

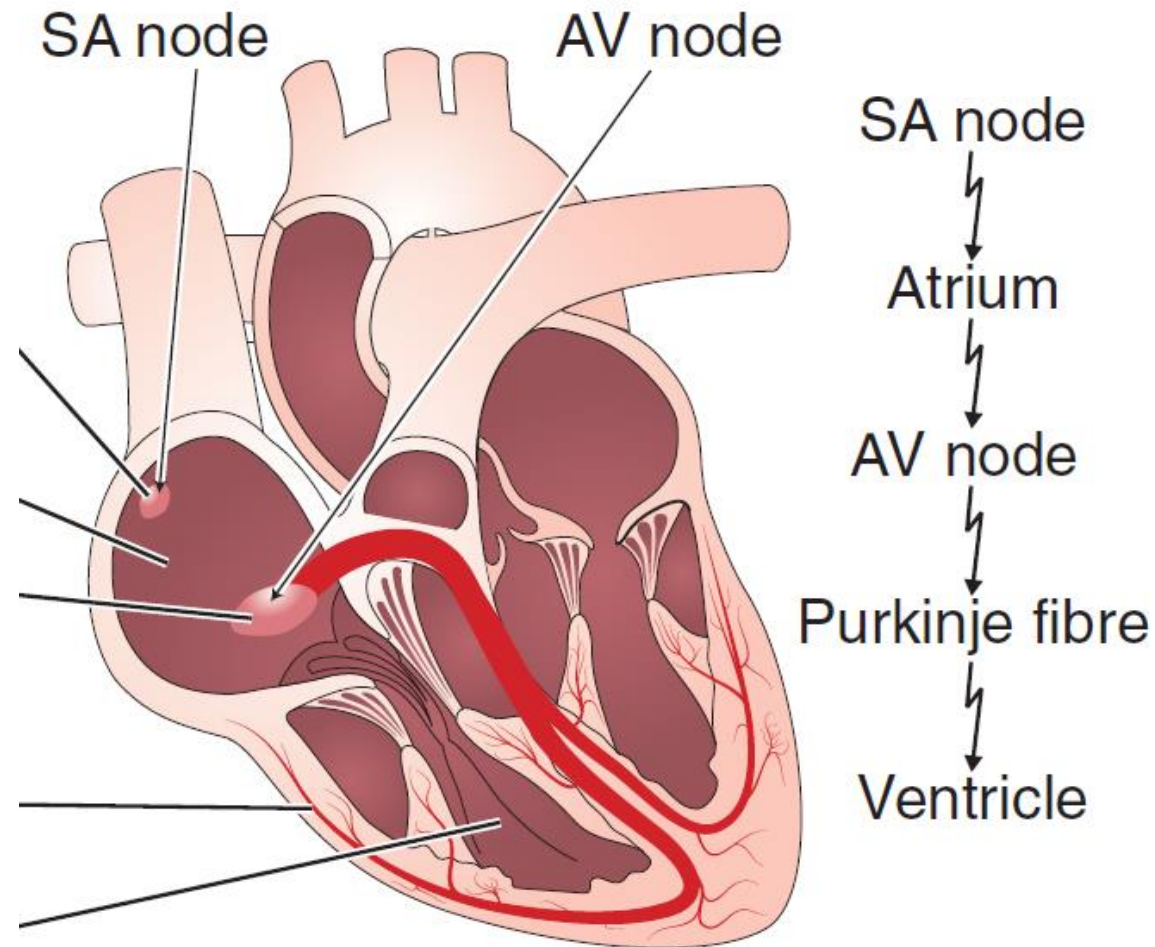
Heart Failure

By

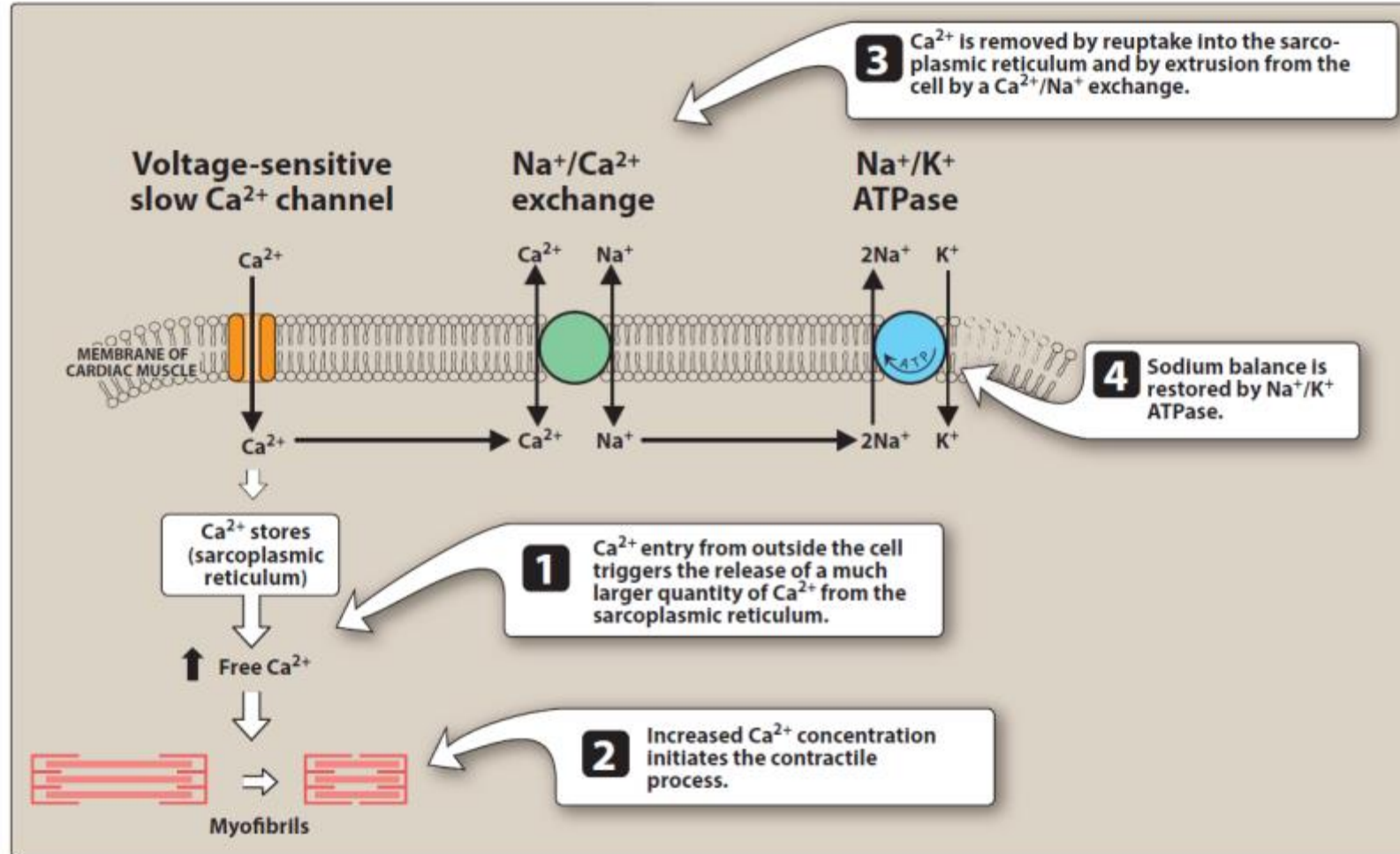
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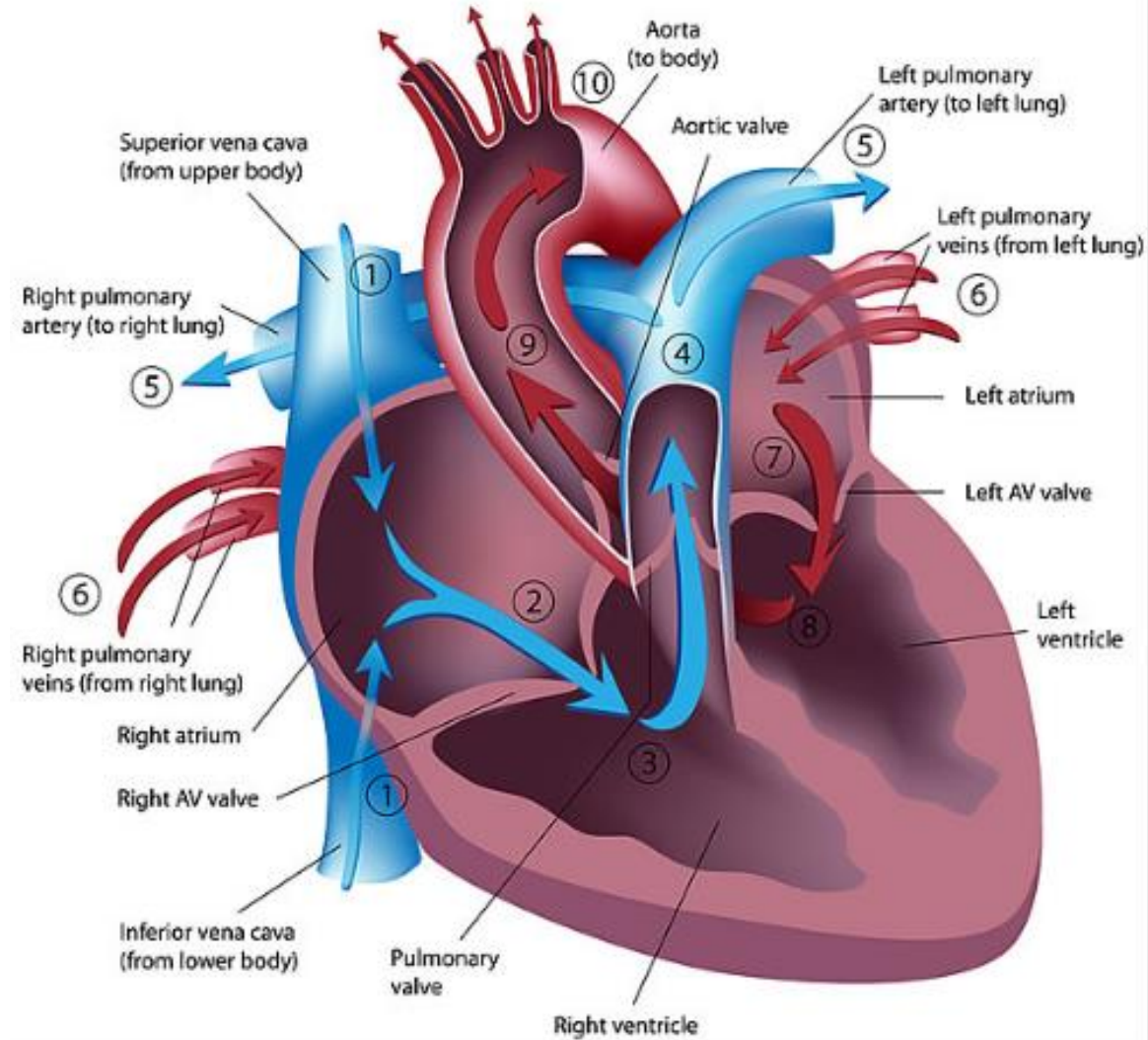
ELECTRICAL CONDUCTION SYSTEM



CARDIAC MUSCLE ACTION

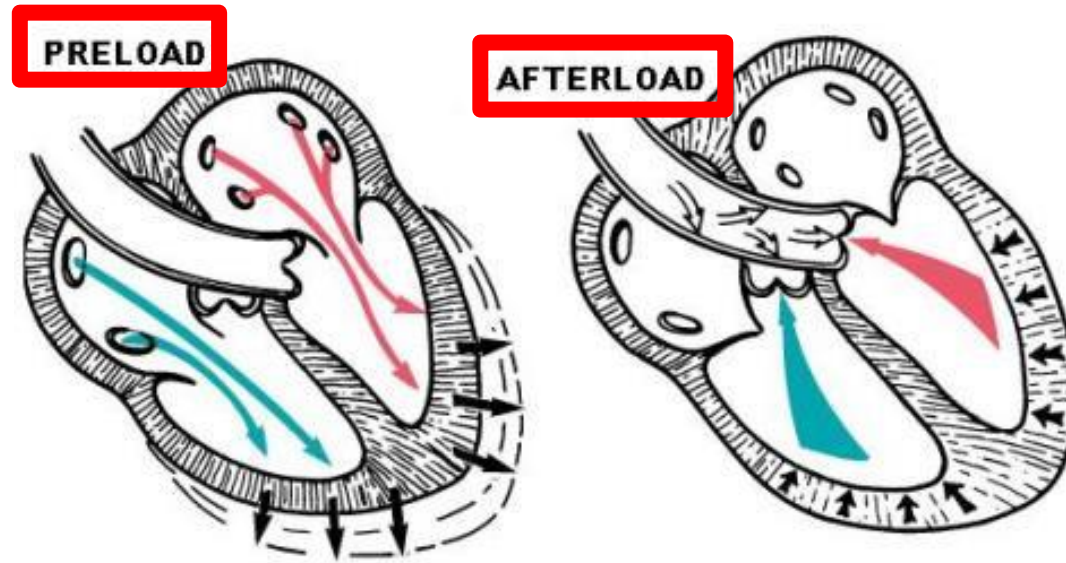


The pathway of blood flow through the heart



HEART FAILURE

- Heart failure, **complex progressive disorder**, is the **heart inability to pump sufficient blood to meet the needs of the body**.
- **Congestive heart failure** = clinical syndrome developed due to **accumulation of the blood in the left or right parts of the heart**.
- The causes of heart failure are still not completely understood.
 - Simple loss of functional myocardium; **myocardial infarction**.
 - Other causes; **chronic hypertension, valvular disease, coronary artery disease,**



- **Preload**, is the amount of ventricular pressure at the end of diastole.

Preload = venous return.

- **Afterload**, the pressure that the heart work against to eject blood during systole.

Afterload = arterial resistance.

TYPES

Low COP failure

High COP failure

Systolic Failure

(Failure due to reduction of **cardiac contractile force**)

Diastolic Failure

(Failure due to **stiffening or other changes** of ventricles that prevent adequate filling during diastole)

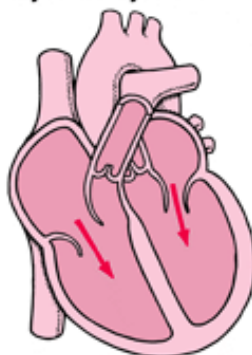
Systolic & Diastolic Failure

Left-sided failure

Right-sided failure

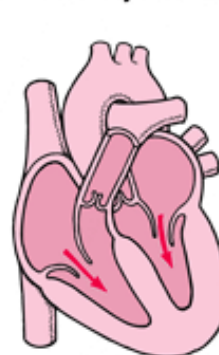
Biventricular failure

Systolic Dysfunction



The enlarged ventricles fill with blood.

Diastolic Dysfunction



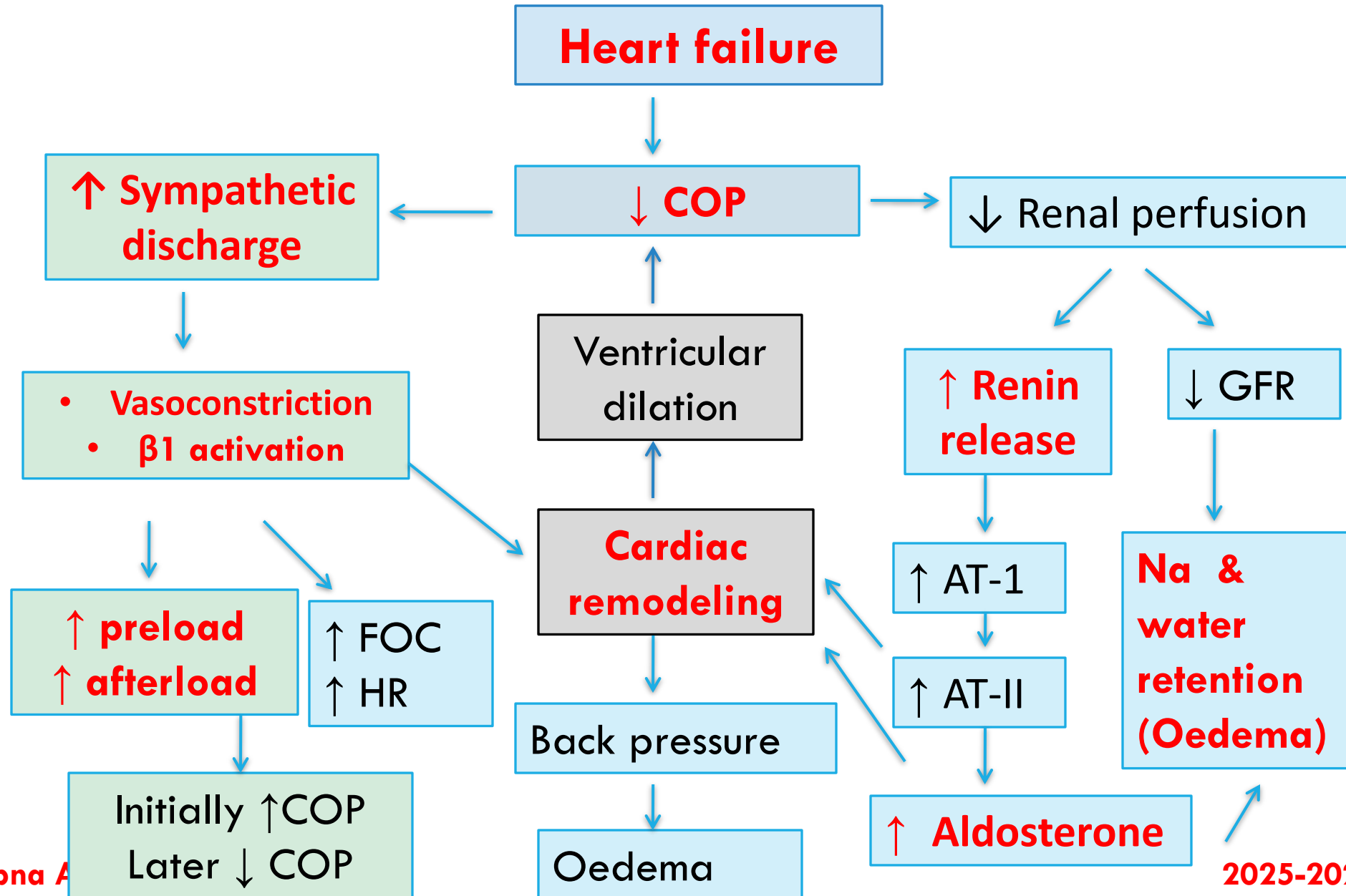
The stiff ventricles fill with less blood than normal.

PATHOPHYSIOLOGY

The homeostatic responses to depressed cardiac output:

- **The Sympathetic nervous system.**
- **The renin-angiotensin-aldosterone system (RAAS).**

Compensatory mechanisms during heart failure



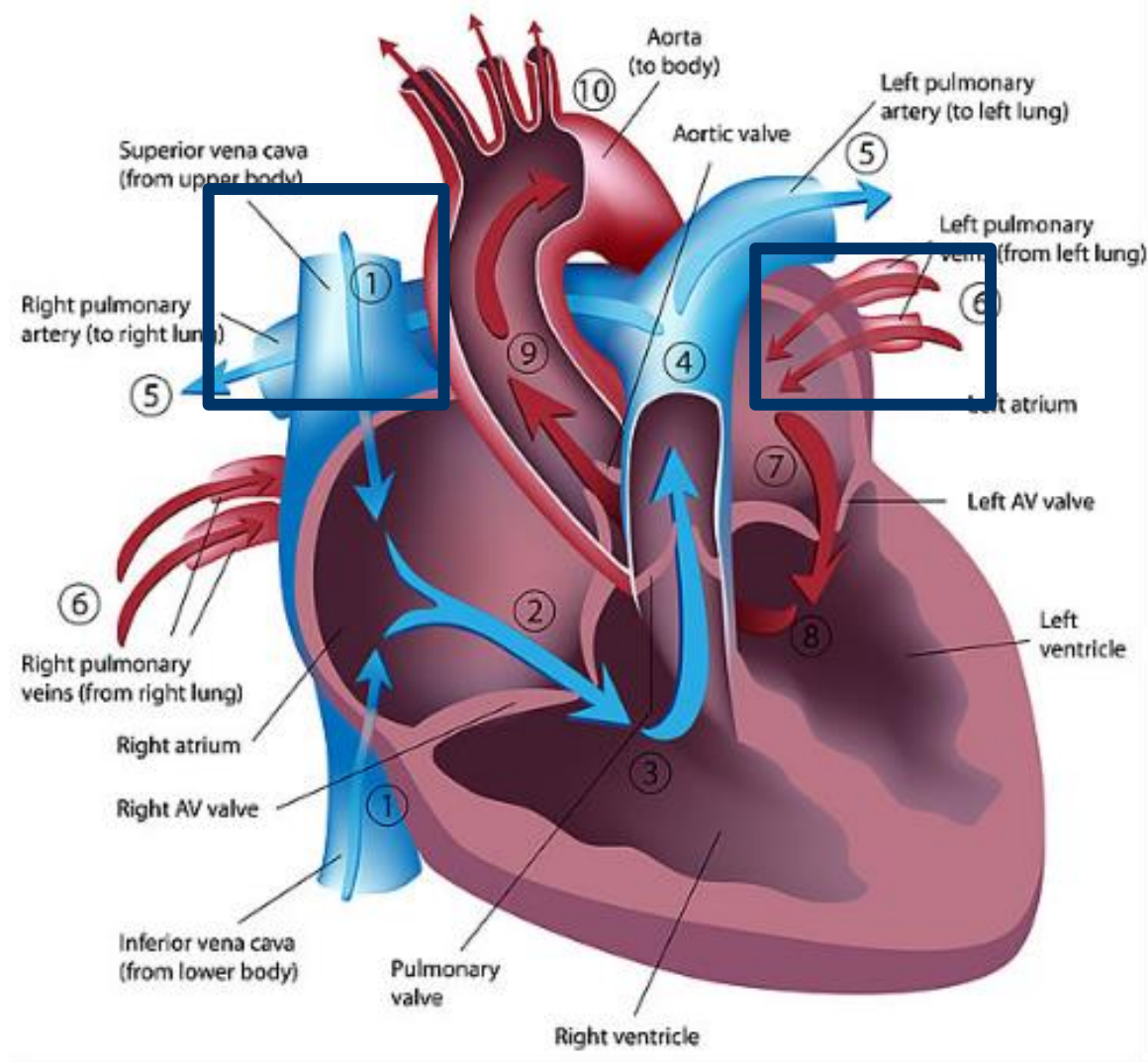
1- Activation of renin angiotensin system	2- Sympathetic stimulation	3- Myocardial hypertrophy & remodelling
Increased aldosterone , salt and water retention (Increased blood volume & improved tissue perfusion).	Increase in myocardial contraction & COP.	Direct effects of angiotensin, aldosterone & norepinephrine cause ventricular remodeling (transient improvement in contractile force & increased COP).

Cardiac Compensation

Compensatory responses can temporarily improve cardiac output, however, they also increase the load on the heart leading to long-term decline in cardiac function

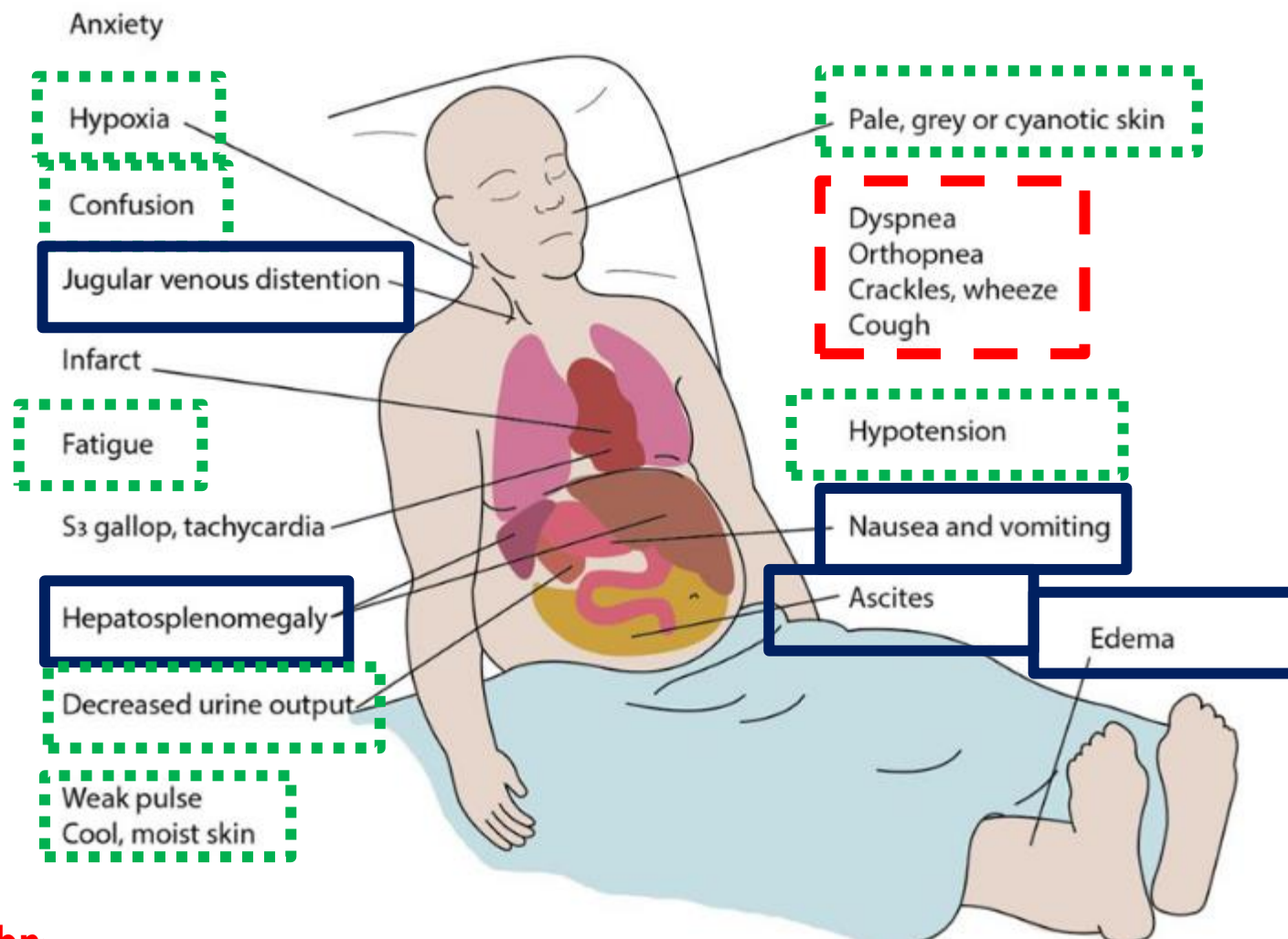
(decompensated).

<ul style="list-style-type: none"> Increased blood volume, increased preload (edema & pulmonary congestion). Increased angiotensin II (vasoconstriction & increased afterload). 	<ul style="list-style-type: none"> Increased peripheral resistance (increased afterload & decreased tissue perfusion). Increase tachyarrhythmia. 	<ul style="list-style-type: none"> Pathological Remodeling (progressive chamber dilation and loss of contractile function). Apoptosis. catecholamines, angiotensin II, & aldosterone play a direct role.
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The Pathway of blood flow through the heart will be reversed in decompensated heart failure

DECOMPENSATED HEART FAILURE



**Left sided
heart failure**

**Right sided
heart failure**

**Low cardiac
output
symptoms**

I-Non-pharmacological measures

- Salt restriction.
- Treat hypertension, diabetes, dyslipidemia and thyrotoxicosis.
- Avoid both physical and mental stressors.

II-Drug treatment

**Myocardial
stimulants**

**Decrease
preload**

**Decrease
afterload**

**Decrease Preload
& afterload**

**Drugs which
decrease mortality**

**Myocardial
stimulants**



In systolic failure, direct augmentation of depressed cardiac contractility:

- **Inamrinone, milirinone** (PDE inhibitors)
- **Dobutamine**
- **Digoxin**

**Decrease
preload**



- Venodilators.....**nitrate.**
- **Diuretics.**

**Decrease
afterload**



- Arterial dilators.....**Hydralazine.**

**Decrease preload
& afterload**



- **ACE inhibitors.**
- **Arterial and venous dilators.**

**Drugs which
decrease mortality**

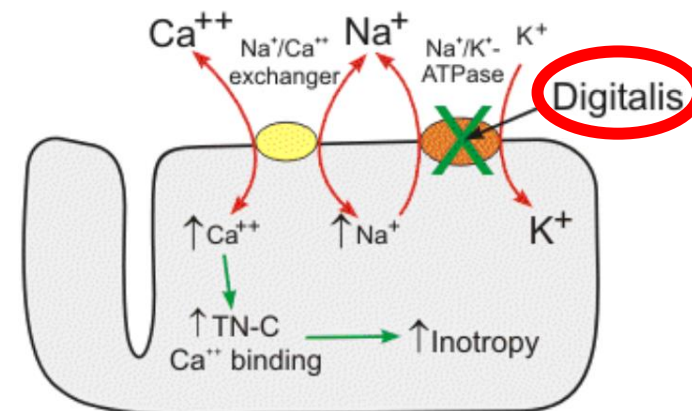
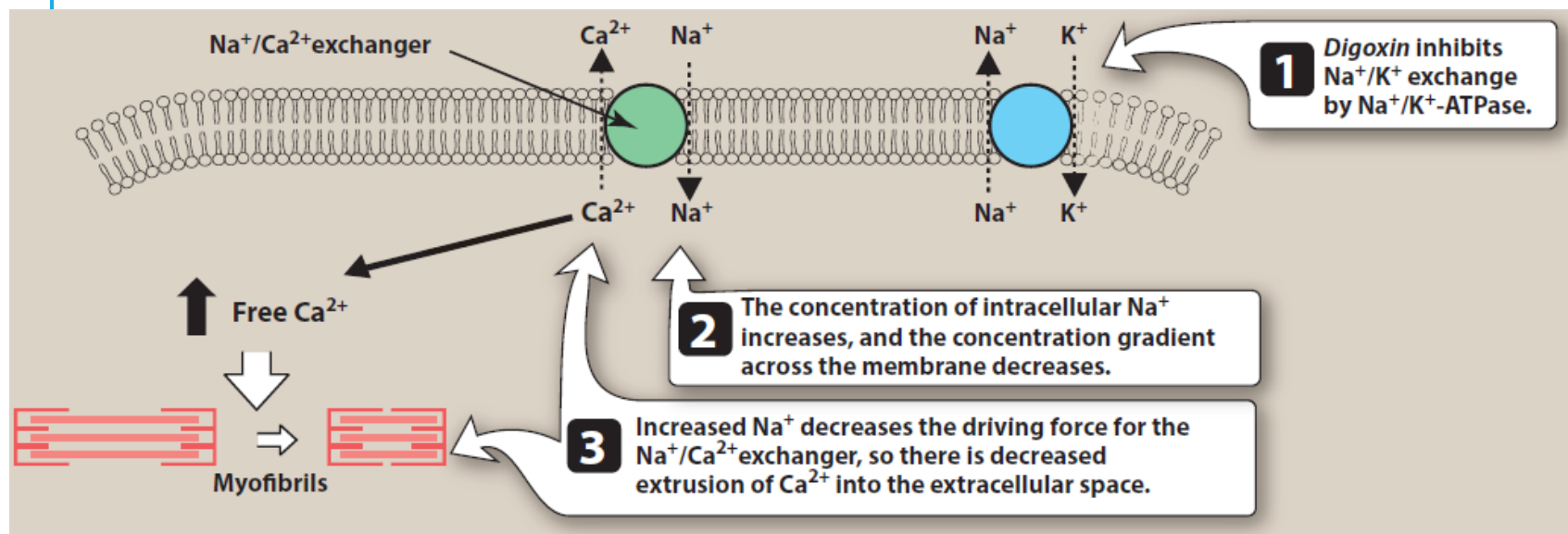


- **Angiotensin Antagonists.**
- **β blockers** (carvedilol, labetalol, metoprolol).
- **Aldosterone antagonist** (spironolactone).

CARDIAC GLYCOSIDES

- **Digitalis glycosides are no longer considered first-line drugs in the treatment of heart failure.**
- **The cardiac glycosides are often called “digitalis” because several come from the digitalis (foxglove) plant.**
- **Digoxin has an oral bioavailability of 60–75%, and a half-life of 36–40 h. Elimination is by renal excretion (about 60%) and hepatic metabolism (40%).**

MECHANISM OF ACTION



- They act by **Inhibition of Na^+/K^+ ATPase** “sodium pump” of the cell membrane results in a small increase in intracellular sodium. **The increased sodium** alters the driving force for sodium-calcium exchange by the exchanger so **that less calcium is removed from the cell (increase intracellular Ca)** & increase release of stored ca from the sarcoplasmic reticulum with increase increases contractile force.
- K^+ compete with digitalis for the binding site on the enzyme, so hypokalemia potentiates digitalis toxicity and K^+ is used for treatment digitalis toxicity

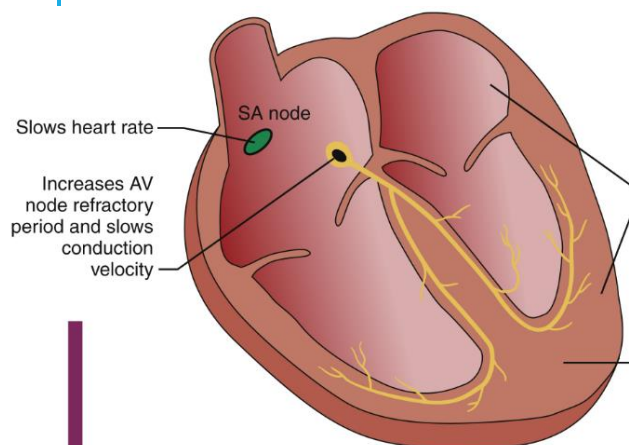
PHARMACOLOGICAL ACTIONS

1- Mechanical effects

- **Increase in force of myocardial contractility** (positive inotropic effect) which decreases the size of the failing dilated heart.
- **Increased cardiac output (COP)** , **decrease heart rate** (negative chronotropic effect) and **increased renal perfusion** (diuretic effect) with diuresis and relief of edema.

N.B. Diuresis is one of the first manifestations of digoxin action in oedematous patients with CHF.

2- Electrical effects



3- Heart rate (HR)

Electrical effects include **early cardiac parasympathomimetic responses** and **later arrhythmogenic actions**:

a- Conduction velocity:

Digoxin **decreases** the conduction velocity in all parts of the heart especially A-V node.

b- Refractory period (RP):

It **increases RP** of A-V node but **decreases RP** of atrium and ventricles.

c- Automaticity:

- It decreases the normal automaticity of S-A node causing bradycardia.
- It enhances the development of ectopic pacemakers (abnormal automaticity), so it increases the incidence of ventricular arrhythmias (extrasystoles,).

Digoxin decreases **HR** through direct and indirect mechanisms.

a) direct effect:

- Prolongation of RP of A-V node.
- Decreased sympathetic activity
- Decreased the sensitivity of S-A node and A-V node to catecholamine (in therapeutic doses)

b) indirect effect:

- Stimulation of vagal activity centrally and peripherally.

THERAPEUTIC USES

1- Congestive heart failure (CHF)

- a) Heart failure patients **complicated with atrial flutter or fibrillation** (control both cases).
- b) Heart failure patients **resistant to other conventional therapy as ACEIs**.

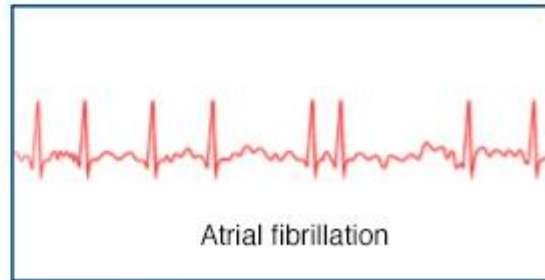
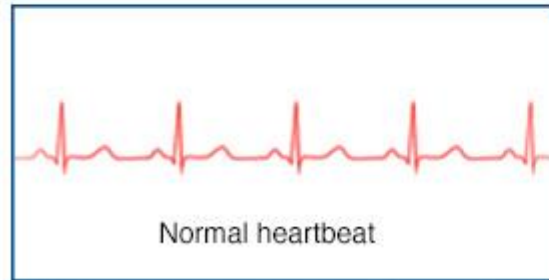
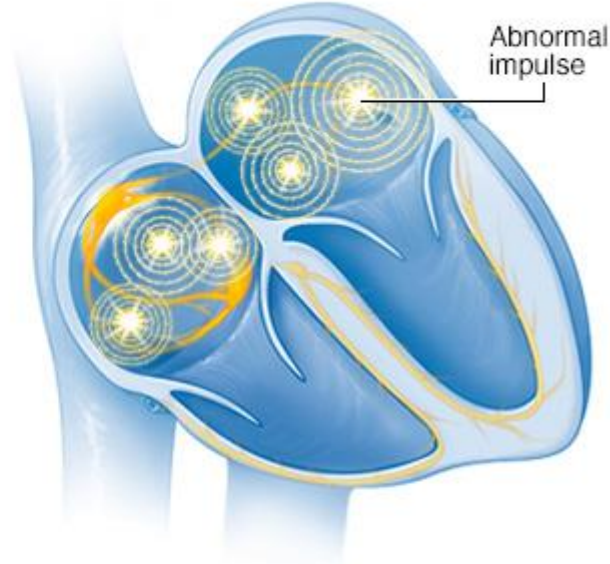
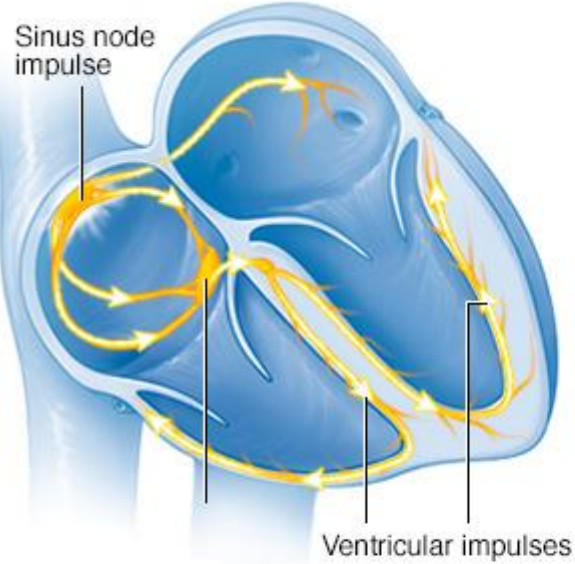
2- Arrhythmias (effective only in atrial arrhythmias)

- a) **Atrial fibrillation and atrial flutter**
Digoxin protects the ventricles from the rapid atrial impulses by decreasing the conduction in A-V node
- b) **Paroxysmal supraventricular tachycardia**. Digoxin vagomimetic effect may be involved.

Atrial Fibrillation

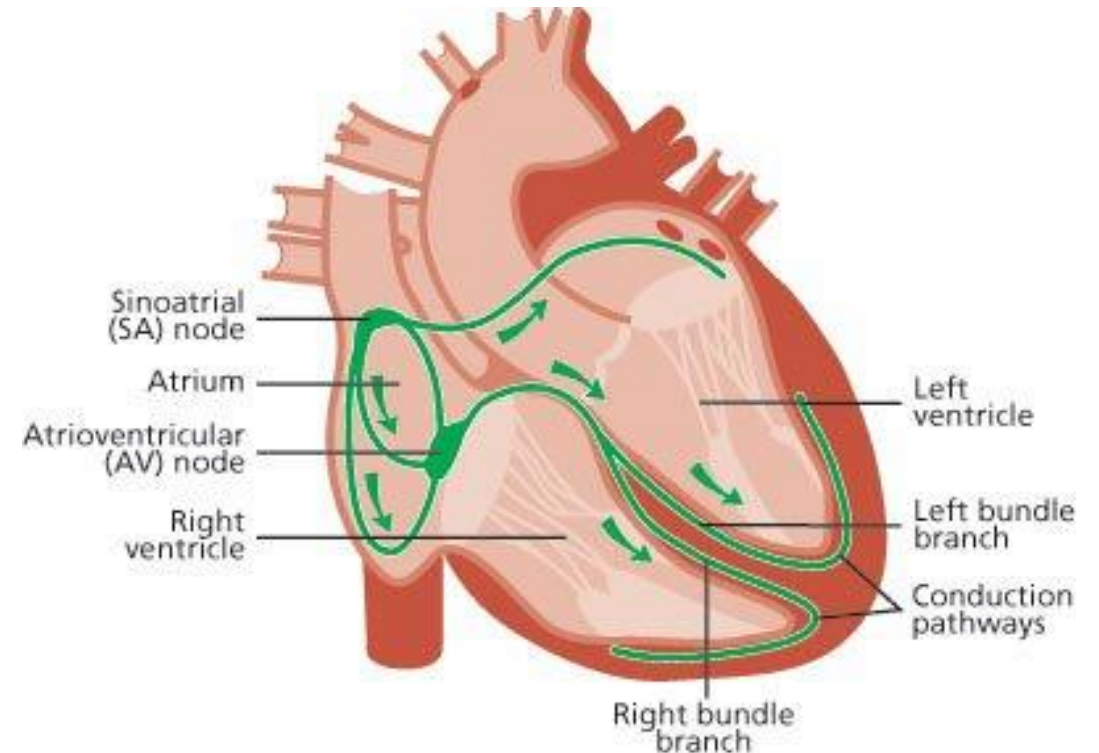
Normal heart rhythm

Atrial fibrillation (AFib)



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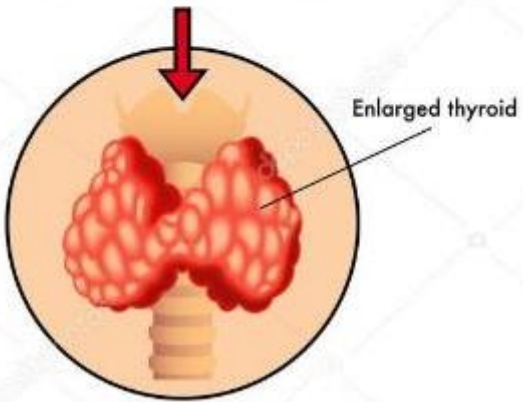
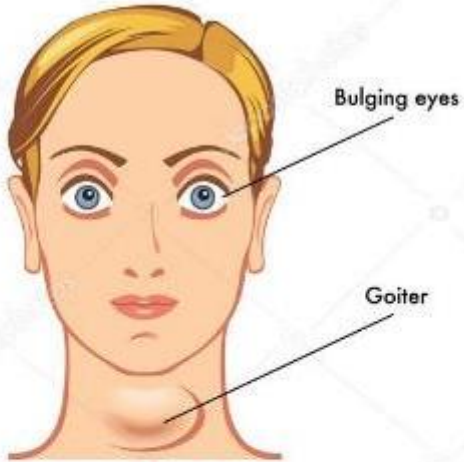
Paroxysmal supraventricular tachycardia





TOXICITY

- It has a **narrow therapeutic index** i.e. i.e. the gap between therapeutic and toxic dose of the drug is narrow.
- Digoxin is a **cumulative drug** and **toxicity is usually due to maintenance doses used over long periods of time without interruption** (one day should be omitted within a week).



- Toxicity Precipitating Factors:

1. **hypokalemia** (K^+ and digoxin compete for the binding site of $Na^+ - K^+ - ATPase$).
2. **Renal failure** (excretion of digoxin is decreased)
3. **Elderly** patients are more liable to toxicity.
4. Use of **K-depleting** diuretics (hypokalemia).
5. **Quinidine** (it decreases the renal excretion of digoxin)
6. I.V **Calcium** administration.
7. **Hypothyroidism** (decrease excretion of digoxin and increase sensitivity of the heart to digoxin).

TOXICITY

I- GIT: anorexia, nausea & vomiting (stimulation of CTZ and irritation of GIT) (**first to appear**).

II- Cardiac toxicity: Can cause **all types of arrhythmias**.

- **Bradycardia** (suppression of S-A node).
- **Partial or complete heart block.**
- Extrasystole.

III- CNS: Headache, Restlessness, Disorientation, Visual disturbance, Abnormal color vision.

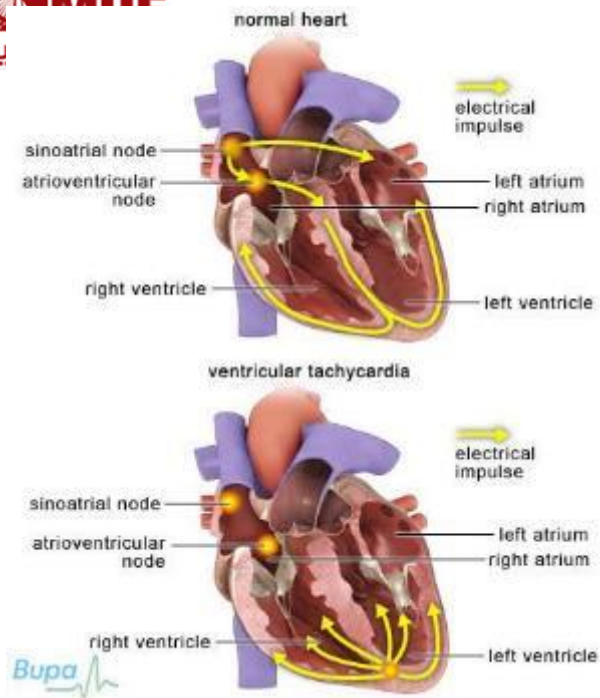
IV- Endocrine: Gynaecomastia due to stimulation of prolactin secretion.

TREATMENT OF TOXICITY

- **Stop** digitalis and diuretics immediately.
 - **TDM (therapeutic drug monitoring).**
 - **Oral or parenteral potassium** supplements [low or normal serum K^+].
 - In severe digitalis intoxication, serum potassium will be high at the time of diagnosis (because of potassium loss from the intracellular compartment of skeletal muscle). Automaticity is depressed, and the use of antiarrhythmic agents may cause cardiac arrest. Treatment should include insertion of a temporary cardiac pacemaker and the use of digitalis antibodies (digoxin immune fab).
 - K^+ is contraindicated in partial A-V block and hyperkalemia.
 - **Ventricular arrhythmia.....**Lidocaine IV drug of choice
 - **Atrial and ventricular arrhythmia.....**Phenytoin
 - **AV block and bradycardia.....**Atropine 0.6 -1.2 mg IM
 - **I.V. Digoxin antibody [Digibind].**
 - **Oral cholestyramine** reduces intestinal absorption of digoxin.
- Digoxin has high Vd (4 - 7 L / Kg), so no value for hemodialysis in cases of toxicity

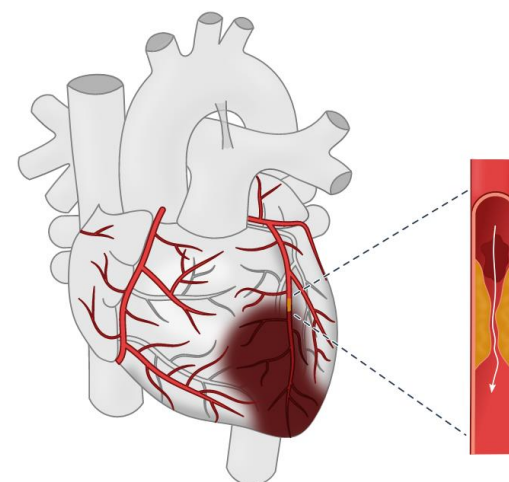
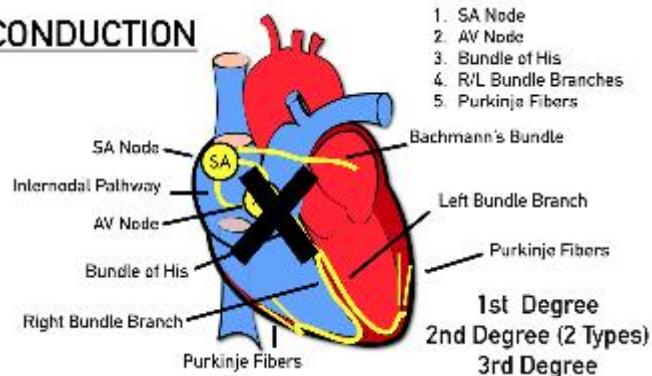
Contraindications

1. **Ventricular tachycardia:** it may convert it into ventricular fibrillation by decreasing the refractory period of the ventricle
2. **Partial heart block:** it may convert it to complete heart block
3. **Recent myocardial infarction:** it increases the tendency of serious dysrhythmia.



Ventricular tachycardia

CONDUCTION

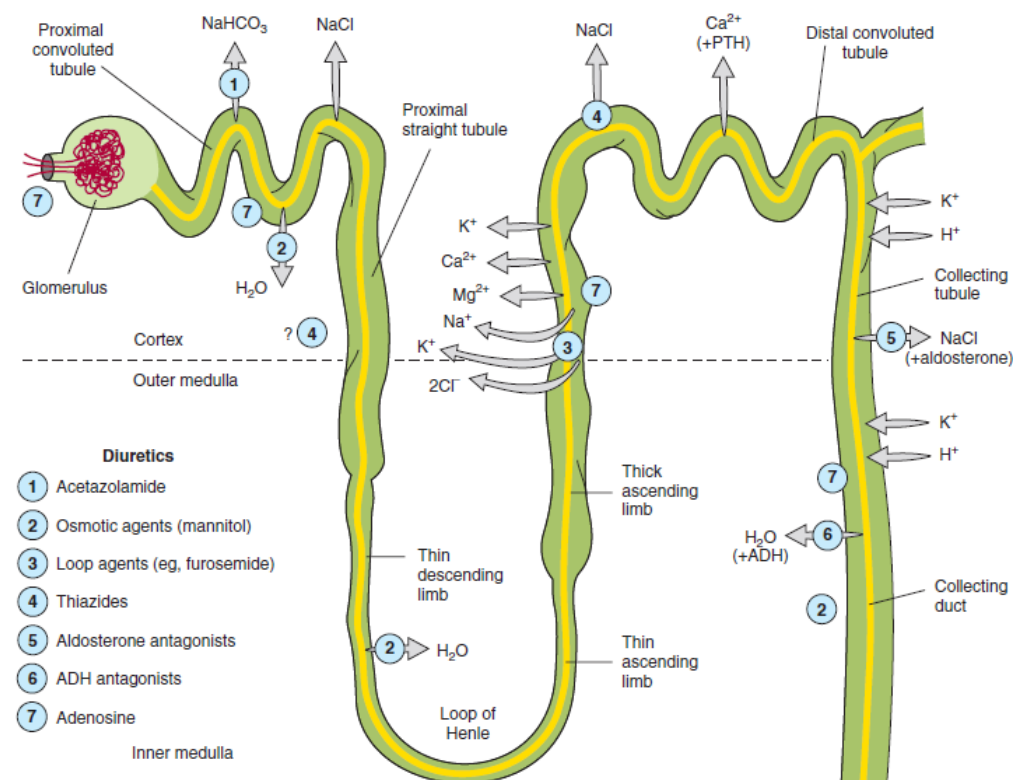


Myocardial Infarction

A. Diuretics

- Diuretics cause salt and water loss, decrease blood volume, venous return and decrease preload

- **Furosemide** is a very useful agent for immediate reduction of the pulmonary congestion and severe edema associated with acute heart failure and for moderate or severe chronic failure.
- **Thiazides** such as hydrochlorothiazide are sometimes sufficient for mild chronic failure.
- **Spironolactone** and **eplerenone** (aldosterone antagonist diuretics) have significant long-term benefits and can reduce mortality in chronic failure.



B. Angiotensin antagonists

- These agents have been shown to reduce morbidity and mortality in chronic heart failure.
- They reduce aldosterone secretion, salt and water retention, and vascular resistance.
- They are now considered, along with diuretics, to be first-line drugs for chronic heart failure.

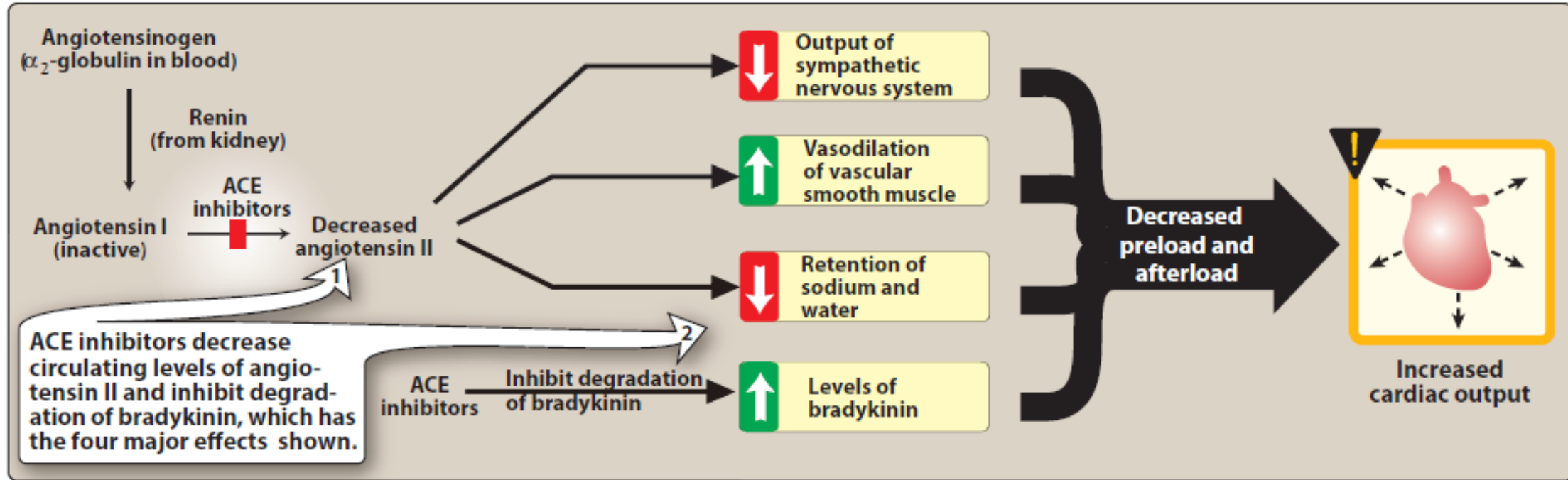
I. Renin inhibitors: Aliskiren.

- Preliminary results suggest an efficacy similar to ACEIs.

II. II- ACEIs: Captopril, enalapril.....

III. III- ARBs: Losartan, valsartan, candesartan.....

- I. Block AT1 receptors → inhibit all the deleterious effects of Ang II mediated through AT1 receptors.
- II. They have arteriodilators, venodilator and antiremodeling effects and
- III. used mainly in patients who cannot tolerate ACEIs because of cough or angioedema.



C. Nesiritide

- It is a new atrial natriuretic peptide.
- It stimulates **guanylate cyclase** and increases **cGMP**.
- It dilates arteries and veins, so decrease afterload and preload

D. Beta1-adrenoceptor agonists (**Dobutamine & Dopamine**)

- **Dobutamine** (selective B1 agonist): **produces an increase in COP**
BUT: B1 stimulation may lead to tachyarrhythmia and increase in myocardial oxygen consumption. **Therefore**, these drugs are **contraindicated** in patients with **coronary artery disease** or **arrhythmias**.
- **Dopamine:** stimulates B1 receptors causing an increase in myocardial contraction, used in combination with dobutamine in acute severe heart failure.

E. Beta-adrenoceptor antagonists

- Several β blockers (**carvedilol, labetalol, metoprolol**) have been shown in long-term studies to **slow progression of chronic heart failure** (but this effect was not observed with another B blockers).
- **They have:**
 - **antiremodeling** effect: by inhibiting the sympathetic nervous system (reflex).
 - **antiarrhythmic** properties.
 - **antioxidant** effect.
- **Beta blockers** are of no value in **acute failure** and **may be detrimental** if **systolic dysfunction** is marked.

F. Phosphodiesterase Inhibitors



- **Milrinone** is the major representative of this infrequently used group.
- These drugs increase cyclic adenosine monophosphate (cAMP) by inhibiting its breakdown by phosphodiesterase.
 - They **increase myocardial contractility** (increase in cardiac intracellular calcium).
 - They cause **vasodilation**, which may be responsible for a major part of their beneficial effect.

G. Vasodilators



- Vasodilator therapy with **nitroprusside** or **nitroglycerin** is often used for acute severe failure with congestion.
- They are used for proper adjustment of venous return (preload) and reduction of impedance to ventricular ejection (afterload).
- Chronic heart failure sometimes responds favorably to oral vasodilators such as **hydralazine** or **isosorbide dinitrate** (or both), and this combination has been shown to reduce mortality due to heart failure in African Americans.

H. ARNI (Angiotensin Receptor-Neprilysin Inhibitors)



- Examples: **Sacubitril/valsartan (Entresto)**.
- **Mechanism of action:** Combine ARB effects with neprilysin inhibition, Increasing natriuretic peptides.
- **Benefits:** Superior to ACE inhibitors in reducing mortality and hospitalization.

I. Other Agents



- Ivabradine: reduce heart rate in patients with elevated HR despite beta-blockers.
- SGLT2 Inhibitors: (e.g., Dapagliflozin, Empagliflozin) shown to reduce cardiovascular death and hospitalization.

CLINICAL TREATMENT OF A CASE OF CHF

1. **Diuretics** and **ACEIs** are the first choice.
2. If the patient cannot tolerate ACEIs due to cough or angioedema, we use **ARBs**.
3. If ARBs are not tolerated, we use **hydralazine-isosorbide dinitrate** combination.
4. when there is hemodynamic stability, we add **B-blockers (carvedilol)** which decrease mortality rate.
5. **Digoxin** is used in:
 - a- the resistant cases to the above treatment (last choice).
 - b- if there is **atrial fibrillation** with the CHF.

