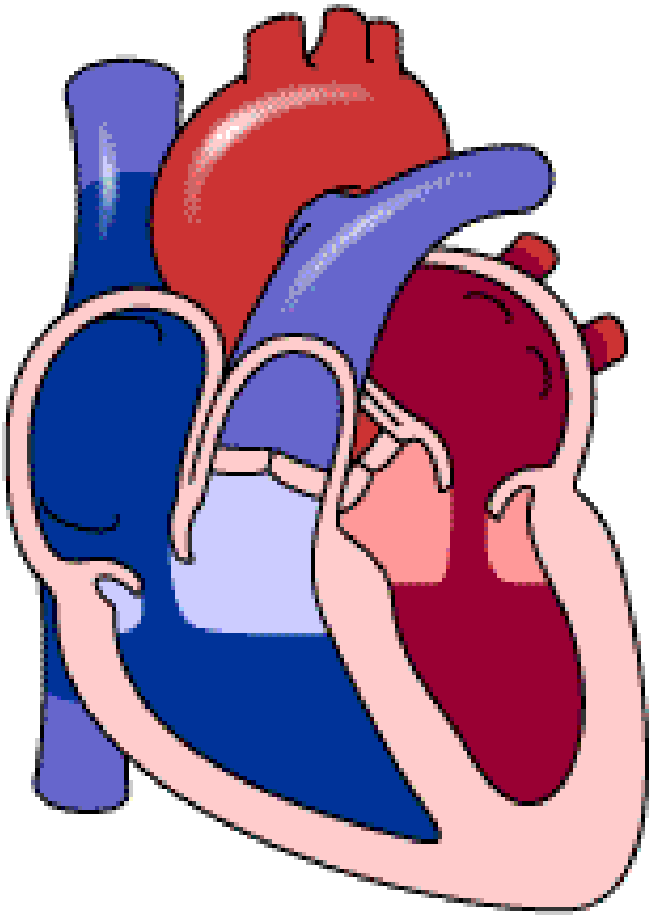
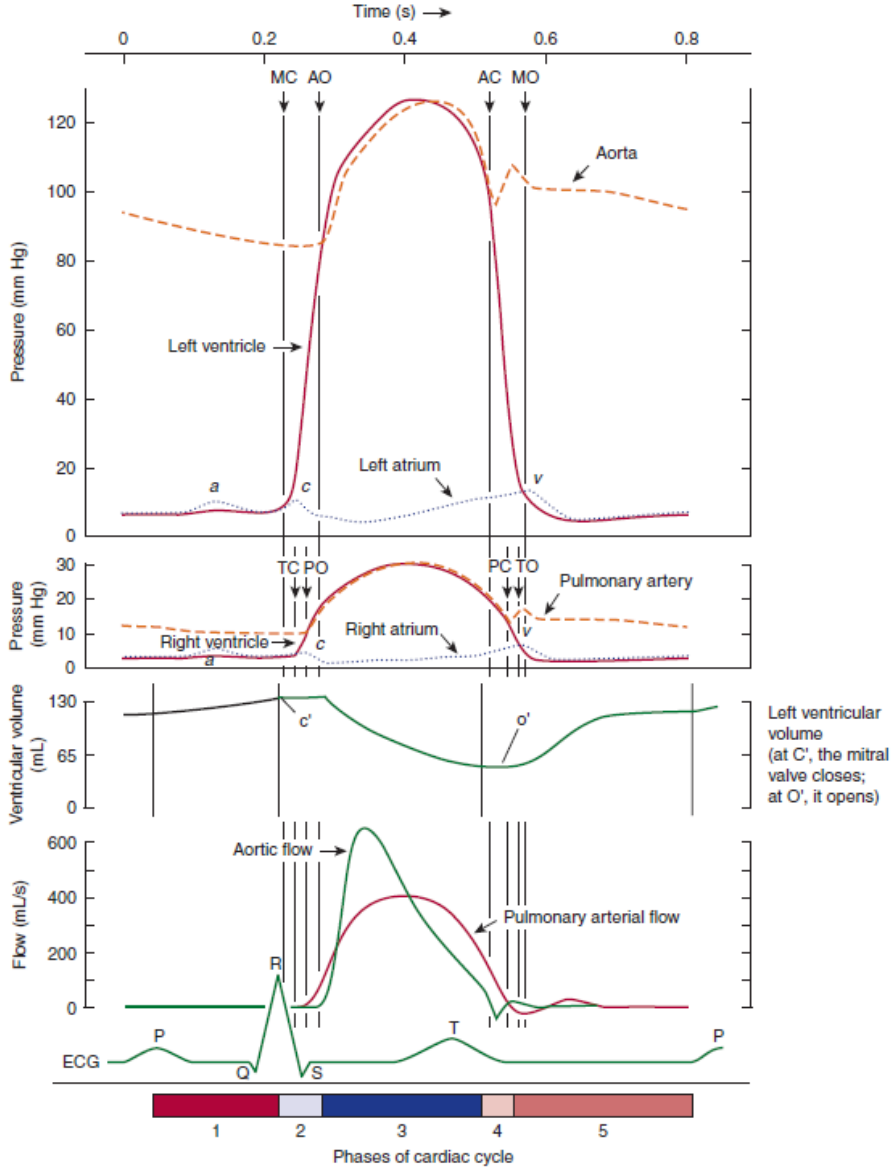
Pathologic contractile function of the heart

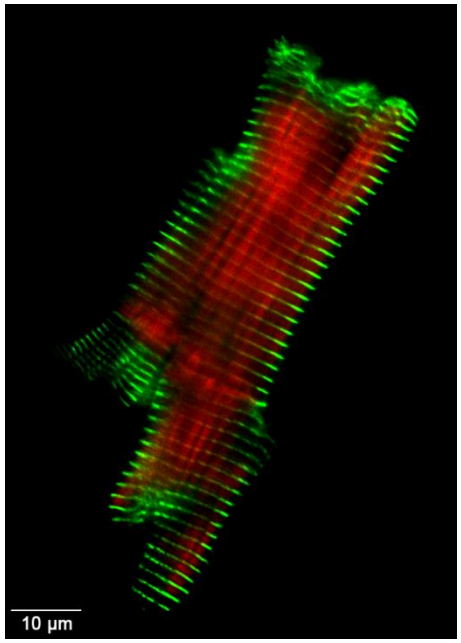
Dr. Zoltán Papp
UD Department of Cardiology
Division of Cinical Physiology

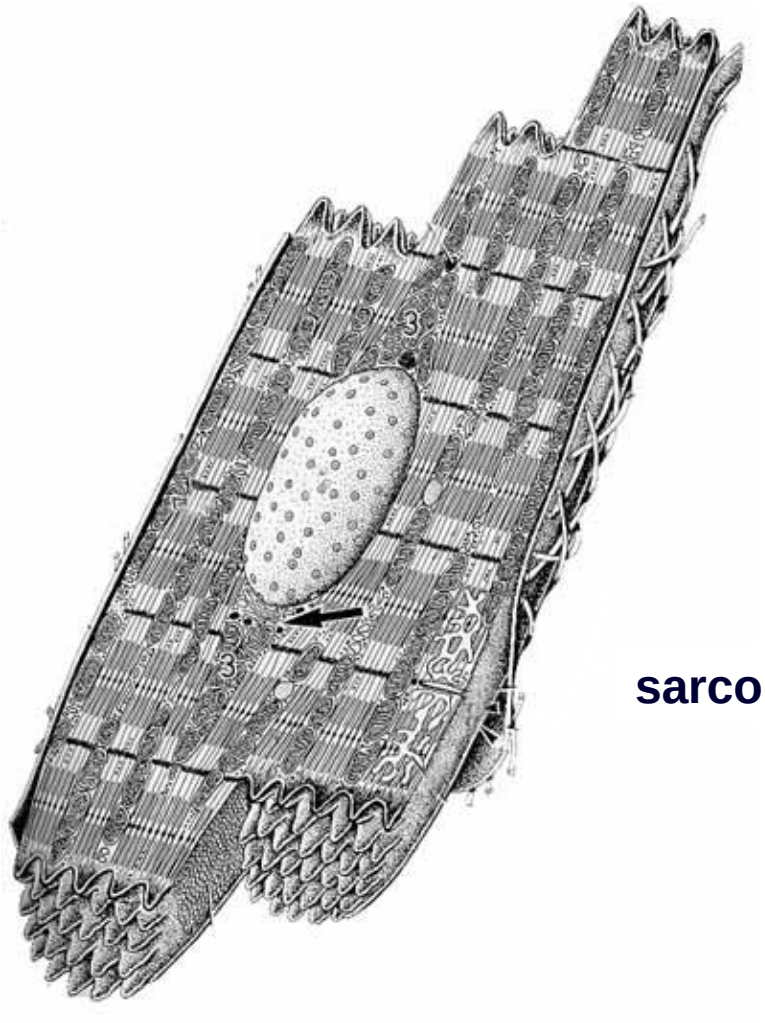
Events of the cardiac cycle





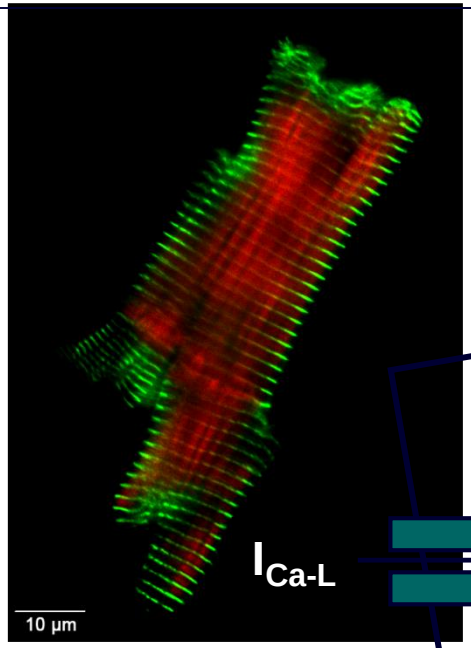
Contractile force is the result of sarcomere shortening

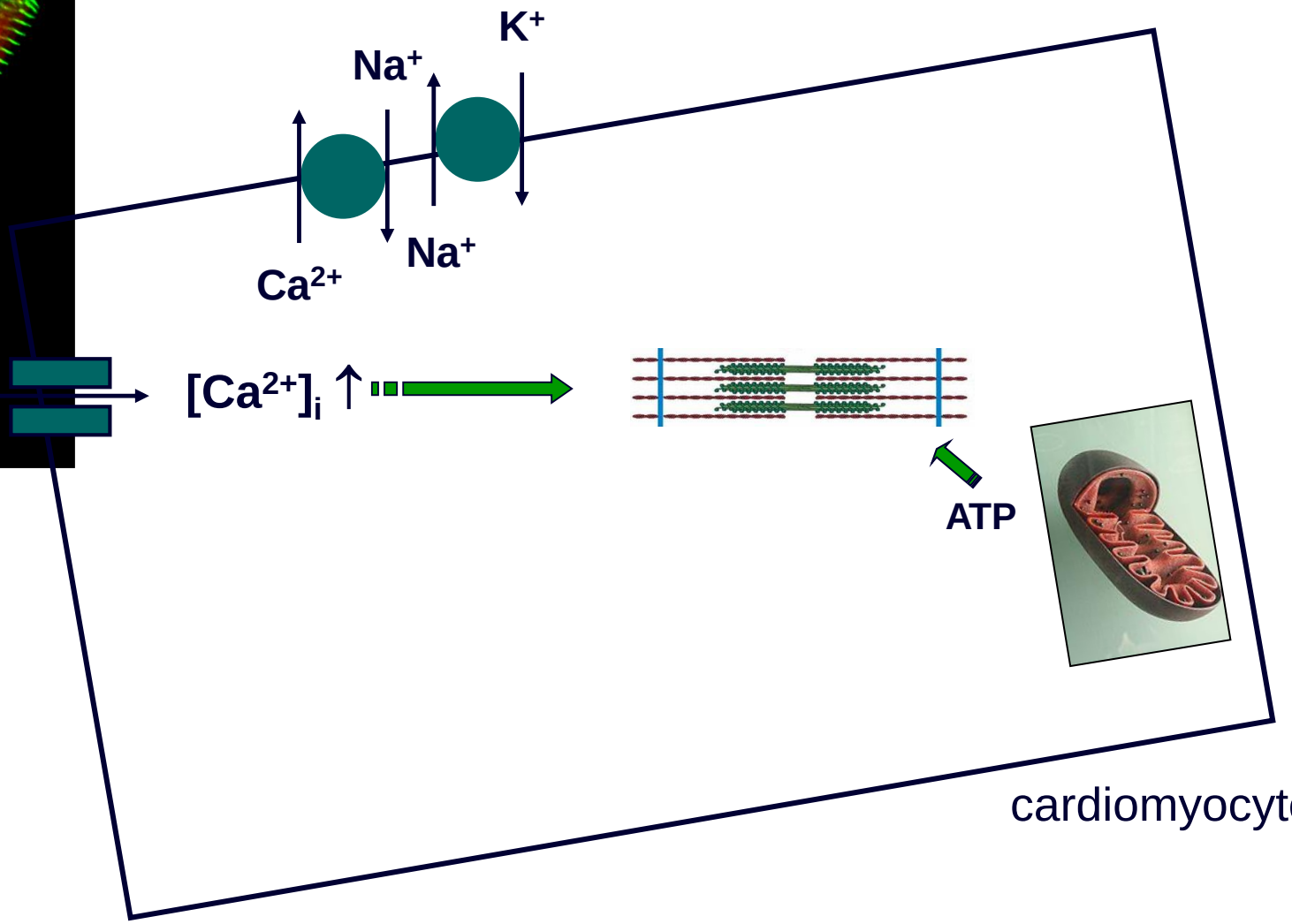




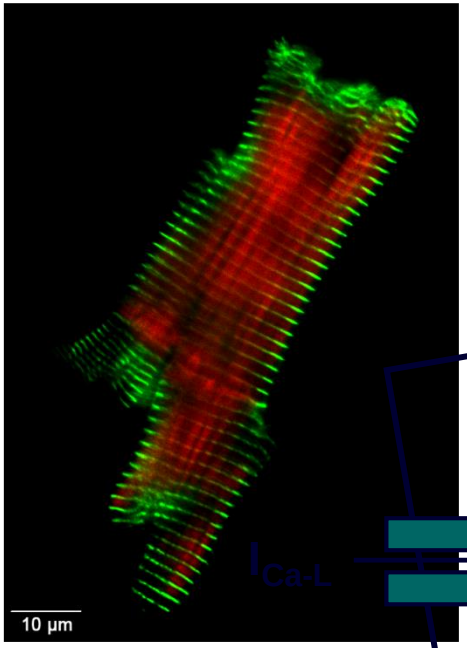
sarcomere

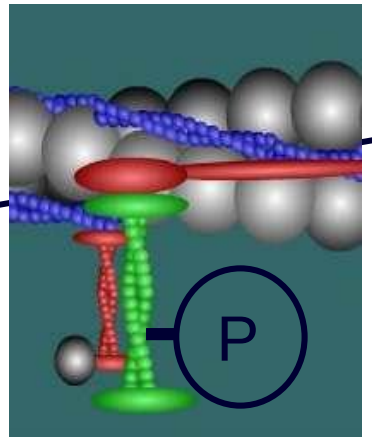
Myocardial contractility = Ca^{2+}-concentration + Ca^{2+}-sensitivity

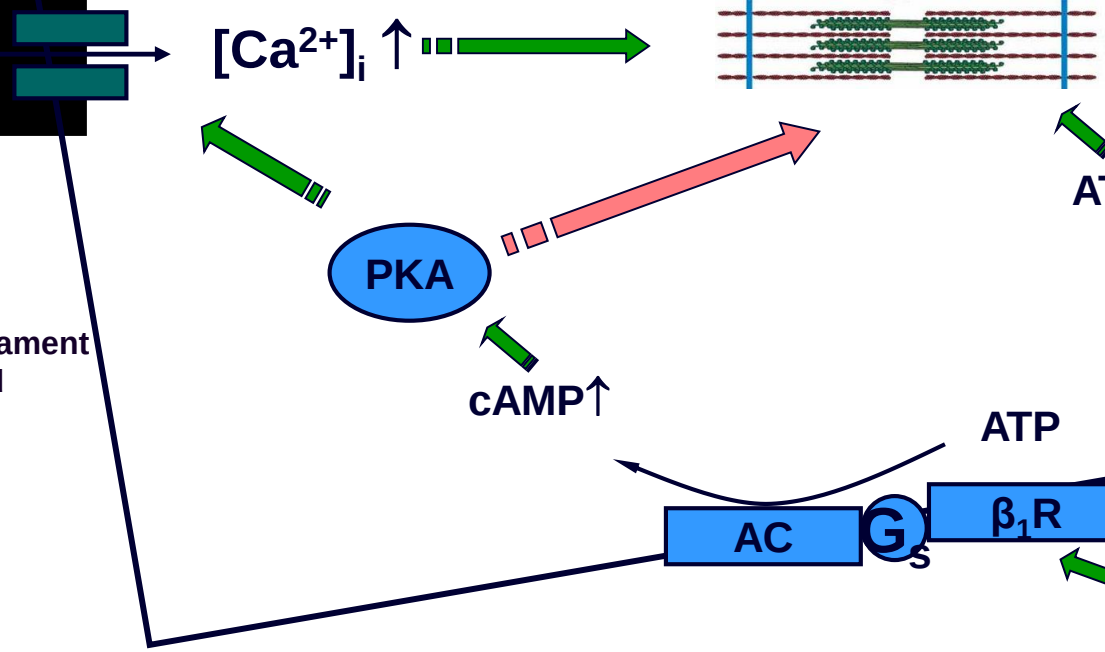




Myocardial contractility = Ca^{2+}-concentration + Ca^{2+}-sensitivity



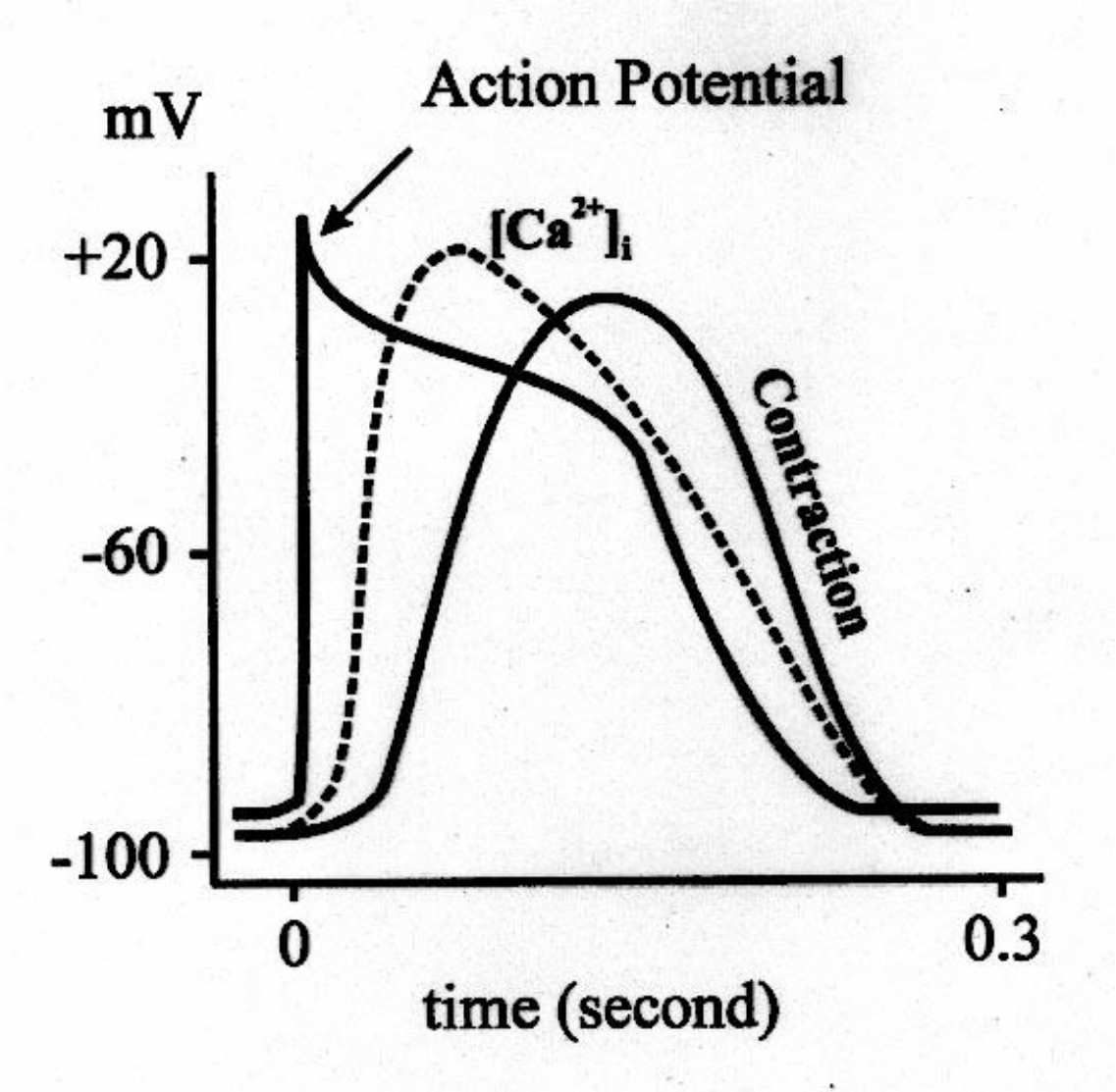




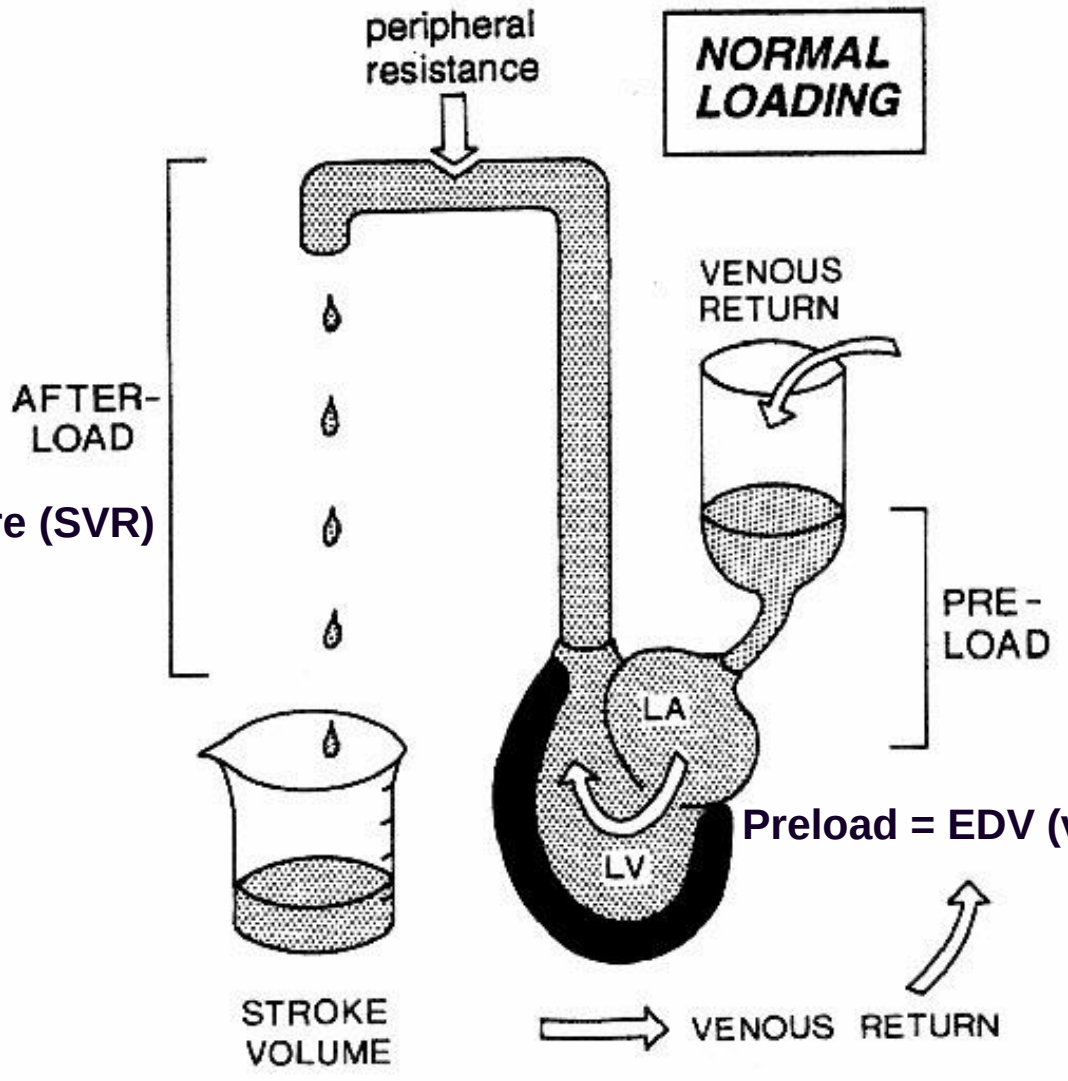
β-stimulation increases $[Ca^{2+}]_i$ and affects myofilament Ca^{2+} responsiveness and these result in:

- **positive inotropy**
- **positive lusitropy**

Action potential, Ca^{2+} transient, contraction



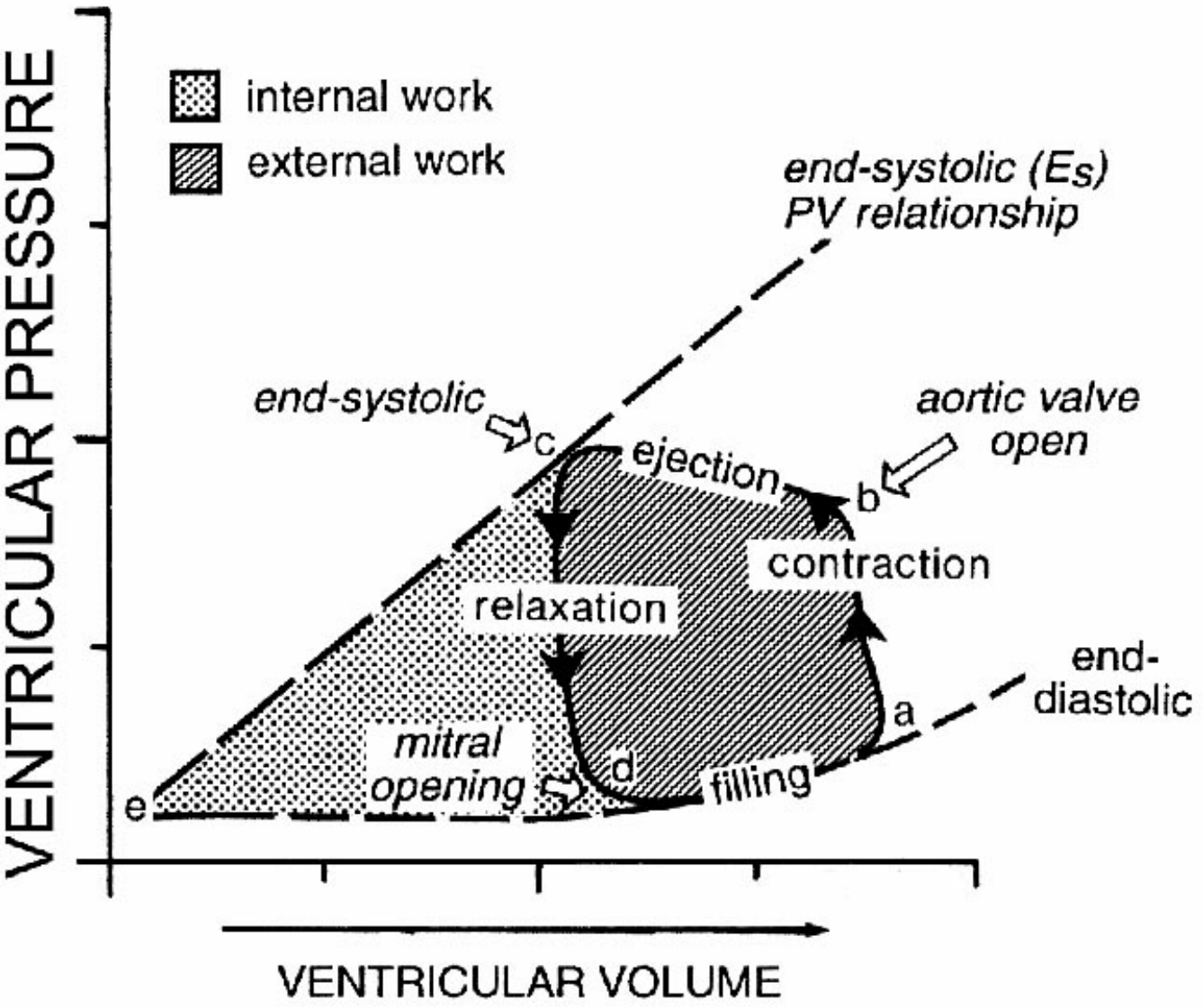
Cardiac preload and afterload



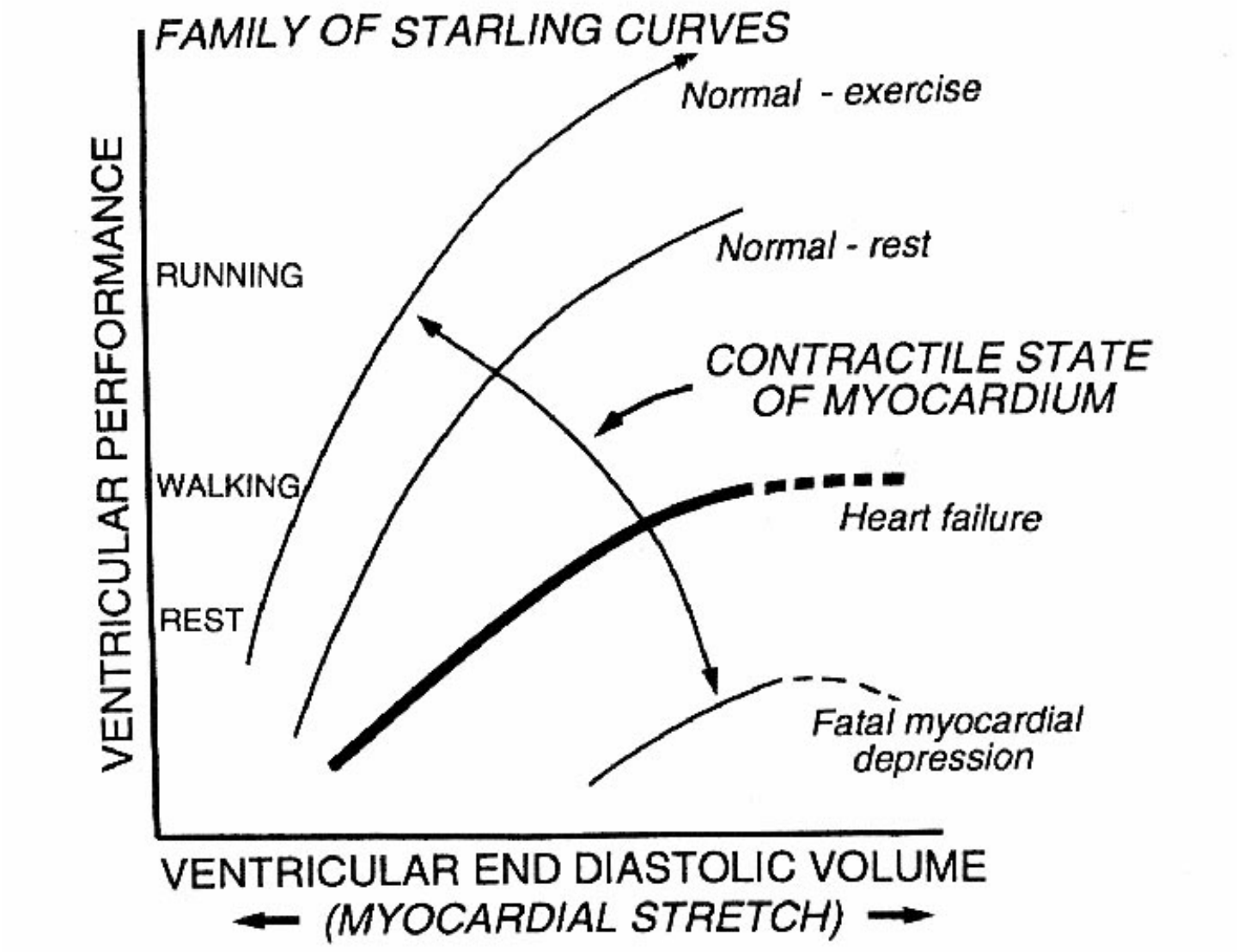
Afterload = Aortic pressure (SVR)

Preload = EDV (venous return)

Cardiac cycle and cardiac work

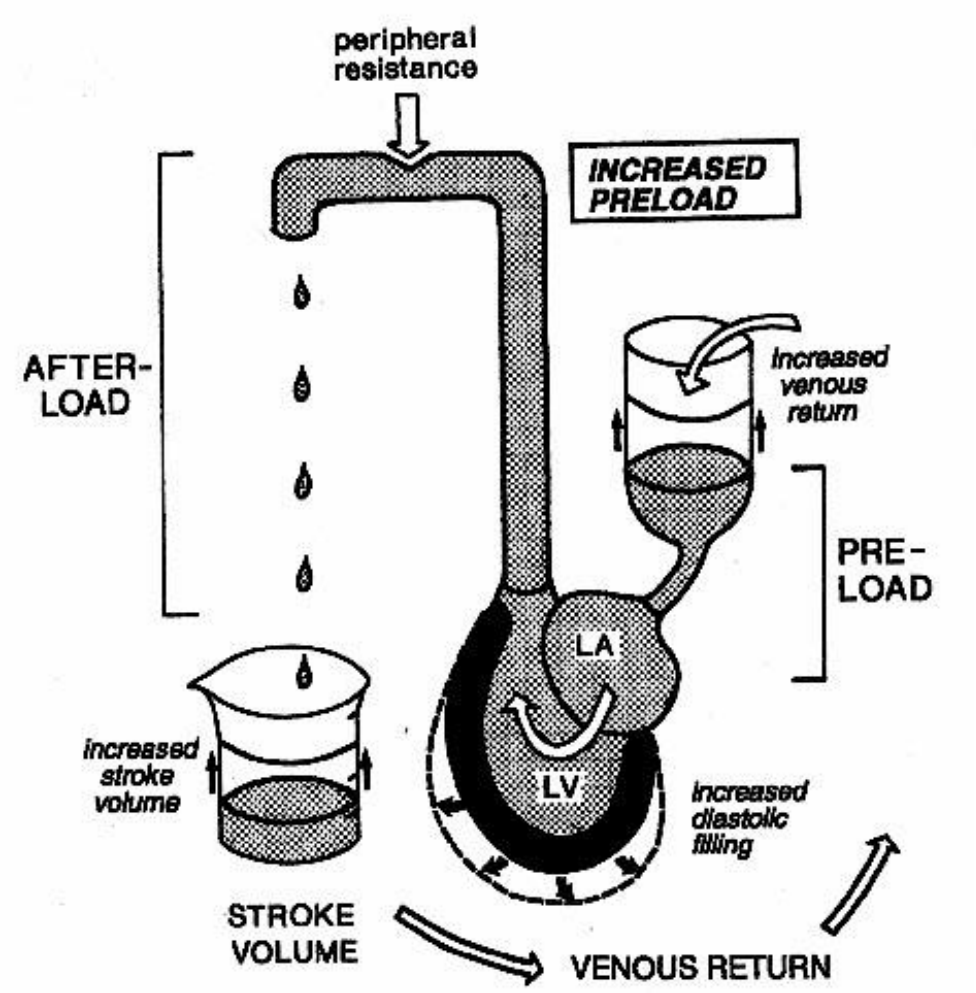


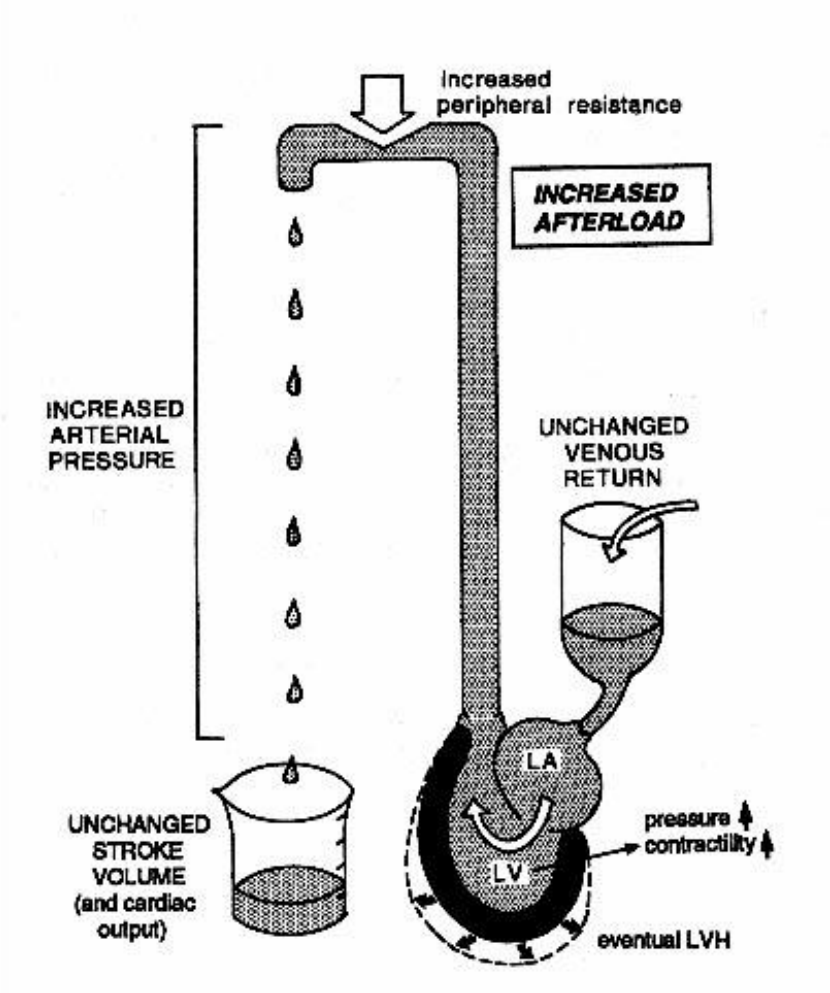
Ventricular function curves



Each curve = different contractile state
Moving along a curve = preload change; moving between curves = contractility change

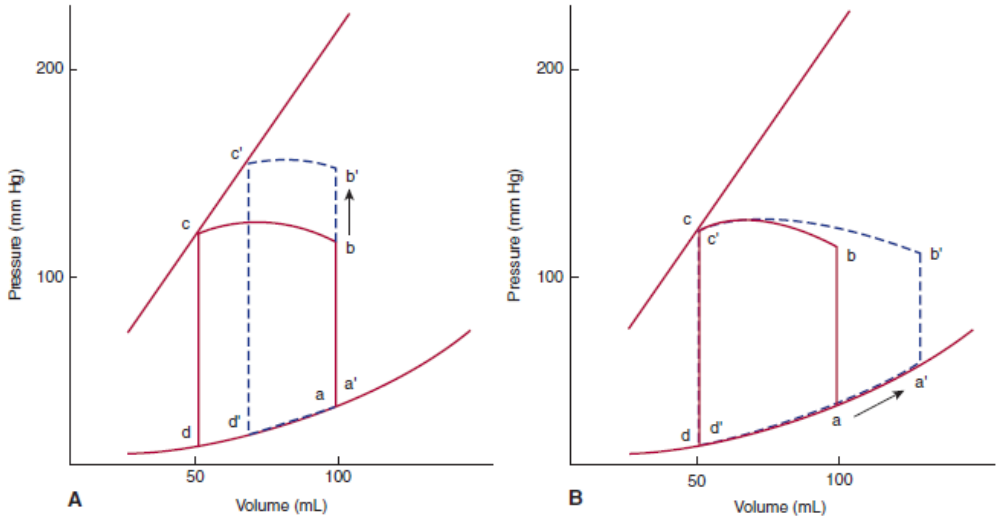
Increased preload and afterload





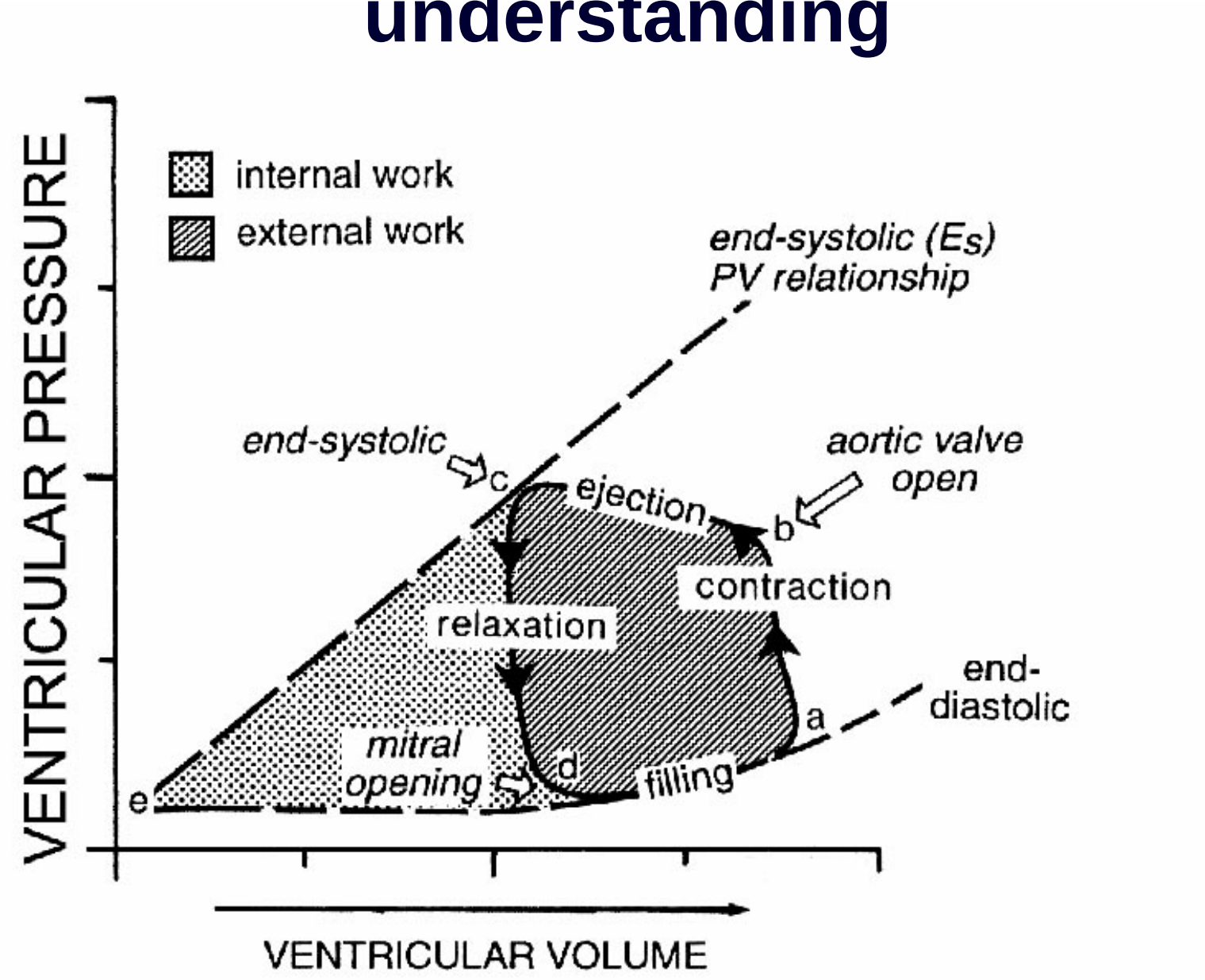
Responses on changes in loading conditions

Increase in afterload



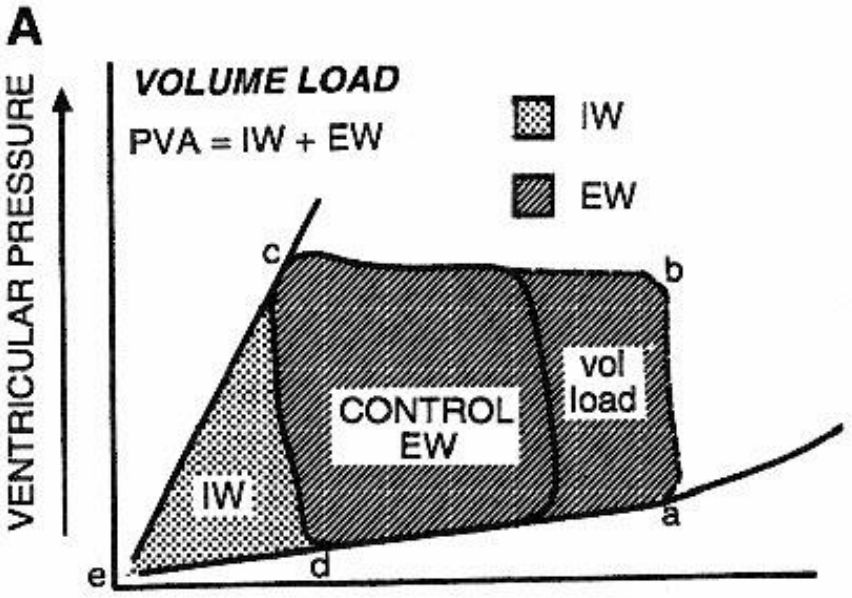
Increase in preload

Revisiting cardiac work with new understanding



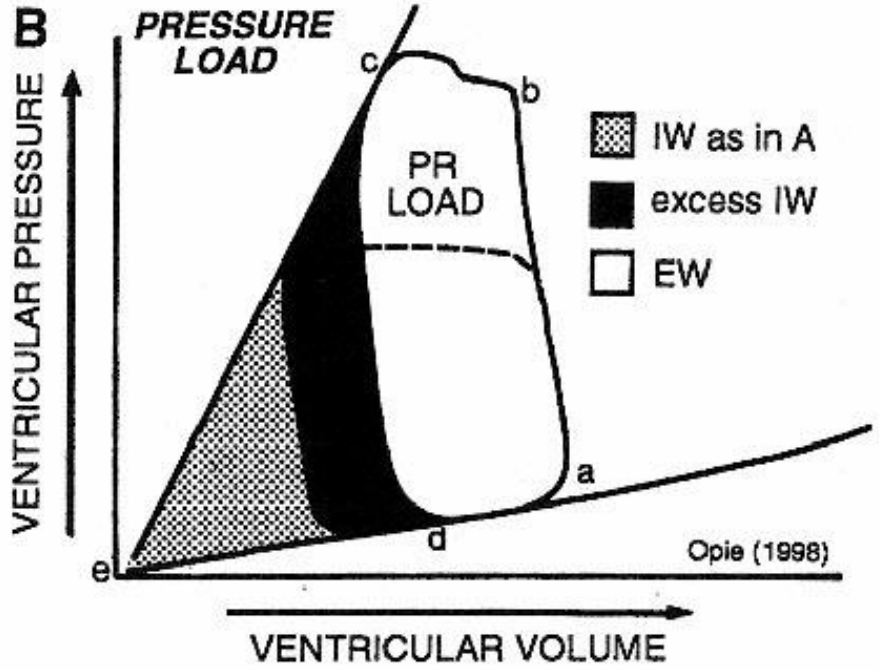
Increased preload

e.g.: mitral regurgitation, aortic regurgitation

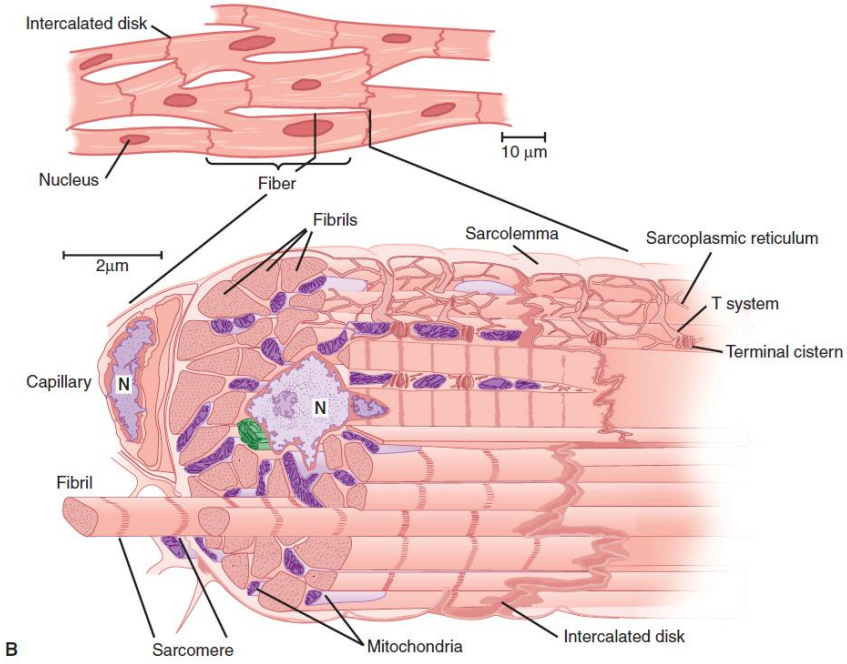


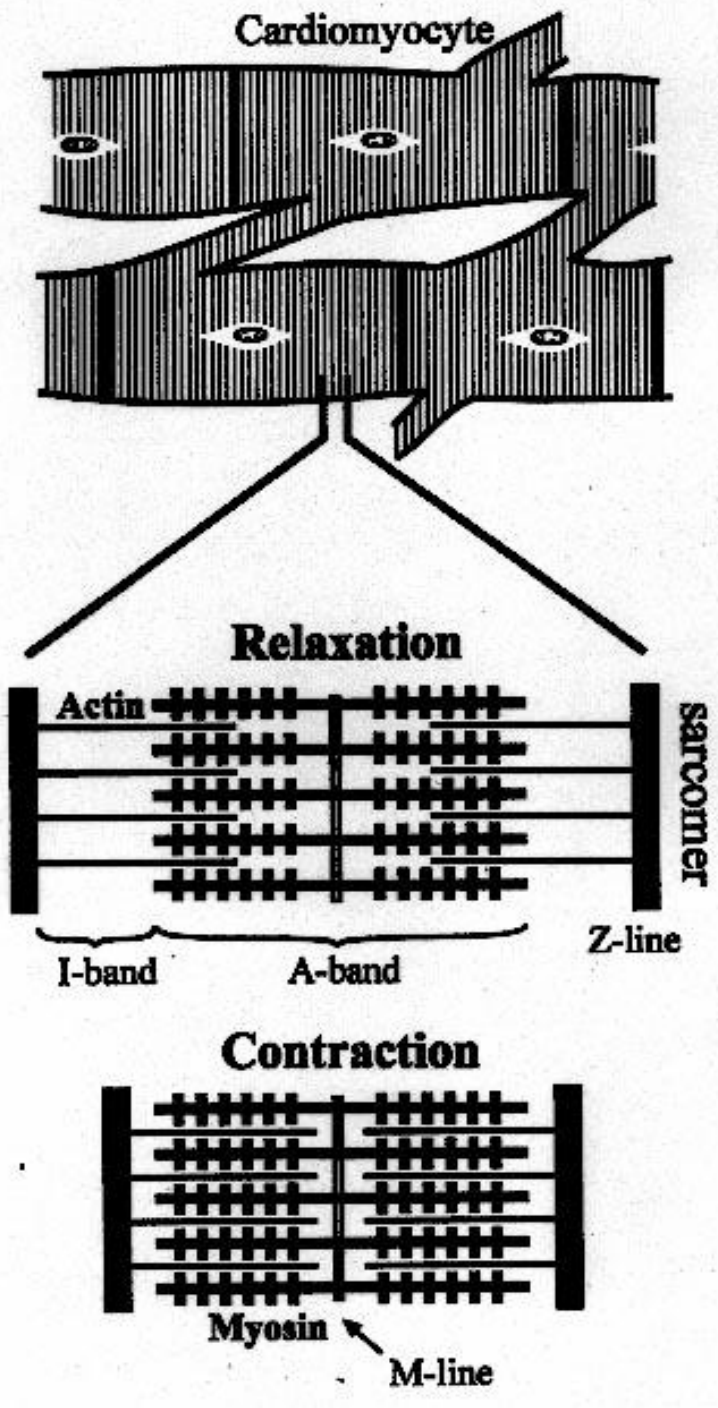
Increased afterload

e.g.: aortic stenosis, hypertension

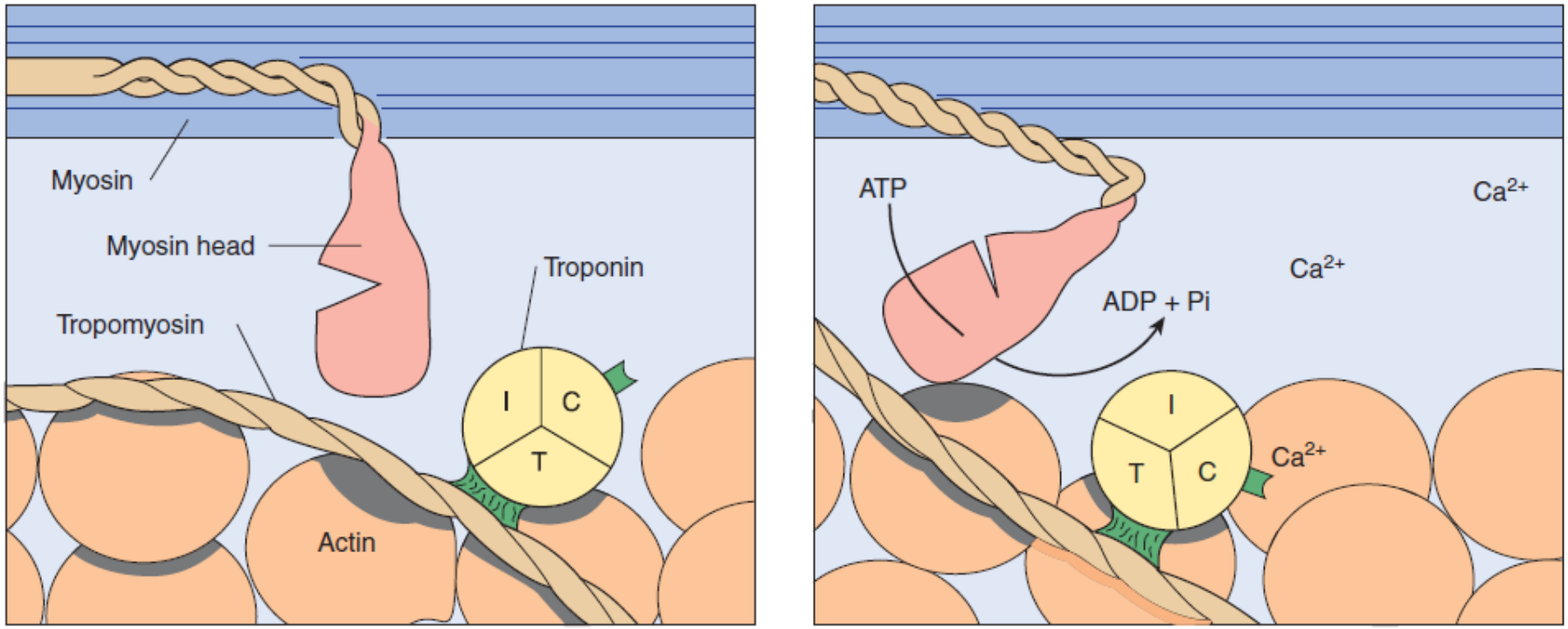


Contractile function and myofilaments

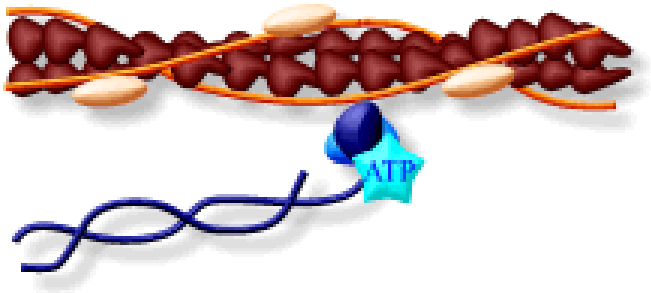


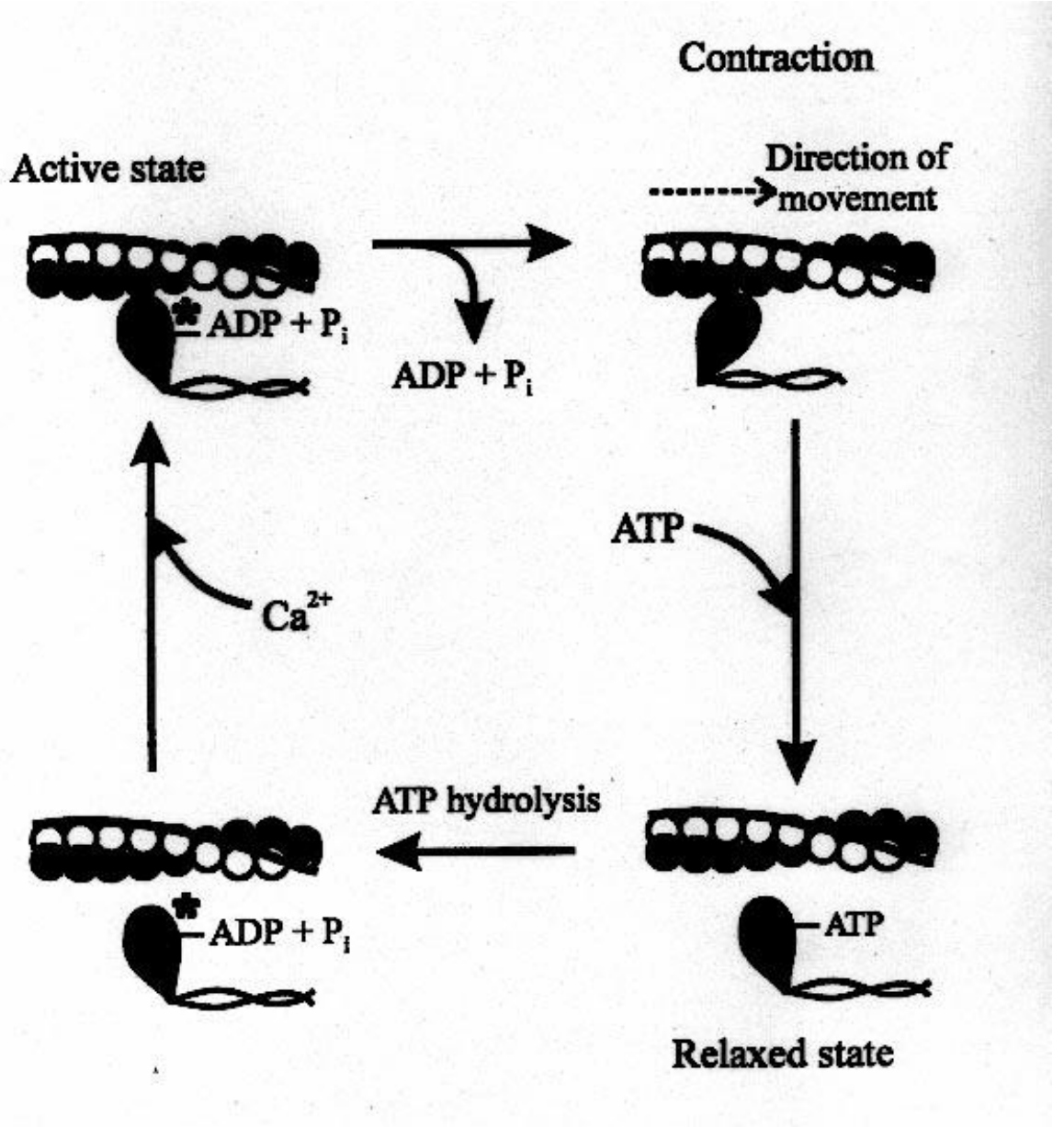


Contractile proteins



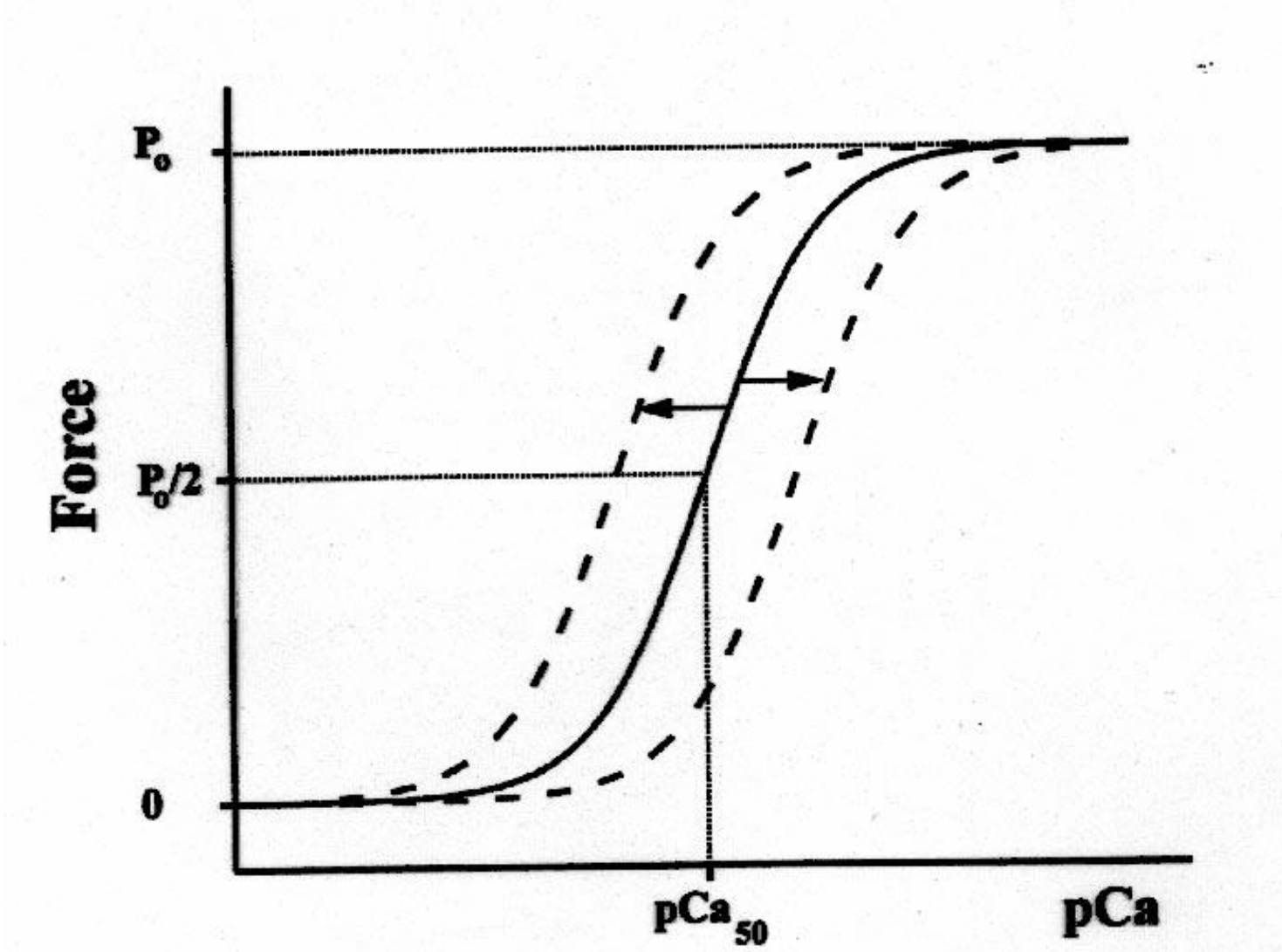
Actin-myosin cycle





ATP required for BOTH contraction AND relaxation.

Ca^{2+} - force relationship

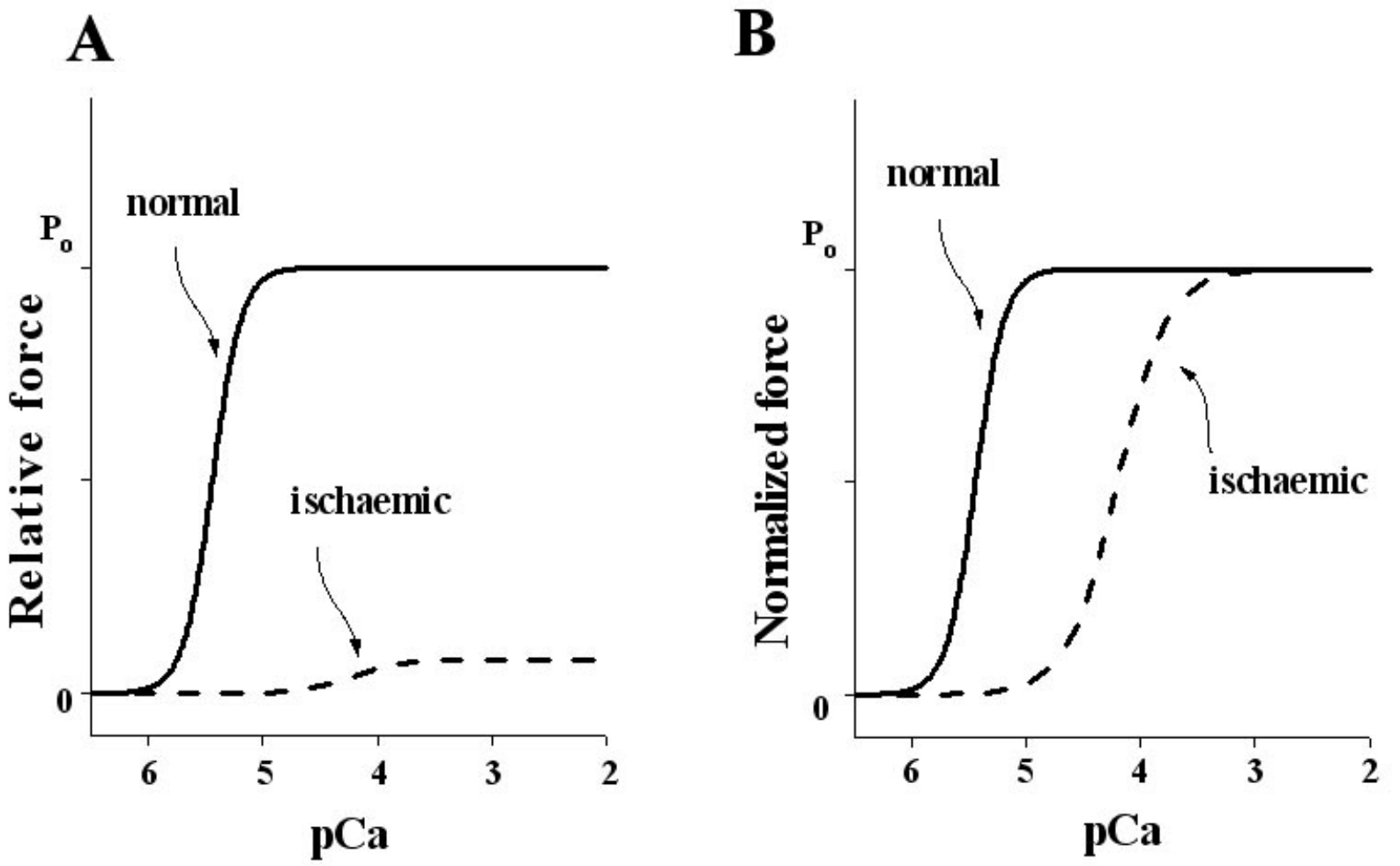


Leftward shift = ↑ sensitivity

Ca^{2+} sensitivity

$pCa = -lg\ [Ca^{2+}]$

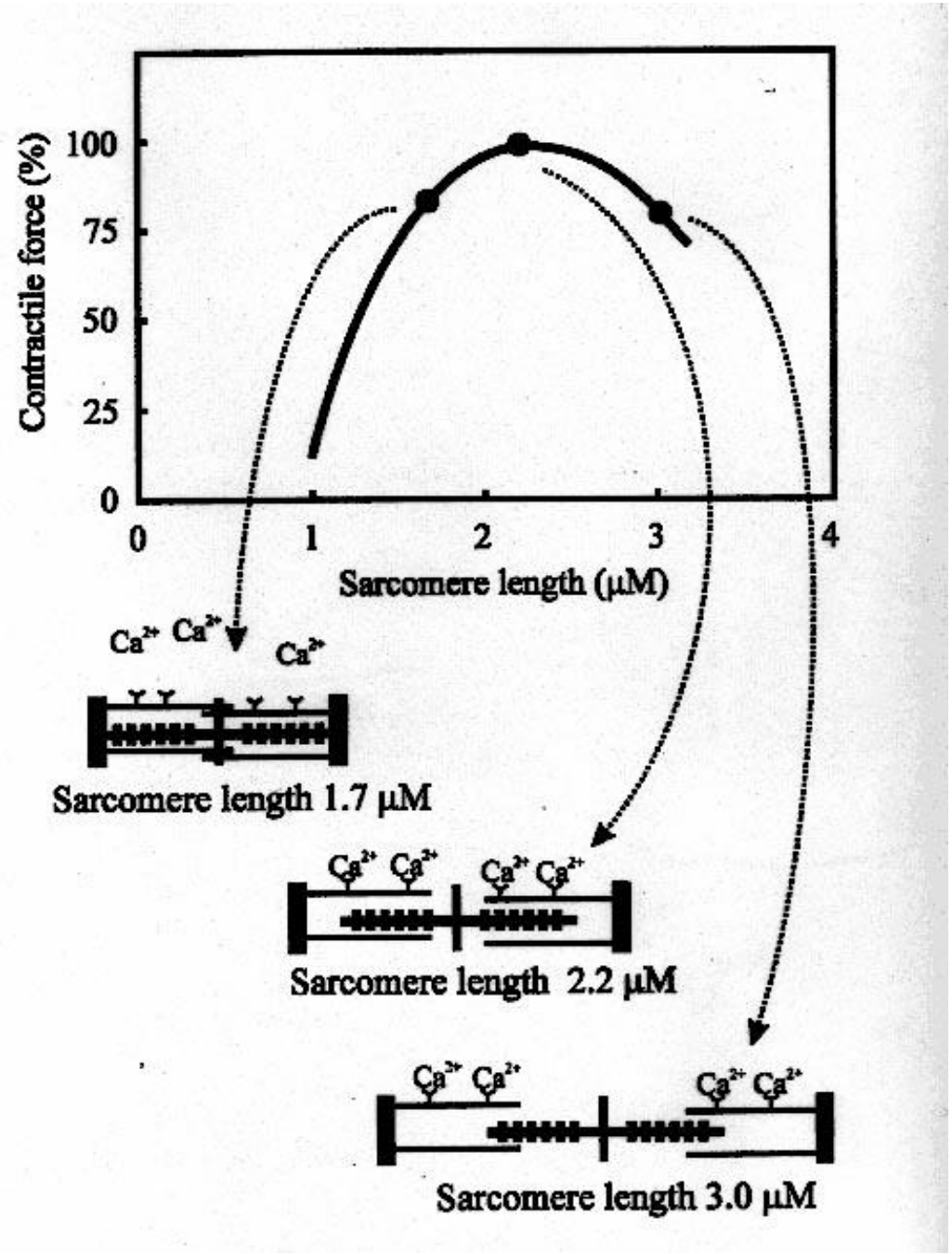
The effects of ischaemic metabolites (P_i and low pH) on the Ca^{2+} - force relationship



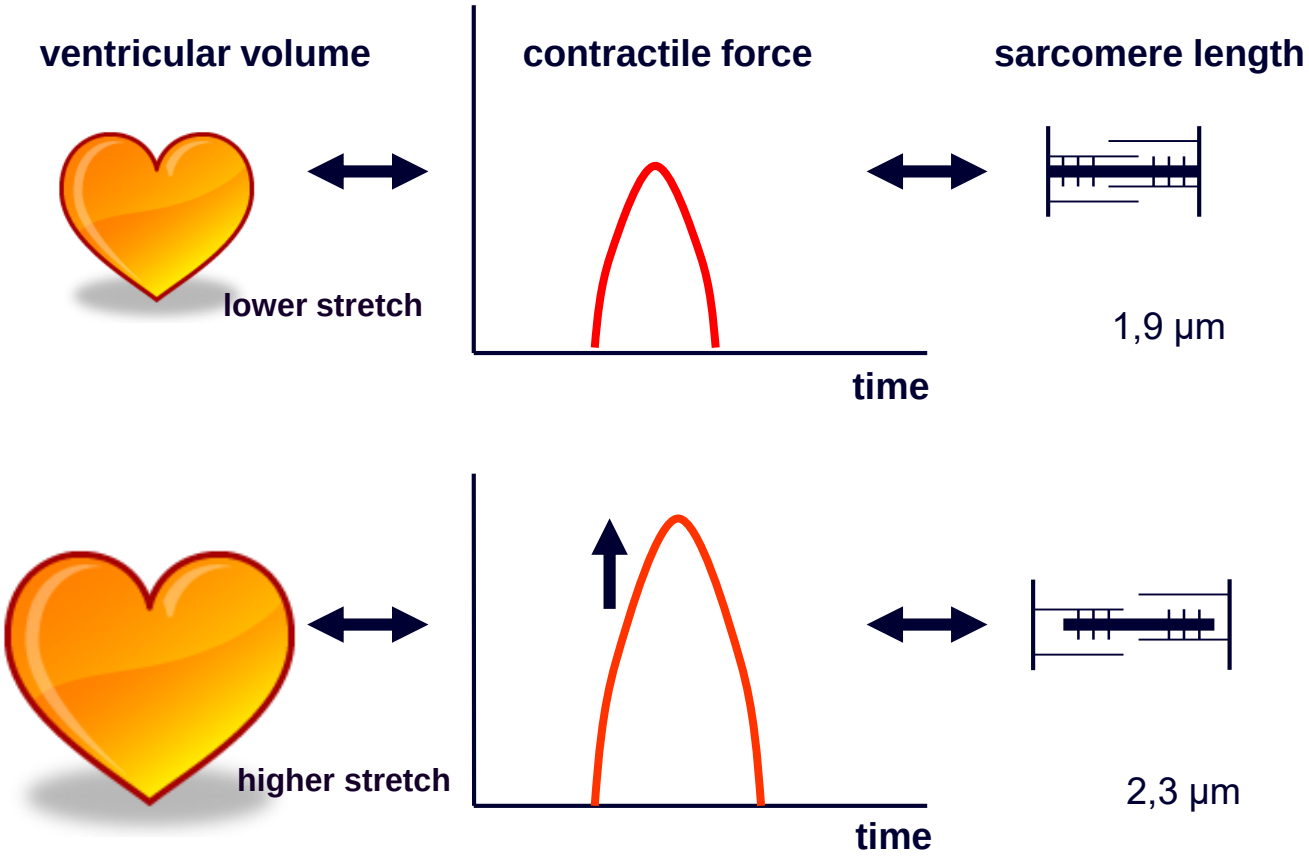
↑P_i and ↓pH → ↓ maximal force (↓ Po)

↑P_i and ↓pH → ↓ Ca^{2+} sensitivity (rightward shift)

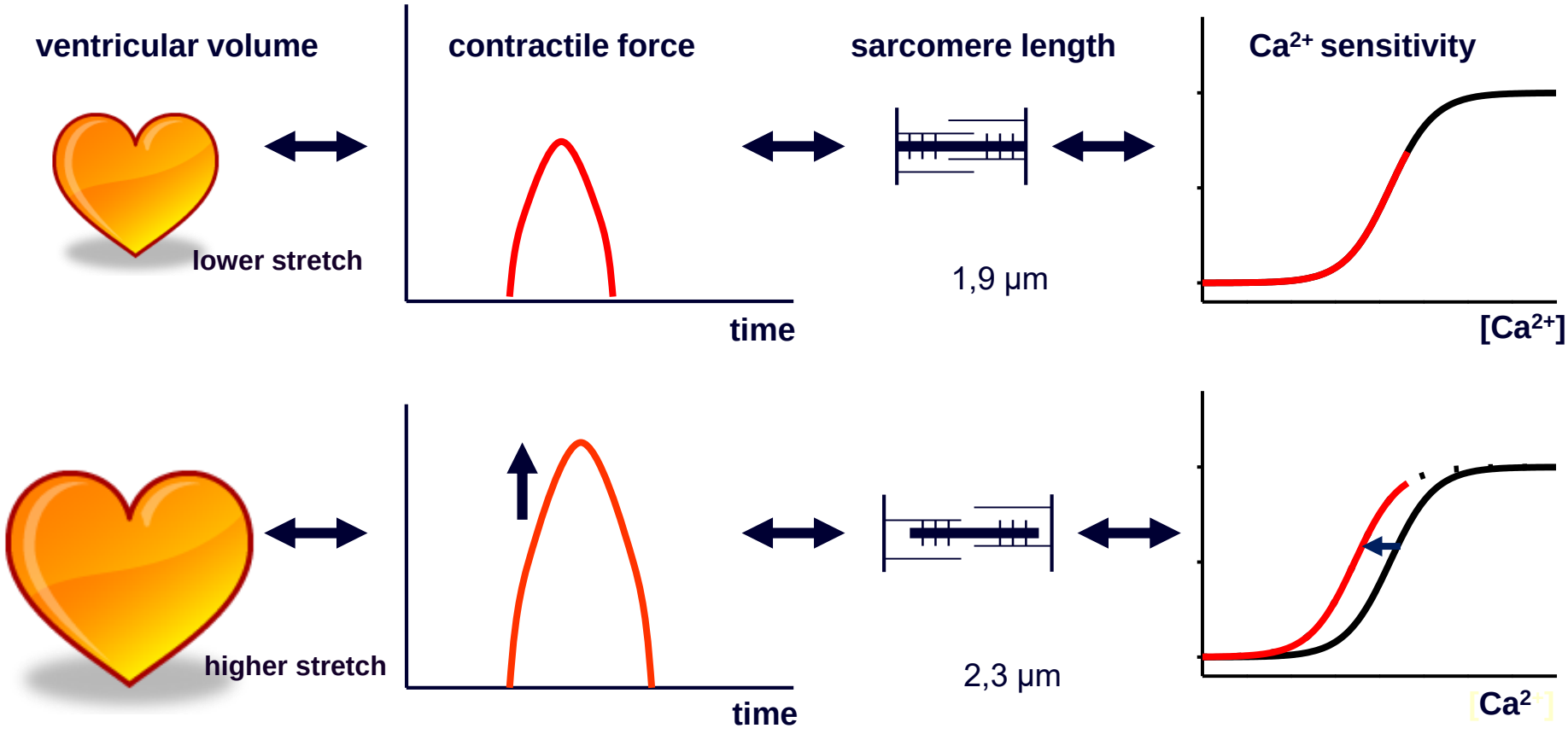
Length – tension relationship and its explanation



Frank-Starling-mechanism and sarcomere length



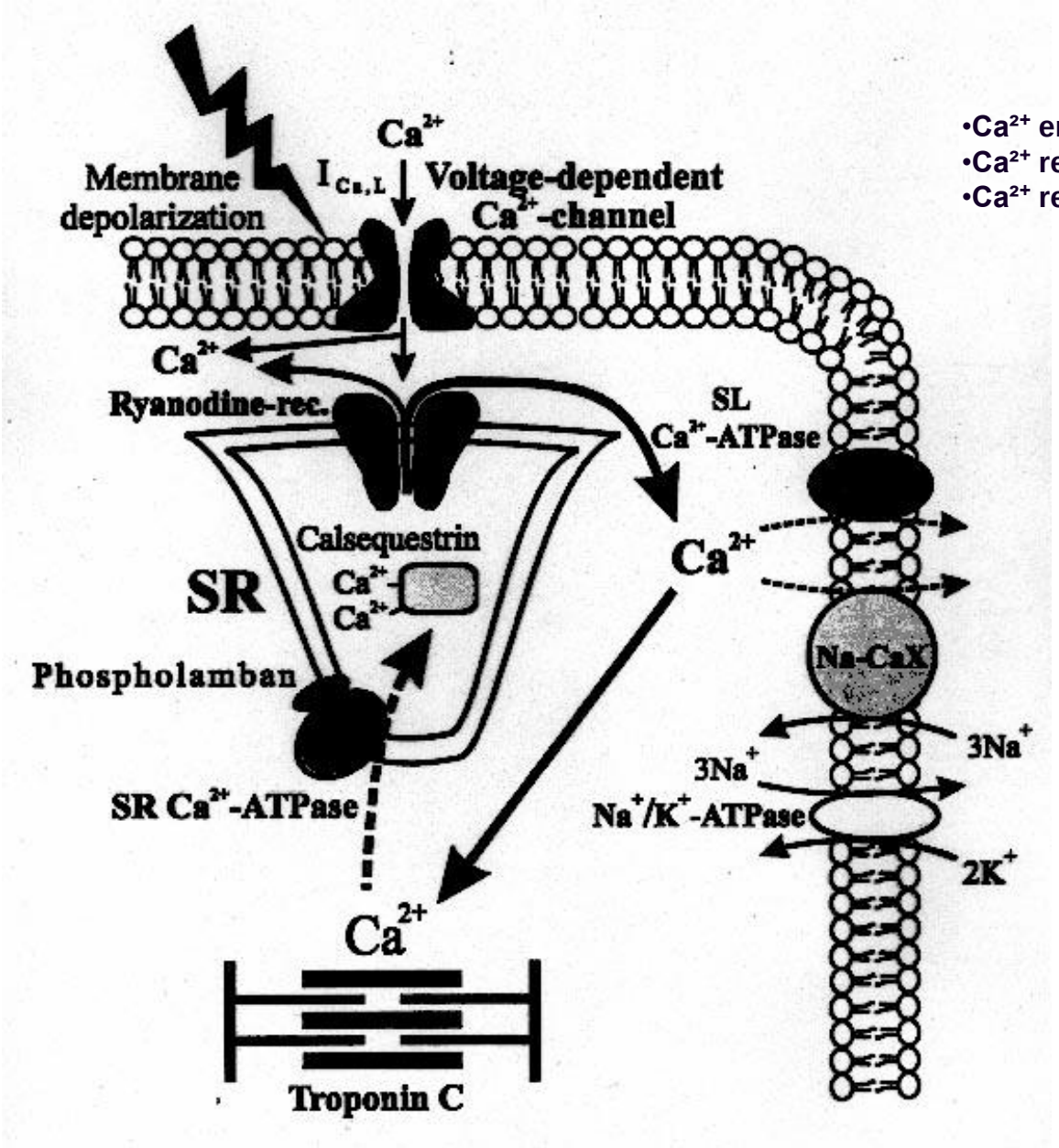
Frank-Starling-mechanism and sarcomere length



Stretch → ↑ Ca^{2+} sensitivity (NOT just ↑ myofilament overlap)

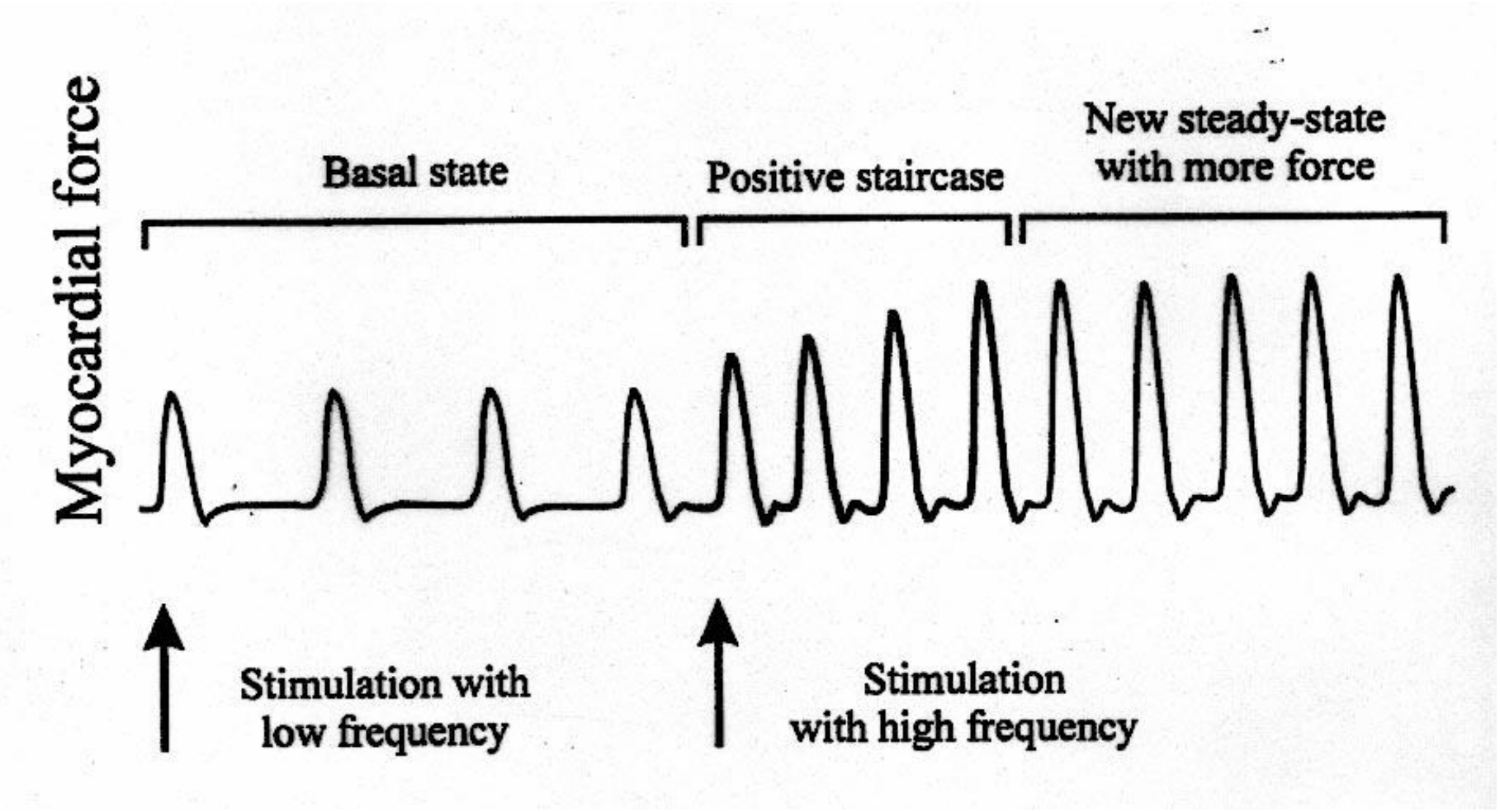
This is the molecular basis of Starling's Law.

Intracellular Ca^{2+} balance



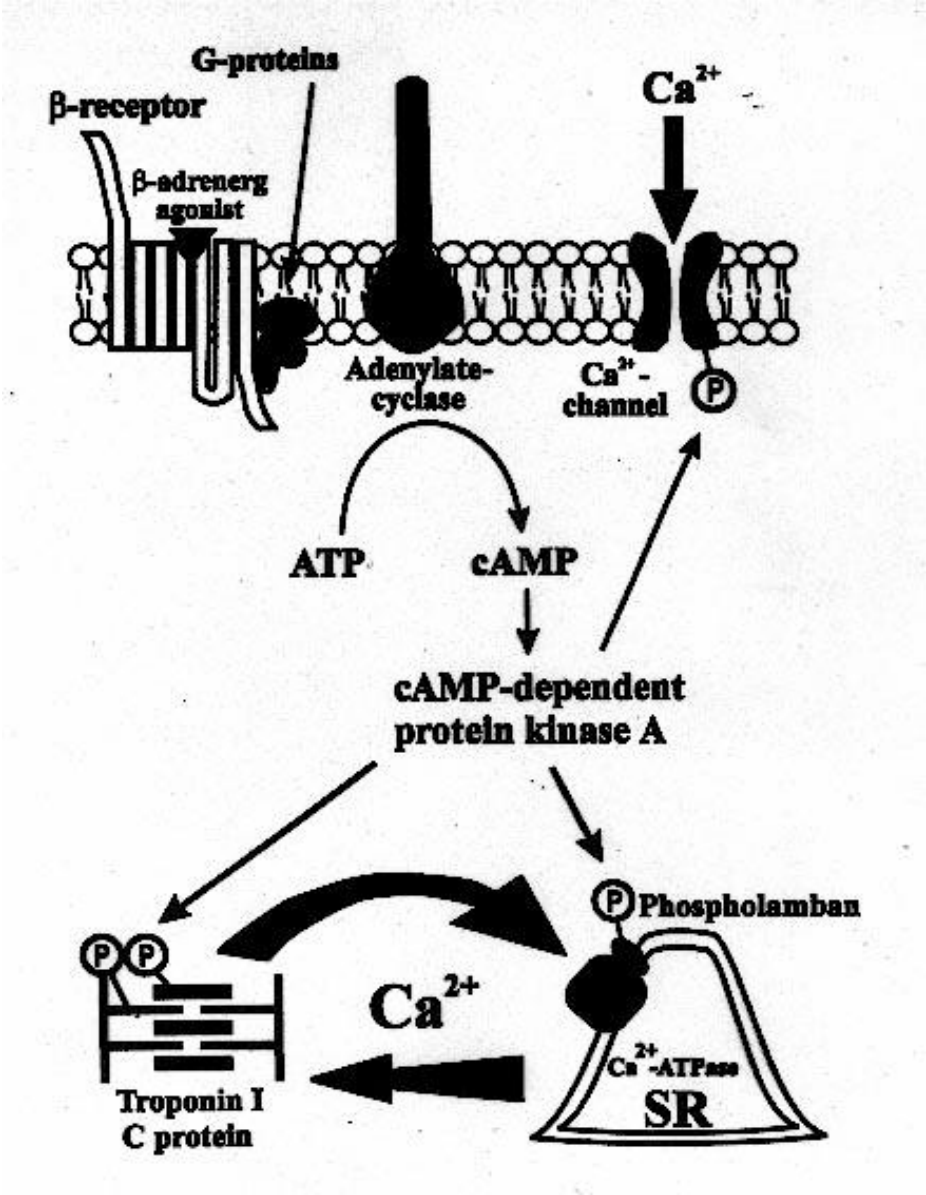
- Ca^{2+} entry: L-type Ca^{2+} channel
- Ca^{2+} release: Ryanodine receptor (CICR)
- Ca^{2+} removal: SERCA (SR), NCX (sarcolemma)

Force – frequency relationship

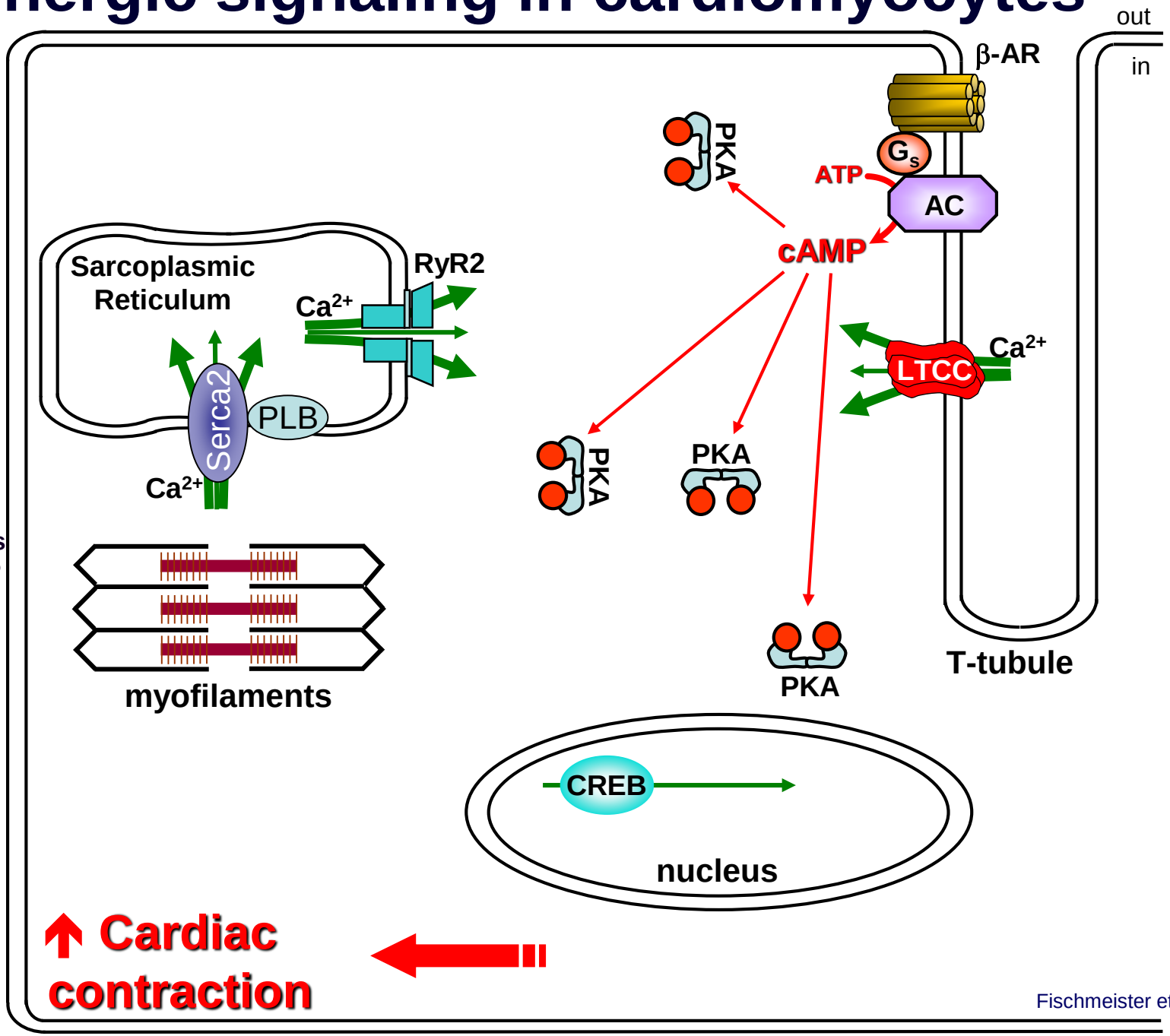


Mechanism: more beats → more Ca^{2+} entry → more SR loading → more force

β - adrenergic regulation of contractility



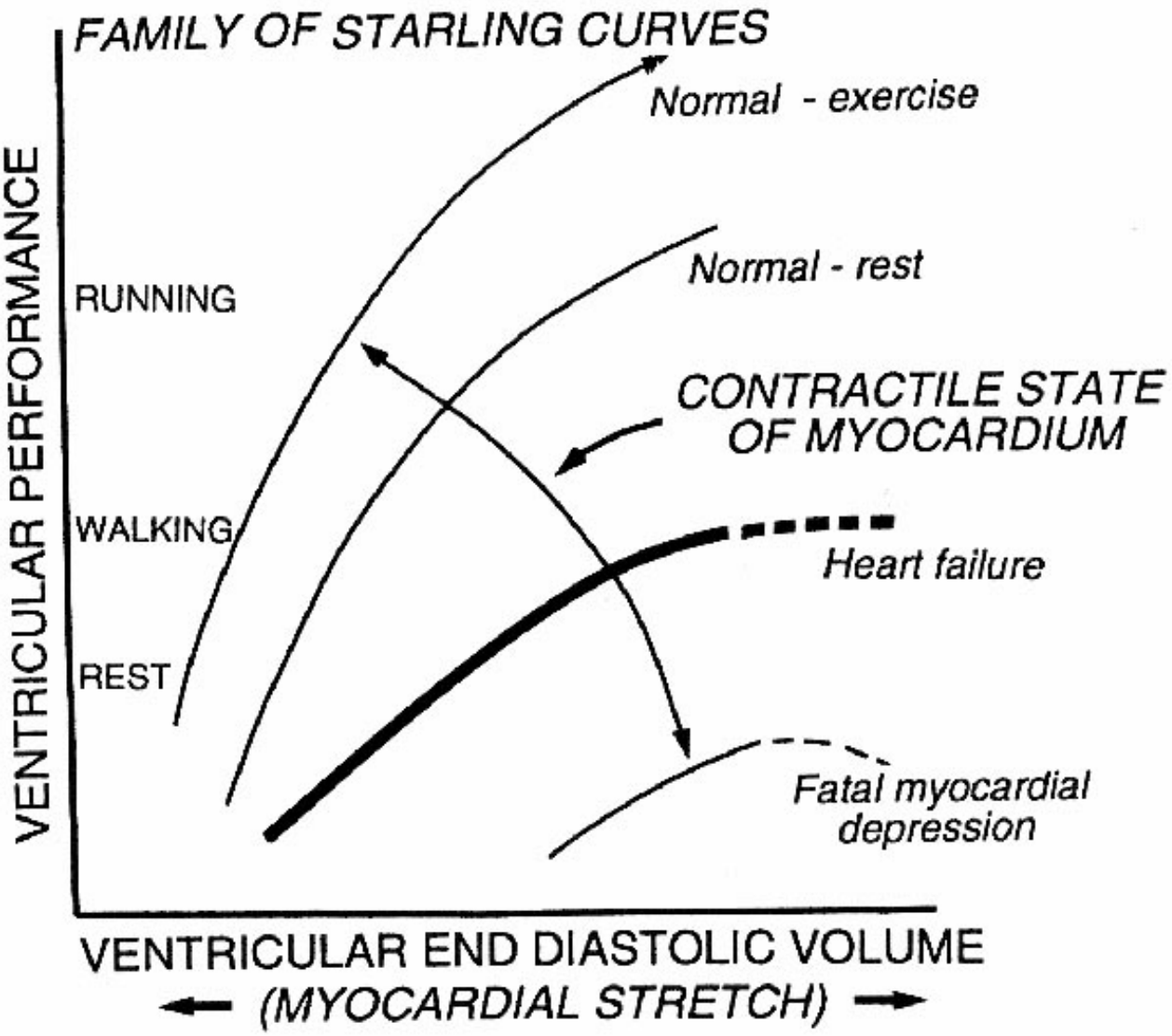
β - adrenergic signaling in cardiomyocytes



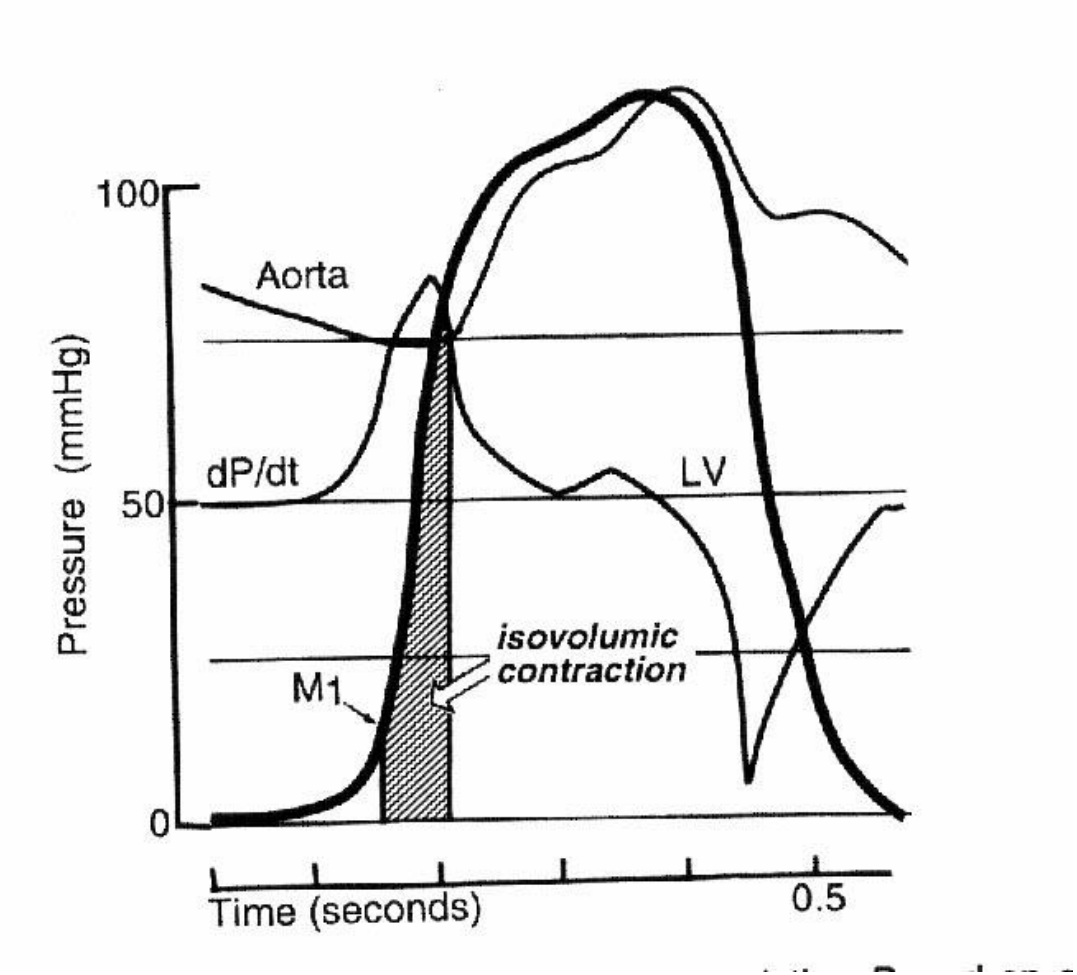
Phosphodiesterases (PDEs) cleave cAMP in subcellular microdomains.

Fischmeister et al.,

Ventricular function curves



Measures of myocardial contractile state



- dP/dt = rate of pressure rise, its maximum (dP/dt_{max}) during isovolumic contraction
- dP/dt_{max} reflects intrinsic contractility (load-independent), but frequency dependent
- Clinical use: catheterization, echocardiography (strain rate)
- EF (ejection fraction) replaces dP/dt in clinical practice

Summary - Perspectives future lectures on ischemia and HF

- Cardiac work requires enormous amounts of ATP
- Normal: oxidative phosphorylation
- Ischemia: ATP ↓, metabolites ↑
- Ischemia disrupts contractility (↓ATP, ↑P_i, ↓pH, Ca^{2+} overload)
- Chronic HF remodels the pathways regulating cardiac contractility
- Contractility disorders: systolic (can't contract) vs. diastolic (can't relax)