Contractile Mechanism in Cardiac Muscle

Physiology Team 439

MED439
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Red : important
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Gray: extra information
Textbook: Guyton

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Objectives

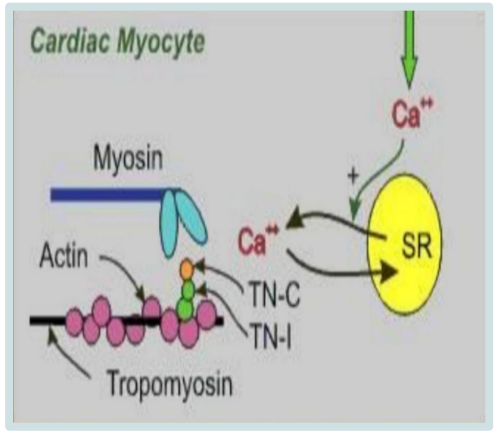
- Define Cardiac Muscle Contractility & Types Of Its Contraction
- Understand The Physiology Of Cardiac Muscle
- Understand The Phases Of Cardiac Action Potential And The Ionic bases
- Identify The Refractory Period Of Cardiac Muscle
- Discuss The Role Of Ca++ In The Regulation Of Cardiac Muscle Function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

Recap:

Skeletal muscle	Cardiac muscle	Smooth muscle
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 + desmosomes	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 contact with reticulum near Z lines	Lack T tubules, SR controlled by second messengers
Membrane lacks Ca+2 channels	**Voltage gated Ca+2 channels** (cause Ca++ induced Ca++ release discussed later)	Voltage gated Ca+2 channels

The Contractility of the Cardiac Muscle

- **Contractility:** the force of contraction for a given fiber length.
  Ability to contract after electrical impulse response
  - Cardiac muscle fiber contracts when stimulated.
  - Strength of contraction determines the pumping power of the heart
  - Ca++ regulates contraction (cause Ca++ induced Ca++ release that will be discussed later)



- **Cardiac contractile filaments** are quite similar to that in skeletal muscle:
  - Thick filaments (myosin): contains 2 heads having ATPase activity.
  - Thin filaments (actin, troponin, tropomyosin) :
    -TN-C binds Ca++ released by sarcoplasmic reticulum (SR).
    -TN-1 inhibits actin-myosin binding until Ca++ binds to TN-C.

Types of Cardiac Muscle Contraction

Explained in more detail in cardiac cycle lecture.

Isometric contraction

The stimulated muscle exerts an internal tension but it cannot be shortened (NO work, **same length**).
Ventricular **pressure rises** to high level due to **closed** aortic and pulmonary **valves**.
Muscle contraction without significant shortening or change in distance.

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**.

Muscle contraction without significant change in force of contraction.

Major Types Of Cardiac Muscle Cells

Specialize Excitatory & **Conductive Cells**

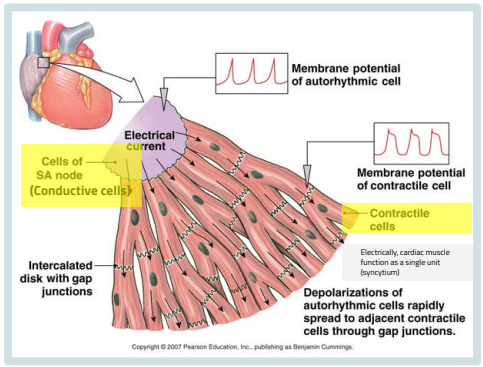
-Contract weakly because they contain few contractile fibrils (e.g. AV, SA node)
-Specialized for initiating and conducting action potentials responsible for contraction of working cells

We will be discussing the **action potential** of these types of cells in the **next lecture**.

Contractile Cells (Atrial & Ventricular)

Make up 99% of cardiac muscle cells
Do the mechanical work of pumping

We will be discussing the **action potential** of these types of cells in **this lecture**.



Features of <u>Conductive</u> Cells (Automatic/Autorhythmic cells)

They are specialized or modified cardiac muscle cells, containing few contractile fibrils and have 3 properties:

But the properties of the whole heart :
1- Excitability, 2-conductivity , 3- AutoRhythmicity , 4- contractility

1-Excitability:

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

2 -Conductivity:

Conducts electrical (impulses)current to another cardiac cells through the heart.

3-Self-stimulating (Automaticity & rhythmicity)

Generate impulses spontaneously in a repetitive,regular. (Rhythmicity)
consistent manner (Automaticity)

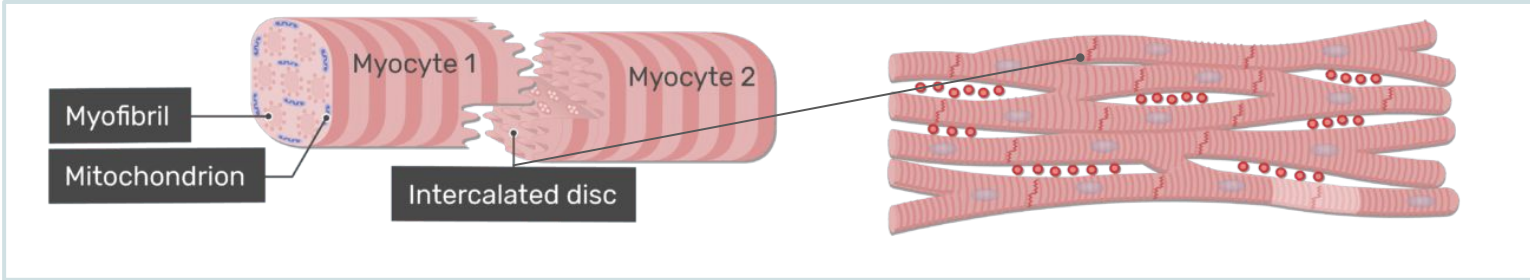
Features of Contractile Cells

- Striated in appearance, with centrally located nuclei
- Elongated (cylindrical)
- Rich in mitochondria (up to 40% of cell volume)
- Functional unit is called Sarcomere (the distance between 2 Z-lines)
- 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. (cause Ca++ induced Ca++ release discussed later)
- Fibers are not anchored at ends; allows for greater sarcomere shortening and lengthening

Features of Contractile Cells

Intercalated Discs are cell membranes that separate individual cardiac muscle cells from one another. They are the dark areas crossin the muscle fibers.

Intercalated discs contain two kinds of membrane junctions: **Gap junctions** & **Desmosomes** (اجسام رابطة)



Gap junctions

They are communicating junctions, or transmembrane channel proteins, that connect the cytoplasm of the cells.

Function:

Ions diffuse freely through them and move with ease in the intracellular fluid along the longitudinal axes of the cardiac muscle fibers.
As a result of the ion diffusion, **action potentials travel from one cardiac muscle cell to another.** Thus, cardiac muscle is a syncytium of many heart muscle cells, action potential spreads to all of them

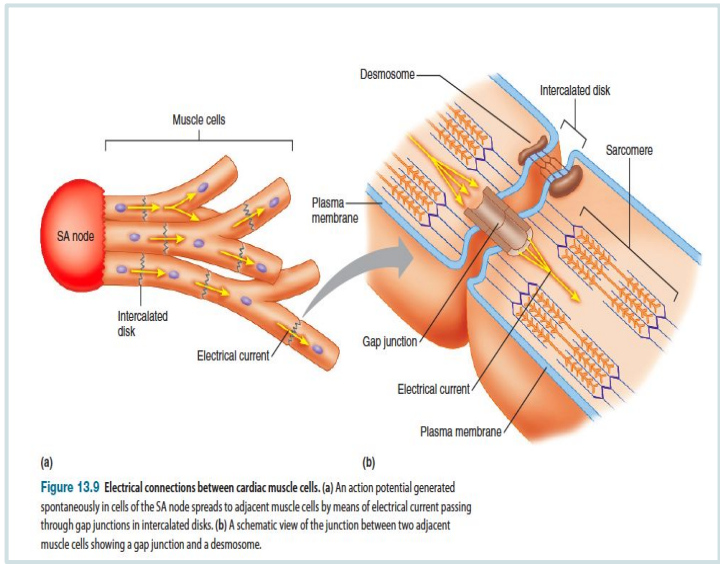


Figure 13.9 Electrical connections between cardiac muscle cells. (a) An action potential generated spontaneously in cells of the SA node spreads to adjacent muscle cells by means of electrical current passing through gap junctions in intercalated disks. (b) A schematic view of the junction between two adjacent muscle cells showing a gap junction and a desmosome.

Functional Syncytia

- Physiological & histological features of cardiac muscle (interconnection by intercalated discs) help it to act as 2 **functional syncytium** (not anatomical syncytium).

- Cardiac muscle cells are so tightly bound that when autorhythmic cells depolarize, action potential spread rapidly to contractile cells

2 Functional Syncytia

- Atrial 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 the 2 syncytia 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). It allows atrial emptying into ventricles (atria and ventricle will never contract at the same time)

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All or none 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 none rule.

Phases of Action Potential in Contractile Cardiac Muscle Fibers

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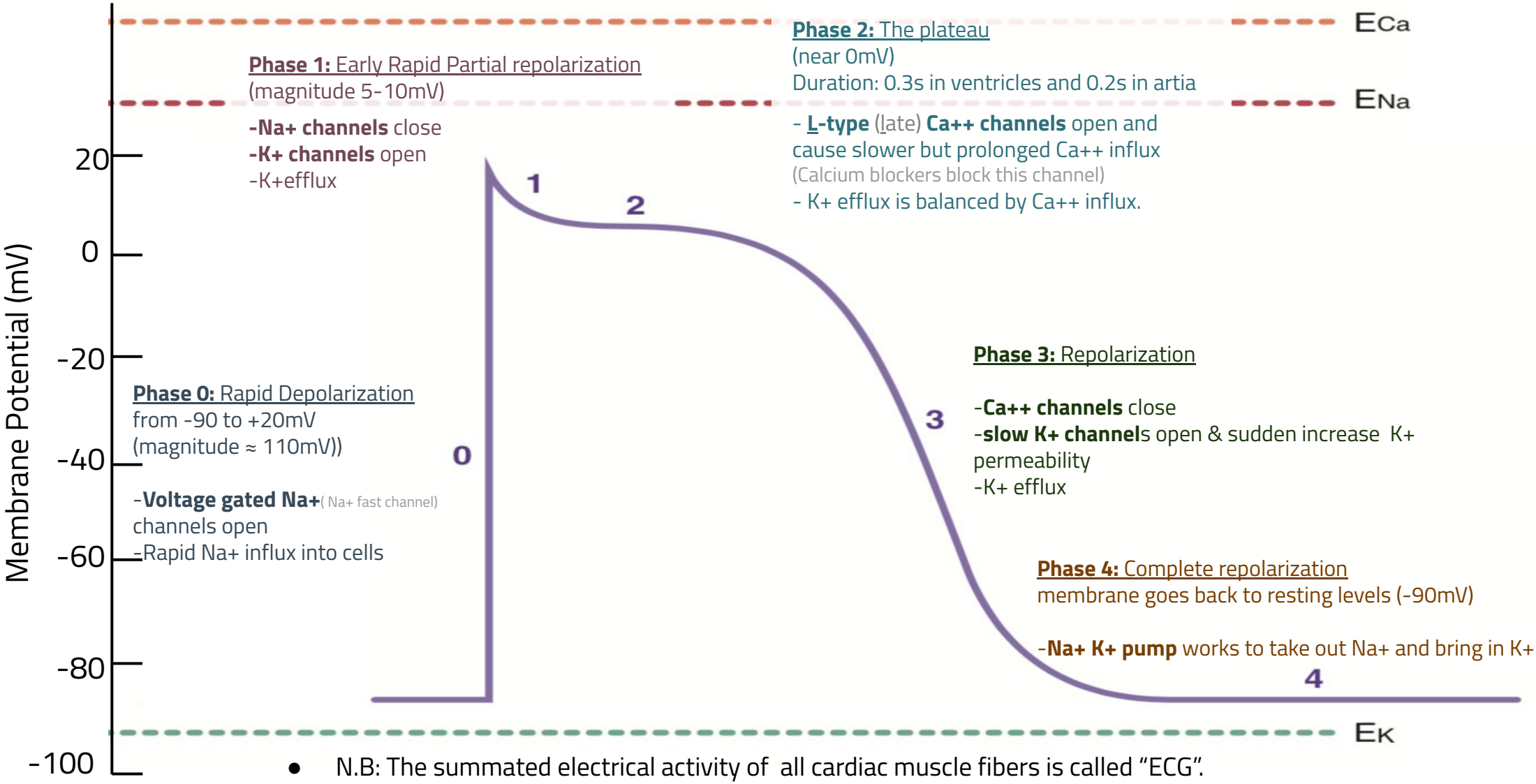
Here, we are talking about **contractile cells action potential only**.
(Excitatory/conductive cell action potential will be discussed next lecture.)

- Resting membrane potential of contractile myocardial fibers is stable **"-90mV"**.
- Duration of action potential is **300-400ms**.
- It has **5 phases** (numbered from 0 to 4)**:**



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

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What causes the Plateau in the Action Potential?

1

Opening of Slow Ca++ channels (slow in comparison to fast Na+ channels of phase 0)

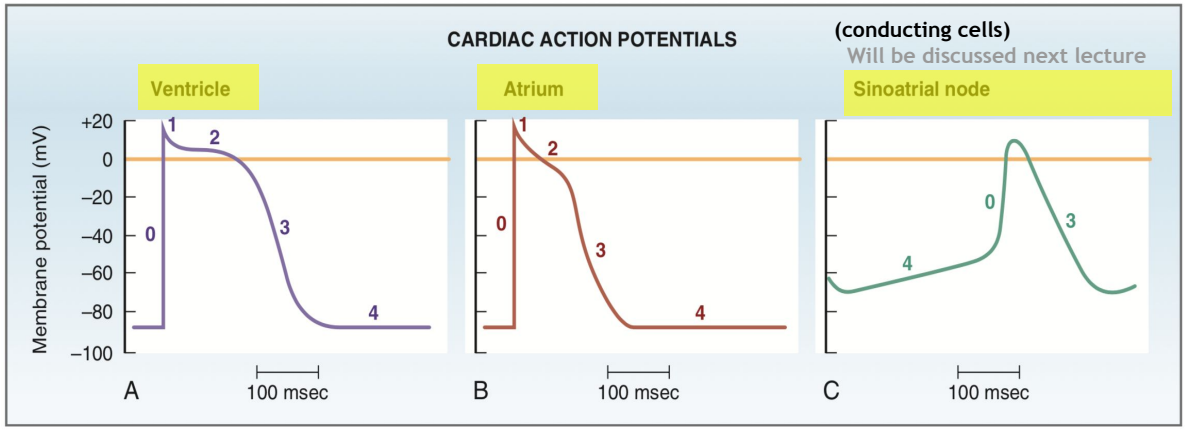
They are voltage-activated Ca++-Na+ channels **(L-type Ca++ channels).** They are slow to open & remain open for several tenths of a second. Prolonged opening of these channels allows large quantity of Ca++ flow to the interior of the cardiac muscle fiber, cause plateau.

2

Decrease K+ outflux during the action potential plateau

This decrease in K+ efflux is caused by the decreased permeability of the cardiac muscle membrane for K+.

- Moreover, voltage-gated K+ channels are slower to open**.** This **delays the return to resting membrane potential** (–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.



Note: In atrial fibers, the plateau is shorter than in ventricular fibers.

EXTRA NOTES

Action Potential in Contractile Cardiac Muscle Fibers

- **KEY CONCEPT:** for the membrane potential to be stable (horizontal line), inward and outward currents must be equal such that there is no net current flow across the membrane.
- (ex: in phase 2 and phase 4 there is no net flow)
- **What determines whether an ion wants to move in or out of a cell?** ElectroChemical gradient

  1-Chemical gradient: an ion wants to move from an area of high concentration to an area of low concentration until it reaches equilibrium.
  (ex: a cell is filled with K+, so if given the chance K+ will try to move out. For the opposite reason, Na+ tries to enter the cell)

  2-Electric gradient:
  If the membrane potential of a cell is negative, positive ions will try to come in **(that's why during phase 0, Na+ enter the cell)**.
  If the membrane potential is positive, positive ions will try to move out **(that's why in phase 1, K+ leave the cell)**.

- **The inward Ca2+ current during phase 2 (plateau) does two things:**

  1.Effects membrane potential (slows down repolarization).

  2. Initiates the release of more Ca2+ from intracellular stores for **excitation-contraction coupling** (this process is called **Ca2+-induced Ca2+release).**

  Basically, during phase 2, the Ca++ that comes in from the ECF stimulates the sarcoplasmic reticulum to release Ca++ into the cytoplasm. This released Ca++ is used for muscle contraction (Ca++ binds to troponin, causing it to release actin. This free actin binds to myosin, resulting in muscle contraction)

- **At the end of phase 3, the outward K+ current is reduced because repolarization brings the membrane potential closer to the K+ equilibrium potential (the green line in the action potential graph), thus decreasing the driving force on K+.**

- **Phase 4=resting membrane potential =electrical diastole: outward current (K+) is balanced by inward current (Na+ and Ca2+)**

  How can the sum of inward Na+ and Ca2+ currents be the same magnitude as the outward K+ current, given that Na and Ca conductance are very low, and K1 conductance is very high?

  current = conductance × driving force

  K1 conductance is high, but the driving force on K+ is low because the resting membrane potential is close to the K+ equilibrium potential; thus, the outward K+ current is relatively small.

  On the other hand, Na and Ca conductance are both low, but the driving forces on Na+ and Ca2+ are high because the resting membrane potential is far from the Na+ and Ca2+ equilibrium potentials; thus, the sum of the inward currents carried by Na+ and Ca2+ is equal to the outward current carried by K+.

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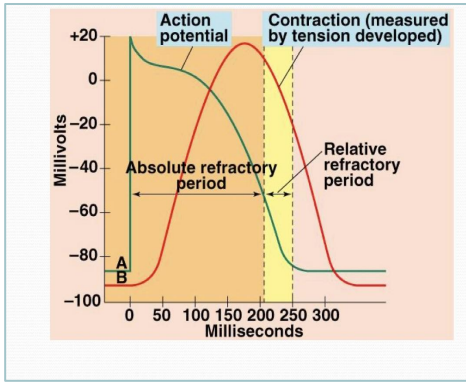
Refractory Period of Cardiac muscle

Refractory period is the interval in 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: prevent tetanus "prolonged spasm" and summation which may stop the circulation, this ensures alternate periods of contraction and relaxation which are essential for pumping blood.

	Absolute	Relative
Description	Cardiac muscle cannot be excited due to the complete depolarization.	Cardiac muscle can be excited only by strong stimulus, producing extra-systole.
Time	During depolarization and the 1st 2/3 of repolarization (phases 0,1,2 and the beginning of phase 3)	During last 1/3 of repolarization (the rest of phase 3)
Mechanically	Occupies whole period of systole & early diastole	Occupies the middle of diastole.
Duration	Long 0.25- 0.3 sec.	Short in ventricles = 0.05 sec in atria = 0.03 sec



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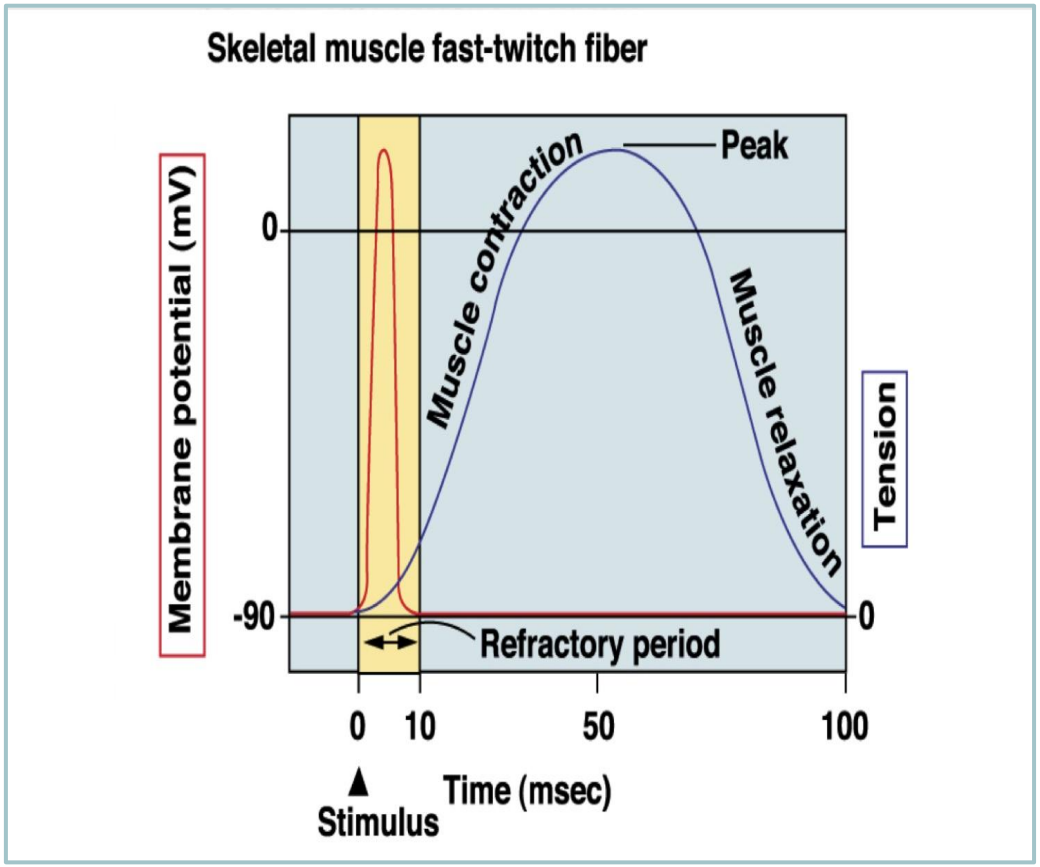
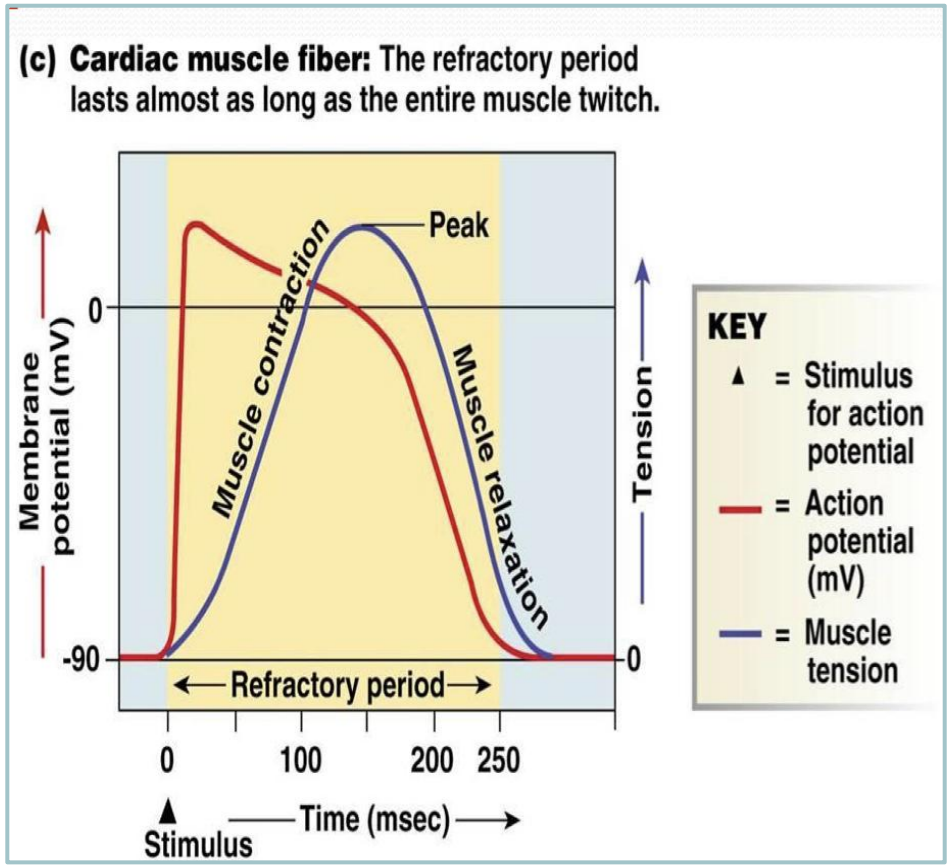
Refractory Period of Cardiac muscle Vs Skeletal muscle





The Refractory period is short in skeletal muscle , but very long in cardiac muscle " 300 msec "
This means that skeletal muscle can undergo summation and tetanus "this feature so important for skeletal muscle and must occur when we carry heavy objects " .
Cardiac muscle **CAN NOT** sum action potentials or contractions so can't be tetanized.

Excitation-Contraction Coupling

Excitation-contraction coupling is the mechanism by which action potential causes muscle contraction.
Excitation of the heart is triggered by **electrical impulse** rather than neurotransmitters.

Contraction of the heart is triggered by elevation of intracellular Ca++ influx.
Contraction requires ATP and Calcium, so we'll briefly talk about the source and role of each.

ATP:

Cardiac muscle 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 1 ATP molecule.

Ca++:

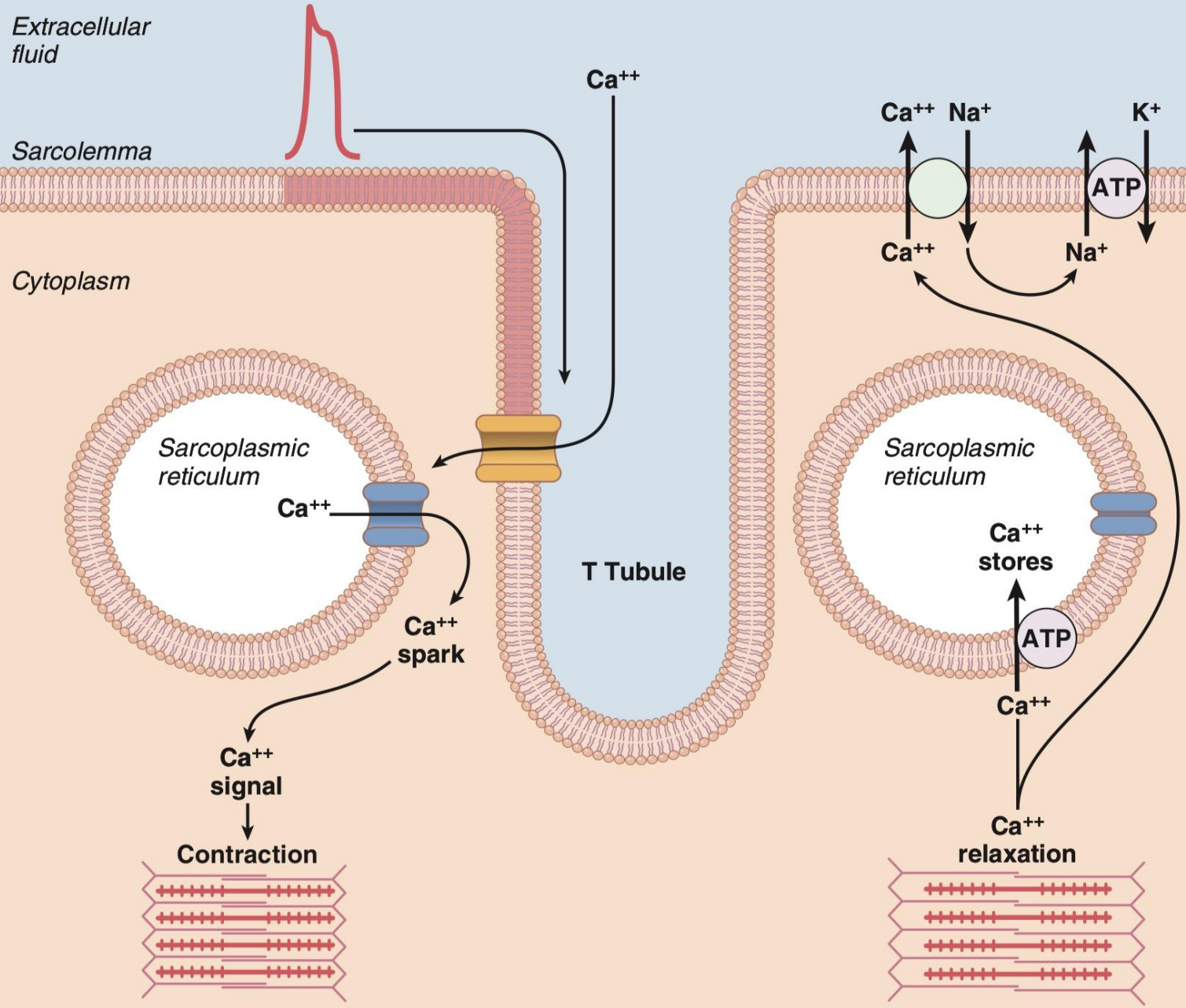
Action potentials spread to the interior of the cardiac muscle fiber along the transverse "T" tubules.

The "T" tubules of cardiac muscles have a diameter 5 times as great as that of the skeletal muscle tubules.
Why?
Without the Ca++ of the T tubules, the strength of cardiac muscle contraction would be reduced considerably because the sarcoplasmic reticulum of cardiac muscle is less well developed than that of skeletal muscles and does not store enough Ca++ to provide full contraction.

Ca++ 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)**, the source of about 95% of Ca++ in cytosol. (Basically, the Ca++ that came in during Phase 2 from ECF into cell causes the sarcoplasmic reticulum to release the Ca++ stored in it. This helps in muscle contraction. More detail in the next slide.)

Excitation-Contraction Coupling



summary

1- Ca++ enter the cell through Ca++ channels on sarcolemma during depolarization(phase 2) and triggers release of Ca++ by terminal cisternae. **=(Ca++ induced Ca++ release)**

2- Ca++ binds to troponin-C inducing a conformational change in the troponin complex. (Ca+ binds to troponin, so troponin releases actin. The free actin can now bind to myosin.)

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

4- Ca++ is re-sequestered(Ca++ reuptake) 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. (muscle relaxation)

EXTRA

Skeletal muscle vs cardiac muscle

Action potential

- Cardiac muscle: Action potential conducted From cell to cell.
- Skeletal muscle : Action potential conducted along length fiber.

Rate of Action potential propagation

- slow in cardiac muscle because of gap junctions and small diameter of fibers.
- Faster in skeletal muscle due to larger diameter fibers.

Calcium release

- calcium-induced calcium release (**CICR**) in cardiac muscle : Movement of extracellular Ca++ Through plasma membrane and T tubules into sarcoplasm stimulates release release of Ca++ from sarcoplasmic reticulum.
- In the skeletal muscle : Action potential in T-tubules stimulates Ca++ from sarcoplasmic reticulum .

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Intrinsic Regulation Of Heart Pumping (Frank-starling Mechanism)

It is the intrinsic ability of the heart to adapt to increasing volumes of inflowing blood.

Initial **length** of cardiac muscle (EDV) $\propto$ **Force** of contraction

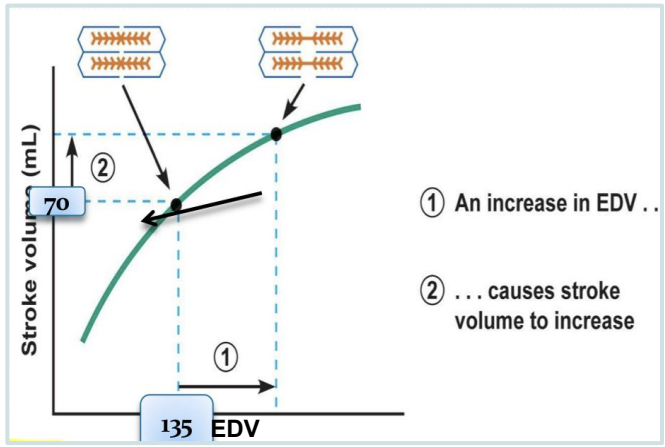
Bigger EDV means strong contraction **within physiological limits** (basically, the more blood the heart receives the harder it pumps to accommodate)

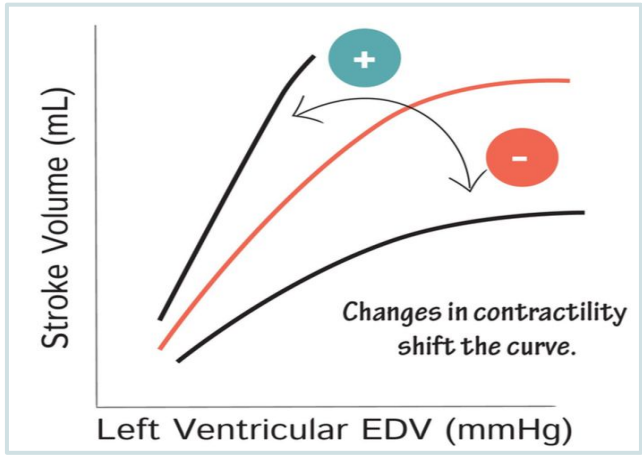
The force of contraction is proportional to the initial length of the cardiac muscle within physiological limits

The initial **length** depends on **end diastolic volume** (we will discuss EDV later in cardiac cycles); 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 (excessive stretch causes damage to heart muscles which decreases the force of contraction)

When an extra amount of blood flows into the ventricles, the cardiac muscle is stretched to a greater length. This stretching in turn causes the muscle to contract with increased force because the actin and myosin filaments are brought to a more nearly optimal degree of overlap for force generation.





Extrinsic Regulation of Heart Pumping

Up until this point, we've been talking about how the heart regulates itself.
Now, we will be talking about other EXTERNAL factors that can affect the heart.

Inotropic effect: mechanism that affects contractility

can be divided into positive inotropes, which stimulate and increase the force of contraction of the heart muscle, and negative inotropes, which weaken the force of muscular contractions, decreasing how hard the heart has to work

Factors Affecting Heart Pumping

Positive Inotropic Effects
↑ Cardiac Contractility

Sympathetic Stimulation: Sympathetic stimulation (neurotransmitter) : binds to b1 receptors on the SA nodal membranes

↑ [Ca++] in ECF
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.

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

Digoxin, digitalis

Negative Inotropic Effects
↓ Cardiac Contractility

Parasympathetic Stimulation: Parasympathetic stimulation (neurotransmitter): binds to muscarinic receptors on nodal membranes increases conductivity of K+ and decreases conductivity of Ca2+.

↑ [K+] in ECF
Excess K+ cause the heart to become dilated and flaccid and also slows the heart rate. These effects result partially from decreasing the resting membrane potential in the cardiac muscle fibers.

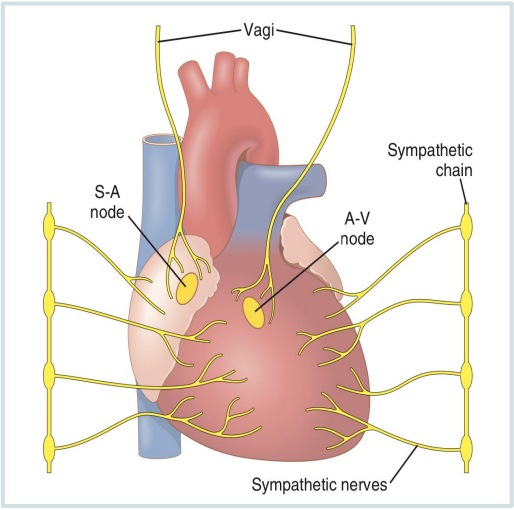
Cooling

Ca++ Channel Blockers
Block Phase 2 L-Type Ca++ channels. Used in hypertension.
β-Blockers

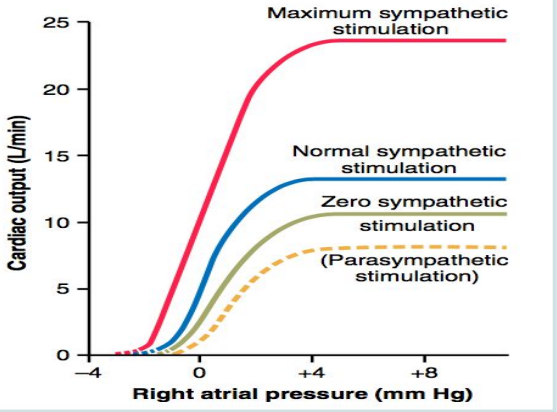
Hypoxia

Extrinsic Regulation of Heart Pumping: Effect of Autonomic Innervation

Autonomic nervous system modulates the frequency of depolarization of pacemaker



Sympathetic	Parasympathetic
- sympathetic nerves are distribute to **both** atria and ventricles	- vagal fibers distributed **mainly to the atria** and not much to the ventricles.
- increase the force of **both** atria & ventricular contractions.	- decrease the force of atrial contraction. - slight decrease in ventricular contraction.
- affects HR (tachycardia) **and** contractility	- only affects HR (bradycardia)



Effect of Sympathetic or Parasympathetic Stimulation on the **cardiac output curve** in different degrees.

This curve demonstrate that at any given right atrial pressure, the cardiac output increases during increased sympathetic stimulation and decreases during increased parasympathetic stimulation. These changes in output caused by autonomic nervous system stimulation result both from changes in heart rate and from changes in contractile strength of the heart.

Quiz

MCQs:

1-Which of these contractions shorten the muscles and preserve its tension?
A. Isotonic
B. Isovolumic
C. Isometric
D. Isotension

2-Which of these is a difference between skeletal and cardiac contraction mechanism?
A. Spread of action potential muscle cells
B. Release of Ca++ from the cisternae
C. Ca++ binding to troponin to form the cross-bridge
D. Diffusion of Ca++ through T-tubule

3- Which of the following induces Ca release from Sarcoplasmic reticulum ?
A-Ca
B-Na
C-K
D-All of the above

4- Which of the following answers present Parasympathetic stimulation?
A- Increase conductivity of K and Decrease conductivity of Ca
B- Decrease conductivity of K and Increase conductivity of Ca
C- Increase conductivity of K and Decrease conductivity of Na
D- None of the Above

SAQs:

1- Define contractility, and mention its different types.

2- When Ca atoms unbind from troponin portion of them leaving the cell instead of going back to the sarcoplasmic reticulum, explain WHY?

Answers:
1- Slide No.4
2- To maintain electricity of the cell membrane

Answer Key:
1-A 2-D 3-A 4-A

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