

# **Drug Therapy of Heart Failure**

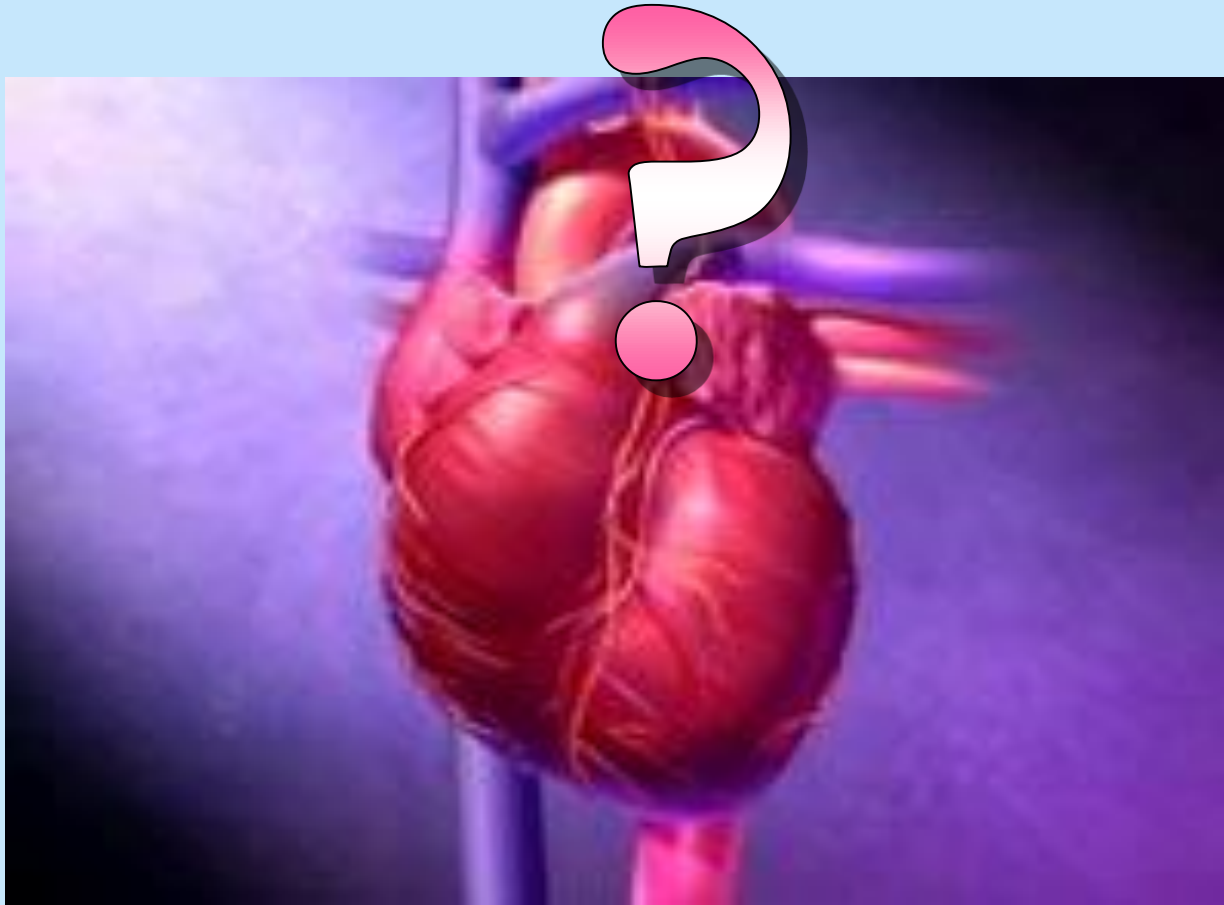
**Prof. Abdulrahman Almotrefi**

# Learning objectives

*By the end of this lecture, students should be able to:*

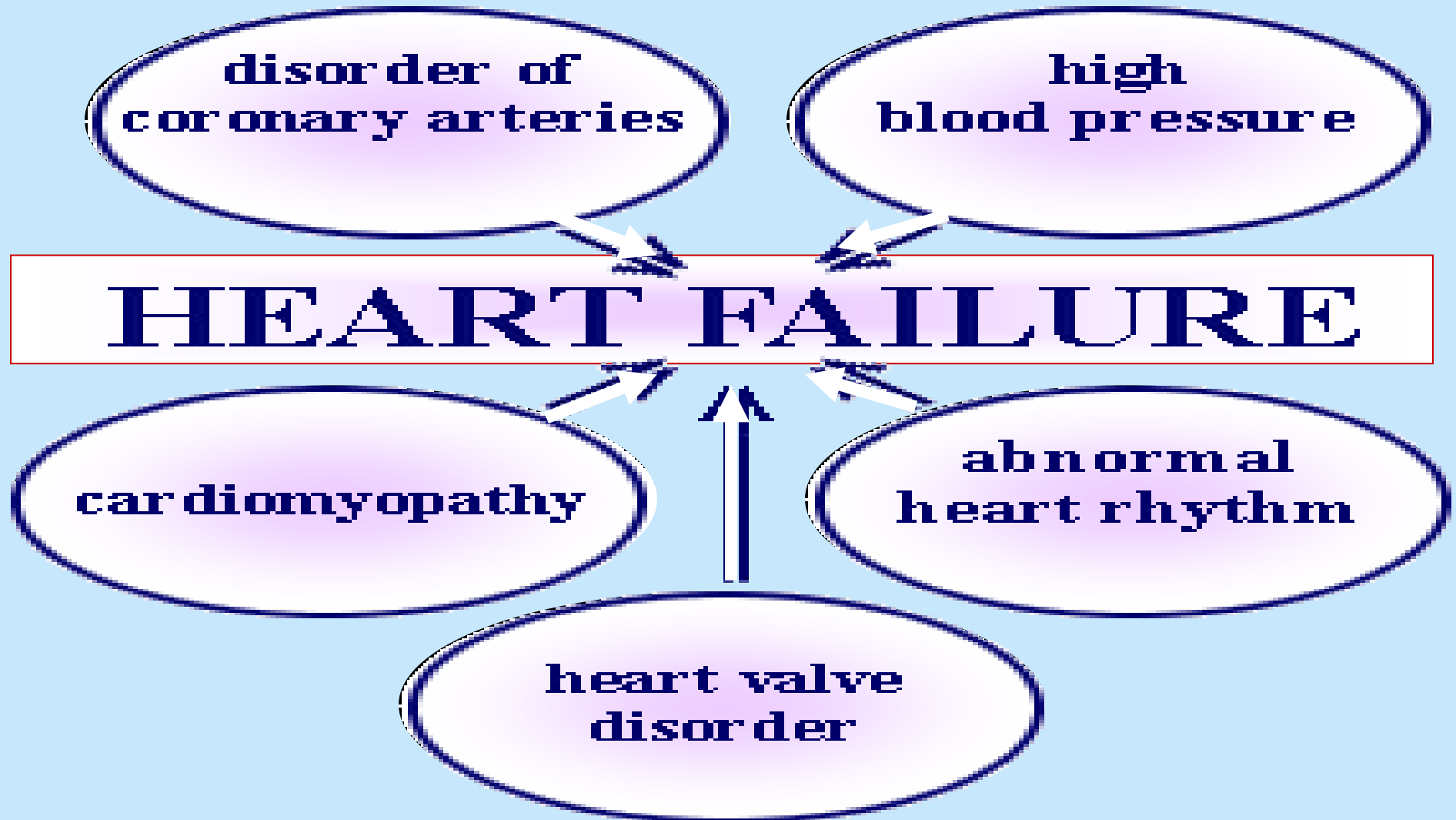
- **Describe** the different classes of drugs used for treatment of acute & chronic heart failure and their mechanism of action
- **Understand** their pharmacological effects, clinical uses, adverse effects and their interactions with other drugs

# HEART FAILURE



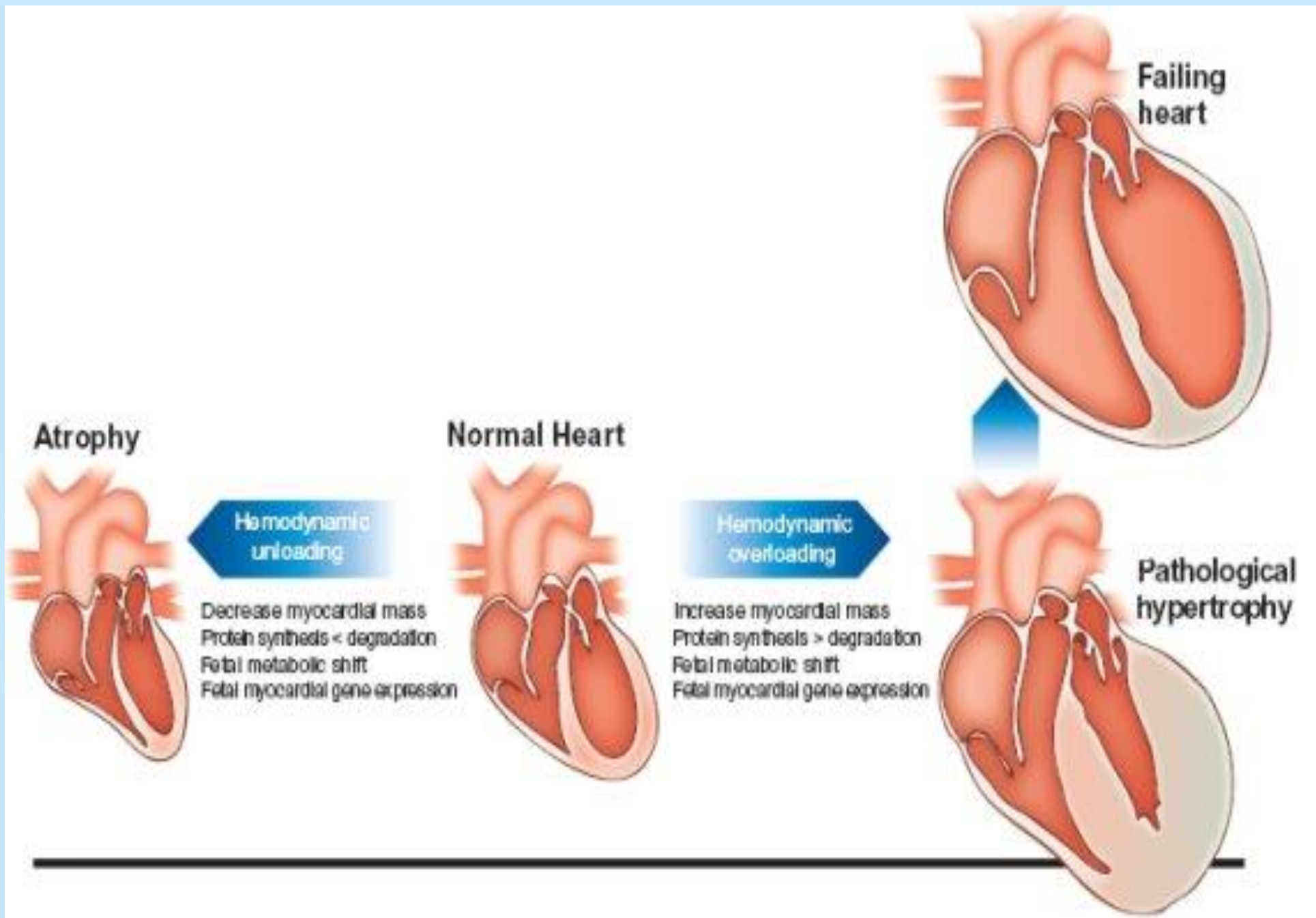
**Inability of the heart to maintain an adequate cardiac output to meet the metabolic demands of the body.**

# CAUSES OF HEART FAILURE



# Symptoms of Heart failure

- **Tachycardia**
- **Decreased exercise tolerance (rapid fatigue)**
- **Dyspnea ( pulmonary congestion )**
- **Peripheral edema**
- **Cardiomegaly**



# Pathophysiology of CHF

↓ Force of contraction

↓  
**Low C.O.**

↓ Renal blood flow

↓ Carotid sinus firing

**Activate renin-angiotensin-  
Aldosterone system**

**Activate sympathetic system  
↑ Sympathetic discharge**

ALDOST.

Ag. II

**Remodeling**

Salt & Water  
Retention

Volume expansion

**Vasoconstriction**

Venous VC

Arterial VC

↑ Force of  
Cardiac .cont.

↑ HR

↑ **Preload**

↑ **Preload**

↑ **Afterload**

# **Factors affecting cardiac output and heart failure**

**1- Preload**

**2- Afterload**

**3- Cardiac contractility**



# Drugs used in the treatment of heart failure

## I- Drugs that decrease preload

- 1 - Diuretics
- 2 - Aldosterone antagonists
- 3 - Venodilators

## II- Drugs that decrease afterload

- 1 - Arteriodilators

# Drugs used in the treatment of heart failure

## III- Drugs that decrease both preload & afterload ( Combined arteriolo- & venodilators )

- 1- Angiotensin converting enzyme (ACE) inhibitors
- 2- Angiotensin receptor antagonists
- 3-  $\alpha_1$ -adrenoceptor antagonists
- 4- Direct vasodilators

# Drugs used in the treatment of heart failure

## IV- Drugs that increase contractility

- 1- Cardiac glycosides (digitalis)
- 2-  $\beta$ - adrenoceptor agonists
- 3- Phosphodiesterase inhibitors

# I- Drugs that decrease preload

## 1-Diuretics:

**Mechanism of action in heart failure :**

**reduce salt and water retention**



**decrease ventricular preload and venous pressure**



**reduction of cardiac size**



**Improvement of cardiac performance**

# I- Drugs that decrease preload

## 1-Diuretics:

### Chlorothiazide

- first-line agent in heart failure therapy
- used in volume overload ( pulmonary and/ or peripheral edema )
- used in mild congestive heart failure

# I- Drugs that decrease preload

## 1-Diuretics:

### **Furosemide**

- a potent diuretic
- used for immediate reduction of pulmonary congestion & severe edema associated with :
  - acute heart failure
  - moderate & severe chronic failure

# I- Drugs that decrease preload

## 2-Aldosterone antagonists:

### **Spironolactone**

- nonselective antagonist of aldosterone receptor
- a potassium sparing diuretic used in congestive heart failure
- improves survival in advanced heart failure

### **Eplerenone**

- a new selective aldosterone receptor antagonists

# I- Drugs that decrease preload

## 3-Venodilators:

**Nitroglycerine**

**Isosorbide dinitrate**

- **used I.V. for severe heart failure when the main symptom is dyspnea due to pulmonary congestion**
- **dilates venous blood vessels and reduce preload**



# II- Drugs that decrease afterload

## 1- Arteriodilators:

### Hydralazine

- used when the main symptom is rapid fatigue due to low cardiac output
- reduce peripheral vascular resistance

### **III- Drugs that decrease both preload & afterload**

#### **1-Angiotensin converting enzyme (ACE) inhibitors:**

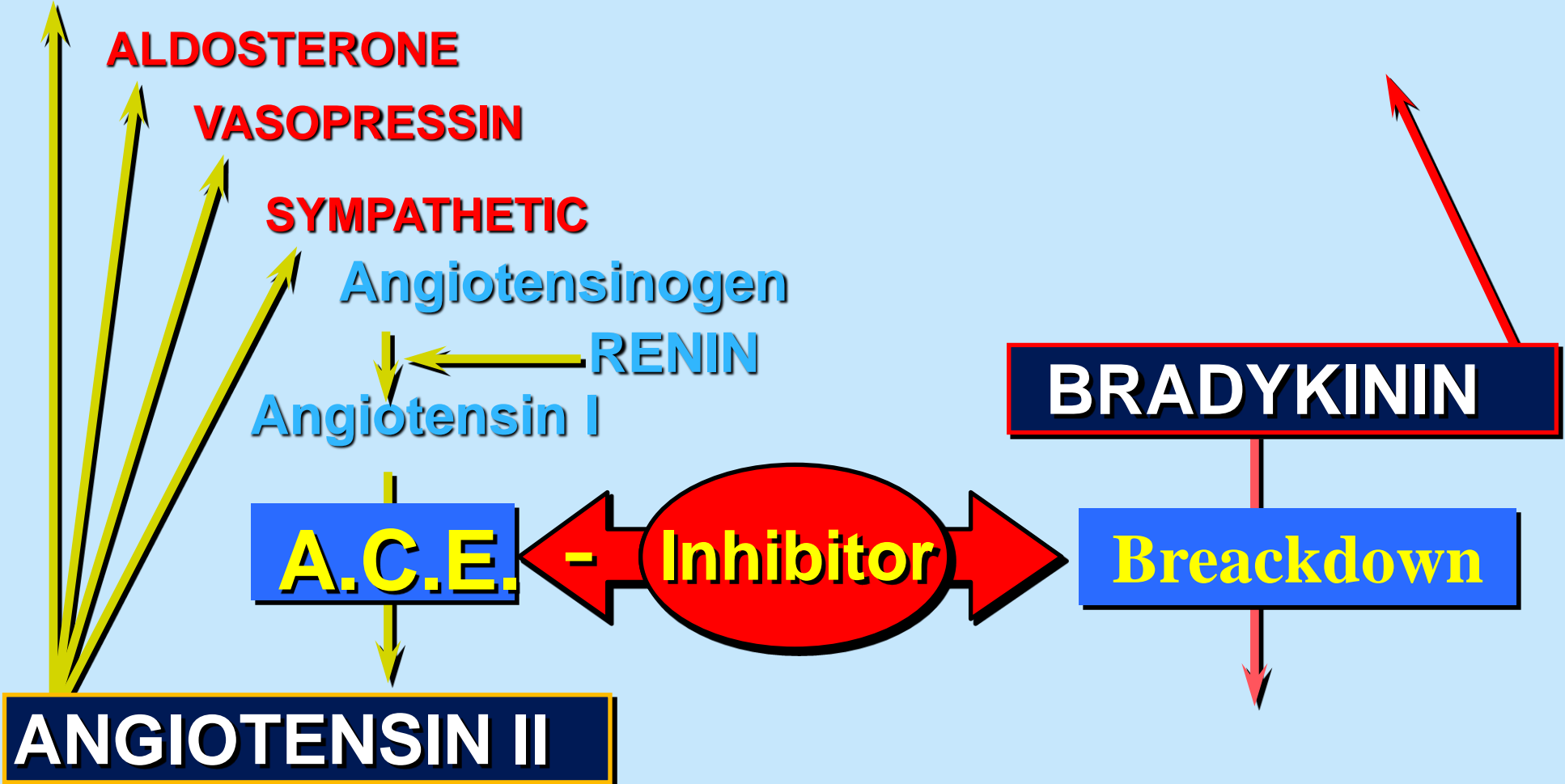
- are now considered as first-line drugs for chronic heart failure along with diuretics**
- first-line drugs for hypertension therapy**

# Angiotensin converting enzyme inhibitors

## MECHANISM OF ACTION

**VASOCONSTRICTION**

**VASODILATATION**



# ACE Inhibitors

## Pharmacokinetics:

### Captopril, Enalapril and Ramipril

- rapidly absorbed from GIT after oral administration.
- food reduce their bioavailability

### Enalapril , Ramipril

- prodrugs, converted to their active metabolites in the liver
- have long half-life & given once daily

### Enalaprilat

- the active metabolite of enalapril
- given I.V. in hypertensive emergency

# ACE Inhibitors

## Adverse effects:

- 1- acute renal failure, especially in patients with renal artery stenosis**
- 2- hyperkalemia, especially in patients with renal insufficiency or diabetes**
- 3- severe hypotension in hypovolemic patients (due to diuretics, salt restriction or gastrointestinal fluid loss)**

# ACE Inhibitors

## Adverse effects:

- 4- dry cough sometimes with wheezing
- 5- angioneurotic edema ( swelling in the nose , throat, tongue, larynx)
- 6- dysgeusia ( reversible loss or altered taste )

# ACE Inhibitors

## Contraindications:

- during the second and third trimesters of pregnancy  
( due to the risk of : fetal hypotension renal failure & malformations )
- renal artery stenosis

### **III- Drugs that decrease both preload & afterload**

#### **2- Angiotensin receptor blockers (ARBs) :**

**Losartan, Valsartan , Irbesartan**

#### **Mechanism of action:**

- block AT<sub>1</sub> receptors**
- decrease action of angiotensin II**



# Useful Effects of ACE Inhibitors & ARBs In Heart Failure

- 1 - Decrease peripheral resistance ( Afterload )
- 2 - Decrease Venous return ( Preload)
- 3 - Decrease sympathetic activity

(By blocking sympathetic nerve release & reuptake of norepinephrine)

4- Inhibit cardiac and vascular remodeling

associated with chronic heart failure



**Decrease in mortality rate**

## **III- Drugs that decrease both preload & afterload**

### **3- $\alpha$ -ADRENOCEPTOR BLOCKERS :**

#### **Prazosin**

- block  $\alpha$ - receptors in arterioles and venules**
- reduce blood pressure by decreasing both afterload & preload which help heart failure patients**

### **III- Drugs that decrease both preload & afterload**

#### **4- Direct acting vasodilators:**

##### **Sodium nitroprusside**

- given I.V. for acute or severe heart failure**
- acts immediately and effects lasts for 1-5 minutes**

## **IV- Drugs that increase contractility**

### **1- Cardiac glycosides ( digitalis) :**

#### **Digoxin**

#### **Pharmacological actions:**

#### **1- increase the force of myocardial contraction**

**( +ve inotropic effect )**



**increase left ventricle emptying**



**increase cardiac output**

## **IV- Drugs that increase contractility**

### **1- Cardiac glycosides ( digitalis ) :**

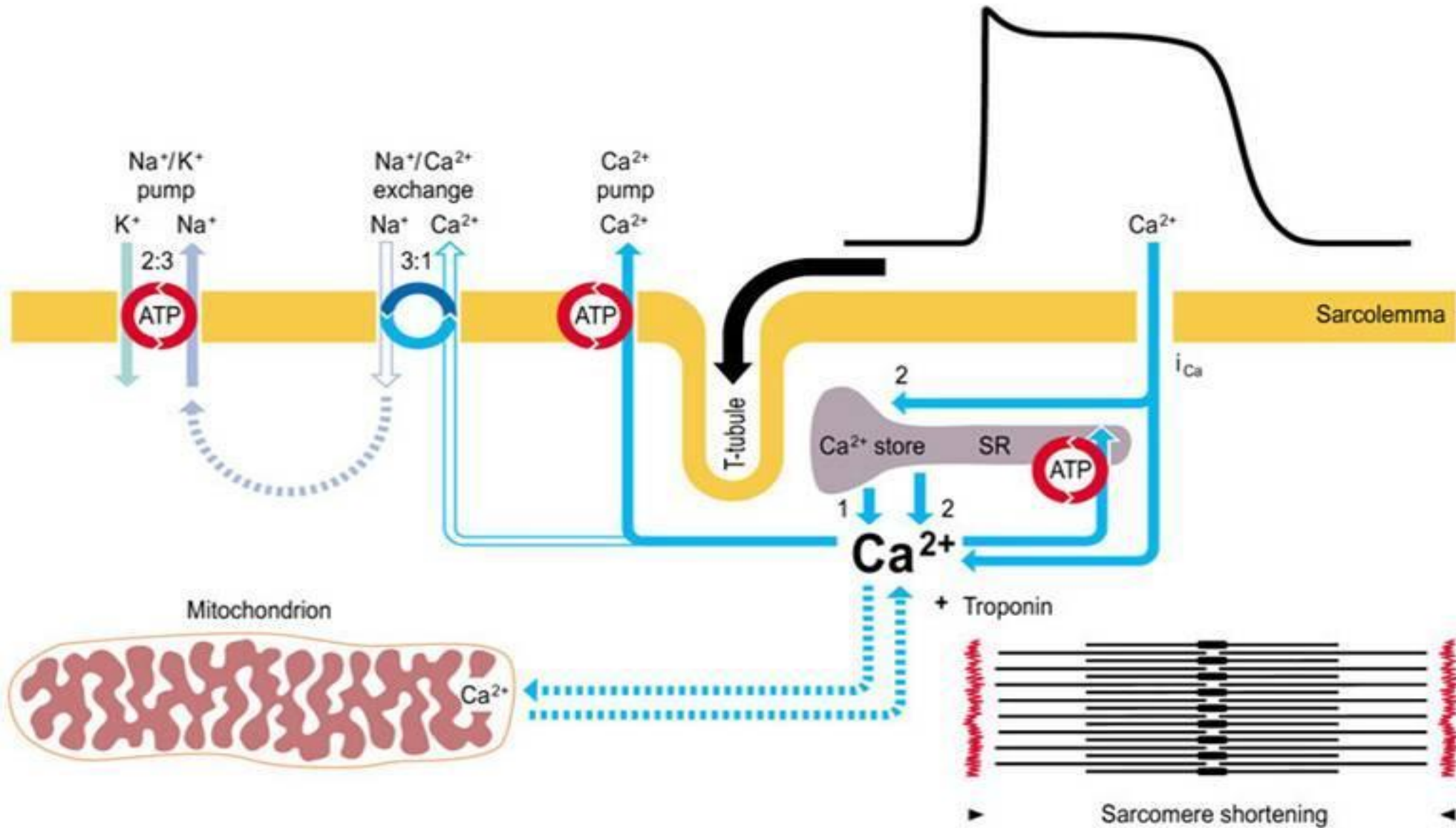
**Digoxin**

**2- Slow heart rate by vagal stimulation  
( -ve chronotropic effect )**

### **Mechanism of action :**

- Inhibit  $\text{Na}^+ / \text{K}^+$  ATPase enzyme  
( the sodium pump )**

# MECHANISM OF ACTION OF DIGOXIN



# IV- Drugs that increase contractility

## 1- Cardiac glycosides ( digitalis) :

### **Digoxin**

#### Therapeutic uses:

- Congestive heart failure
- Atrial arrhythmias:
  - Atrial flutter
  - Atrial fibrillation
  - Supraventricular tachycardia

## IV- Drugs that increase contractility

### 1- Cardiac glycosides ( digitalis) :

#### **Digoxin**

#### Pharmacokinetics of digoxin:

- has narrow therapeutic index
- oral absorption: 40-80% (**variable bioavailability**)
- 85% is excreted unchanged in the urine



## IV- Drugs that increase contractility

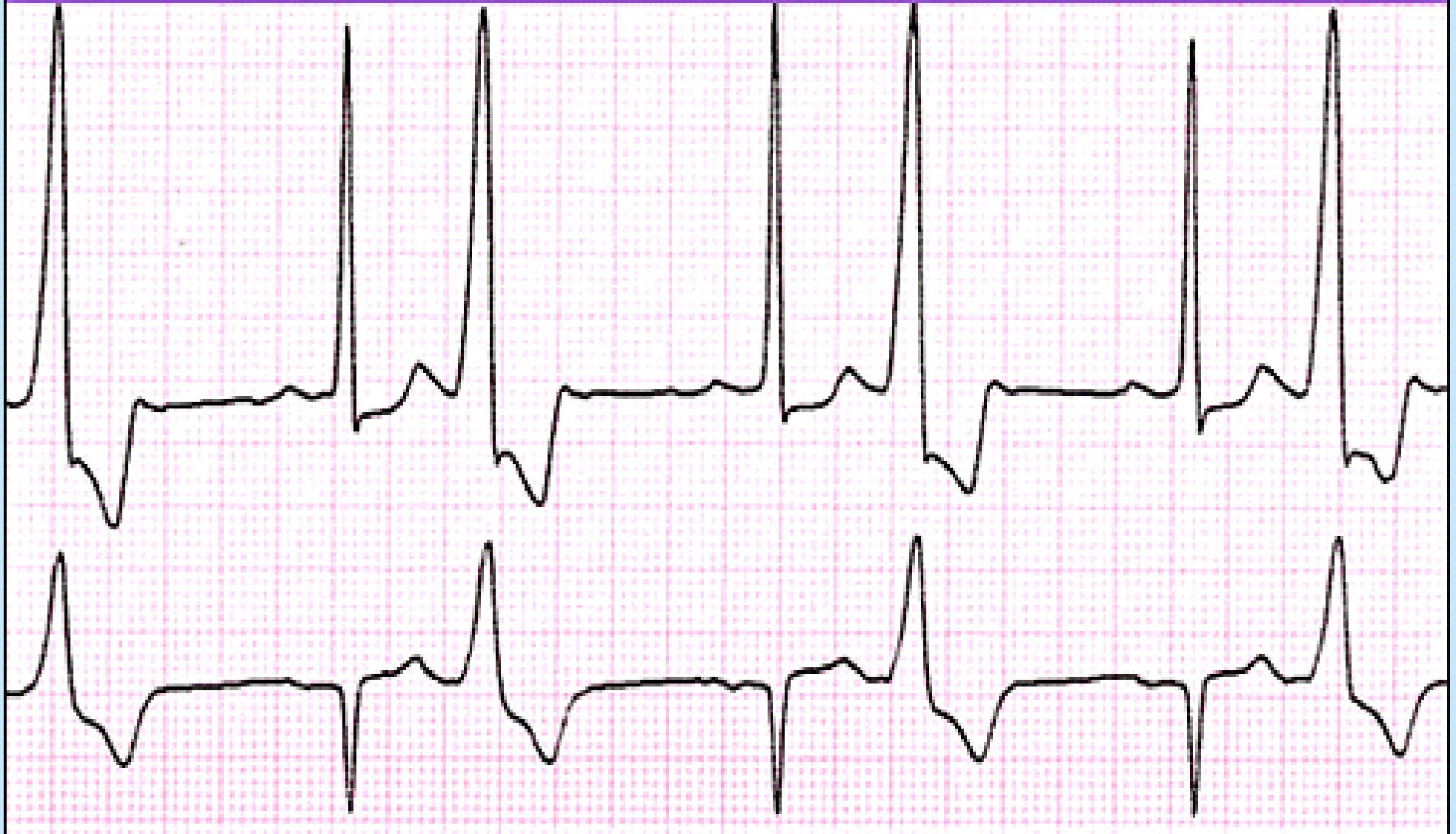
### 1- Cardiac glycosides ( digitalis) :

#### **Digoxin**

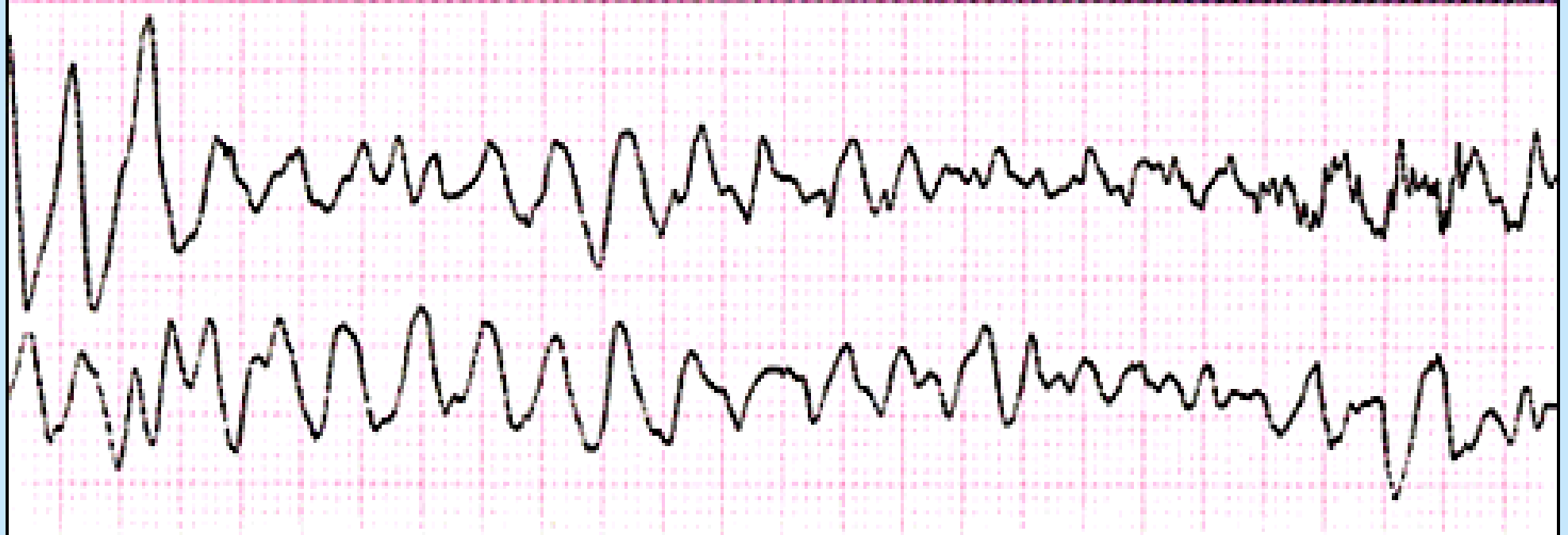
#### **Adverse effects (Cardiac):**

- digitalis-induced arrhythmias
  - extrasystoles
  - coupled beats (**Bigeminal rhythm**)
  - ventricular tachycardia or fibrillation
  - cardiac arrest

## Bigeminal PVC's: every other beat is a PVC.



## Ventricular Fibrillation



Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
300-600	Extremely irregular	Absent	N/A	Fibrillatory baseline

## **IV- Drugs that increase contractility**

### **1- Cardiac glycosides ( digitalis) :**

#### **Digoxin**

#### **Adverse effects (non-cardiac) :**

#### **GIT :**

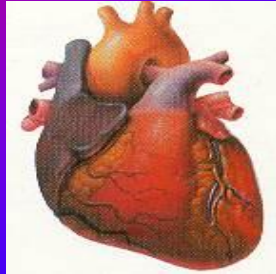
**anorexia ,nausea, vomiting, diarrhea  
( the earliest signs of toxicity )**

#### **CNS:**

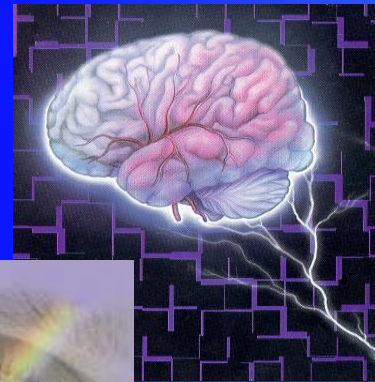
**headache, visual disturbances, drowsiness**

# Treatment OF ADVERSE EFFECTS

HEART



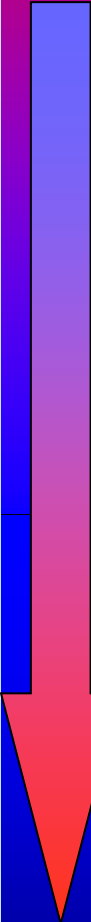
CNS



Vision



GIT



Digoxin , diuretic

- ◆ Atropine
- ◆ Antiarrythmics
- ◆ K supplements
- ◆ FAB fragment

## **IV- Drugs that increase contractility**

### **1- Cardiac glycosides ( digitalis) :**

#### **Digoxin**

#### **Factors that increase toxicity:**

- Renal diseases**
- Hypokalemia**
- Hypomagnesemia**
- Hypercalcemia**

## **IV- Drugs that increase contractility**

### **2- $\beta$ -Adrenoceptor agonists:**

#### **Dobutamine**

- **Selective  $\beta_1$  agonist**
- **Uses : Treatment of acute heart failure in cardiogenic shock**

## IV- Drugs that increase contractility

### 3- phosphodiesterase -III inhibitors:

**Amrinone & Milrinone**

#### Mechanism of action:

- Inhibit phosphodiesterase -III ( cardiac & B. Vessels)



inhibit cAMP degradation (↑ cAMP )



Increase cardiac  
Contractility



dilatation of arteries & veins  
(reduction of preload & afterload )



## IV- Drugs that increase contractility

### 3- phosphodiesterase -III inhibitors :

#### Therapeutic uses:

- **Milrinone** is the PDE-III inhibitor in clinical use
- used only intravenously for management of **acute heart failure**
- not safe or effective in the longer ( > 48 hours) treatment of patients with heart failure
- **Amrinone** not used now because it causes thrombocytopenia

## **IV- Drugs that increase contractility**

### **3- phosphodiesterase -III inhibitors :**

#### **Adverse effects:**

- nausea ,vomiting**
- thrombocytopenia**
- liver toxicity**
- Enoximone & vesnarinone are new drugs in clinical trials**

# The use of $\beta$ -adrenoceptor blockers in heart failure

- The elevated adrenergic activity in chronic heart failure patients cause structural remodeling of the heart (cardiac dilatation & hypertrophy)

## $\beta$ -blockers:

- reduce the progression of chronic heart failure
- not used in acute heart failure

# The use of $\beta$ -adrenoceptor blockers in heart failure

## Mechanism of action:

### $\beta$ -blockers:

- 1- attenuate cardiac remodeling
- 2- slow heart rate, which allows the left ventricle to fill more completely
- 3- decrease renin release



**reduce mortality & morbidity of patients with HF**

# The use of $\beta$ -adrenoceptor blockers in heart failure

## $\beta$ -blockers:

- **Second generation:**

cardioselective (  $\beta_1$ -receptors )

e.g. **Bisoprolol, Metoprolol**

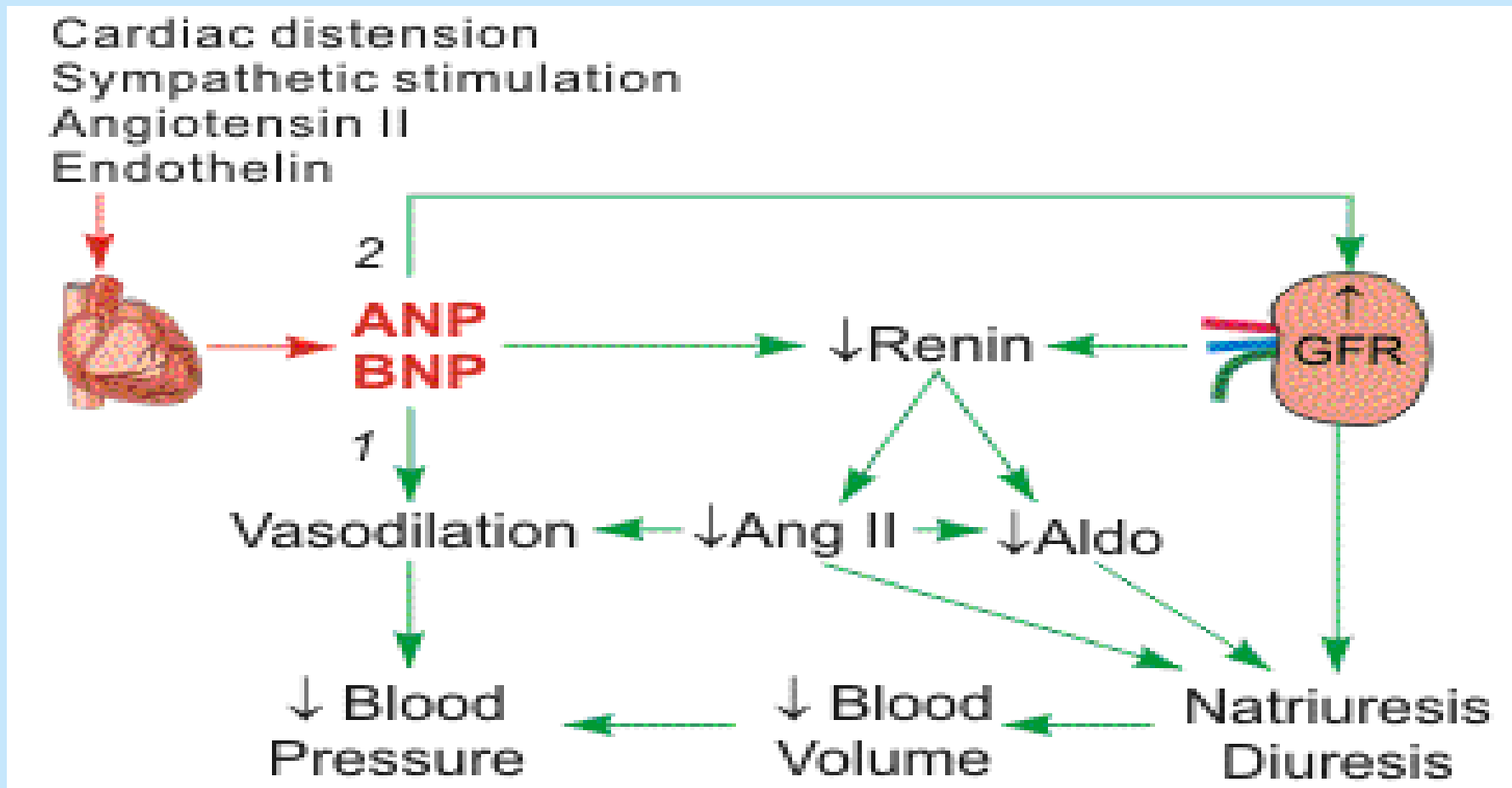
- **Third generation:**

have vasodilator actions (  $\alpha$ - blocking effect)

e.g. **Carvedilol , Nebivolol**

# Natriuretic Peptides

- BNP is secreted by the ventricular myocardium in response to stretch
- elevated BNP is associated with advanced heart failure ( **compensatory mechanism in HF** )



# Natriuretic Peptides

## Nesiritide

- **purified preparation of human BNP, manufactured by recombinant DNA technology**
- **increases cyclic-GMP in vascular smooth muscle, leading to smooth muscle relaxation, & reduction of preload and afterload**
- **indicated for the treatment of patients with acutely decompensated heart failure who have dyspnea at rest or with minimal activity**

# Management of chronic heart failure

- **Reduce work load of the heart**
  - **Limit patient activity**
  - **Reduce weight**
  - **Control hypertension**
- **Restrict sodium**
- **Stop smoking**



# Heart Failure Functional Classification

NYHA Class	Symptoms
I	<b>Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.</b>
II	<b>Mild symptoms (mild shortness of breath and/or angina), slight limitation during ordinary activity.</b>
III	<b>Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.</b>
IV	<b>Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.</b>

# Management of chronic heart failure

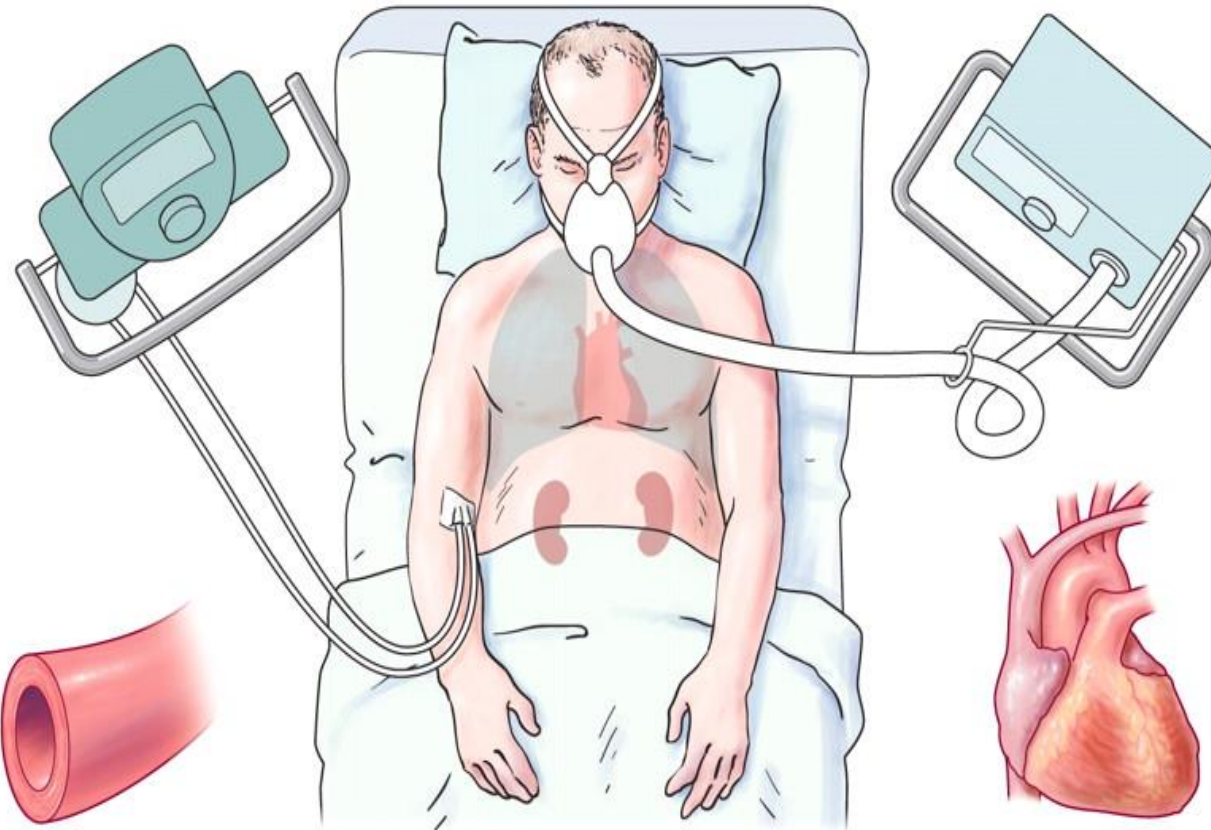
	For Survival/Morbidity	For Symptoms
NYHA I	Continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI add beta-blocker if post-MI	reduce / stop diuretic
NYHA II	ACE inhibitor as first-line treatment/ARB if ACE inhibitor intolerant add beta-blocker and aldosterone antagonist if post MI	+/- diuretic depending on fluid retention
NYHA III	ACE inhibitor plus ARB or ARB alone if ACE intolerant beta-blocker add aldosterone antagonist	+ diuretics + digitalis If still symptomatic
NYHA IV	Continue ACE inhibitor/ARB beta-blocker Aldosterone antagonist	+diuretics + digitalis + consider temporary inotropic support

# Use of vasodilators

## hydralazine and isosorbide dinitrate :

- should be considered black patients with advanced heart failure due to left ventricular systolic dysfunction in addition to standard therapy.
- should be considered patients who are intolerant of an angiotensin converting enzyme inhibitor and an angiotensin II receptor blocker due to renal dysfunction

# Management of acute heart failure



**Ultrafiltration:**  
*Aqua/natriuresis*

**Bilevel or continuous positive airway pressure:**  
*Preload reduction*

**Nitrates, nitroprusside, dobutamine:**  
*Arterial vasodilation*

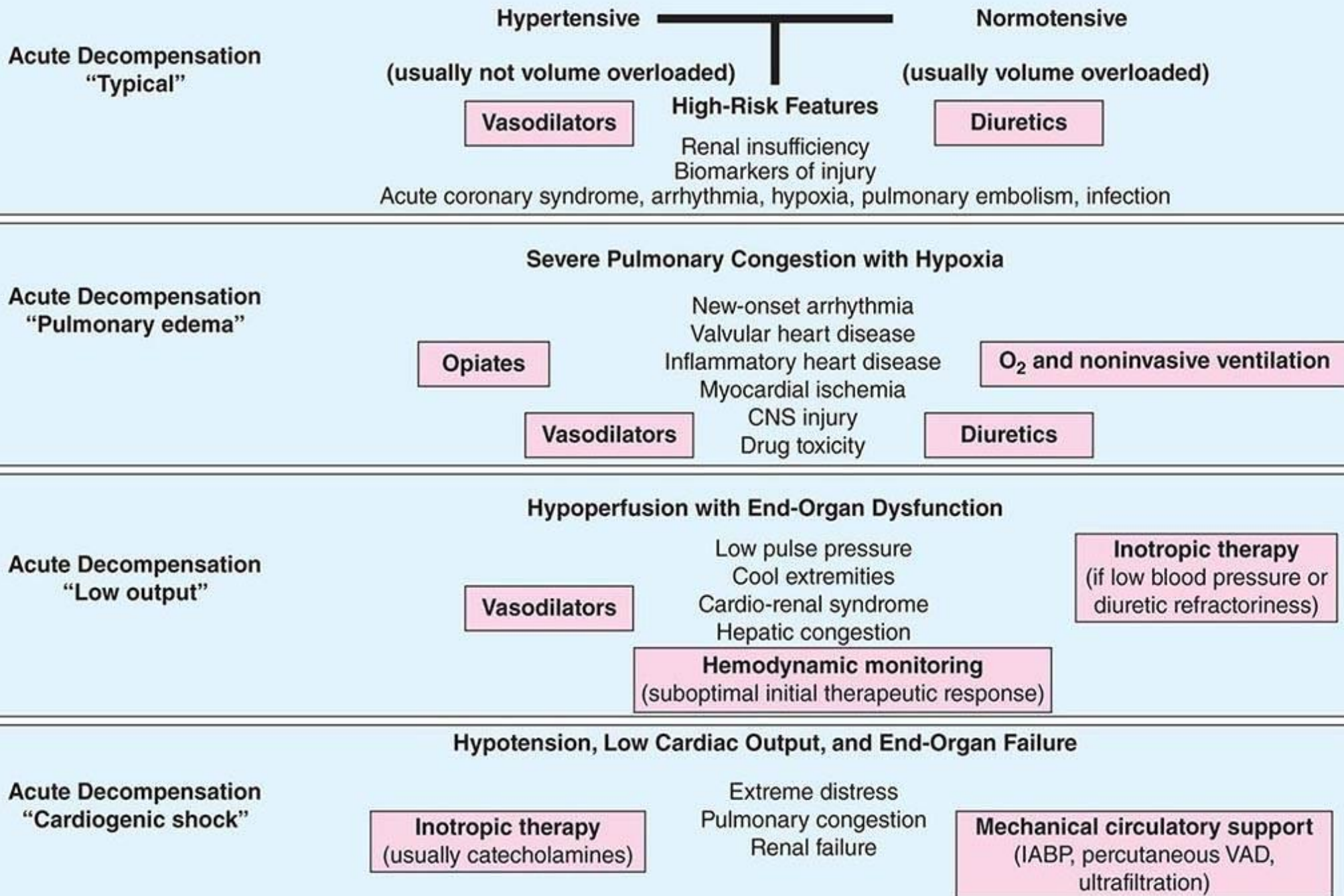
**Dobutamine, dopamine, milrinone:**  
*Increased inotropy*

**Nitrates, morphine:**  
*Venodilation*

**Furosemide:**  
*Natriuresis*



# Heterogeneity of ADHF: Management Principles





**Thank you**

