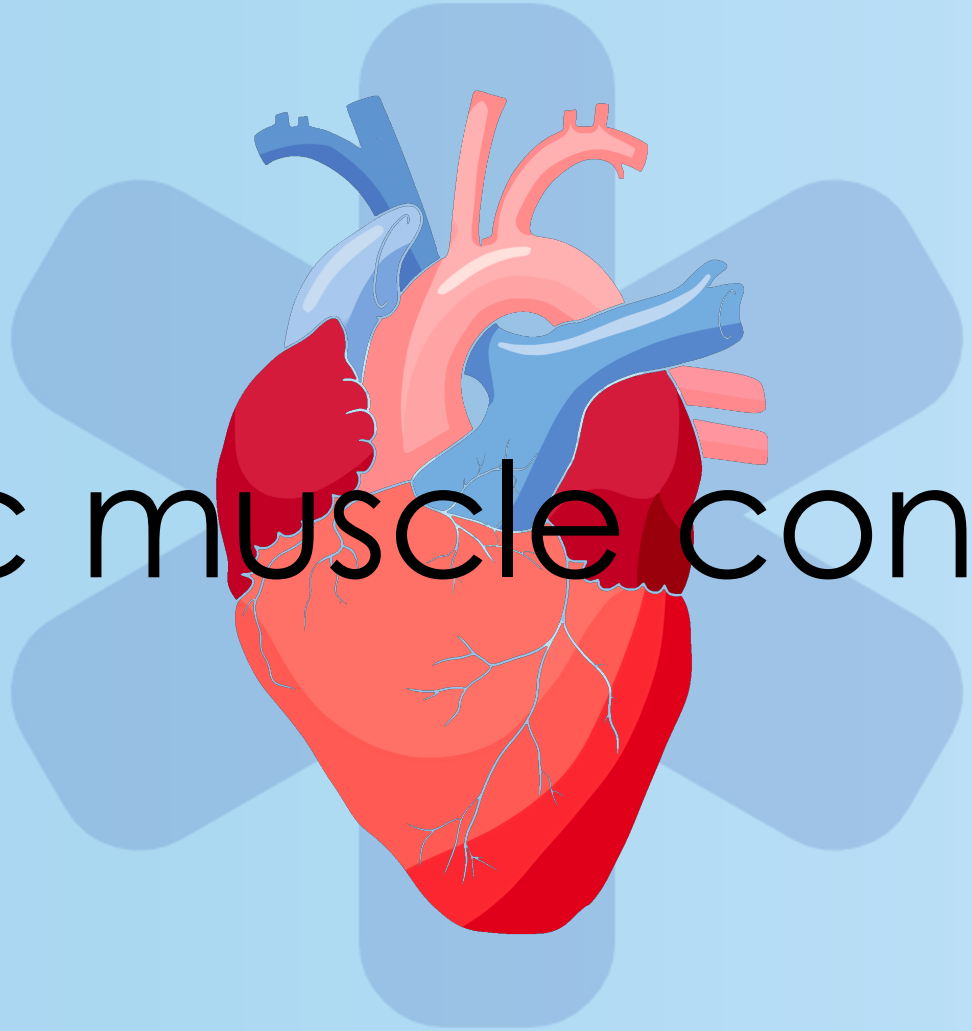
Cardiac muscle contraction



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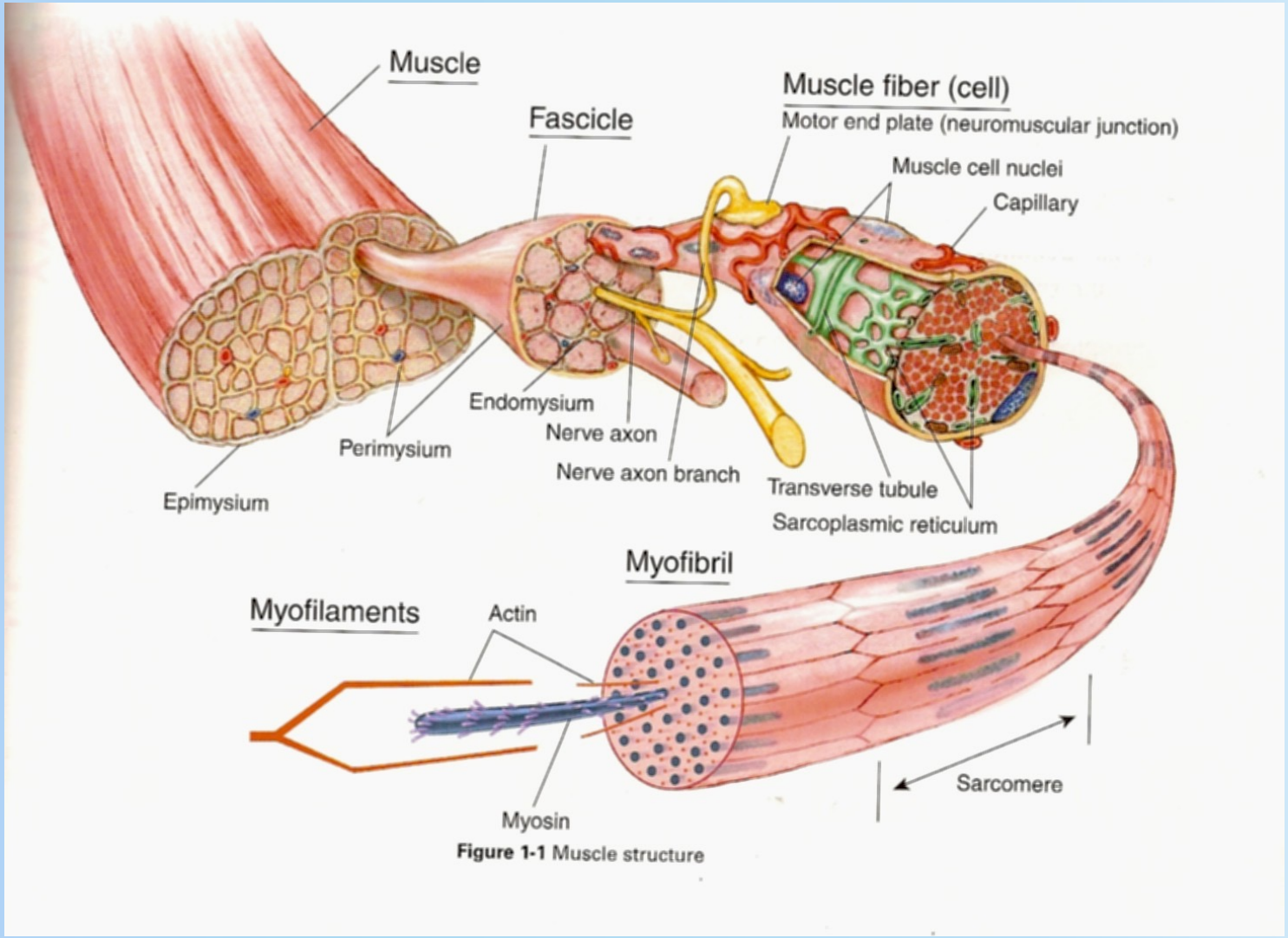
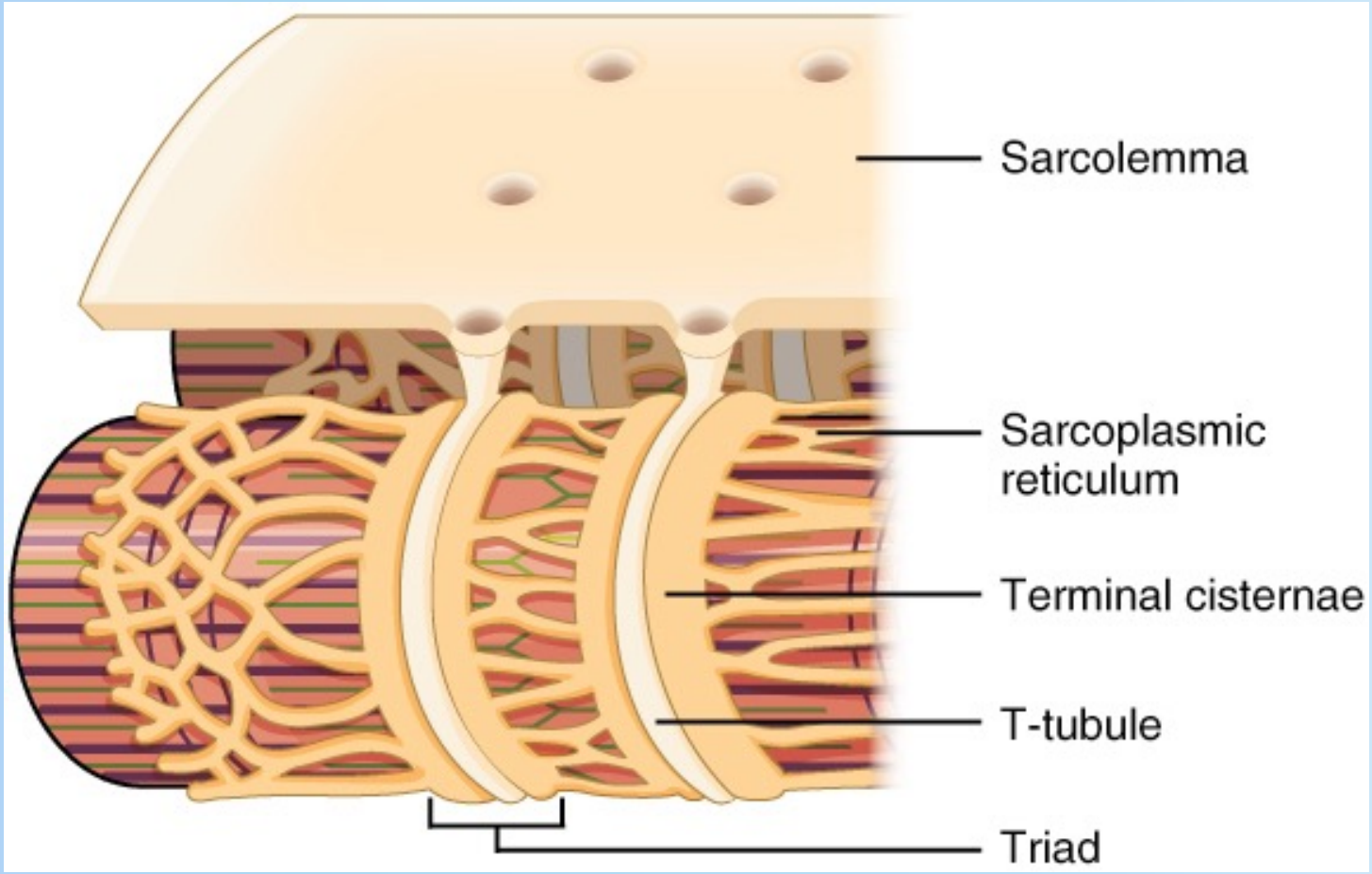


Figure 1-1 Muscle structure

The Cardiac Muscle Cell



The Cardiac Muscle Cell

The movement of the signal:

Presynaptic membrane

↓

Sarcolemma

↓

T-tubule

↓

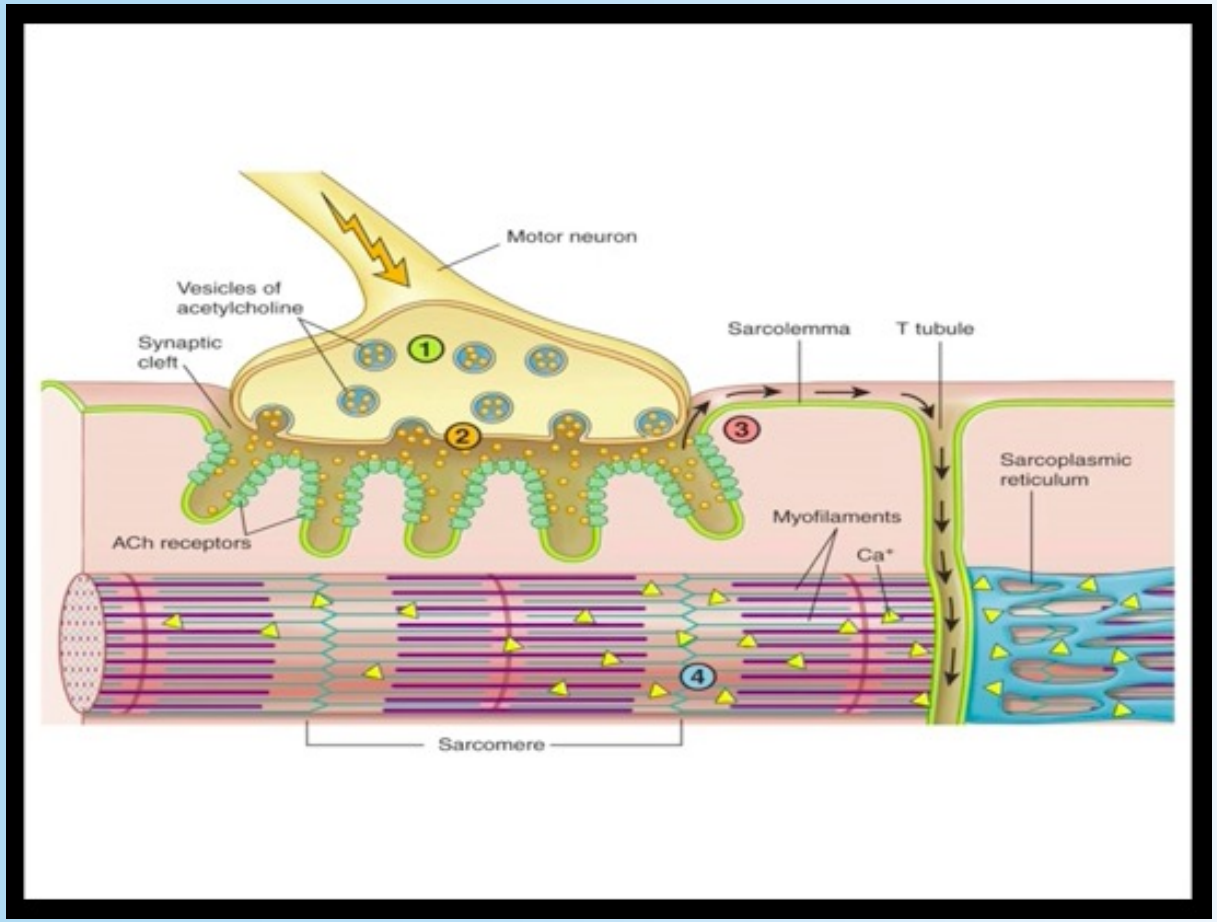
Terminal Cisternae

↓

Sarcoplasmic Reticulum (SR)

↓

Sarcomere



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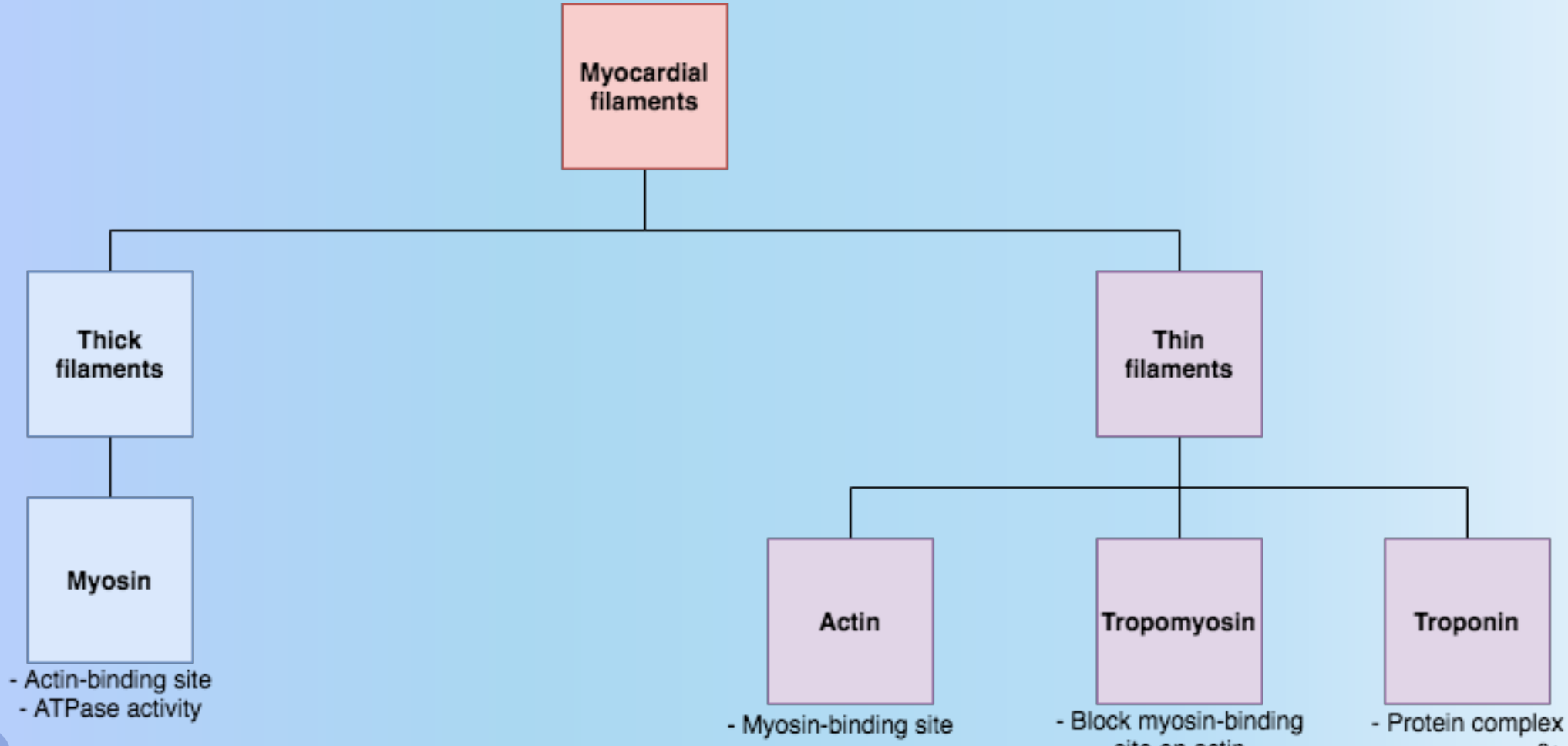
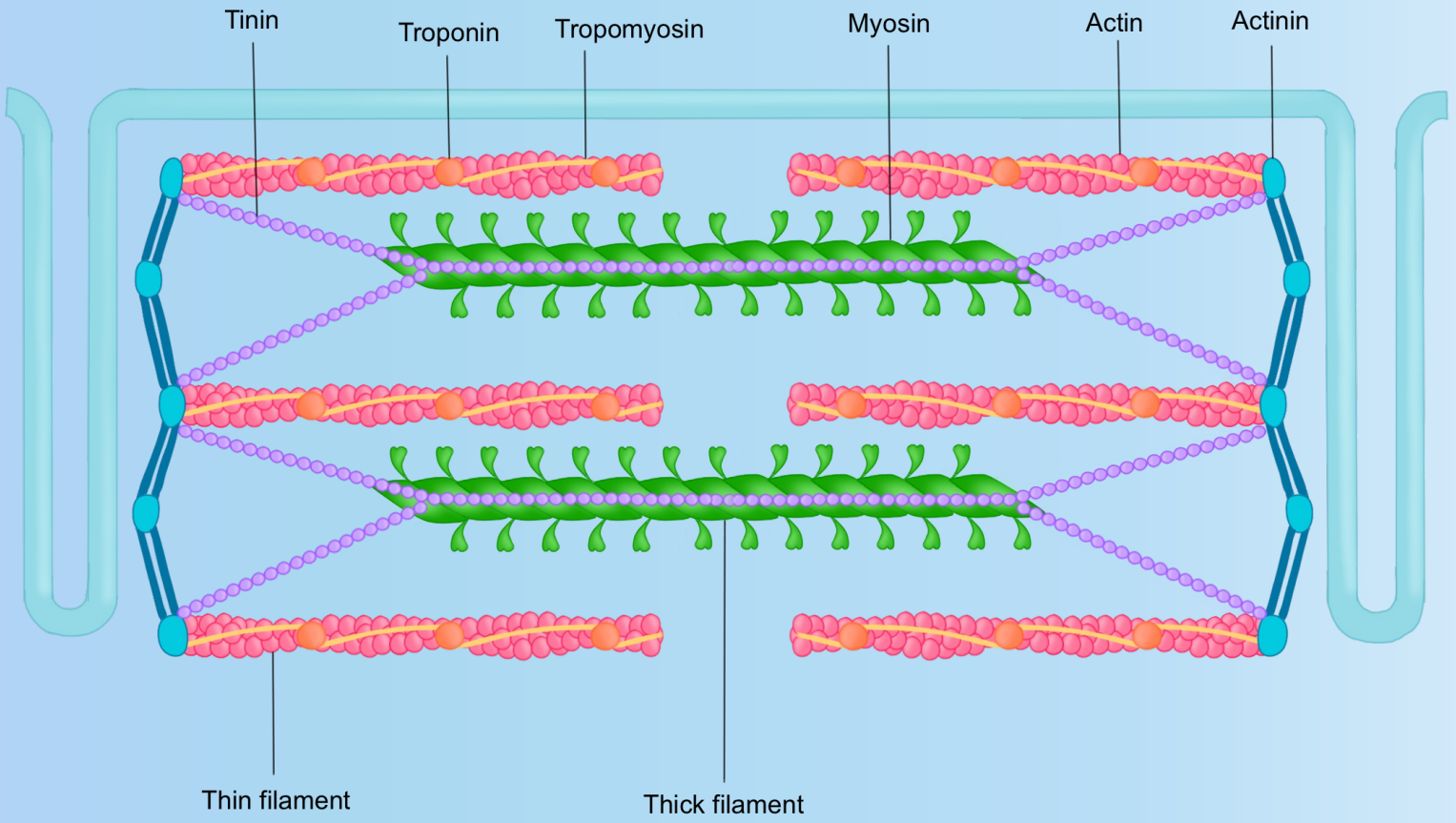
The Sarcomere



The Sarcomere

The essential contractile unit



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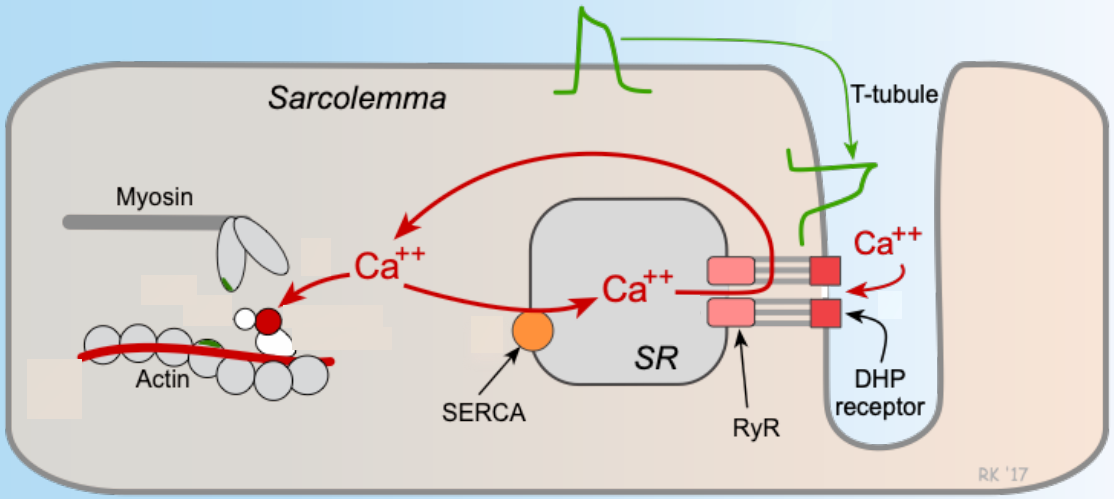
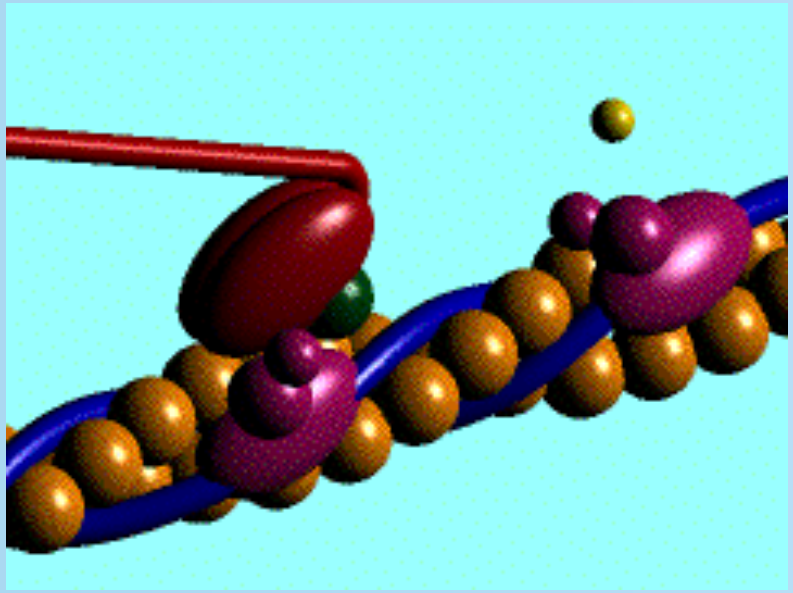
Excitation-Contraction Coupling

- Signal transmission into cell
  - Action potential opens L-type Ca^{2+}-channel (dihydropyridine receptor/DHPR) in t-tubules
  - → «trigger Ca^{2+}» released into cell
- Signal amplification
  - Ca^{2+} stimulates ryanodine receptors (RyR) on SR
  - → *Calcium-induced calcium release (CICR)*
- Contraction
  - Ca^{2+} from SR and DHPR/L-type Ca^{2+}-channel diffuse to the sarcomere
  - Ca^{2+} binds to troponin, which removes tropomyosin from the myosin binding sites



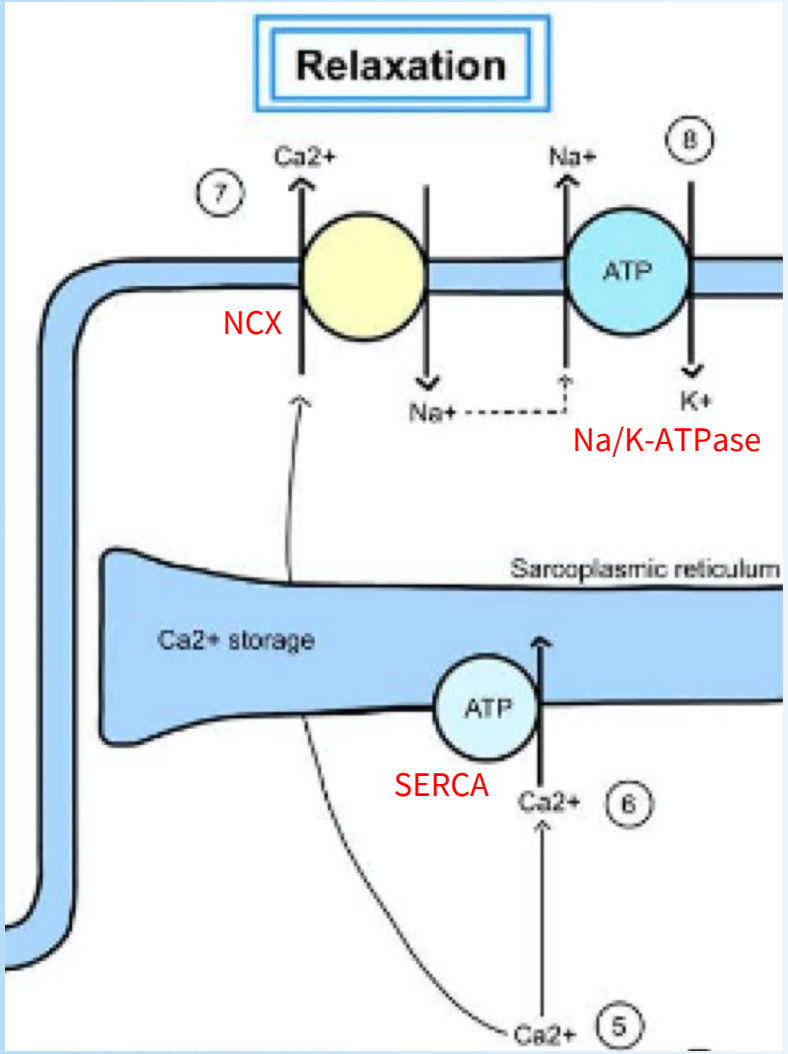
Contraction



http://www.sci.sdsu.edu/movies/actin_myosin_gif.html

Relaxation

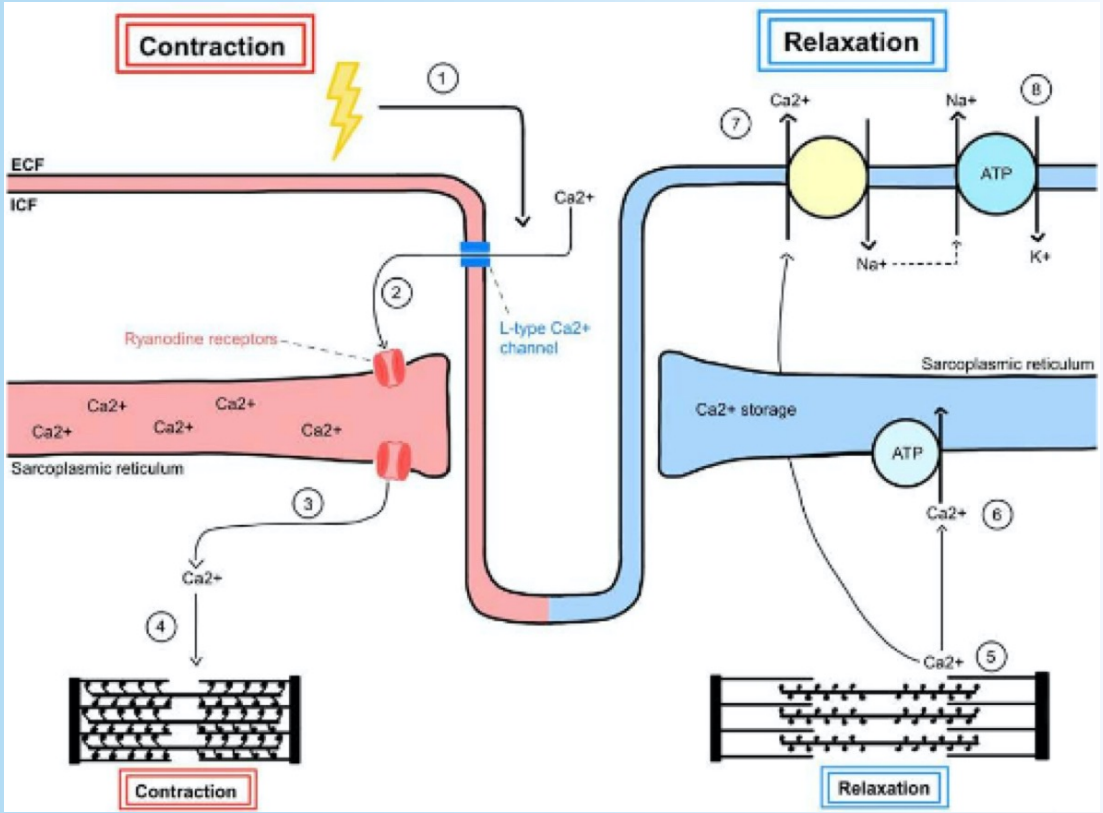
- Calcium disengagement
  - Ca^{2+} releases from troponin, and tropomyosin returns to the default state of blocking the myosin binding site
  - Passive lengthening
- Calcium removal
  - Ca^{2+}-ATPase (SERCA) pumps Ca^{2+} into the SR
  - Ca^{2+}-$3Na^{+}$-exchanger (NCX) pumps Ca^{2+} out of cell
  - Na^{+}/K^{+}-ATPase restores Na^{+} gradient of sarcolemma
- Regulation
  - Unphosphorylated (inactive) phospholamban inhibits SERCA function
  - $ß_1$ - adrenergic stimulation phosphorylates (activates) phospholamban → *increased rate of relaxation*



Recap...

Contraction	
Stage	**Event**
1	**Action Potential –** An action potential is initiated and the wave of depolarization is conducted to interior of the cell membrane through **t-tubules**
2	**Trigger Ca^{2+} -** During the plateau phase of the ventricular action potential, Ca^{2+} enters the cardiomyocyte through L-type Ca^{2+}channels (*dihydropyridine receptors*)
3	**Ca^{2+} induced Ca^{2+} release (CICR) -** Trigger Ca^{2+} activates ryanodine receptors on the SR and Ca^{2+} is subsequently released from the SR
4	**Cross-bridge formation -** Ca^{2+} binds Troponin C, leading to removal of the tropomyosin inhibition on myosin. Actin binds myosin, allowing cross-bridge formation and contraction

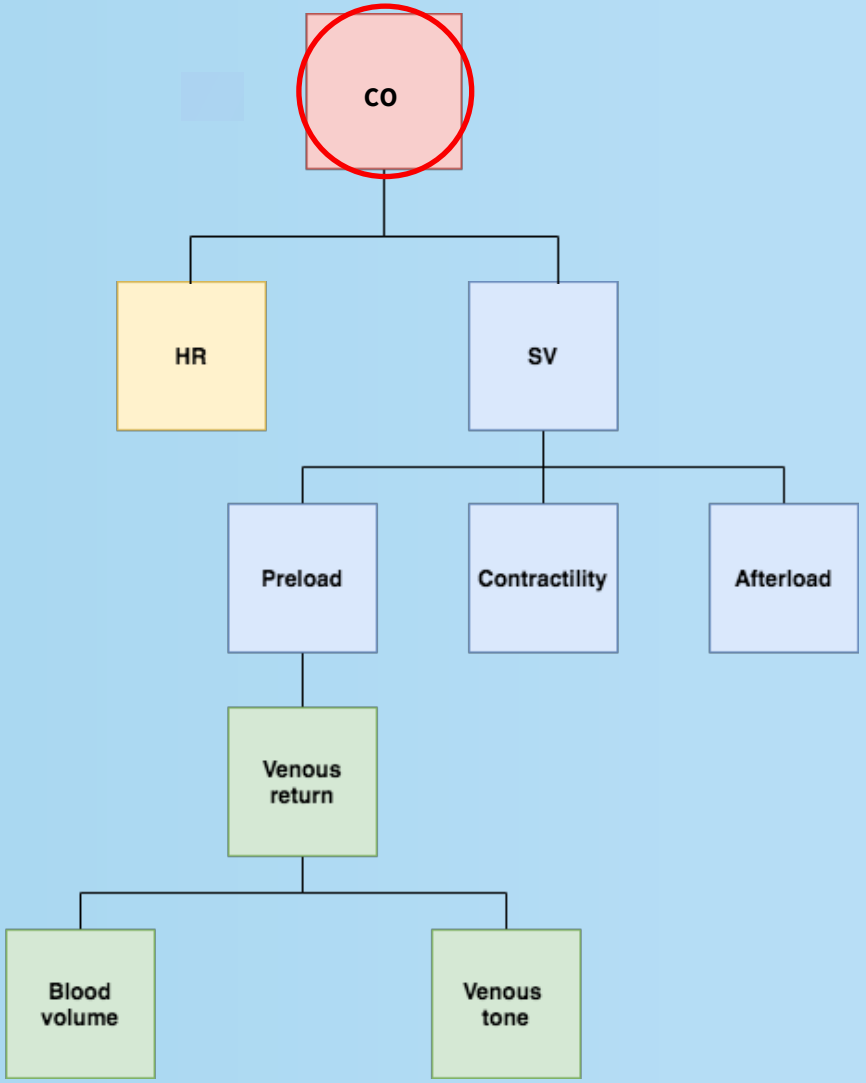
Relaxation	
Stage	**Event**
5	**Ca^{2+} detaches from troponin C**
6	**Ca^{2+} reuptake into SR by Ca^{2+}- ATP-ase –** Intracellular Ca^{2+} levels decrease
7	**Ca^{2+} - $3Na^{+}$ exchanger in sarcolemmal membrane** - Extrudes Ca^{2+} out of the cell, contributing to a further decrease in intracellular Ca^{2+}
8	**Na^{+}/K^{+} ATP-ase** – Restoration of the Na^{+} gradient



Drugs that Affect Inotropy

Drug class	Glycosides	Cathecholamines	Calcium Channel Blockers
Drug examples	• Digoxin • Digitoxin	• Epinephrine • Norepinephrine	«dipine»-suffix: • Amlodipine • Nifedipine
Mechanism of action	Inhibits Na^+/K^+-ATPase → ↑ intracellular Ca^{2+}	$ß_1$ – adrenergic receptor agonist → phospholamban phosphorylation	Blocks Ca^{2+}-channels in cardiac muscle & arteriolar smooth muscle
Effects	• Positive inotrope	• Positive inotrope • ↑ Heart rate	• Negative inotrope • Vasodilation

Cardiac Contraction Measurements



Cardiac Output

- Cardiac output = the amount of blood ejected *per minute* (L/min)
- Determined by stroke volume (SV = L/beat) & heart rate (HR = beats/min)
- Normal range: 4 - 8 L/min

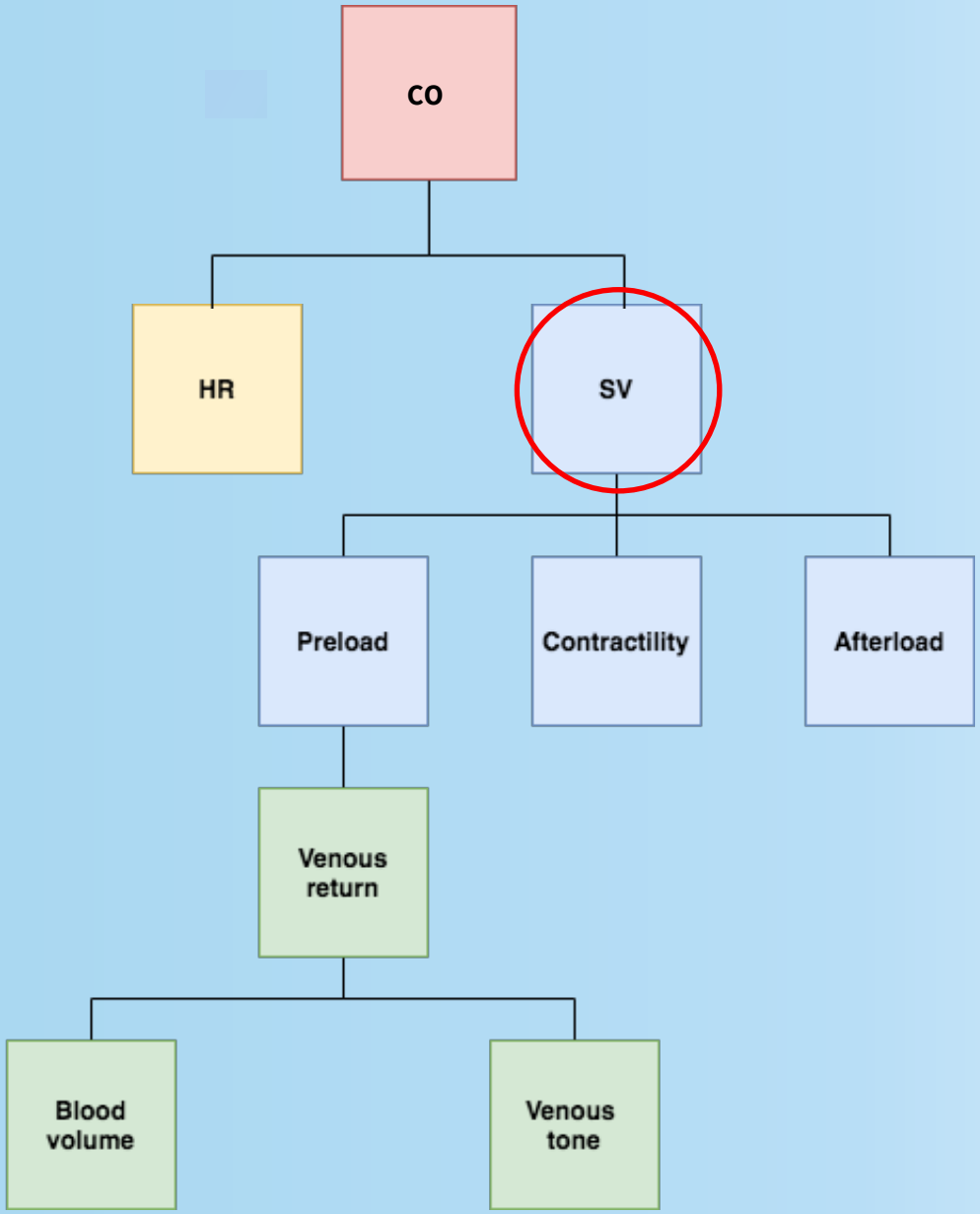
$$CO = SV \times HR$$

$$\frac{L}{min} = \frac{L}{beat} \times \frac{beat}{min}$$

Clinical correlate:

In situations where there is a decrease in blood flow throughout the body *(bleeding from trauma, severe infections, allergic reactions)*, your body will attempt to compensate for the loss in cardiac output by increasing your heart rate.

Takeaway: Patients with a fast heart rate may be in need of urgent intervention!


CO
HR
SV
Preload
Contractility
Afterload
Venous return
Blood volume
Venous tone

Stroke Volume

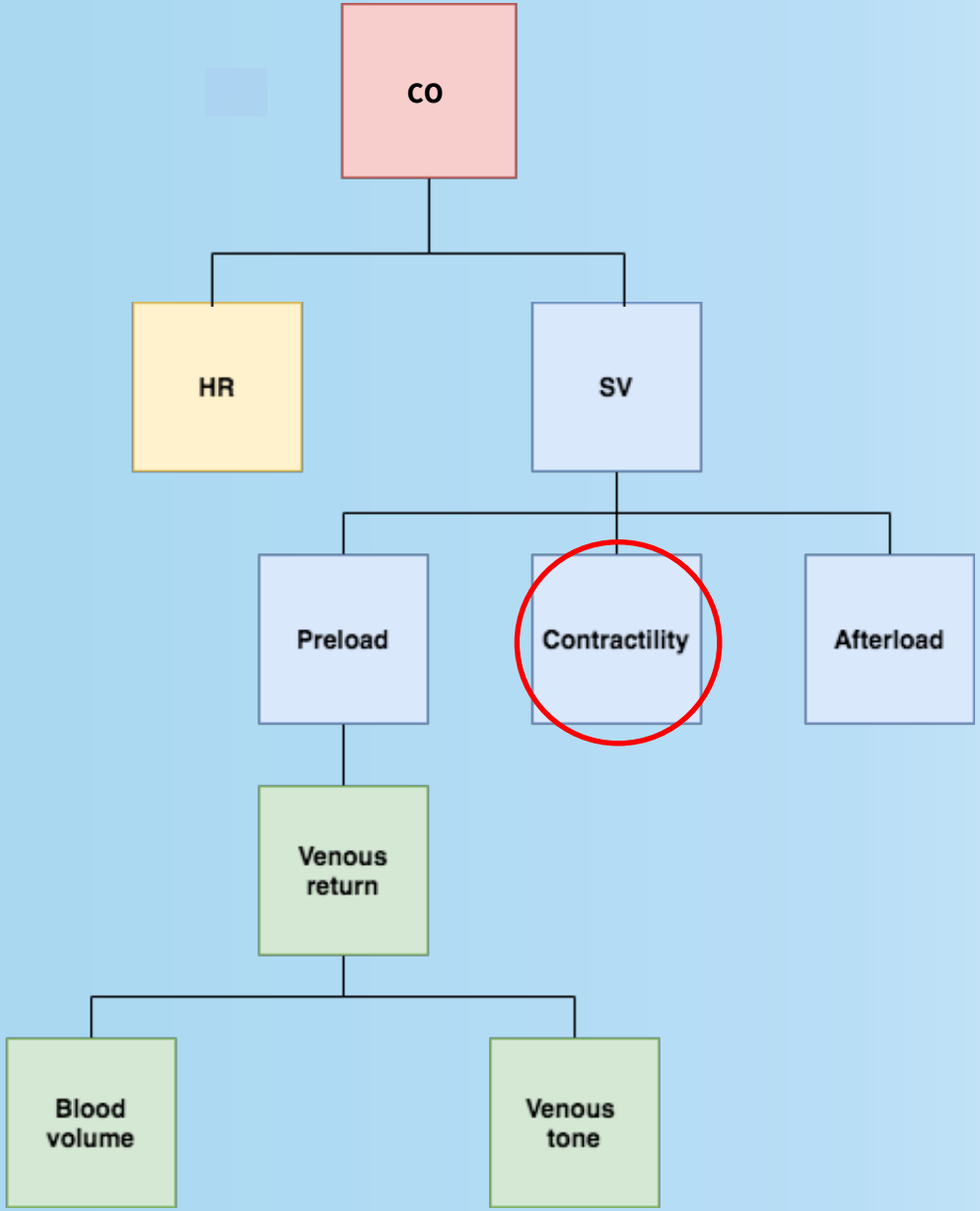
- Stroke volume (SV) = amount of blood ejected *per beat*
- Normal range: 60-100 mL

$$SV = EDV - ESV$$

EDV = end-diastolic volume
ESV = end-systolic volume

Stroke volume is dependent on contractility, preload and afterload:

- ↑ Contractility → ↑ SV
- ↑ Preload → ↑ SV
- ↑ Afterload → ↓ SV


CO
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Contractility - inotropism

↑ Contractility → ↑ SV

- Contractility = strength of contraction of the cardiomyocytes
- Proportional to intracellular Ca^{2+} concentration
- Measured by ejection fraction (EF), or percentage of blood ejected per beat
- Normal range: 50 - 70%

$$EF = \frac{SV}{EDV}$$

- SV (stroke volume) = blood volume ejected per beat
- EDV (end-diastolic volume) = blood volume present before each beat

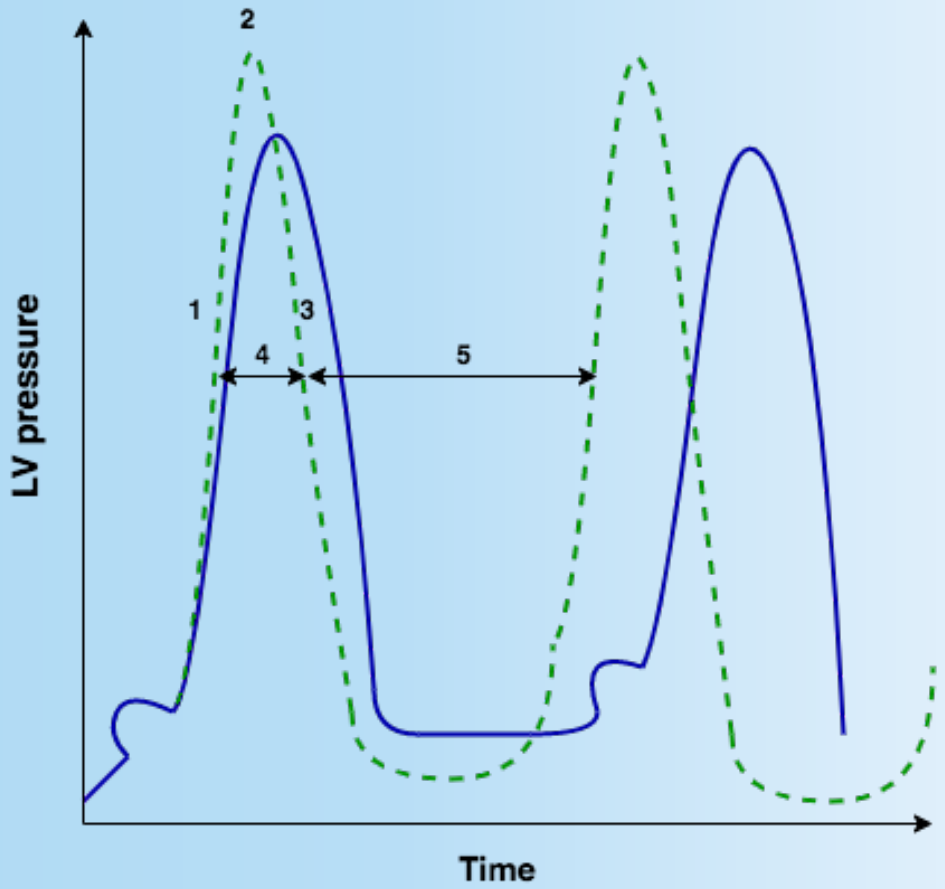
Contractility - inotropism

Increased contractility

- Sympathetic stimulation
- Increased heart rate
  - $\uparrow HR \rightarrow \uparrow Ca^{2+}$ *in SR*

Decreased contractility

- Parasympathetic stimulation
- Decreased heart rate



Green dotted line: ↑ contractility
Purple line: ↓ contractility

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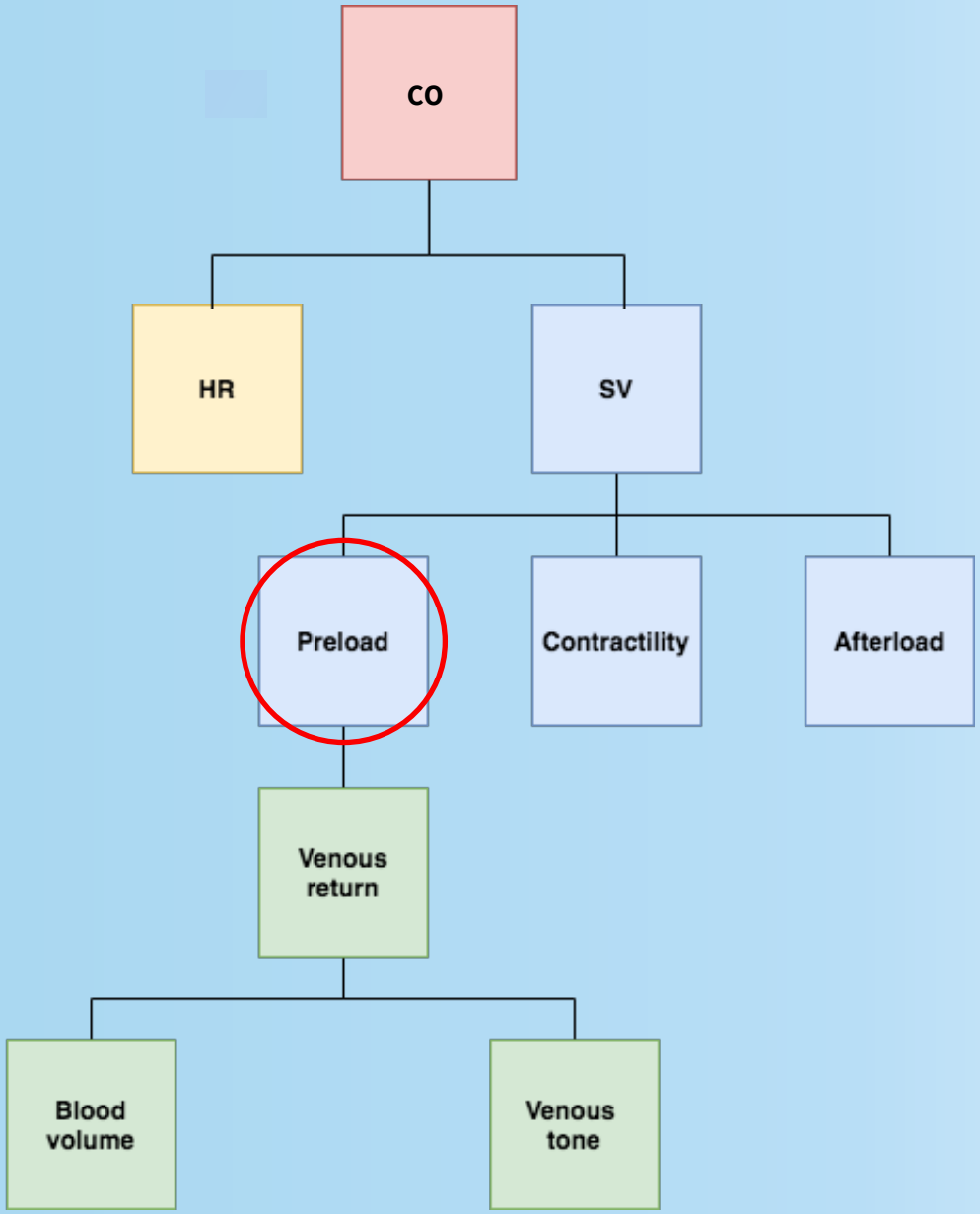
CO
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Preload

↑Preload → ↑SV

- *Degree of sarcomere stretch* before ventricular contraction
- Preload = LVEDP (≈ EDV)

LVEDP = Left Ventricular End-Diastolic Pressure (mmHg)
EDV = End Diastolic Volume (L)

- Dependent on venous tone and blood volume:
  - ↑ Venous tone → ↑ VR → ↑ Preload
  - ↑ Blood volume → ↑ VR → ↑ Preload

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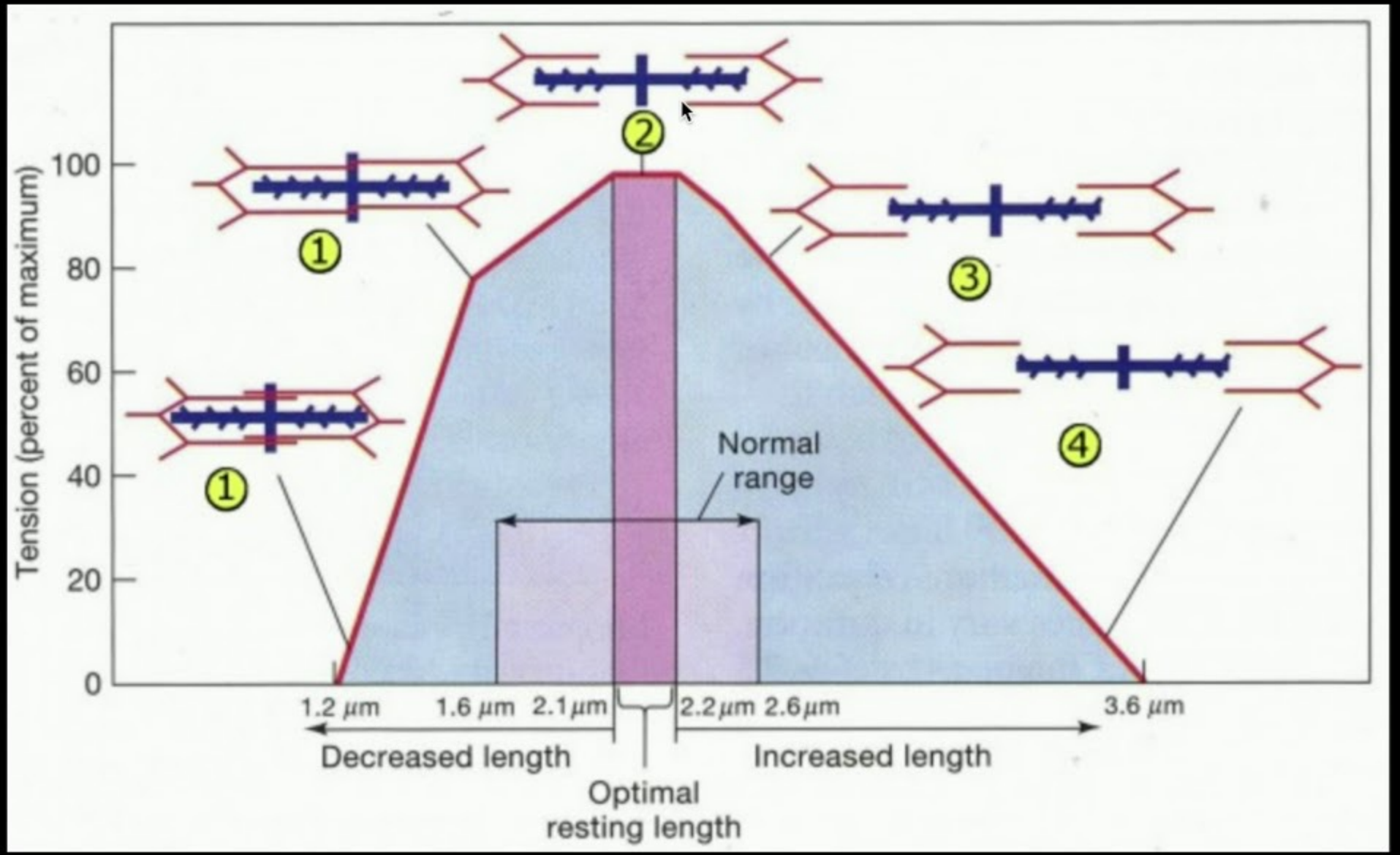
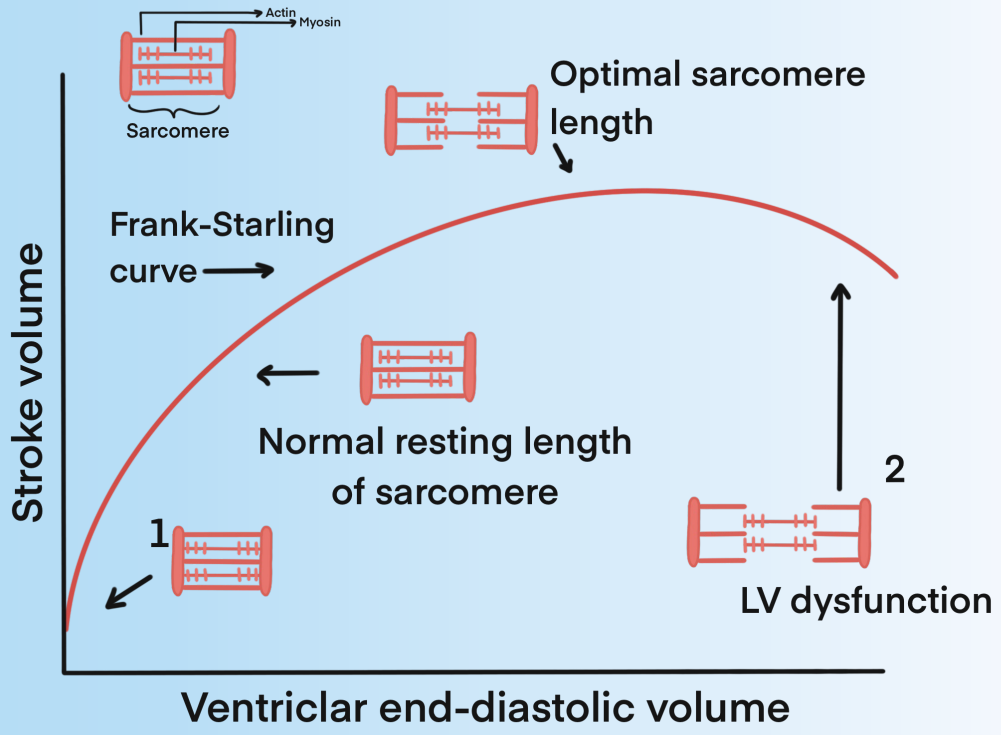
The Length-Tension Relationship of Muscle



Frank-Starling curve

Describes how changes in preload affects stroke volume:

- ↑ Preload → ↑ Sarcomere stretch → ↑ SV
  - Heterometric autoregulation:
    The heart responds to increased preload by increasing stroke volume
- Excessive stretch decreases SV



Frank-Starling curve

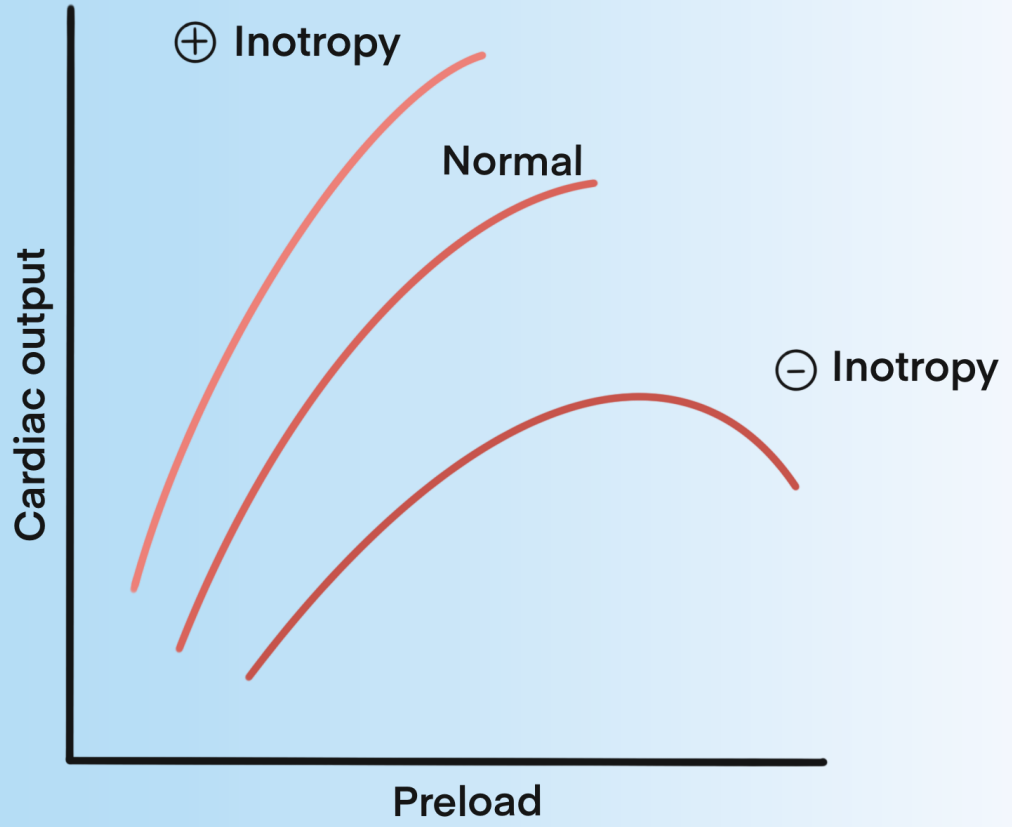
In relation to contractility

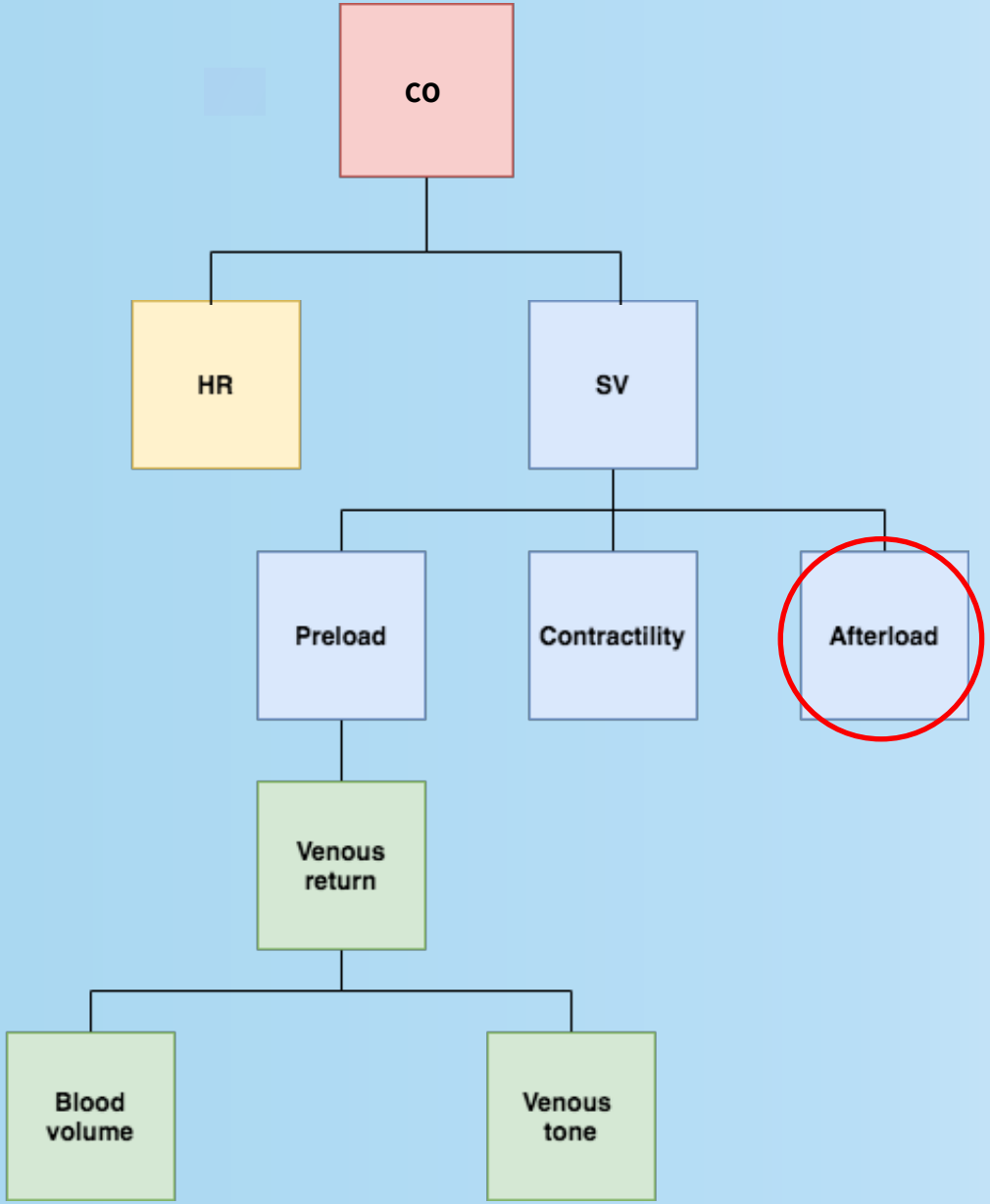
Increased contractility – curve to the ***left***

- Sympathetic stimulation
- Increased heart rate

Decreased contractility – curve to the ***right***

- ß-blockers
- Heart failure




CO
HR
SV
Preload
Contractility
Afterload
Venous return
Blood volume
Venous tone

Afterload

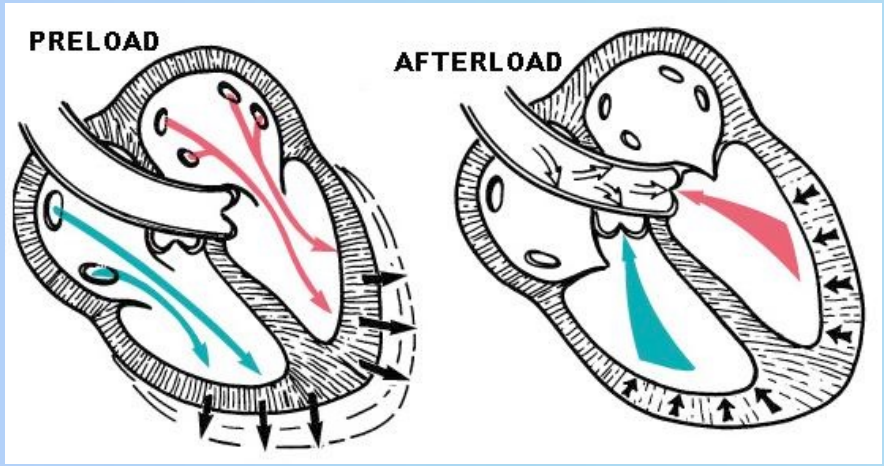
↑ *Afterload* → ↓ *SV*

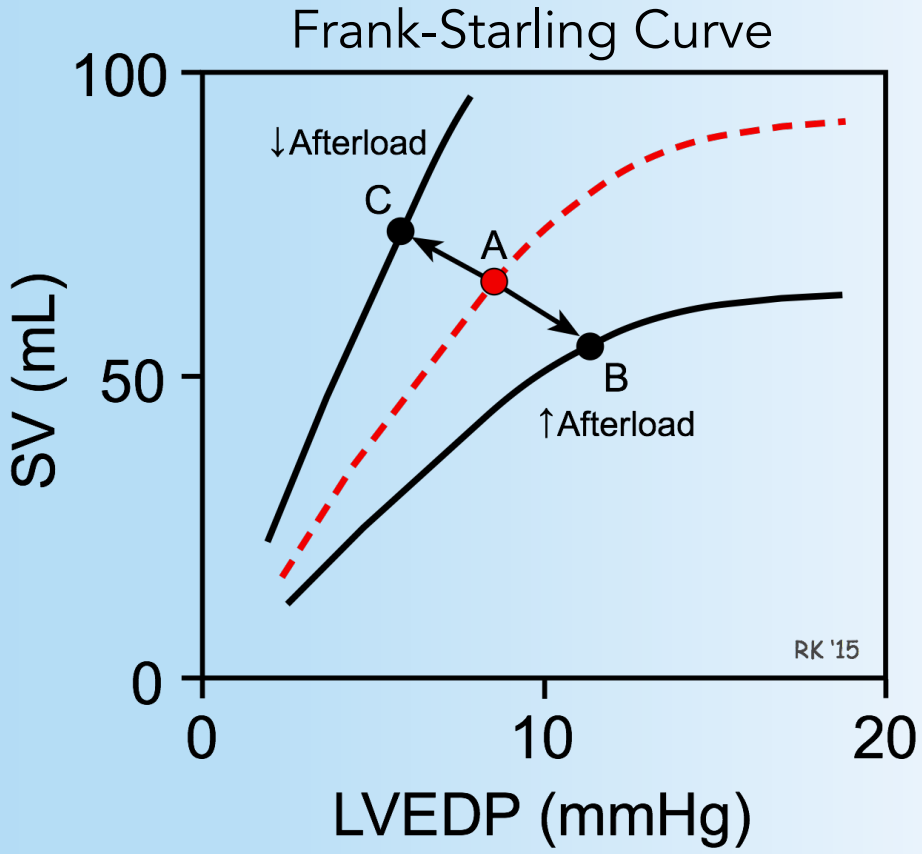
- The pressure the *ventricles are pushing against* during systole:
  - The pressure in the aorta
  - Hypertension → ↑ afterload
- Dependent on *total peripheral resistance* (TPR), which is regulated by constriction of the arterioles:
  - Arteriolar constriction → ↑ TPR → ↑ afterload

Preload vs. Afterload

- ↑ Afterload → ↓ Stroke volume
- ↓ Afterload → ↑ Stroke volume

- ↑ Preload → ↑ Stroke volume
- ↓ Preload → ↓ Stroke volume





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To which point (from N) will you end up:

- During exercise?
- In aortic valve stenosis?
- During exams (stress)?
- When you lay on your back with legs raised?
- When arterioles constrict?
- In a trauma patient with blood loss?