Cardiovascular System Block
Contractile Mechanism in Cardiac Muscle
(Physiology)

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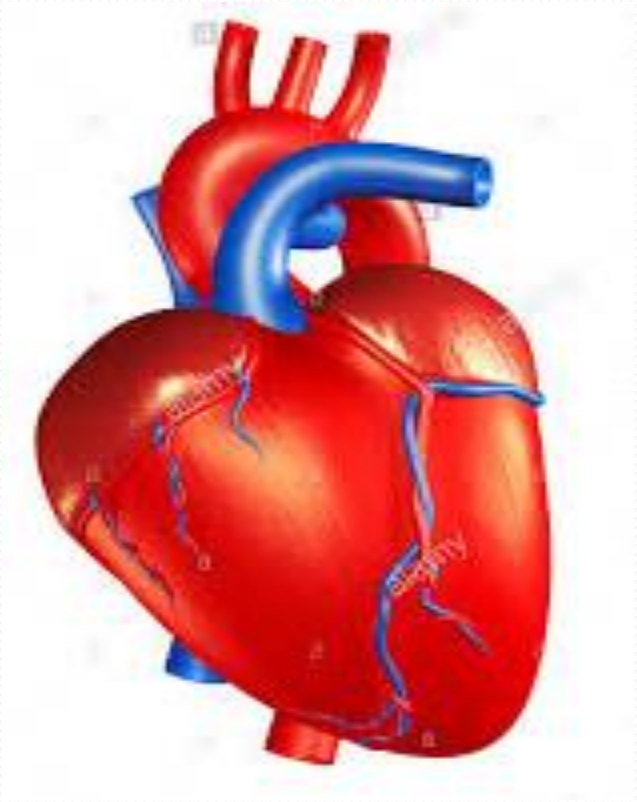
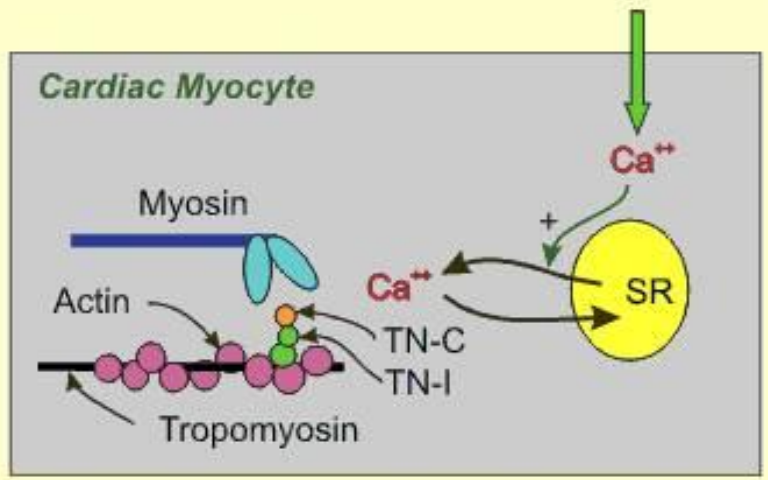


Learning Objectives

- Define Cardiac Muscle Contractility & Types Of Its Contraction
- Understand The Physiology Of Cardiac Muscle
- Understand The Phases Of Cardiac Action Potential And The Ionic Bases
- Identify The Refractory Period Of Cardiac Muscle
- Discuss The Role Of Ca^{++} In The Regulation Of Cardiac Muscle Function
- Describe The Mechanism Of Excitation Contraction Coupling
- Discuss Factors Affecting Cardiac Contractility

The Contractility of the Cardiac Muscle

- **Contractility:** Is the force of contraction for a given fiber length.
- Cardiac muscle fiber contracts when stimulated.
- Strength of contraction determines the pumping power of the heart.
- Cardiac contractile filaments are quite similar to that in skeletal muscle:
  - Thick filaments: (myosin)
  - Thin filaments: (actin, troponin, tropomyocin)
- Ca^{++} regulates contraction: (Will be discussed later)

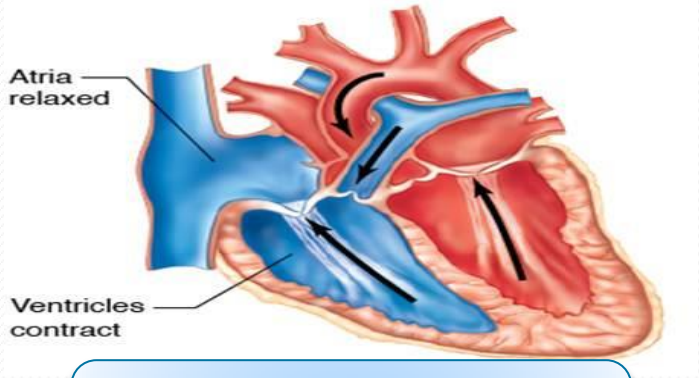


Cardiac myofilaments. Myosin (thick filament) contains 2 heads having ATPase activity. Thin filament is made up of actin, tropomyosin and troponin (TN). TN-C binds Ca^{++} released by sarcoplasmic reticulum (SR). TN-1 inhibits actin-myosin binding until Ca^{++} binds to TN-C.

The Contractility of the Cardiac Muscle

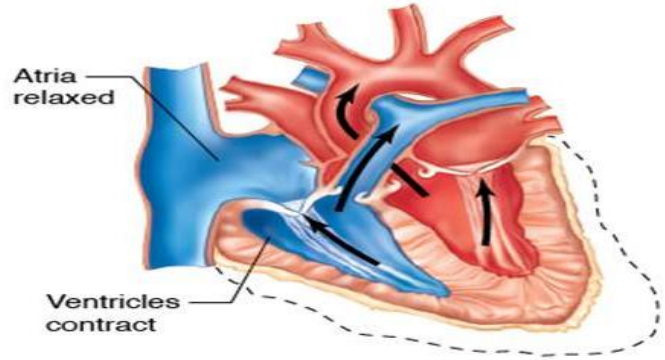
- **Cardiac muscle can perform both isometric (isovolumic) & isotonic types of contractions**

Isometric contraction: The stimulated muscle exerts an internal tension but cannot be shortened (NO work, with same length). Ventricular pressure rises to high level to open aortic & pulmonary valves.



Aortic & pulmonary valves closed

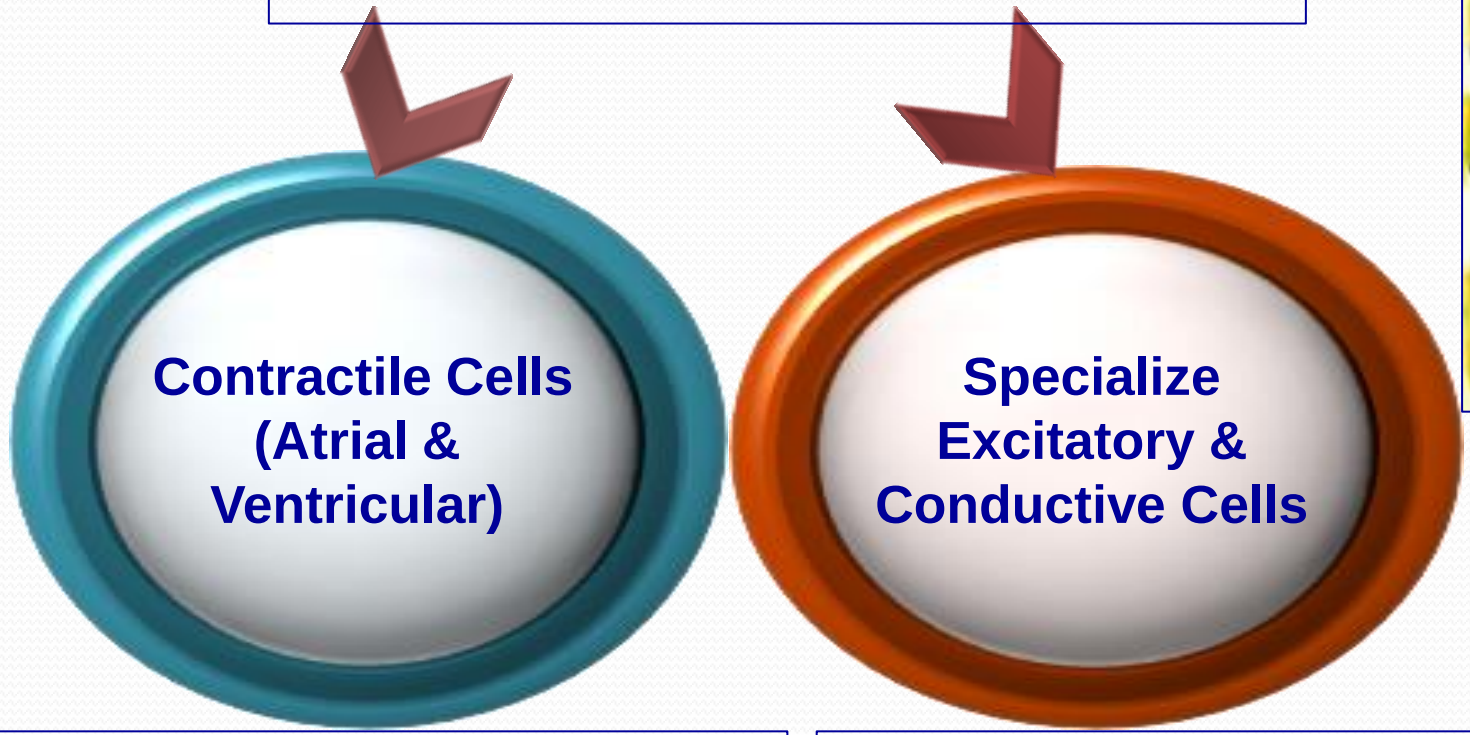
Isotonic contraction: The stimulated muscle is allowed to shorten with same tension. Volume of heart diminishes & ventricles pumps blood into lung or body through opened aortic & pulmonary valves.

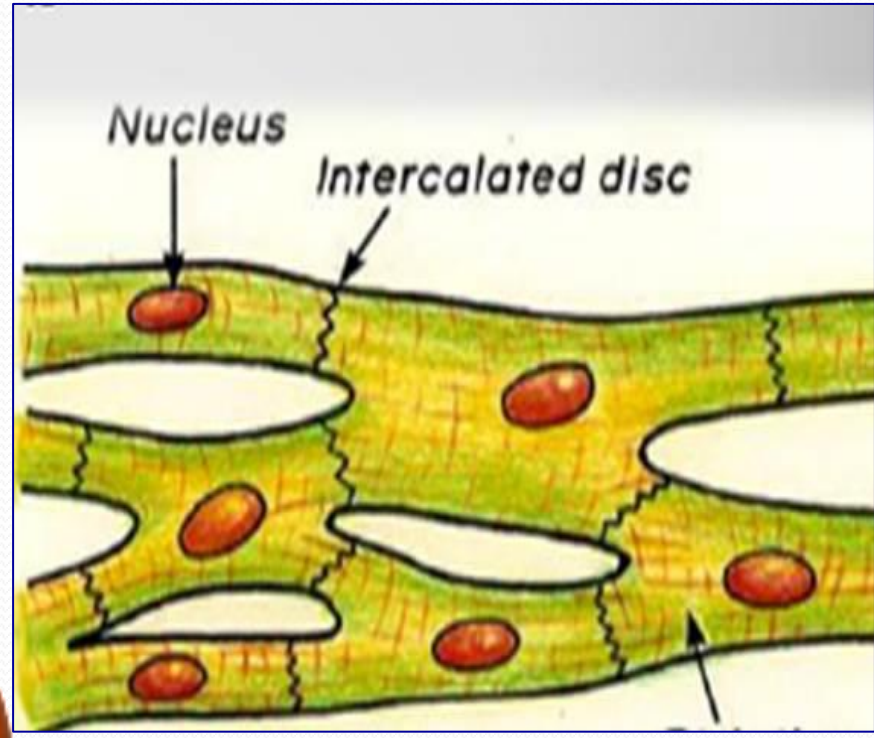


Aortic & pulmonary valves opened

Physiology of Cardiac Muscle

2 Major Types Of Cardiac Muscle Cells



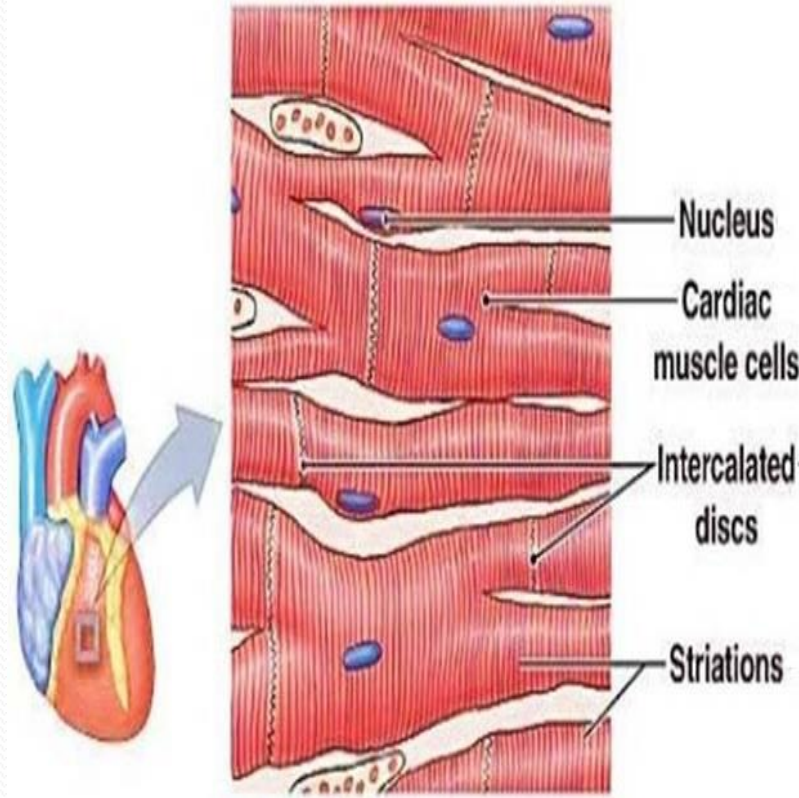


99% of cardiac muscle cells
Do mechanical work of pumping

Contract weakly because they contain few contractile fibrils

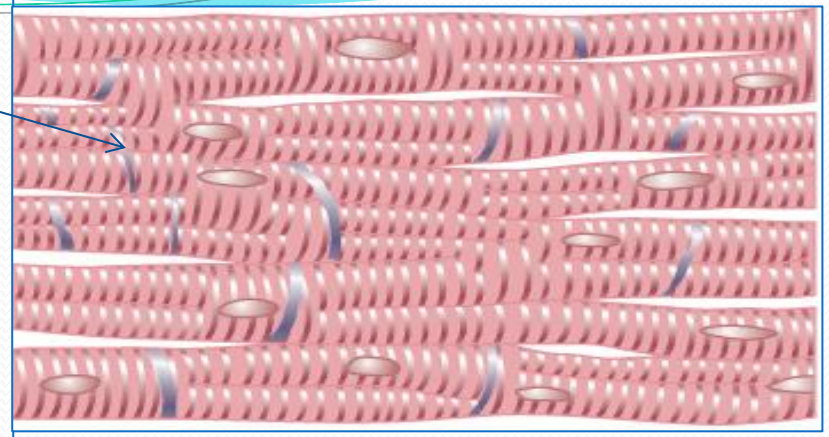
I: Contractile Cells

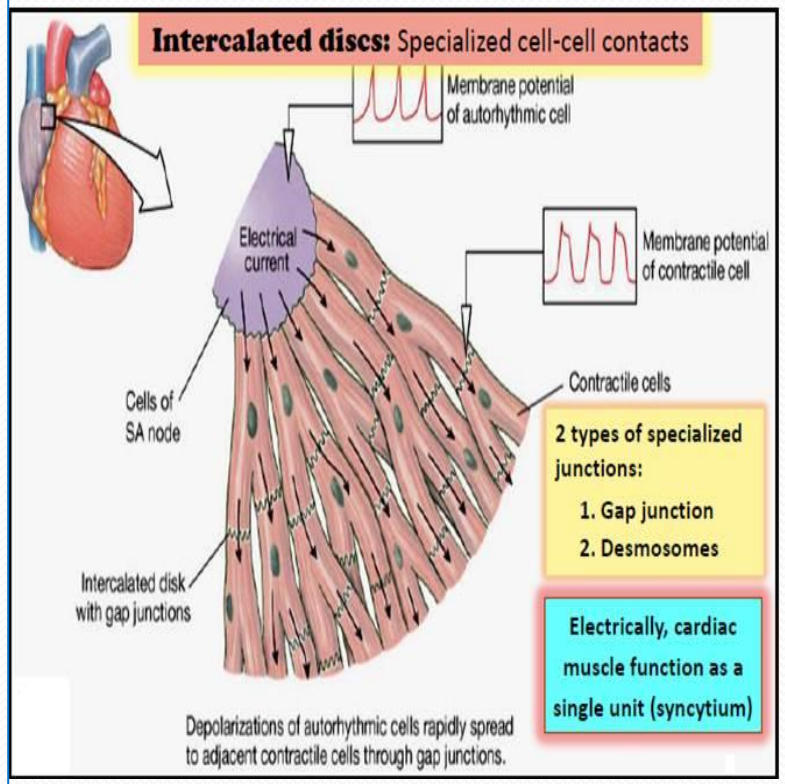
- ✓ Striated in appearance, with centrally located nuclei
- ✓ Elongated (cylindrical)
- ✓ Rich in mitochondria (up to 40% of cell volume)
- ✓ Functional unit is called Sarcomere
- ✓ Fibers are branched & interdigitated
- ✓ Sarcoplasmic reticulum is less abundant than in skeletal muscle, but greater in density than smooth muscle.
- ✓ Sarcolemma has specialized voltage-gated Ca^{++} channels that skeletal muscle does not have.
- ✓ Fibers are not anchored at ends (غير مثبتة); allows for greater sarcomere shortening and lengthening



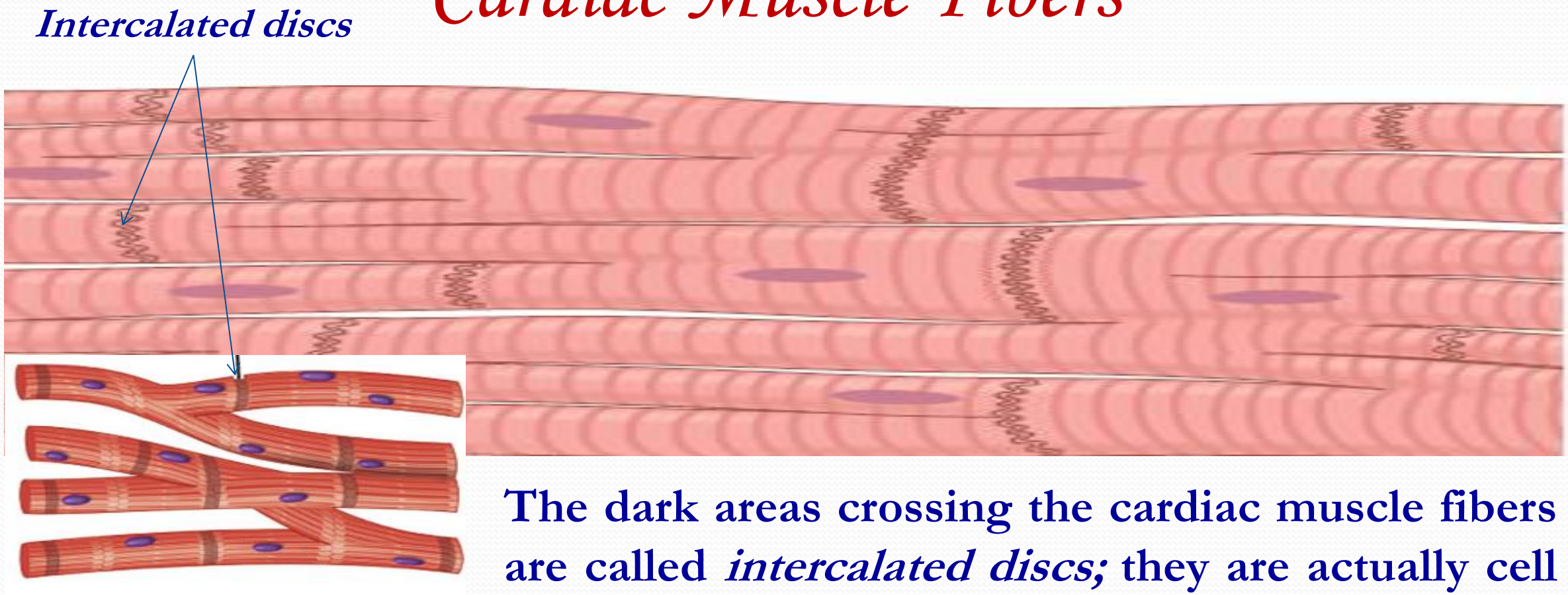
I: Contractile Cells….Cont.

- Fibers connect to one another at "**Intercalated Discs**": cell membranes, separate individual cardiac muscle cells from one another
- Within intercalated discs, two kinds of membrane junctions
  - Desmosomes (اجسام رابطة)
  - Gap junctions
- **"The Gap junctions"** are communicating junctions, trans-membrane channel proteins, connecting the cytoplasm of the cells
- Ions diffuse freely through them and move with ease in the intracellular fluid along the longitudinal axes of the cardiac muscle fibers
- Action potentials travel from one cardiac muscle cell to another



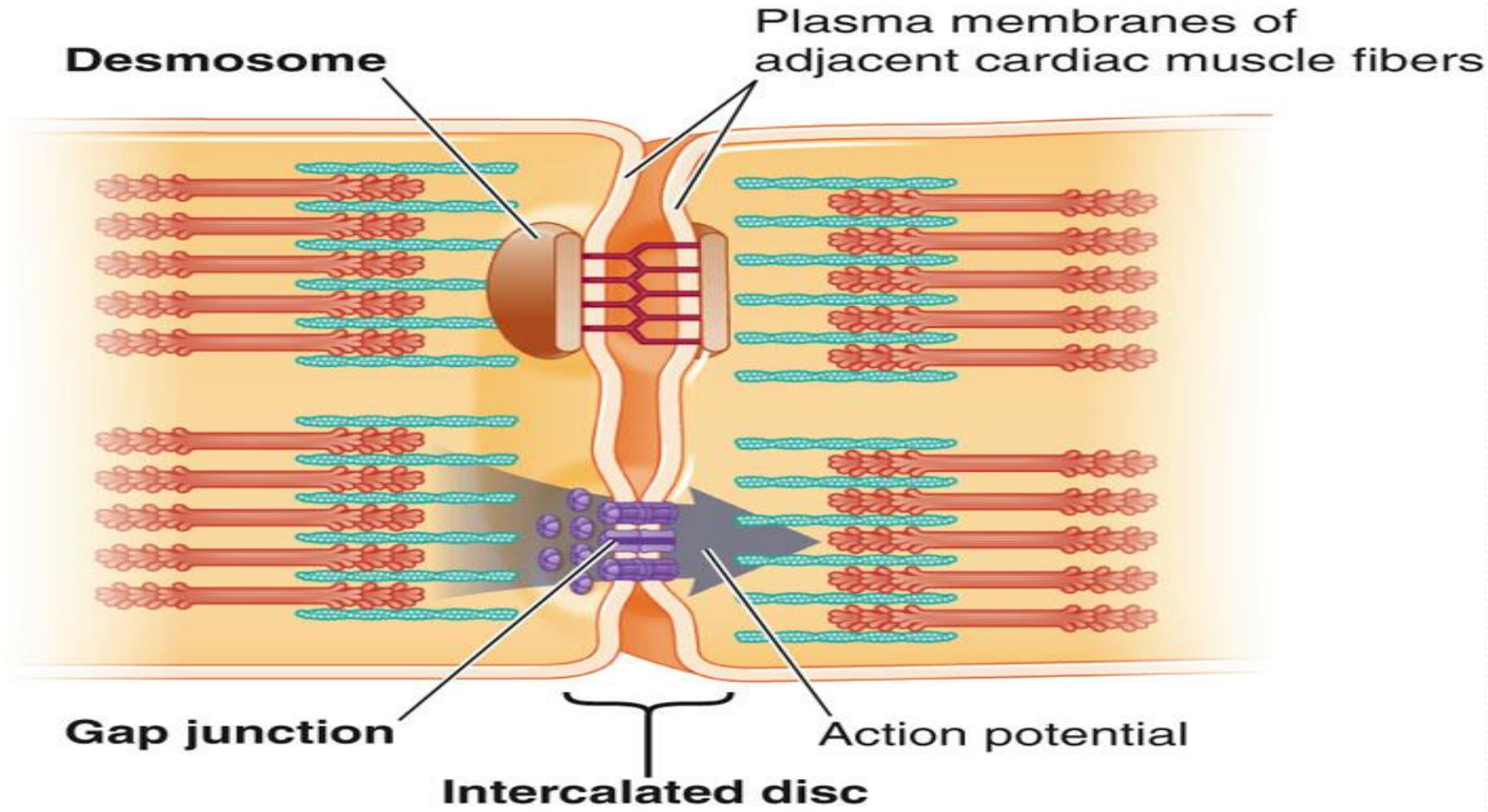


Intercalated Discs and Gap Junctions of Cardiac Muscle Fibers



The dark areas crossing the cardiac muscle fibers are called *intercalated discs;* they are actually cell membranes that separate individual cardiac muscle cells from one another.

Two Kinds of Membrane Junctions Within the Intercalated Discs

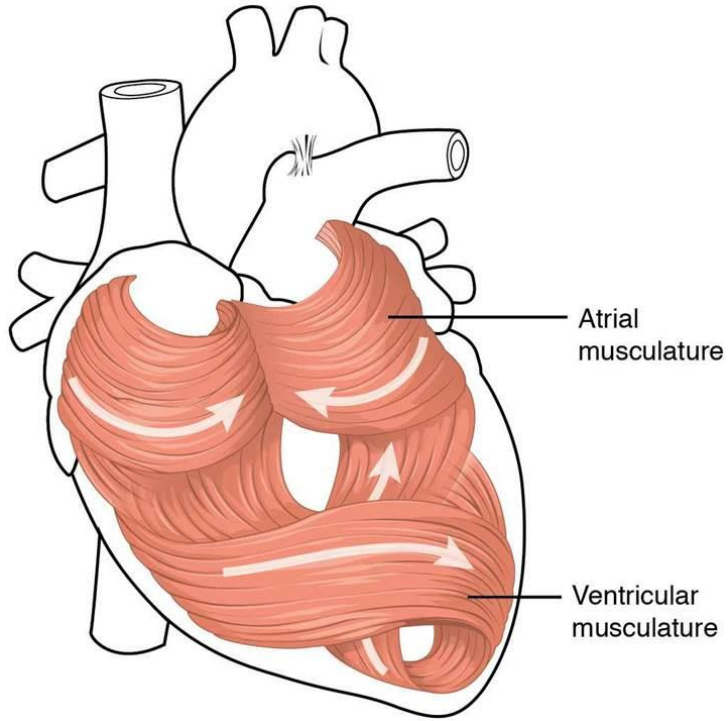


Histologic Features of Skeletal, Cardiac and Smooth Muscle

Skeletal	Cardiac	Smooth
Striated	Striated	Non-striated
Actin and myosin form sarcomeres	Actin and myosin form sarcomeres	Actin and myosin not organized into sarcomeres
Sarcolemma lacks junctional complexes between fibers	Junctional complexes between fibers including gap junctions	Gap junctions
Each fiber is innervated	Electrical syncytium	Electrical syncytium
Troponin to bind calcium	Troponin to bind calcium	Calmodulin to bind calcium
High ATPase activity (fast muscle)	Intermediate ATPase activity	Low ATPase activity (slow muscle)
Extensive sarcoplasmic reticulum	Intermediate sarcoplasmic reticulum	Limited sarcoplasmic reticulum
T tubules form triadic contacts with reticulum at A-I junctions	T tubules form dyadic contacts with reticulum near Z lines	Lack T tubules, SR controlled by second messengers
Membrane lacks Ca^{+2} channels	Voltage gated Ca^{+2} channels	Voltage gated Ca^{+2} channels

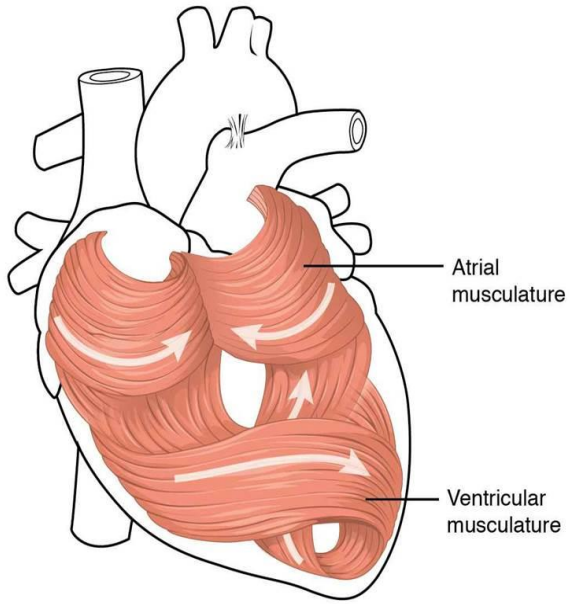
Functional Syncytia

- ✓ Physiological & histological features of cardiac muscle help it to act as a functional (not anatomical) syncytium
- ✓ Cardiac muscle cells are so tight bound that when autorhythmic cells depolarize, action potential spread rapidly to contractile cells.



Functional Syncytia….Cont.

- ✓ Cardiac muscle tissue forms 2 functional (NOT anatomical) syncytia:
  - ***Atria syncytium*** (2 atria): Both atria act as one unit.
  - ***Ventricular syncytium*** (2 ventricles): Both ventricles act as another unit.
  - Action potential can be conducted between them by specialized conducting system "A-V bundle".
  - The division of cardiac muscle mass into 2 separate syncytia allows atria to contract before ventricular contraction (for effectiveness of heart pumping).



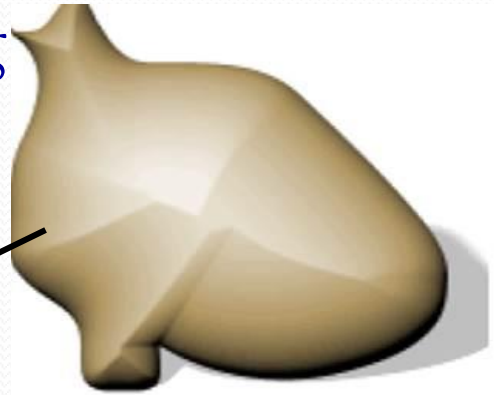
All or non principle as applied to heart

- Stimulation of a single atrial muscle fiber causes action potential to travel over entire atrial mass from cell to cell through the gap junctions leading to contraction of all the muscle fibers.
- Also stimulation of any ventricular muscle fiber causes excitation of all ventricular muscle mass.
- So, cardiac muscle sheet behave like a functional syncytium and obeys the all or non rule.

II: Conducting cells:

(Automatic/Autorythmic)

✓ Specialized or modified cardiac muscle cells, containing few contractile fibrils and have 3 properties



Self-stimulating (Automaticity) & rhythmicity

- Generate impulses spontaneously in a repetitive, regular, constant manner

Conductivity

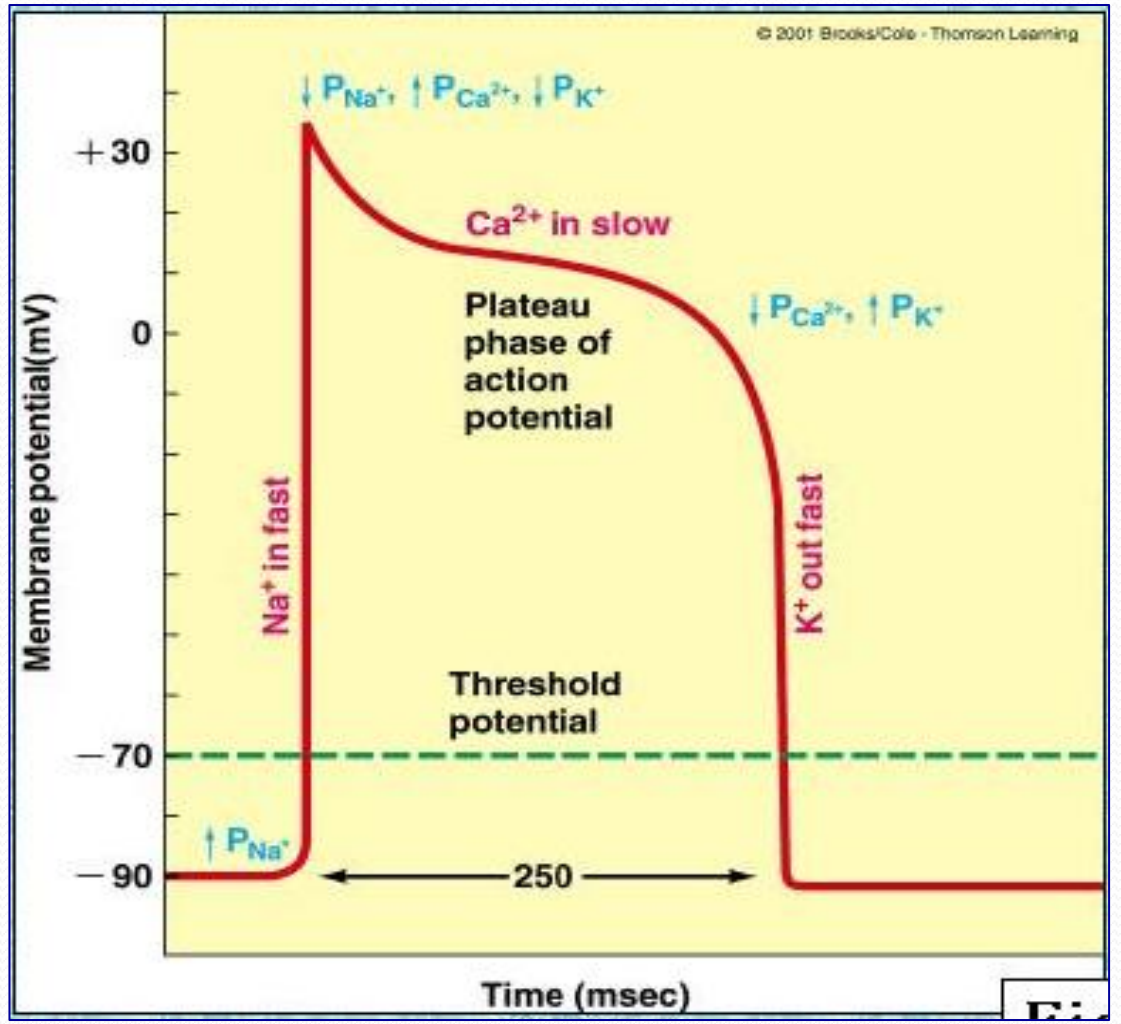
- Conducts electrical current to another cardiac cells throughout the heart

Excitability

- Respond to an electrical impulse and provide an excitatory system to the heart

Action Potential of Contractile Cardiac Muscle Fibers

- Resting membrane potential of contractile myocardial fibers is stable **"-90 mV".**
- Duration of action potential is **300-400 ms.**
- It has 5 phases



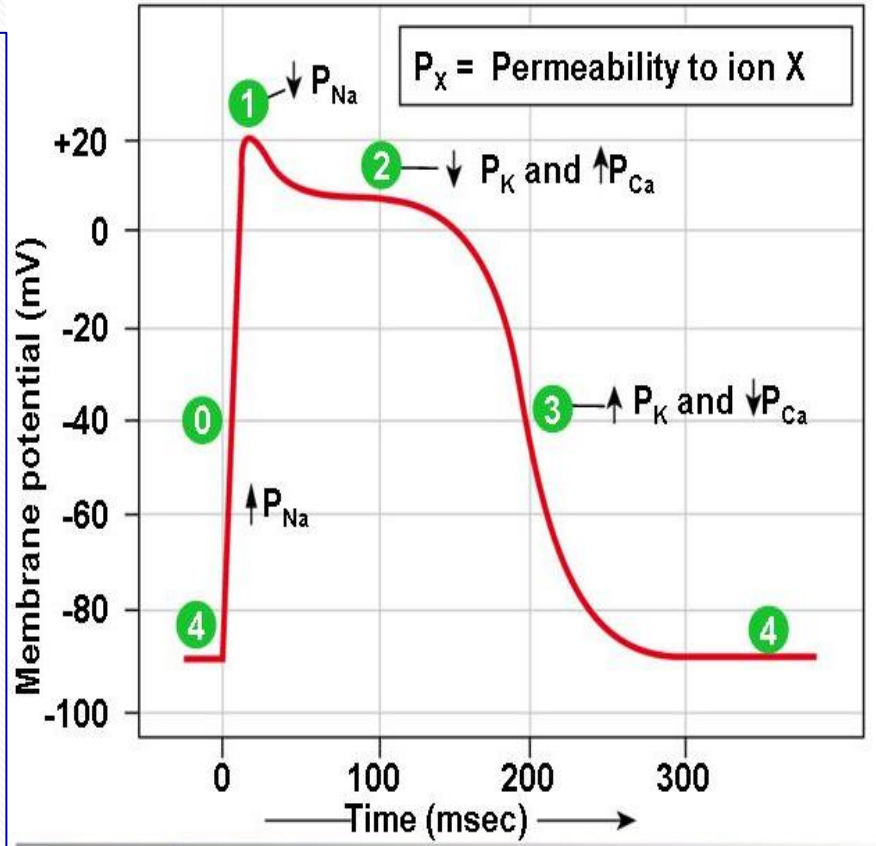
Phases of Action Potential in Cardiac Muscle

Phase 0:- Rapid depolarization (from -90 to +20 mv), caused by opening of fast voltage gated Na^+ channels → rapid Na^+ influx into cells. (magnitude ≈ 110 mv).

Phase 1:- The early rapid partial repolarization (5-10 mV) due to K^+ efflux through open K^+ channels. This phase is also caused by closure of Na^+ channels.

Phase 2:- The plateau (near 0 mV), is the flat portion of the curve. Ca^{++} channels open and cause slower but prolonged Ca^{++} influx, balanced by efflux of an equal amount of K^+. Its duration is 0.3 sec in ventricles and 0.2 sec in atria.

K^+ efflux and increased Ca^{++} influx causes the action potential to plateau.



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

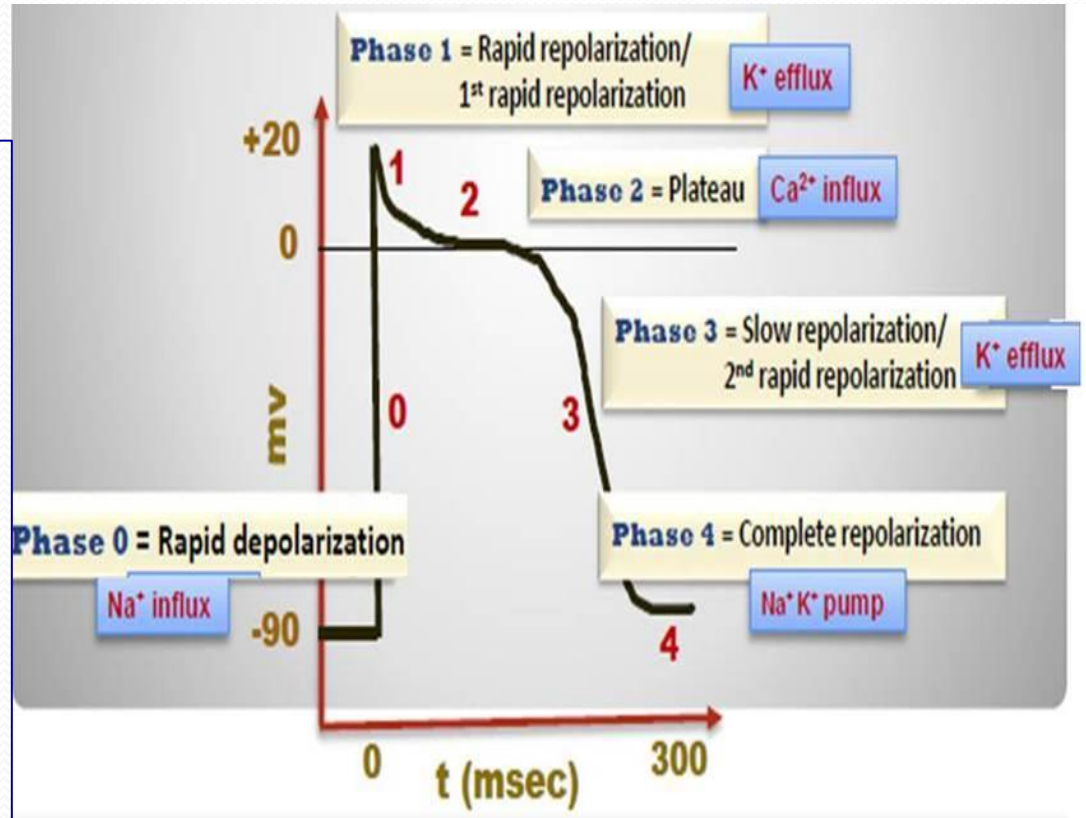
Phases of Action Potential in Cardiac Muscle….Cont.

Phase 3:- Repolarization is caused by closure of Ca^{++} channels, and opening of slow K^+ channels with sudden increase in K^+ permeability, permitting K^+ efflux outside the cell

Phase 4:- Complete repolarization, where membrane goes back to resting levels "-90 mv".

Na^+- K^+ pump works to derive excess Na^+ out and excess K^+ into.

N.B: The summated electrical activity of all cardiac muscle fibers is called "ECG".



Phase	Membrane channels
0	Na^+ channels open
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2	Ca^{2+} channels open; fast K^+ channels close
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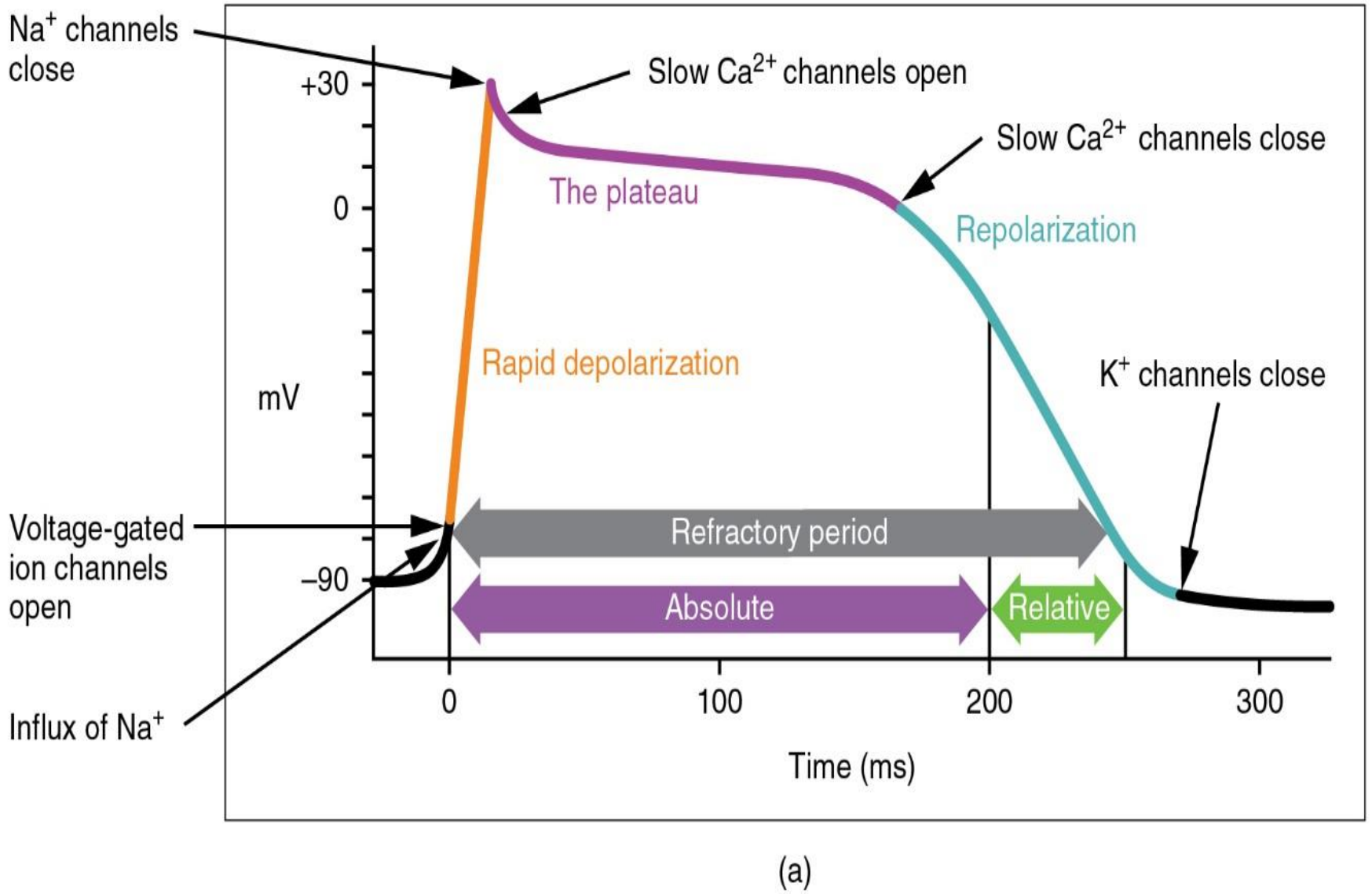
4	Resting potential

What causes the Plateau in the Action Potential?

1. **Slow Ca^{++} channels are** voltage-activated Ca^{++}-Na^{+} channels (L-type Ca^{++} channels) slow to open & remain open for several tenths of a second. Prolonged opening of the slow Ca^{++}-Na^{+} channels allows large quantity of Ca^{++} flow to the interior of the cardiac muscle fiber, cause plateau.
2. Decreased permeability of the cardiac muscle membrane for K^{+} → decrease K^{+} outflux during the action potential plateau.

- Moreover, voltage-gated K^{+} channels are slower to open. This delays the return of the membrane potential to −80 to −90 millivolts.
- The presence of plateau in the action potential causes ventricular contraction to last as much as 15 times as long in cardiac muscle as in skeletal muscle.

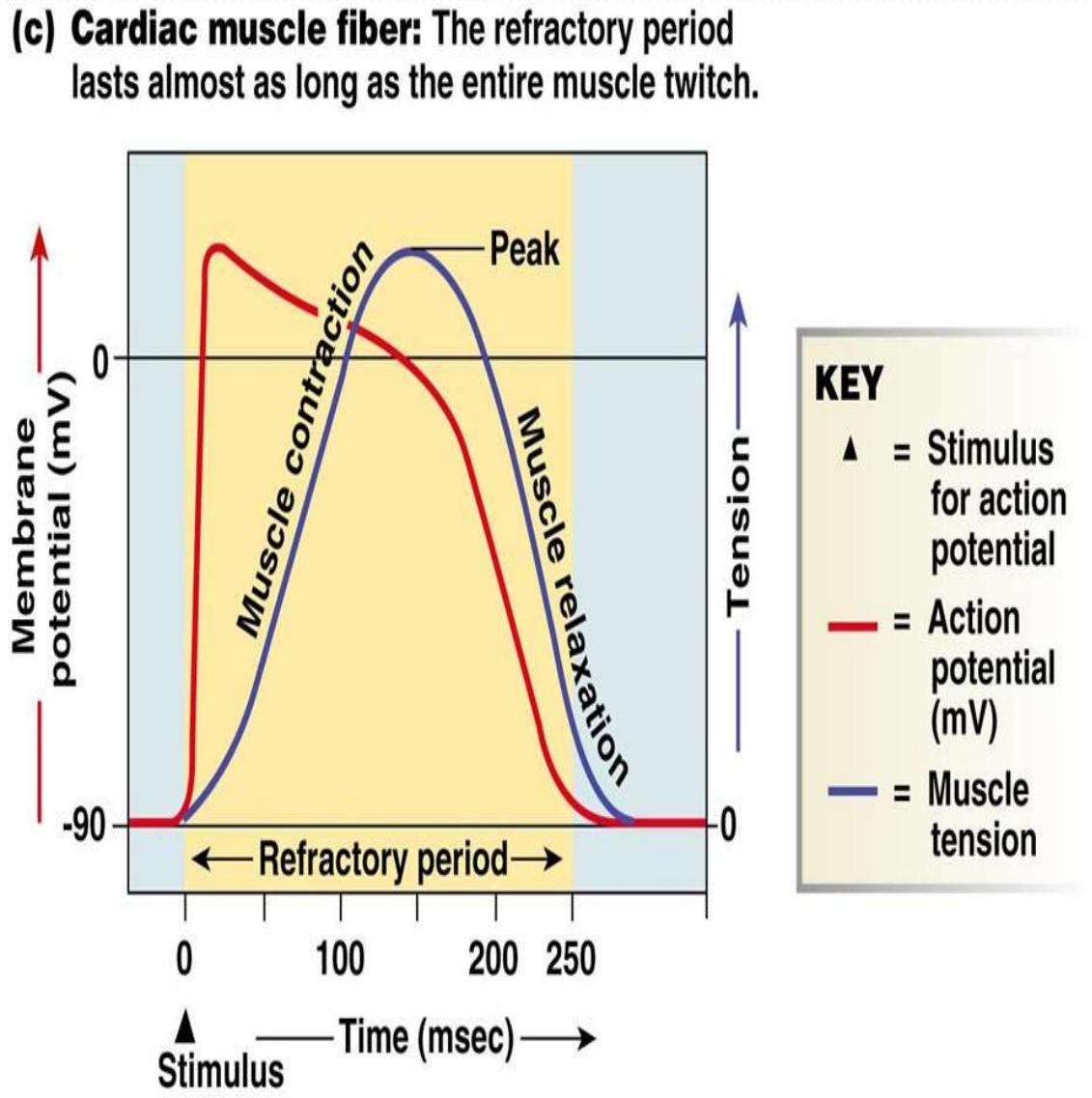
Action Potential & refractory periods in Cardiac Muscle



(a)

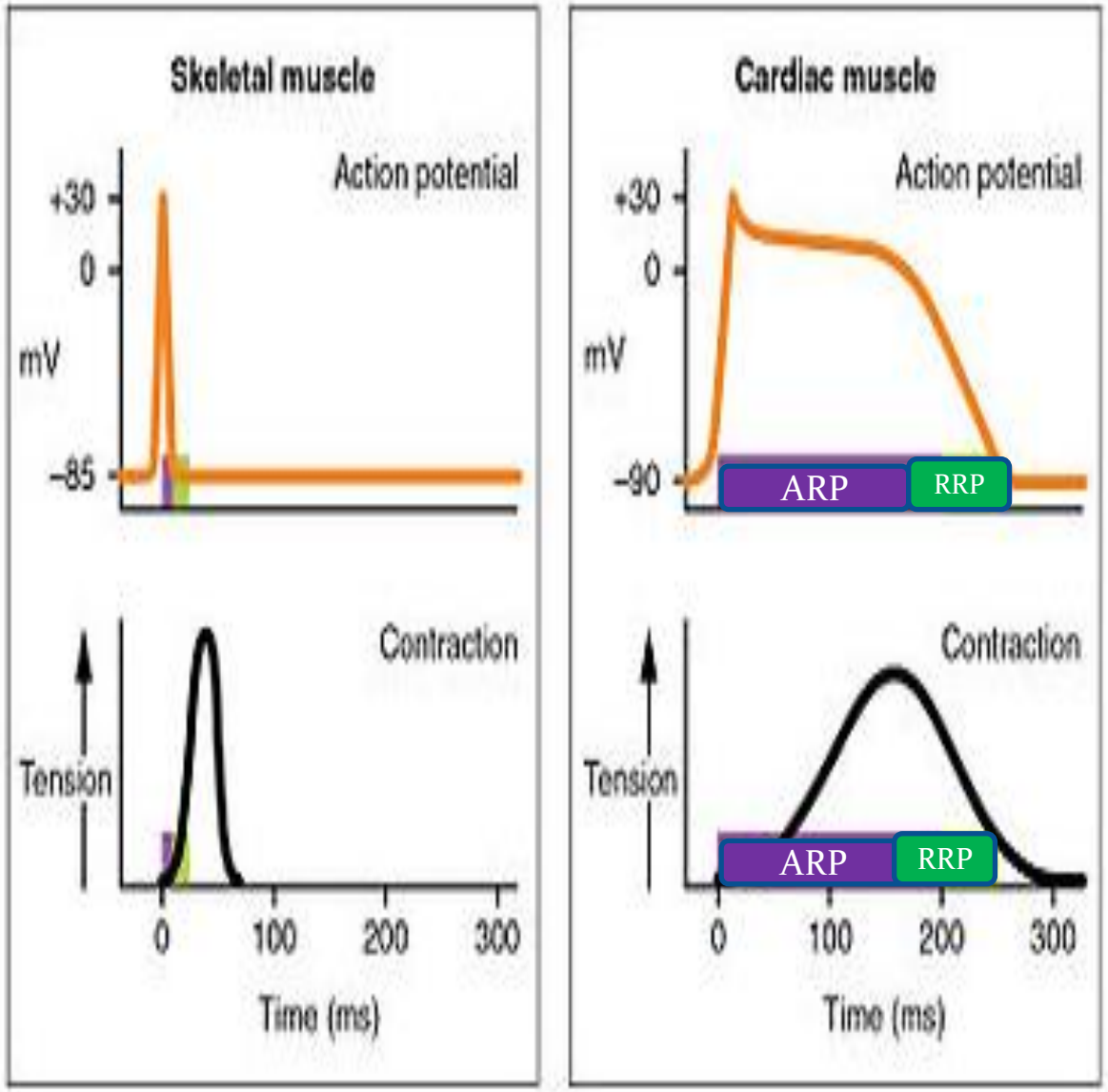
Refractory Period of Cardiac Muscle

- Is the interval of time during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle.
- Cardiac muscle is refractory to re-stimulation during the action potential.
- In cardiac muscle fiber, the refractory period lasts almost as long as the entire muscle contraction (almost 300 msec).
- ***Significance***: Cardiac muscle can't be tetanized i.e. Summation cannot occur. This ensures alternate periods of contraction and relaxation which are essential for pumping blood
- If tetanus in heart continued for few seconds, circulation would stop.



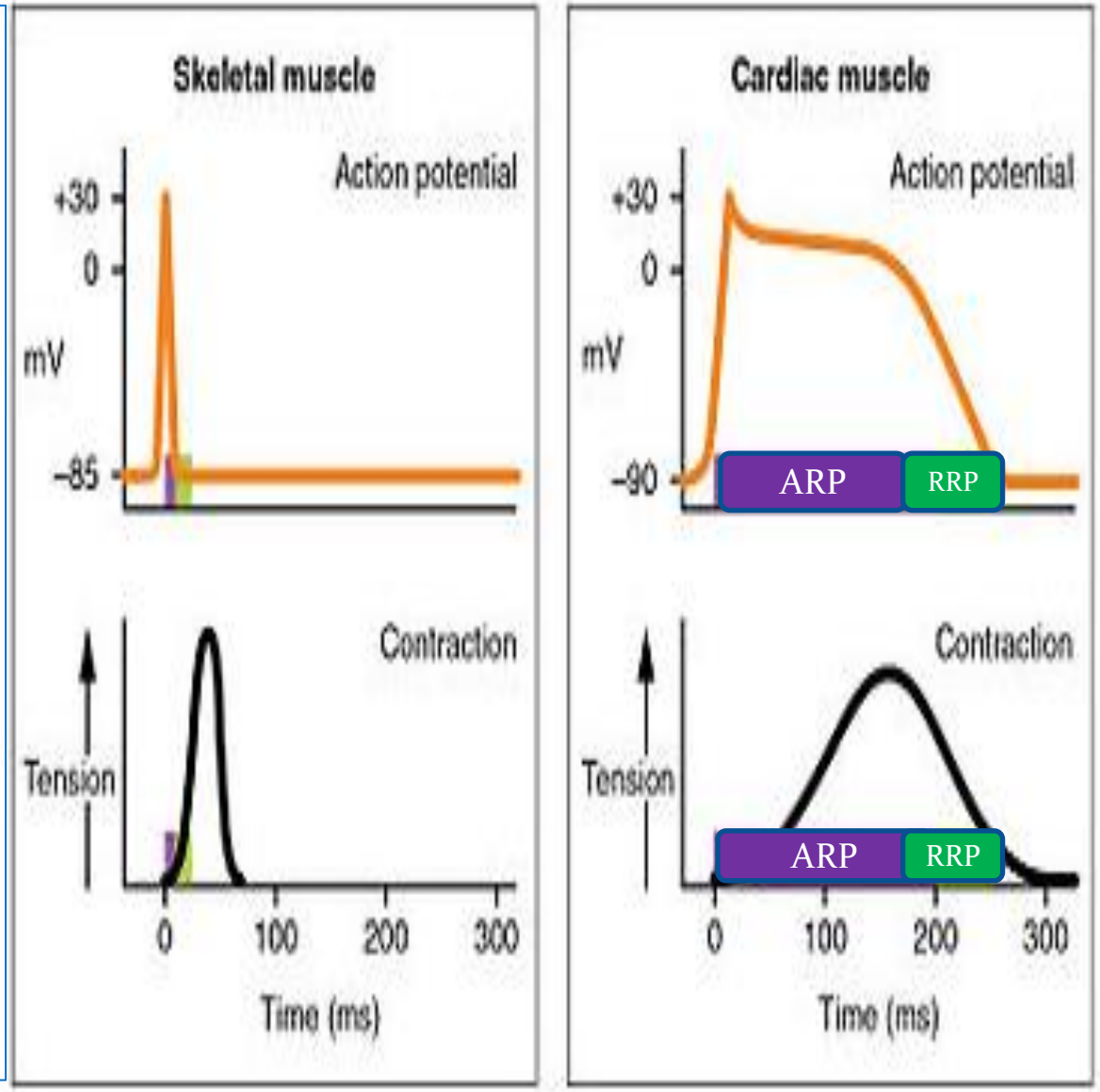
Cardiac Muscle has two Refractory Period s:

- ***Absolute refractory period***
  - Cardiac muscle cannot be excited while it is contracting (due to complete depolarizationa)… benefit?
  - Time: depolarization and the 1st 2/3 of repolarization (phases 0, 1, 2 and beginning of phase 3).
  - Mechanically, it occupies whole period of systole & early diastole.
  - Duration: Long (0.25- 0.3 sec).

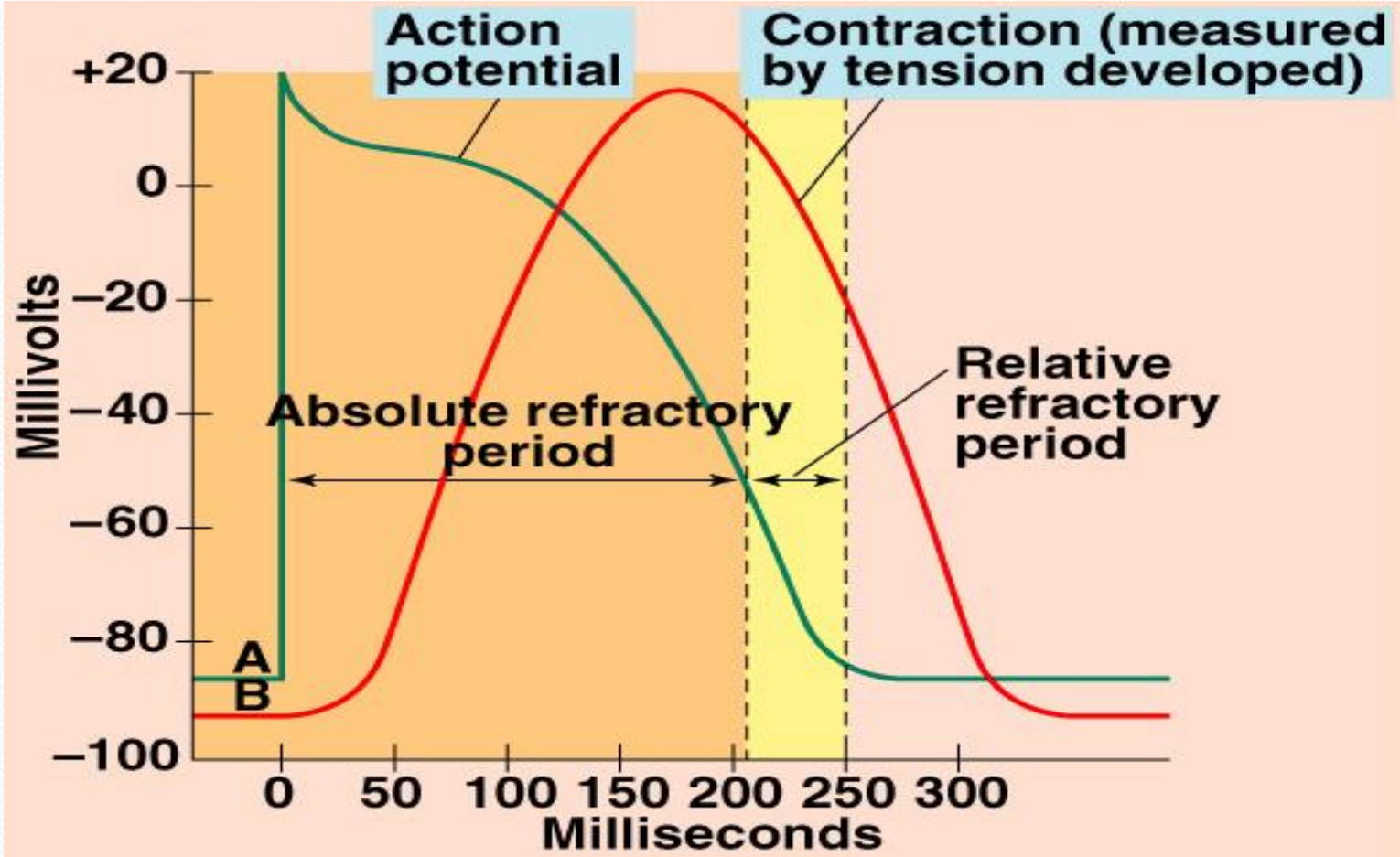


Cardiac Muscle has two Refractory Period s….Cont.

- ***Relative refractory period***
  - Cardiac muscle can be excited by strong stimulus to produce a new systole called extra-systole.
  - Time: the last 1/3 of repolarization (the rest of phase 3)
  - Mechanically, it occupies the middle of diastole.
  - Duration: 0.05 sec. in ventricles and 0.03 sec in atria.

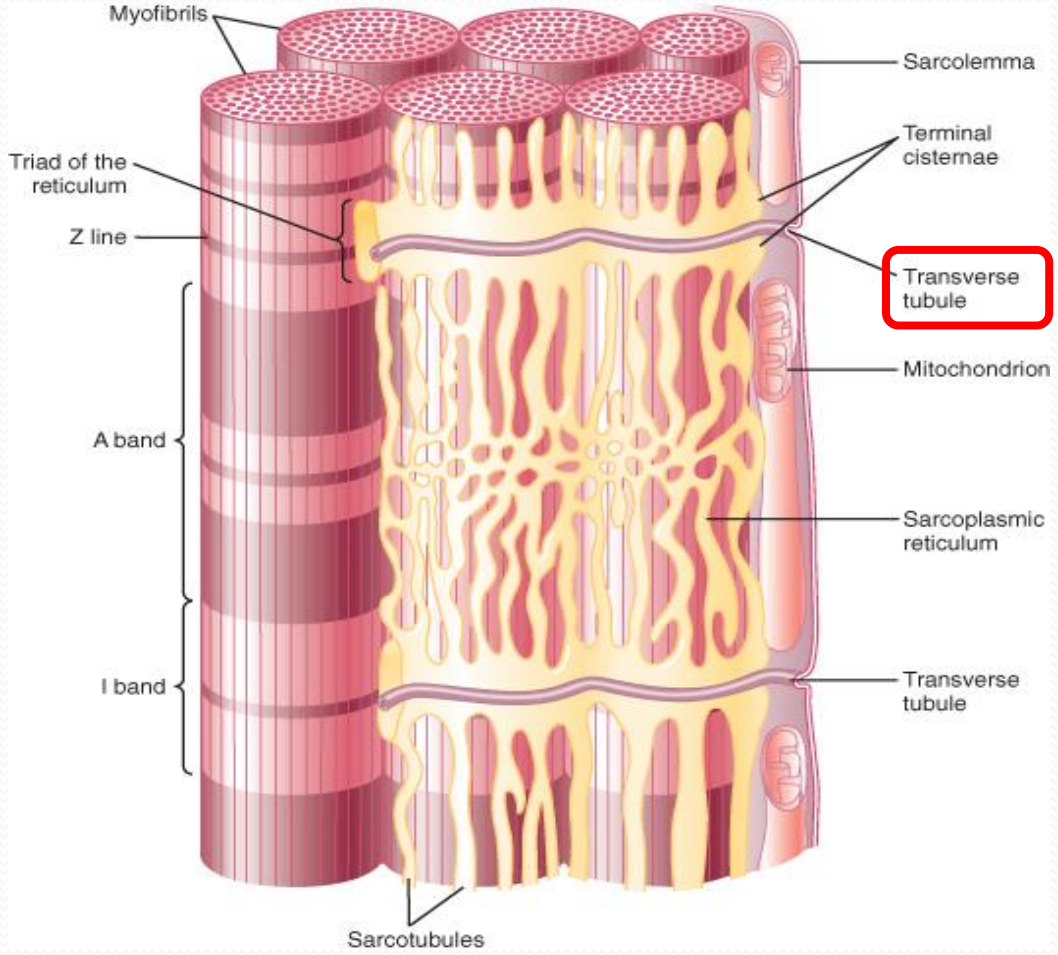


The Refractory Period s of cardiac Muscles



Excitation – Contraction Coupling in Cardiac Muscle

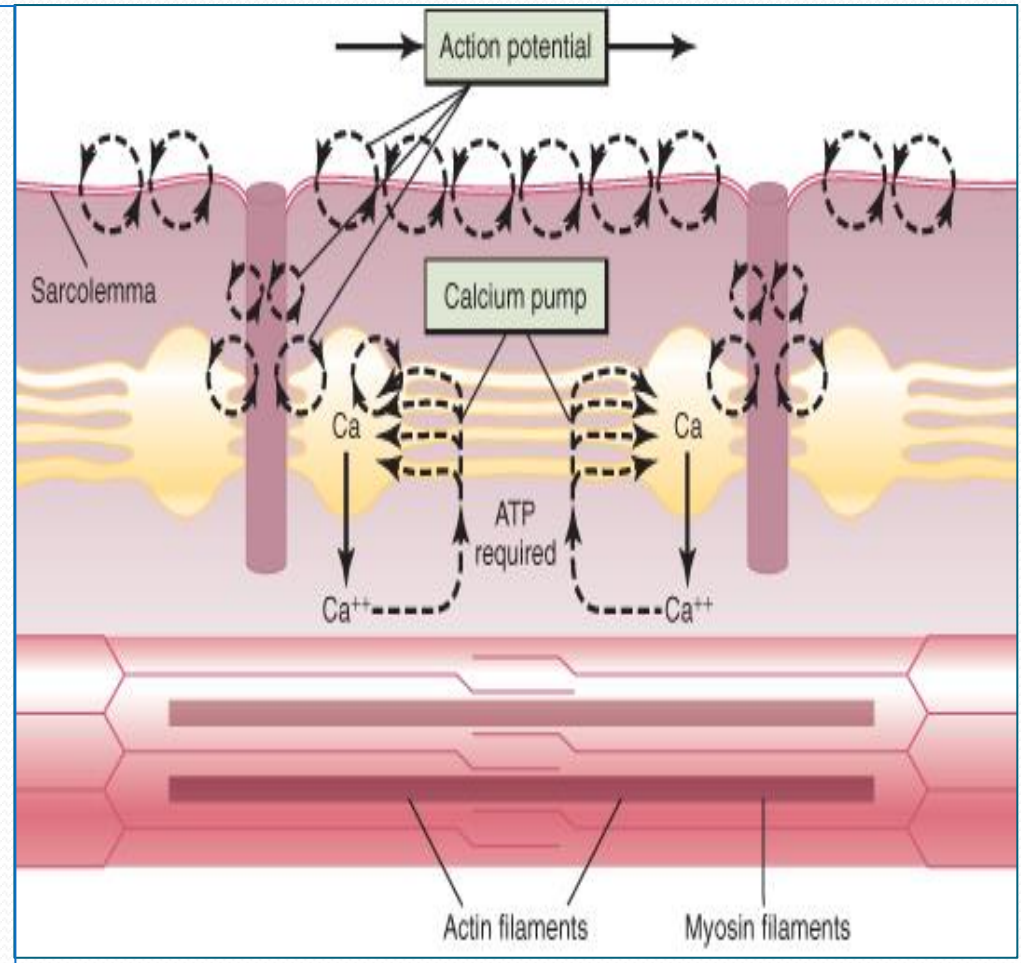
- ***Excitation – Contraction Coupling*** is the mechanism by which the action potential causes muscle contraction.
- Excitation of the heart is triggered by electrical impulse rather than neural transmitters.



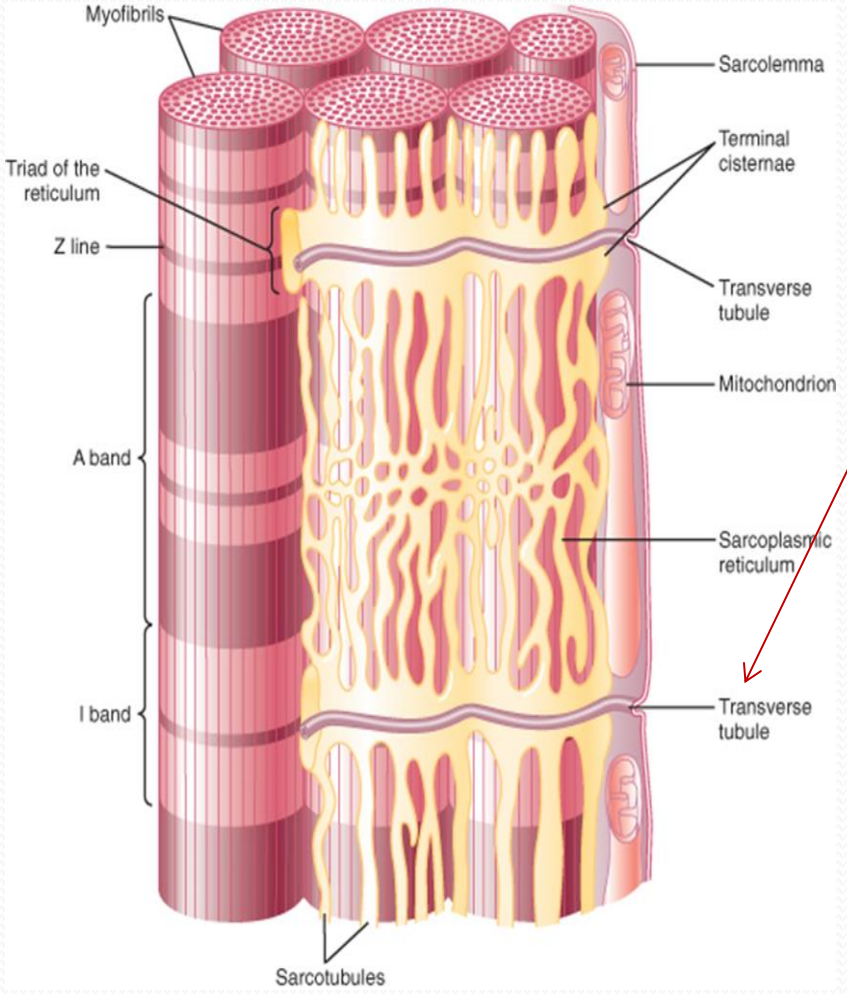
Transverse (T) tubule-sarcoplasmic reticulum system

Excitation – Contraction Coupling…Cont.

- Contraction of the heart is triggered by elevation of intracellular Ca^{++} influx.
- Cardiac muscle are continually contracting and require substantial amounts of energy for the process of contraction and sliding mechanism.
- The energy is derived from ATP generated by oxidative phosphorylation in the mitochondria (the myocytes contain large numbers of mitochondria).
- Each contraction involves the hydrolysis of an ATP molecule.



Excitation – Contraction Coupling…Cont.



- 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.
- Ca^{++} ions regulate the contraction of cardiac muscle, so the strength of muscle contraction depends to a great extent on the concentration of Ca^{++} in the extracellular fluids
- Entry of extracellular Ca^{++} causes the release of Ca^{++} from the sarcoplasmic reticulum (Ca^{++} - induced Ca^{++} release), source of about 95% of Ca^{++} in cytosol.

Summary of Excitation – Contraction Coupling

1- Ca^{++} enter the cell during depolarization and triggers release of Ca^{++} by terminal cisternae.

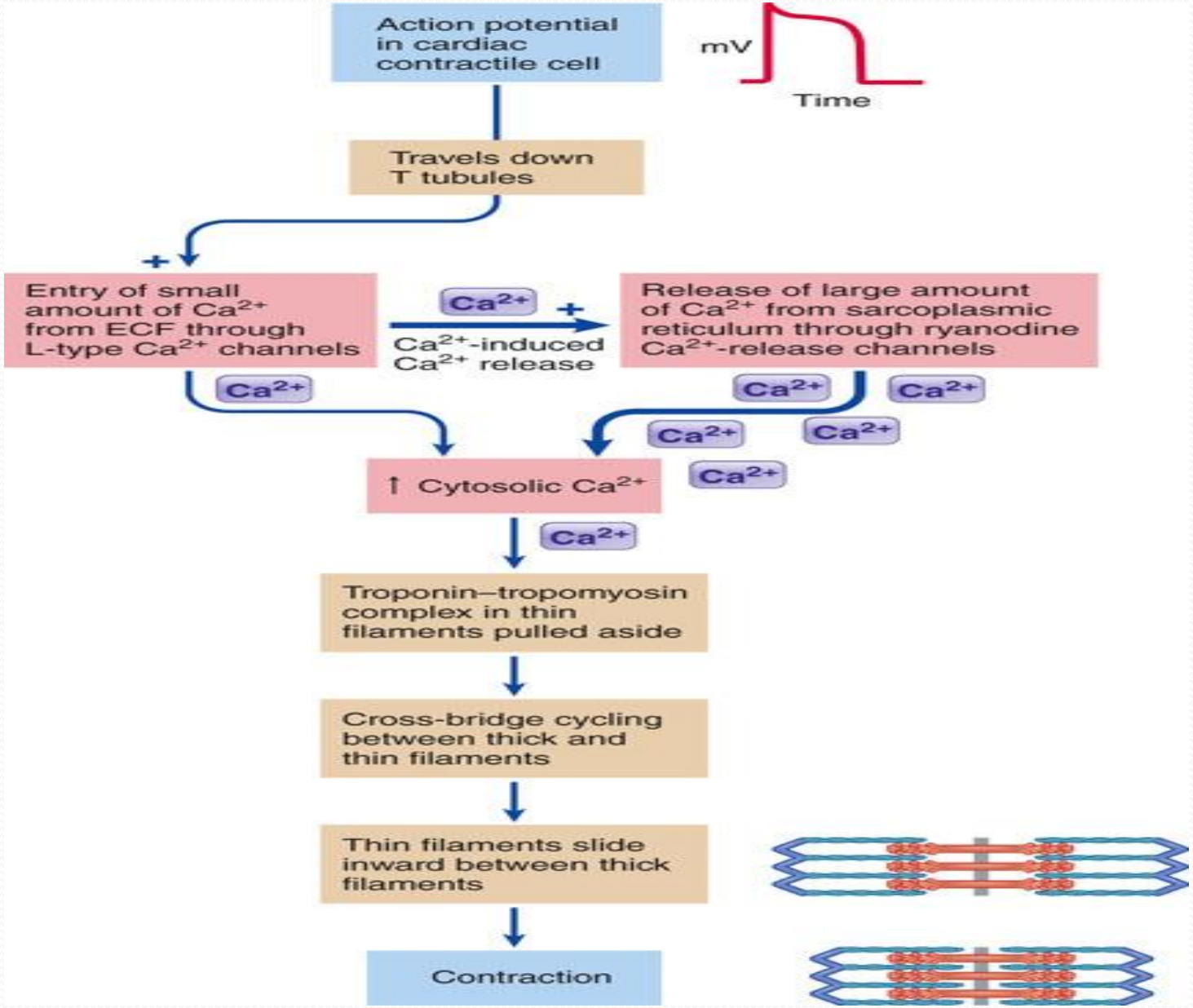
2- Ca^{++} binds to troponin-C inducing a conformational change in the troponin complex.

3- Myosin heads bind to actin, leading to cross-bridge movement (requires ATP hydrolysis) and reduction in sarcomere length.

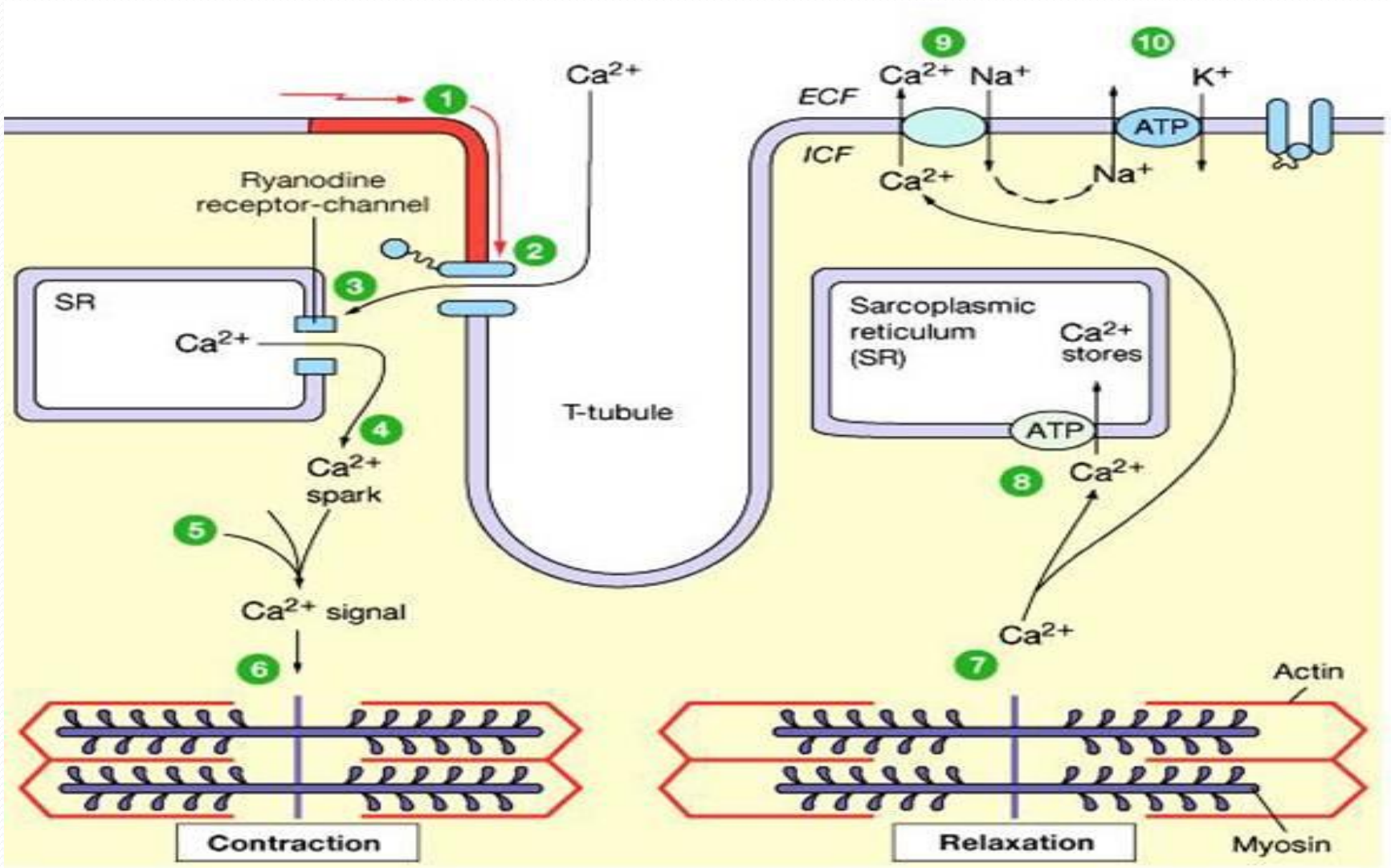
4- Ca^{++} is re-sequestered by sarcoplasmic reticulum by sarco-endoplasmic reticulum calcium ATPase (SERCA) pump.

5- Ca^{++} is removed from troponin-C and myosin unbinds from actin (requires ATP hydrolysis); this allows the sarcomere to resume its original, relaxed length.

Excitation – Contraction Coupling in Cardiac contractile Cells

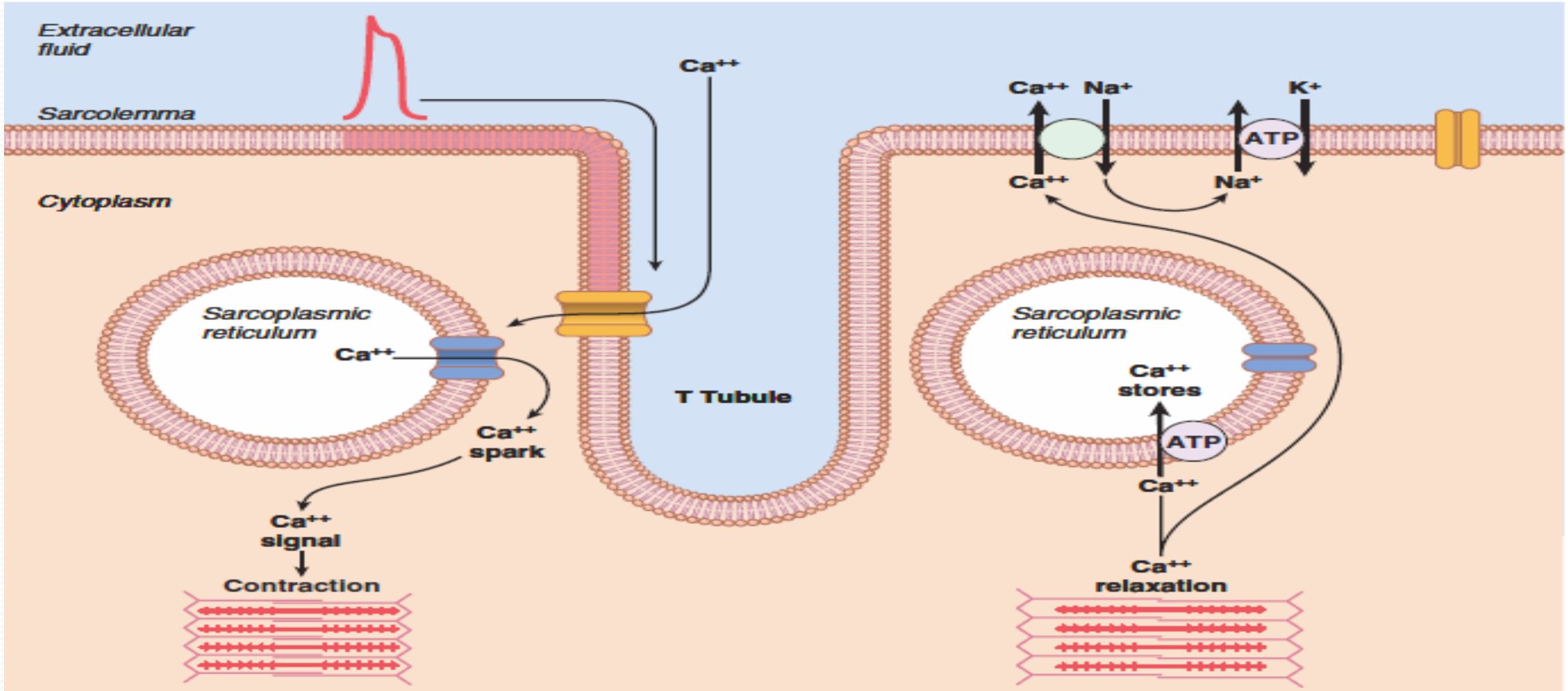


Excitation – Contraction Coupling…Cont.



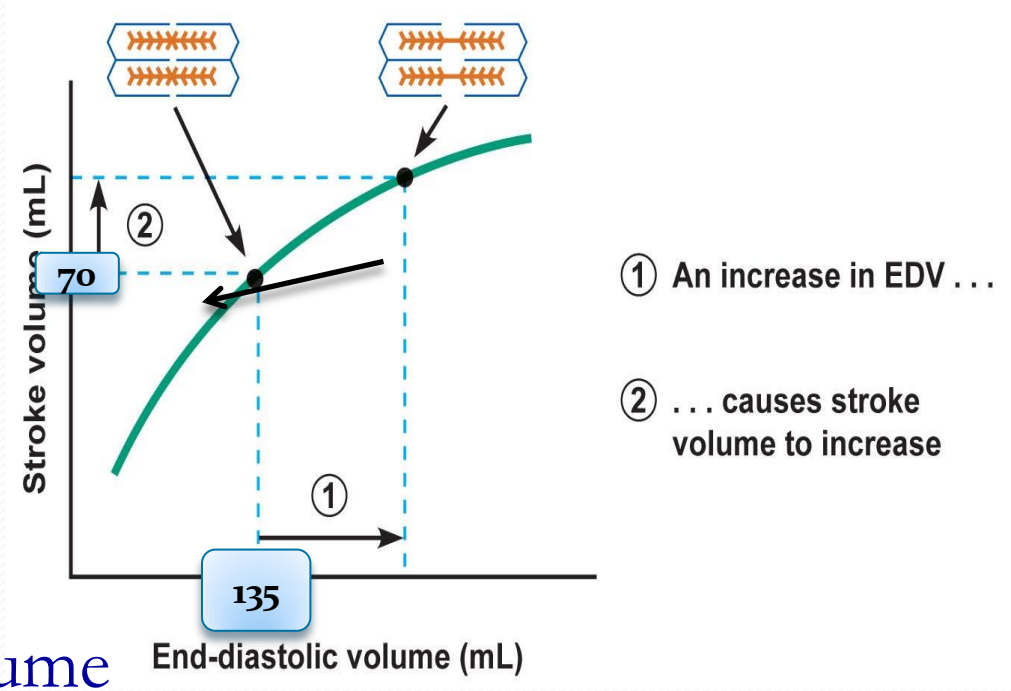
1. Action potential enters from adjacent cell.
2. Voltage-gated Ca^{2+} channels open. Ca^{2+} enters cell.
3. Ca^{2+} induces Ca^{2+} release through ryanodine receptor-channels (RyR).
4. Local release causes Ca^{2+} spark.
5. Summed Ca^{2+} sparks create a Ca^{2+} signal.
6. Ca^{2+} ions bind to troponin to initiate contraction.
7. Relaxation occurs when Ca^{2+} unbinds from troponin.
8. Ca^{2+} is pumped back into the sarcoplasmic reticulum for storage.
9. Ca^{2+} is exchanged with Na^{+}.
10. Na^{+} gradient is maintained by the Na^{+}-K^{+}-ATPase.

Mechanism of Excitation – Contraction Coupling in Cardiac Muscle



Intrinsic Regulation Of Heart Pumping the Frank-starling Mechanism

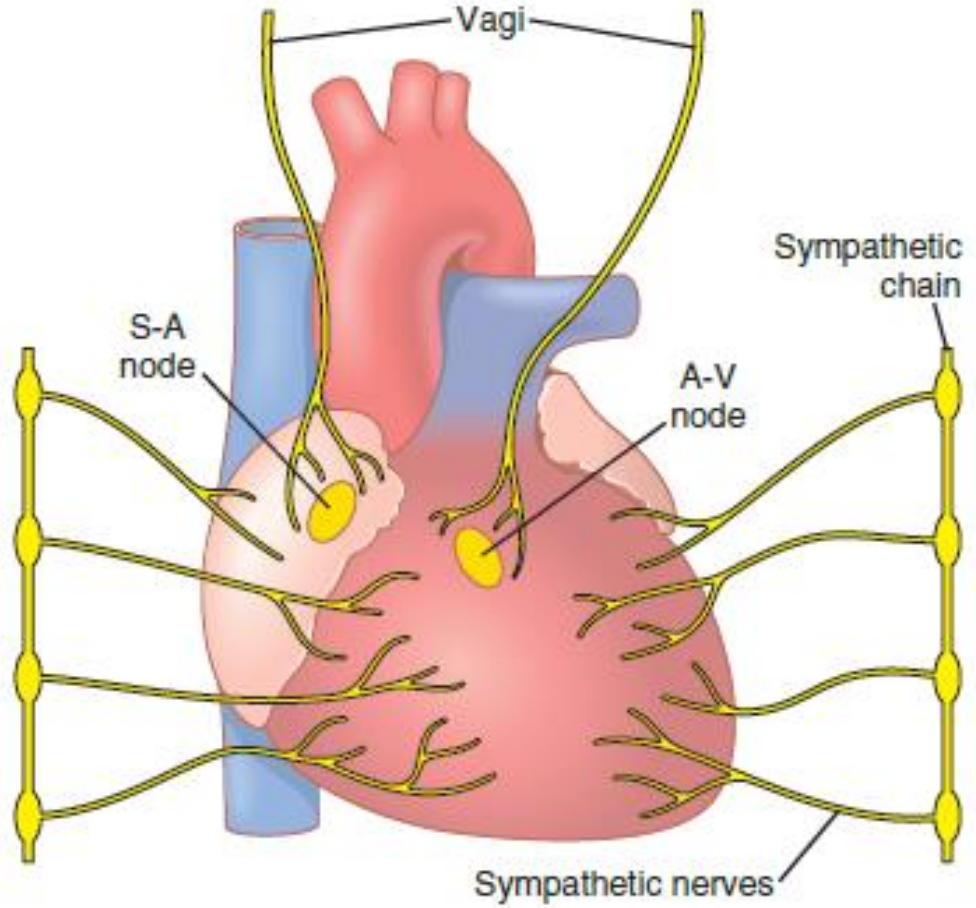
- It is the intrinsic ability of the heart to adapt to increasing volumes of inflowing blood
- The force of contraction is proportional to the initial length of the cardiac muscle within physiological limits



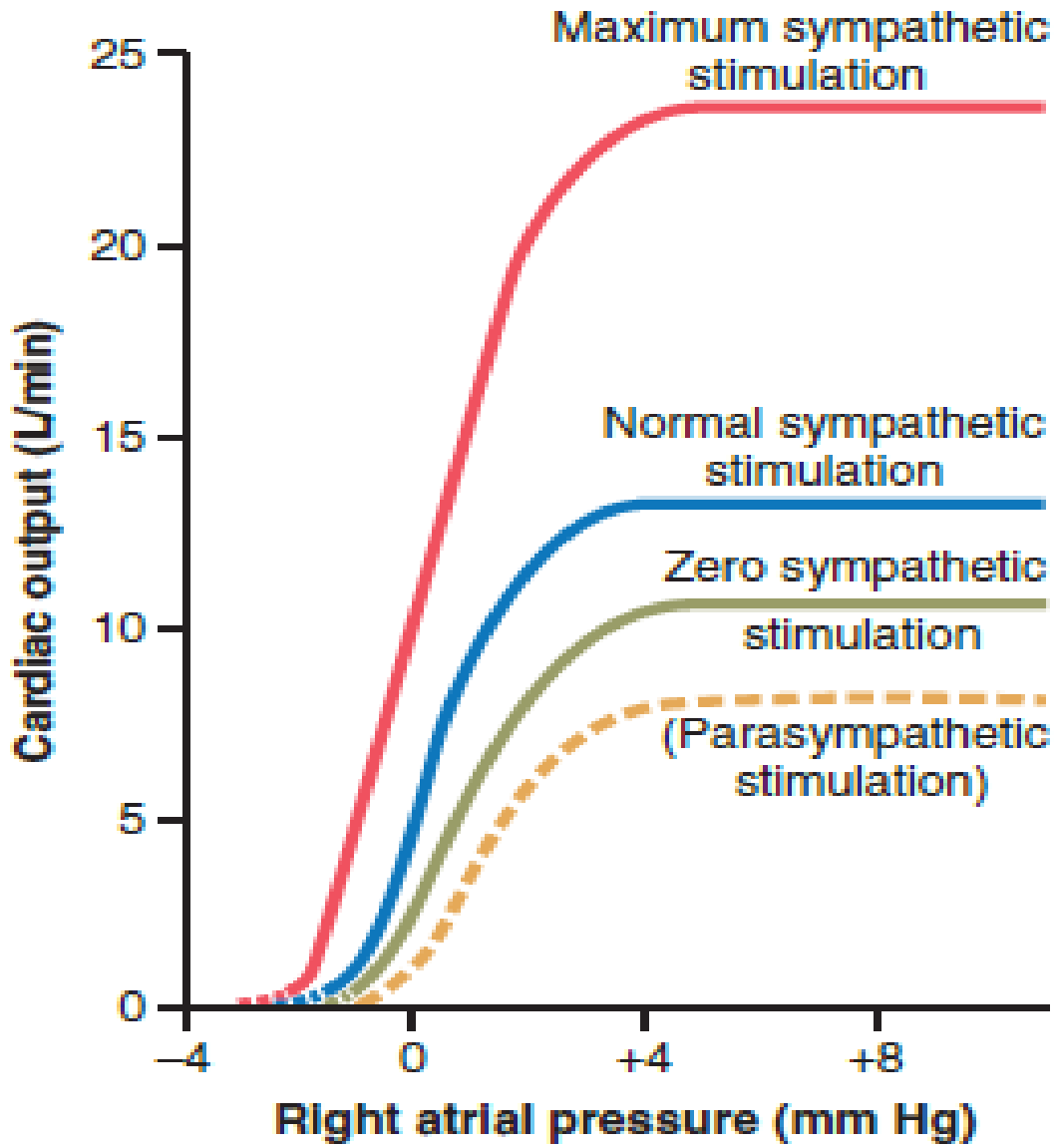
- The initial length depends on end diastolic volume
- Therefore, the ventricle, because of its increased pumping, automatically pumps the extra blood into the arteries.
- Cardiac muscle accommodates itself to the changes in venous return up to certain limits

Effects of Autonomic Innervation on Heart Pumping

- Sympathetic nerves are distributed to both atria and ventricles. So, they increase the force of both atria & ventricular contractions.
- In contrast, The vagal fibers are distributed mainly to the atria and not much to the ventricles. So, vagus nerves decrease the force of atrial contraction (with a slight decrease in ventricular contraction).



Effect on the cardiac output curve of different degrees of sympathetic or parasympathetic stimulation.



Effects of other factors on Heart Pumping

- ***Oxygen supply:***

  Hypoxia: ↓Contractility

- ***[Ca^{++}]& [K^{+}] ion concentration in ECF:***

  ↑[Ca^{++}]:↑ Contractility. Excess Ca^{++} cause the heart to move toward spastic contraction. This effect is caused by a direct effect of Ca^{++} to initiate the cardiac contractile process.

  ↑[K^{+}]: ↓ Contractility. Excess K^{+} causes the heart to become dilated and flaccid and also slows the heart rate. These effects result partially from decrease the resting membrane potential in the cardiac muscle fibers.

- ***Physical factors:***

  Warming: ↑ Contractile strength of the heart temporarily such as that which occurs during body exercise,

  Cooling: ↓ Contractility

Summary: Regulation Of Heart Pumping

Ionotropic effect: mechanism that affect the contractility

Positive Inotropic Effects

↑ Cardiac contractility

- **Sympathetic stimulation**
- **Calcium ions**
- **Digoxin, digitalis**
- **Warming (exercise)**

Negative Inotropic Effects

↓ Cardiac contractility

- **Parasympathetic stimulation**
- **Ca^{++} channel blockers**
- **Potassium ions**
- **Beta Blockers**
- **Cooling**

For further readings and diagrams:

Textbook of Medical Physiology by Guyton & Hall

Chapter 9 (Heart Muscle)


Thank you