Pathophysiology of heart failure

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Regulation of Cardiac Performance and Output

- Cardiac output (the efficiency of the heart as a pump =SV *HR = 3,5-8,0 l/minute
- Cardiac reserve
- Preload (ventricular filling)
- After load (resistance to ejection of blood from the heart
- Cardiac contractility
- Heart rate

Heart rate

It determines the frequency with which blood is ejected from the heart

Stroke volume

It is a function of preload, afterload, and myocardial contractility

Preload

The volume or loading conditions of the ventricles at the end of diastole; just before the onset of systole;

After load

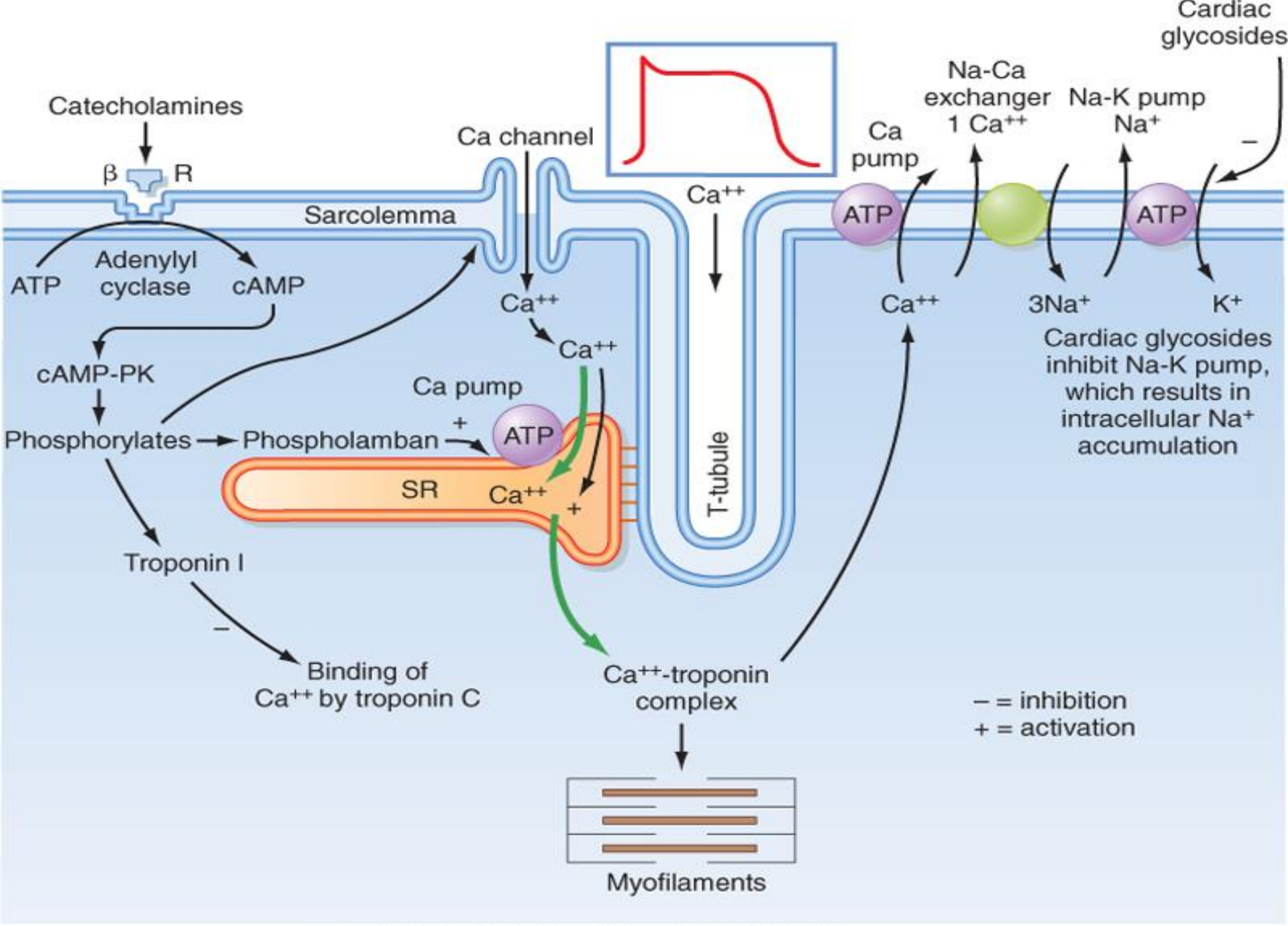
Pressure or tension work of the heart; the pressure that the heart must generate to move blood from the filled heart

Systemic (peripheral vascular resistance)

Ventricular wall tension

Cardiac contractility

Ability of the heart to change its force of contraction without changing its resting (diastolic length)



Heart failure

It reflects a fundamental abnormality in effective mechanical performance of the heart, resulting in cardiac output inadequate to meet the body s needs

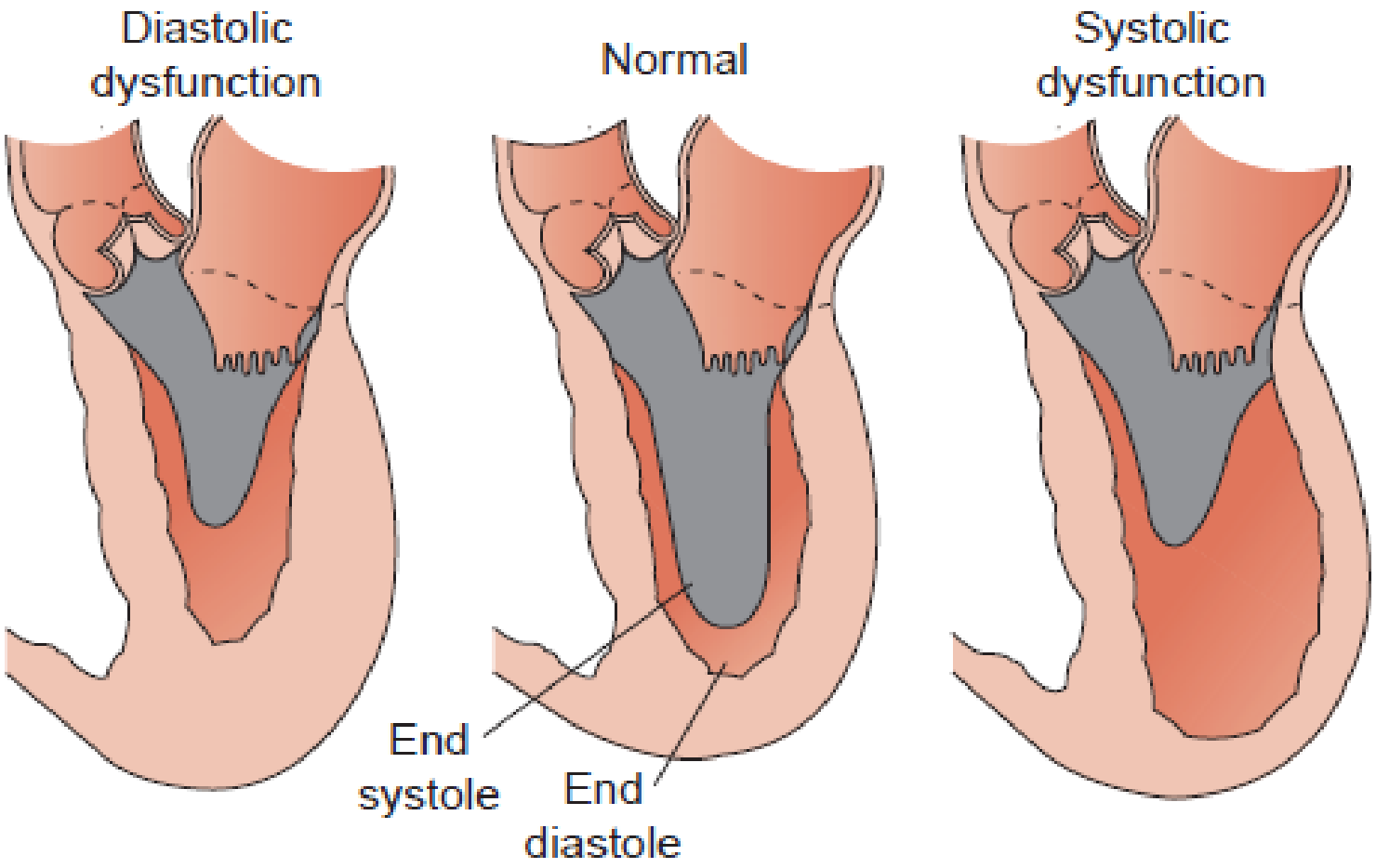
Heart failure

May be manufest by :

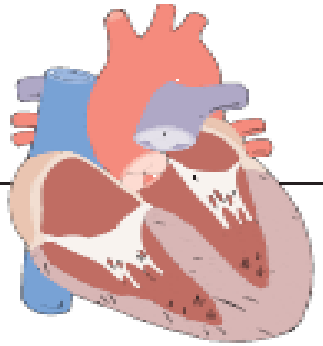
a) decrease in cardiac output and/or

b) damming of blood in the veins behind the left or right side of the heart

Systolic Versus Diastolic Dysfunction



Right versus Left ventricular Dysfunction



- Right heart failure
  - Congestion of peripheral tissues
    - Dependent edema and ascites
    - GI tract congestion
      - Anorexia, GI distress, weight loss
    - Liver congestion
      - Signs related to impaired liver function
- Left heart failure
  - Decreased cardiac output
    - Activity intolerance and signs of decreased tissue perfusion
  - Pulmonary congestion
    - Impaired gas exchange
      - Cyanosis and signs of hypoxia
    - Pulmonary edema
      - Cough with frothy sputum
      - Orthopnea
      - Paroxysmal nocturnal dyspnea

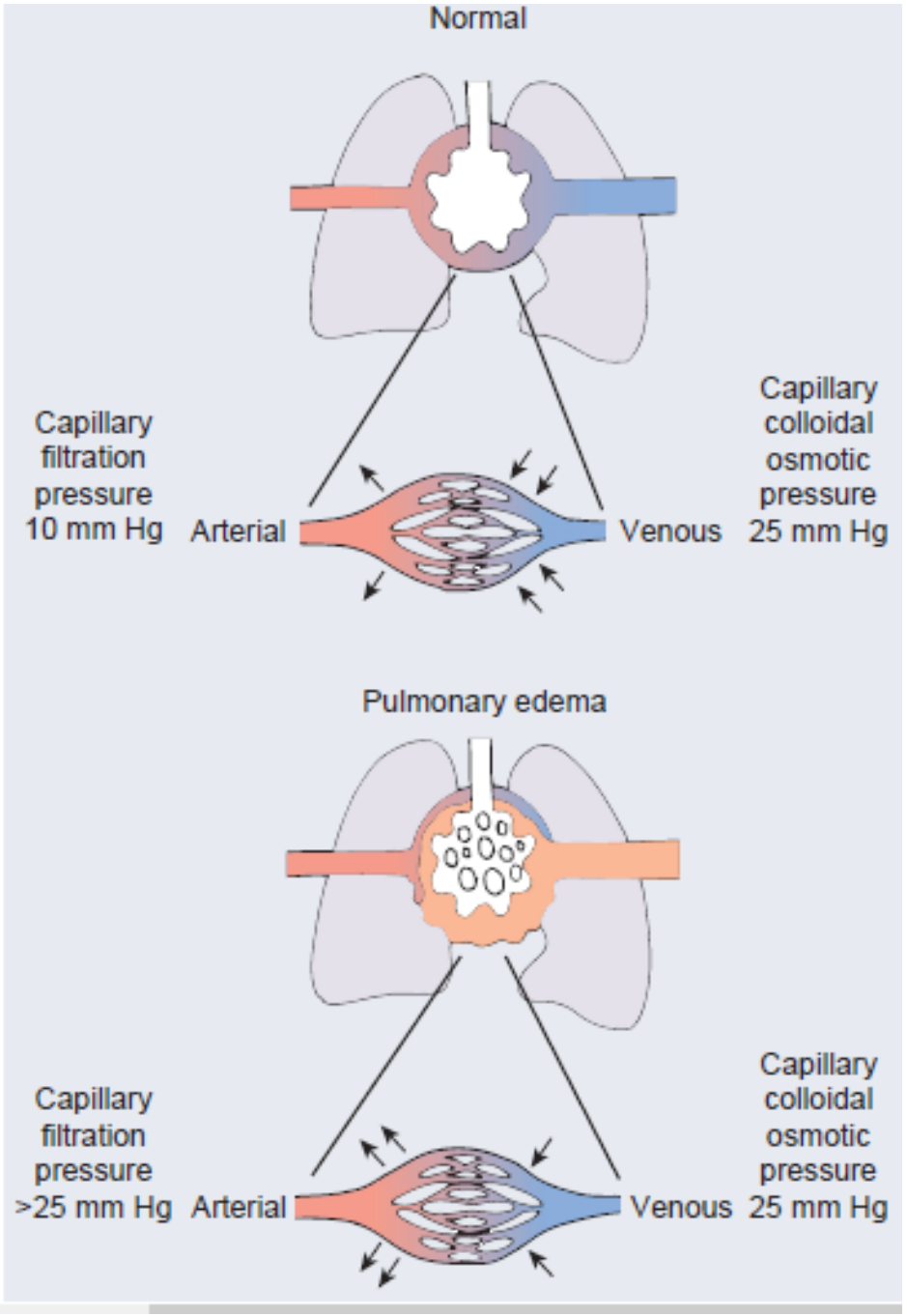

Normal
Capillary filtration pressure 10 mm Hg
Arterial
Venous
Capillary colloidal osmotic pressure 25 mm Hg
Pulmonary edema
Capillary filtration pressure >25 mm Hg
Arterial
Venous
Capillary colloidal osmotic pressure 25 mm Hg

TABLE 28-1 Causes of Heart Failure

Impaired Cardiac Function	Excess Work Demands
Myocardial Disease	**Increased Pressure Work**
Cardiomyopathies	Systemic hypertension
Myocarditis	Pulmonary hypertension
Coronary insufficiency	Coarctation of the aorta
Myocardial infarction	
Valvular Heart Disease	**Increased Volume Work**
Stenotic valvular disease	Arteriovenous shunt
Regurgitant valvular disease	Excessive administration of intravenous fluids
Congenital Heart Defects	**Increased Perfusion Work**
	Thyrotoxicosis
	Anemia
Constrictive Pericarditis	

PRECIPITATING CAUSES

- **Cardiac factors:**
- *Inflammatory causes* (rheumatic myocarditis, infective endocarditis)
- *Negative inotropic agents* (beta blockers, Ca channels blockers, antiarrhytmics)
- *Myocardial ischemia*
- *Acute mechanic injuries*
- **Extra cardiac factors**
- *Systemic or pulmonary hypertension*
- *Hypervolemia*
- *Hyperkinetic states*

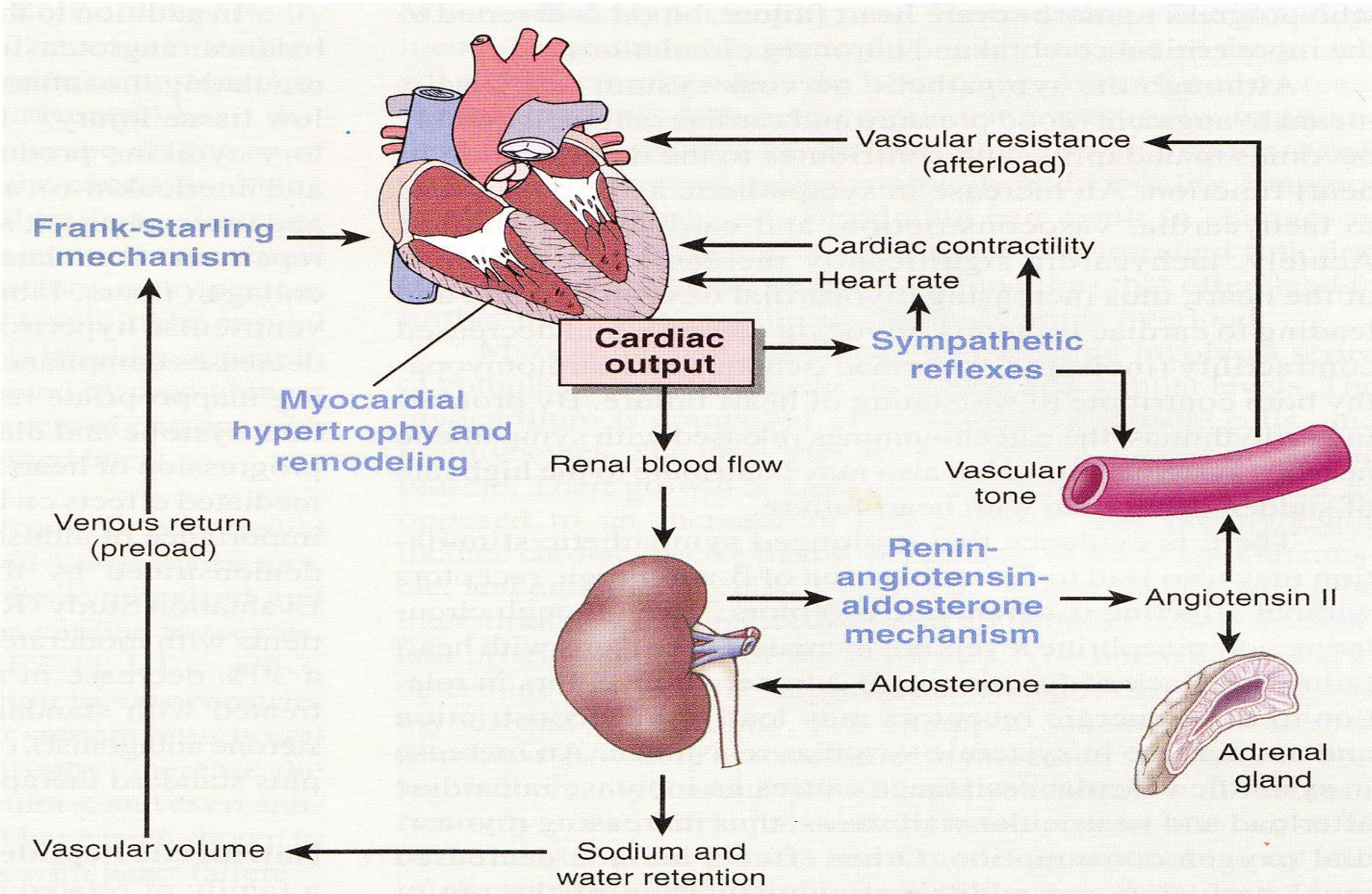
Causes of heart failure (underlying causes)

- **Impaired contraction** (systolic failure- myocardial infarction, cardiomyopathies, ventricular hypertrophy)
- **Work overload** (**pressure**: systemic hypertension, aortic stenosis, pulmonary hypertension; **volume**: mitral, aortic regurgitation, ventricular septal defect
- **Inadequate heart filling** due to diastolic failure and constrictive pericarditis, cardiac tamponade

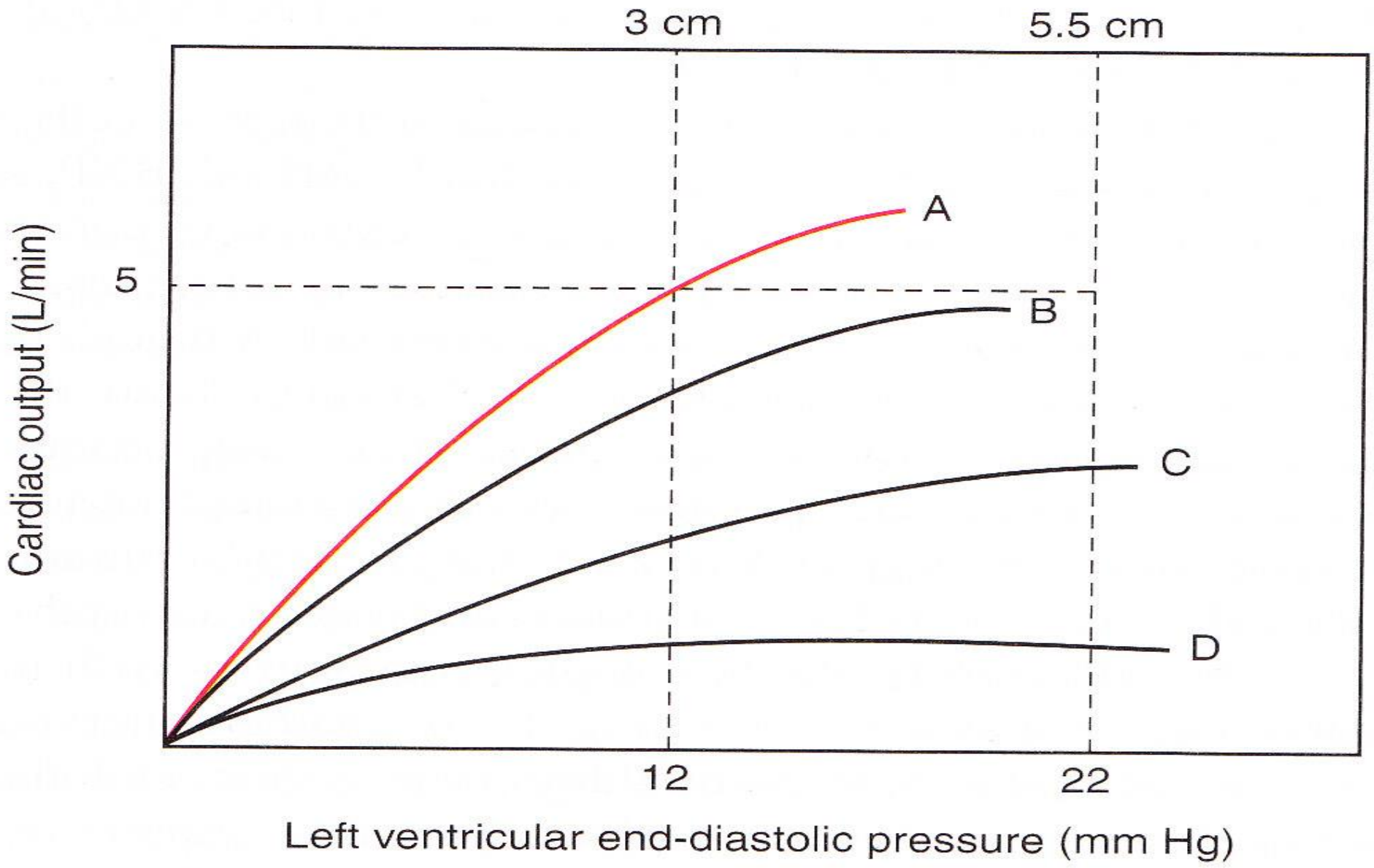
COMPENSATORY MECHANISMS IN HEART FAILURE

- **Immediate (emergent)**
- **1. Central** (tachycardia, length tension-Frank-Starling mechanism)
- **2. Peripheral** (redistribution of cardiac output; increased hemoglobin desaturation)
- **Delayte mechanisms**
- **1. Central** (hypertrophy, cardiac remodeling)
- **2. Peripheral** (renal retention of fluid)

Compensatory Mechanisms



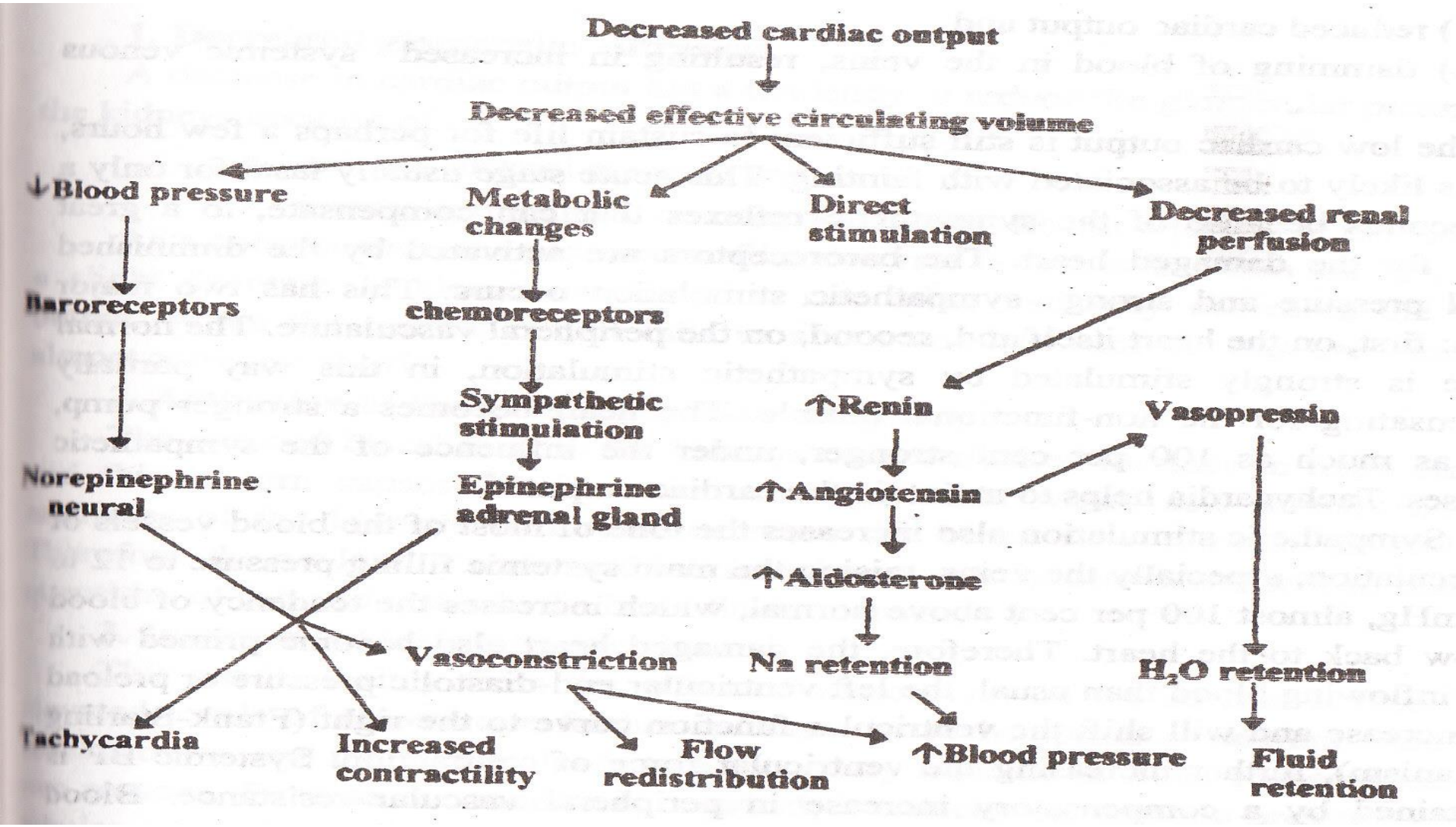
FRANK-STARLING MECHANISM



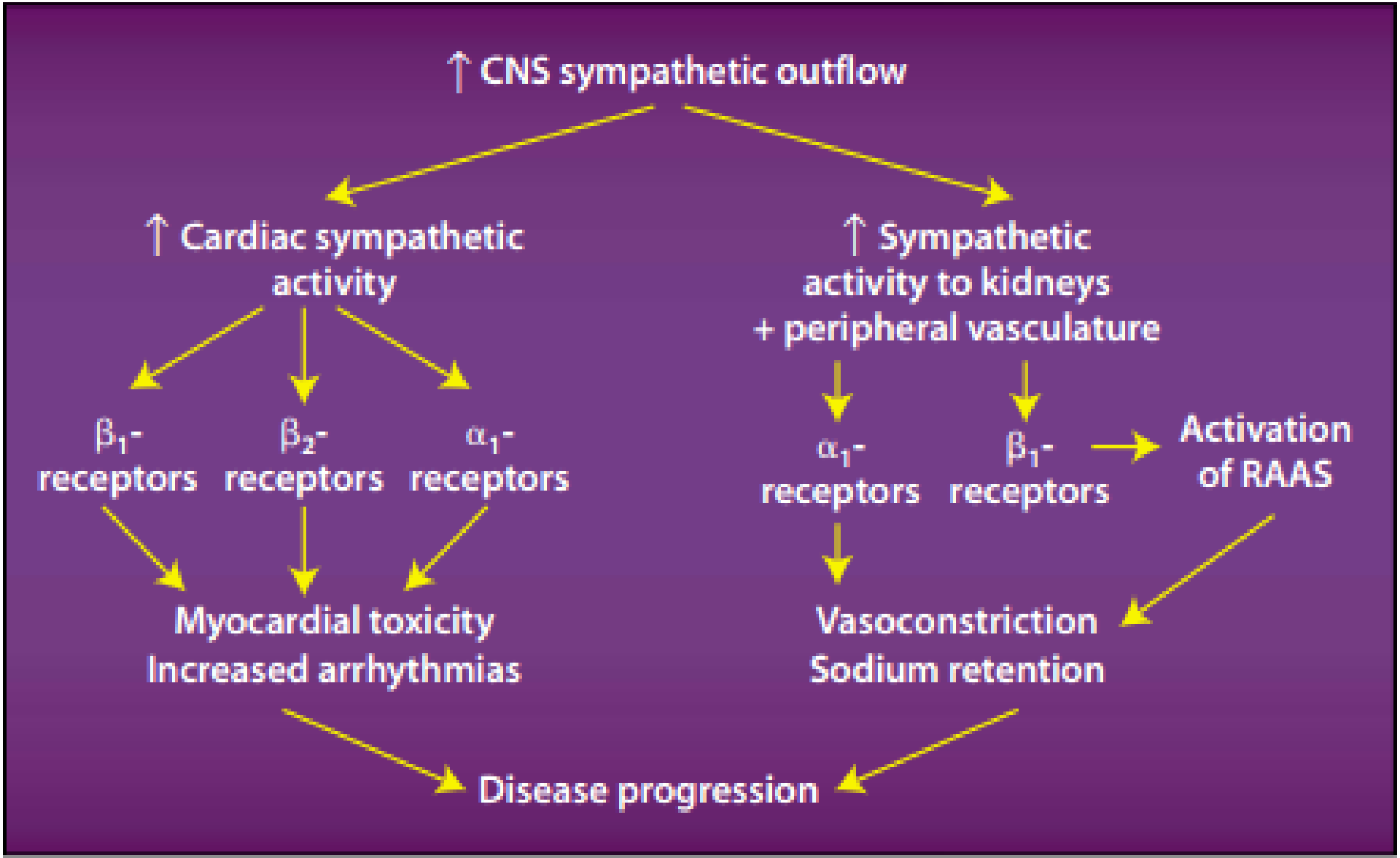
NEURO ENDOCRINE REGULATION OF THE COMPENSATORY MECHANISMS

- **1. The sympathetic stimulation:**
- **Central effects:** tachycardia , increased contractility, increased diastolic relaxation
- **Peripheral effects:** selective vasoconstriction and flow redistribution; renin release
- **2. The renin-angiotensin-aldosterone system**
- **3. The antidiuretic hormone**
- **4. The prostaglandines**
- **5. The atrial natriretic peptide**
- **6. Endothelins**
- **7. Inflammatory Mediators (CRP, cytokines)**

The compensatory mechanisms triggered by a decrease in cardiac output



The sympathetic stimulation



NEURO ENDOCRINE REGULATION OF THE COMPENSATORY MECHANISMS

- **Vasoconstrictor:**

1. sympathetic stimulation
2. renin-angiotensin aldosterone system
3. ADH

- **Local**

- **Vasodilator**

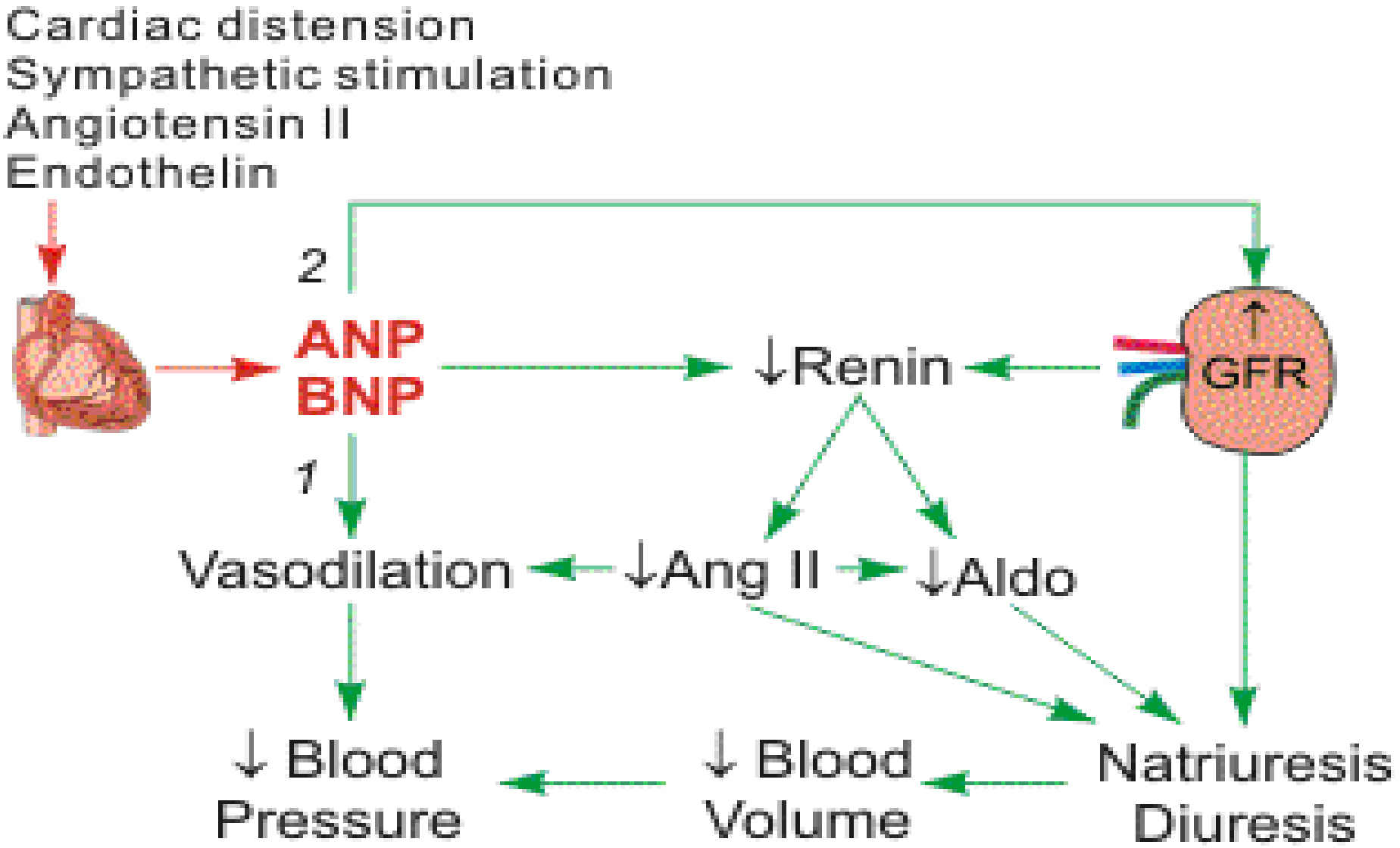
atrial natriuretic peptide

nitric oxide

prostaglandins

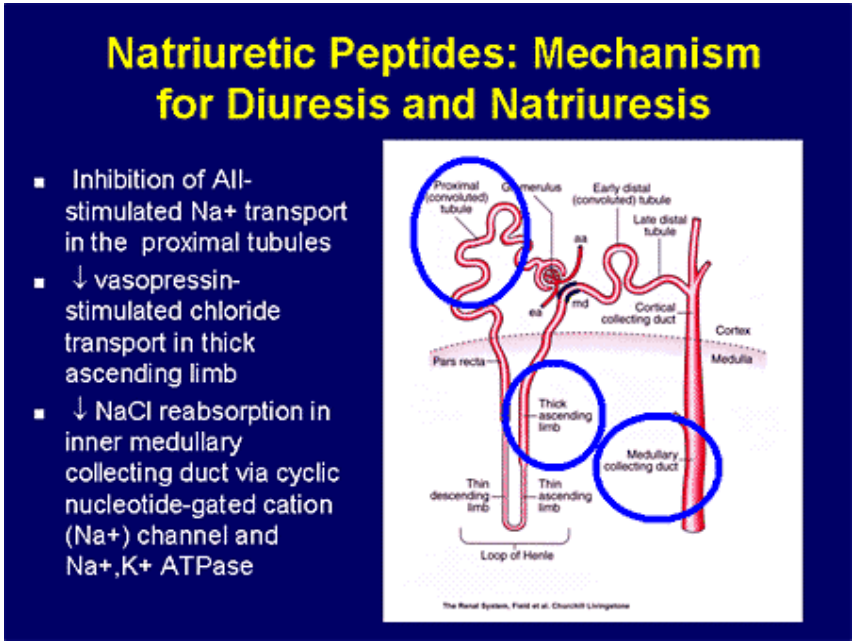
- **Vasodilator**

Natriuretic Peptides

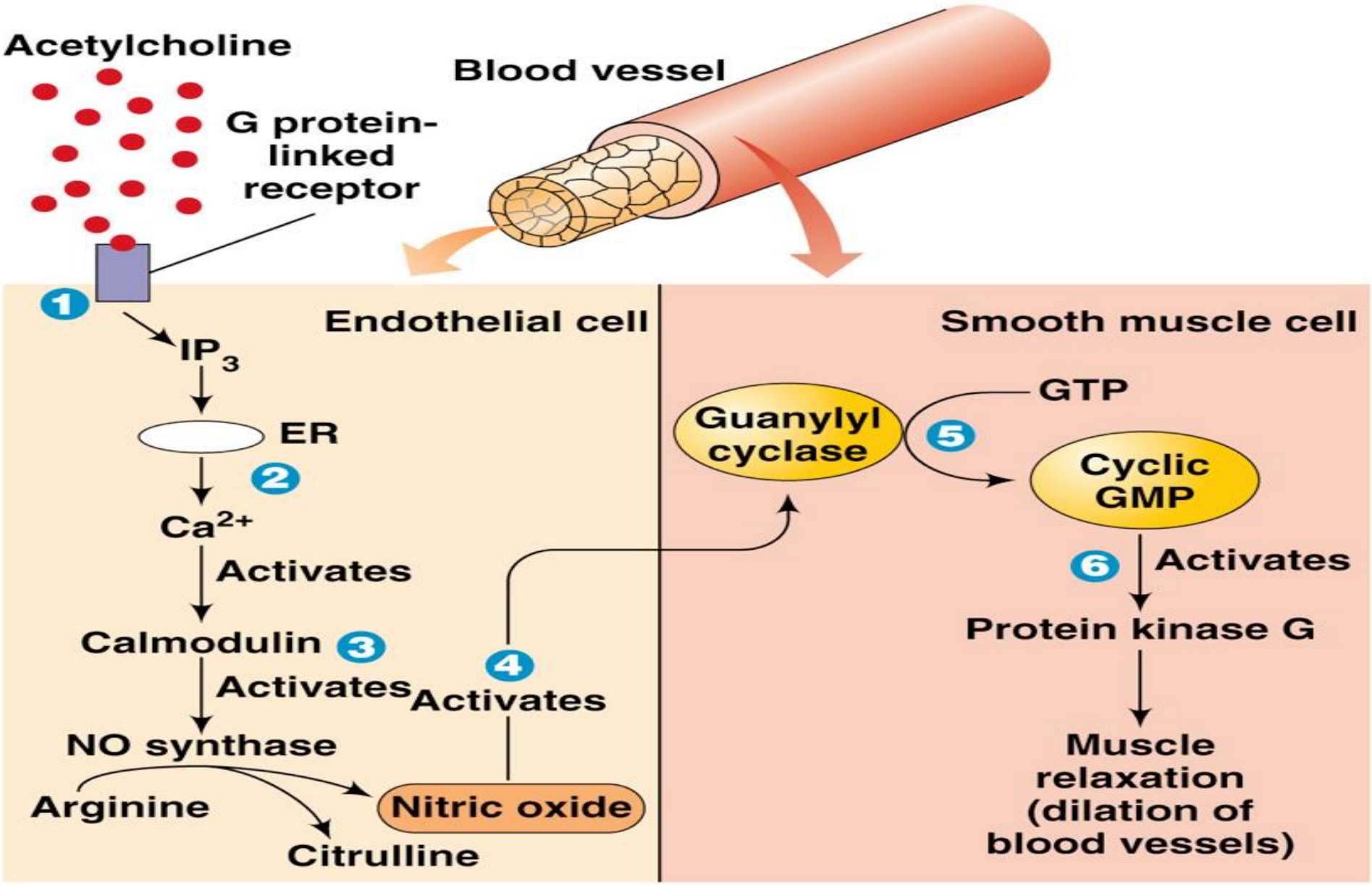


Antihypertropic Signaling Pathways

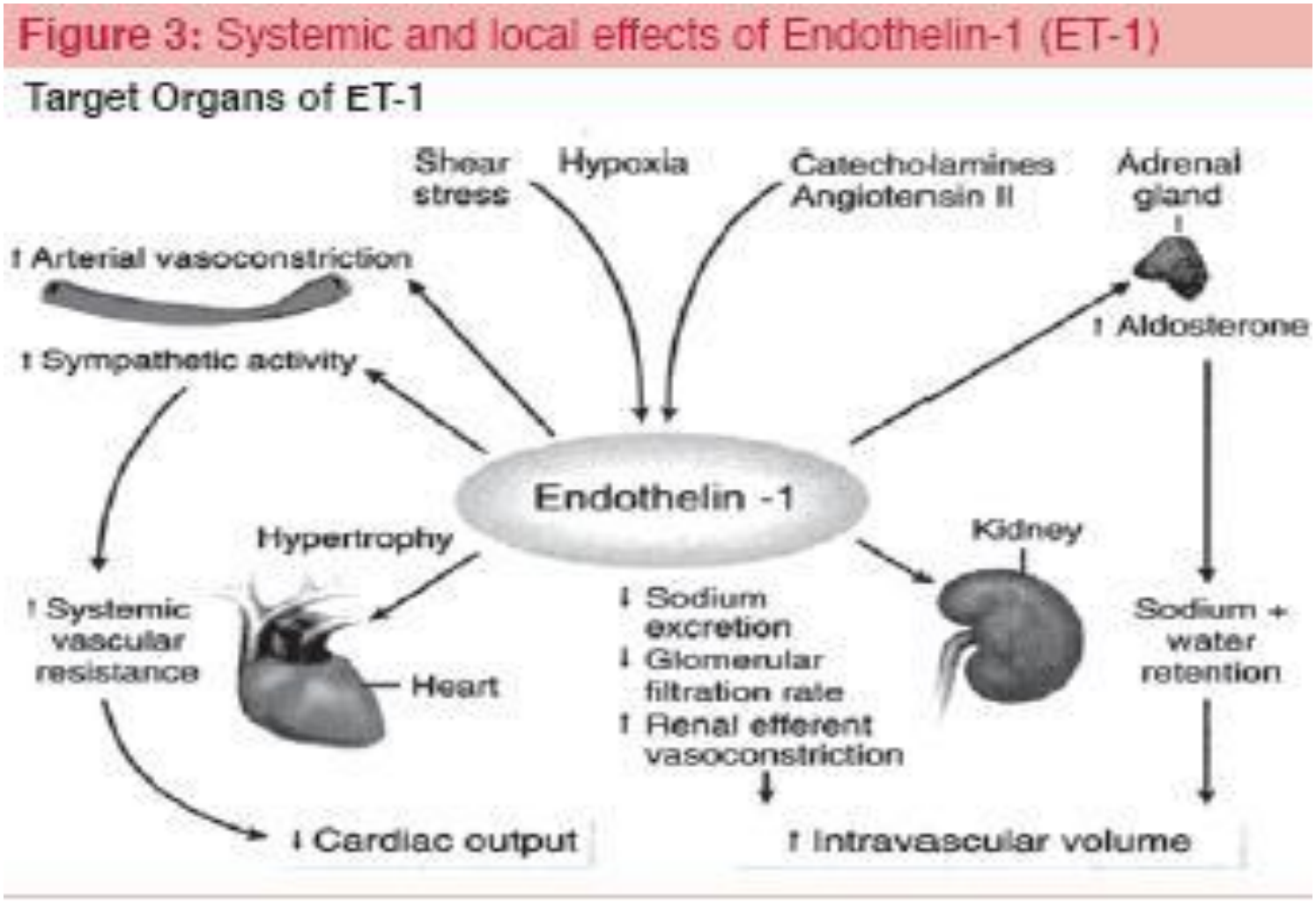
- Have potent natriuretic
- Diuretic
- Vascular smooth muscle effects
- Interact with other neurohumoral mechanisms
- ANP and BNP



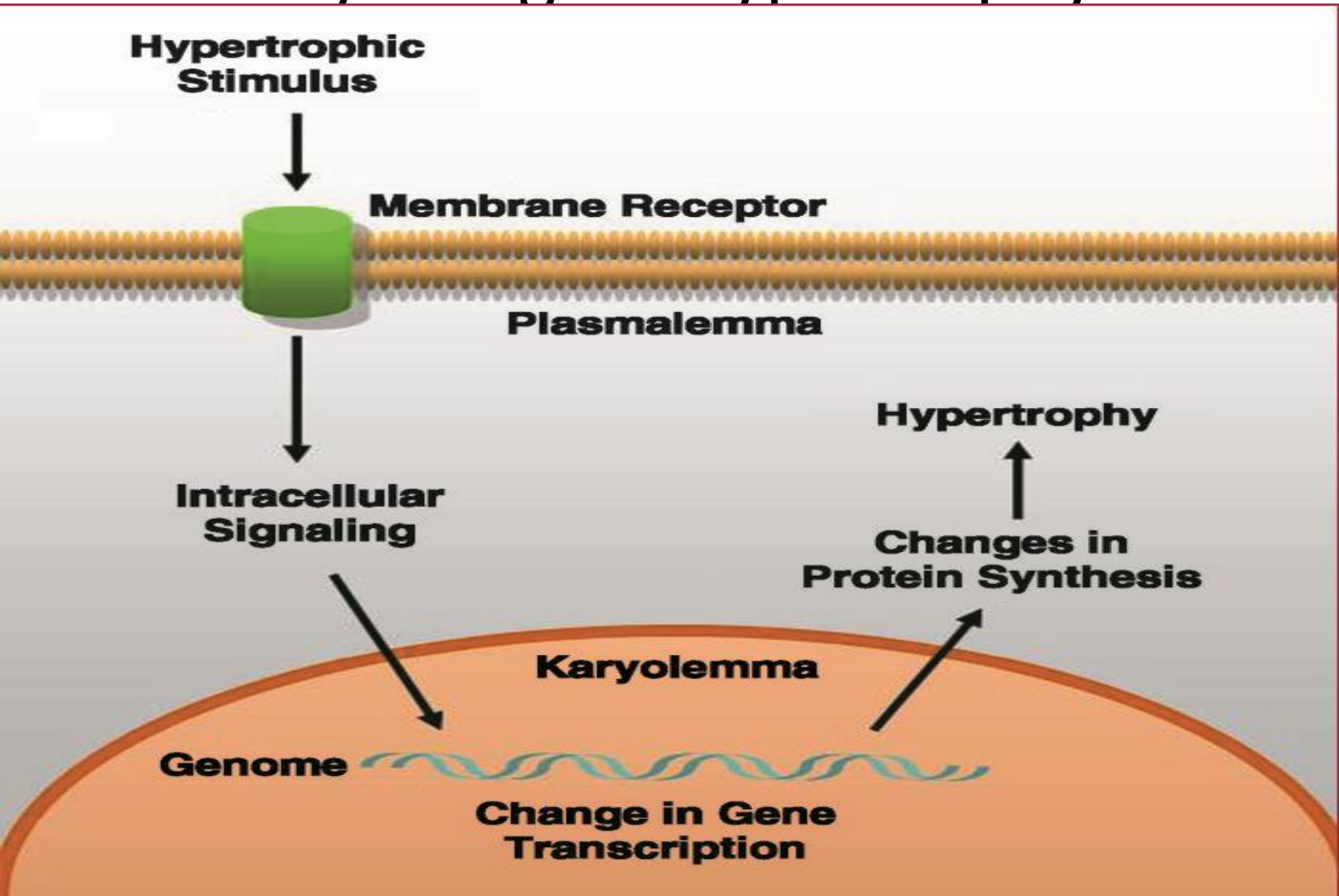
Nitric oxide

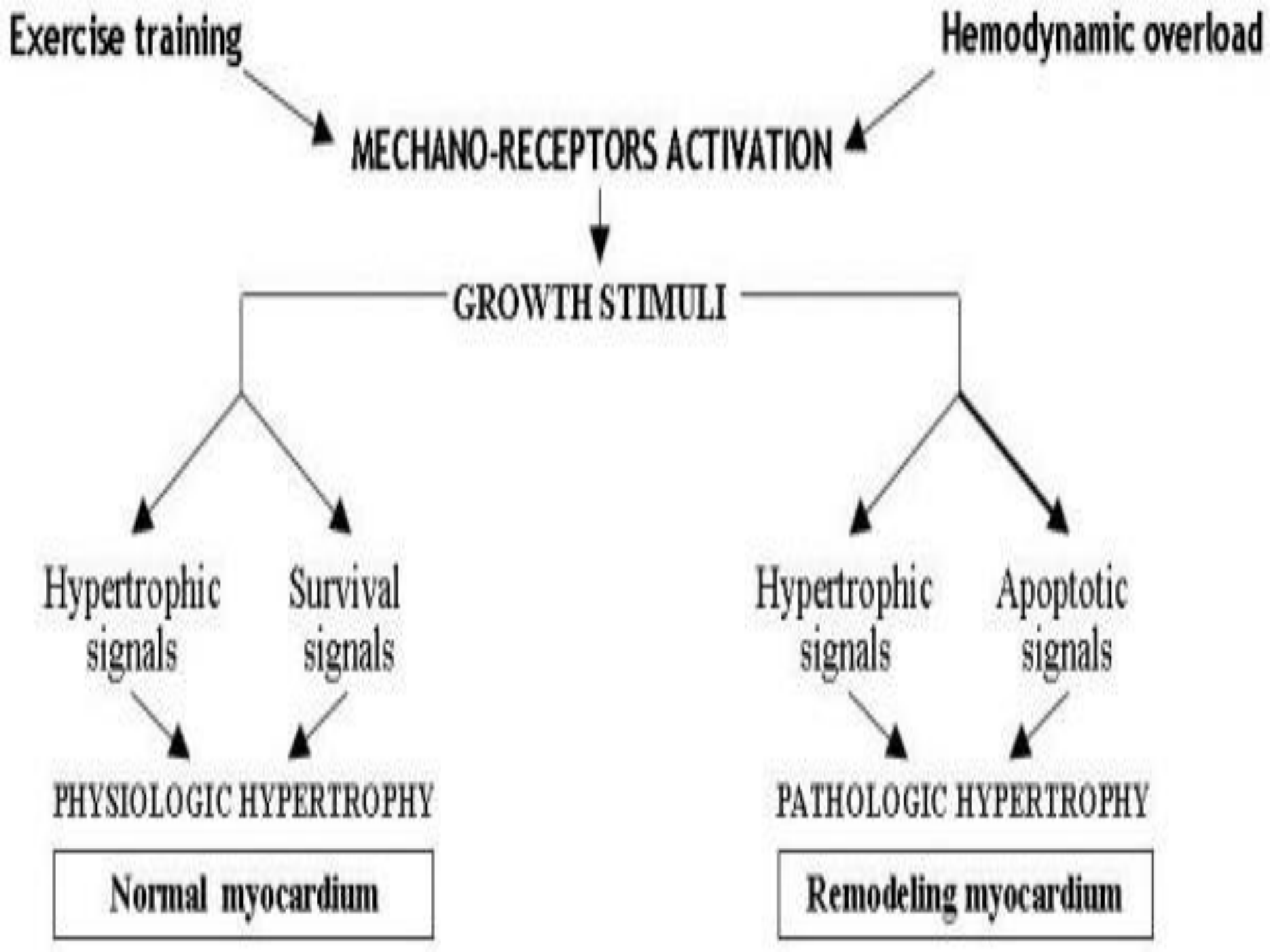


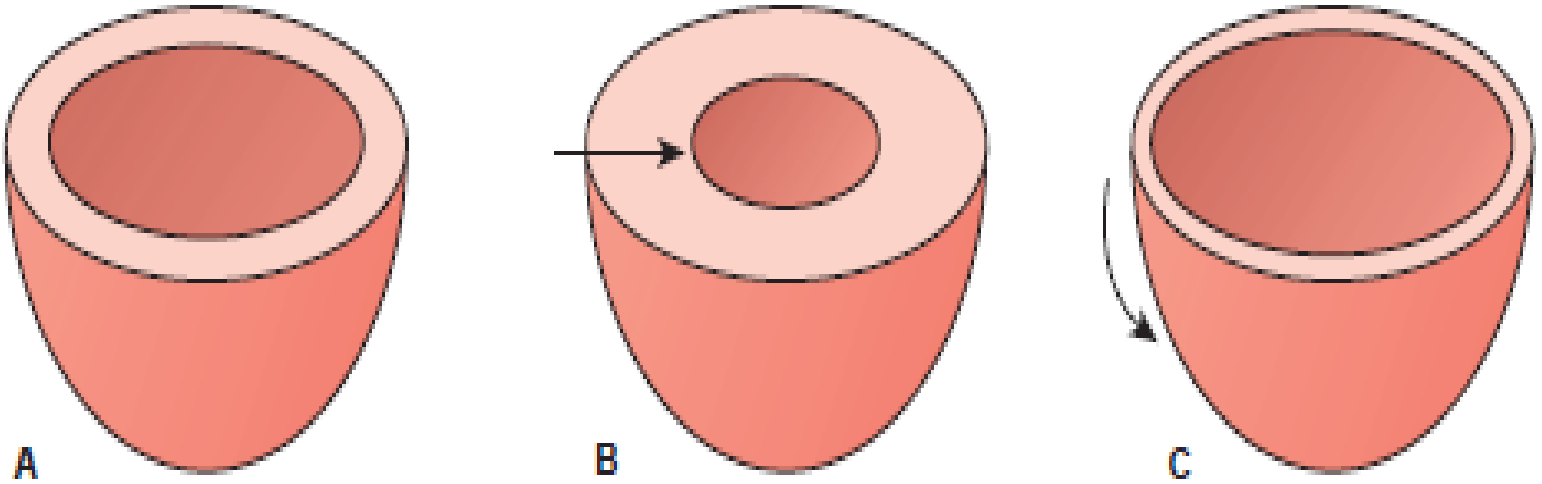
Endothelins



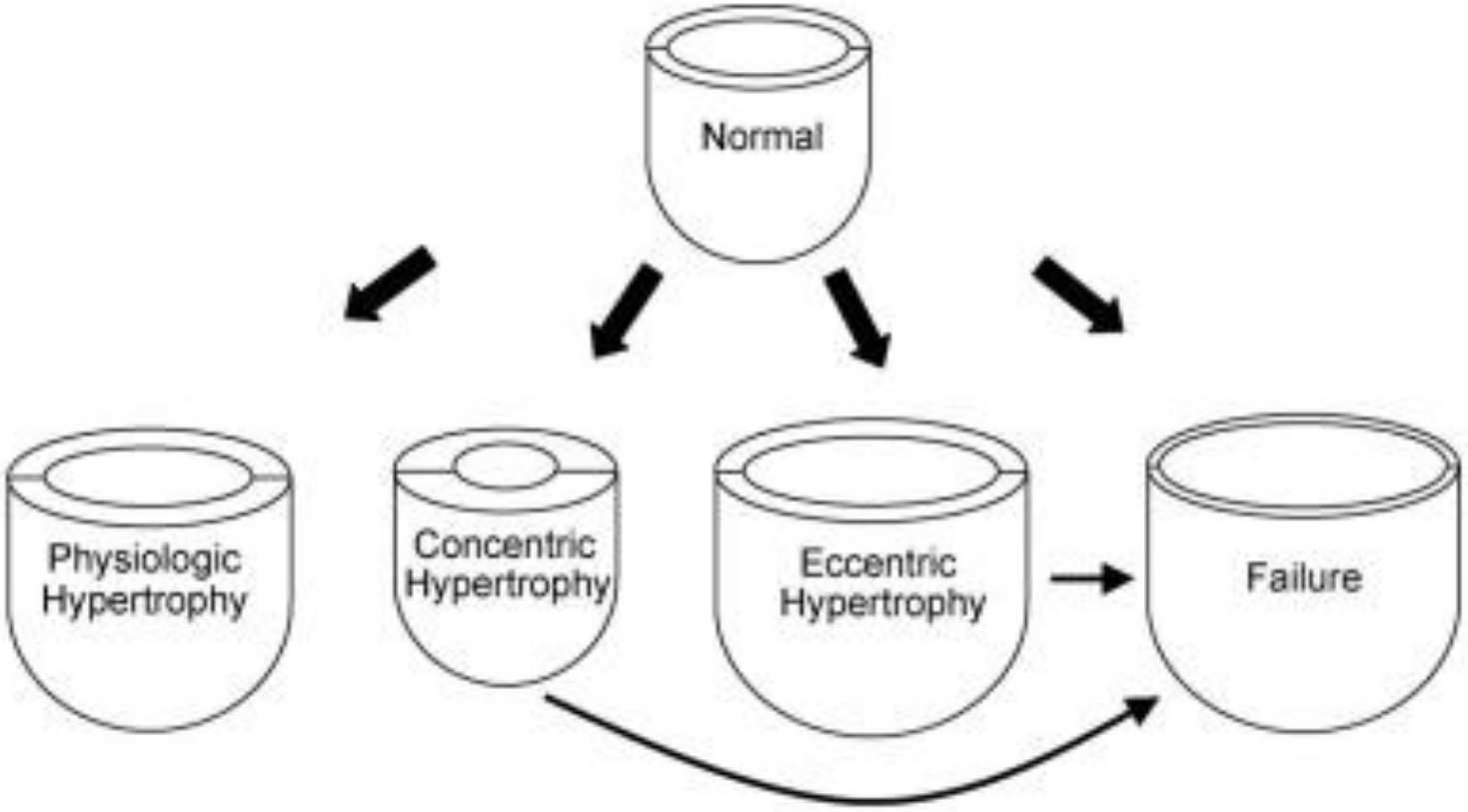
Physiological hypertrophy




Exercise training
Hemodynamic overload
MECHANO-RECEPTORS ACTIVATION
GROWTH STIMULI
Hypertrophic signals
Survival signals
Hypertrophic signals
Apoptotic signals
PHYSIOLOGIC HYPERTROPHY
PATHOLOGIC HYPERTROPHY
Normal myocardium
Remodeling myocardium

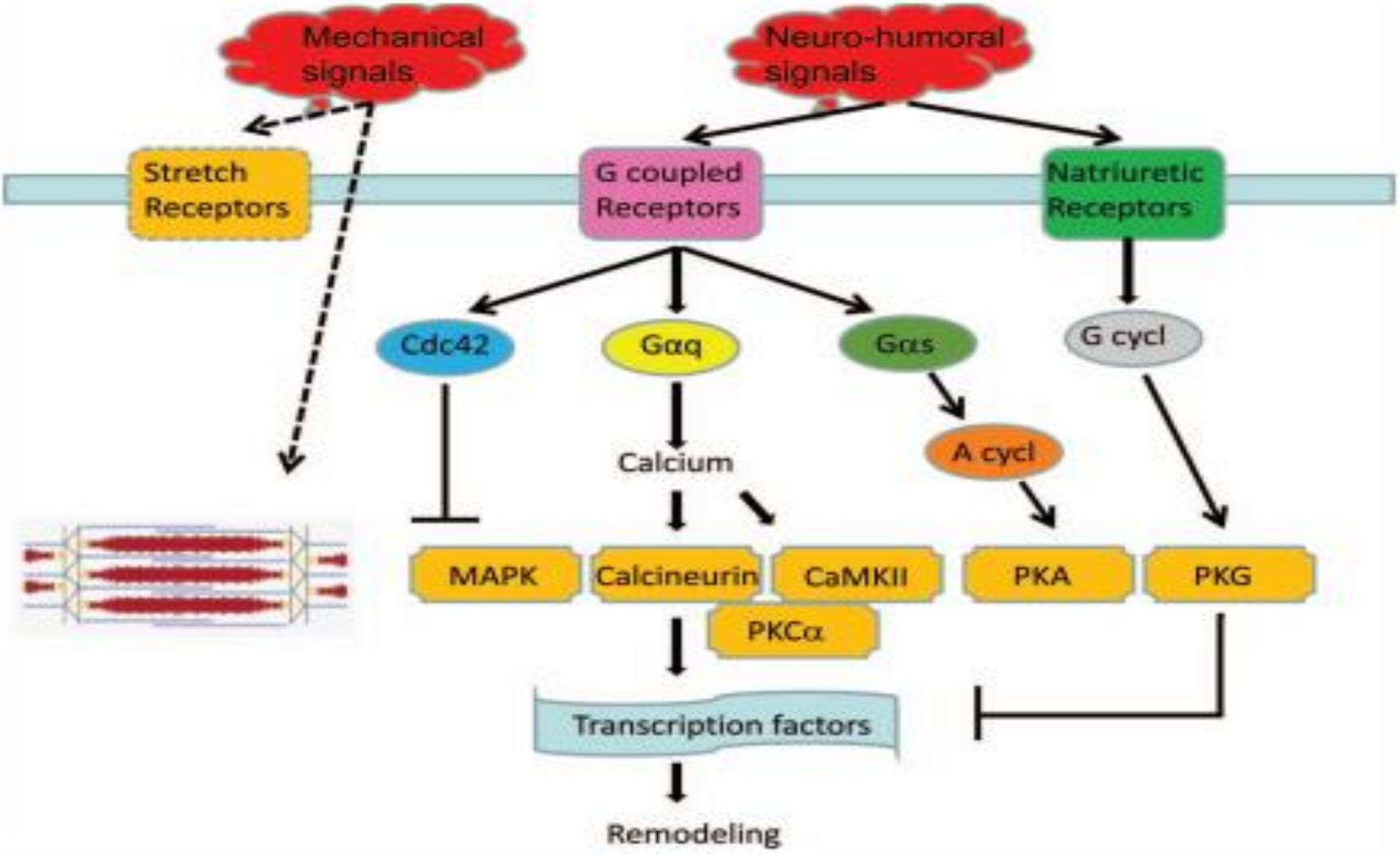

A
B
C

Types of hypertrophy



Fetal genes:	-	+	+	+
Fibrosis:	-	+++	-/+	++
Cellular dysfunction:	-	-/+	-/+	++

Concentric hypertrophy



Eccentric hypertrophy

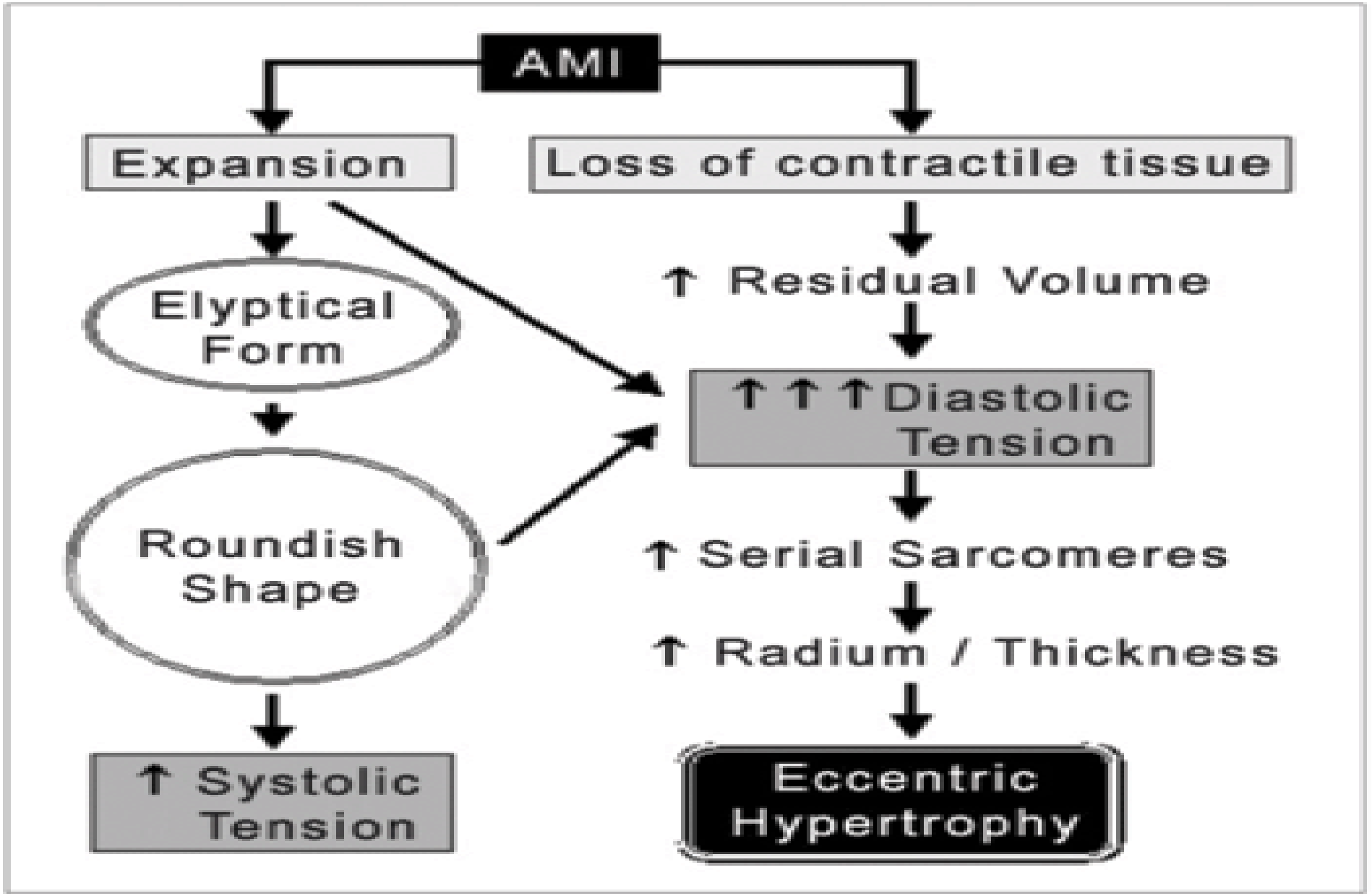
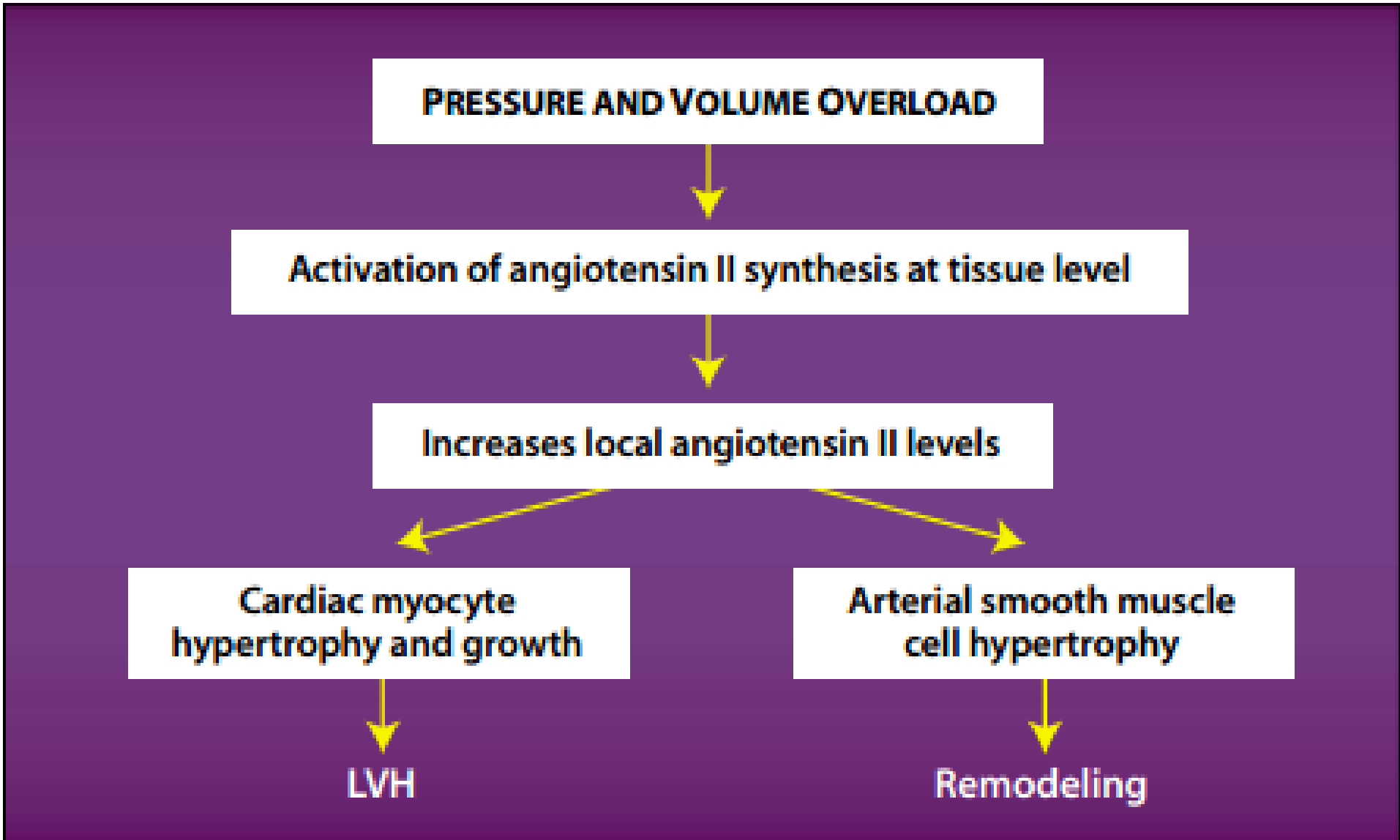


Figure 2 - Chronic phase of left ventricle remodeling.

Response to pressure and volume overload



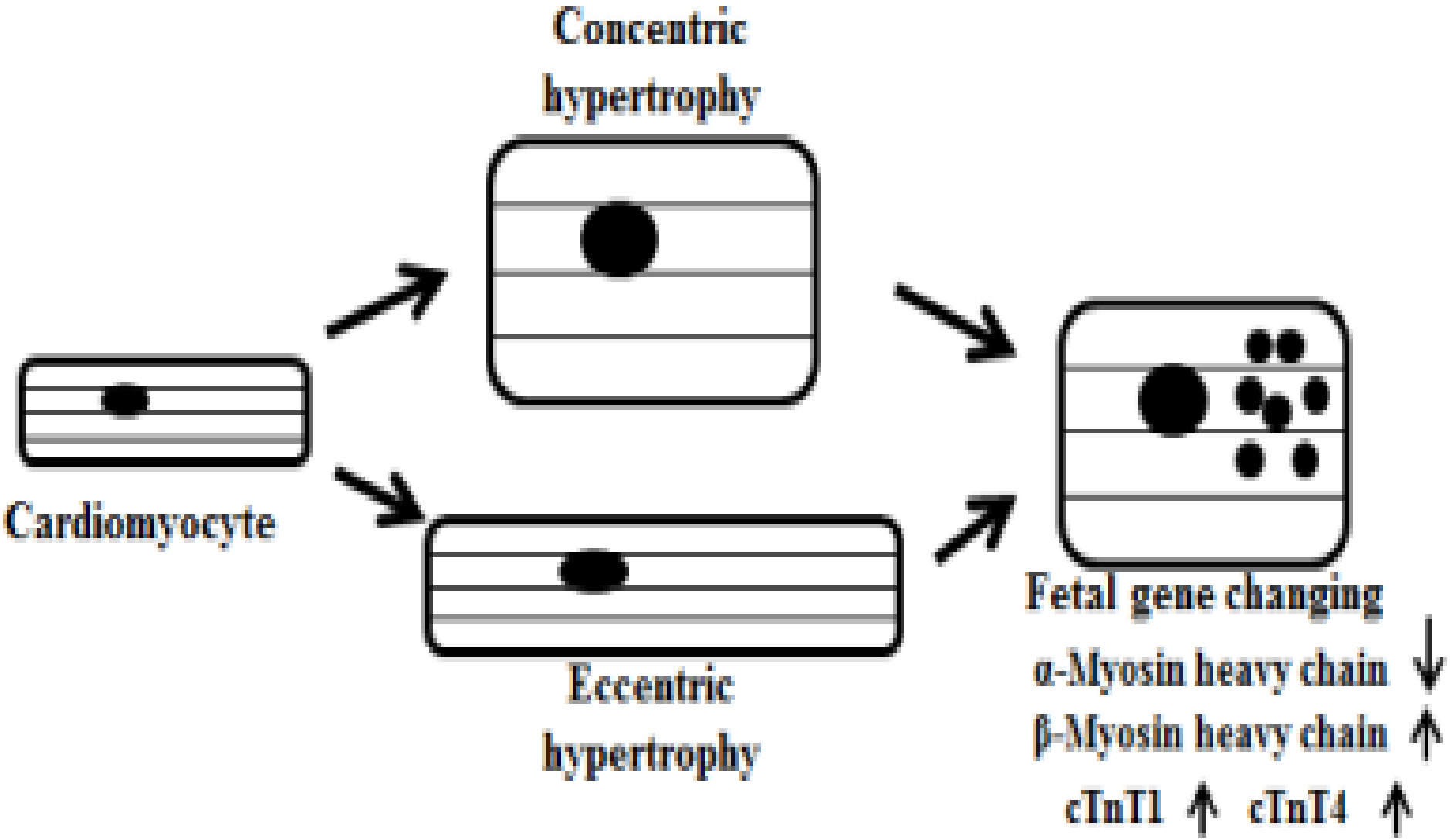
Cardiac remodeling

Clinically manifest as changes in size, shape, and function of the heart after injury or stress stimulation

Myocardial Hypertrophy

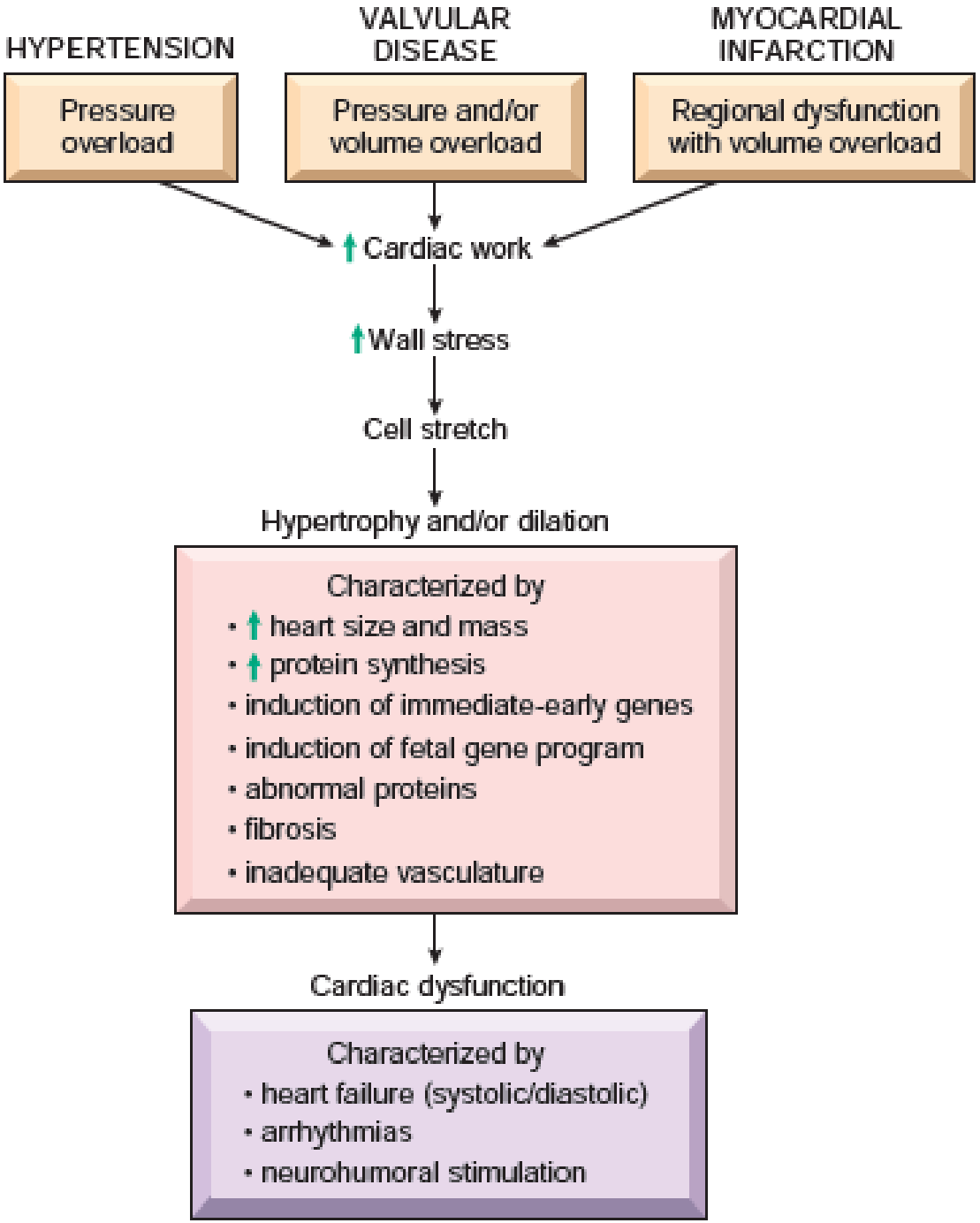
- **Cellular and molecular remodeling**
- myocyte growth without significant proliferation
- re expression of fetal genes
- alterations in the expression of proteins involved in excitations-contraction coupling
- changes in the energetic and metabolic state of myocyte

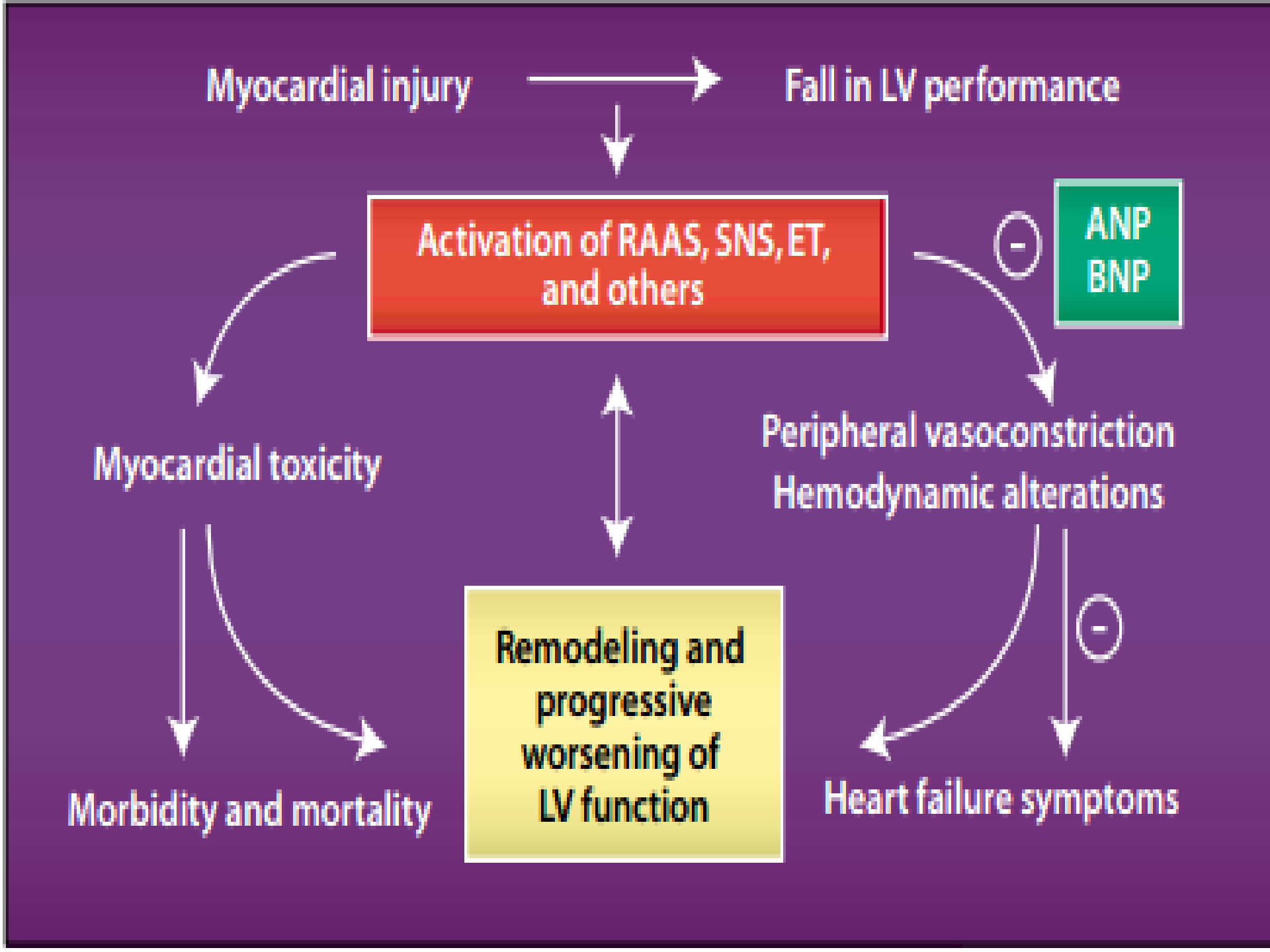
- **Changes in the extra cellular matrix (ECM)-** cardiac macrophages, fibroblasts, vasclar smooth muscle, endothelial cells)
- hyperplasia
- uncontrolled cardiac fibroblast growth
- increased synthesis of collagen fibers
- Myocardial fibrosis
- ventricular wall stiffnes

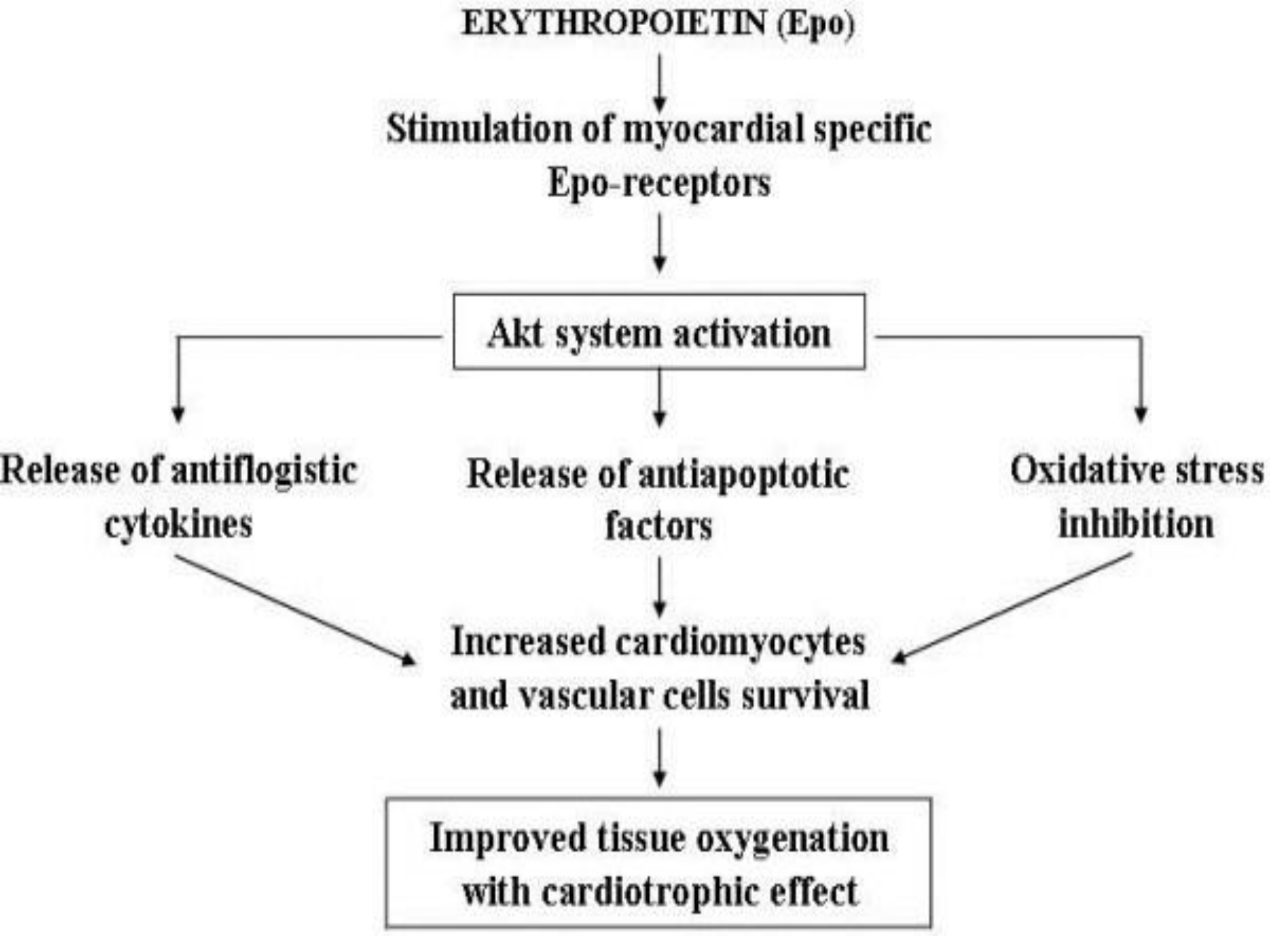


Process of ventricular remodeling

Figure 4


HYPERTENSION
Pressure overload
VALVULAR DISEASE
Pressure and/or volume overload
MYOCARDIAL INFARCTION
Regional dysfunction with volume overload
↑ Cardiac work
↑ Wall stress
Cell stretch
Hypertrophy and/or dilation
Characterized by
• ↑ heart size and mass
• ↑ protein synthesis
• induction of immediate-early genes
• induction of fetal gene program
• abnormal proteins
• fibrosis
• inadequate vasculature
Cardiac dysfunction
Characterized by
• heart failure (systolic/diastolic)
• arrhythmias
• neurohumoral stimulation


Myocardial injury
Fall in LV performance
Activation of RAAS, SNS, ET, and others
ANP
BNP
Myocardial toxicity
Peripheral vasoconstriction
Hemodynamic alterations
Remodeling and progressive worsening of LV function
Morbidity and mortality
Heart failure symptoms

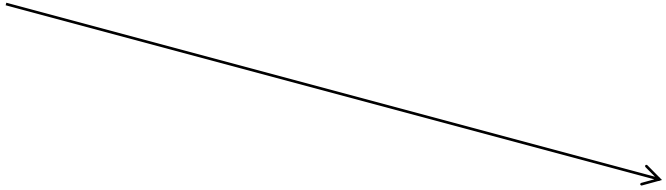

ERYTHROPOIETIN (Epo)
Stimulation of myocardial specific Epo-receptors
Akt system activation
Release of antiflogistic cytokines
Release of antiapoptotic factors
Oxidative stress inhibition
Increased cardiomyocytes and vascular cells survival
Improved tissue oxygenation with cardiotrophic effect

Myocardium **Vessels**

Noxious stimuli

Increased biomechanical stress to the cardiomyocytes

Increased workload



Adaptive hypertrophic growth

Or undergo apoptosis

Organ enlargement

Cardiac dilation and increased sphericity.

↓

Increased ventricular wall stress

↓

Decreased coronary blood flow

↓

Impaired pump function

↓

Diminished cardiac output

↓

Moreover, interstitial fibrosis is observed, further hindering systolic and diastolic cardiac function

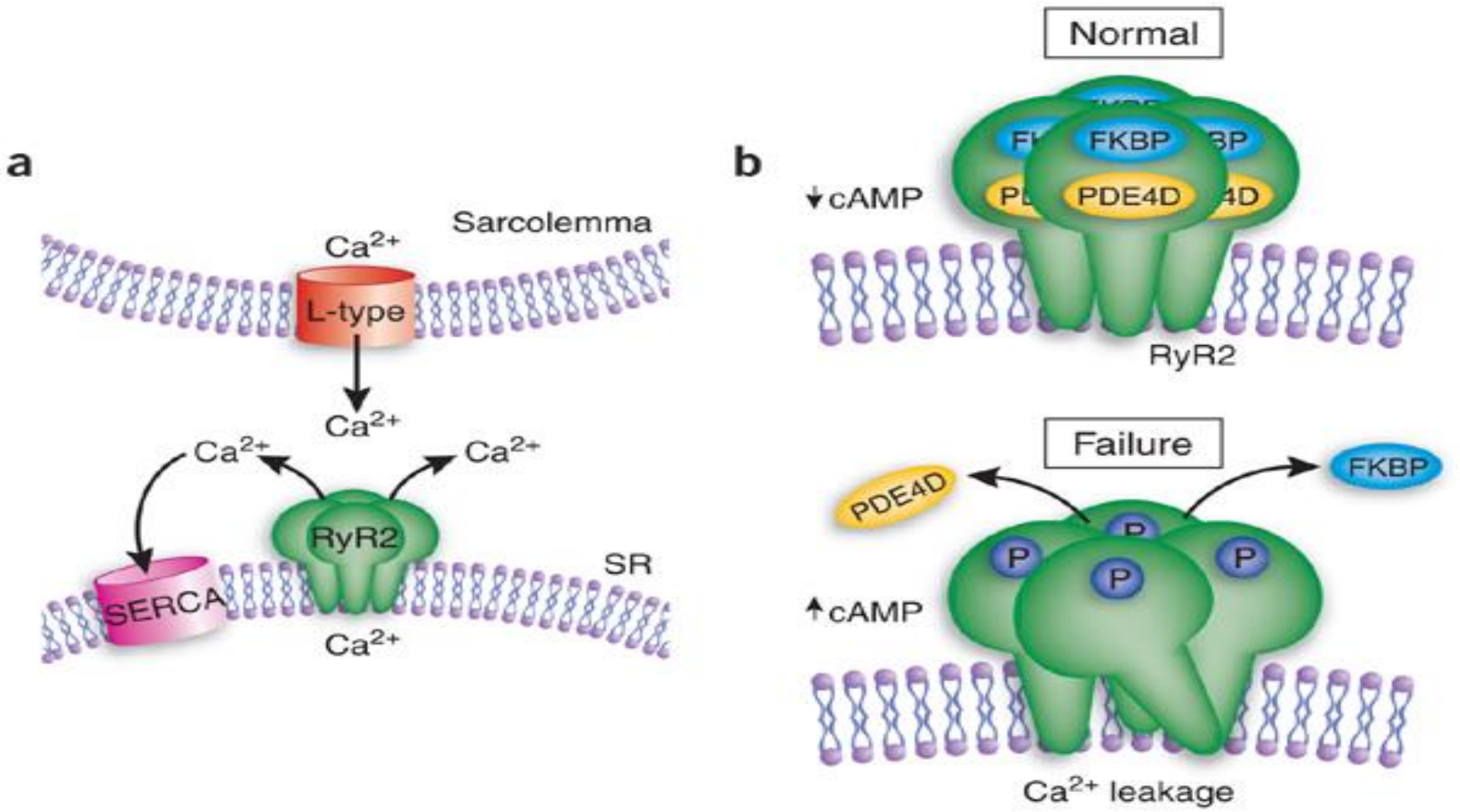
↓

Hypertrophy eventually becomes a maladaptive process

↓

Chronic heart failure and cardiac mortality

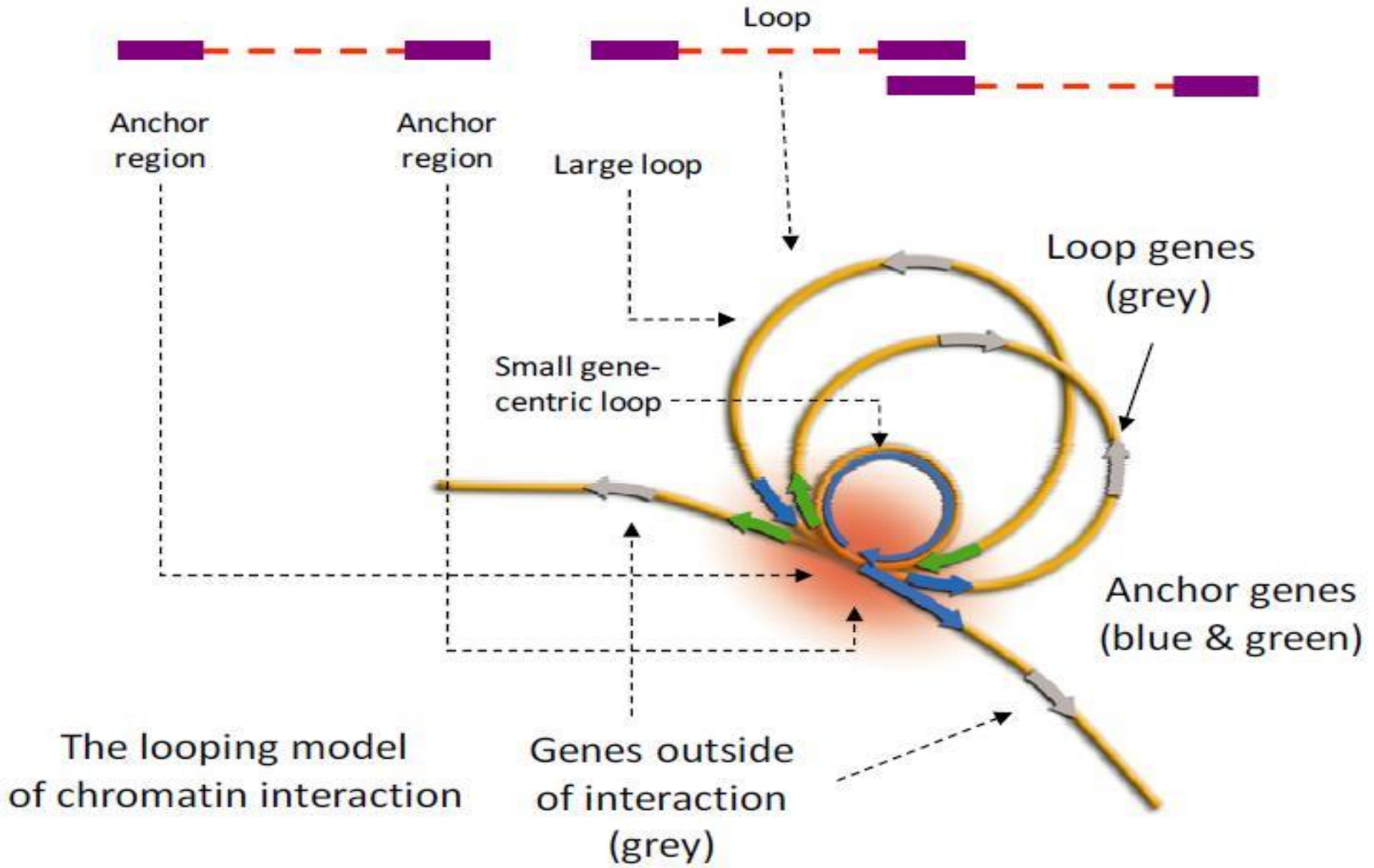
L-type calcium channel



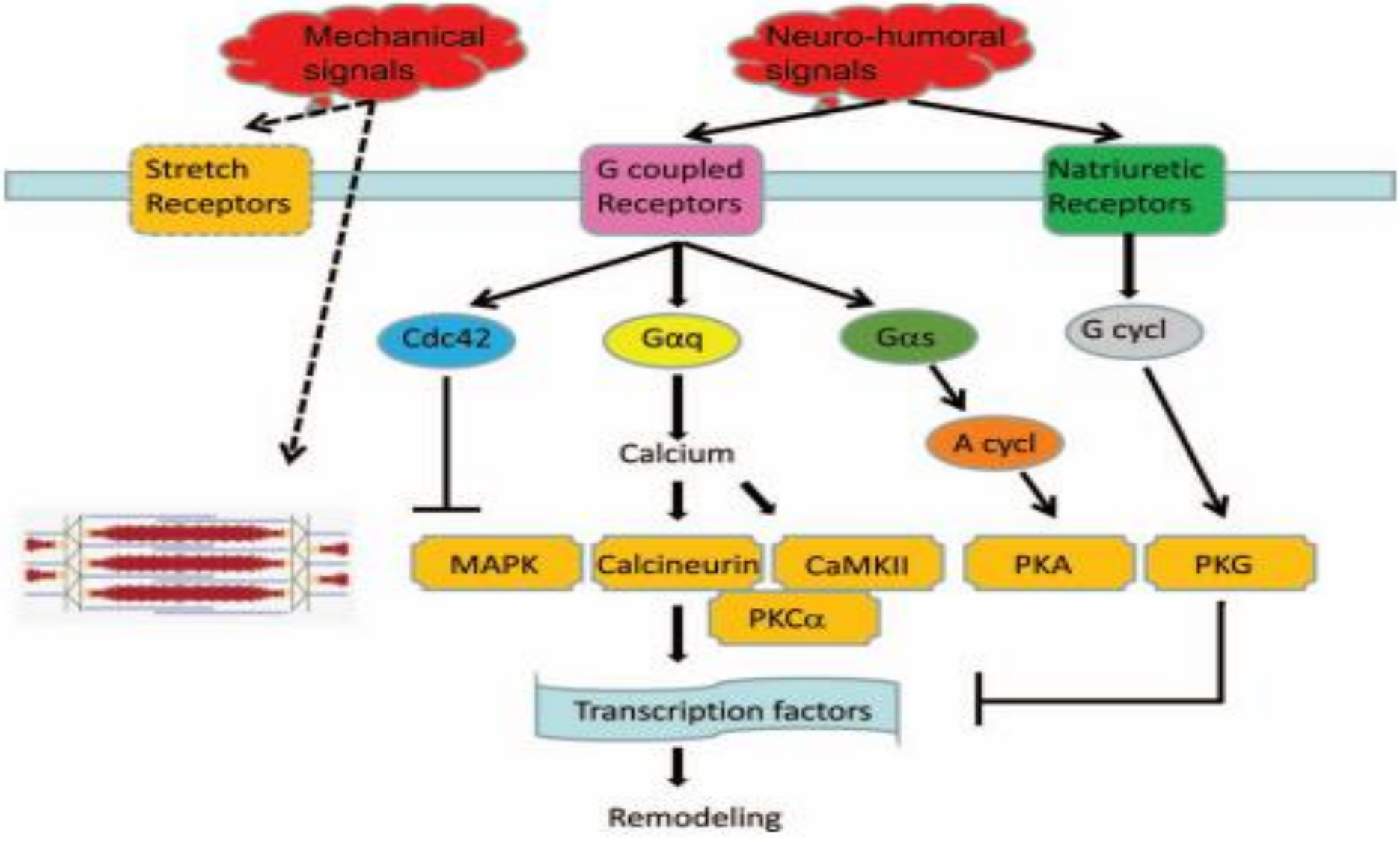
Molecular Changes Underlying a Transition to Heart Failure

- Intrinsic changes in the cardiomyocyte (reexpression of fetal genes)
- Alterations in the expression of proteins involved in excitation-contraction coupling
- changes in the energetic and metabolic state of the myocyte
- a mismatch between vascular and cardiomyocyte growth
- myocyte death caused by necrosis and apoptosis
- changes in the extra cellular matrix.

Chromatin Alterations in Cardiac Hypertrophic Signaling



Impaired Excitation-Contraction Coupling



Apoptotic changes

Apoptosis is believed to contribute to cardiomyocyte dropout and progressive decline in left ventricular function during chronic heart failure, contributing factors are:

-Extrinsic Death Receptor Pathway

There is evidence that the Fas/FasL system participates in various types of stress-induced apoptosis in the heart, where cellular stressful stimuli sensitize cardiomyocytes to Fas in vitro. Elevated levels of soluble Fas ligand and Fas mRNA have been found in failing hearts.

- Intrinsic Mitochondrial Pathway

Release of cytochrome c from the mitochondria and activation of caspase 3 occurs in chronic heart failure patients.

-Bcl-2 Family

These proteins show either pro-apoptotic (Bcl-2 and Bcl-x_L) or anti-apoptotic properties (Bax, Bad, Bid, Bnip3), primarily acting through the mitochondrial pathway. Upon hypoxia or mechanical stretch, both kinds of Bcl-2 family proteins were found to be induced during terminal chronic heart failure

Changes in Heme Oxygenase-1

Heme oxygenase-1 (HO-1, HSP 32) is a member of family of heat shock proteins induced by noxious stimuli.

Heme oxygenase-1 acts as a cell-protective and anti-apoptotically, which means its increased expression indicates increased cell stress.

In chronic heart failure, Heme oxygenase-1 is significantly increased in cardiomyocytes and, to a lesser extent, in arterial smooth muscle cells, endothelial cells and inflammatory cells

Changes in Metallothionein

Metallothionein is a cell stress protein involved in the inactivation of free reactive oxygen species.

Metallothionein expression is increased in chronic heart.

Changes in the Cytoskeletal Architecture

-Tubulin

Tubulin is clearly increased as compared to control tissue from normal human hearts while contractile filaments are reduced.

-Desmin

There is an increase and disorganization of desmin filaments seen in chronic heart failure, using immunocytochemistry. The irregular distribution of desmin and its mRNA by in situ hybridization in individual myocytes coincided with the occurrence of Z-line streaming and with a lack of contractile filaments.

-Membrane-associated proteins

These proteins are involved in fixation of sarcomeres to the lateral sarcolemma and stabilization of the T-tubular system.

Vinculin links the cell membrane and actin filaments via talin, paxillin and a-actinin. Dystrophin is part of a group of proteins (a protein complex) that work together to strengthen muscle fibers and protect them from injury as muscles contract and relax, while Spectrin maintains the plasma membrane integrity and cytoskeletal structure.

In failing human hearts vinculin is increased as are dystrophin, talin, and spectrin.

Data also indicate that some of these changes are found during the compensated stage of heart failure; whereas other changes are found during overt decompensation and are associated with changes in systolic and diastolic function.

The transition from compensated to decompensated heart failure is more than likely related to the overexpression of neurohormones and peptides such as norepinephrine, angiotensin II, and proinflammatory cytokines

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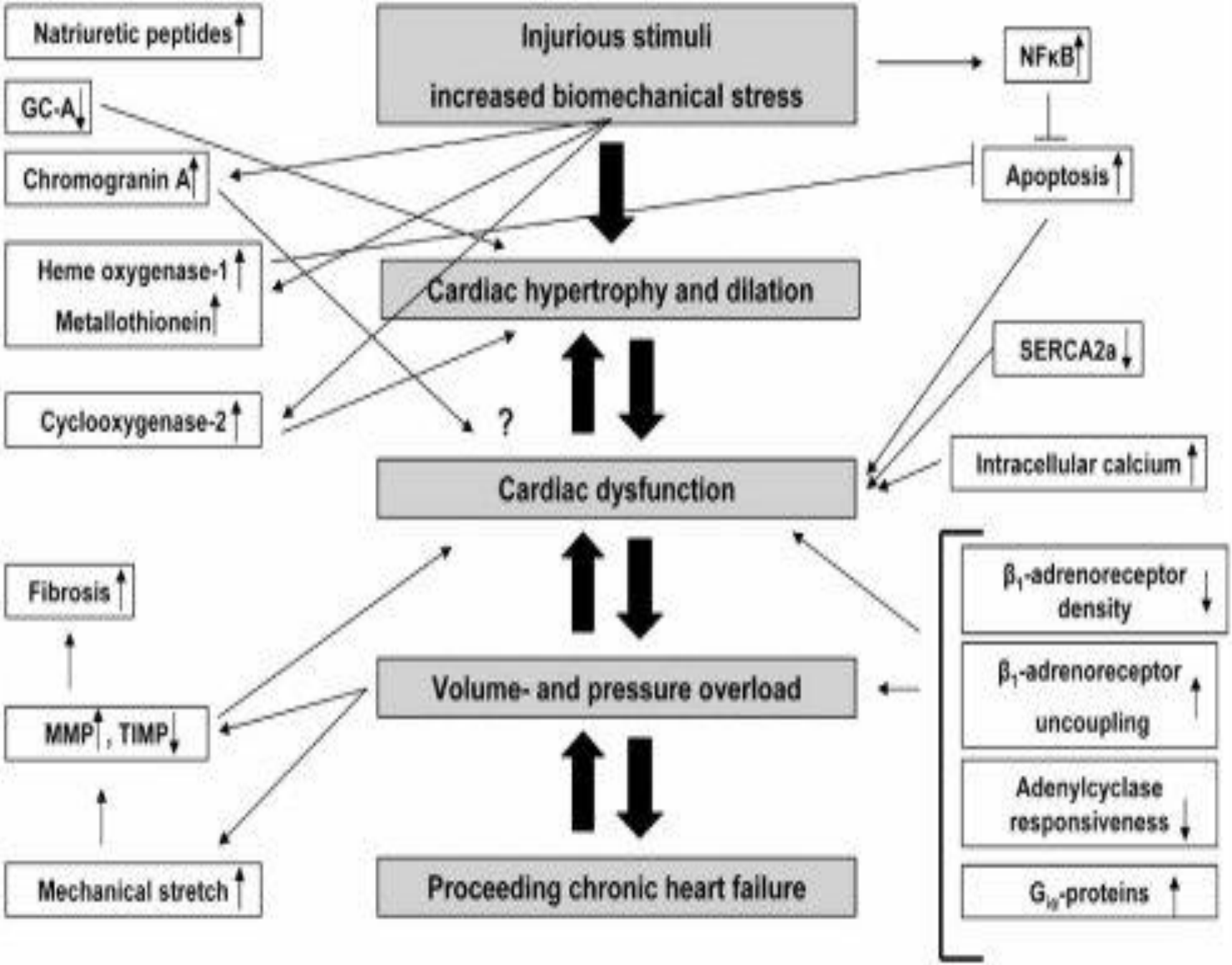
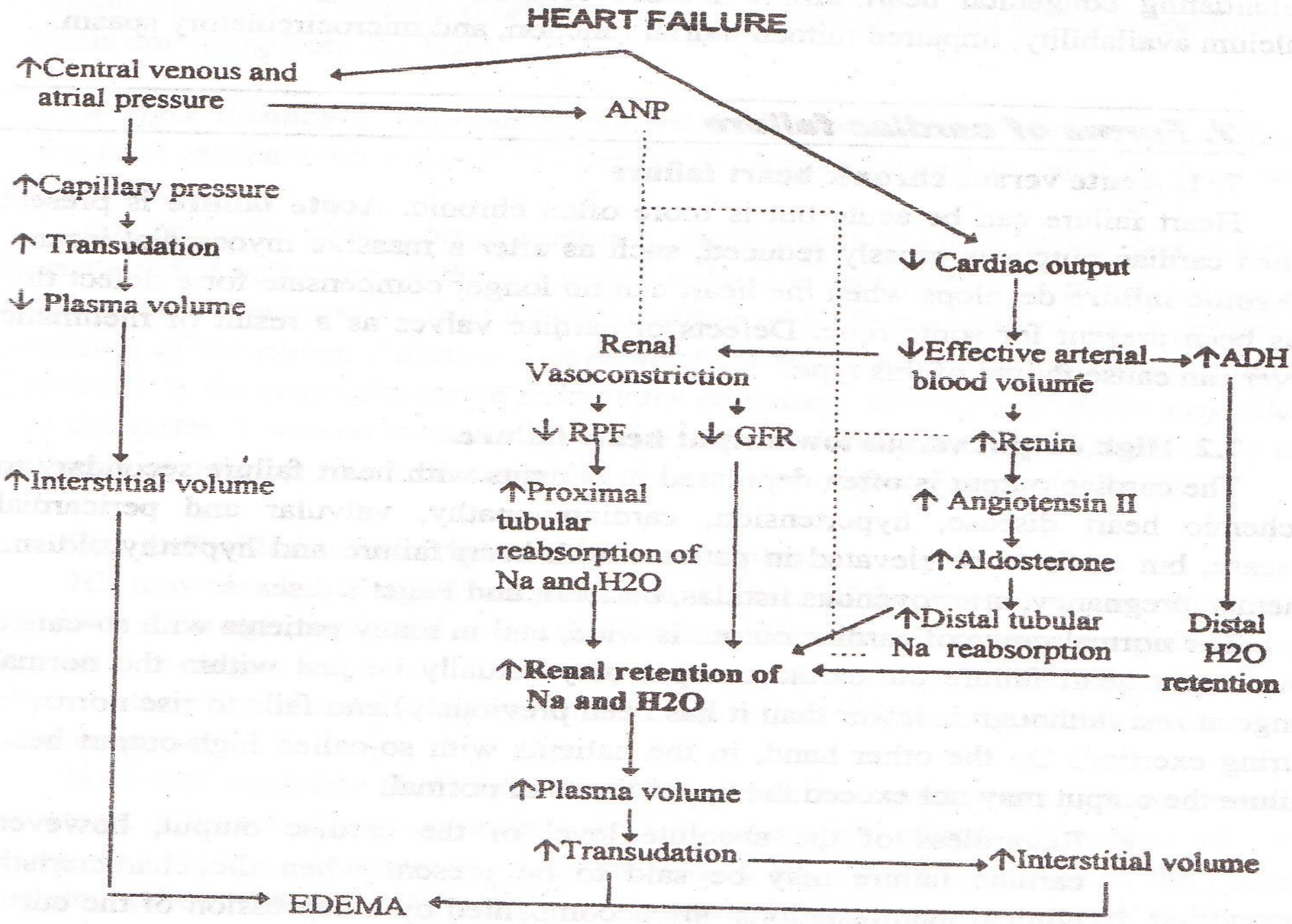

Natriuretic peptides
GC-A
Chromogranin A
Heme oxygenase-1
Metallothionein
Cyclooxygenase-2
Injurious stimuli
increased biomechanical stress
NFκB
Apoptosis
Cardiac hypertrophy and dilation
SERCA2a
?
Intracellular calcium
Cardiac dysfunction
Fibrosis
MMP, TIMP
Volume- and pressure overload
Mechanical stretch
Proceeding chronic heart failure
β1-adrenoreceptor density
β1-adrenoreceptor uncoupling
Adenylcyclase responsiveness
Gi-proteins


HEART FAILURE
↑Central venous and atrial pressure
ANP
↑Capillary pressure
↑ Transudation
↓ Plasma volume
↓ Cardiac output
Renal Vasoconstriction
↓Effective arterial blood volume
↑ADH
↓ RPF
↓ GFR
↑Renin
↑Interstitial volume
↑Proximal tubular reabsorption of Na and H2O
↑ Angiotensin II
↑Aldosterone
↑Distal tubular Na reabsorption
Distal H2O retention
↑Renal retention of Na and H2O
↑Plasma volume
↑Transudation
↑Interstitial volume
EDEMA


Thank you!