Cardiovascular Physiology

Contractile Mechanism in Cardiac Muscle

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At end of this lecture you should be able to:

- ✓ Define cardiac muscle contractility
- ✓ Describe the mechanism of 'Excitation-Contraction Coupling'
- ✓ Understand the mechanism of isovolumetric & isometric contraction
- ✓ Factors affecting cardiac contractility
- ✓ Understand what's ment by inotropics (+ve & -ve)

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PROPERTIES OF THE CARDIAC MUSCLE

I. Excitability
II. Conductivity
III. Contractility
IV. Rhythmicity

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Contractility:

Is the force of contraction for a given fiber length

- Or/ is the ability of cardiac muscle to convert chemical energy into mechanical work
- **Its essential for the pumping action of the heart**

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Excitation-Contraction Coupling:

The mechanism by which the action potential triggers contraction of the myofibrils

- Is almost similar to that of skeletal ms
- It depends more on ECF [Ca^{2+}]

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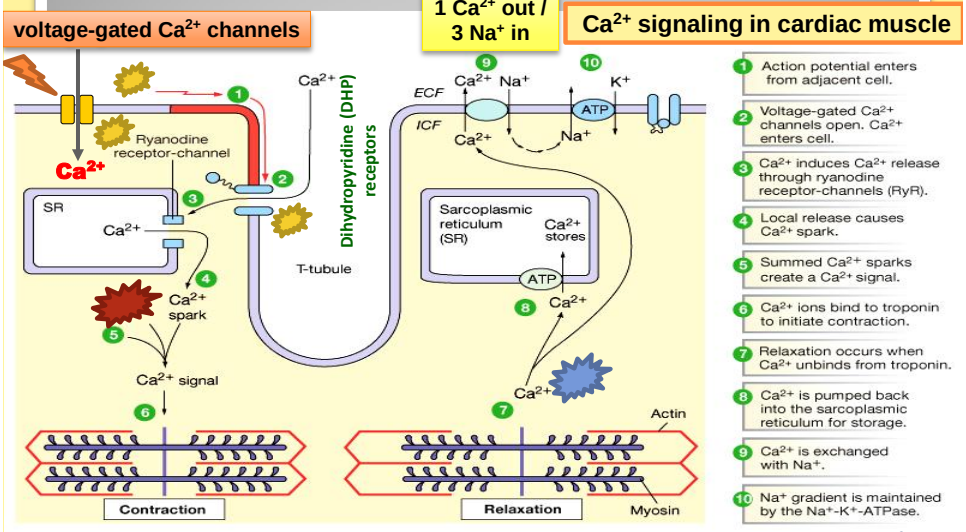
Excitation-Contraction Coupling in Heart Muscle



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In resting muscle fibers:

- Ca^{2+} is stored in the endoplasmic 'sarcoplasmic' reticulum (SR)
- Along the plasma membrane 'sarcolemma' there are membrane invaginations that form transverse tubules 'T tubules' (TT), which are long & tortuous
- TT terminate near the Ca^{2+} -filled sacs of SR

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Excitation-Contraction Coupling:

- Initiated by impulse (AP) on the surface of myocardium
- Depolarization wave passes through TT
- Ca^{2+} enters through Ca^{2+} voltage channel in exterior membrane & dihydropyridine receptors (DHPRs) in TT
- Ca^{2+} entry triggers the release of Ca^{2+} from SR
- causes ↑ in intracellular Ca^{2+}

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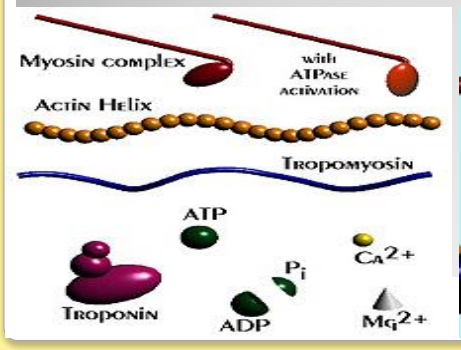
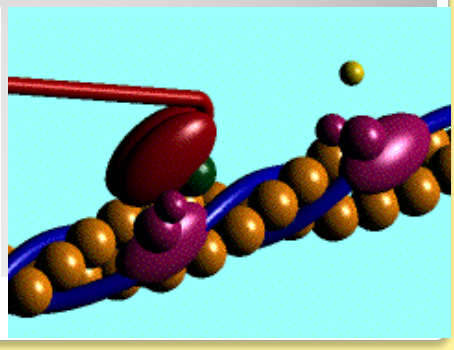
Excitation-Contraction Coupling … (Cont.)

- Ca^{2+} then binds to troponin C on thin filaments to start cross bridge cycle
- hydrolysis of ATP occurs to provide the energy for sliding of myosin over actin, causing contraction





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Excitation-Contraction Coupling … (Cont.)

- Relaxation occurs when Ca^{2+} is removed from troponin C:
  - Ca^{2+} will actively re-uptaken by the SR … (using a Ca^{2+} ATPase)
  - Ca^{2+} will also pumped out of cell via Na^{+}-Ca^{2+} exchanger
- Resulting in cessation of contraction until new AP occurs

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Factors Affecting Myocardial Contractility: (Inotropic Effectors)

1. **Cardiac innervation:** (ANS)
2. **Oxygen supply**
3. **[Ca^{2+}] & [K^{+}] ions in ECF**
4. **Physical factors:** (e.g. warming; cooling)
5. **Hormonal & Chemical factors**
6. **Mechanical factors**

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Factors Affecting Myocardial Contractility: (Inotropic Effectors)

- Inotropes are agents that ↑ or ↓ the force of musclular contraction:

  Negatively Inotropic agents weaken the force of muscular contractions

  Positively Inotropic agents increase the strength of muscular contraction

- Inotropes work via the autonomic nervous system (ANS)

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How do they work?

- **'Ach'** is the neurotransmitter of the parasympathetic nervous system (PNS)
- **'NA'** is the primary neurotransmitter released by the sympathetic nervous system (SNS)
- **When SNS is stimulated, Noradrenaline & adrenaline levels ↑, leading to stimulation of adrenergic receptors that located in the endothelium:**
  - **Alpha1 (α_1), Alpha2 (α_2)**
  - **Beta1 (β_1), Beta2 (β_2), &**
  - **Dopamine (D)**

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Adrenergic Receptors

Alpha Receptors		Beta Receptors		Dopamine
Alpha1 (α_1)	**Alpha2 (α_2)**	**Beta1 (β_1)**	**Beta2 (β_2)**	**Dopamine (D)**
Cardiac	In peripheral vessels	Heart	• Bronchial smooth muscles • Skeletal muscles	
↑ Contractility w/out ↑ in rate	Mediate vasoconstriction	↑ Contractility w ↑ in HR	• Dilation of BSM • Vasodilation in SM • ? Some cardiac effects	• ↑ Renal & ↑ Coronary blood flow • Arterial vasodilatation

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Factors Affecting Myocardial Contractility:

1. Cardiac innervation: (ANS)

- Sympathetic NS → ↑ force of contraction
- Parasympathetic NS (vagus) → ↓ atrial force of contraction w no significant effect on ventricular ms

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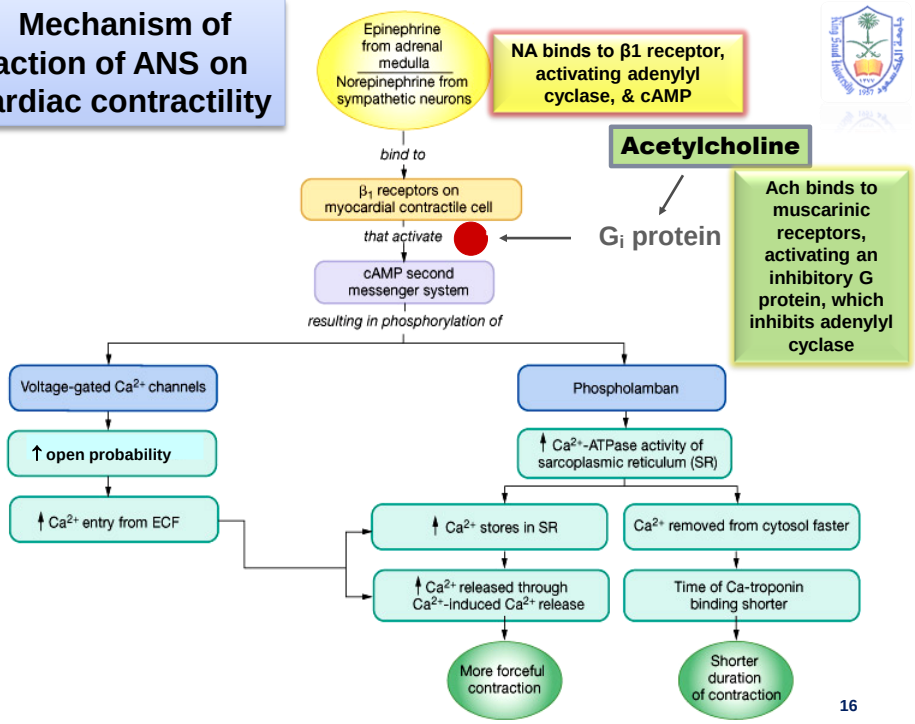
Mechanism of action of ANS on cardiac contractility



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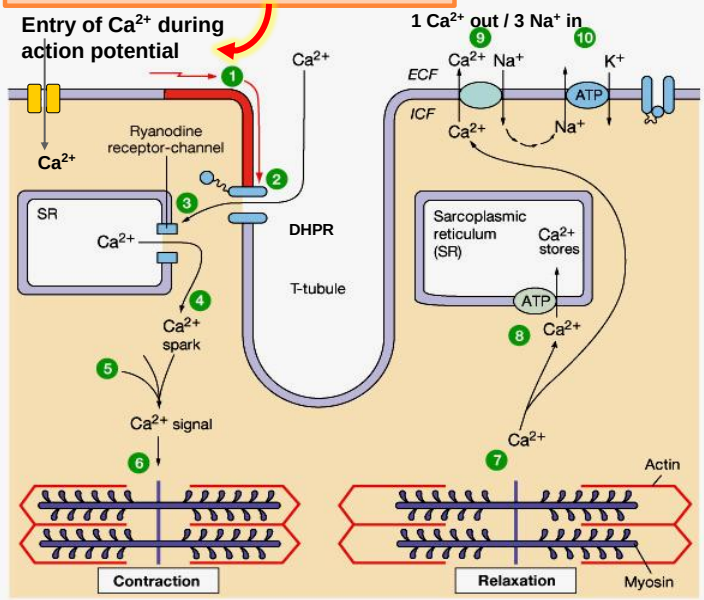
Effect of autonomic innervation on cardiac contractility

Affected by epinephrine (↑) & ACh (↓)



1. Action potential enters from adjacent cell.
2. Voltage-gated Ca^{2+} channels open. Ca^{2+} enters cell. (DHPR)
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.

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Factors Affecting Myocardial Contractility … (Cont.)

2. Oxygen supply:

- Hypoxia → ↓ contractility

3. [Ca^{2+}] & [K^{+}] ions in ECF:

- ↑ Ca^{2+} → ↑ contractility
- ↑ K^{+} → ↓ contractility

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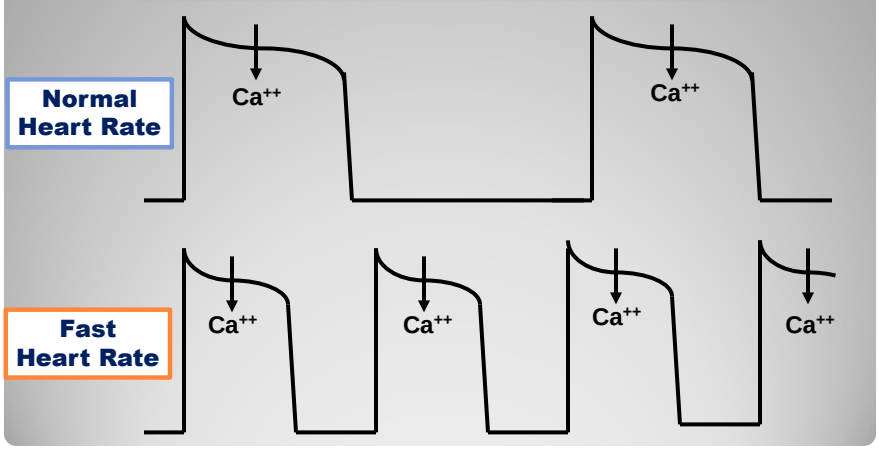
Effect of Ca^{2+} on cardiac contractility

- Ca^{2+} ↑ force of contraction- ? systolic arrest
- Ca^{2+} ↑ Heart rate



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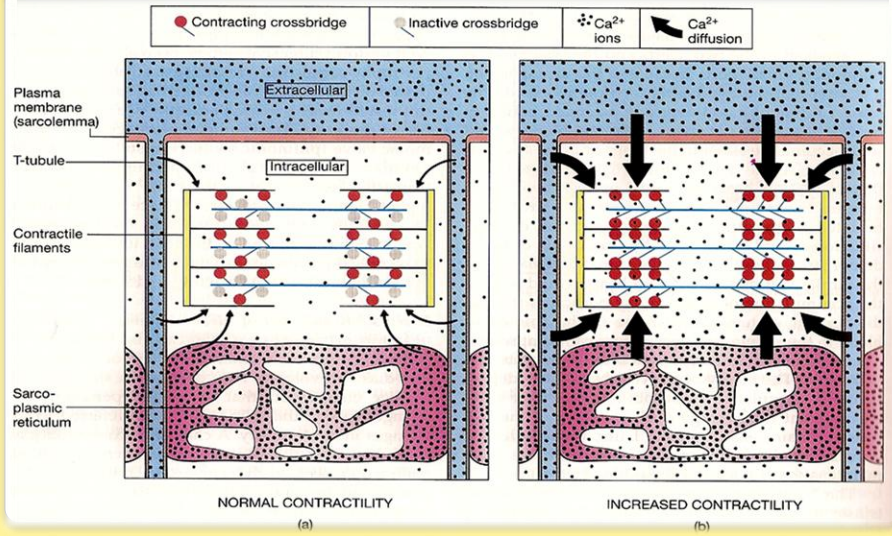
↑ Ca^{2+} , ↑ force of contraction- ? systolic arrest



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Factors Affecting Myocardial Contractility … (Cont.)

4. Physical factors:

- Warming → ↑ contractility
- Cooling → ↓ contractility

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Factors Affecting Myocardial Contractility … (Cont.)

5. Hormonal & Chemical factors:

Positive (↑Cardiac Contractility)	Negative (↓Cardiac Contractility)
Digoxin, digitalis	Beta blockers (β blockers)
Adrenaline & Noradrenaline	Acetylcholine
Dobutamine	Ether
Dopamine	Some bacterial toxins (e.g. diphtheria toxins)
Isoprenaline	K^+
Alkalosis	Acidosis
Ca^{2+}	Ca^{2+} channel blockers
Caffieen	

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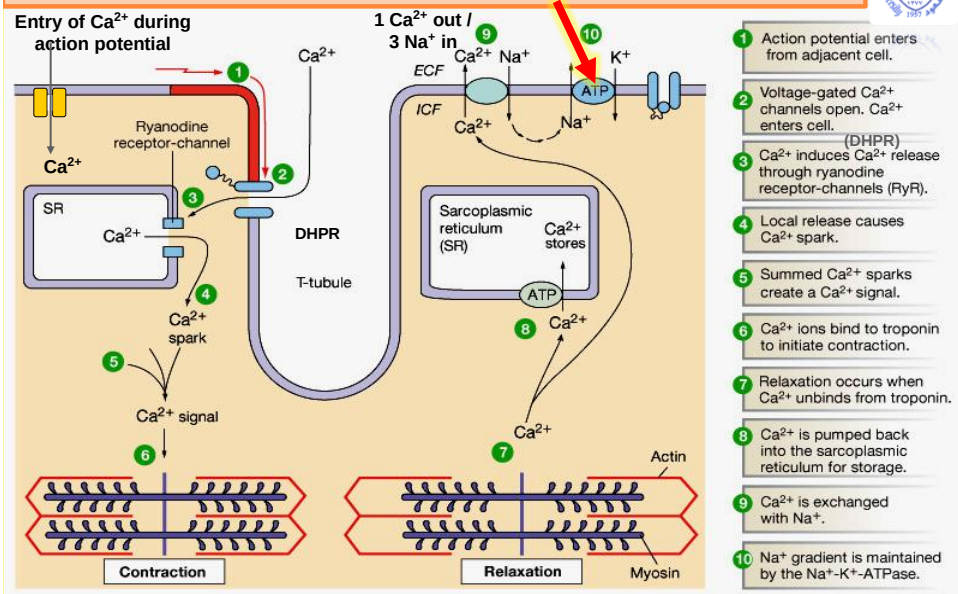
Drugs: Digitalis & ouabain → inhibit Na^+/K^+ pump (indirectly inhibiting Na^+/Ca^{2+} exchange) → ↑$[Ca^{2+}]_{in}$



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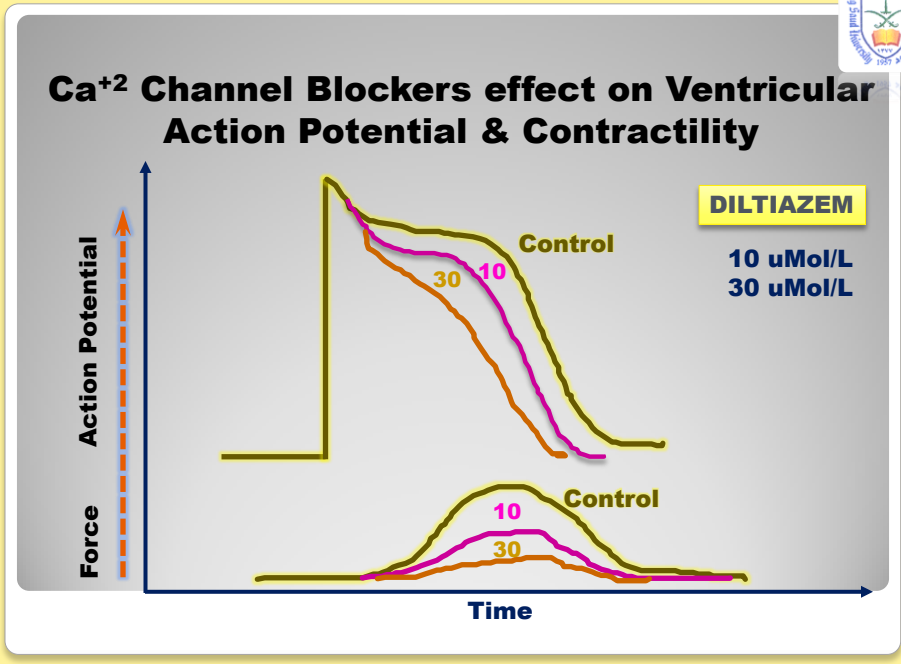

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Risk & Benefits of Inotropes

Benefits	Risk
Improves cardiac performance	↑ Heart rate, causing further deterioration of failing heart pump
Improves myocardial contractility	↑ Myocardial oxygen requirements
↑ Blood pressure	Potentially arrythmogenic
	Can ↑ ischemia

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Factors Affecting Myocardial Contractility … (Cont.)

6. Mechanical factors:

a. Cardiac ms obeys 'all or none law'

b. Cardiac ms can perform both isometric & isotonic types of contractions

c. Staircase phenomenon

d. Cardiac ms can't be tetanized

e. Starling's law of the heart

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Mechanical Factors … (Cont.)

a. Cardiac ms obeys 'all or none law'

- Action potential fails to occur if the stimulus is subthreshold in magnitude
- It occurs with constant amplitude & form regardless of the strength of the stimulus if the stimulus is at or above the threshold
  - This is made possible through rapid spread of excitation from cell to cell (as cardiac ms behaves as a syncytium)

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Mechanical Factors … (Cont.)

b. Cardiac ms Can perform both isometric & isotonic types of contractions

- **Isometric 'same length' contraction:**
  Occurs when the muscle is stimulated after its ends has been fixed 'held'. It contracts & exerts an internal tension but cannot be shortened, so it does no external work
- **Isotonic 'same tension' contraction:**
  Occurs when stimulated muscle is allowed to shorten

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Mechanical Factors … (Cont.)

c. Staircase Phenomenon

- **After brief rest, on stimulation at regular frequency, the force of contraction ↑ progressively to a maximum & then is maintained at a plateau**
- Causes of staircase effect:
  - ↑ accumulation of Ca^{2+}
  - ↑ temperature
  - ↓ viscosity

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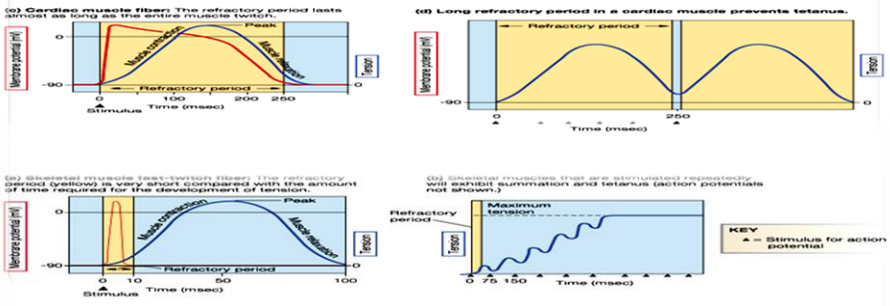
Mechanical Factors … (Cont.)

d. Cardiac ms can't be tetanized

- Cardiac ms can't be stimulated while it's contracted
- Its excitability during contraction is zero, due to long ARP



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Mechanical Factors … (Cont.)

e. Starling's law of the heart

- **Effect of load on contractility:**
  - **Pre-load:**
    the load acting on heart before it starts contracting
  - **After-load:**
    the load acting on heart after it starts contracting … (resistance)

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Mechanical Factors … (Cont.)

e. Starling's law of the heart … (Cont.)

- **Starling's law of the heart states that the force of contraction is proportional to the initial length of the muscle within the physiological limits**
  - Initial length depends on pre-load, i.e. end-diastolic volume (EDV) ≈ 130 ml
- Cardiac ms accommodates itself (up to certain limit) to the changes in venous return

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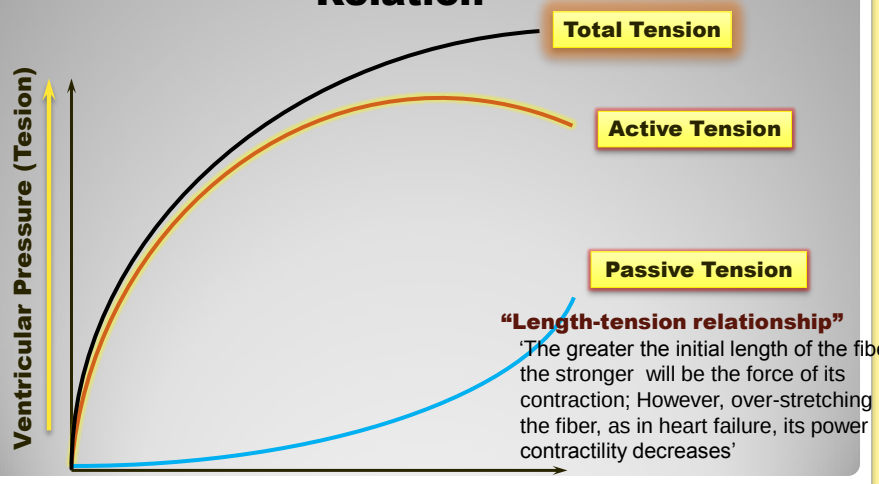
Length/ Tension and the Frank-Starling Relation



"Length-tension relationship"
'The greater the initial length of the fiber, the stronger will be the force of its contraction; However, over-stretching the fiber, as in heart failure, its power of contractility decreases'

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Length - Tension Relationship

- **As the pre-load ↑, the tension ↑**
- **Passive tension** is given by diastolic intraventricular pressure
- **Active tension** is given by systolic intraventricular pressure
- **Total tension** is the sum of the parallel elastic tension, i.e. 'passive' & 'active' tension
- **Descending limb at high degree of stretch is due to disruption of myocardial fibers**

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Thank You