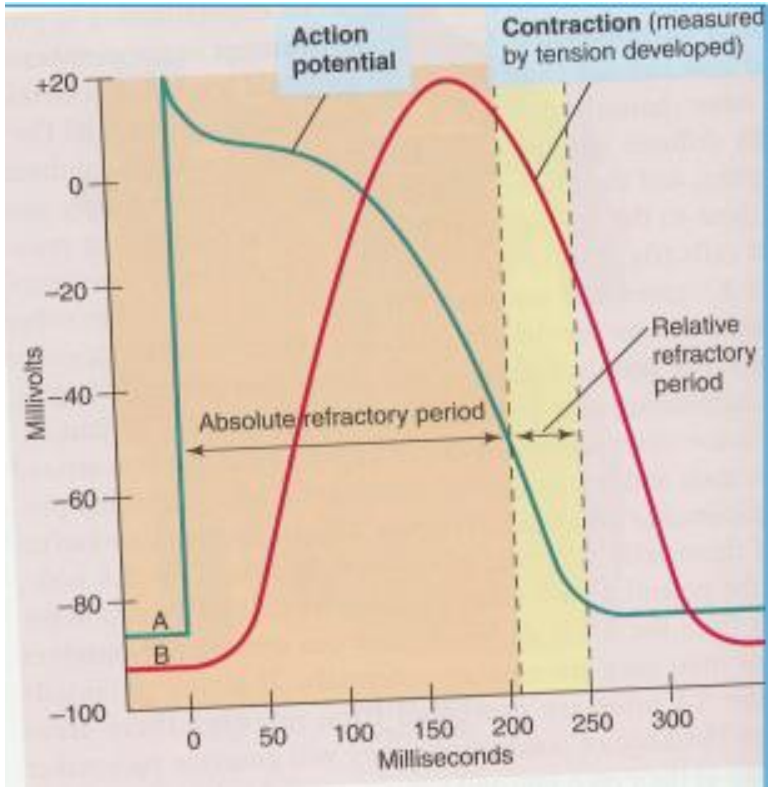
Refractory Period of Cardiac Muscle

Video of (cardiac AP &refractory period)
Duration: (7)mins

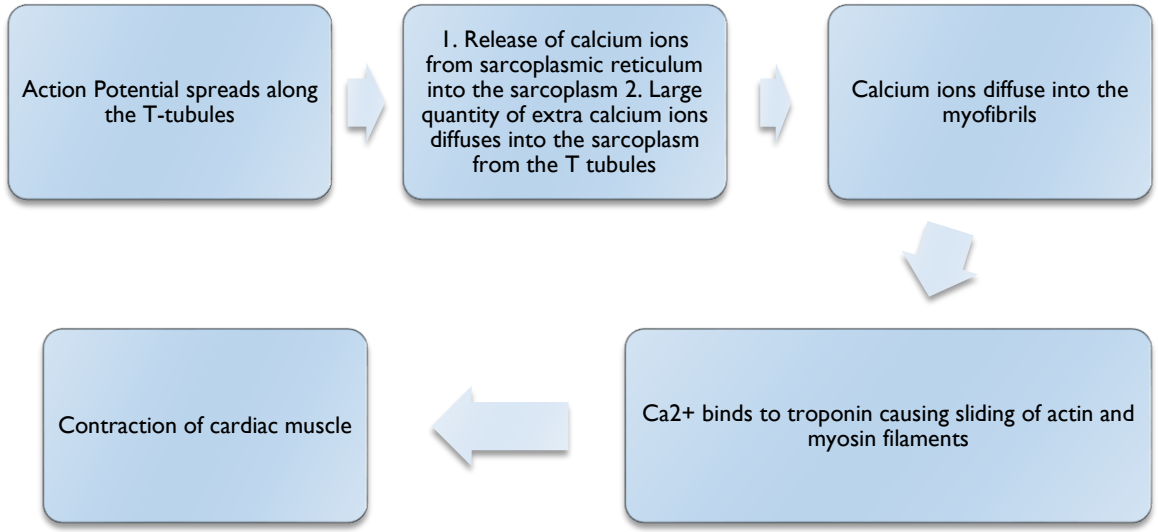
- Cardiac muscle is refractory to re-stimulation during the action potential.
- The refractory period of the heart: is the interval of time during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle.

	Absolute Refractory Period	**Relative Refractory Period**
Definition	Cardiac muscle cannot be excited while it is contracting	Cardiac muscle can be excited by **strong** stimulus
Benefit	Long ARP	-
Time	Depolarization and 2/3 repolarization	Repolarization
Duration	0.25 - 0.3 sec	0.05 sec
In SKm	Longer than that of SKm	

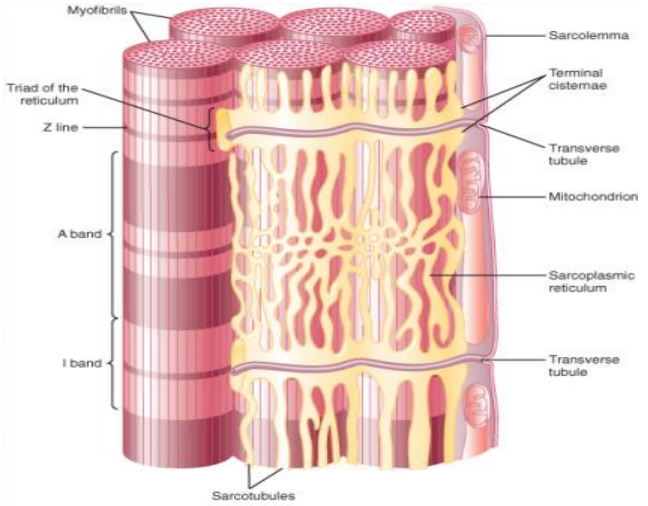


Excitation Contraction Coupling

- Excitation – Contraction Coupling: is the mechanism by which the action potential causes muscle contraction.
- Action potential spreads to the interior of the cardiac muscle fiber along the transverse (T) tubules.

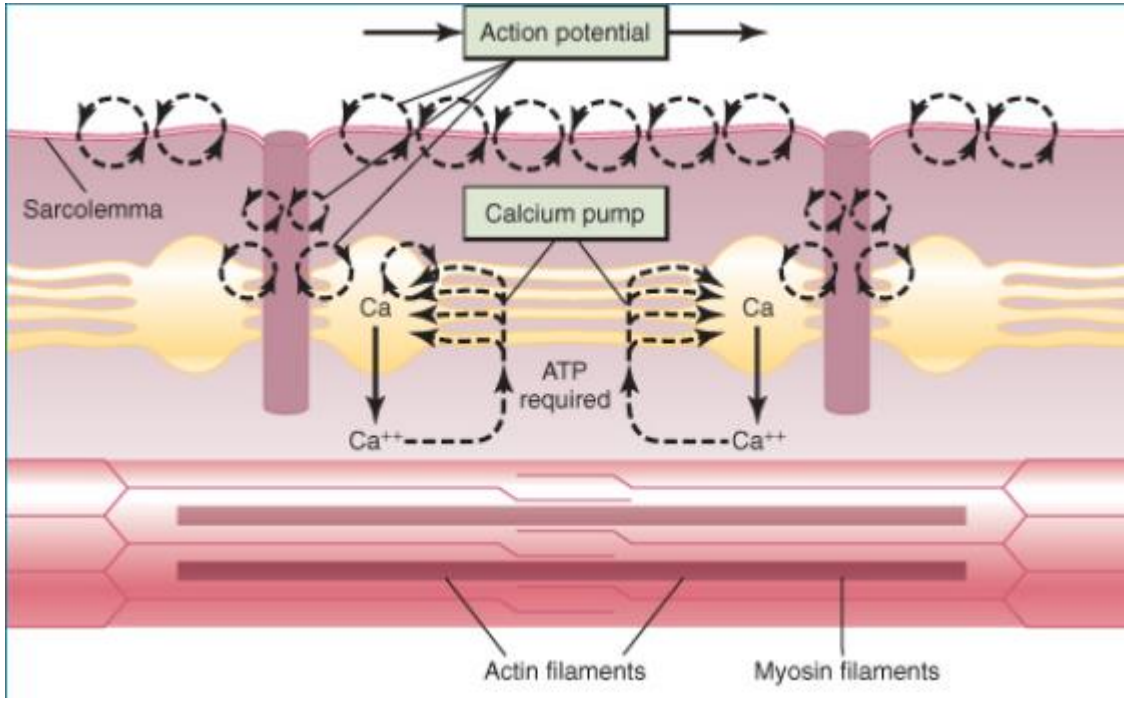


- The T tubules of cardiac muscle have a diameter 5 times as great as that of the skeletal muscle tubules.
- The strength of contraction of cardiac muscle depends to a great extent on the concentration of calcium ions in the extracellular fluids.
- At the end of the Plateau of the action potential → calcium ions are pumped back into the sarcoplasmic reticulum and the T-tubules → contraction ends (repolarization)



Excitation Contraction Coupling

- Each contraction involves the hydrolysis of an ATP molecule for the process of contraction and sliding mechanism.
- Cardiac muscles are continually contracting and require substantial amounts of energy.
- The energy is derived from ATP generated by oxidative phosphorylation in the mitochondria.
- The myocytes contain large numbers of mitochondria.



Excitation Contraction Coupling

- Excitation-contraction coupling is similar in cardiac and skeletal muscles. Increased intracellular Ca^{2+} triggers contraction by binding to troponin C on the thin filament.

- Tension generation in cardiac, but not in skeletal muscle is profoundly influenced by:

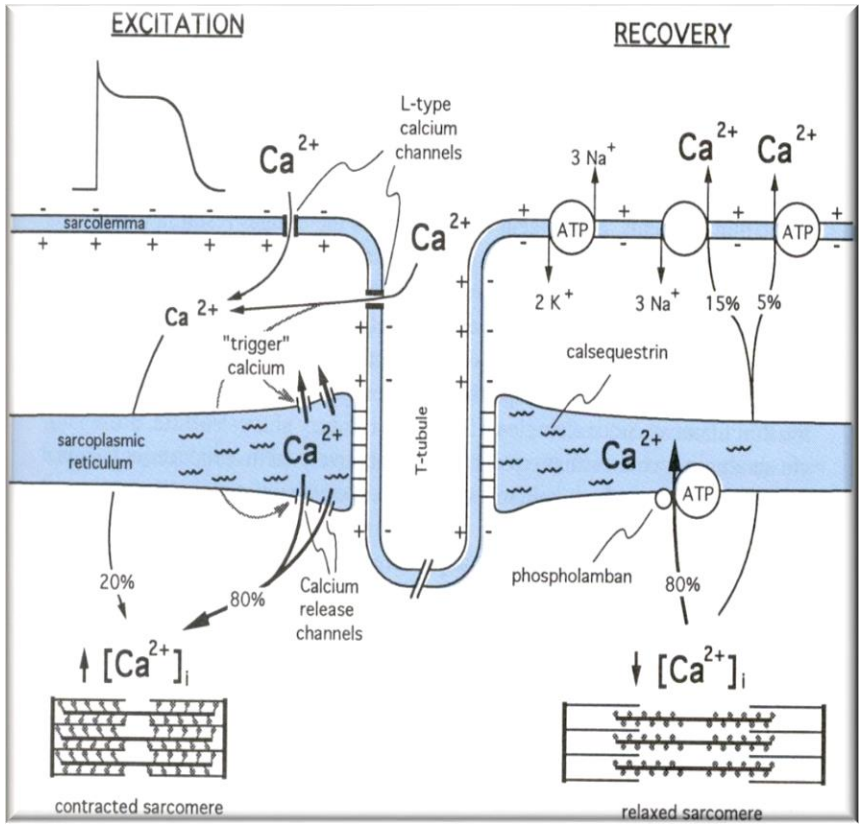
  1. **Extracellular calcium levels.**

     For example: doubling the extracellular calcium concentration may nearly double the maximum cardiac contractile force.

  2. **Factors that affect the magnitude of the inward calcium current.**

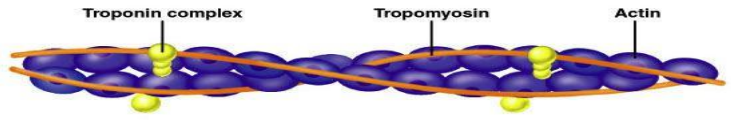
     For example: Sympathetic nervous system will increase the contraction by increasing the calcium influx. And visa versa with parasympathetic.

  - Drugs which reduce calcium influx have profound negative inotropic effects on the myocardium (↓ contractility), but affect skeletal muscle only when present in massive overdose.

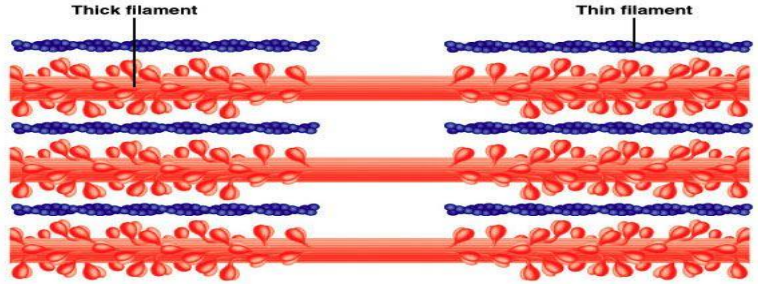


Excitation Contraction Coupling

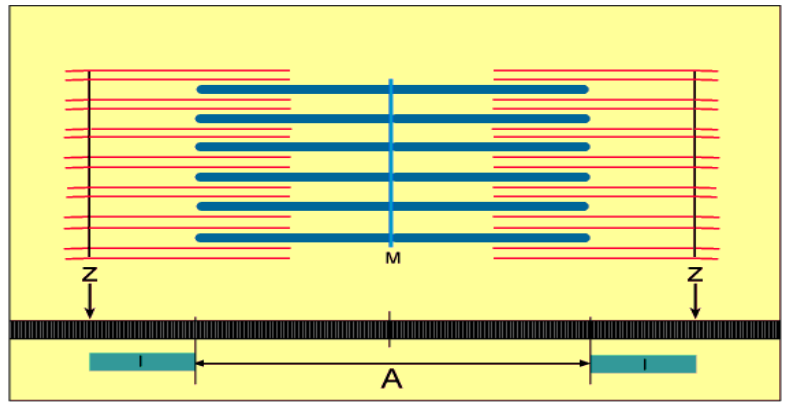
- The myocardial fibers (cells) contain many myofibrils.
- The myofibrils consist of thick myosin filaments and thin actin filaments.
- When the myocyte is relaxed the sarcomere is long, while when the myocyte is contracted the sarcomere is short.
- The calcium released from sarcoplasmic reticulum by calcium-induced calcium release process will trigger the Contraction cycle. (will be discussed in the next slides)



(c) Portion of a thin filament

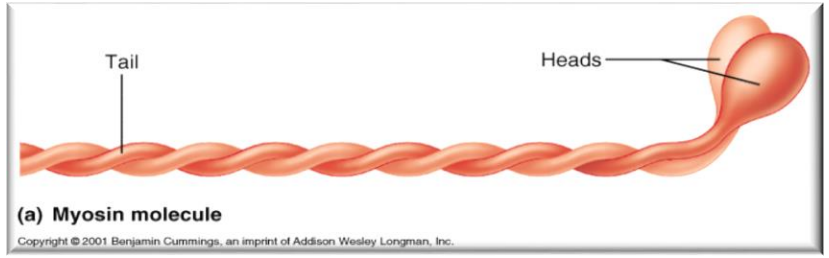


(d) Longitudinal section of filaments within one sarcomere of a myofibril

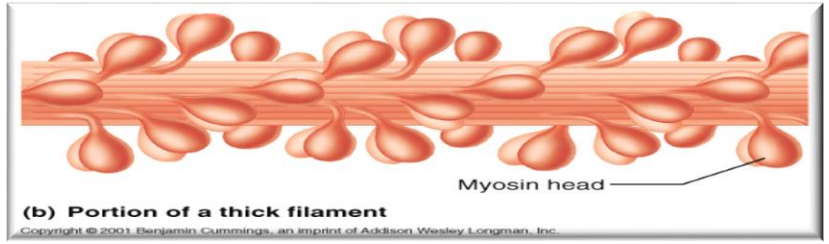


Animation

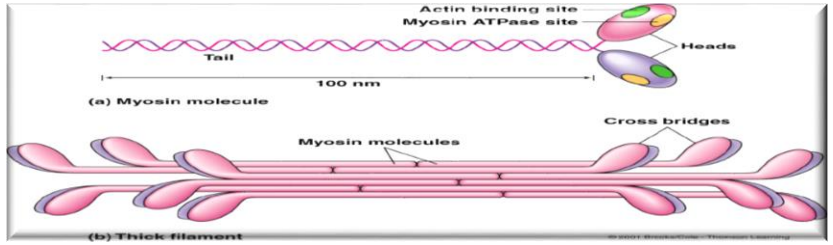
Thick Filaments (Myosin)



Each myosin molecule has a tail and 2 globular heads.



The myosin molecules combine to form a Thick filament (myosin filament)

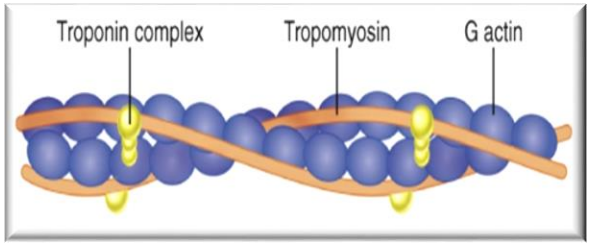


KEY POINT: The heads of each myosin molecule have an ACTIN binding site and an ATPase site (splits ATP)

1) Actin binding site binds to actin.
2) Atpase site binds to Atp and splits it to Adp +p.

Thin Filaments
Sliding-filament Mechanism of Contraction

In the relaxed state, myosin binding sites on actin molecules are covered by tropomyosin.

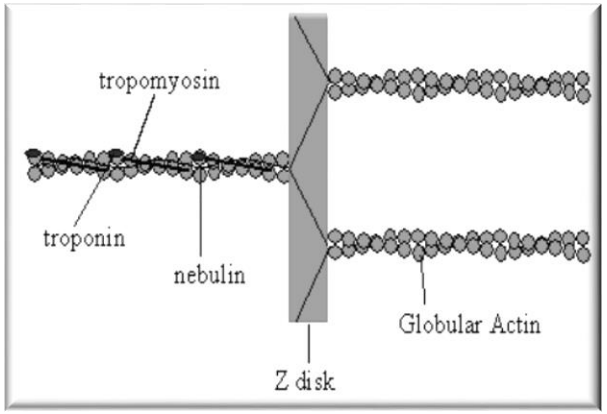


↓

Excitation rises calcium level.

↓

Ca^{2+} binds to troponin C.



↓

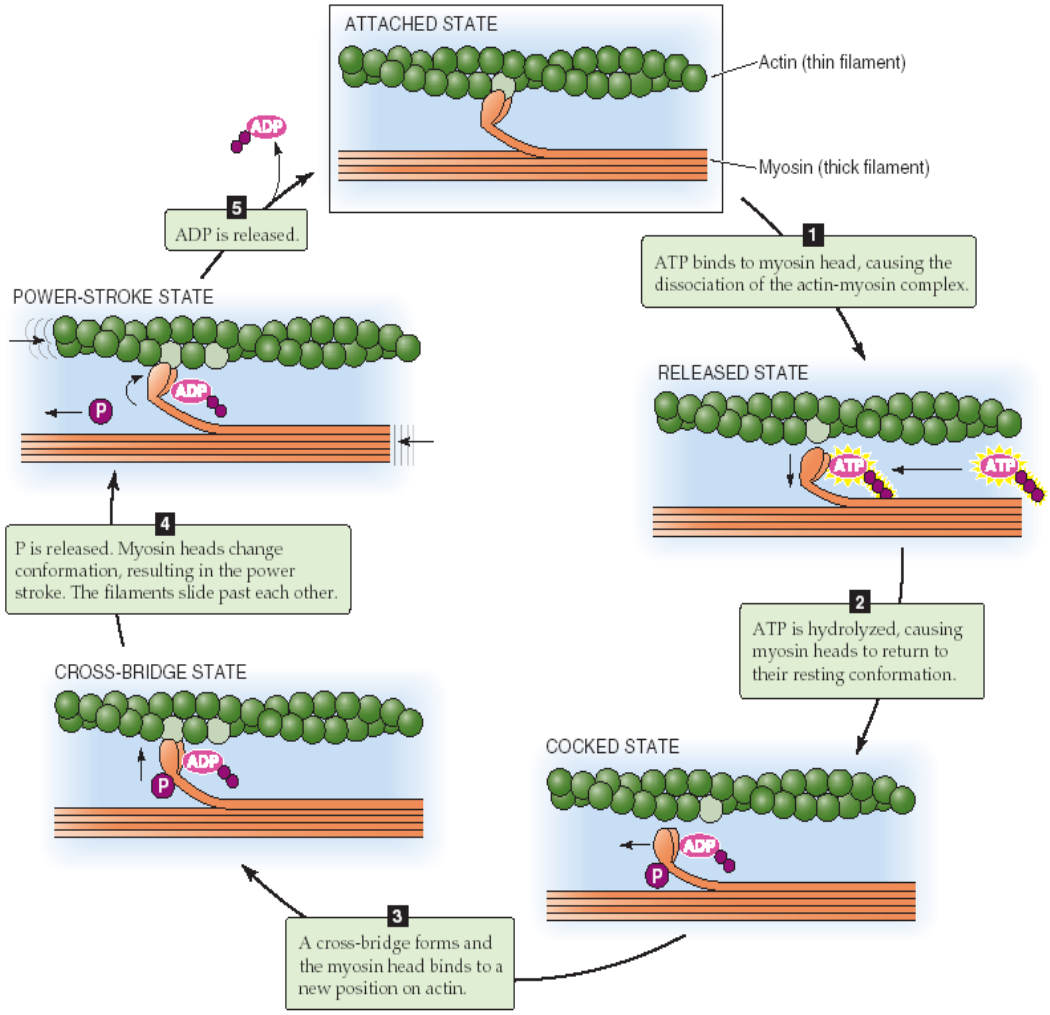
Ca-troponin C complex interacts with tropomyosin → uncovering the myosin binding sites on actin molecules.

→ **Myosin head binds to actin.**

Contraction Cycle

- **Contraction cycle:** it is the continuous cycling of cross-bridges.
- As long as calcium concentrations remain high, actin and myosin cross-bridges interact to produce contraction of the muscle, similar to that seen in skeletal muscle.
- ↑ Ca → ↑ contraction ↓ Ca → ↓ contraction
- Skeletal muscle is susceptible to rigor (تيبس) if no ATP is present in the muscle cell to bind to the myosin head and allow it to **detach** from the actin filament.
- Cardiac muscle is unlikely to ever undergo rigor, due to the large amounts of mitochondria producing ATP.

Example: in death (rigor mortis) happens which is the absolute stiffness of the skeletal muscle due to the loss of ATP.
In normal states, ATP binds to myosin to cause attachment and detachment of myosin head to/from actin



ONLY IN MALES' SLIDES

Mechanisms Maintaining Low Intracellular Ca2+ Between Successive Action Potentials

1. Calcium-ATPase pumps: SERCA

(sarco/endoplasmic reticulum Ca^{2+}-ATPase)

- Found in Sarcolemma and Sarcoplasmic Reticular membrane (SR)

Catecholamines → increase Adenylyl Cyclase → increase cAMP → activation of cAMP protien kinase

Activation of cAMP protien kinase will lead to:

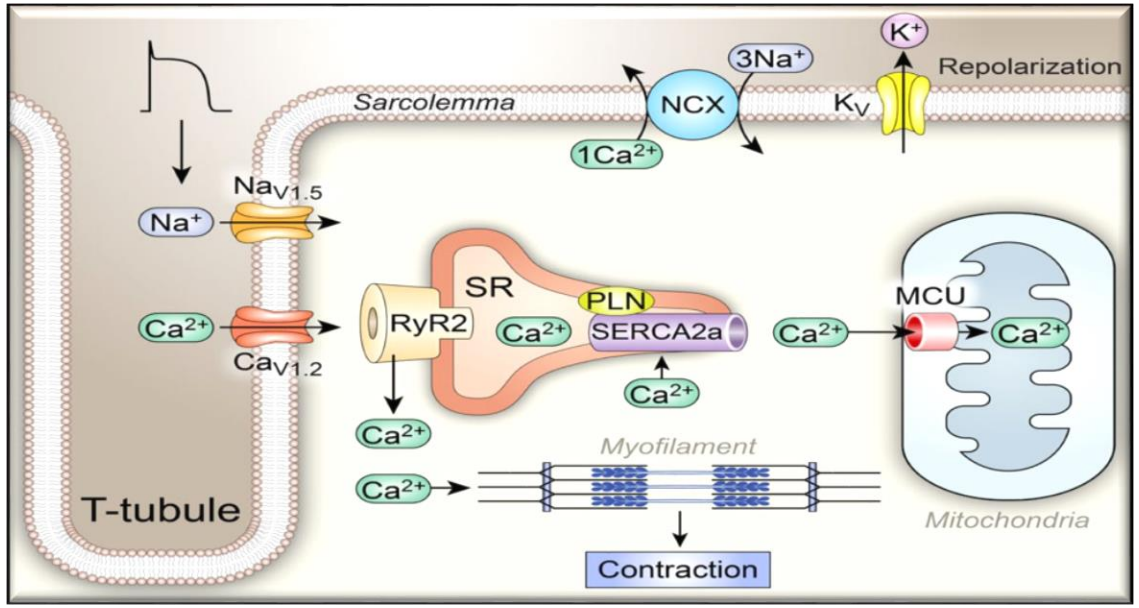
1-Phosphorylation of phospholamban → speed up action of SERCA (faster calcium removal from cytoplasm to SR).	2-Phosphorylation of DHPR→ more influx of Ca → more release of Ca → stronger contraction.

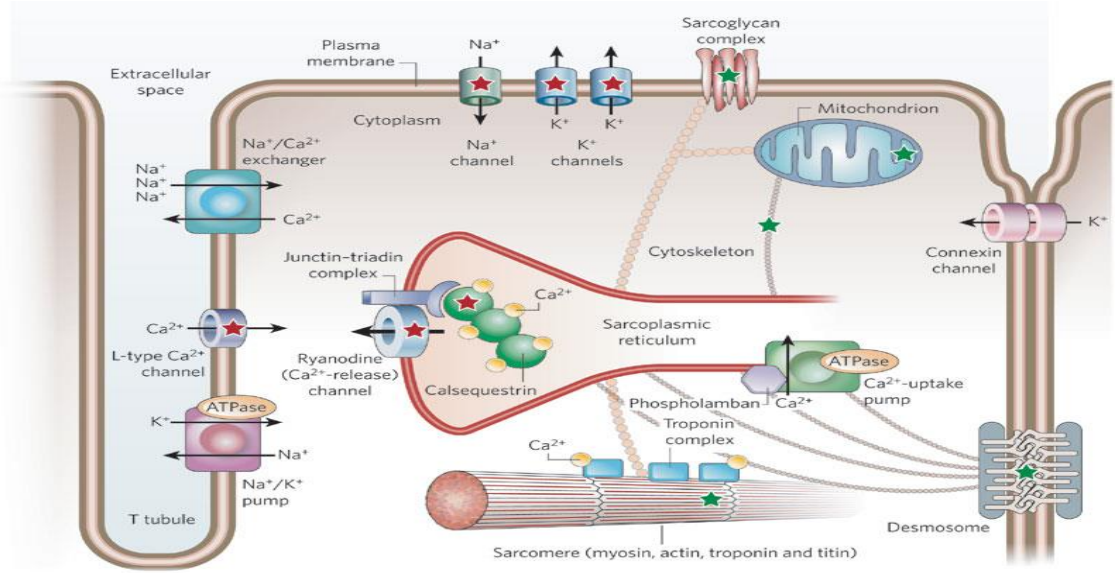
2. Sodium-Calcium exchanger:

- Found in plasma membrane (sarcolemma)

No block in Sodium-Potassium pump:	Block in Sodium-Potassium pump:
Sodium potassium pump pumps Na outside the cell creating low intracellular Na concentration. The exchanger uses the electrochemical gradient (created by sodium potassium pump) to remove 1 Ca2+ ion (efflux) for every 3 Na+ ions which enter the cell.	High Na inside the cell, the exchanger will work to bring in 1 Ca2+ ion for every 3 Na+ ions removed.

Cont.





Mechanism of action of digitalis (digoxin) used in the management of cardiac failure: These agents block the sodium pump and thereby allow such an increase in intracellular sodium concentration → reverse Na+-Ca2+ exchanger.

If there's a high intracellular sodium concentration, the electrochemical gradient driving sodium ion entry decreases. This results in removal of Na and an increased internal calcium concentration and contractile force.

Factors Affecting Cardiac Contractility

- Cardiac contractility is an intrinsic property of the contractile cardiac muscle cells and is defined as the force of contraction of the heart. It is essential for the pumping action of the heart.
- In physiological terms, cardiac contractility is referred to as the inotropic state of the myocardium. An inotropic effect is an effect or a mechanism that affects cardiac contractility.

Positive ionotropic effects:	Negative Ionotropic effects:
• These are the factors/mechanisms that increase the cardiac contractility. • Sympathetic stimulation (catecholamines) • Calcium ions	• These are the factors/mechanisms that decrease the cardiac contractility. • Parasympathetic stimulation (vagal –of the vagus nerve- stimulation) • Acetylcholine

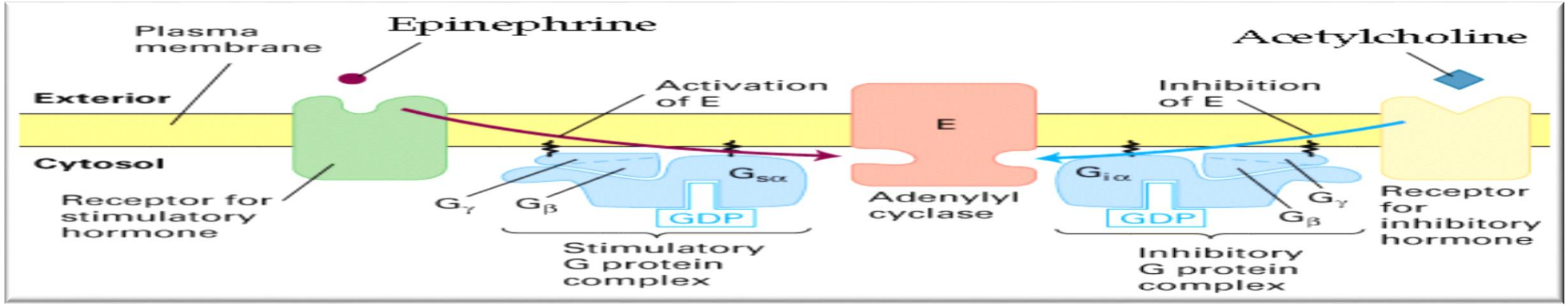
Factors Affecting Cardiac Contractility

1. Sympathetic stimulation:

- Catecholamines interact with beta-adrenergic receptors → activation of adenylyl cyclase. This increases intercellular levels of cAMP.
- cAMP activates protein kinases which promote the phosphorylation of L-type Ca2+ channels.
- Phosphorylation of L-type Ca2+ channels increases the influx of Ca2+ during the action potential and hence more Ca2+ is released from the sarcoplasmic reticulum.

2. Parasympathetic stimulation:

- Interaction of acetylcholine with muscarinic receptors on cardiac muscle cell, and Inhibition of the release of norepinephrine from neighboring sympathetic neurons.
- Interaction of acetylcholine with muscarinic receptor inhibits adenylyl cyclase → ↓ intracellular levels of cAMP.
- The reduction in cAMP leads to a reduction in Ca2+ influx during the action potential , and thus a decrease in contractility.
- The reduction in contractility induced by parasympathetic stimulation is seen primarily in the atria.



Quiz

- https://www.onlineexambuilder.com/contractile-mechanisms-in-cardiac-muscle/exam-136425

Link to Editing File

(Please be sure to check this file frequently for any edits or updates on all of our lectures.)

References:

- Girls' and boys' slides.
- Guyton and Hall Textbook of Medical Physiology (Thirteenth Edition.)

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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