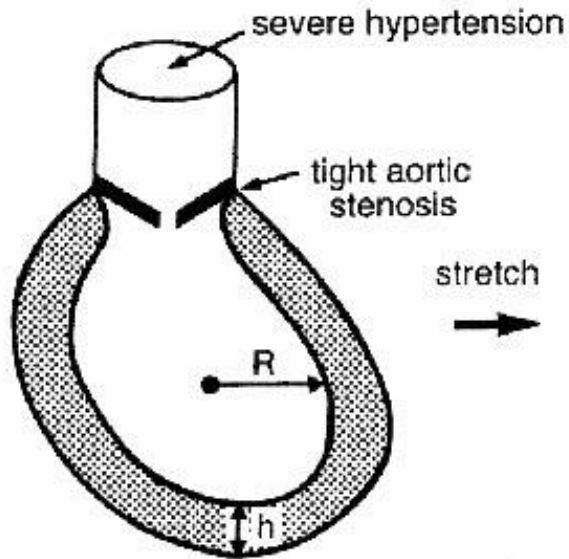


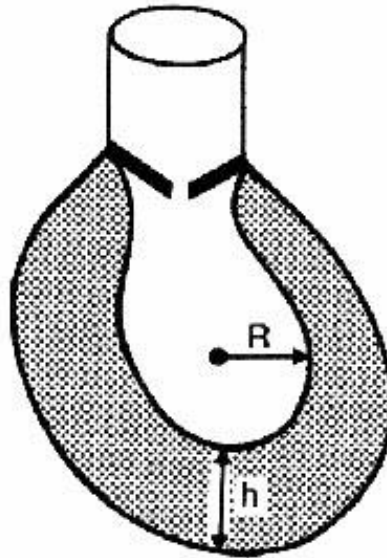
# **Chronic heart failure (molecular pathophysiology)**

**Dr. Zoltán Papp  
University of Debrecen  
Faculty of Medicine  
Division of Clinical Physiology**

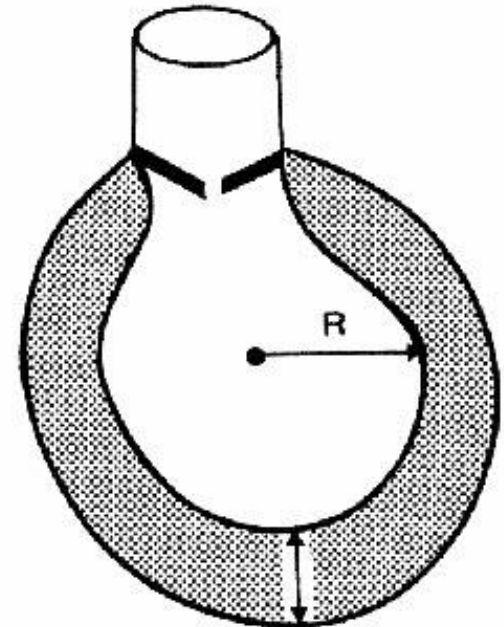
# Pressure overload hypertrophy



stretch  
→



fibrosis  
→  
slippage



LV PRESSURE (P)

Wall stress ↑

$$\text{Stress} = \frac{P \uparrow \times R}{h}$$

CONCENTRIC HYPERTROPHY

Wall stress normalized

$$\text{Stress} = \frac{P \uparrow \times R \downarrow}{h \uparrow \uparrow}$$

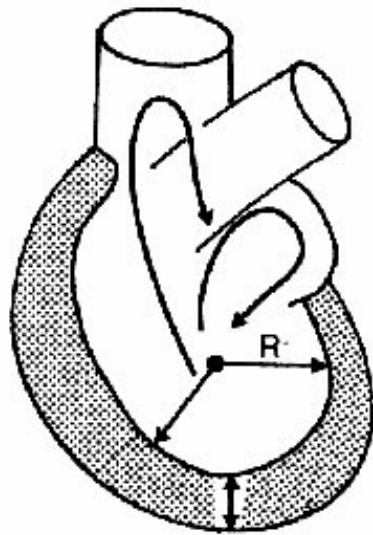
HYPERTROPHY + DILATION

Wall stress ↑

$$\text{Stress} = \frac{P \uparrow \times R \uparrow}{h \uparrow}$$

# Volume overload hypertrophy

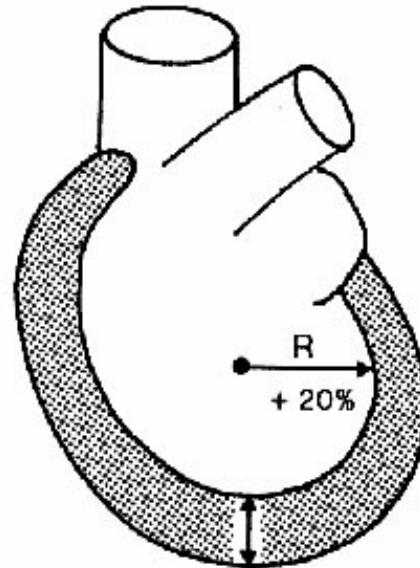
(AORTIC OR MITRAL REGURGITATION)



Volume load

VALVE REGURGITATION

$$\text{Wall stress} = \frac{P \times R}{h}$$

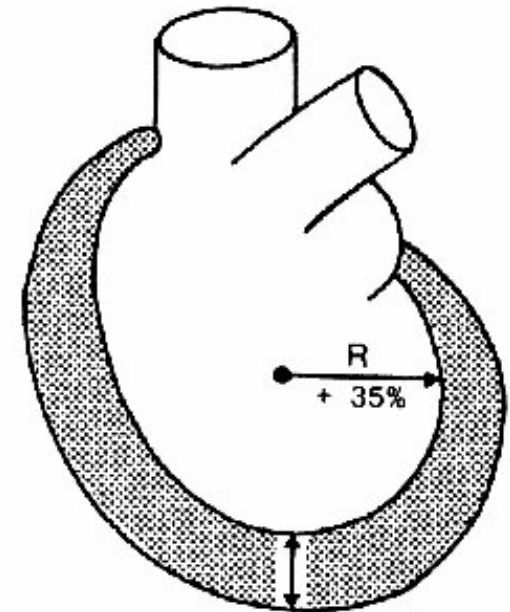


$h + 20\%$

DILATED HYPERTROPHIC MYOCARDIUM

- Compensated
- Wall stress normalized

$$\text{Stress} = \frac{P \times R \uparrow}{h \uparrow}$$



$h + 20\%$

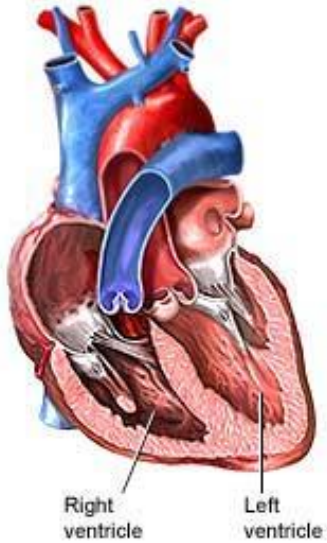
MYOCARDIAL FAILURE

Wall stress increased

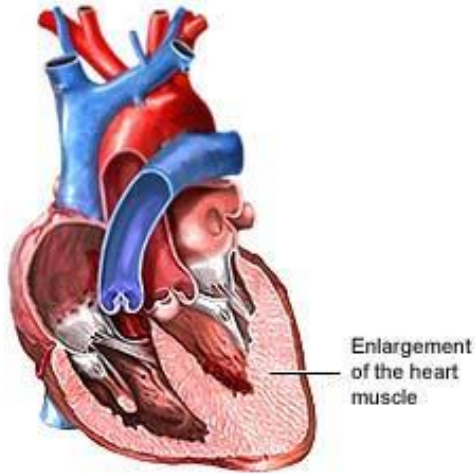
$$\text{Stress} \uparrow = \frac{P \times R \uparrow \uparrow}{h \uparrow}$$

# Hypertrophic cardiomyopathy

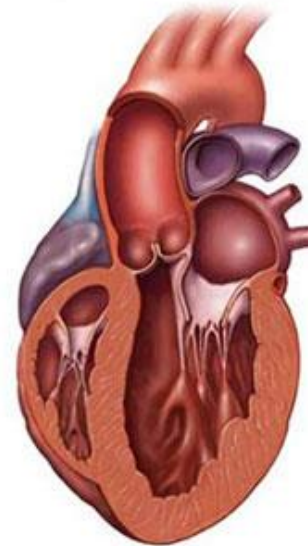
Normal heart



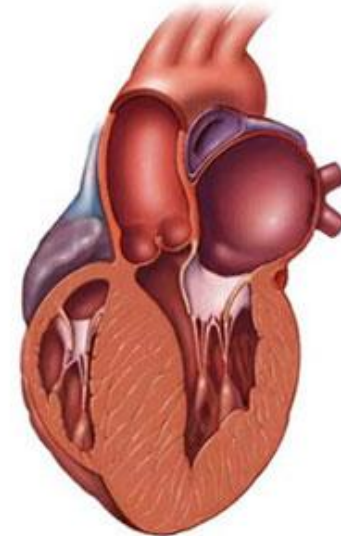
Hypertrophic cardiomyopathy



Normal heart

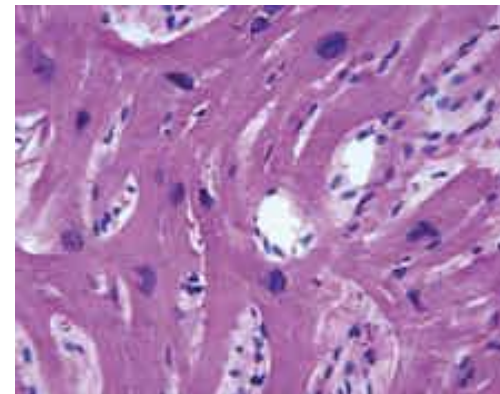
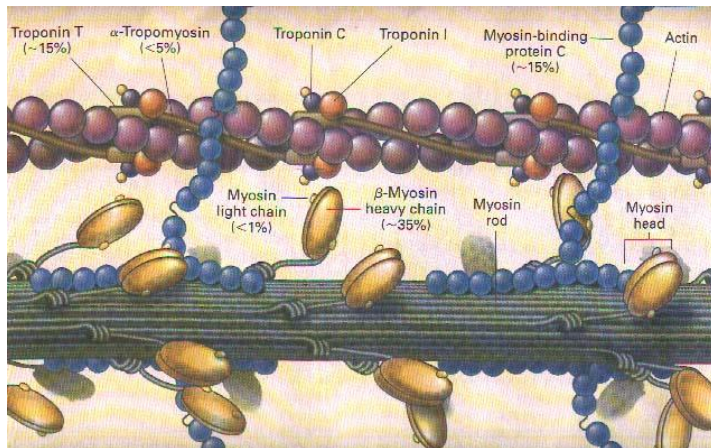


Heart with Hypertrophic Cardiomyopathy



ADAM.

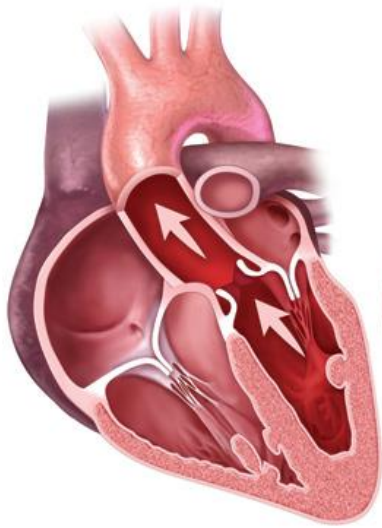
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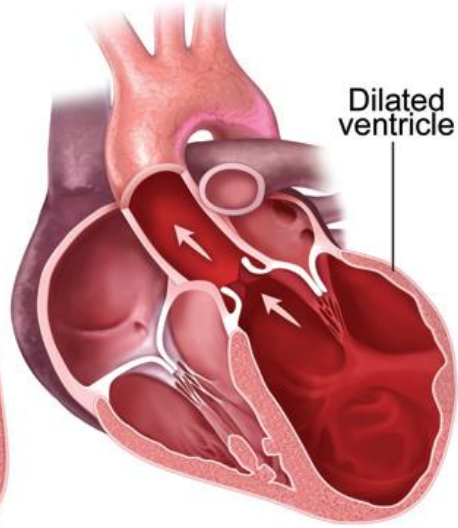
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# Dilated cardiomyopathy

Normal Heart

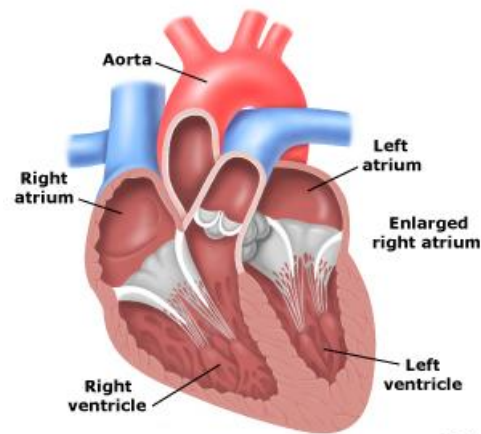


Dilated Cardiomyopathy

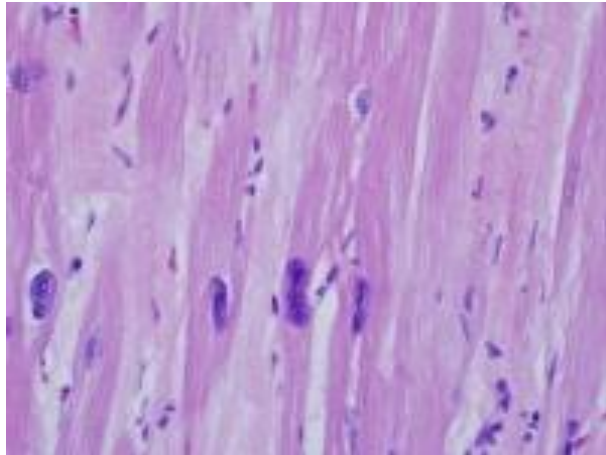
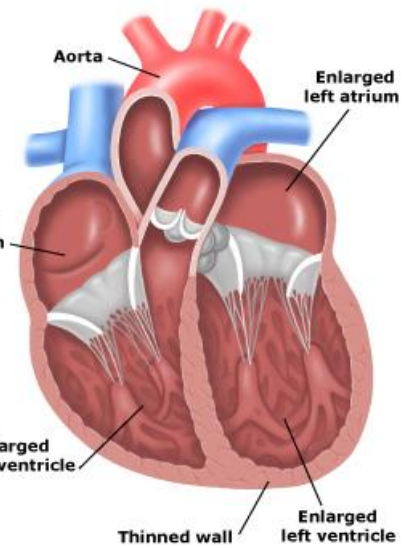


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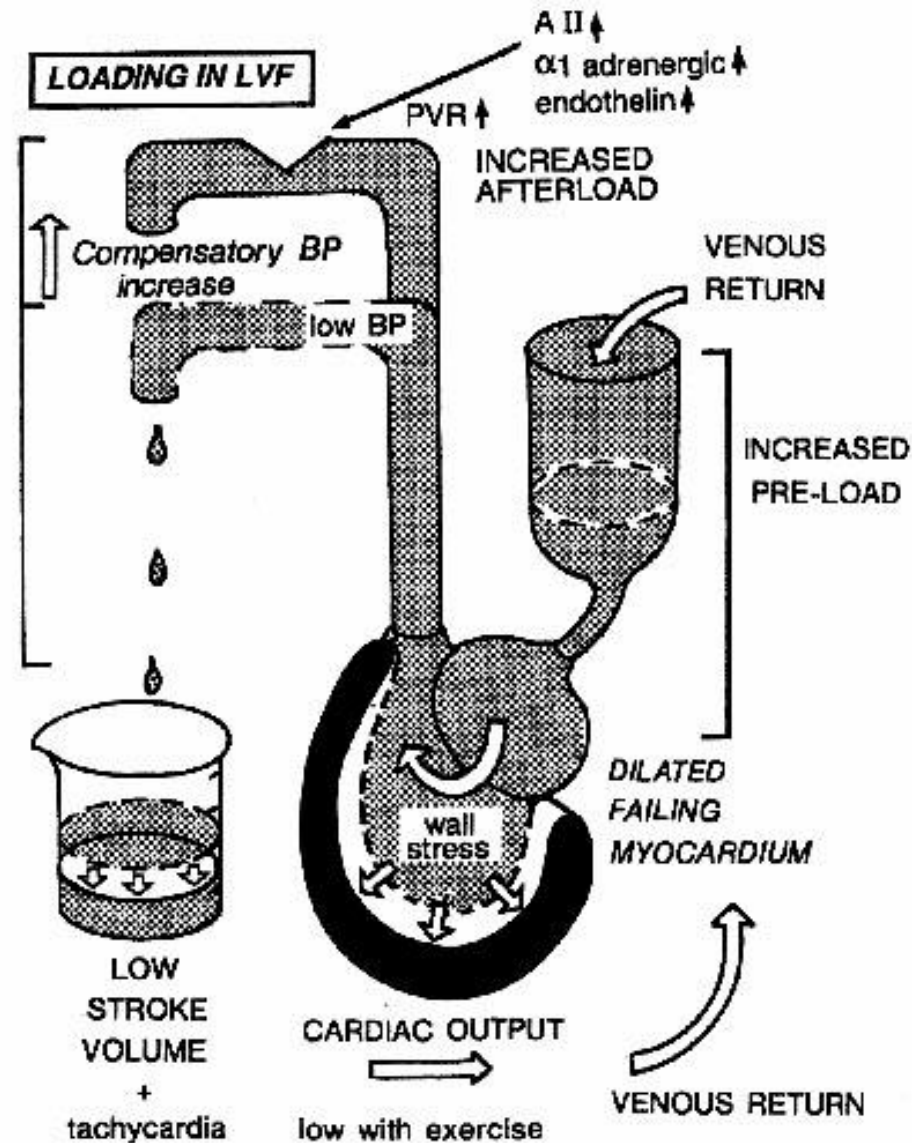
Normal



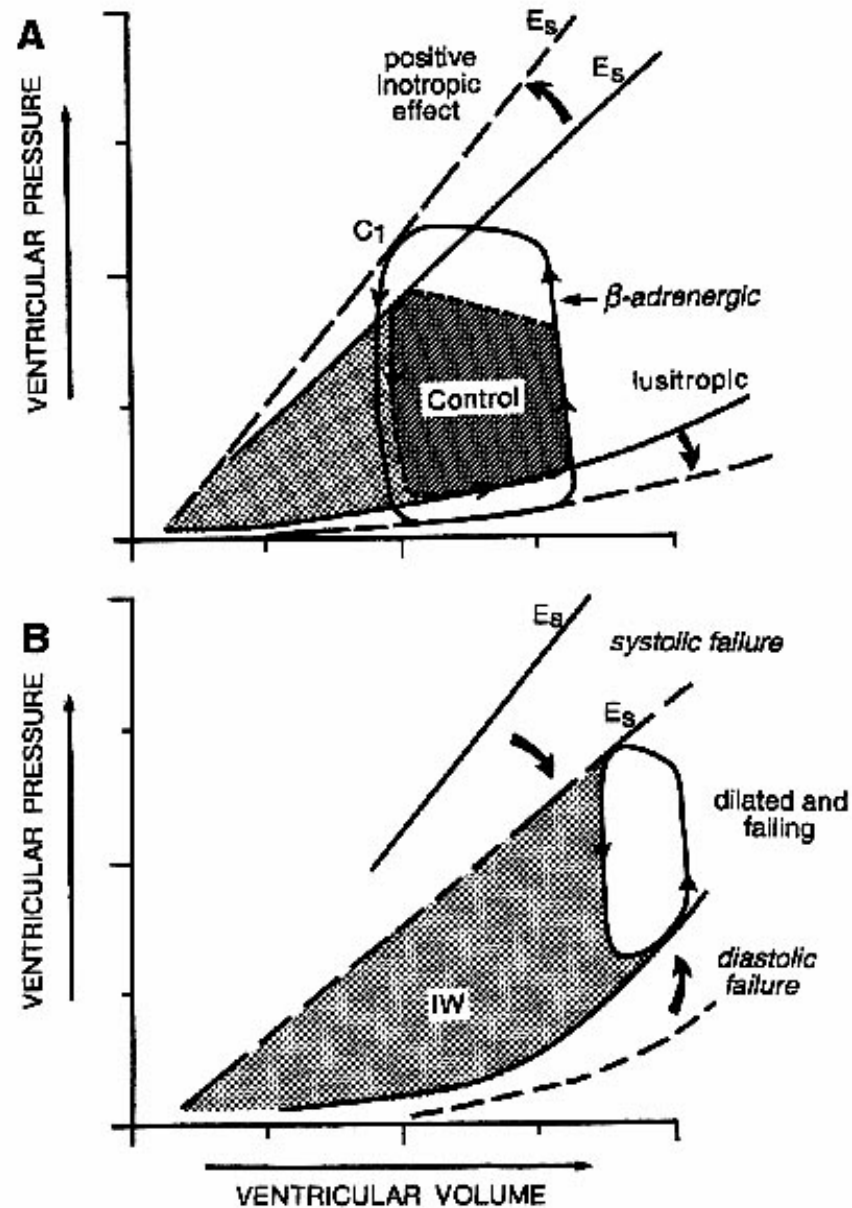
Dilated cardiomyopathy



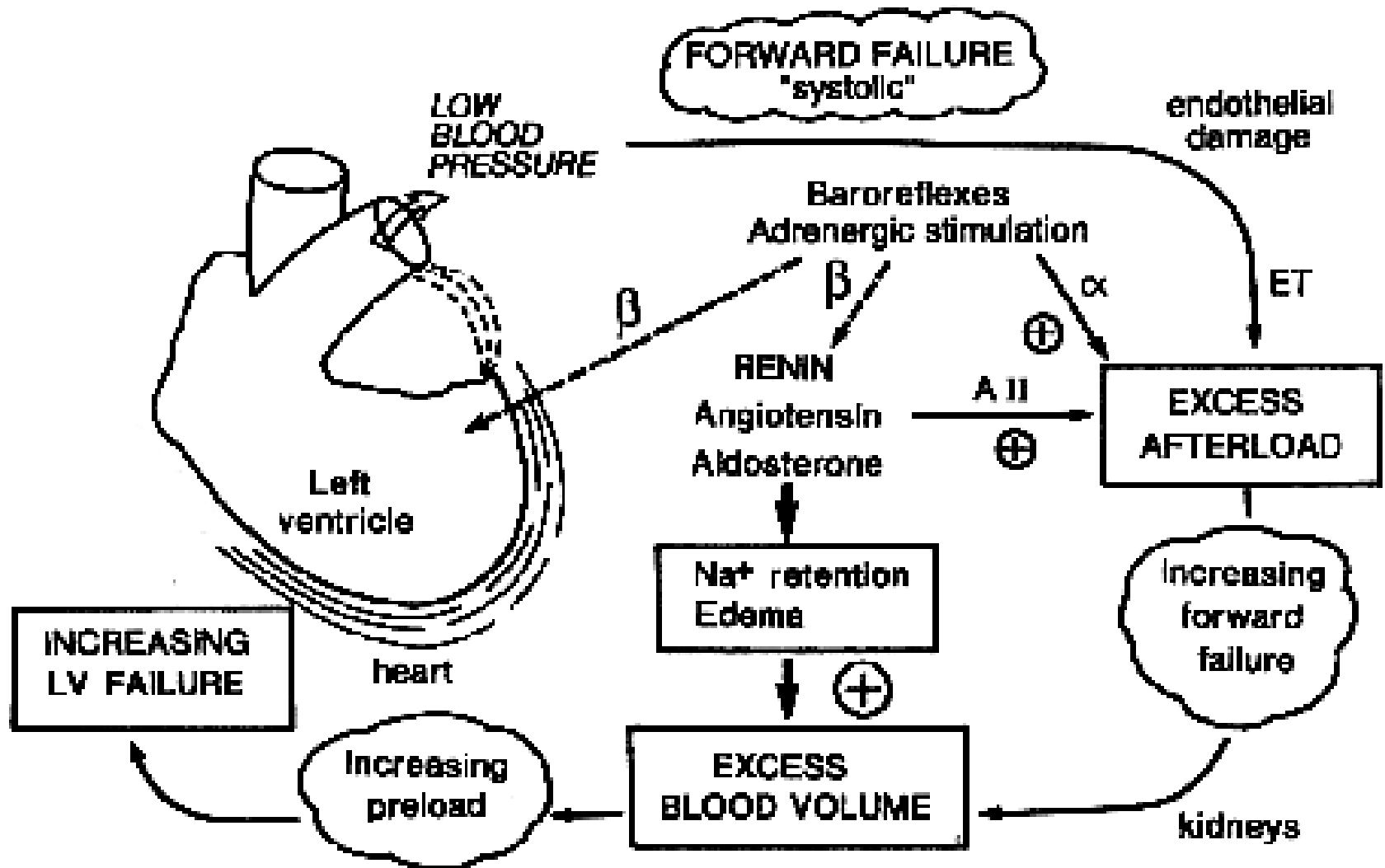
# Haemodynamic changes during chronic heart failure



# Healthy vs. failing myocardial energetics

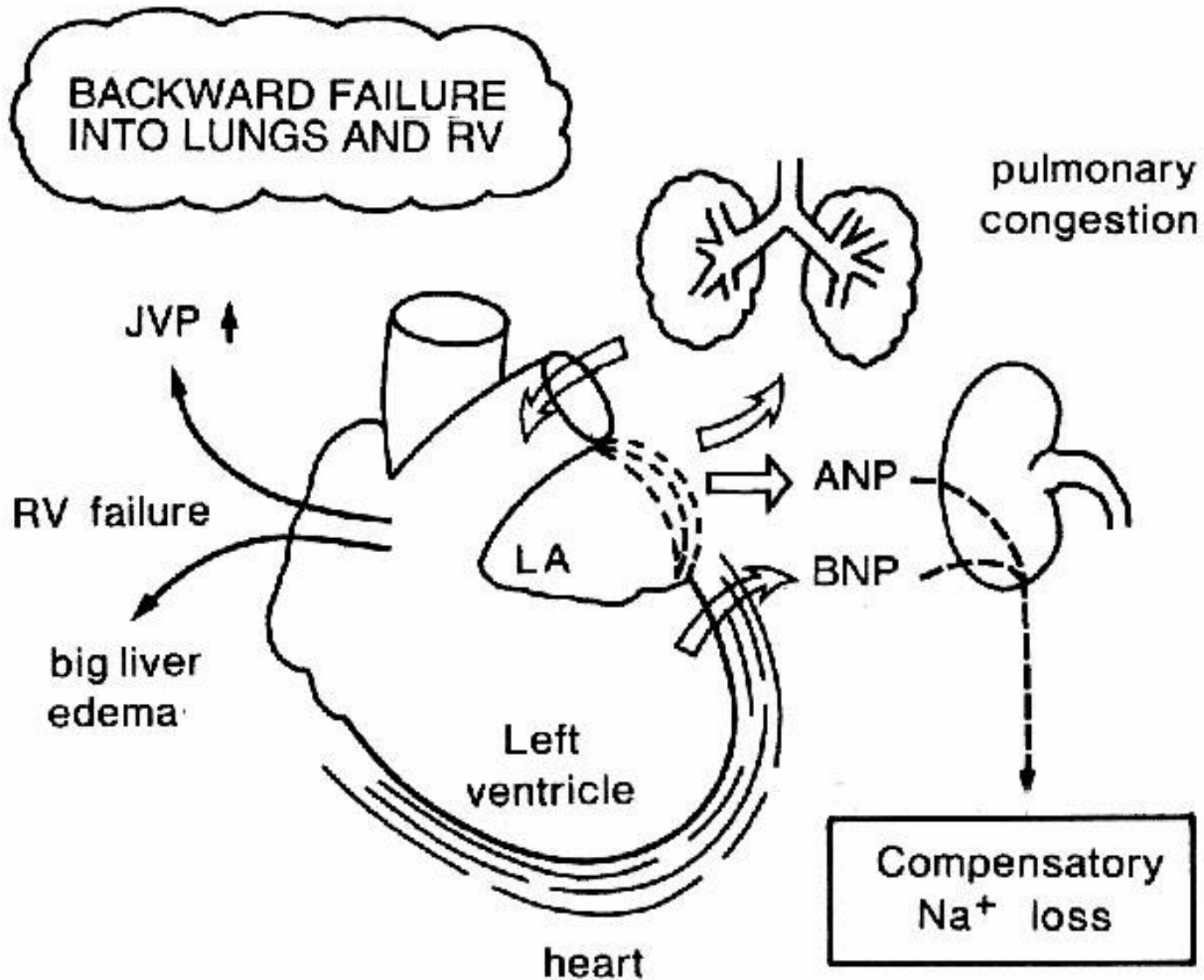


# Forward left ventricular failure

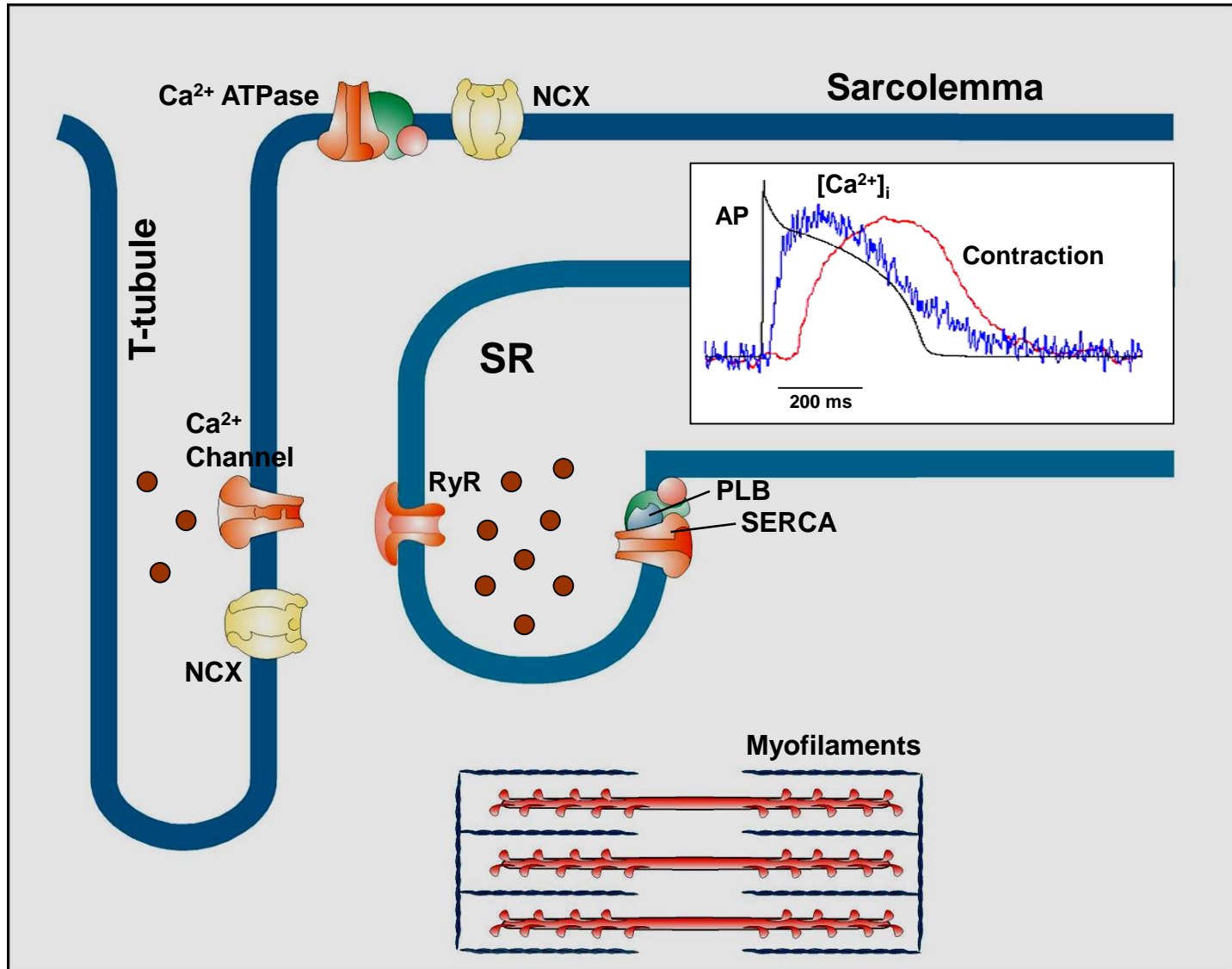




# Backward left ventricular failure

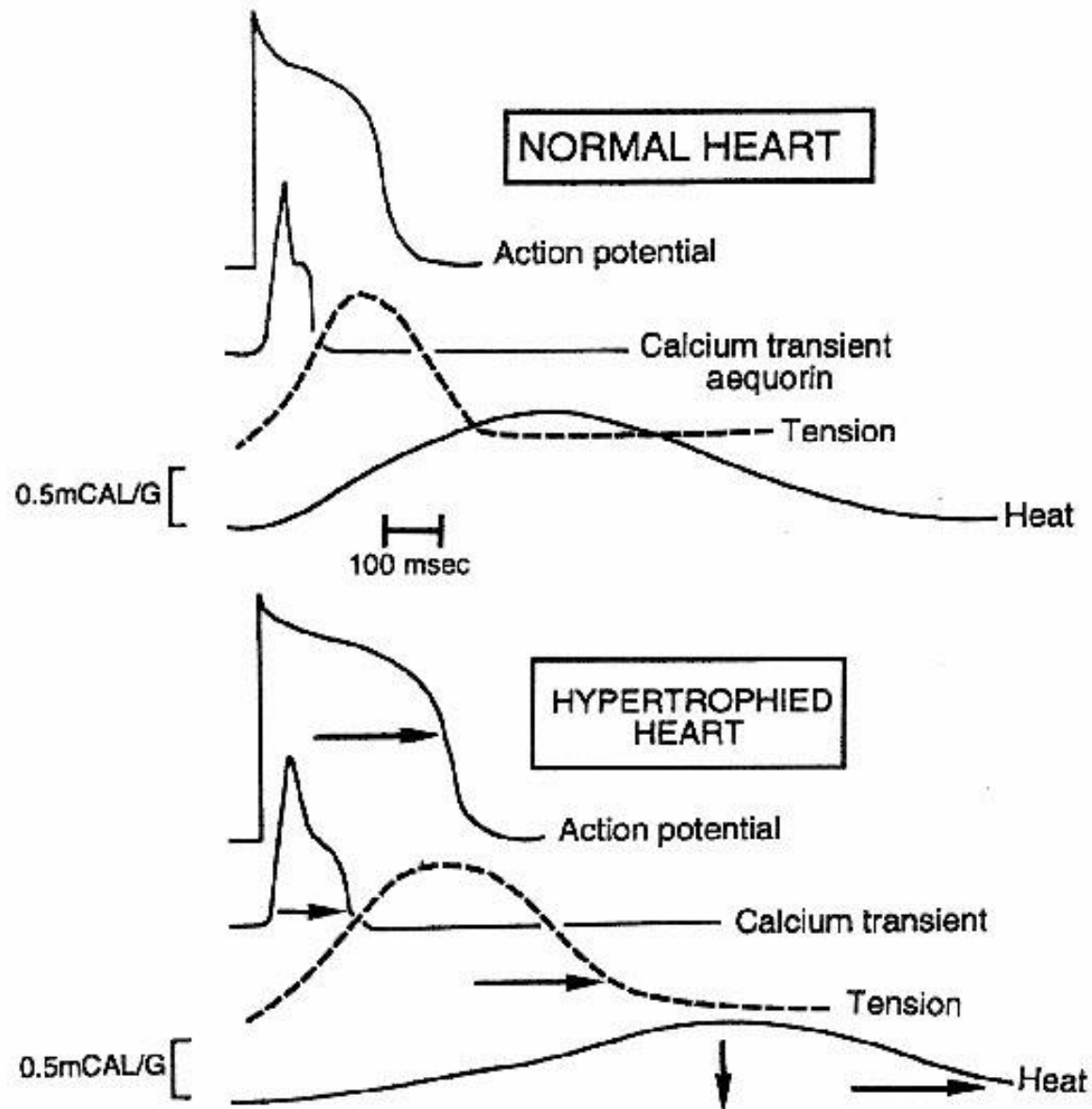


# Ca<sup>2+</sup> fluxes during excitation-contraction coupling

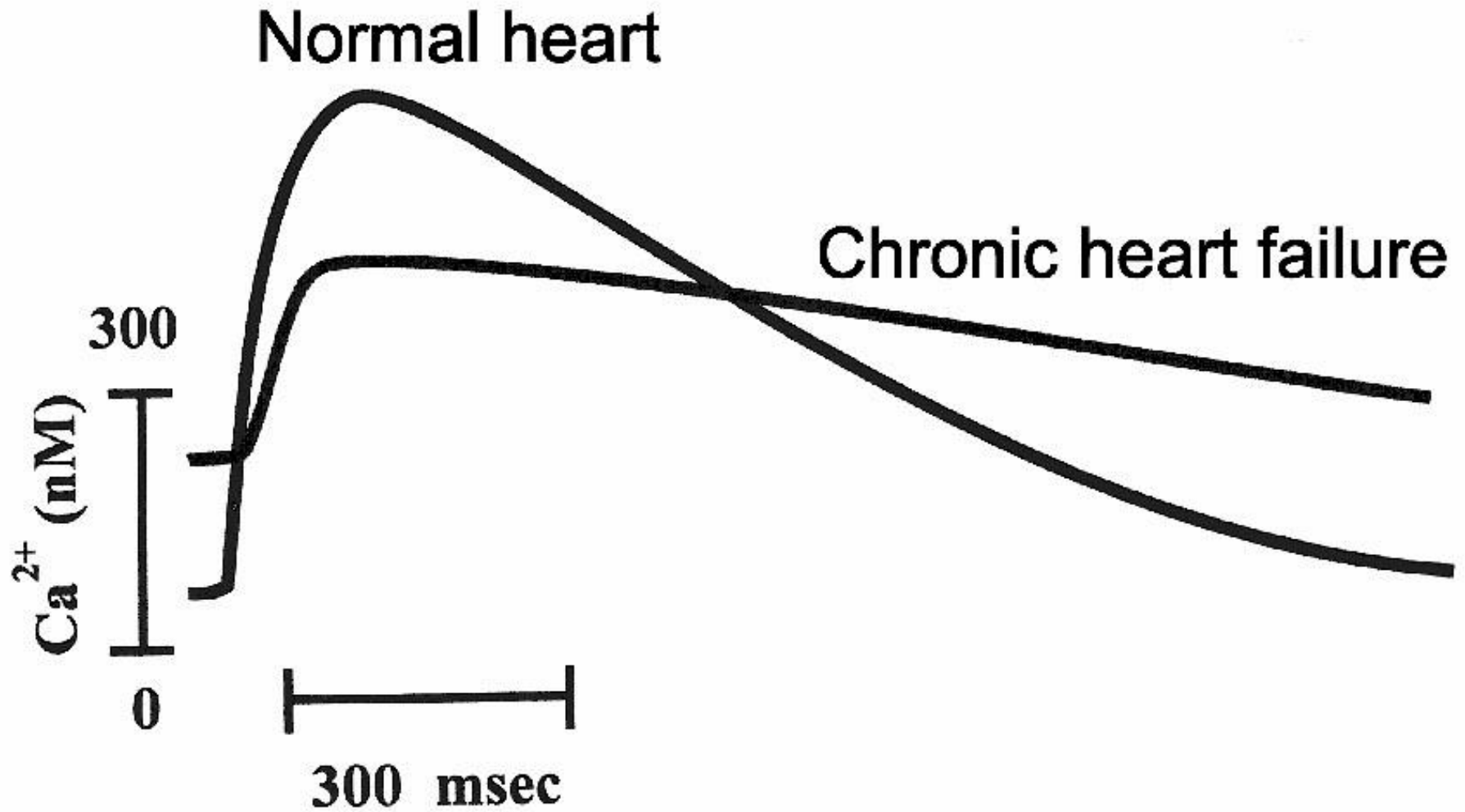


Adapted from Sjaastad et al., 2003

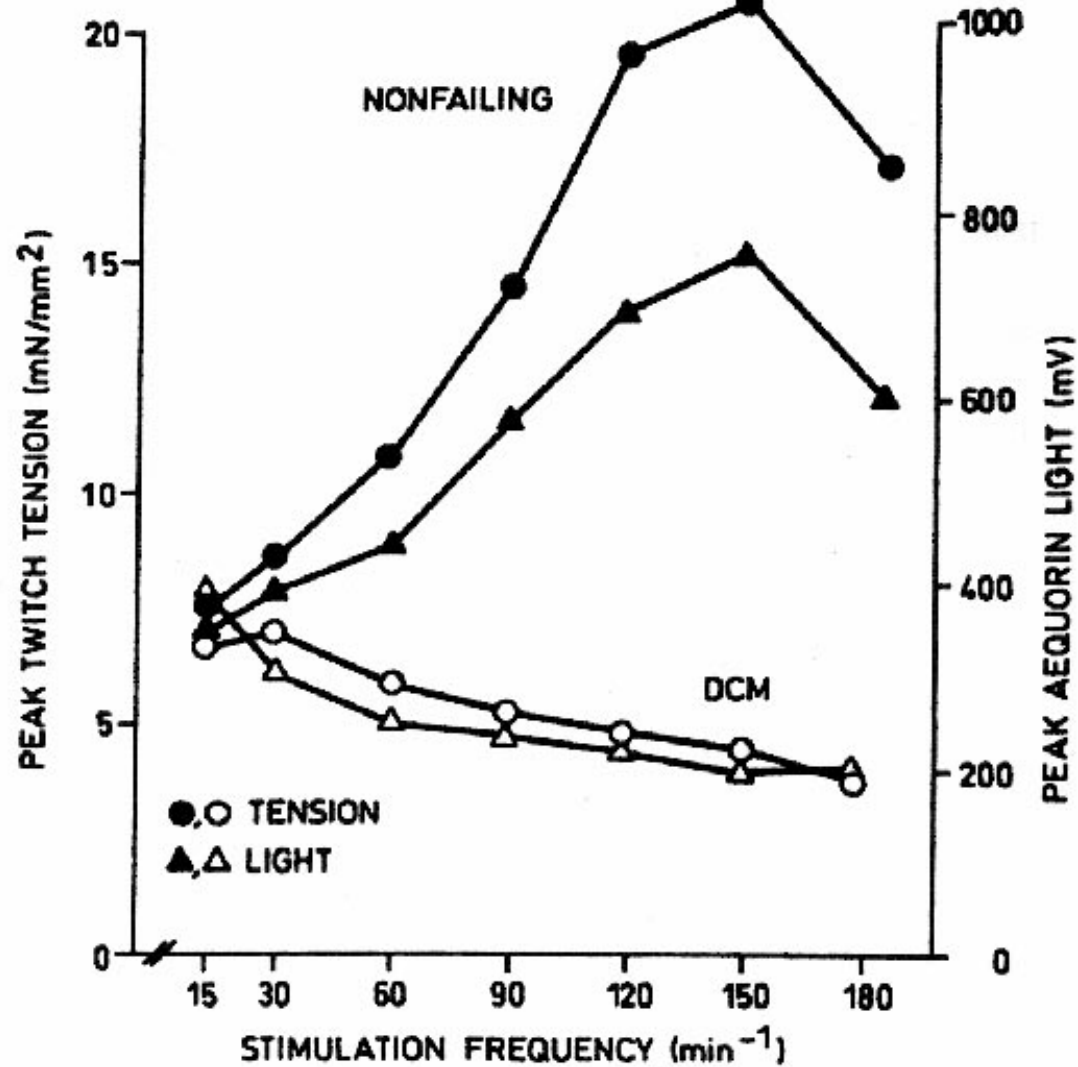
# Cellular determinants of contractility during chronic heart failure



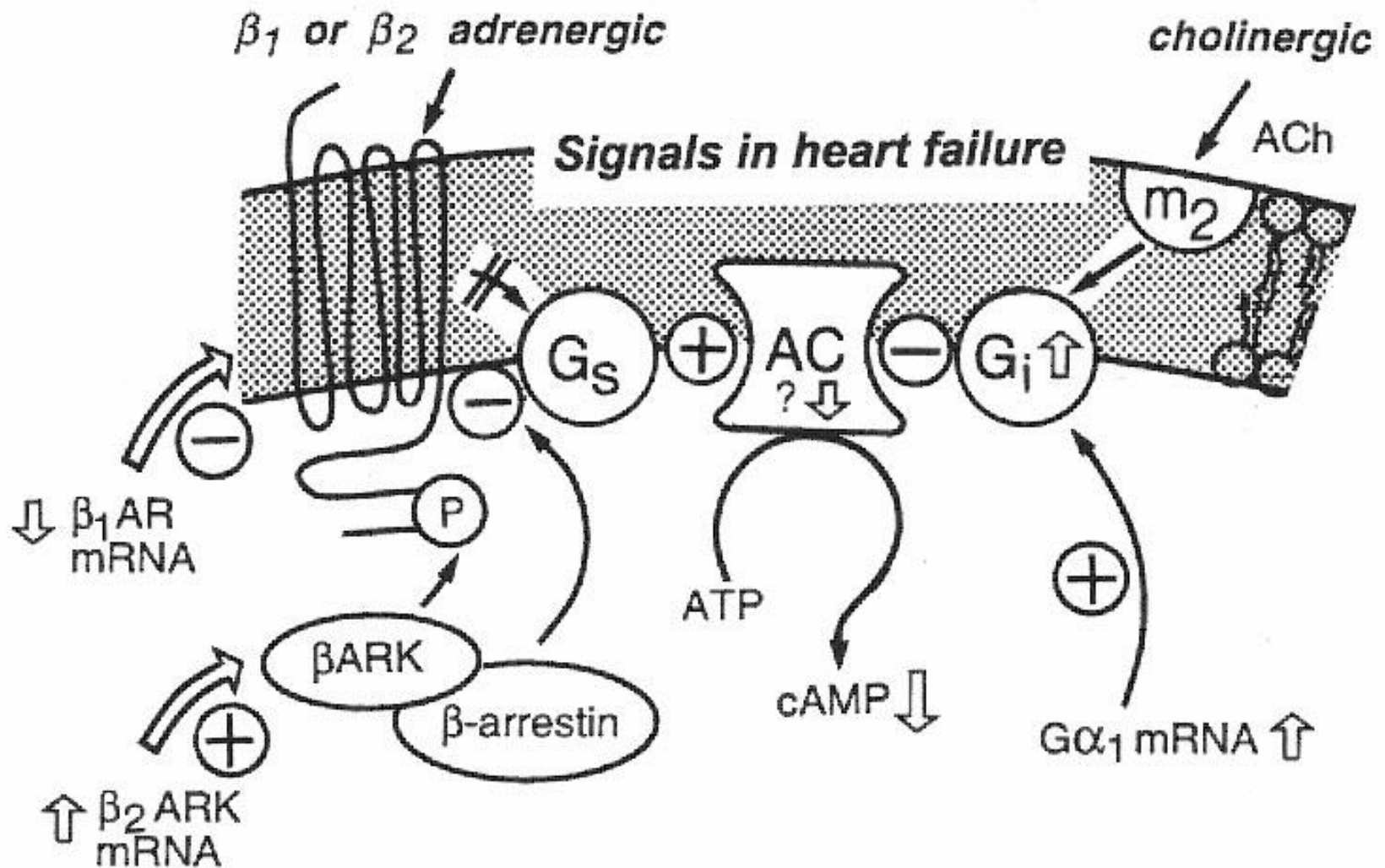
# Ca<sup>2+</sup>-transients during chronic heart failure



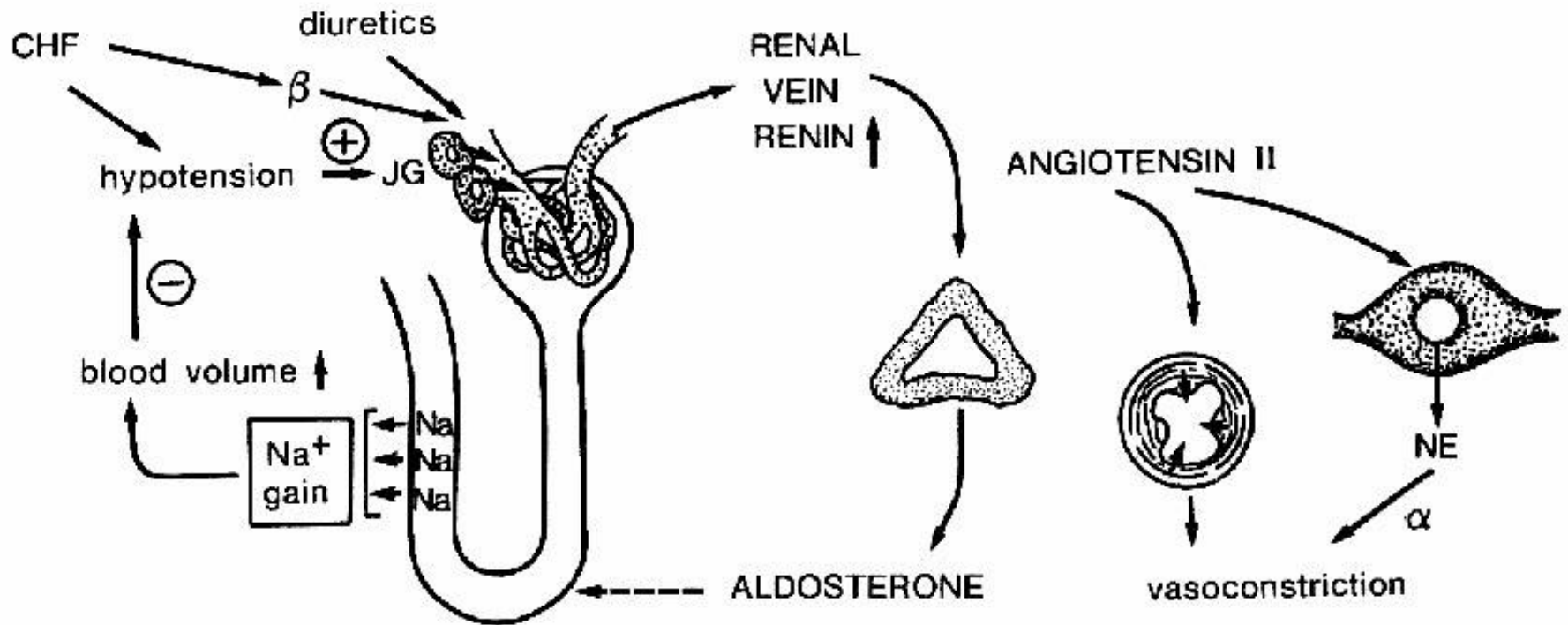
# Blunted force-frequency relationship during chronic heart failure



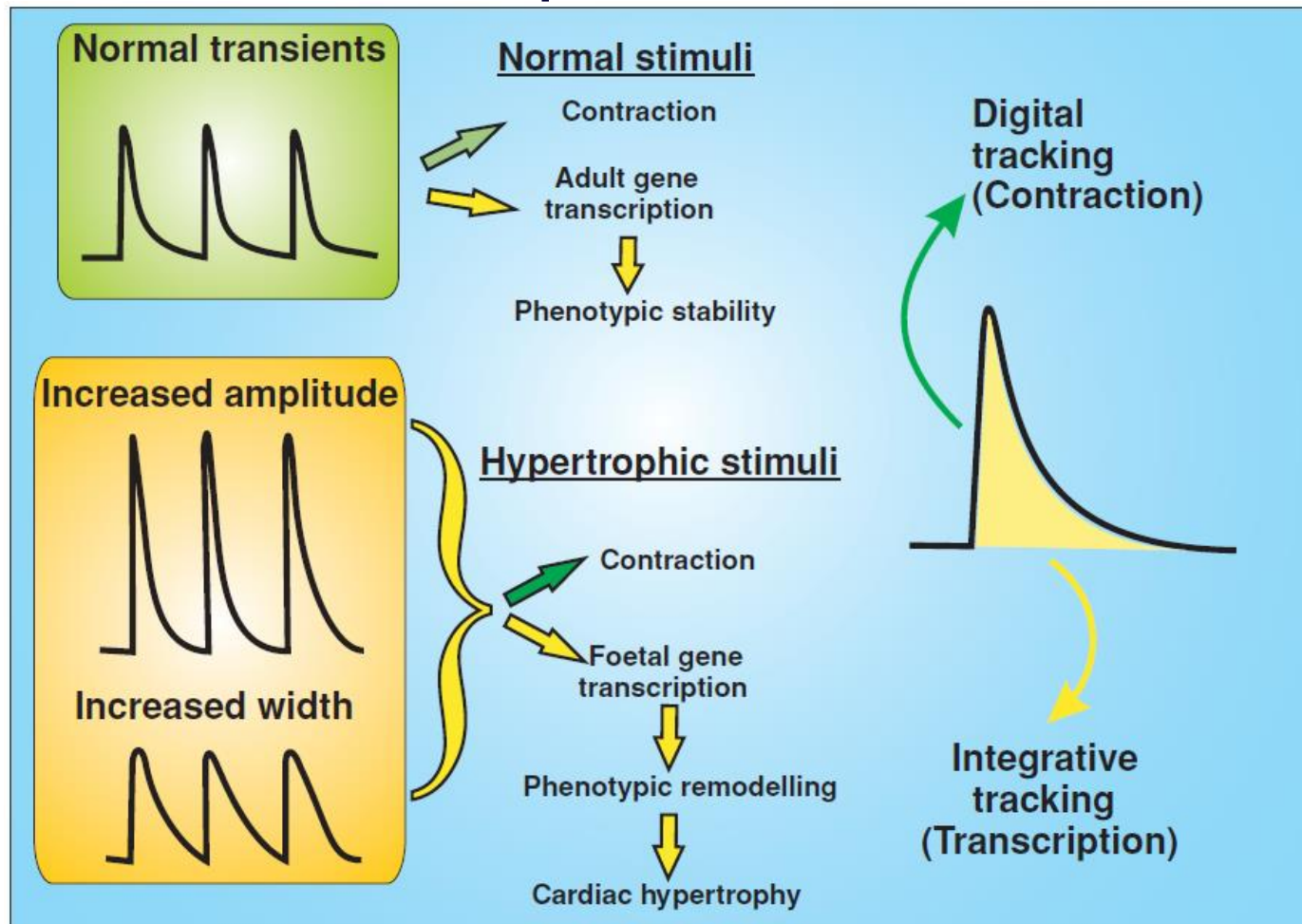
# The $\beta$ - adrenergic system during chronic heart failure



# Renin-angiotensin system activation during chronic heart failure



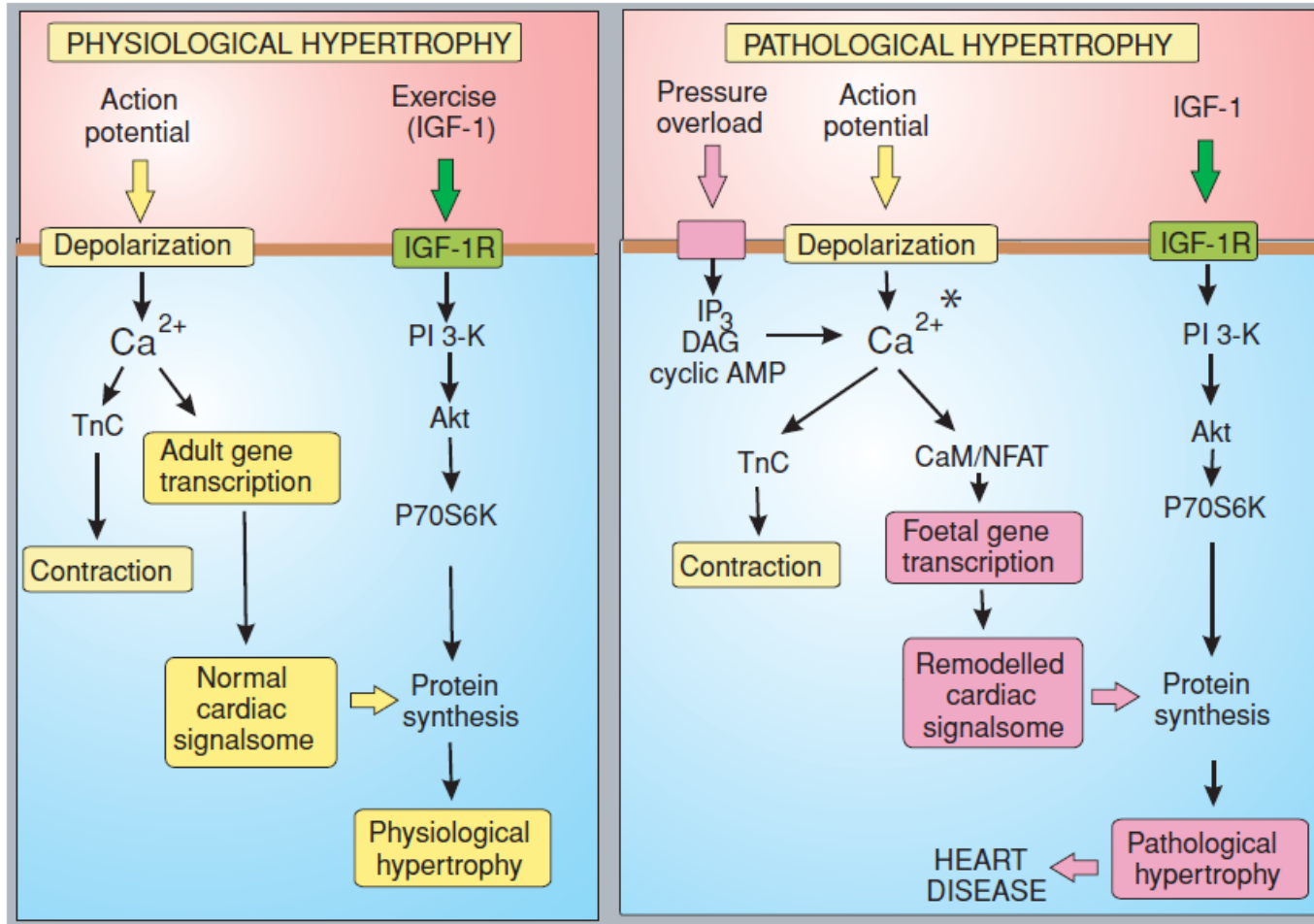
# Hypothetical explanation for the hypertrophic process



The normal transients drive both contraction and the transcription of adult genes to maintain phenotypic stability. Under conditions that induce hypertrophy, the modified  $\text{Ca}^{2+}$  transients (increase in amplitude or width) are such that they can induce both contraction and the activation of foetal genes that bring about the phenotypic remodelling that leads to cardiac hypertrophy.

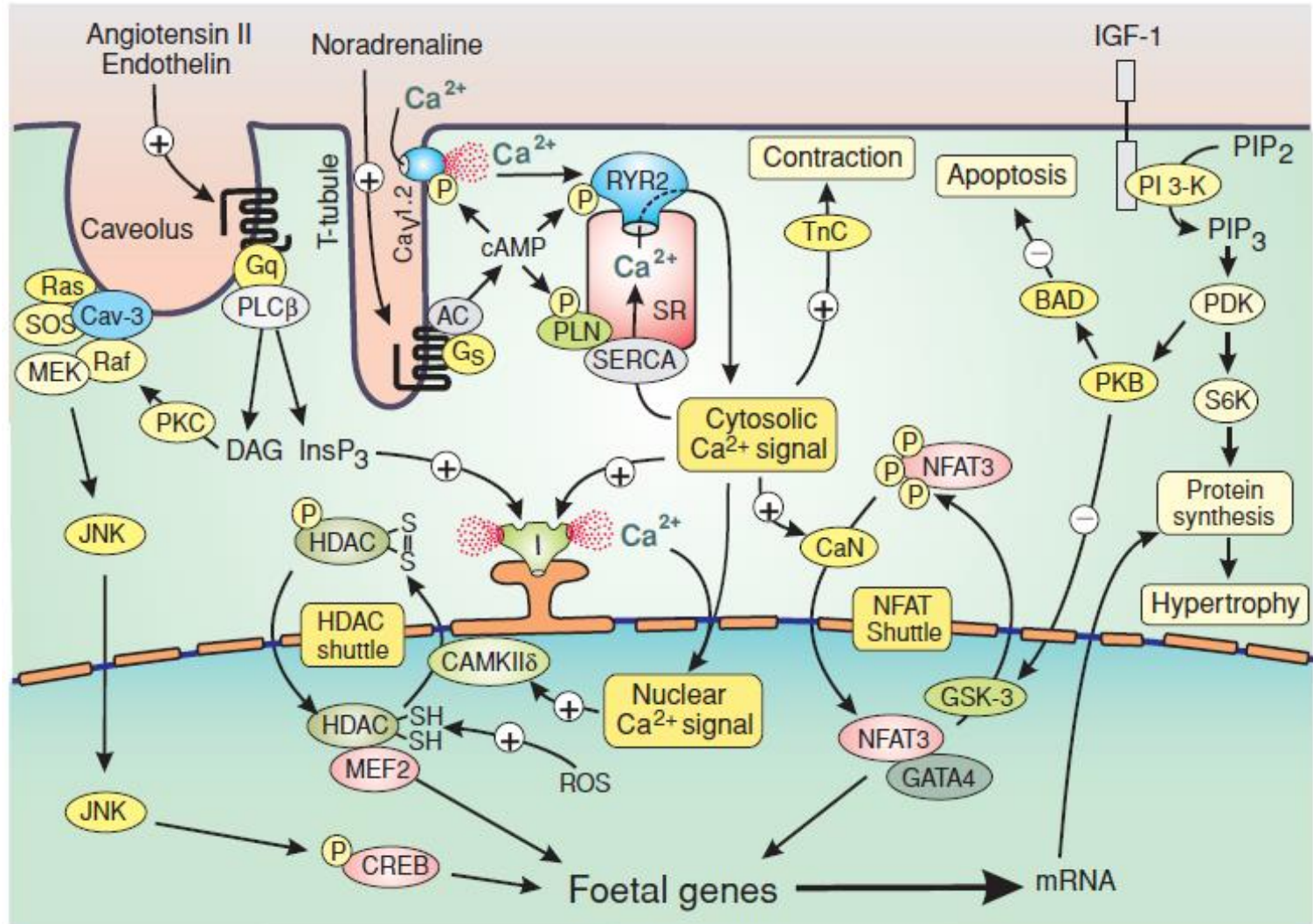


# Physiologic and pathologic myocardial hypertrophy

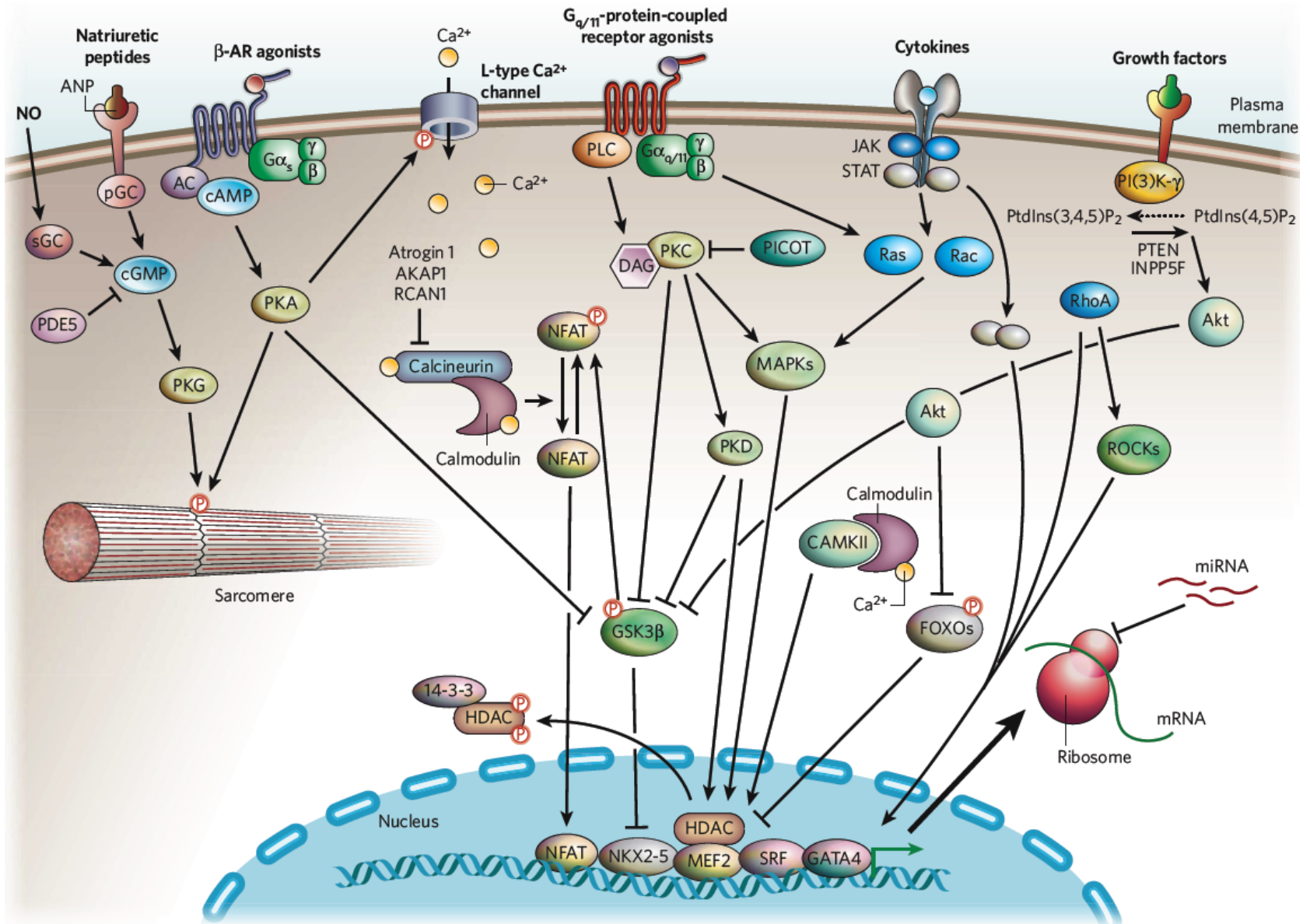


In physiological hypertrophy, action potentials generate a  $Ca^{2+}$  signal that controls contraction and may also stabilize the normal cardiac signalsome by maintaining the adult genes. The insulin-like growth factor 1 (IGF-1) that is produced during exercise uses this adult template when it activates protein synthesis, acting through the PtdIns 3-kinase (PI 3-K) signalling pathway. During pathological hypertrophy, pressure overload activates signalling pathways that alter the nature of the  $Ca^{2+}$  signal (\*), which activates a foetal set of genes that results in a remodelled cardiac signalsome that results in heart disease.

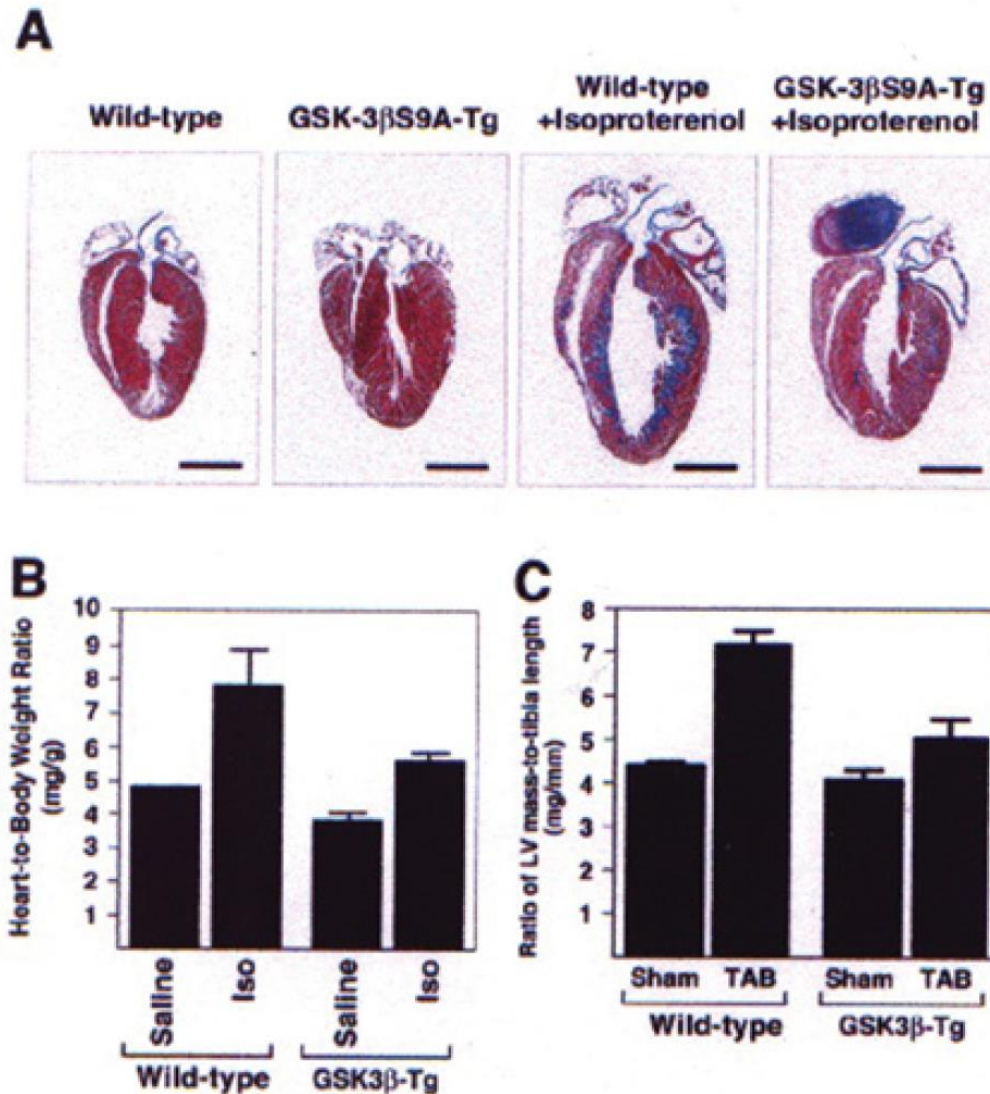
# Signaling processes involved in cardiac remodelling



# Parallel pathways and nodes in HF signaling



# GSK-3 $\beta$ and cardiac hypertrophy



# Molecular changes during chronic heart failure

