

Drug Therapy Of Heart Failure

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Assistant Professor

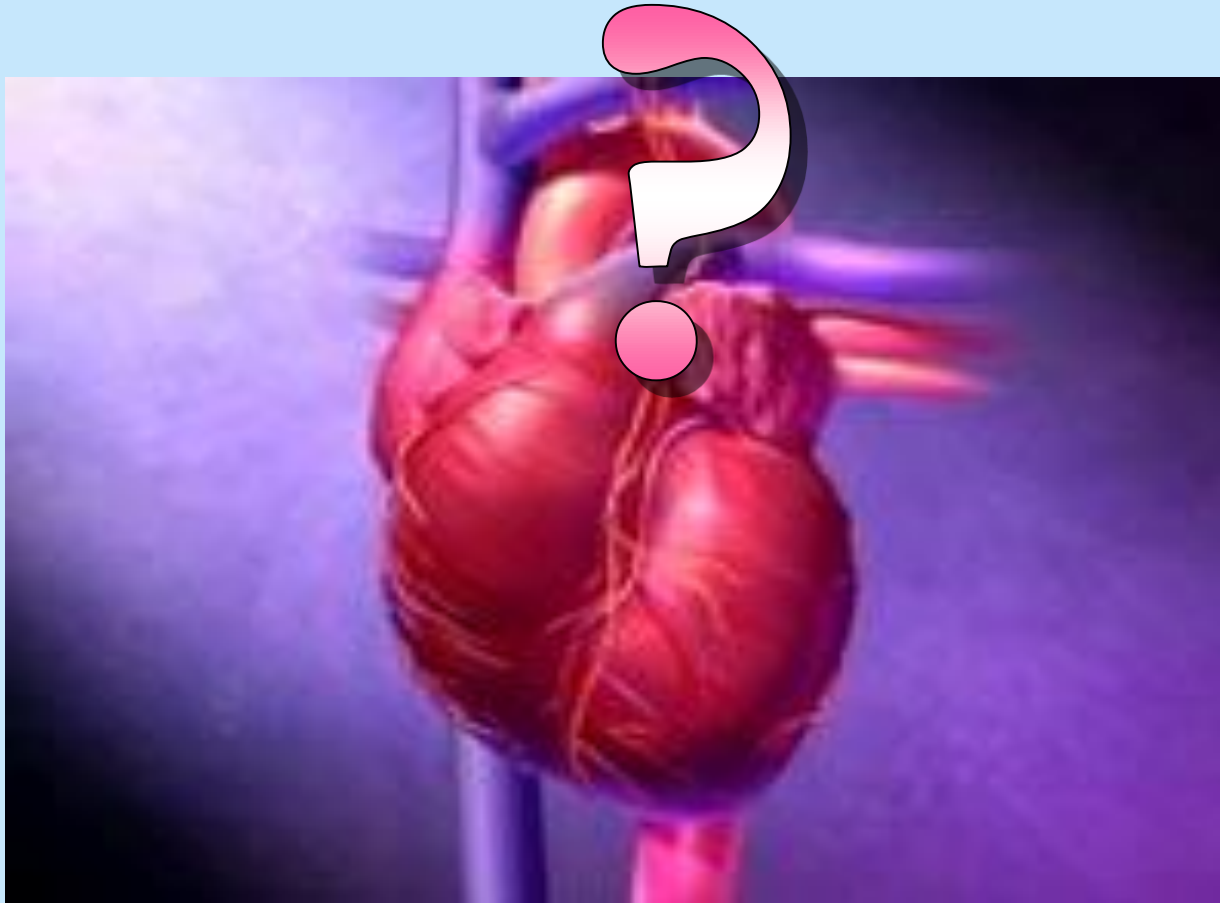
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Learning objectives

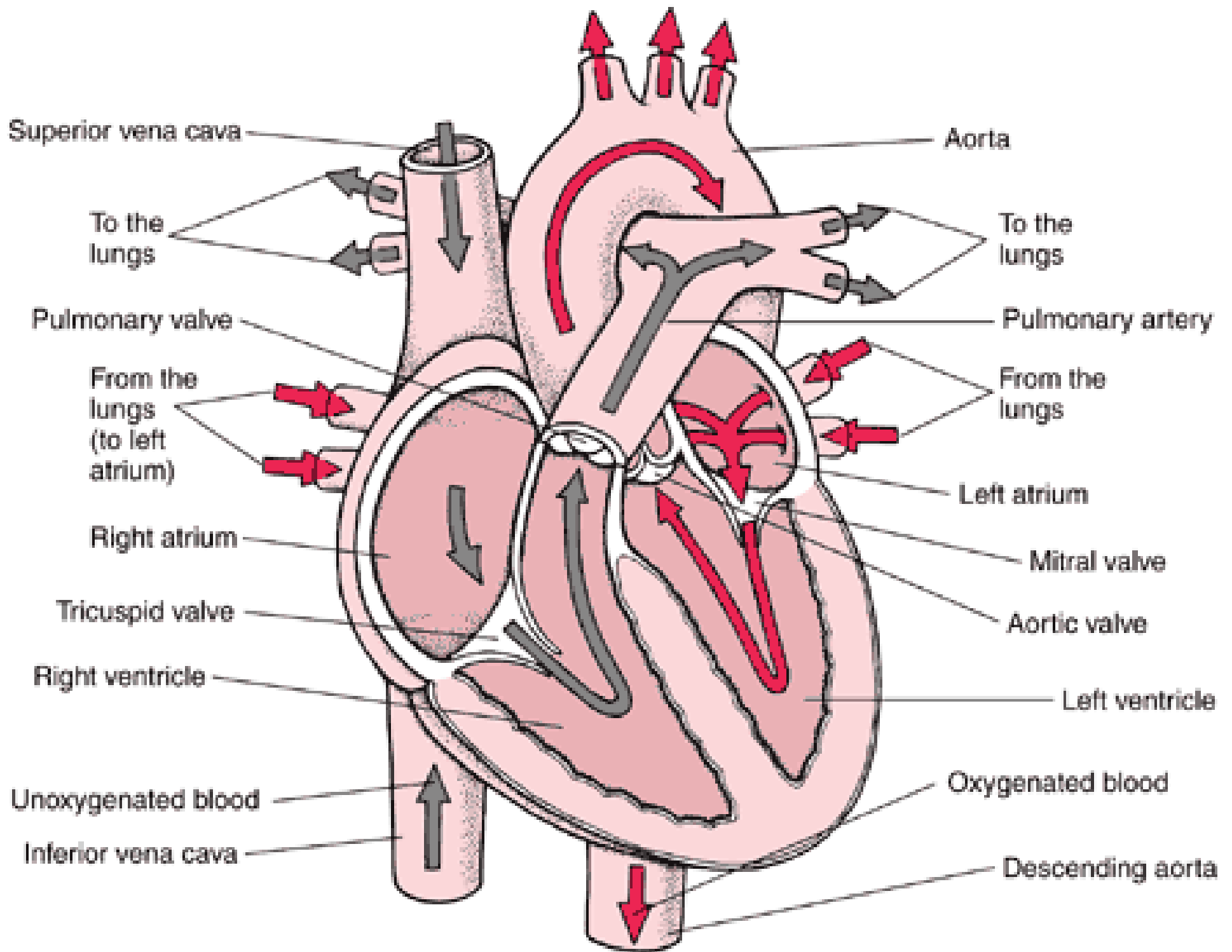
By the end of this lecture, students should be able to:

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

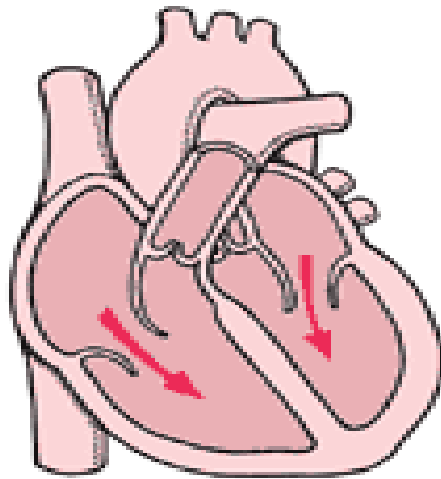


Normal

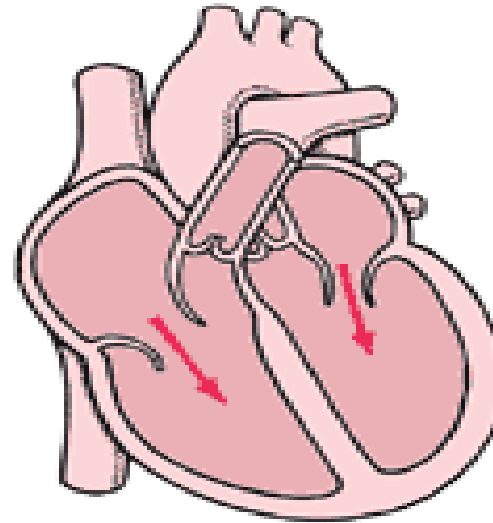
Systolic Dysfunction

Diastolic Dysfunction

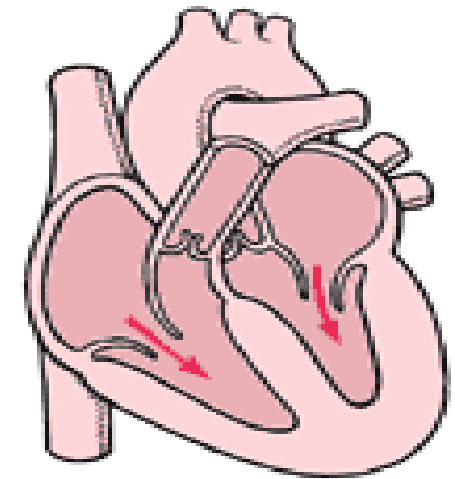
Diastole
(filling)



The ventricles fill normally with blood.

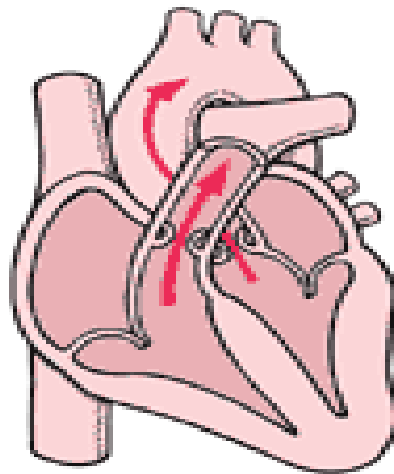


The enlarged ventricles fill with blood.

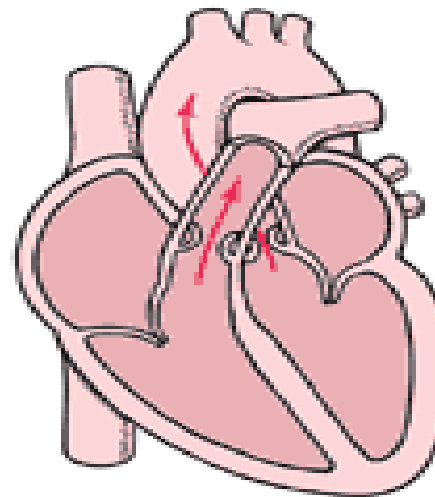


The stiff ventricles fill with less blood than normal.

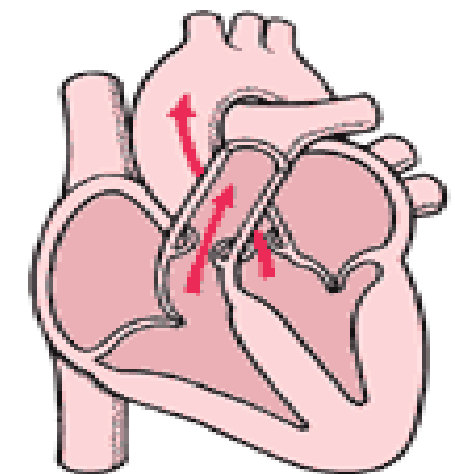
Systole
(pumping)



The ventricles pump out about 60% of the blood.



The ventricles pump out less than 40 to 50% of the blood.

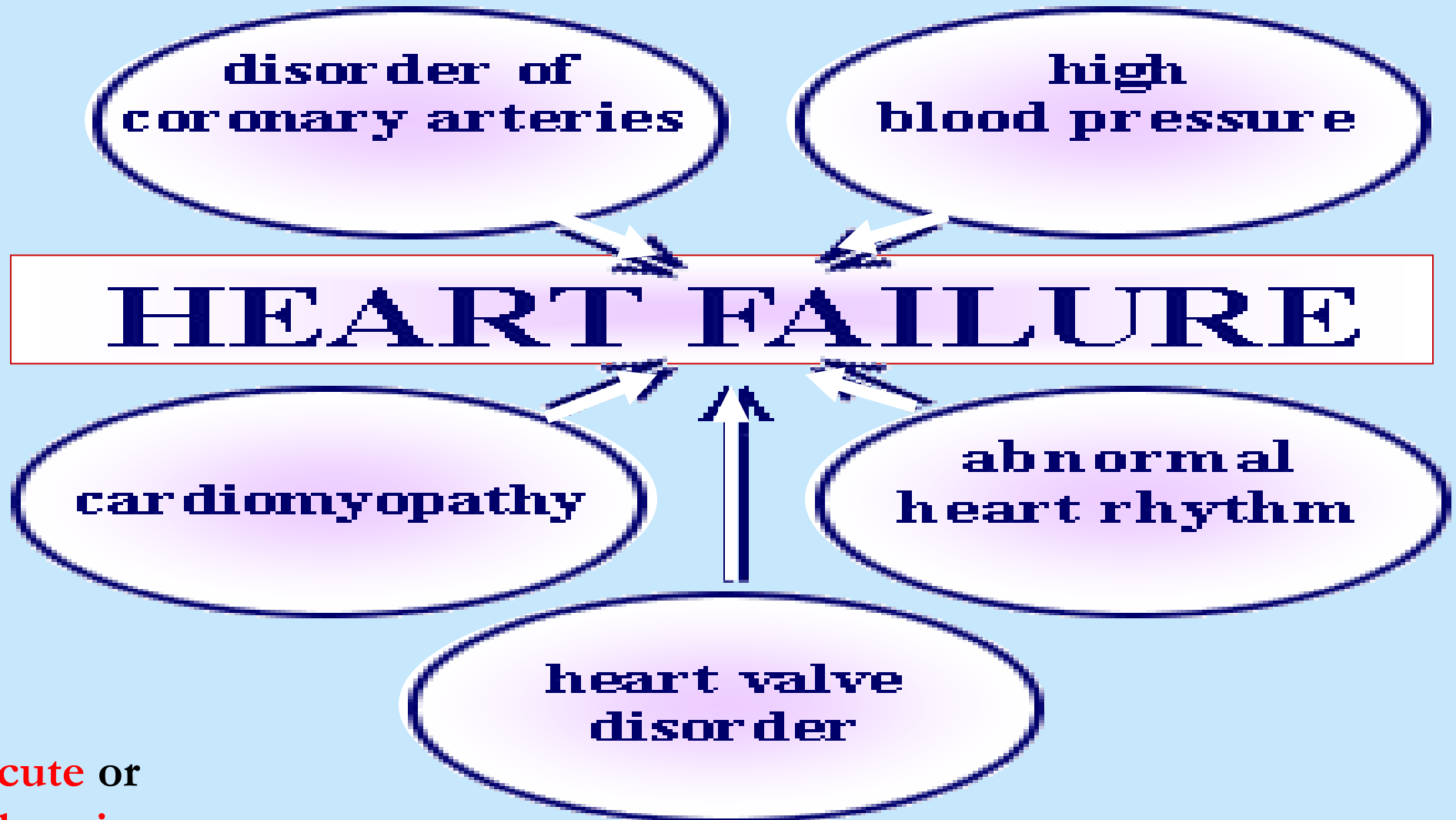


The ventricles pump out about 60% of the blood, but the amount may be lower than normal.

Heart Failure Classification

- The severity of heart failure is usually described according to a scale devised by the **New York Heart Association (NYHA)**:
 - **Class I failure**: no limitations in activities; symptoms occur only with greater than ordinary exercise.
 - **Class II**: slight limitation of ordinary activities- which result in fatigue and palpitations.
 - **Class III**: no symptoms at rest, but fatigue, etc., with less than ordinary physical activity.
 - **Class IV**: symptoms even when the patient is at rest.

CAUSES OF HEART FAILURE



Acute or
Chronic

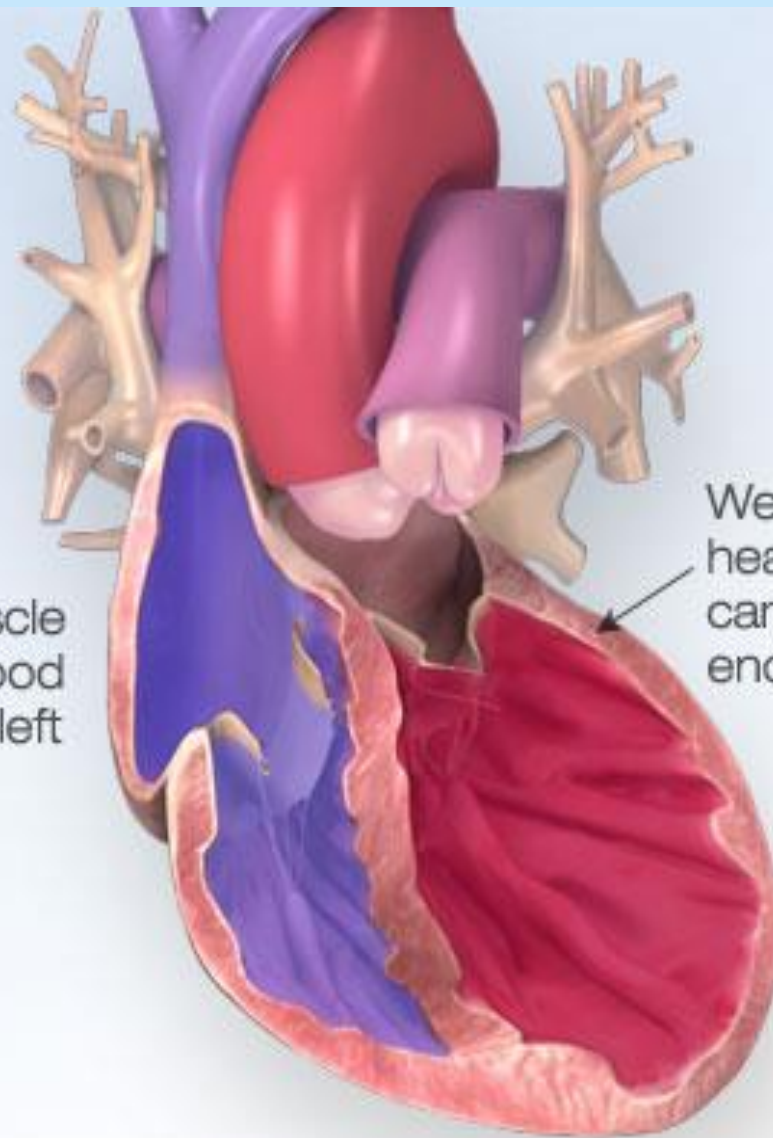
Symptoms of Heart failure

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



Heart muscle pumps blood out of the left ventricle.

Normal Heart



Weakened heart muscle cannot pump enough blood.

Heart Failure

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

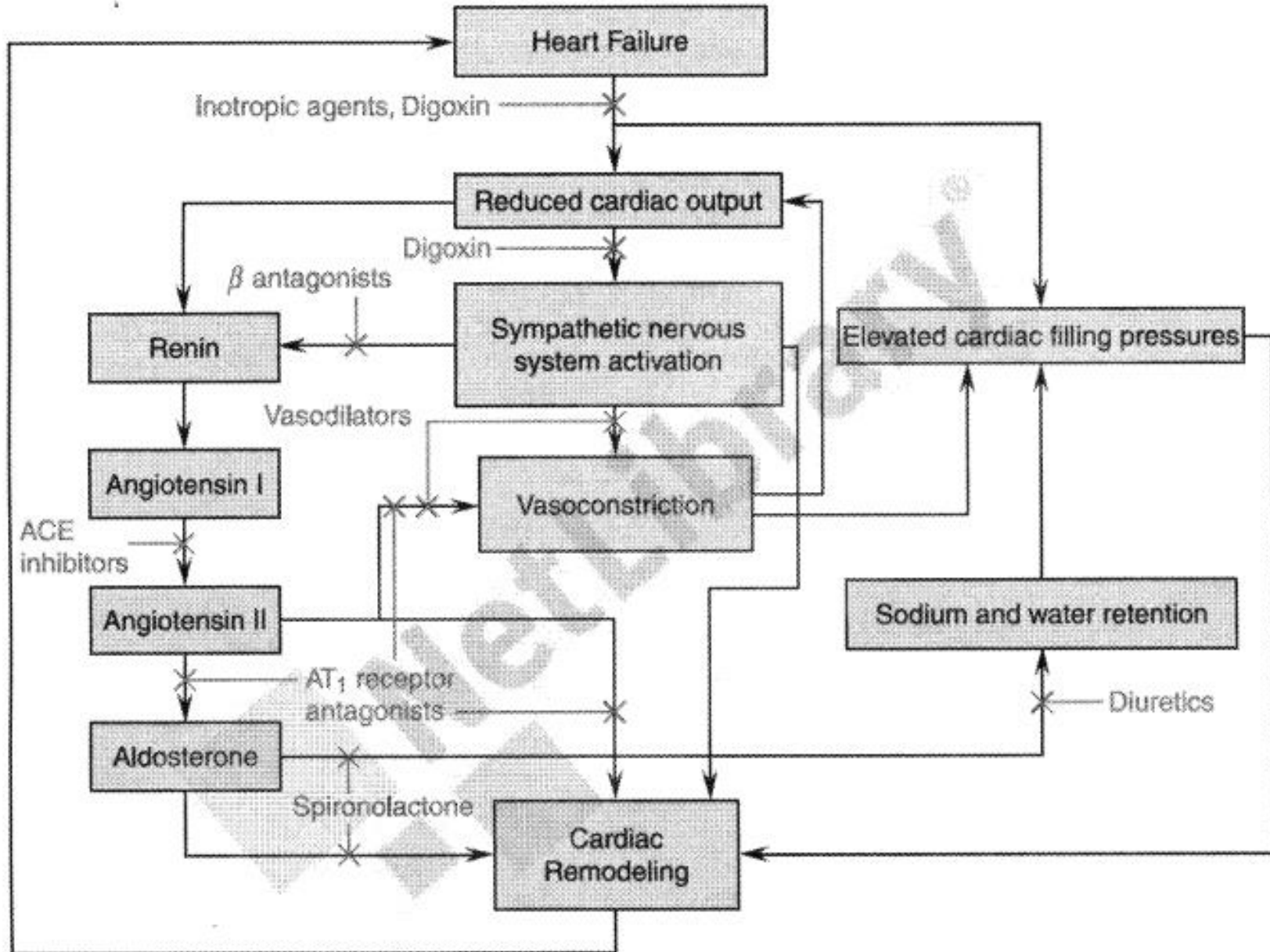
Factors affecting cardiac output and heart failure

1- Preload

2- Afterload

3- Cardiac contractility

Site of Drug Action



Drugs used in 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 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- α_1 -adrenoceptor antagonists
- 4- Direct vasodilators

Drugs used in treatment of heart failure

IV- Drugs that increase heart contractility:

- 1- **Cardiac glycosides (digitalis)**
- 2- **β - 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



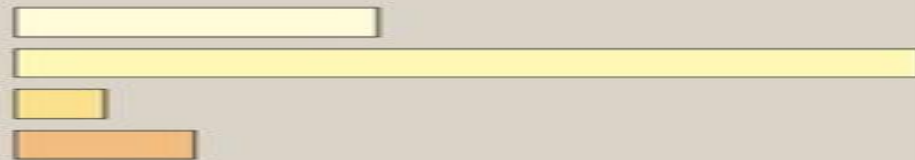
Improvement of cardiac performance

KEY

- Thiazide diuretics
- Loop diuretics
- K⁺-sparing diuretics
- Acetazolamide



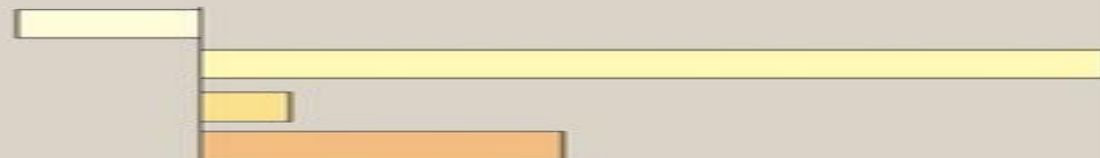
Na⁺ excretion



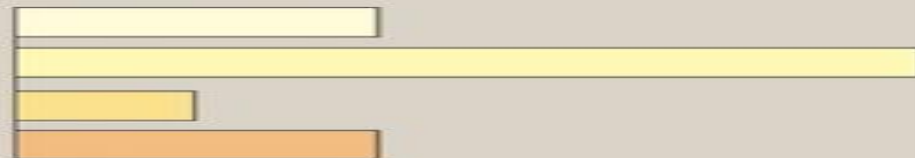
K⁺ excretion



Ca²⁺ excretion



Volume of urine



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

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

2-Aldosterone antagonists:

Spironolactone

- non-selective antagonist of aldosterone receptor
- a potassium sparing diuretic
- improves survival in advanced heart failure

I- Drugs that decrease preload

2-Aldosterone antagonists:

Eplerenone

- a new selective aldosterone receptor antagonist

(does not inhibit other hormones such as estrogens & androgens)

- indicated to improve survival of stable patients with congestive heart failure.

I- Drugs that decrease preload

3-Venodilators:

A- Nitroglycerine

B- Isosorbide dinitrate

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

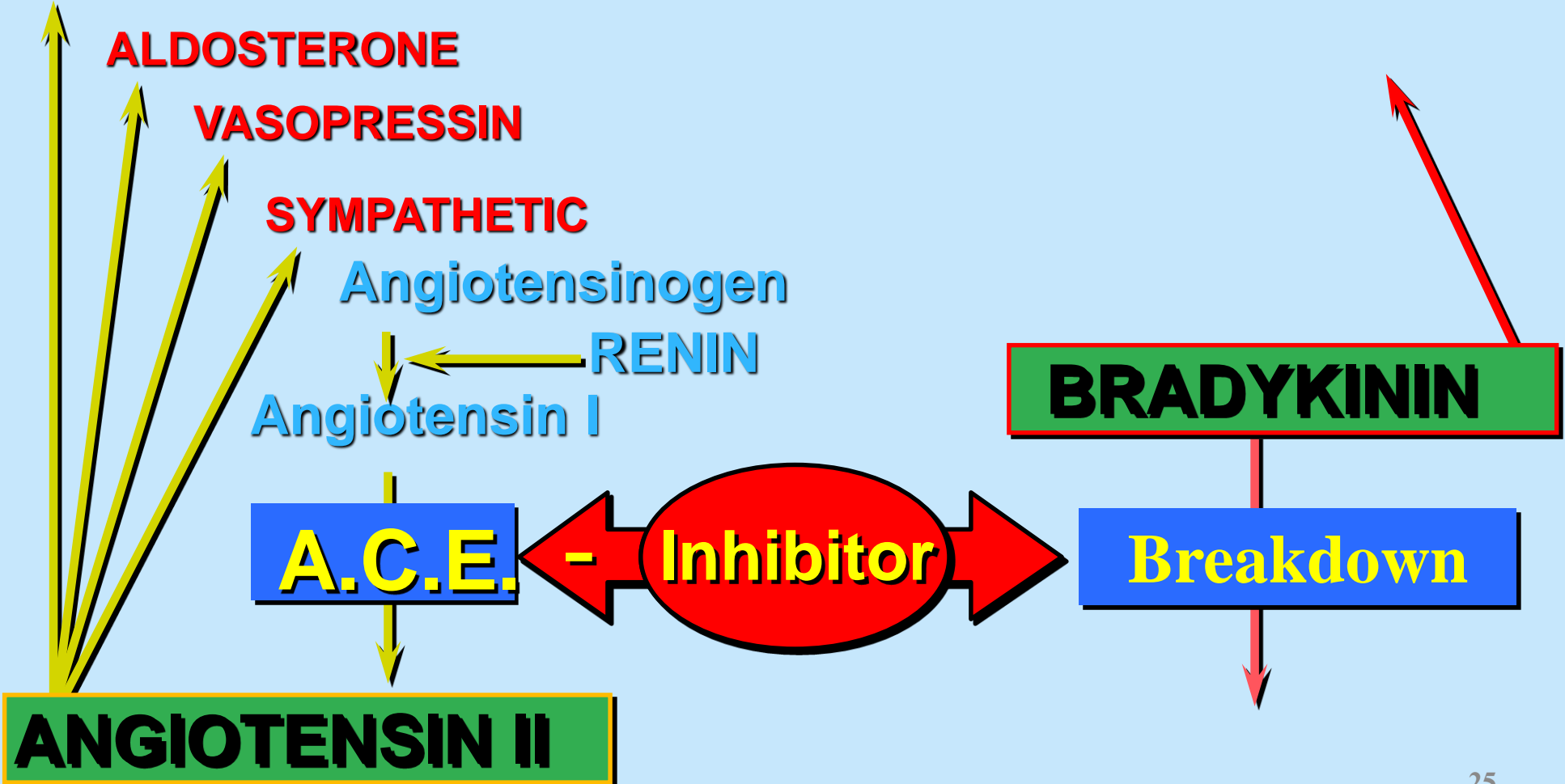
- considered as first-line drugs for chronic heart failure along with diuretics**
- first-line drugs for hypertension therapy.**

Angiotensin converting enzyme inhibitors

MECHANISM OF ACTION

VASOCONSTRICTION

VASODILATATION



ACE Inhibitors

Pharmacological actions:

- 1 - Decrease peripheral resistance (Afterload)
- 2 - Decrease Venous return (Preload)
- 3 - Decrease sympathetic activity
- 4- Inhibit cardiac and vascular remodeling
associated with chronic heart failure



Decrease in mortality rate

ACE Inhibitors

Captopril, Enalapril and Ramipril

Pharmacokinetics:

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

Enalapril , Ramipril

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

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 & 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 AT₁ receptors**
- decrease action of angiotensin II**

III- Drugs that decrease both preload & afterload

3- α -ADRENOCEPTOR BLOCKERS :

Prazosin

- blocks α - receptors in arterioles and venules**
- decrease both afterload & preload**

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 min.

IV- Drugs that increase contractility

1- Cardiac glycosides (digitalis) :

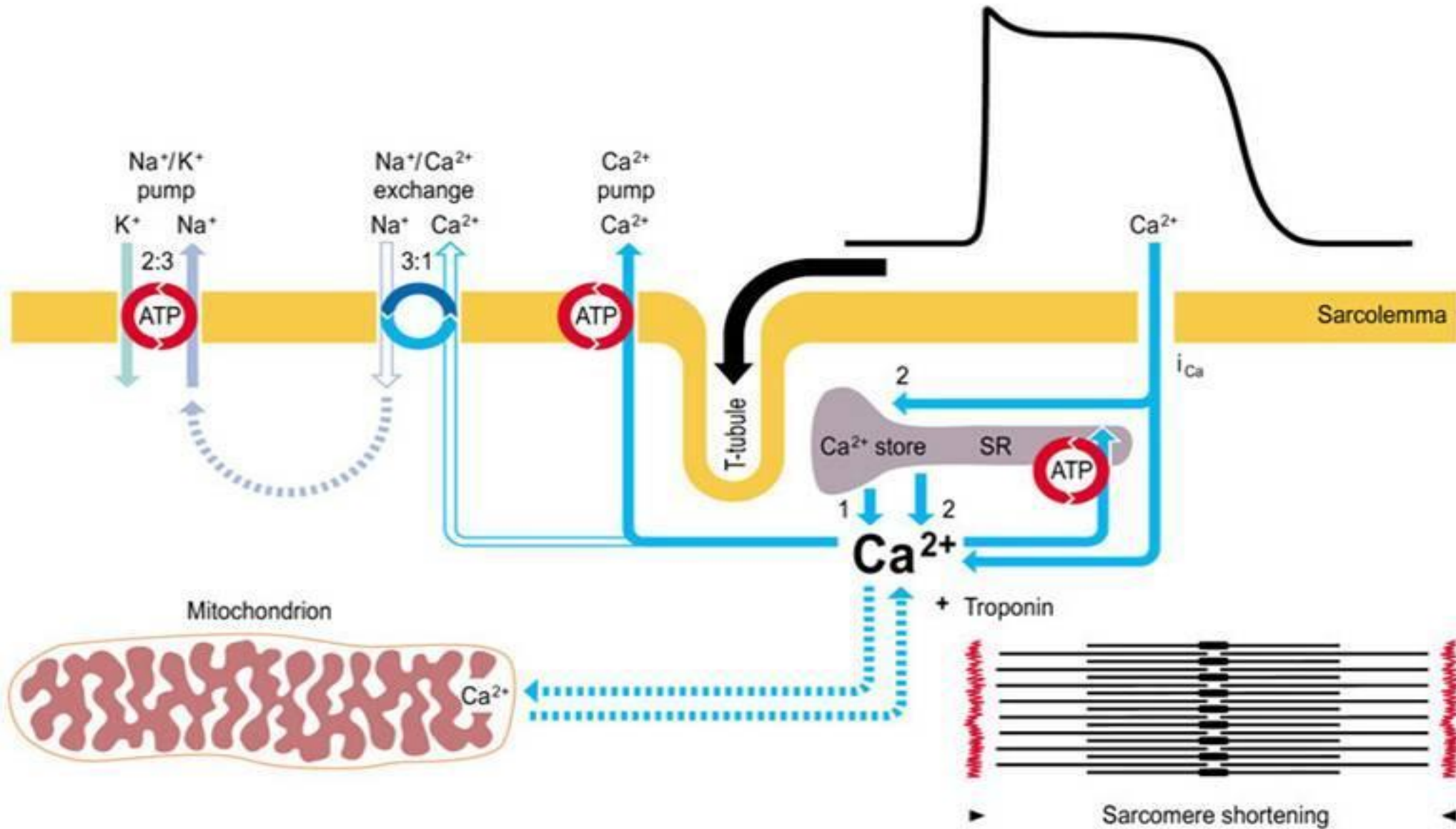
Digoxin

- increases the force of myocardial contraction
(+ve inotropic effect)

Mechanism of action :

- Inhibit Na^+ / 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
- has narrow therapeutic index

IV- Drugs that increase contractility

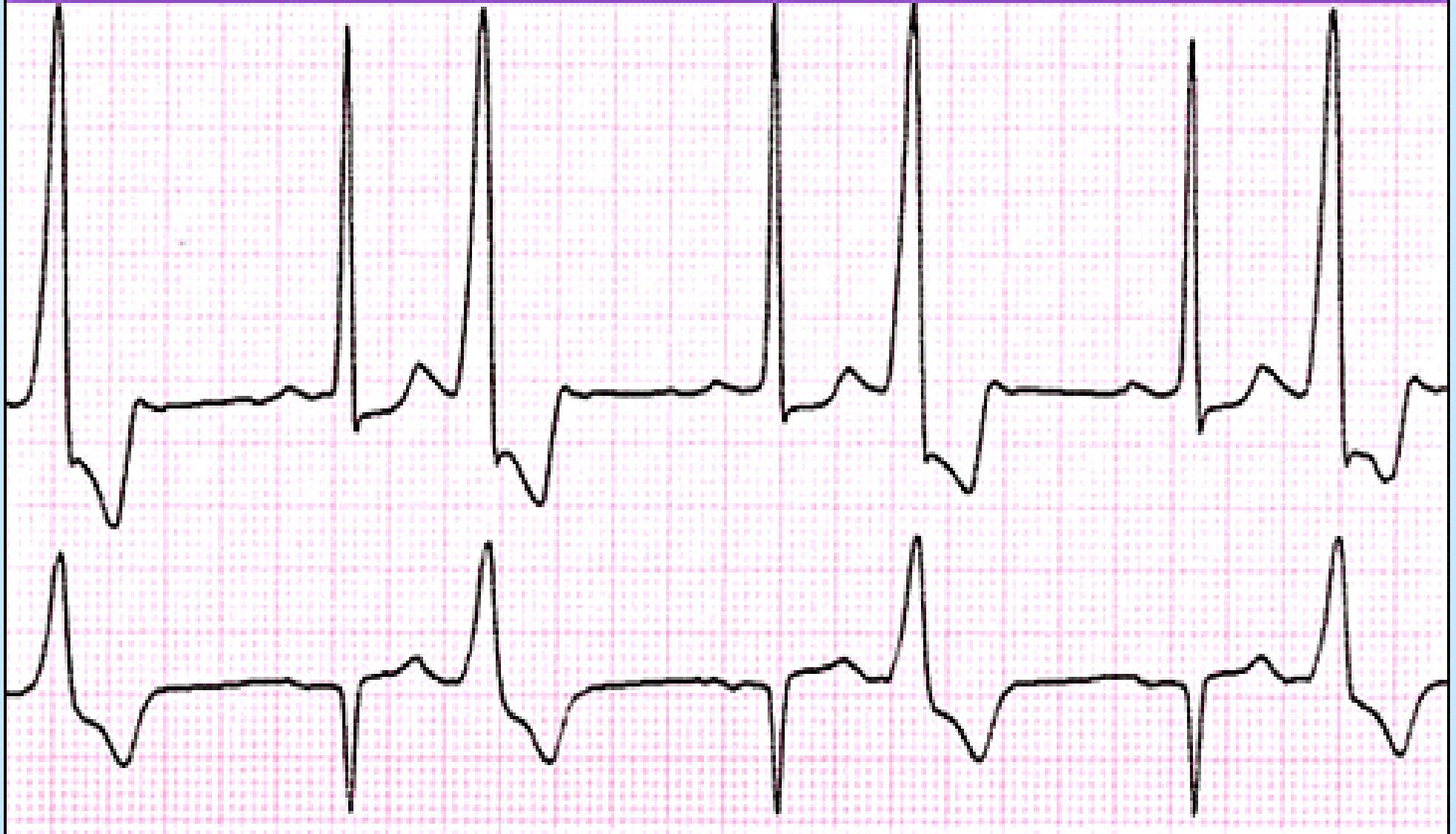
1- Cardiac glycosides (digitalis) :

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.



IV- Drugs that increase contractility

1- Cardiac glycosides (digitalis):

Digoxin

Adverse effects (non-cardiac):

GIT:

anorexia, nausea, vomiting, diarrhea

CNS:

headache, visual disturbances, drowsiness.

IV- Drugs that increase contractility

1- Cardiac glycosides (digitalis) :

Digoxin

Factors that increase its toxicity:

- Renal diseases
- Hypokalemia
- Hypomagnesemia
- Hypercalcemia

IV- Drugs that increase contractility

2- β -Adrenoceptor agonists:

Dobutamine

- **Selective β_1 agonist**
- **Uses : Treatment of acute heart failure in cardiogenic shock**

IV- Drugs that increase contractility

3- phosphodiesterase -III inhibitors:

Milrinone

Mechanism of action:

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



Increase cardiac
Contractility



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

IV- Drugs that increase contractility

3- phosphodiesterase -III inhibitors :

Milrinone

Therapeutic uses:

- used only IV for management of
acute heart failure
- not safe or effective in the longer (> 48 hours)
treatment of patients with heart failure

IV- Drugs that increase contractility

3- phosphodiesterase -III inhibitors :

Milrinone

Adverse effects:

- Hypotension and chest pain (angina)

Chemical interaction:

- furosemide should not be administered in I.V. lines containing milrinone due to formation of a precipitate

- **Enoximone & Vesnarinone**
new drugs in clinical trials.

The use of β -adrenoceptor blockers in heart failure

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

β -blockers:

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

The use of β -adrenoceptor blockers in heart failure

Mechanism of action of β -blockers in HF:

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 β -adrenoceptor blockers in heart failure

- Second generation:

cardioselective (β_1 -receptors)

e.g. **Bisoprolol, Metoprolol**

- Third generation:

β_1 -receptors blocker & have vasodilator actions
(α - blocking effect)

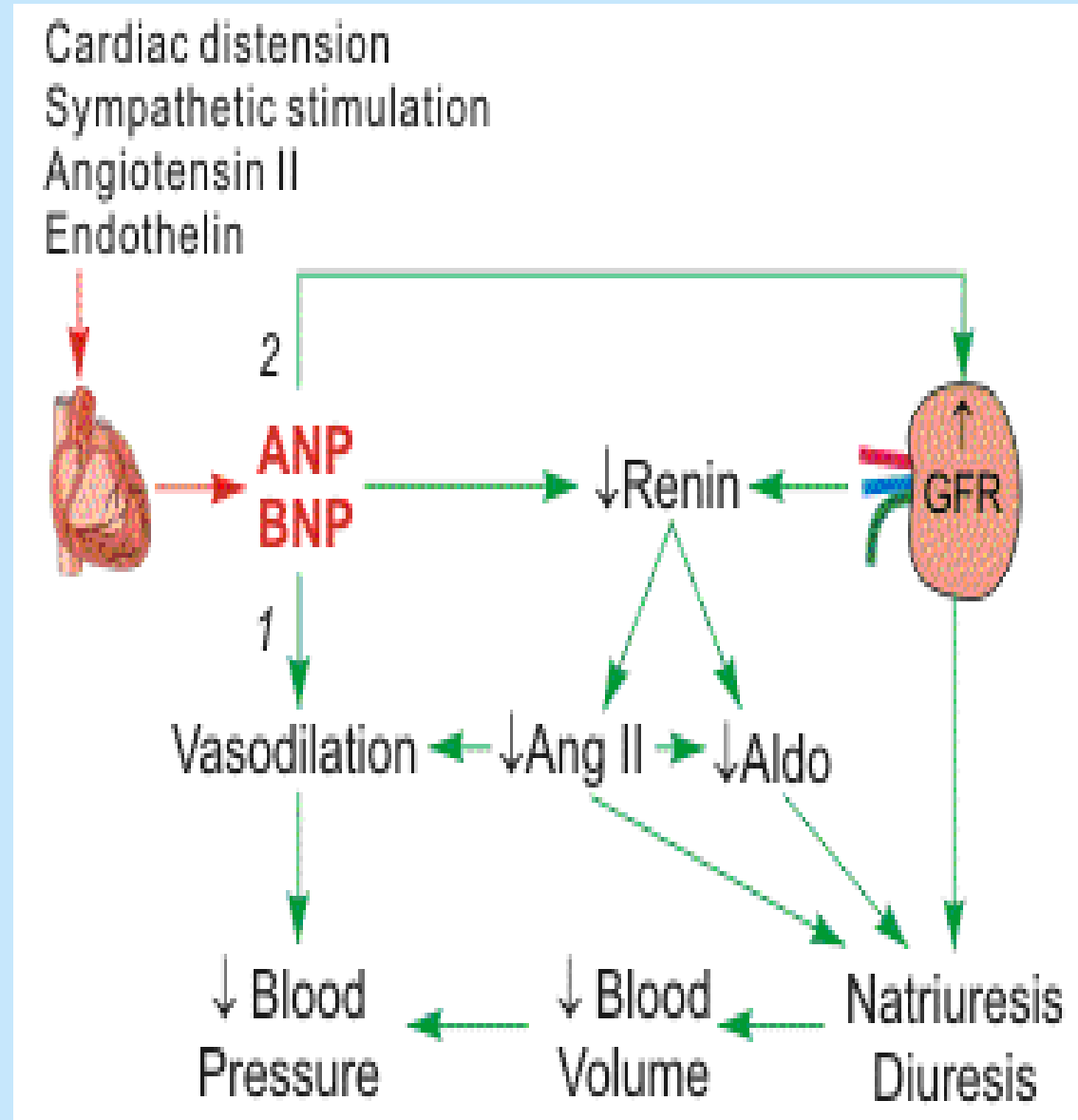
e.g. **Carvedilol, Nebivolol.**

New drugs for heart failure

1- Natriuretic Peptides:

Nesiritide

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



Natriuretic Peptides

Nesiritide

- a purified preparation of human BNP, manufactured by recombinant DNA technology
- ↑ cyclic-GMP in vascular smooth muscle, leading to smooth muscle relaxation & reduction of preload and afterload
- indicated (IV) for the treatment of patients with acute decompensated heart failure (ADHF) who have dyspnea at rest or with minimal activity.

New drugs for heart failure

2- Calcium sensitisers:

Levosimendan

- used in the management of ADHF

New drugs for heart failure

Levosimendan

mechanism of action:

- Calcium sensitization

(improves cardiac contractility without increasing oxygen consumption)

- potassium-ATP channel opening

(cause vasodilation, improving blood flow to vital organs)

These effects reduce the risk of worsening ADHF or death compared with dobutamine.

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	Cardiac disease, but no symptoms & no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc
II	Mild symptoms (mild shortness of breath &/or angina), slight limitation during ordinary activity
III	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
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

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

Congestive Heart Failure in Black patients

Hydralazine/isosorbide dinitrate fixed dose combination

- FDA approved to add to standard therapy for black Americans with congestive heart failure

(due to poor response to ACE inhibitors)
- should be considered for patients intolerant to ACE inhibitors & ARBs due to

renal dysfunction

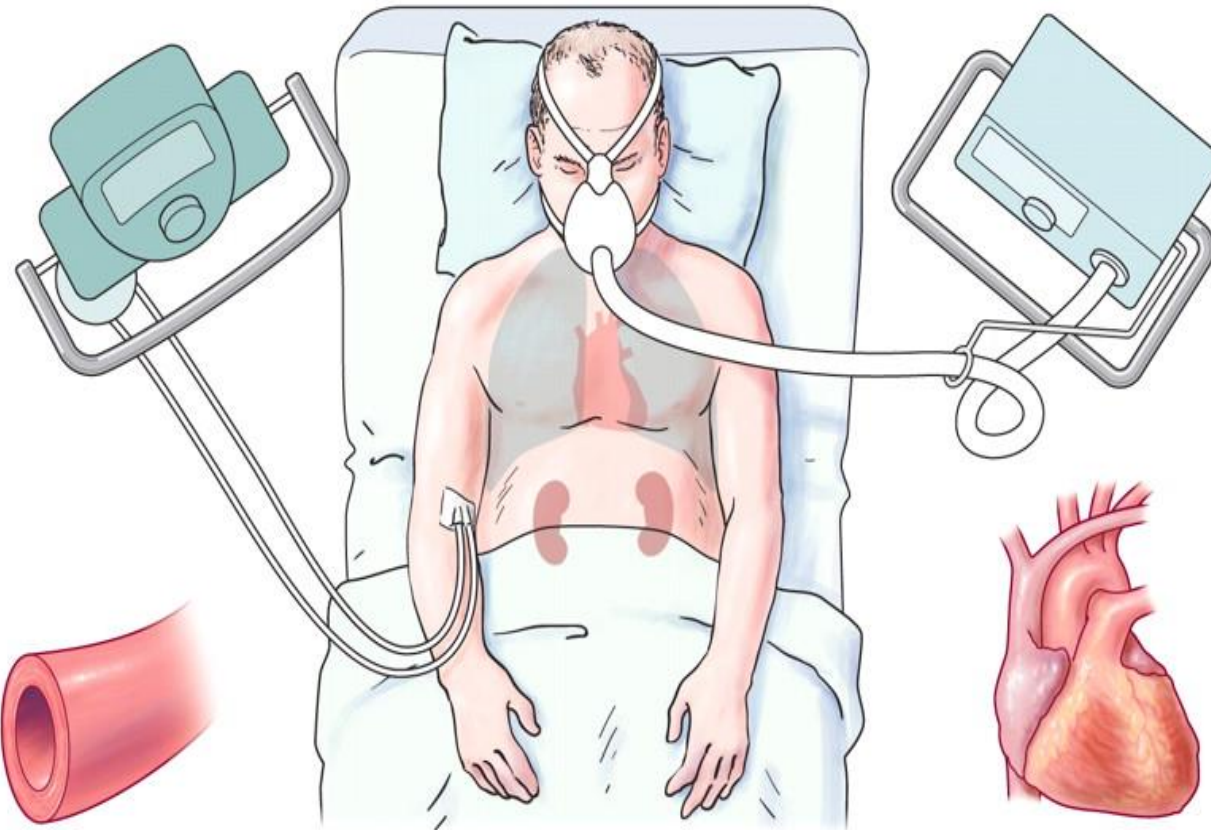
Acute decompensated heart failure (ADHF)

A sudden worsening of the signs & symptoms of heart failure, which typically includes:

- **difficulty breathing (dyspnea)**
- **leg or feet swelling**
- **fatigue**

- **ADHF is a common & potentially serious cause of acute respiratory distress.**

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

Table 1. FDA Drug Risk Classification

Category	Description
A	Controlled studies in humans show no risk to the fetus
B	No controlled studies have been conducted in humans; animal studies show no risk to the fetus
C	No controlled studies have been conducted in animals or humans
D	Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations
X	Controlled studies in both animals and humans demonstrate fetal abnormalities; the risk in pregnant women outweighs any possible benefit

Source: References 4-7.

Thank you

