Drugs for treatment of cardiac failure

by

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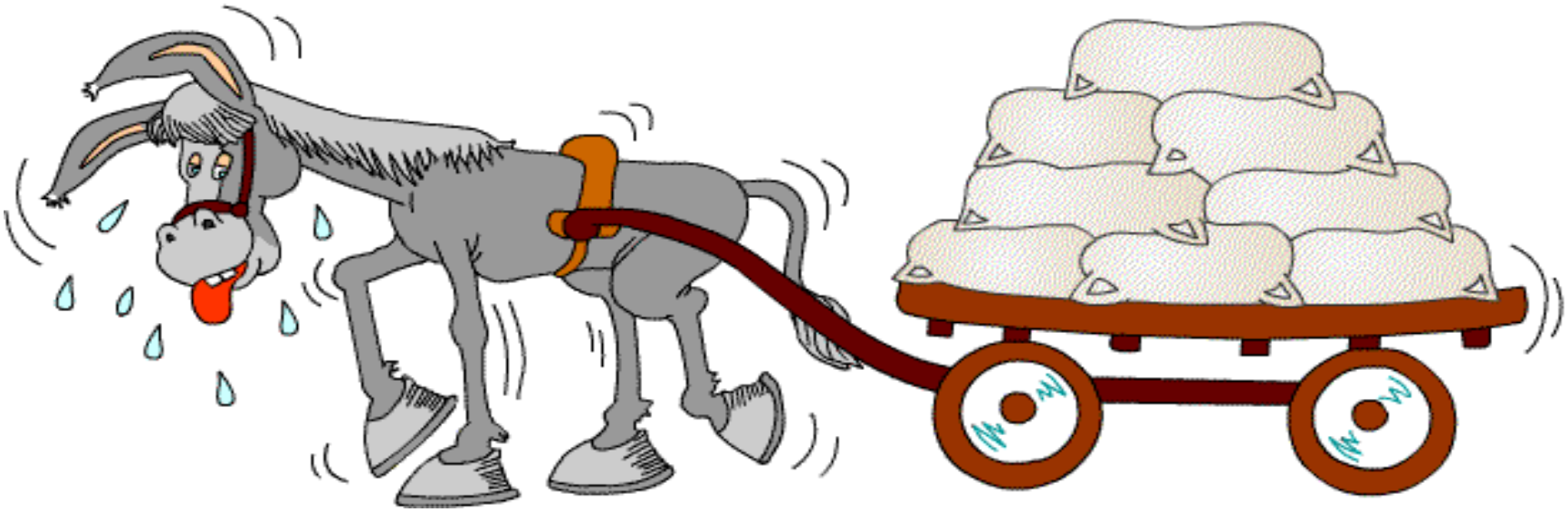
Objectives

- 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

What is heart failure



Definition of heart failure:

Heart failure is a condition in which the heart has lost the ability to pump enough blood to the body's tissues.

With too little blood being delivered, the organs and other tissues do not receive enough oxygen and nutrients to function properly.

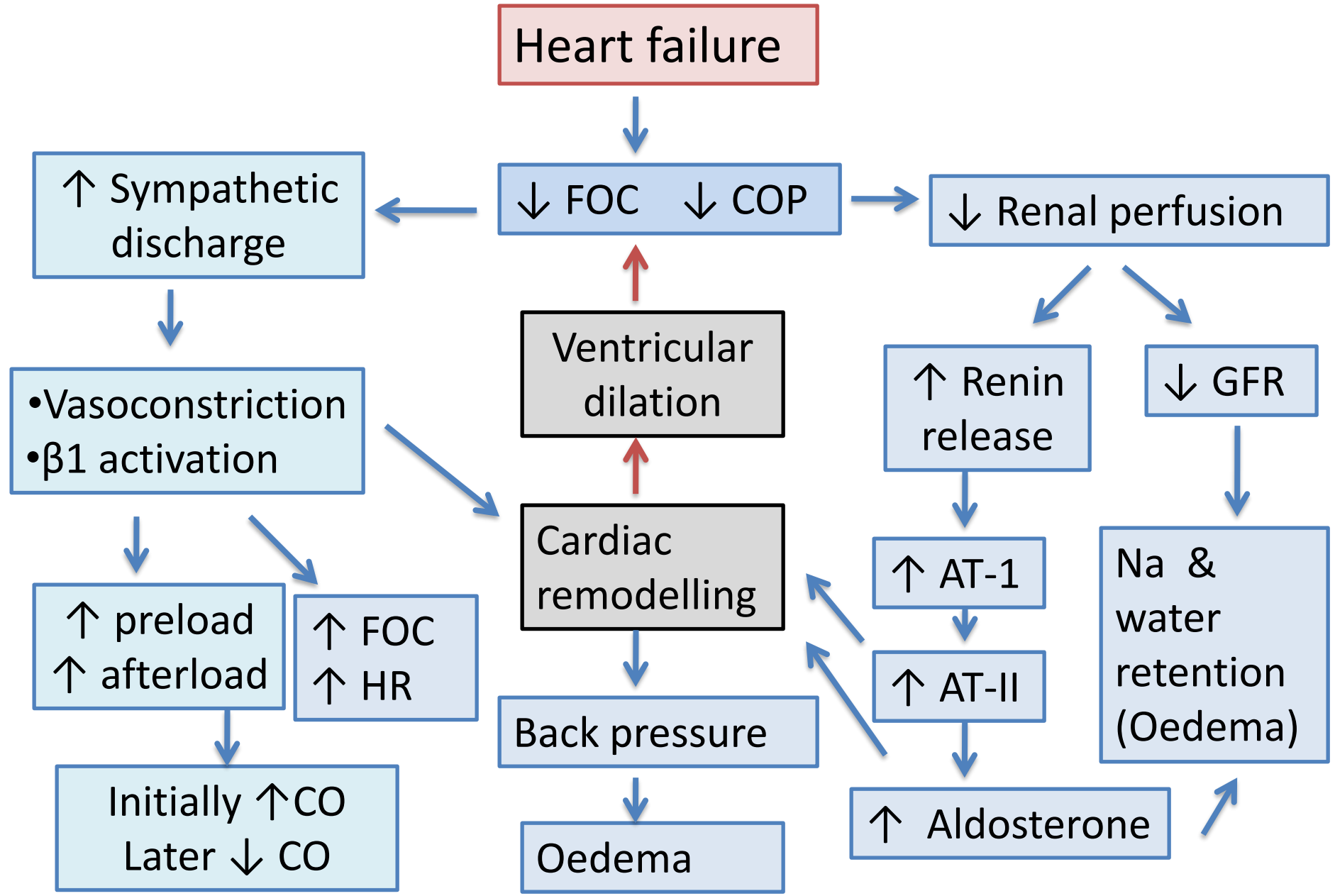
Causes of HF

- **Coronary artery disease** and heart attack (which may be "silent"): the most common cause
- **Cardiomyopathy:** is a chronic disease of the heart muscle (myocardium), in which the muscle is abnormally enlarged, thickened, and/or stiffened.
- High blood pressure (hypertension)
- Heart valve disease
- Congenital heart disease
- **Drug-induced heart failure**:

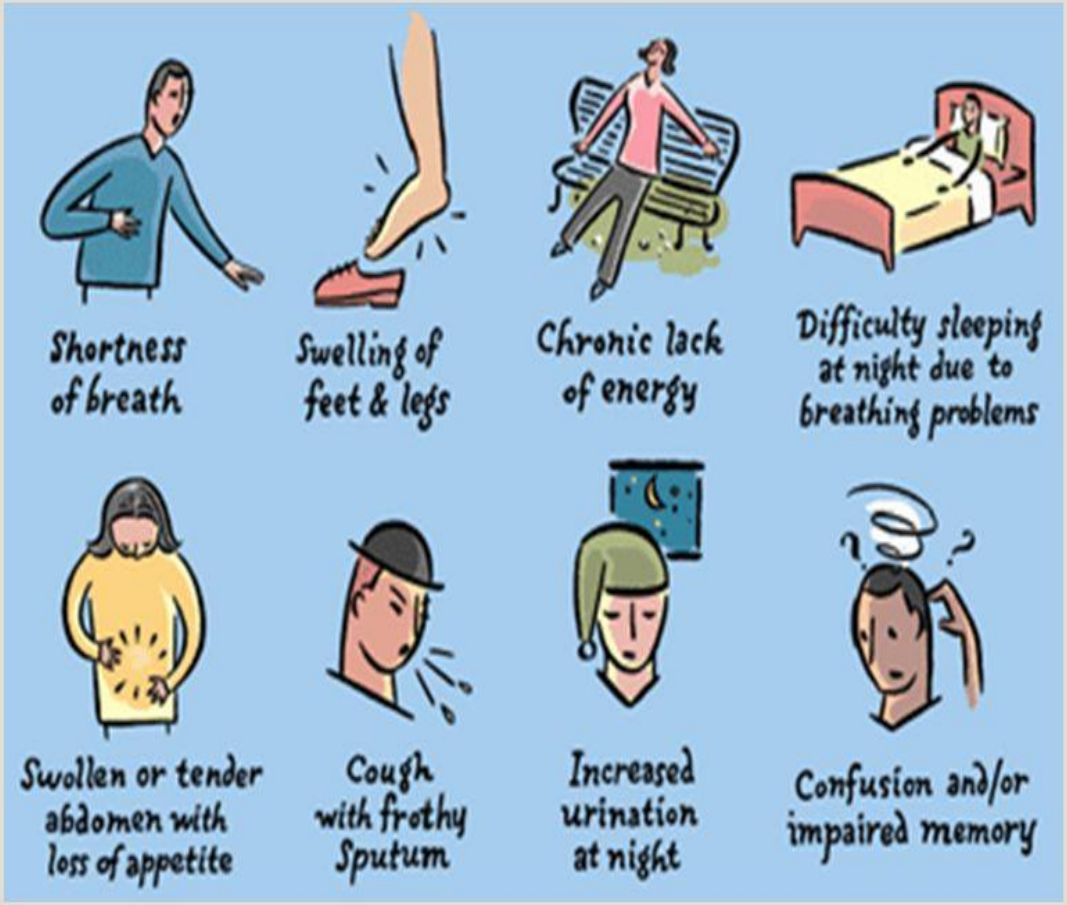
Drug-induced HF

- 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



Signs and Symptoms of heart failure

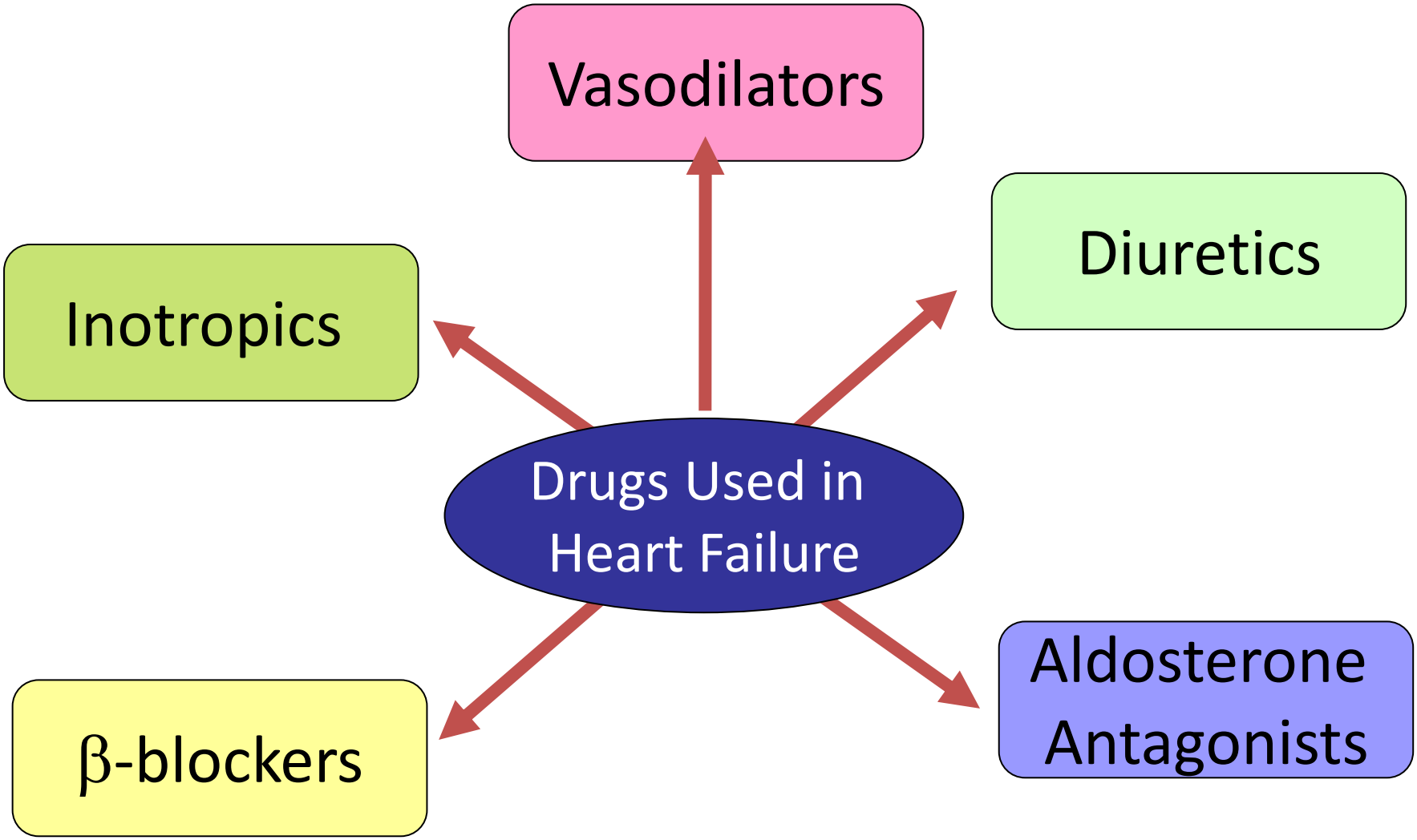


Symptoms:

- Dyspnoea
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Fatigue
- Cough (pink, frothy sputum)
- Nocturia

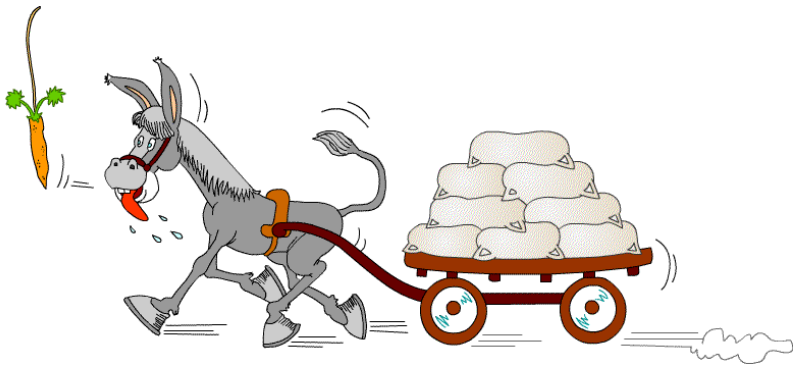
Signs:

- Resting tachycardia
- JVP elevation
- Lung crackles
- Wheezing
- 3rd heart sound
- Peripheral oedema
- Ascites


Vasodilators
Diuretics
Inotropics
Drugs Used in Heart Failure
Aldosterone Antagonists
β-blockers

Inotropic drugs

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



Like the carrot placed in front of the donkey

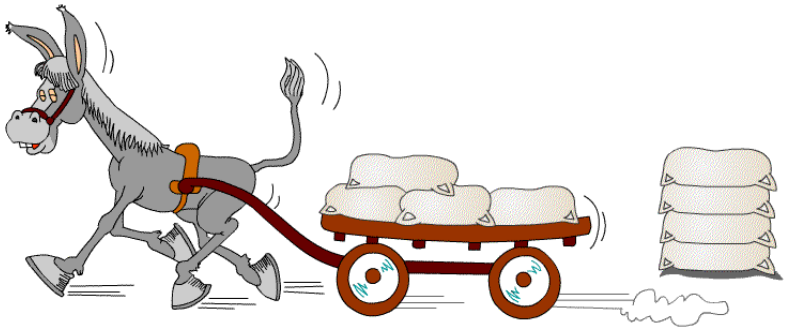
Vasodilators

- Arteriolar: hydralazine , minoxidil, nicorandil
- Venodilators: nitrates
- Arteriolar and venodilators: ACE inhibitors, angiotensin receptor blockers

Increase the donkey's efficiency

Diuretics

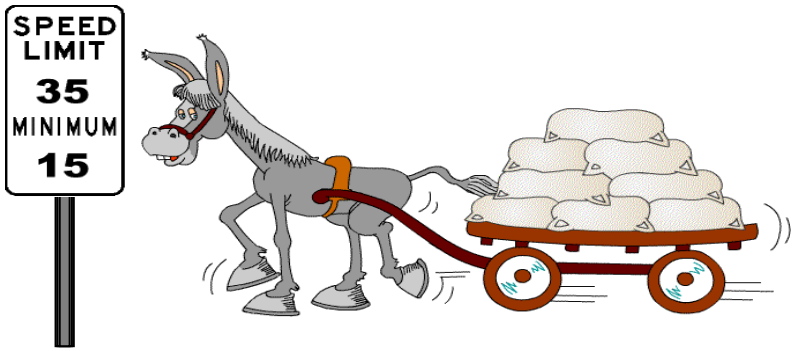
- Loop diuretics: furosemide, torsemide
- Thiazide diuretics: hydrochlorthiazide
- K+ Sparing diuretics:
  - Spironolactone (Also is aldosterone antagonist)
  - Amiloride



Reduce the number of sacks on the wagon

Beta Blockers

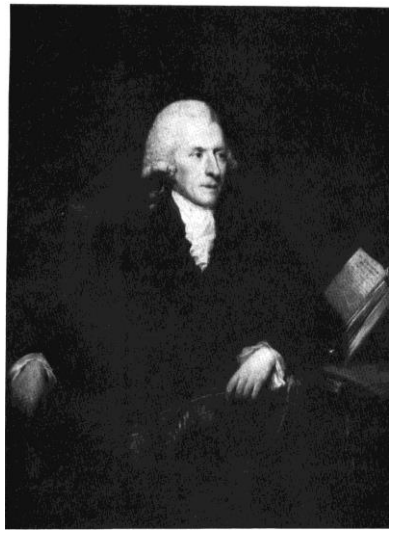
- Metoprolol, bisoprolol, carvedilol



Limit the donkey's speed,
thus saving energy

Inotropic Agents

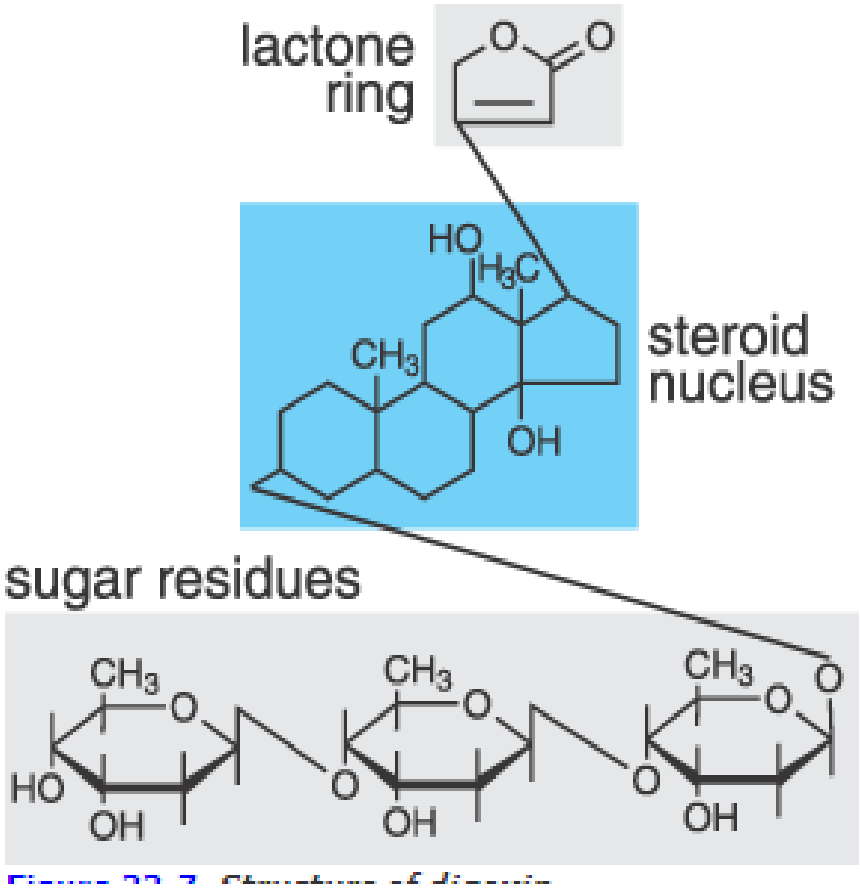
- Cardiac glycosides: Digoxin



William Withering 1785

Foxglove plant

Chemistry of cardiac glycosides



Aglycone (genin)
Responsible for pharmacodynamic activity

(glycon)Sugar influence pharmacokinetics

What is positive inotropic effect?

- (increase the contractile force of the cardiac muscles)
- This effect is manifested in patients with heart failure, this results in:
- increased C.O.P,
- decreased heart size,
- decreased pulmonary and systemic venous congestion,
- decreased blood volume, diuresis and relief of edema,
- also, digitalis increase mechanical efficiency of cardiac muscles as it increase C.O.P without increase in O2 consumption by cardiac muscles.

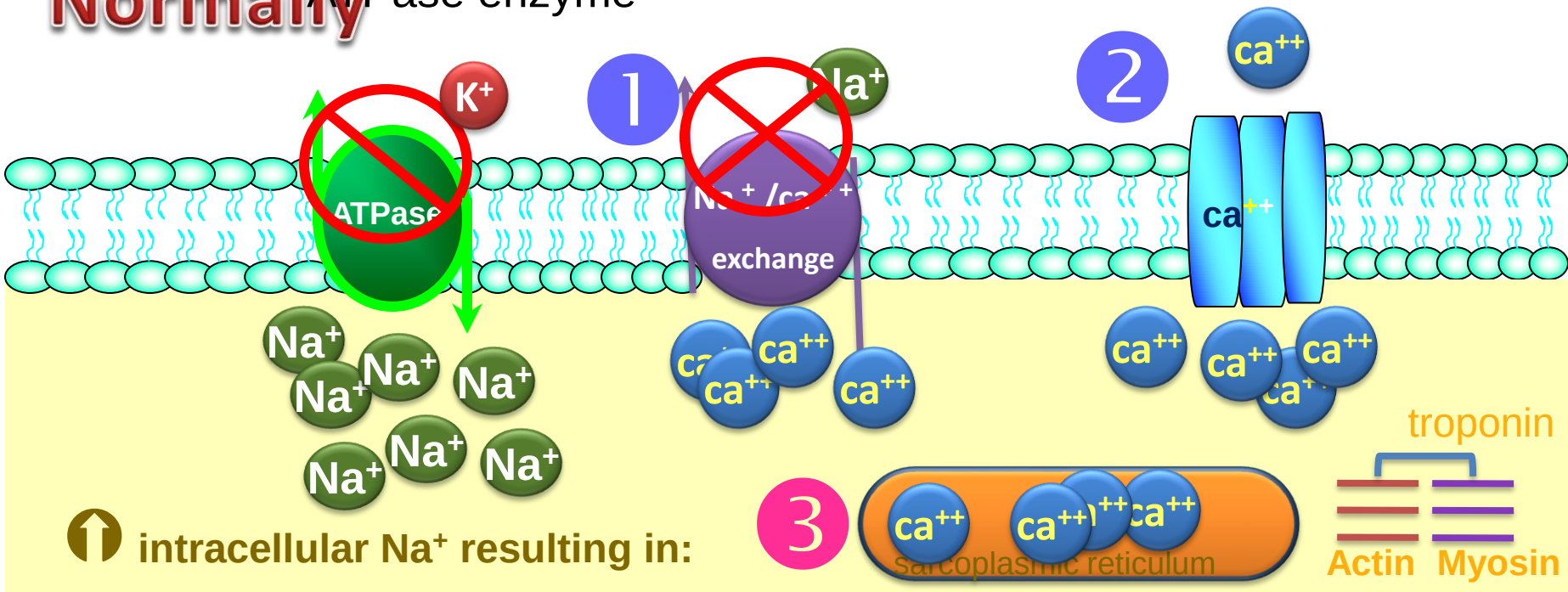
Digitalis

Mechanism of the +ve inotropic action:

Digitalis

Normally

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



⬆ intracellular Na^+ resulting in:

⬆⬆ Force Of Contractility

Digitalis increase intracellular free Ca+2 in the vicinity of the contractile proteins 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 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.

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

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.

Effect of digitalis on HR

Digitalis decrease heart rate in cases of congestive heart failure, atrial fibrillation, atrial flutter and Supraventricular tachycardia through:

(a) Indirect effect:

vagal and antiadrenergic effects (in therapeutic doses)

(b) direct effects.

Refractory period (RP) and conduction velocity (CV)

a- Atria: decrease of RP by direct and vagal effects and increase of CV.

b- A-V node: increase of RP by vagal and antiadrenergic & DIRECT effects and decrease of CV.

c- Ventricles: decrease of RP by direct effects and increase in CV

Cardiac glycosides - Digoxin

- Effects of digoxin on electrical properties of cardiac tissues:

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

Pharmacological actions

CARDIAC

- ↑force of contraction & Cardiac Output
- ↓ Heart rate
- ↓ Refractory period (RP) & ↑ Conduction velocity (CV) in atria/ventricles
- ↑ RP & ↓ CV in AV node
- Increased automaticity
- ECG: ↑PR interval , ↓ QT interval

EXTRA CARDIAC

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

Pharmacokinetic properties

Property	Digoxin	Digitoxin
Oral absorption	60 -80 %	90 -100 %
Plasma protein binding	25 %	95%
Onset of action	15 -30 min	½ to 1 hour
Duration of action	2-6 days	2-3 weeks
Plasma t ½	40 hrs	5-7 days
Route of elimination	Renal excretion	Hepatic metabolism
Time for digitalization	5-7 days	25-30 days
Daily maintainence dose	0.125 – 0.5 mg	0.05 -0.2 mg
Administration	Oral / IV	Oral

Cardiac Glycosides (Digitalis)

- Two glycosides:

Used

  - Short acting **Digoxin** (t½: **1.5** days)

  - Long acting **Digitoxin** (t½: **5** days)

Severely limited Use

Uses of Digoxin

Congestive heart failure

Cardiac arrhythmias

- Atrial fibrillation
- Atrial flutter
- Paroxysmal supraventricular tachycardia

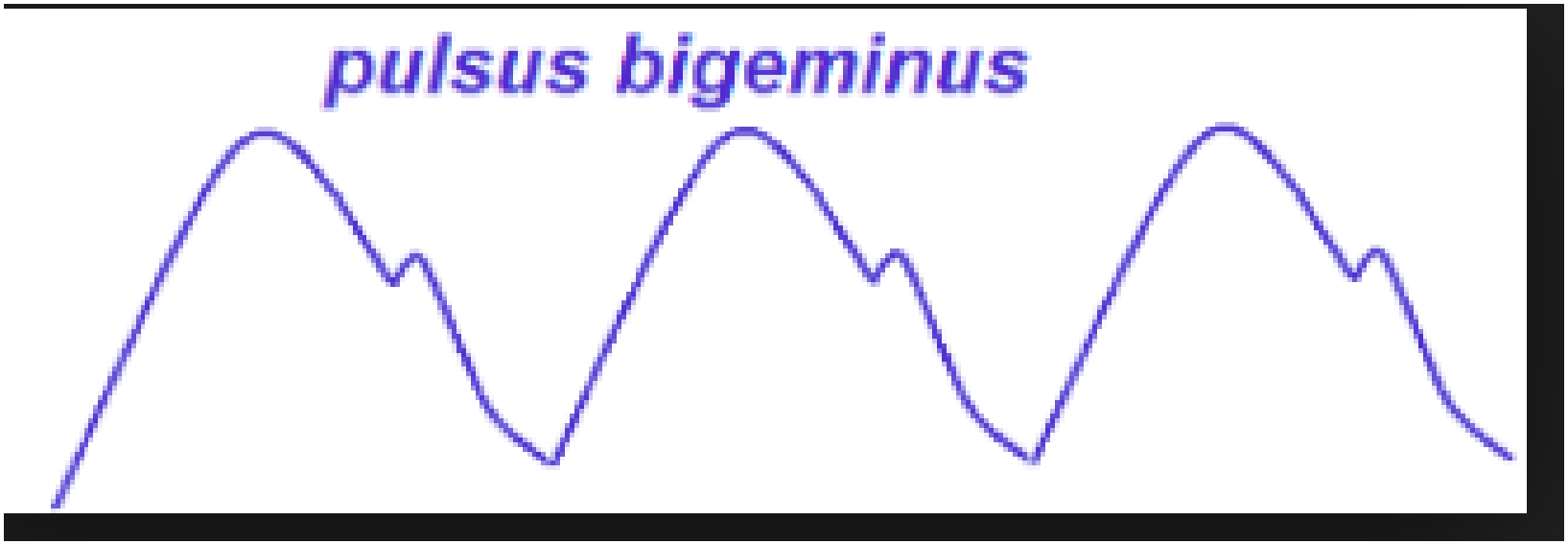
Adverse effects of digoxin

Extra-Cardiac

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

Cardiac

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


pulsus bigeminus

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 0.6 -1.2 mg IM
- Digoxin antibody

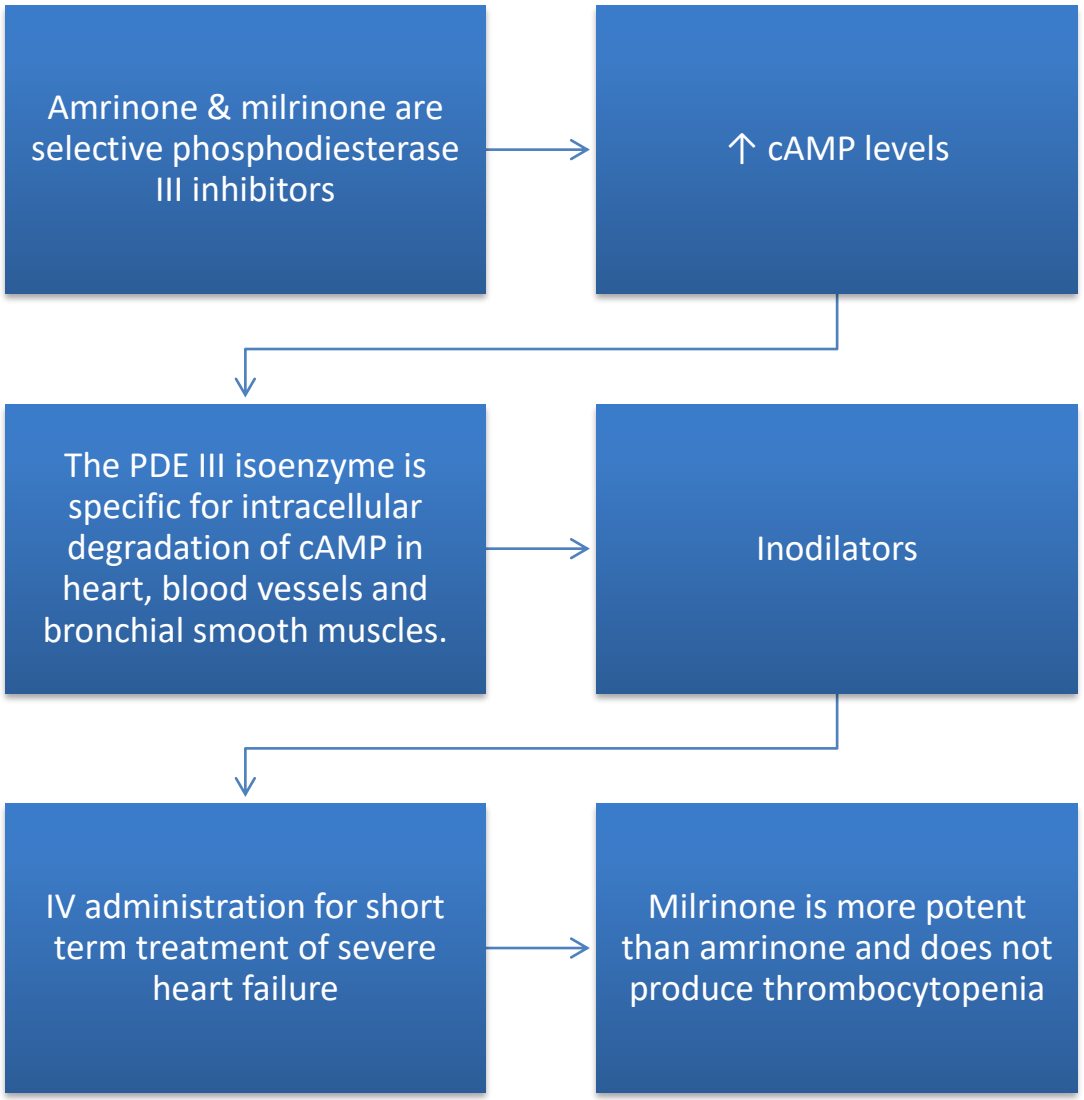
Contraindications of Digitalis

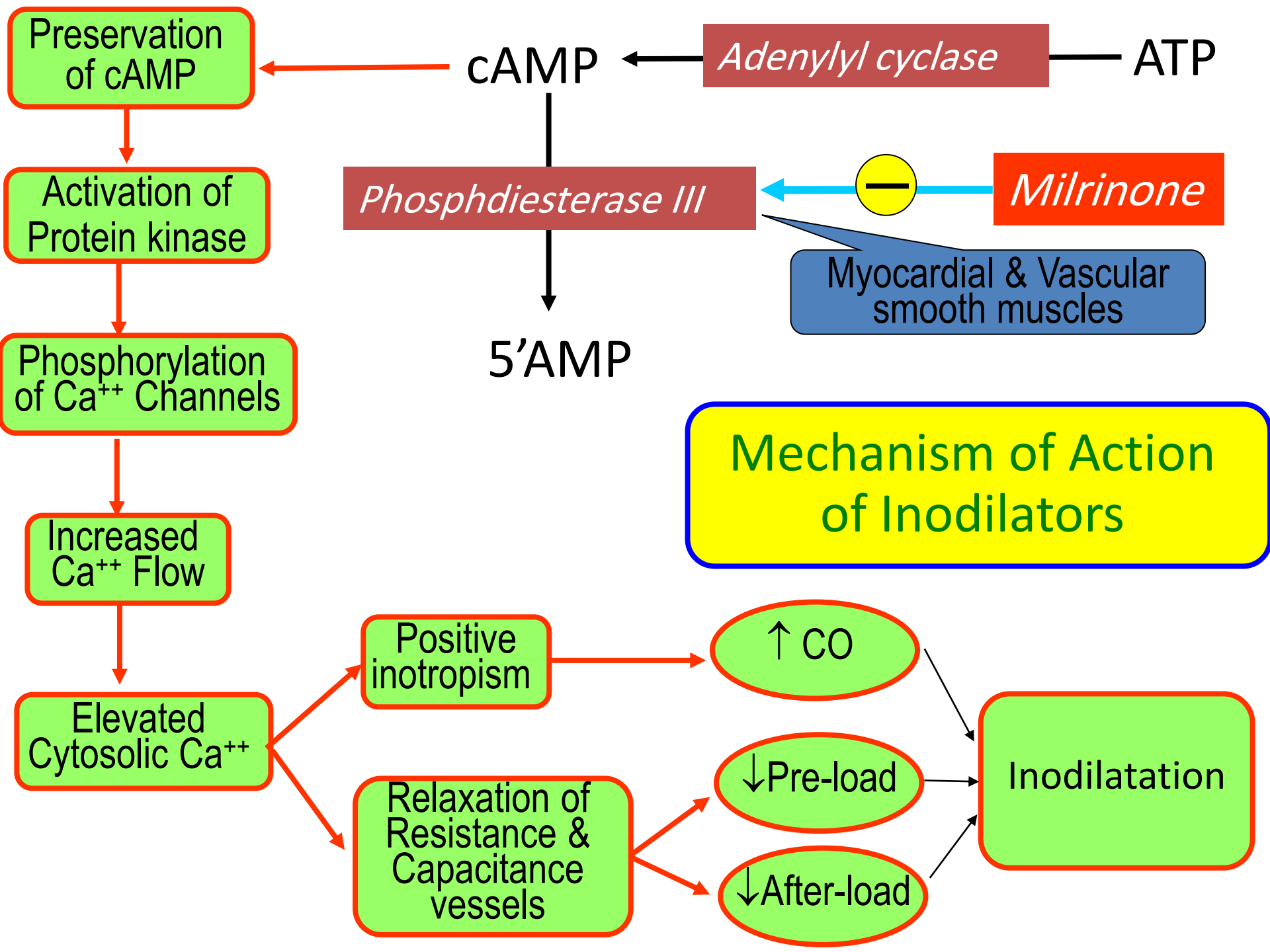
Carditis (myocarditis)
Increased calcium
WPW syndrome
Hypokalemia & **H**ypomagnesemia
Elderly
AV block (partial)
Renal failure
Thyroid (hyper or hypo)

"Contraindicated In Weak HEART"

Phosphodiesterase inhibitors in heart failure

Phosphodiestrase inhibitors




Preservation of cAMP
cAMP
Adenylyl cyclase
ATP
Activation of Protein kinase
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

Other inotropic drugs

Dopamine

Dobutamine

Role of diuretics in heart failure

Role of diuretics

Almost all symptomatic Patients treated with a diuretic

High ceiling diuretics (loop diuretics) preferred

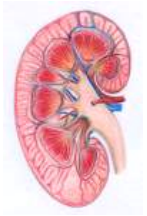
- Low dose therapy for maintainence

They increase salt and water excretion & reduce blood volume

- Reduce preload & venous pressure
- Improve cardiac performance & relieve edema

ACE Inhibitors in heart failure

- Angiotensin converting enzyme inhibitors
  - Captopril, enalapril, ramipril, lisinopril
- Act by
  - Reduction of after load
  - Reduction of preload
  - Reversing the compensatory changes
- ACE inhibitors are the most preferred drugs for treatment of Congestive cardiac failure



Angiotensinogen

Renin

Angiotensin I

Angiotensin Converting Enzyme (ACE)

Synthesis Blocker

ACE inhibitor

Angiotensin II

AT2

AT1

Angiotensin Receptor Blocker

Receptor Blocker

Angiotensin III

Angiotensin receptor blockers in heart failure

- Losartan , candesartan, valsartan, telmisartan
- 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

Drugs used in heart failure

Chronic heart failure

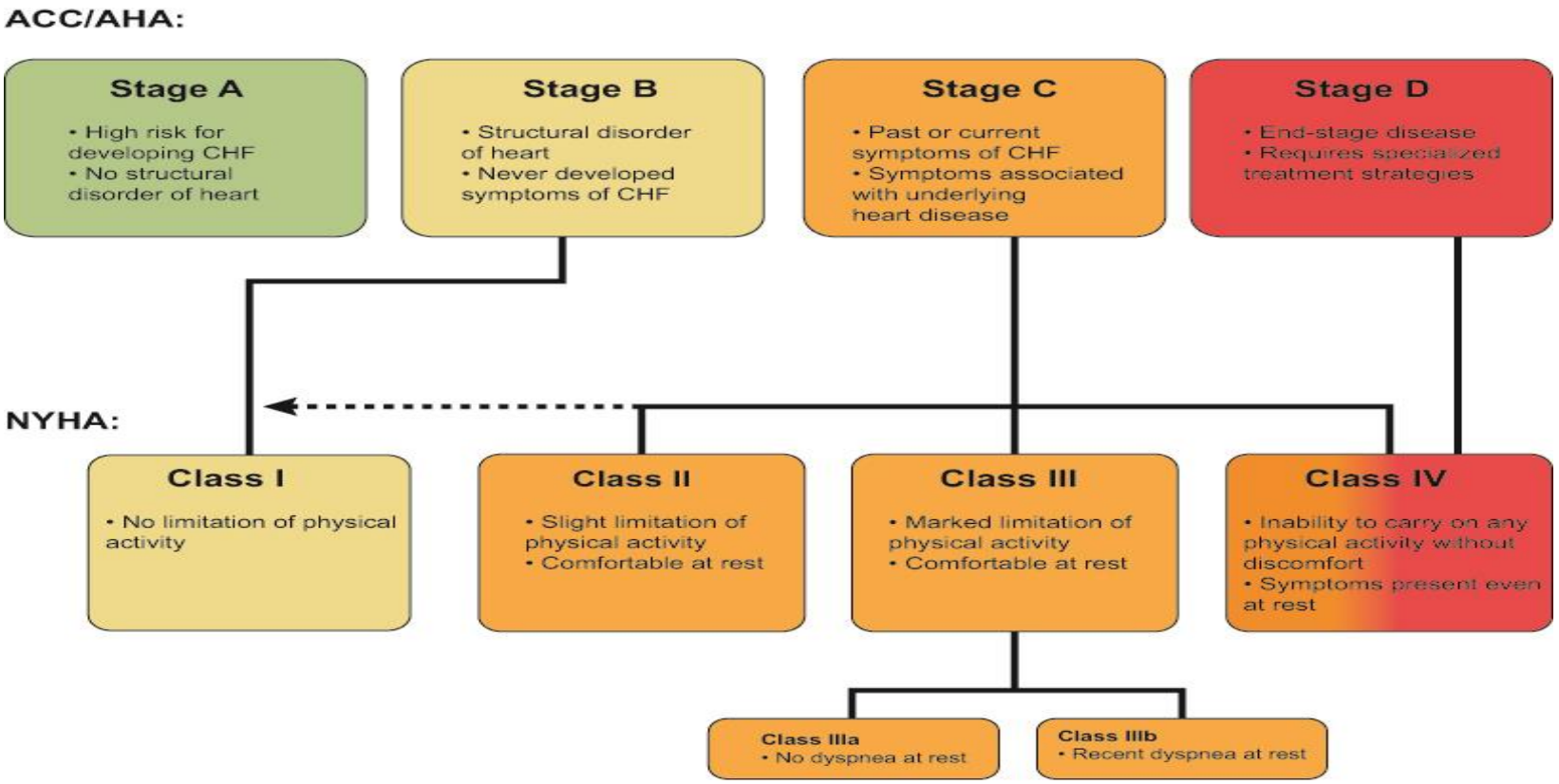
- Diuretics
- Aldosterone receptor antagonist
- ACE inhibitors
- Angiotensin receptor blockers
- Cardiac glycosides
- Vasodilators

Acute heart failure

- Diuretics
- Vasodilators
- Dopamine, dobutamine
- Amrinone

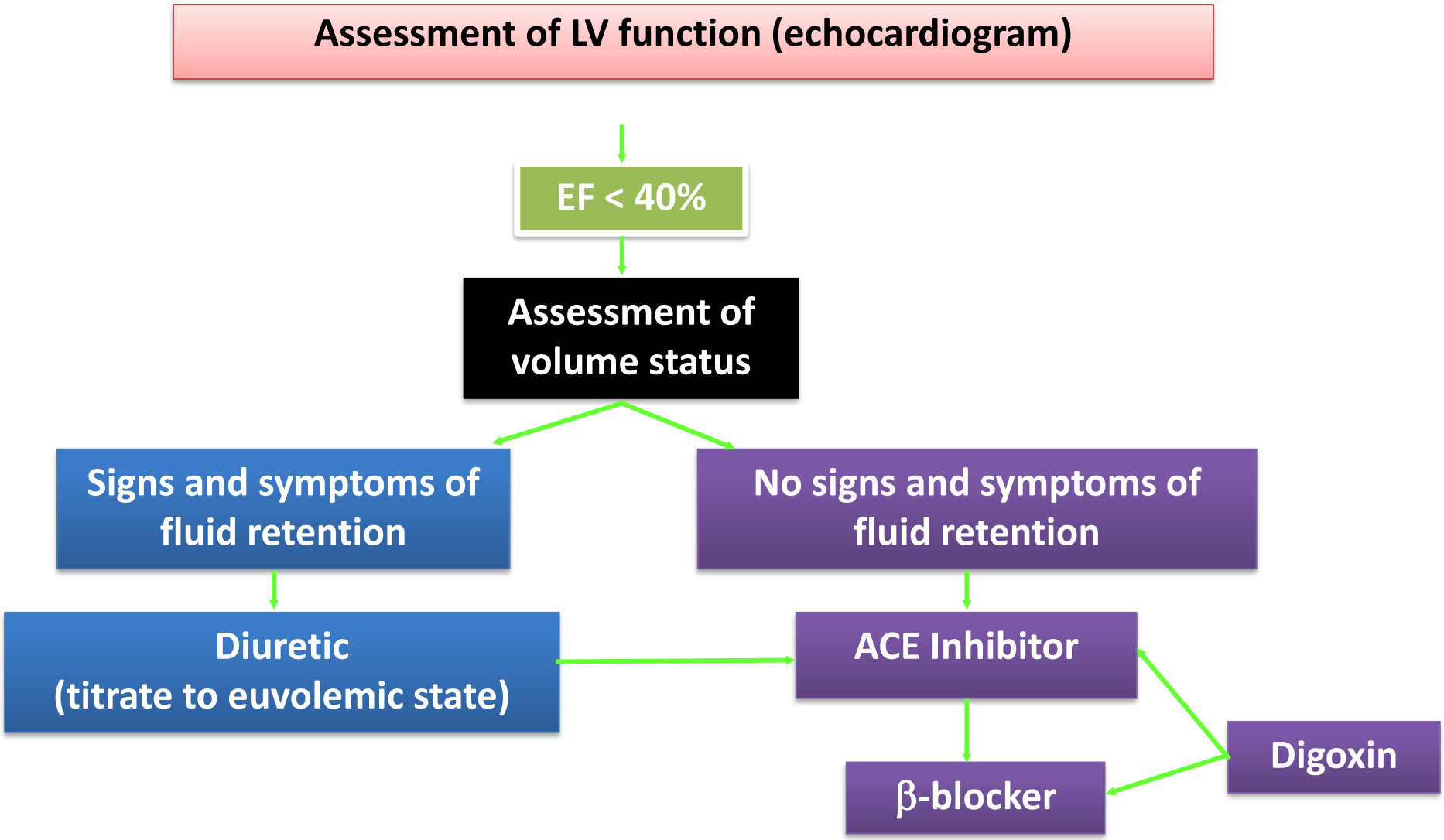
-

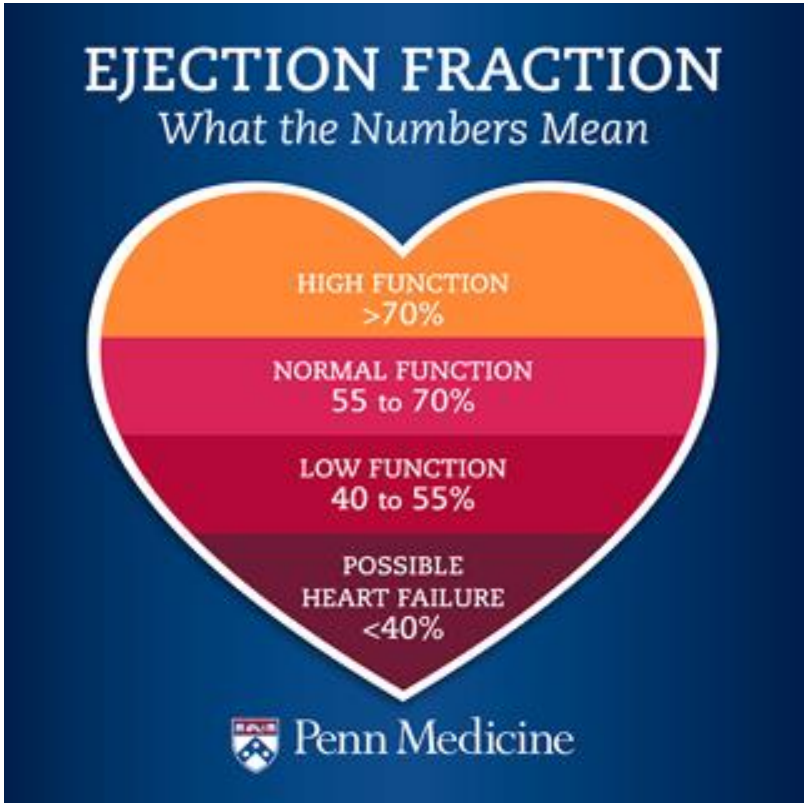
Stages and classes of heart failure:

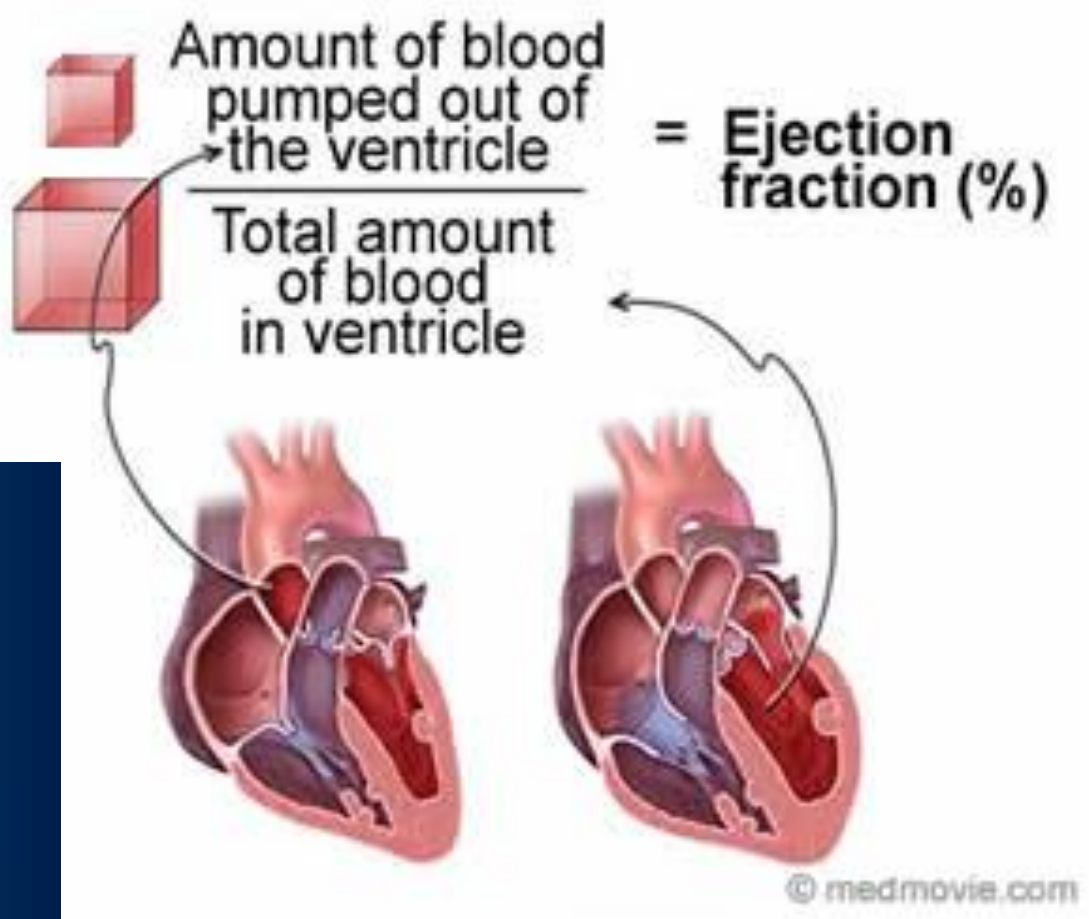


ACC/AHA: The American College of Cardiology/American Heart Association.
NYHA: New York Heart Association (NYHA)

Approach to the Patient with Heart Failure




EJECTION FRACTION
What the Numbers Mean
HIGH FUNCTION
>70%
NORMAL FUNCTION
55 to 70%
LOW FUNCTION
40 to 55%
POSSIBLE
HEART FAILURE
<40%
Penn Medicine


Amount of blood pumped out of the ventricle
Total amount of blood in ventricle
= Ejection fraction (%)
© medmovie.com

Treatment of 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

Thank you