Drug Therapy of Heart Failure

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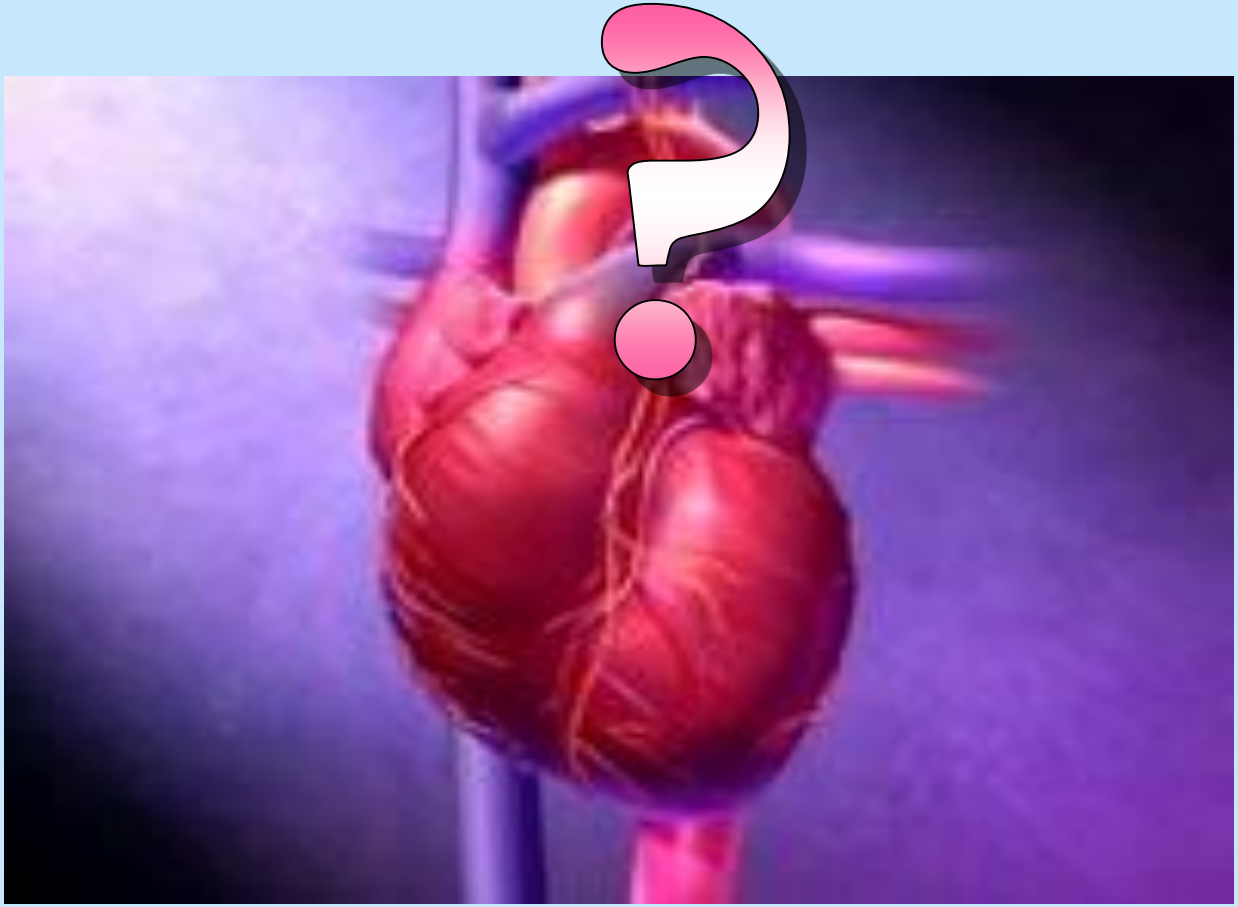
Learning objectives

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 and their mechanism of action

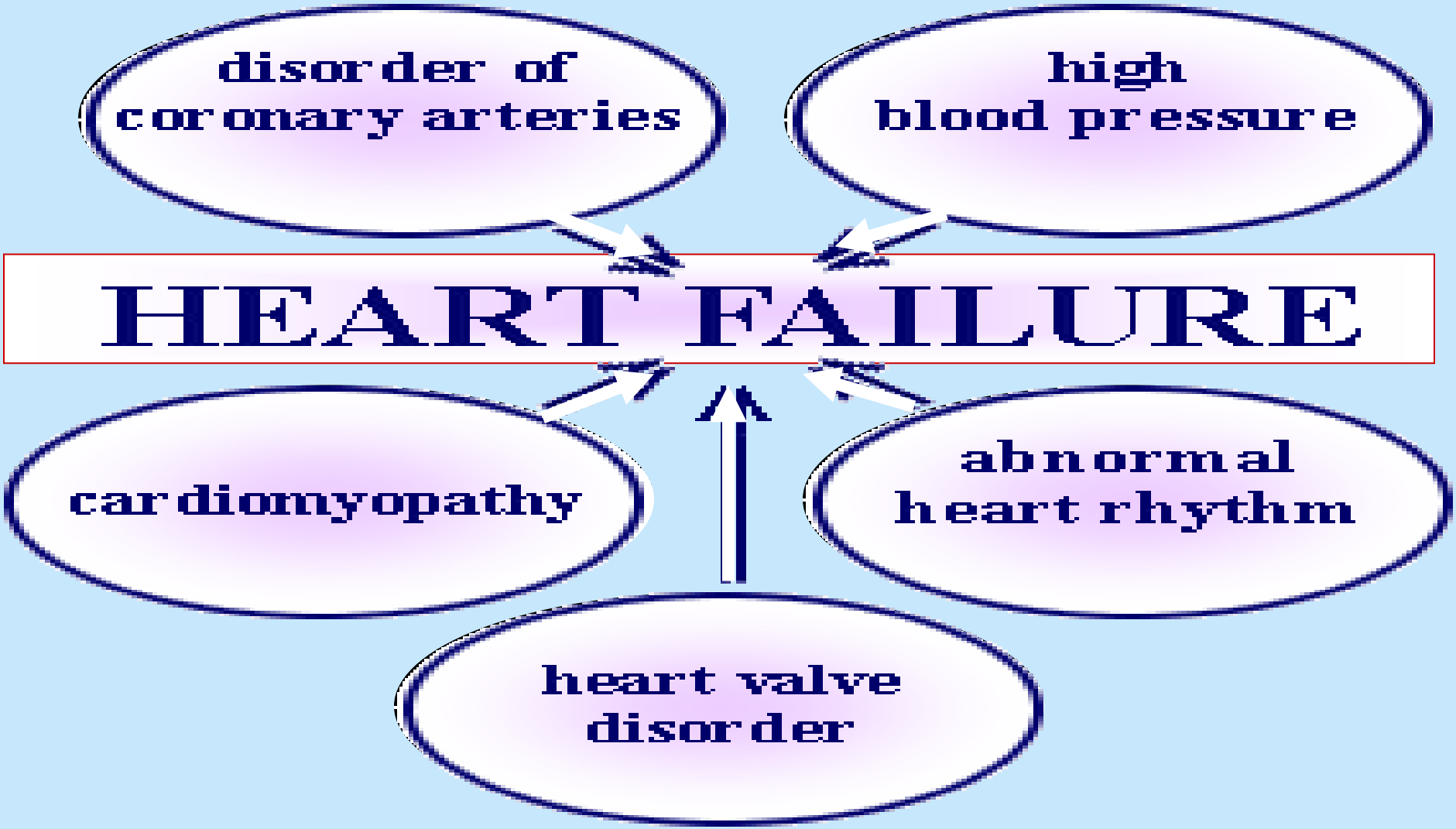
- Understand their pharmacological effects, clinical uses, adverse effects and their interactions with other drugs

HEART FAILURE



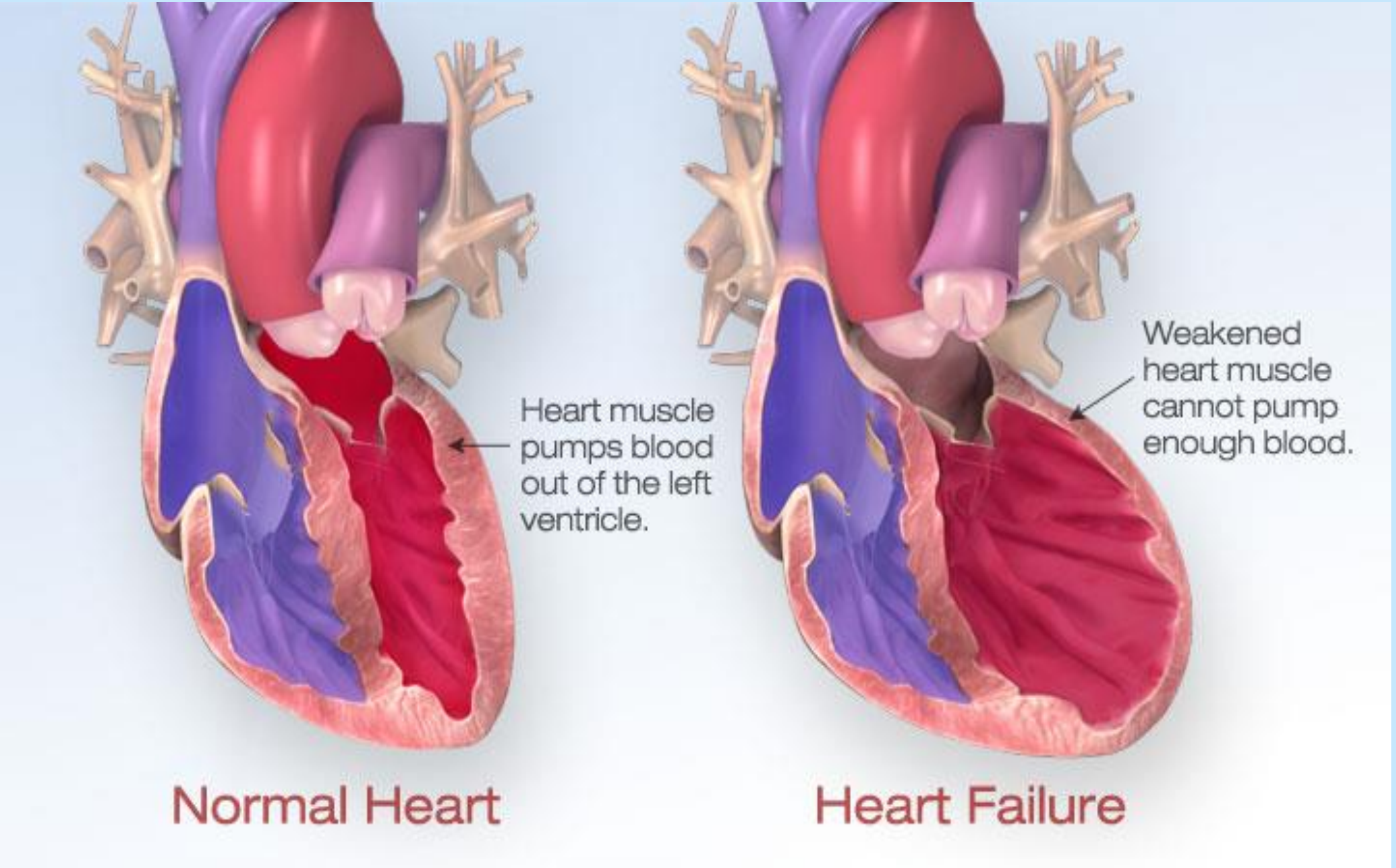
Inability of the heart to maintain an adequate cardiac output to meet the metabolic demands of the body.

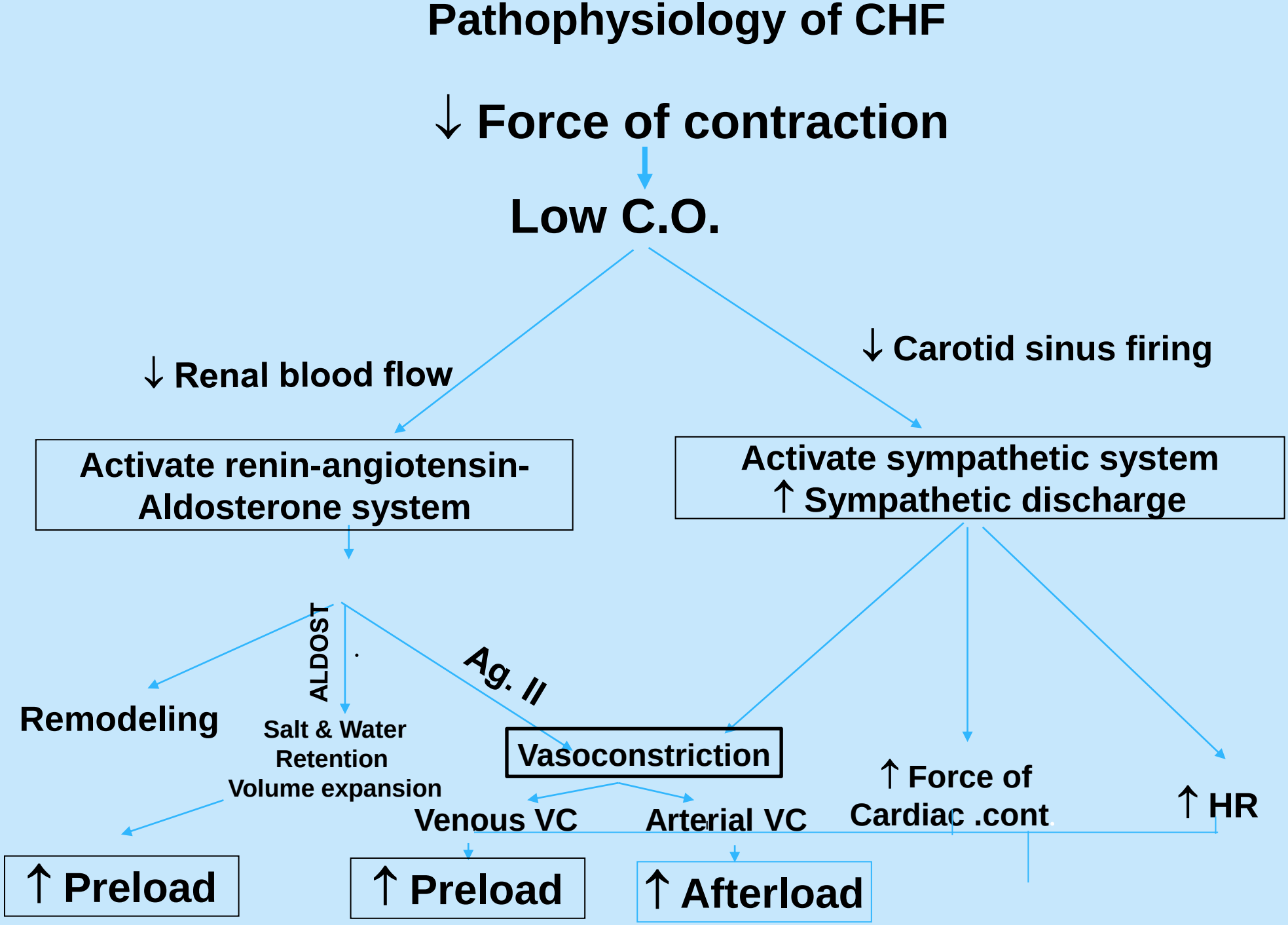
CAUSES OF HEART FAILURE



Symptoms of Heart failure

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


Heart muscle pumps blood out of the left ventricle.
Weakened heart muscle cannot pump enough blood.
Normal Heart
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
↑ Force of Cardiac .cont
↑ HR
Venous VC
Arterial VC
↑ Preload
↑ Preload
↑ Afterload

Factors affecting cardiac output and heart failure

1- Preload

2- Afterload

3- Cardiac contractility

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 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

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
- 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:

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

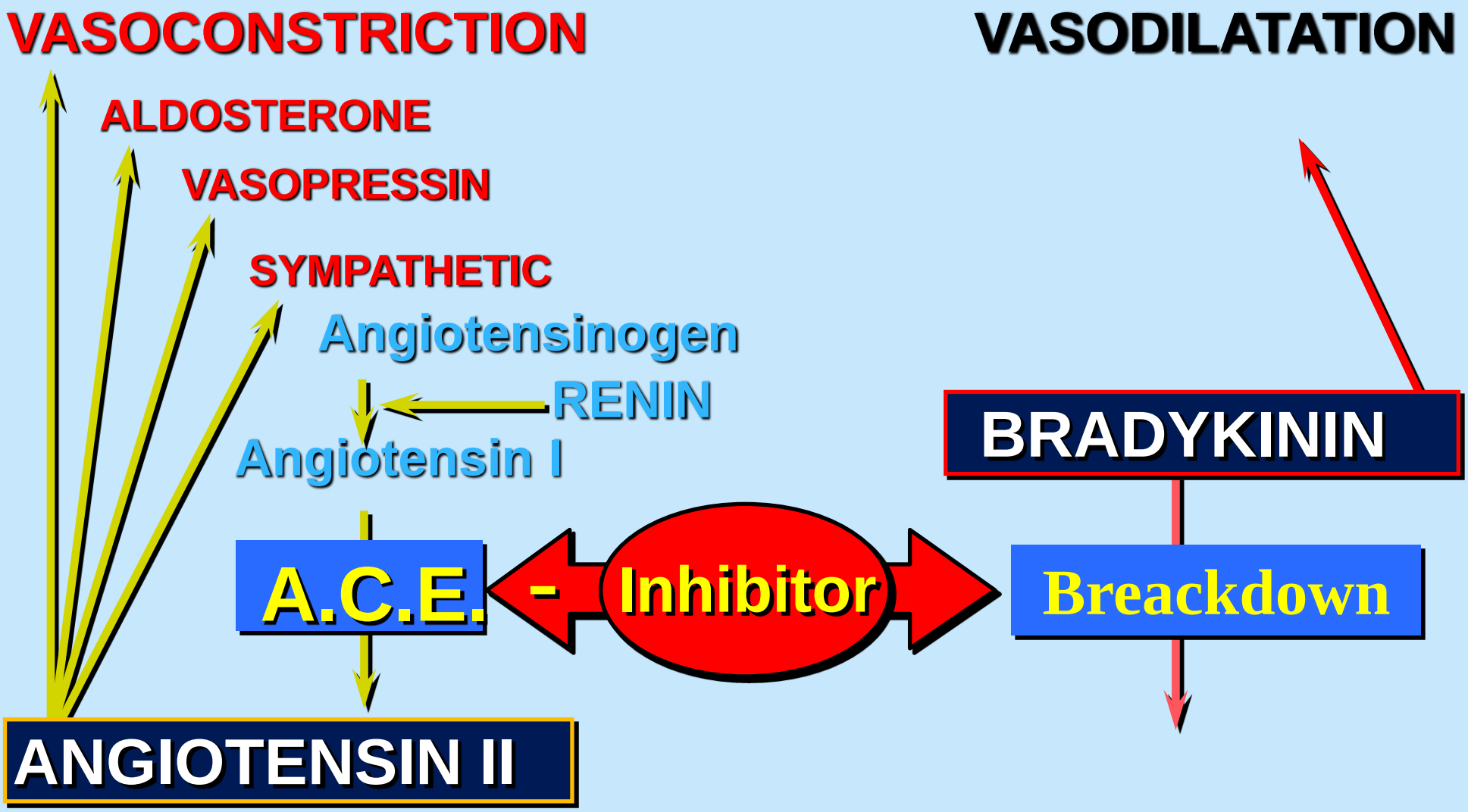
1-Angiotensin converting enzyme (ACE) inhibitors:

- 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



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

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 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 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_1 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

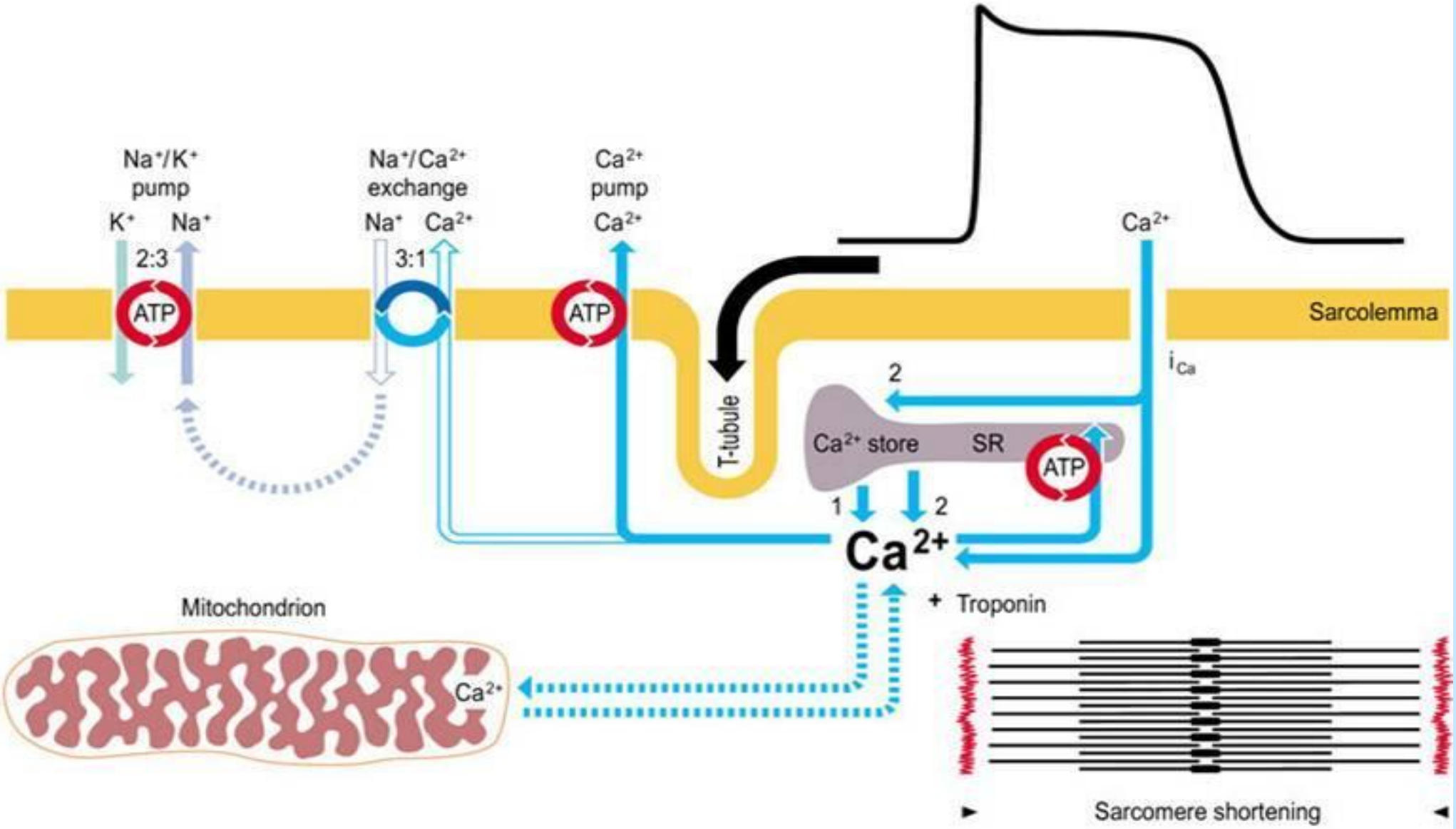
(+ve inotropic effect)

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**
- **Hypercalemia**

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)

Which inhibits cAMP degradation (↑ cAMP)

↓ ↓

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 intravenously 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:**

  have vasodilator actions (α- blocking effect)

  e.g. Carvedilol , Nebivolol

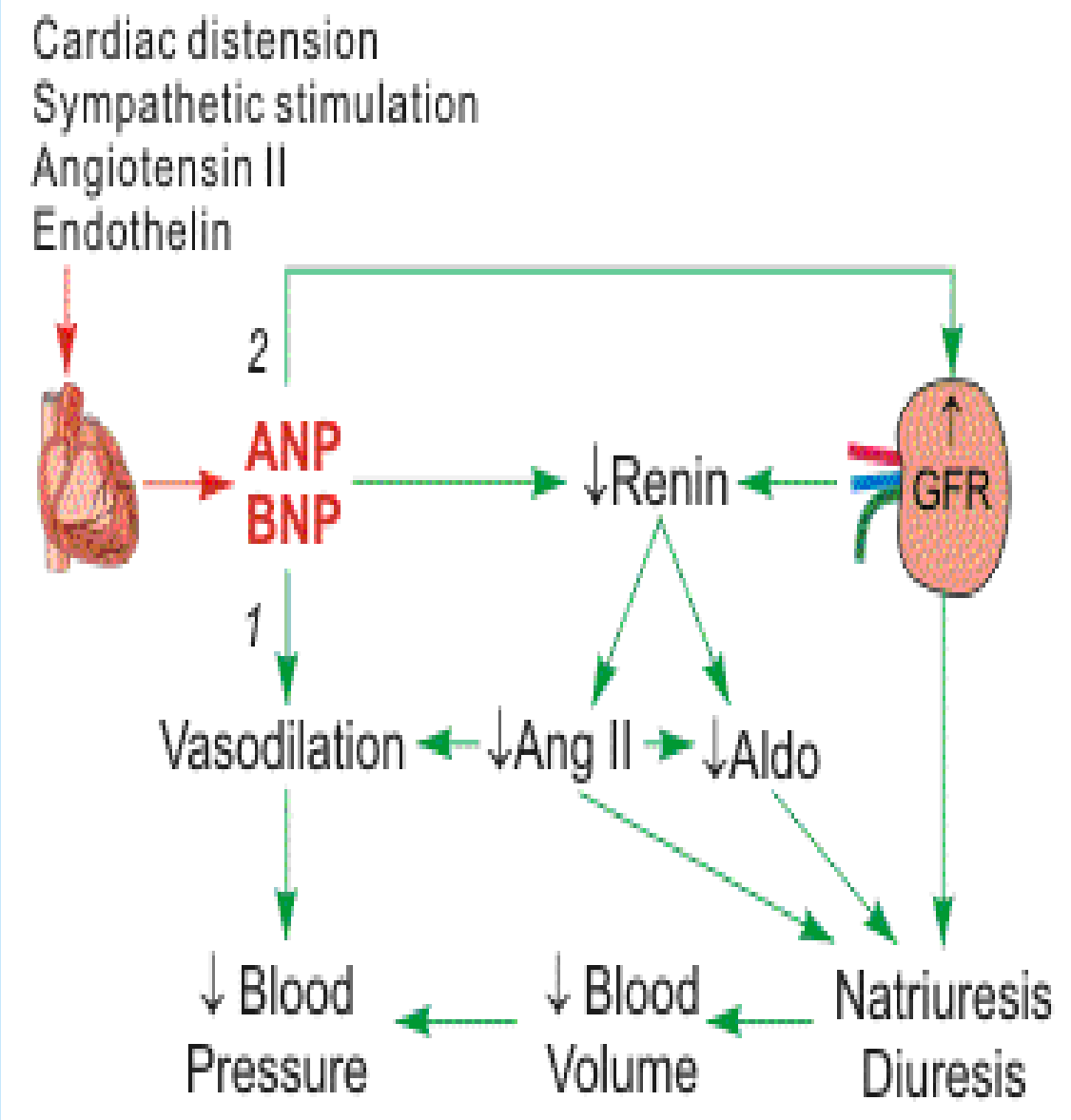
New drugs for heart failure

1- Natriuretic Peptides:

Nesiritide

- **BNP is secreted by the ventricules 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 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

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 CHF 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 and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/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

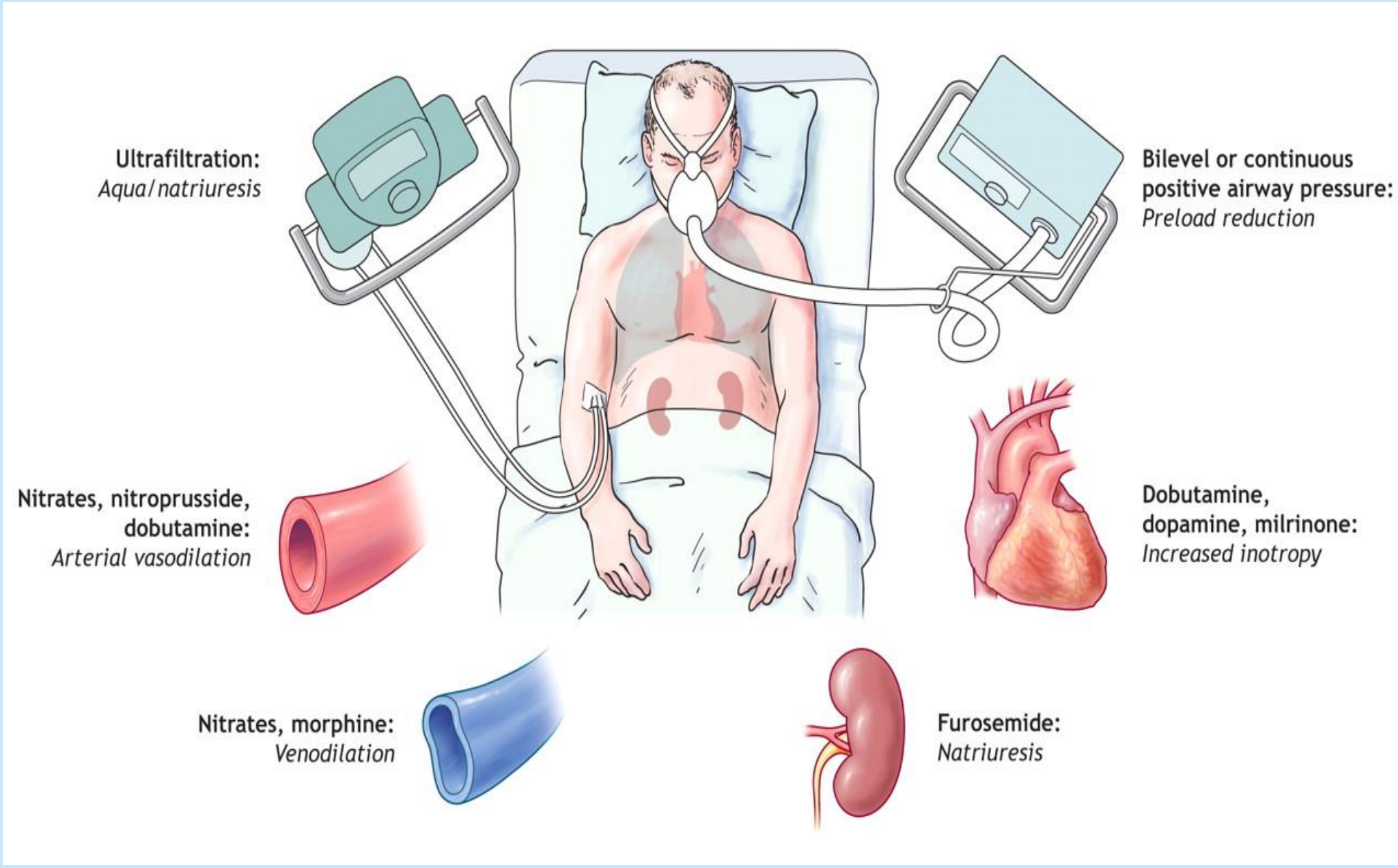
Hydralazine/isosorbide dinitrate fixed dose combination

- **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**

Management of acute heart failure




Thank you