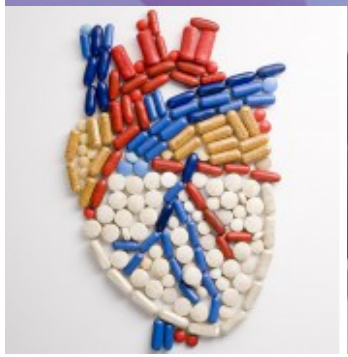
King Saud University
College of Medicine
1st Year, 4th Block

Drug Therapy for Heart Failure 5&6



Cardiovascular Block

Objectives :

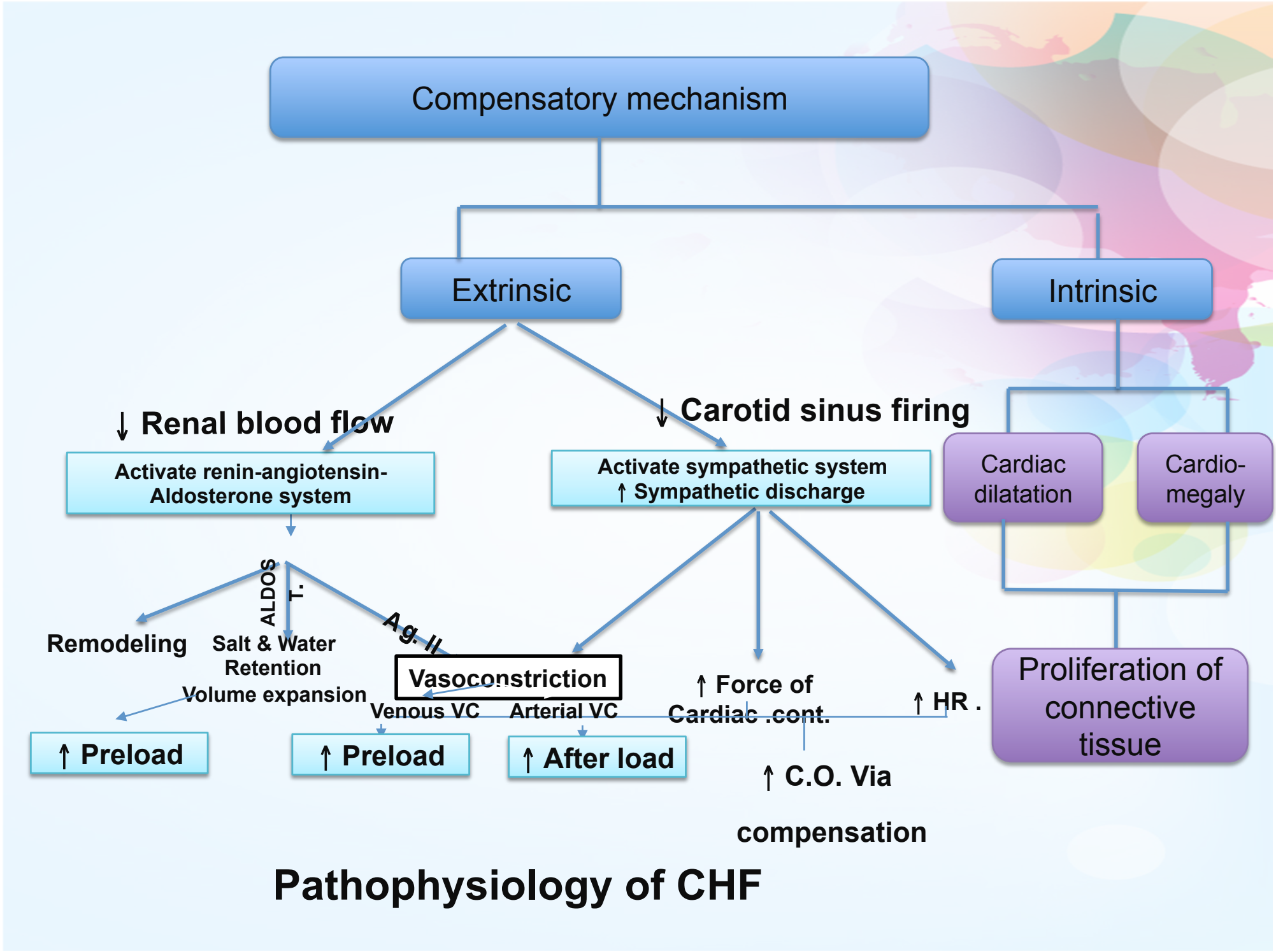
1	Describe the different classes of drugs used for treatment of acute & chronic heart failure
2	Describe the mechanism of action , therapeutic uses , side effects & drug interactions of individual drugs used for the treatment of heart failure

Remember That :

HEART FAILURE (HF) : Inability of the heart to maintain an adequate cardiac output to meet the metabolic demands of the body (low cardiac output HF)

- High cardiac output although it is high but it can't meet the metabolic demand also it is RARE.

HF causes: disorder of coronary arteries (common) – hypertension – cardiomyopathy – arrhythmia – heart valve disorder.



Pathophysiology of CHF

Heart failure symptoms

- Tachycardia
- rapid fatigue → **Low C.O**
- Peripheral edema → Especially in R and L HF
- Cardiomegaly
- pulmonary congestion → **Dyspnea**

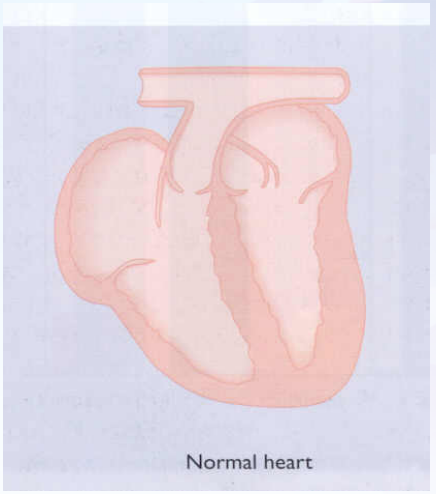
Factors affecting cardiac output and Heart Failure:

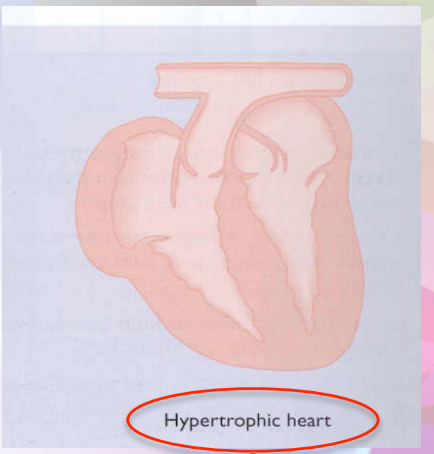
Cardiac contractility

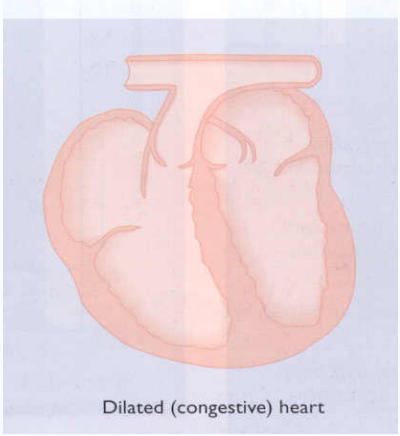
Preload (high in HF patients)

Afterload (high in HF patients)

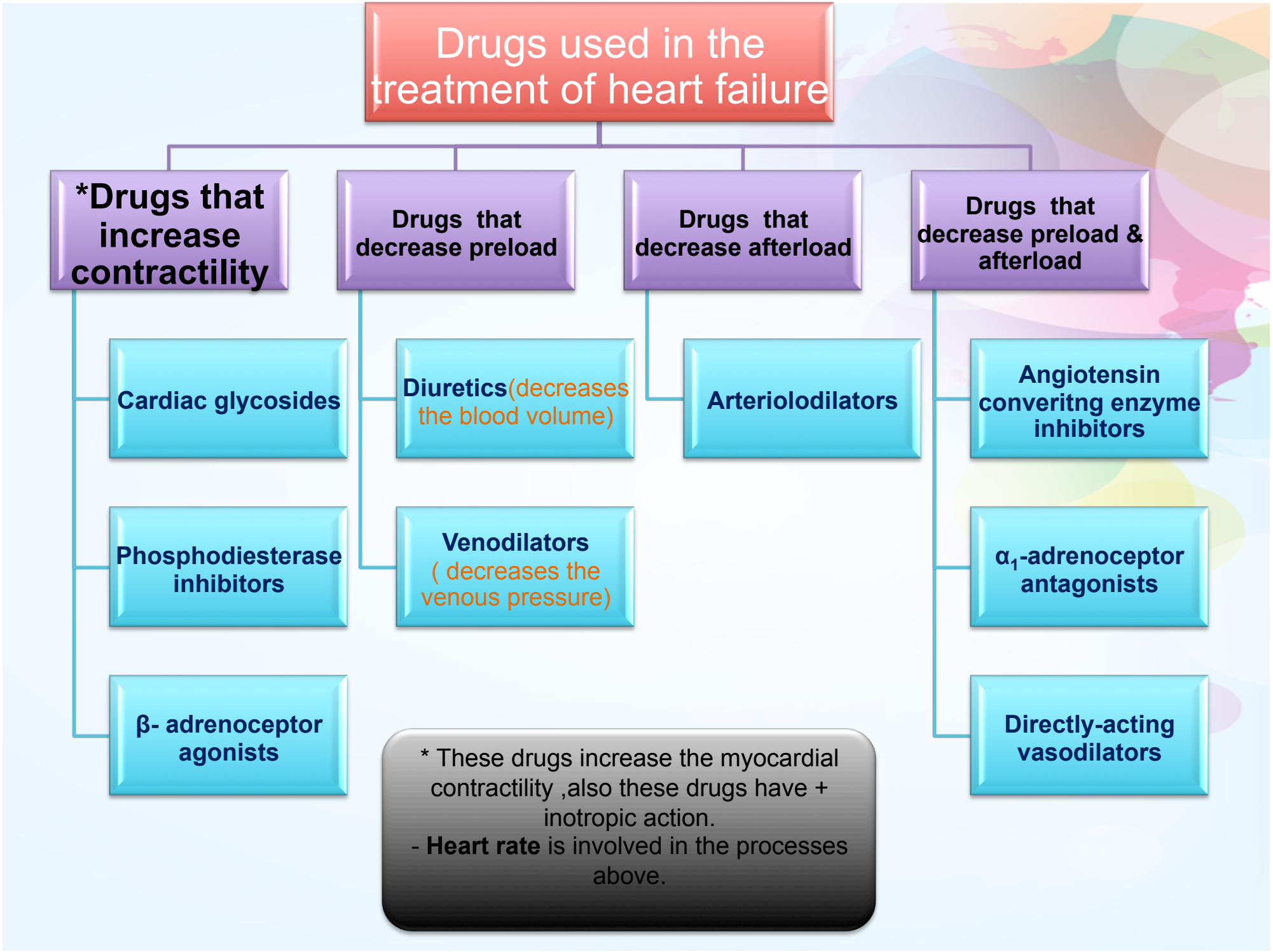
Heart rate.







Connective tissue **NOT** muscles.


Drugs used in the treatment of heart failure
*Drugs that increase contractility
Drugs that decrease preload
Drugs that decrease afterload
Drugs that decrease preload & afterload
Cardiac glycosides
Phosphodiesterase inhibitors
β- adrenoceptor agonists
Diuretics(decreases the blood volume)
Venodilators (decreases the venous pressure)
Arteriolodilators
Angiotensin converitng enzyme inhibitors
α1-adrenoceptor antagonists
Directly-acting vasodilators
* These drugs increase the myocardial contractility ,also these drugs have + inotropic action.
- Heart rate is involved in the processes above.

Cardiac glycosides (**Digoxin**, Digitoxin, Oubain)

Source	Digitalis lanata (a plant)
Chemical structure	Sugar & steroid like
Mechanism of actions	Inhibits Na+ / K+ ATPase enzyme
Pharmacological actions	1- Direct increase in force of contraction of the myocardium (+ve inotropic effect). 2- Increase of heart excitability and automaticity (a sign of digoxin toxicity) 3- A- slowing of conduction and prolongation of atrial & A.V. node refractory period → (In ECG : prolongation of the PR interval) B- shortening of ventricular refractory period → (In ECG : reduced QT interval) EXTRACARDIAC EFFECTS:increases vagal activity on the heart : 1- Decrease of atrial refractory period leading to conversion of atrial flutter to fibrillation. 2- Slowing of A.V. conduction. 3- Bradycardia
Therapeutic uses	1- Congestive heart failure → right or left. 2- Atrial arrhythmias → Atrial flutter - Atrial fibrillation - Supraventricular tachycardia
Digoxin Pharmacokinetic	1- Drug has narrow therapeutic index. 2- **Absorption: orally : 40-80% leading to variable bioavailability. - I.V. acts within 15 min-3hrs** 3- metabolized in liver to cardioactive metabolite 4- excreted mainly by kidney.
Cardiac Adverse effects.	digitalis-induced arrhythmias can cause any type of arrhythmia especially: extrasystoles, coupled beats _ ventricular tachycardia or fibrillation _ A.V.block, cardiac arrest.
Extra-cardiac adverse effects(Other organs)	GIT : are common and among the earliest signs of toxicity : (Anorexia ,nausea,vomiting, diarrhea) C.N.S. :Headache, visual disturbances, drowsiness (in old age)
contraindications	Toxic myocarditis (viral- bacteria) - Constrictive pericarditis – Cardioversion (pacemaker)
Drugs interactions	Diuretics→ hypokalemia (arrhythmia) - Quinidine : ↑plasma level of digitalis With diuretics we should stop the drug or shift to K-sparing diuretics.

The physiological mechanism of Na^{+}/K^{+}ase enzyme

It activates:

1. Na^{+}/K^{+} pump.
2. Na^{+}/Ca^{+} exchange (Na in and Ca out)

Digoxin

1- it inhibits Na^{+}/K^{+}ase enzyme as a result:
Na^{+}/K^{+} pump and Na^{+}/Ca^{+} exchange will be inhibited, this will increase the Ca and increases the contraction.
2- it facilitates the entry of Ca through Ca channels→ ↑ intracellular Ca.
3- it triggers the sarcoplasmic reticulum to release Ca then increases the intracellular Ca.

Factors increase digitalis toxicity:

1. Small Lean body mass→(the store of digoxin is the skeletal muscles so if the body mass is small there will be no store for digoxin and the free level of digoxin in the plasma will increase)
2. Renal diseases→ (the main excretion site of digoxin is kidney)
3. Hypothyroidism→ (they already have decreased metabolic rate of some drugs including digoxin)
4. Hypokalemia- Hypomagnesemia→ They increases the action of digoxin, because that patients who take diuretics(diuretics decrease potassium) and also take digoxin they may develop digitalis toxicity so they must take K supplements
5. Hypercalemia→ They increases the action of digoxin

Treatment OF Adverse effects:

1) Stop the drug.
2) If they take diuretics (not certain type) they have to stop it
3) But if they take k sparing diuretics they don't have to stop it.

- FAB fragments : a very expensive antibodies that stop the mechanism of digoxin immediately (by binding to digoxin)

- **Antiarrythmics**

	β-Adrenoceptor agonists	Phosphodiesterase Inhibitors
Examples	Dopamine- Dobutamine	Bipyridines :(Amrinone **,Milrinone**) only available in parenteral form. It excreted in urine.
Mechanism of action	**Dopamine** → Acts on: α ,β1 and dopamine receptors. **Dobutamine** → Selective β1 agonist	Inhibit phosphodiesterase isozyme 3 in cardiac & smooth muscles → :↑ cAMP* **This results in:** In the heart : Increase myocardial contraction In the peripheral vasculature : Dilatation of both arteries & veins → ↓ afterload & preload
Therapeutic uses	**Dopamine** →acute L.H.F. mainly in patients with impaired renal blood flow (because it makes vasodilatation) **Dobutamine** →in the treatment of acute heart failure (the most used drug because it is cardio selective)	**Used only intravenously for management Of:** Short –term treatment of heart failure (acute heart failure) * Has + inotropic action.

Phosphodiesterase Inhibitors Adverse effects

1. Nausea ,vomiting
2. Arrhythmias (less than digitalis)
3. **Thrombocytopenia**
4. **Liver toxicity**
5. Milrinone less hepatotoxic and less bone marrow depression than amrinone.

Reduction of preload

1. Diuretics

General Diuretics → give k supplements.	potassium sparing diuretics → no need for k supplements.
Action	• Reduce salt and water retention → ↓ventricular preload and venous pressure. • Reduction of edema and its symptoms. • Reduction of cardiac size → improve cardiac performance.
Drug	hydrochlorothiazide

2. Venodilator

Action	Dilate venous capacitance vessels and reduce venous pressure and preload.
Drug	Nitroglycerine → used for short term IV treatment of severe heart failure when the main symptom is dyspnea due to pulmonary congestion.

Afterload=systemic vascular resistance.

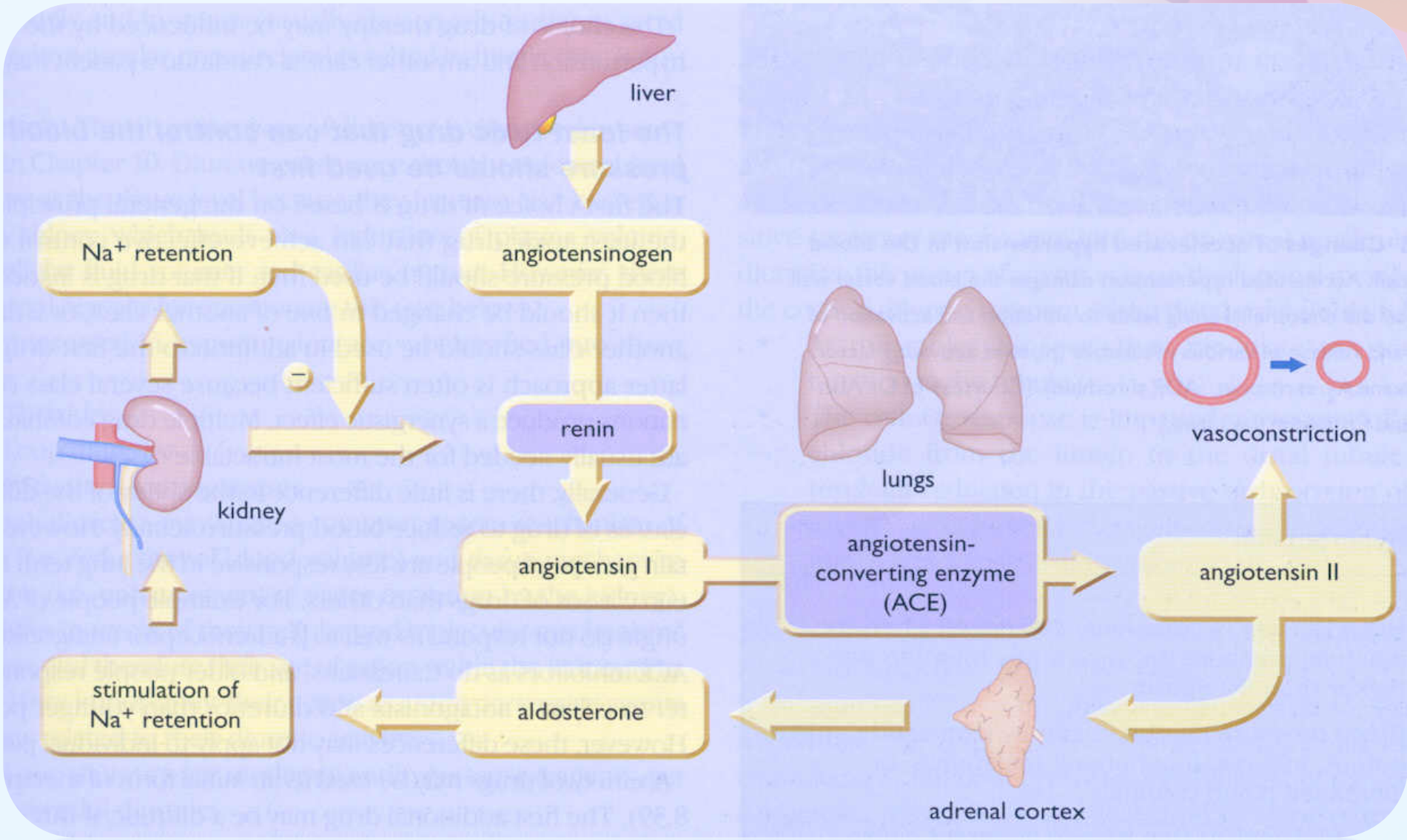
Reduction of afterload

Arteriolodilators

Action	Reduce peripheral vascular resistance.
Drug	hydralazine → selective arteriolodilators , used when the main symptome is rapid fatigue due to low cardiac output.

Reduction of preload and afterload

1. Renin-angiotensin-aldosteronne system.



Reduction of preload and afterload

1. Renin-angiotensin-aldosteronne system.

Drugs acting on the renin- angiotensin - aldosterone system		
Drugs	1- Angiotensin-converting enzyme inhibitors (ACEI)	2- Angiotensin receptor blockers (ARBs)
e.g.	captopril - enalapril - lisinopril	losartan - valsartan - irbesartan
Mechanism of action	Inhibit angiotensin II production leading to: - vasodilatation. (reduction of peripheral resistance) - Fall in aldosterone production.	- block AT1 receptors. - decrease actions of angiotensin II.
Uses of ACEIs & ARBS in HF	↓ Peripheral resistance (Afterload). ↓ Venous return (Preload) . ↓ sympathetic activity . ↓ remodeling→ ↓mortality rate (improve survival rate).	

2. Direct acting vasodilators.

- e.g. : Sodium nitropruside.
- given I.V. in acute or severe refractory heart failure, acts immediately and effects lasts for 1-5 minutes.

Uses of β- adrenoceptor antagonists (β blockers) in HF

Not all (β blockers), just 3 drugs

- Cardioselective: (β1 receptors). e.g. Bisoprolol, Metoprolol
- Non cardioselective: (β1 &β2) & α1-adrenoceptor blocking effect . e.g carvedilol .

Mechanism of beneficial β- blockers effects in HF:

- Reduce remodeling through inhibition of the mitogenic activity of catecholamines.
- Reduce oxidative stress (carvedilol).
- Decrease heart rate .
- Attenuate the adverse effects of catecholamines.
- Inhibit renin release .
- Reduce the mortality rate.

Using β-blockers in HF patients with comorbidities

Comorbidity is the presence of one or more additional disorders (or diseases) *with* a primary disease or disorder.

- After MI.
- Chronic obstructive pulmonary disease: treat with cardioselective.
- Diabetes mellitus : Reduce morbidity & mortality rate in diabetic patients with HF They have favorable metabolic effects.
- Peripheral vascular disease : Carvedilol due to its α1- blockade effect improve tolerability in patients with symptomatic claudication .

Management of chronic and acute HF

Chronic	Acute
Reduce work load of the heart. • Limits patient activity. • Reduce weight. • Control hypertension.	Volume replacement
Restrict sodium	Positive inotropic drugs (Phosphodiesterase inhibitors and Dobutamine)
ACEI or ARBs	Vasodilators (Na nitropruside)
Digitalis	Antiarrhythmic drugs
β- blockers	Treatment of myocardial infarction
Direct vasodilators	-------
Orally ← Diuretics →	IV

MCQs

1. Drugs that decrease preload only :
a. Venodilators
b. Arteriolodilators
c. Directly-acting vasodilators
d. Cardiac glycosides

2. the drug which has Direct acting vasodilators and use for acute or severe refractory heart failure is :
a. Sodium nitropruside
b. Enalapril
c. valsartan
d. Cardiac glycosides

3. The Drugs use for management of Short term treatment of heart failure :
a. Venodilators
b. Bipyridines
c. Directly-acting vasodilators
d. Cardiac glycosides

1. a 2.a 3.b 4.d 5.a 6.c

4. The Management of acute heart failure :
a. Digitalis
b. Restrict sodium
c. Reduce weight
d. Antiarrhythmic drugs

5. the heart failure patient come to the emergency department. the doctor is dignosis Him by hepatotoxicity . What is the most likely drug to cause those symptoms :
a. Amrinone
b. Diuretics
c. Directly-acting vasodilators
d. Venodilators

6. In ECG : the slowing of conduction and prolongation of atrial and A.V. node refractory period show as :
a. Decrease R-R interval
b. reduced QT interval
c. prolongation of the PR interval
d. NO P WAVE

PHARMACOLOGY 433

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We hope that we made this lecture easier for you

Good Luck !