DRUG THERAPY OF CONGESTIVE HEART FAILURE

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OBJECTIVES

- 1- List major drug groups used in treatment of heart failure
- 2- Explain mechanism of action of digitalis and its major effects
- 3- Explain the nature and mechanism of digitalis toxic effects
- 4- Describe the clinical implications of diuretics, vasodilators, ACE inhibitors and other drugs that lack positive inotropic effects in heart failure
- 5- Describe the strategies used in the treatment of heart failure

HEART FAILURE

Inability of the heart to maintain sufficient cardiac output inspite of good venous return.

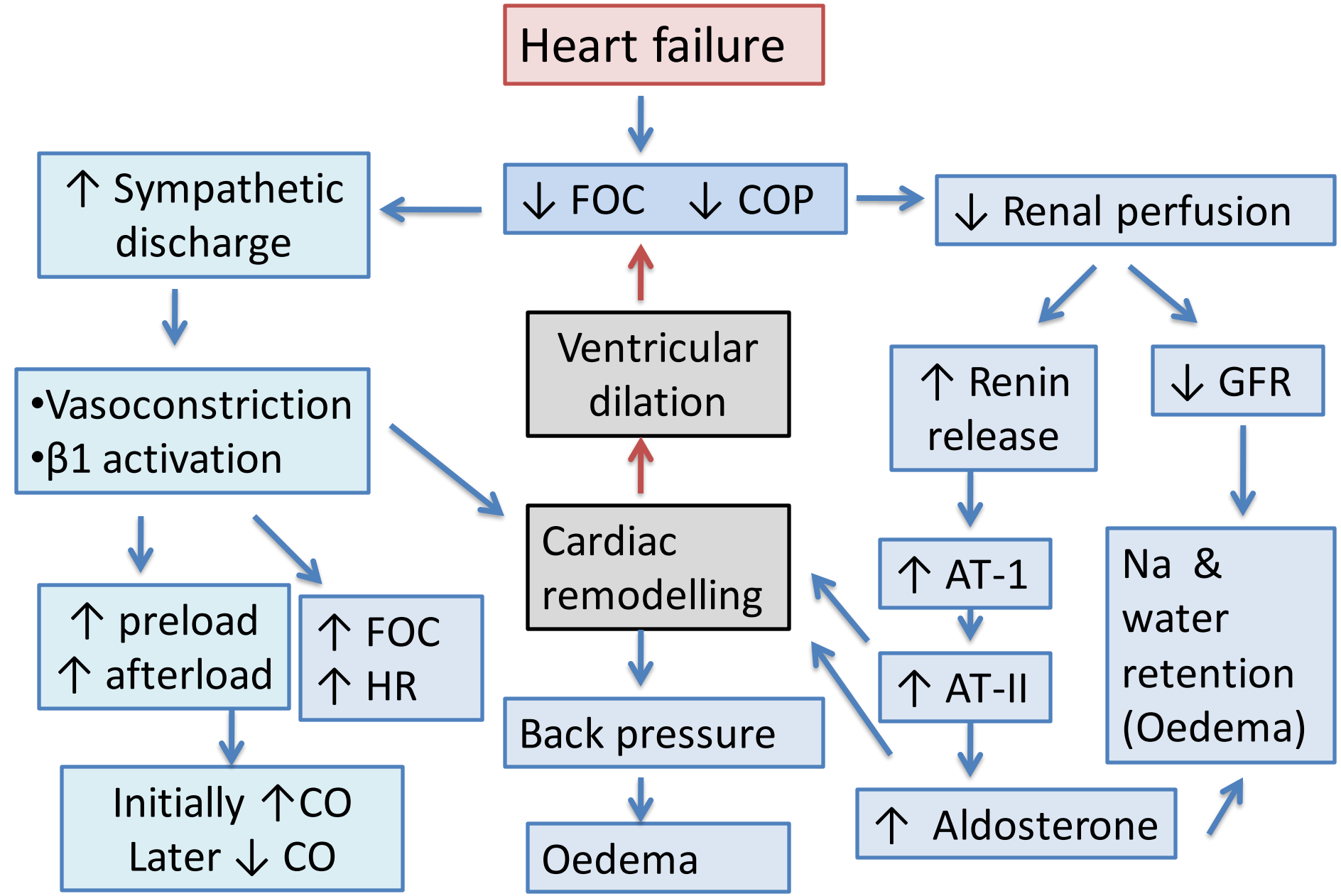
CAUSES OF HF (CLASSIFICATION)

Etiology	Left-sided HF	Right-sised HF
Increased preload	AR, MR, VSD, hyperdynamic circulation	TR, PR, VSD, hyperdynamic circulation
Increased afterload	AS, Aortic cortication, systemic hypertension	PS, Pulmonary hypertension, COPD
Decreased contractility	Coronary ischemia, cardiomyopathy, myocarditis	

DRUG-INDUCED HF

- Alcoholism and drug abuse
- Calcium channel blockers
- Potassium supplements and other drugs associated with hyperkalemia
- Antiarrhythmic agents
- Androgens
- Sodium-containing preparations
- TNF-alpha inhibitors

Compensatory responses during heart failure

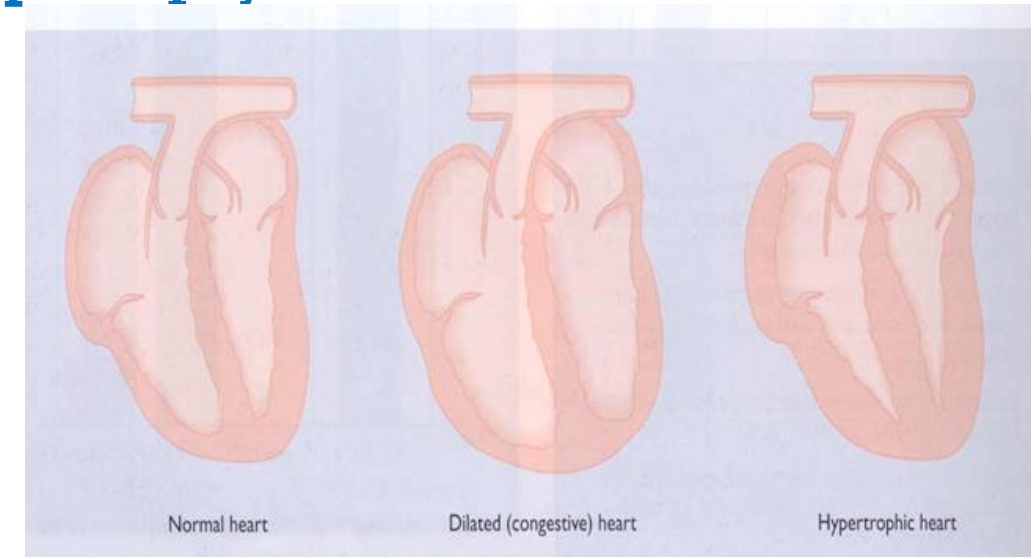


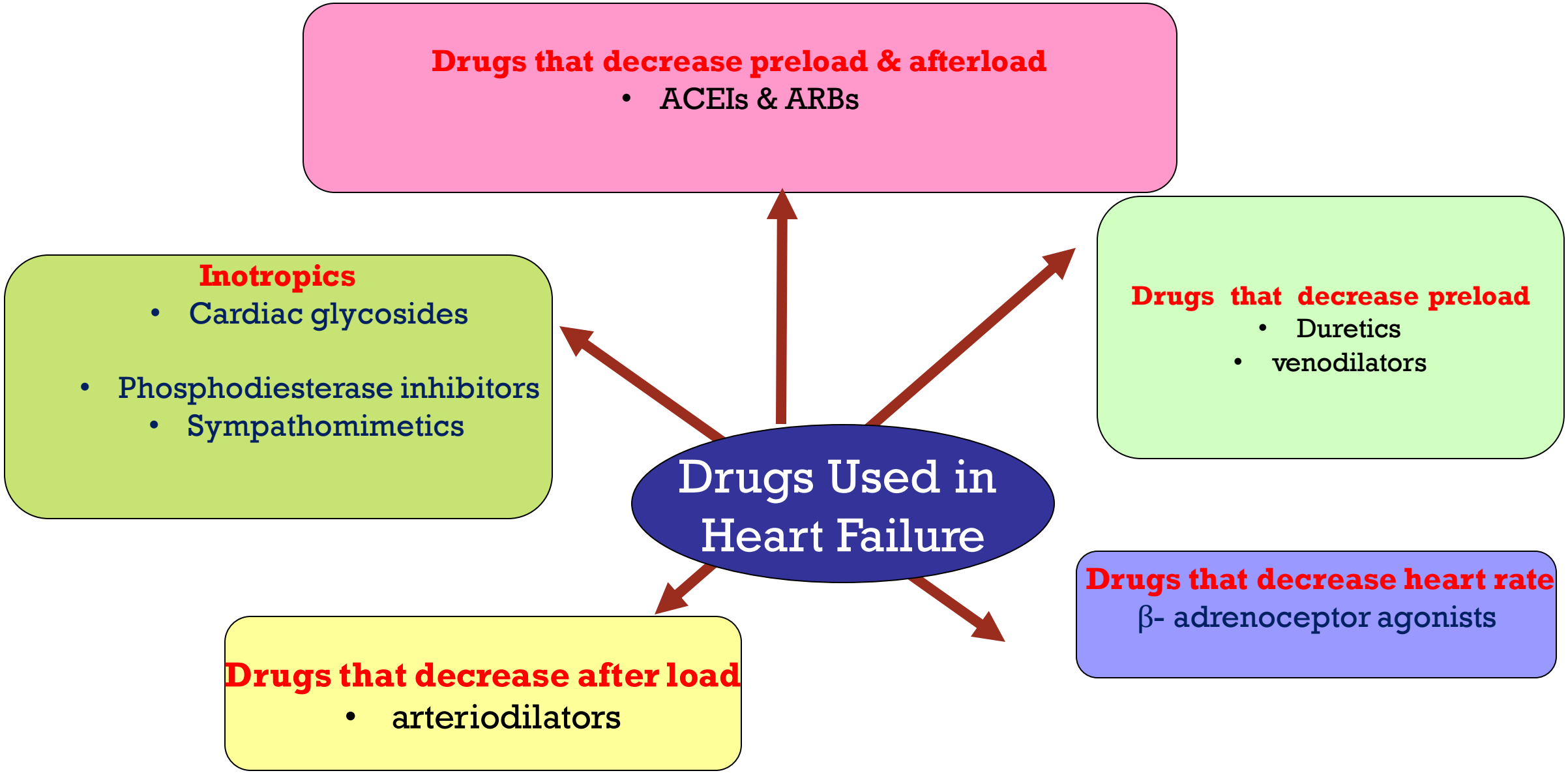
DIAGNOSTIC CRITERIA OF HF

- Triade of:
- Symptoms: shortness of breath, physical fatigue
- Signs: tachycardia, tachypnea, edema
- Evidence of structural or functional abnormality of heart, example: cardiomegaly

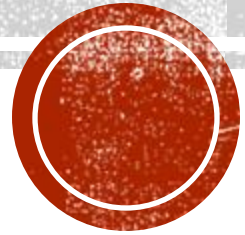
Factors affecting cardiac output and Heart Failure

- **Cardiac contractility**
- **Preload: volume overload: cardiac dilatation**
- **Afterload: tension overload: cardiac hypertrophy**
- **Heart rate: tachycardia**




Drugs that decrease preload & afterload
• ACEIs & ARBs
Inotropics
• Cardiac glycosides
• Phosphodiesterase inhibitors
• Sympathomimetics
Drugs that decrease preload
• Duretics
• venodilators
Drugs Used in Heart Failure
Drugs that decrease after load
• arteriodilators
Drugs that decrease heart rate
β- adrenoceptor agonists

DRUGS THAT INCREASE CONTRACTILITY

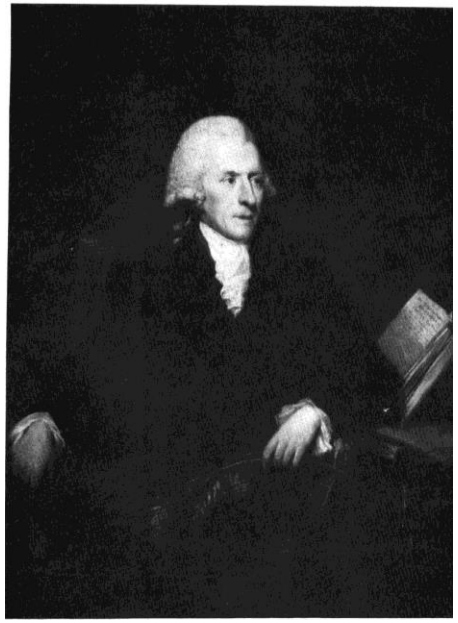


INOTROPIC DRUGS

- Cardiac glycosides:
  - Digoxin, digitoxin
- Sympathomimetic amines:
  - Dopamine , dobutamine
- Phosphodiesterase inhibitors:
  - Amrinone , milrinone

Inotropic drugs

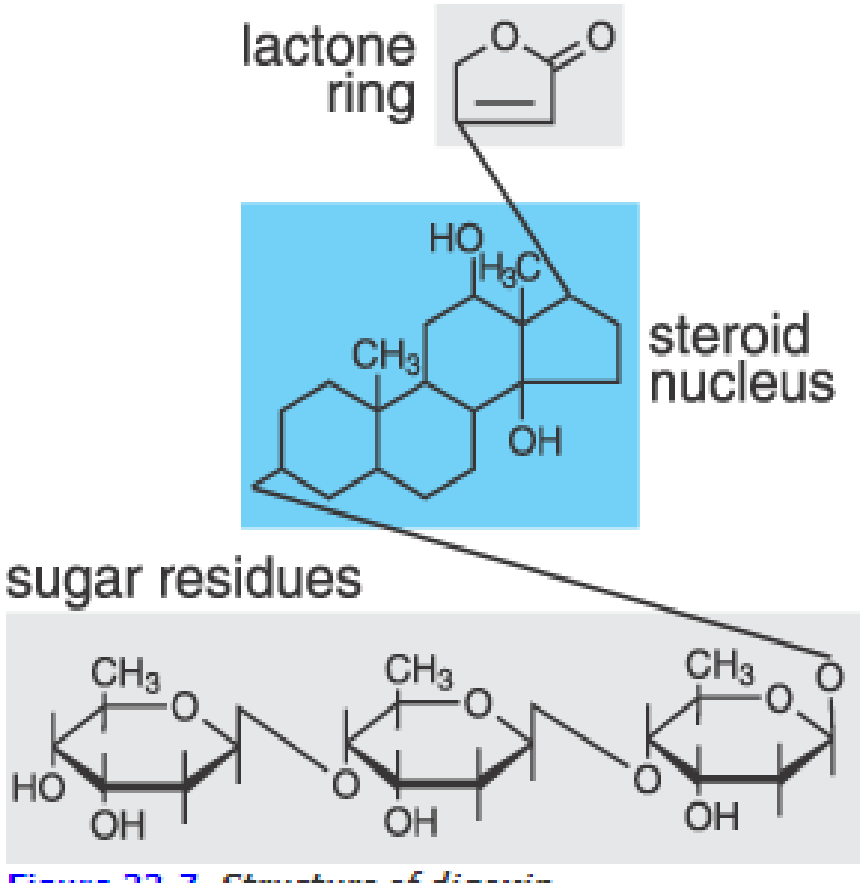
- Cardiac glycosides: Digoxin



William Withering 1785

Foxglove plant

CHEMISTRY OF CARDIAC GLYCOSIDES



Aglycone (genin) Responsible for pharmacodynamic activity

(glycon)Sugar influence pharmacokinetics

BENEFICIAL EFFECTS OF DIGOXIN IN HF

- **(increase the contractile force of the cardiac muscles)**
- **<u>This effect is manifested in patients with heart failure, this results in:</u>**
- 1- Increased C.O.P: increasing renal blood flow, decreasing renin release: decreasing systemic & pulmonary congestion
- Diuresis, relief of edema
- Improving tissue hypoxia
- 2- Bradycardia: diminishing tachycardia: increasing filling time
- 3- Decreased heart size

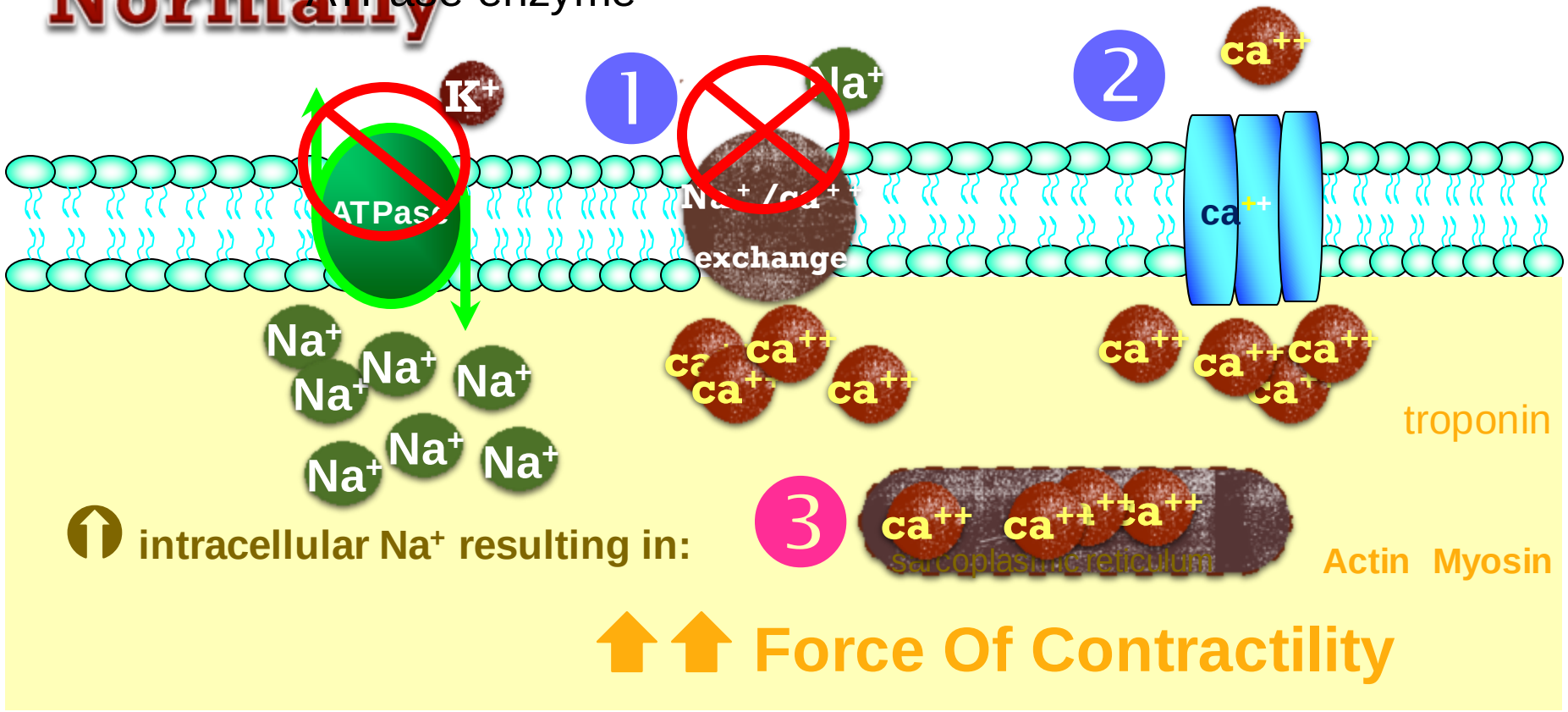
Digitalis

Mechanism of the +ve inotropic action:

N.B. Digitalis inhibit Na+/K+ ATPase by competition with K+ , So hypokalemia increase Digitalis toxicity , while K+ administration improve toxicity of digitalis.

Digitalis In therapeutic dose leads to partial inhibition of Na^+/K^+ ATPase enzyme

Normally



DIGITALIS MECHANISM OF ACTION

- Digitalis increase intracellular free Ca+2 in CARDIAC CELL, during systole .
- Ca+2 inhibits troponin (relaxing protein), thus
- Facilitates excitation -contraction coupling between actin and myosin leading to increased cardiac contractility.

DIGITALIS INCREASE INTRACELLULAR FREE CA+2 IN CARDIAC CELLS BY :

- 1- Inhibition of membrane bound phosphorylated α sub unit of sarcolemal Na+ K+ Atpase enzyme; inhibition of this enzyme by digitalis results in an increase in intracellular Na+ which Leads to increase in free intracellular Ca+2 through:
- Increased intra- cellular Na+ leads to diminished exchange of extracellular Na+ for intracellular Ca+2, this increase concentration of Ca+2 into the sarcoplasm.
- The accumulated intracellular Na+ displaces Ca+2 from its binding sites, thus increases free Ca +2 intracellulary.
- 2- Digitalis may directly facilitate the entry of Ca+2 into cardiac cells during the plateau of the action potential.
- 3- Digitalis may increase the release of stored Ca +2 from the sarcoplasmic reticulum.

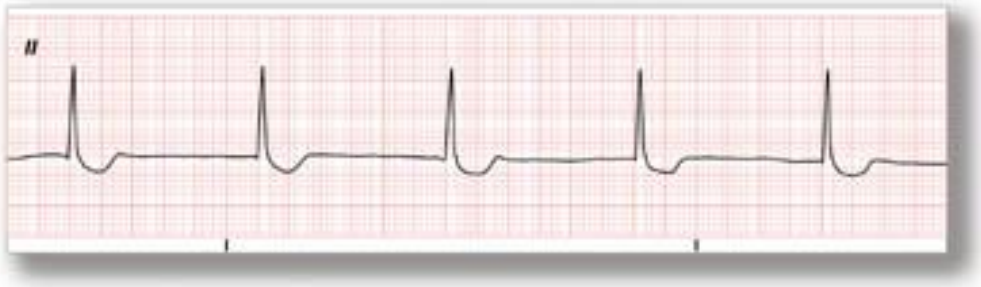
Pharmacological actions

CARDIAC

- ↑force of contraction & Cardiac Output
- ↓ Heart rate : vagal stimulation: by direct and indirect mechanisms
- ↑ Conduction velocity (CV) in atria/ventricles
- ↓ CV in AV node
- Increased automaticity: ectopic foci
- ECG: ↑PR interval , high R wave, inverted T wave, depressed ST segment, arrhythmias of any type, bradycardia

EXTRA CARDIAC

- Kidney:
  - Due to improvement in circulation and renal perfusion
  - Retained salt and water is gradually excreted
- CNS:
  - Nausea, vomiting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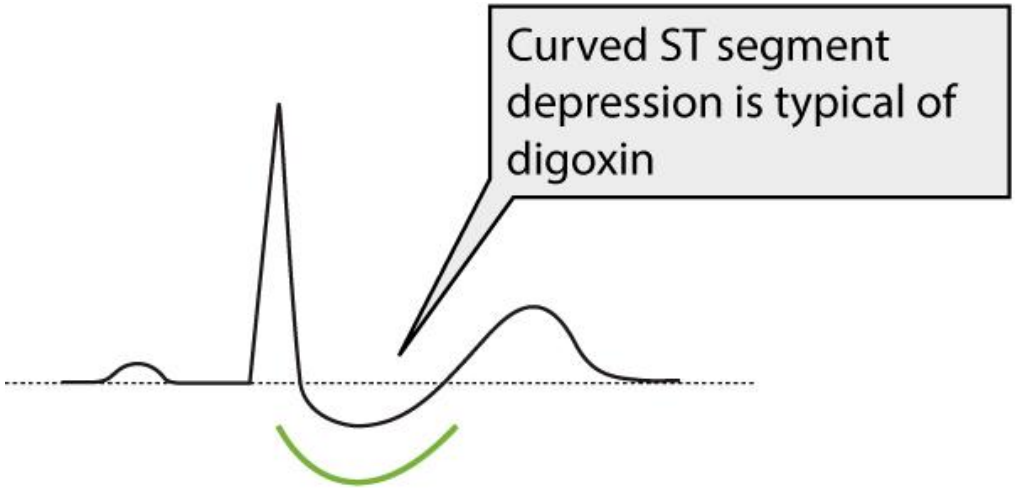
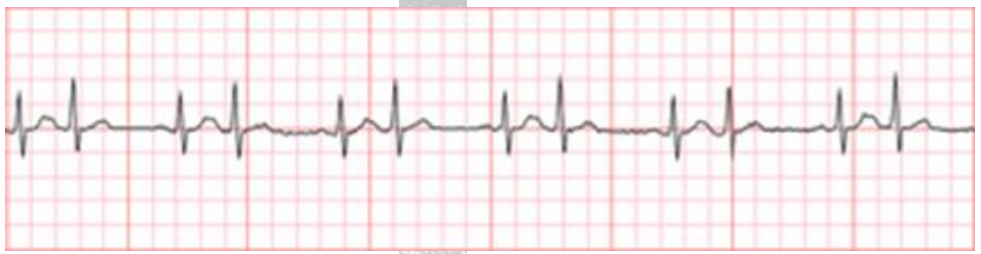

Curved ST segment depression is typical of digoxin



CLINICAL USES OF DIGOXIN

- Congestive heart failure
- Cardiac arrhythmias
- Atrial fibrillation
- Atrial flutter
- Paroxysmal supraventricular tachycardia
- **DOSE**: Lanoxin tablet 0.25 mg once in the morning 5 days/ week
- Sever HF:
- Loading dose: 2 tab. Twice daily for 2 days or
- 2 tab, thrice daily for 1 day
- Then maintenance dose

CONTRAINDICATIONS

Absolute

- 1- Heart block
- 2- WPW syndrome
- 3- Hypertrophic obstructive cardiomyopathy
- 4- Ventricular arrythmia

Relative

- 1- Bradycardia: beta blockers, verapamil, myxedema, sick sinus syndrome.
- 2- Systemic or pulmonary hypertension
- 3- Renal and hepatic impairment
- 4- Ventricular arrythmias
- 5- DC cardioversion
- 6- MI
- 7- Acute myocarditis of rheumatic fever

DRUG INTERACTIONS OF DIGITALIS

- 1- Antacids: decrease digitalis absorption
- 2- Atropine: increases digitalis absorption while metoclopramide decrease
- 3- Quinidine: decreases digitalis clearance
- 4- K- losing diuretics: increase digitalis toxicity

Toxicity of digoxin

Extra-Cardiac

- GIT: Nausea & vomiting (first to appear)
- CNS: Vomiting Restlessness, Disorientation, Visual disturbance, convulsions
- Endocrine: Gynaecomastia

Cardiac

- Bradycardia (first cardiac toxic sign)
- Pulsus bigemini
- Atrial flutter → fibrillation
- Ventricular extra-systole → tachycardia → fibrillation
- Partial heart block → complete block

FACTORS INCREASE DIGITALIS TOXICITY

- Small (Lean) body mass
- Old age
- Renal diseases
- Hypokalemia
- Hypercalemia
- Drug interactions:
- Diuretics→ hypokalemia (arrhythmia)

- Quinidine : ↑plasma level of digitalis

TREATMENT OF DIGITALIS TOXICITY

- Stop digitalis
- Oral or parenteral potassium supplements
- For ventricular arrhythmias:
  - Lidocaine IV drug of choice
- For supraventricular arrhythmia:
  - Propranolol may be given IV or orally
- For AV block and bradycardia
  - Atropine IM
- Digoxin antibodies: (digibind) **FAB fragment life saving**

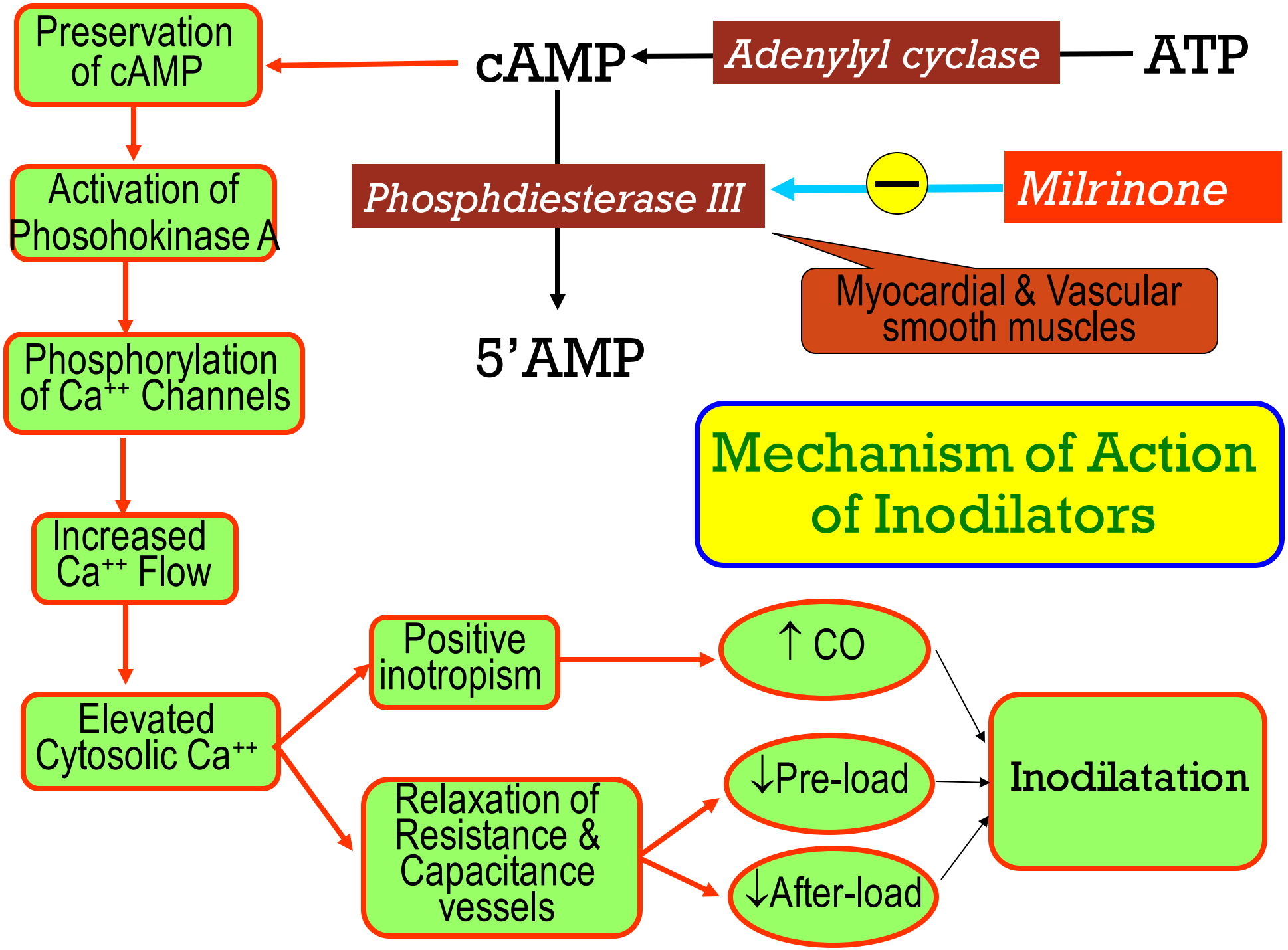
PHOSPHODIESTERASE INHIBITORS

- **Inhibit phosphodiesterase isozyme III in cardiac, smooth muscles & platelets → :**
- **↑ cAMP**

In the heart : Increase myocardial contraction

In the peripheral vasculature : Dilatation of both arteries & veins → ↓ afterload & preload.

Platelets: **↓aggregation**


Preservation of cAMP
cAMP
Adenylyl cyclase
ATP
Activation of Phosohokinase A
Phosphdiesterase III
Milrinone
Myocardial & Vascular smooth muscles
Phosphorylation of Ca++ Channels
5'AMP
Mechanism of Action of Inodilators
Increased Ca++ Flow
Positive inotropism
↑ CO
Elevated Cytosolic Ca++
↓Pre-load
Inodilatation
Relaxation of Resistance & Capacitance vessels
↓After-load

PHOSPHODIESTRASE INHIBITORS

- **Clinical uses: (2nd choice after digitalis)**
- IV administration for short term (24-48 Hs) treatment of sever heart failure (acute)
- **Adverse effects:**
- **Arrhythmias: ↑ A-V conduction**
- **Thrombocytopenia**
- **Liver toxicity**
- **Milrinone less toxic than amrinone.**
- Milrinone is more potent than amrinone and does not produce thrombocytopenia

DRUGS THAT DECREASE PRELOAD

- **Diuretics**

- **Venodilators: nitrates**
- **<u>How nitrates are helpful in CHF</u>?**
- Reduce preload
- Coronary artery dilatation- reperfusion
- **Given alone their efficacy is limited due to**:

✓limited effect on systemic resistance

✓Nitrate tolerance

- **Often combined with other vasodilators for better results:**
- Hydralazine/isosorbide dinitrate(Bidil) is a fixed-dose combination: improve motrality in some cases of HF.

DIURETICS

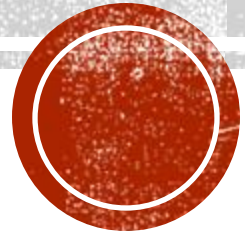
- **Among First-line therapy of heart failure**
- **<u>role in HF</u>:**
- **1- Remove the signs and symptoms of volume overload (pulmonary congestion/ peripheral edema).**
- **2- Reduce salt and water retention (Natriuresis)→↓ventricular preload and venous pressure.**
- **3- Reduction of cardiac size →improve cardiac performance**
- **Loop diuretics** – furosemide
- increase K^+ excretion (hypokalemia)
- **Thiazide Diuretics-** chlorthiazide, hydrochlorthiazide- limited value in CHF
- K^+ loss occurs more than that with loop diuretics (hypokalemia)
- Diuretics do not improve upon the mortality rate in patients

- **K^+ Sparing Diuretics-** Spironolactone, triamterene, amiloride are weak diuretics-for achieving volume reduction with minimal K^+ loss
- **Advantages of spironolactone**:
- 1- Preserve K: prevents hypokalemia
- 2- Decreases mortality in cases of sever HF by unknown mechanism other than diuresis
- Dose: one tablet lasilactone 50 mg in the morning 5 days a week.
- 3- Antagonize aldosterone effects

DRUGS THAT DECREASE AFTERLOAD

- Arteriolodilators: hydralazine , minoxidil, nicorandil
- **Hydralazine**:
- Direct acting vasodilator
- Reduces both right and left ventricular afterload by reducing pulmonary and systemic vascular resistance
- Results in increased cardiac output
- Also has moderate direct positive inotropic activity independent of its afterload reducing effects
- Reduces renal vascular resistance and increases renal blood flow
- Increases renal blood flow more than any other vasodilator except ACE inhibitors
- Preferred drug in CHF (ACE intolerant) with renal impairment

REDUCTION OF AFTERLOAD & PRELOAD



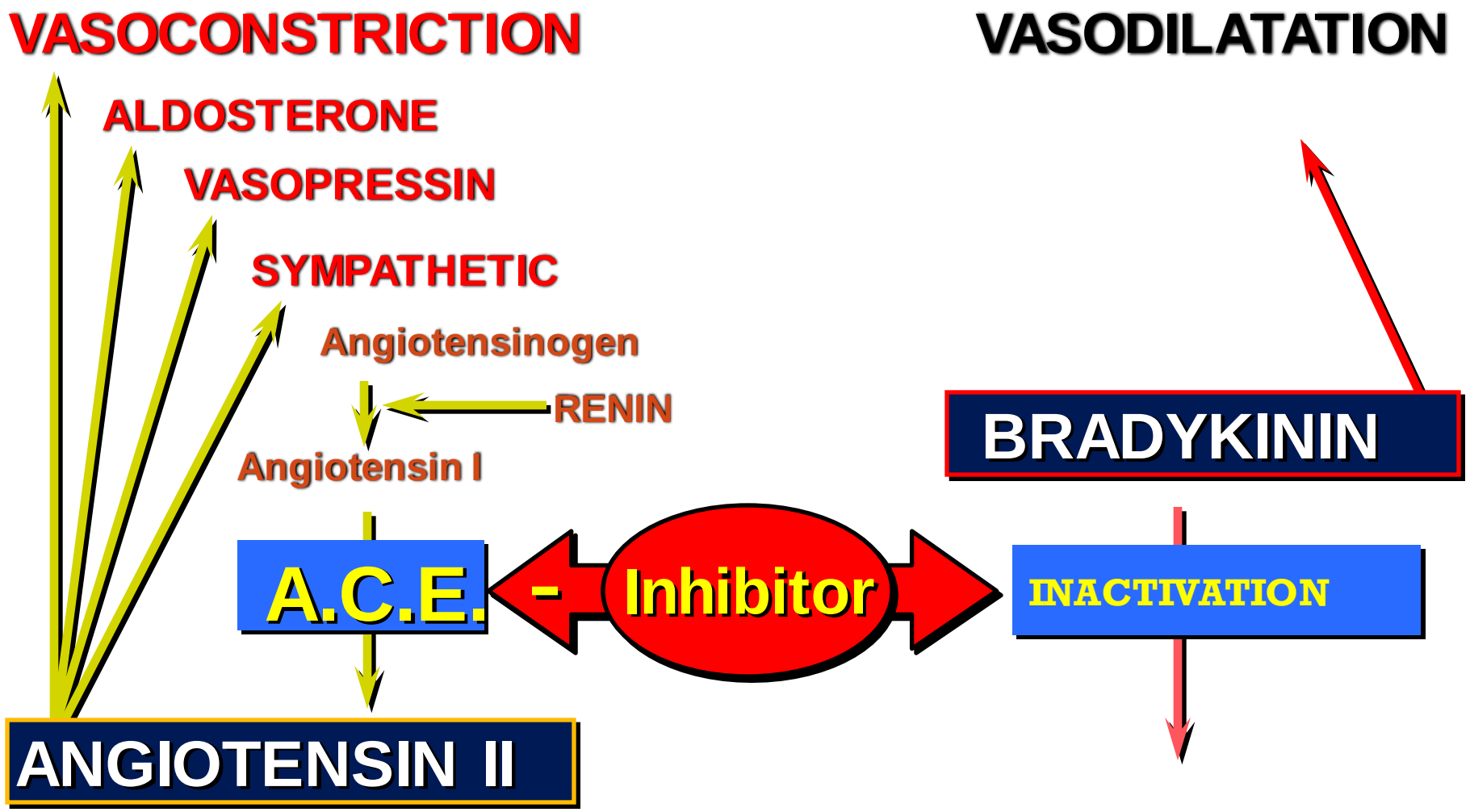
ACE INHIBITORS & ANGIOTENSIN RECEPTOR BLOCKERS

- **Along with digitalis and diuretics are now considered as first –line drugs for heart failure therapy**
- ACEIs: Captopril, enalapril, ramipril, lisinopril
- AT1 receptor blockers: Losartan , candesartan, valsartan, telmisartan
- **Effects of converting enzyme inhibitors (ACEIs)**
- **↓angiotensin II and aldosterone leading to:**
- **1- ↓Peripheral resistance (Afterload)**
- **2- ↓Venous return (Preload)**
- **3- ↓cardiac remodeling →↓mortality rate**

- **Angiotensin receptor blockers**: Block AT_1 receptor on the heart, peripheral vasculature and kidney
- As effective as ACE inhibitors
- Used mainly in patients who cannot tolerate ACE inhibitors because of cough, angioedema, neutropenia

Angiotensin converting enzyme inhibitors

MECHANISM OF ACTION



B-ADRENOCEPTOR BLOCKERS IN HEART FAILURE

- **Benefits in HF:**
- **Reduce catecholamine myocyte toxicity (remodeling)**
- **Decrease mortality rate**
- **Decrease heart rate**
- **Inhibit renin release**
- **Contraindications in HF:**
- **1- Beta blockers in large dose**
- **2- Acute HF**
- **Beta blockers approved in HF:**

1- Bisoprolol

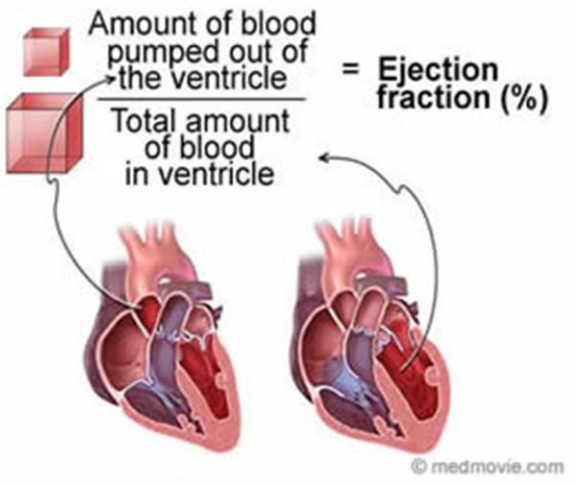
2- Metoprolol

3- Carvedilol

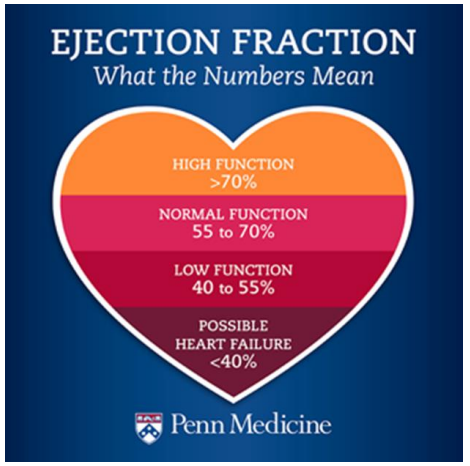
MANAGEMENT OF CHRONIC HEART FAILURE

- Lifestyle changes
- Drug therapy
- Surgery for correctable problems
- Implantable devices
- Heart transplant
- **Diet and lifestyle measures**
- Moderate physical activity, when symptoms are mild or moderate; or bed rest when symptoms are severe.
- Weight reduction
- Sodium restriction – excessive sodium intake may precipitate or exacerbate heart failure, thus a "no added salt" diet (60–100 mmol total daily intake) is recommended for patients with CHF.
- Stop smoking

Approach to the Patient with Heart Failure



Assessment of LV function (echocardiogram)



EF < 40%

Assessment of volume status

Signs and symptoms of fluid retention

Diuretic

No signs and symptoms of fluid retention

ACE Inhibitor

β-blocker

Digoxin

Thank you