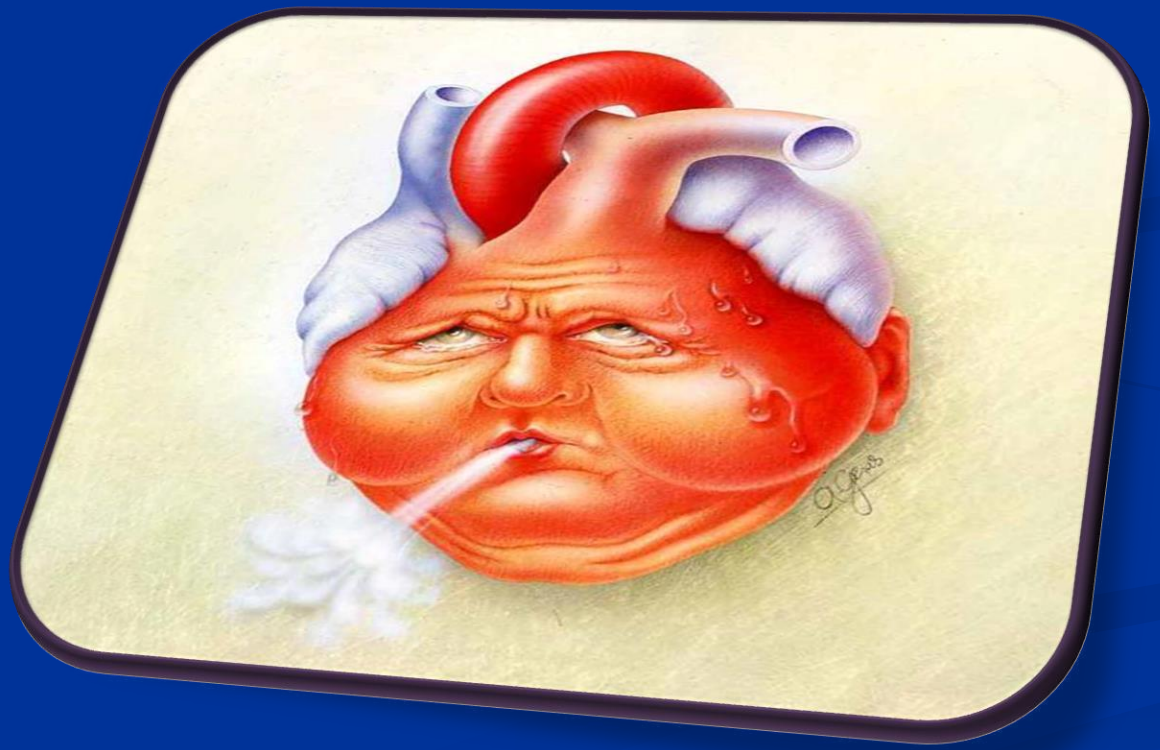
The Islamic University
College of Pharmacy
Pharmacology & Toxicology Dep.

Pharmacology –II

CVS-Acting Drugs

Drugs for Treatment of Heart Failure



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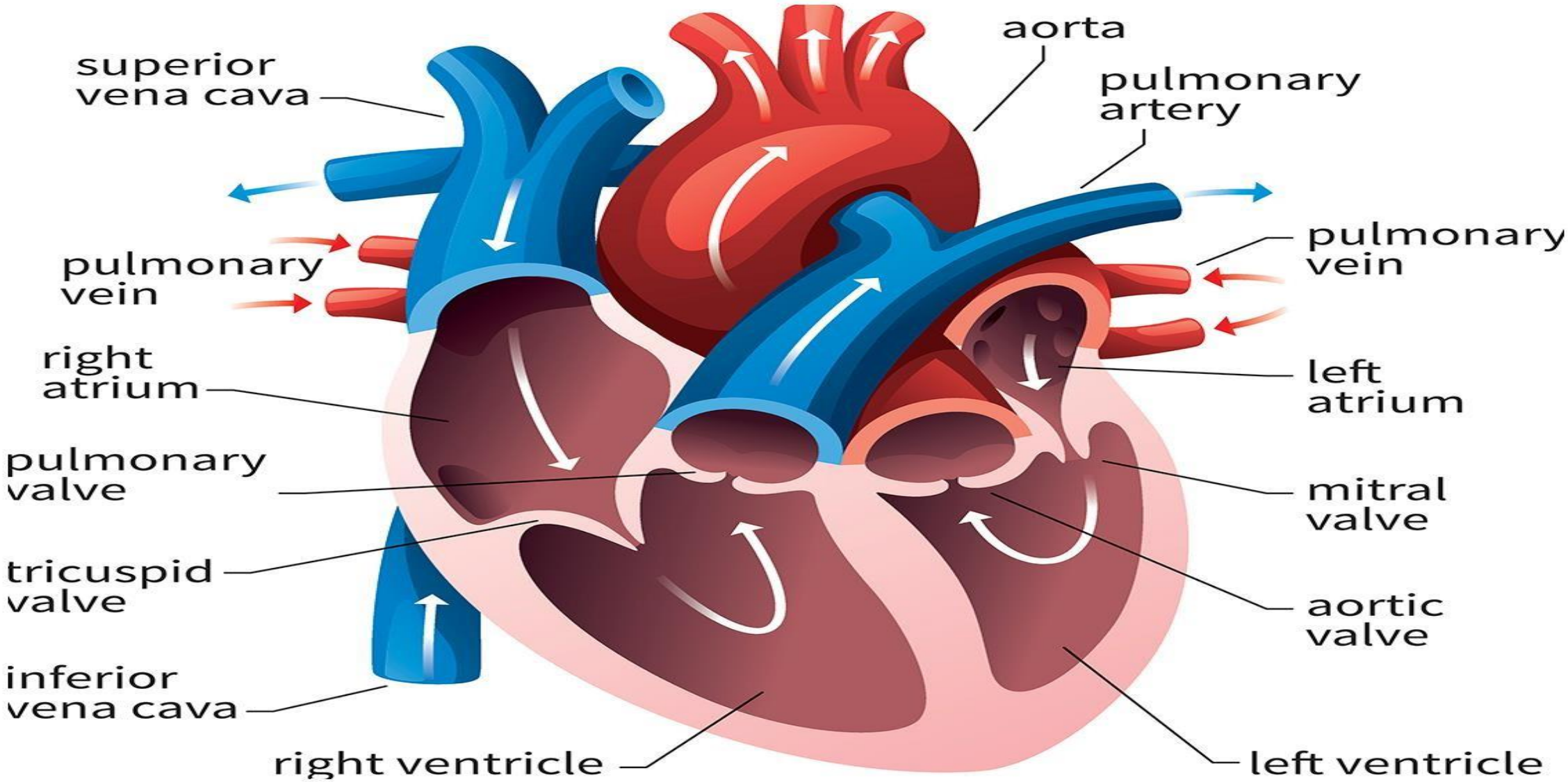
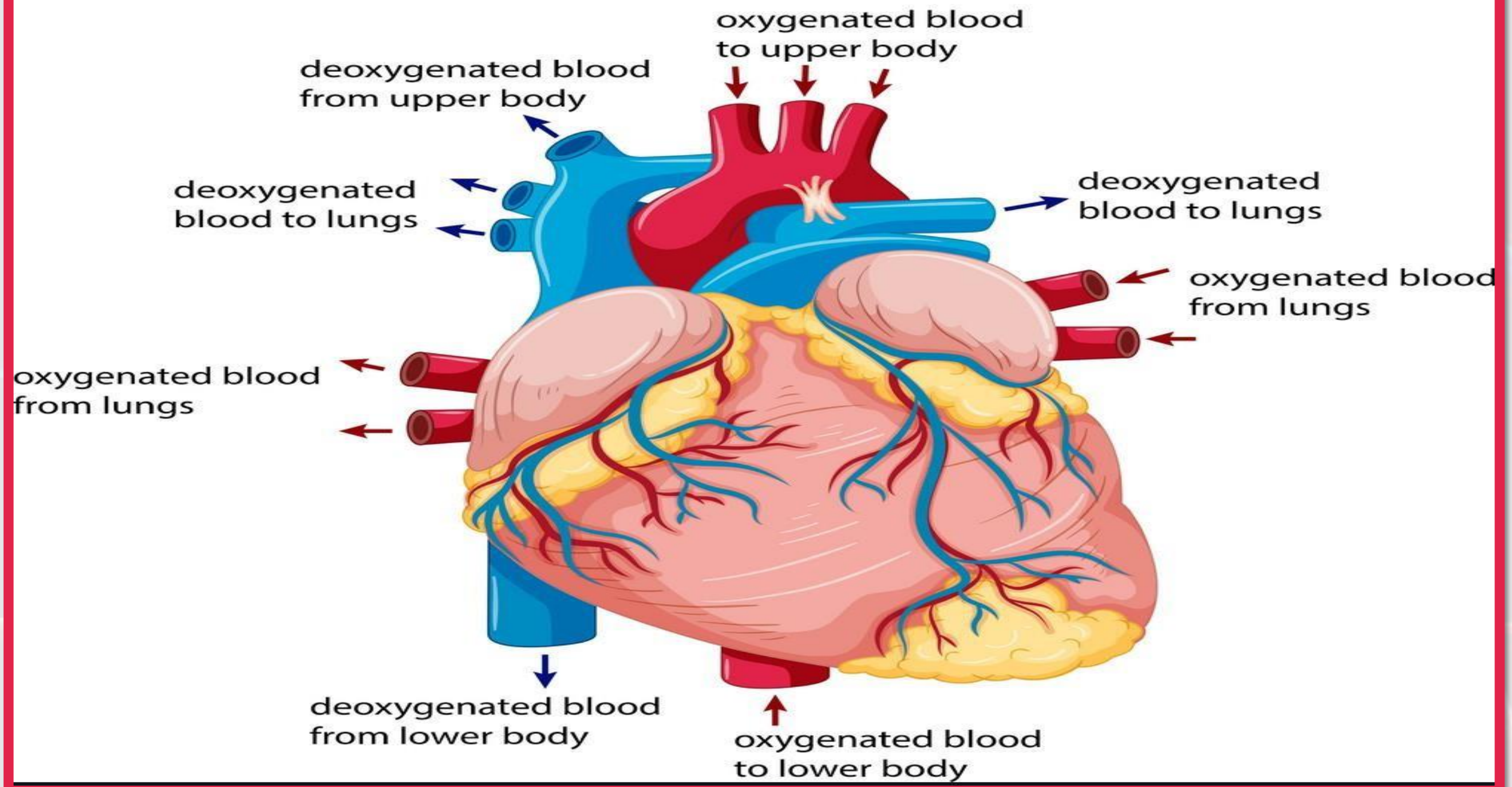
Dr: Mohamed R. Elnagar


superior
vena cava
aorta
pulmonary
artery
pulmonary
vein
pulmonary
vein
right
atrium
left
atrium
pulmonary
valve
mitral
valve
tricuspid
valve
aortic
valve
inferior
vena cava
right ventricle
left ventricle

Blood Flow of the Human Heart



Heart Failure

- Heart failure (HF) is a progressive clinical syndrome caused by **inability of the heart to pump sufficient blood to meet the body's metabolic demands**.
- HF can result from any disorder that **reduces ventricular filling** (diastolic dysfunction) and/or **myocardial contractility** (systolic dysfunction).

Causes

- Coronary artery disease
- Cardiomyopathy
- Long-term Hypertension
- Valve diseases

Risk factors

- High fat diet
- Family history
- Smoking
- Alcohol intake

Heart Failure types

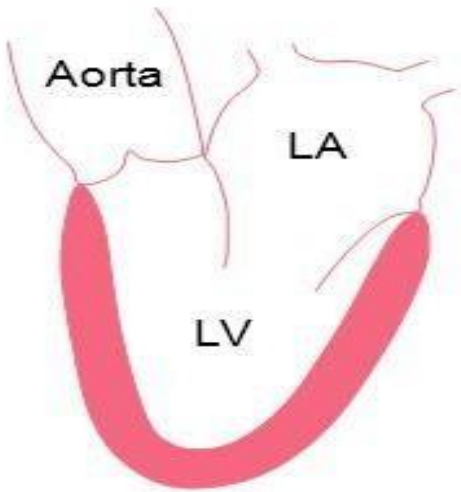
(Acc. to dysfunction and ejection fraction)

Systolic heart failure. The heart muscle becomes weak and enlarged. It can't pump enough blood forward when the ventricles contract. Ejection fraction is lower than normal.

Diastolic heart failure. The heart muscle becomes stiff. It doesn't relax normally between contractions, which keeps the ventricles from filling with blood. Ejection fraction is often in the normal range.

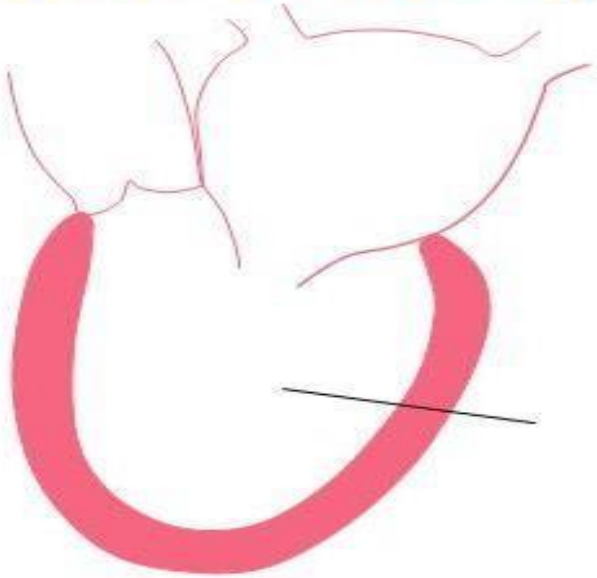
Types of Heart Failure: Difference Between Systolic and Diastolic Heart Failure

(Click for each type)



Normal

Normal ejection (squeeze) =Systolic function
Normal relaxation (filling) =Diastolic function

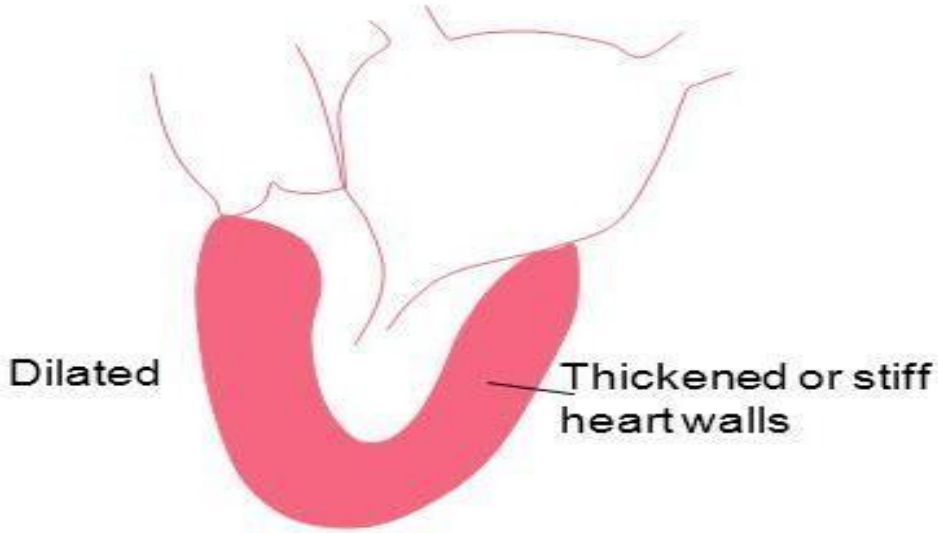


Systolic Heart Failure

Weakened pump

Relaxation ± abnormal

→ Blood backs up and overloads the heart



Diastolic Heart Failure

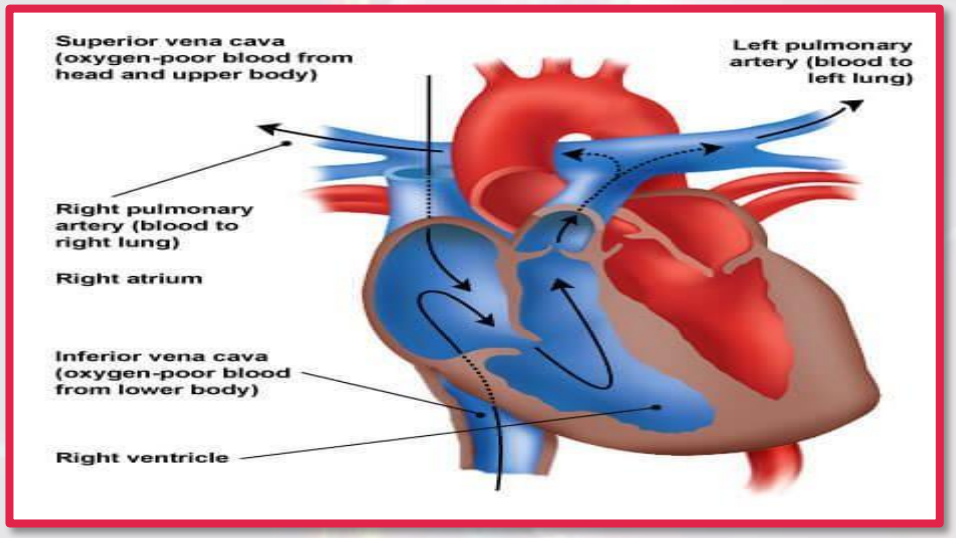
Normal ejection

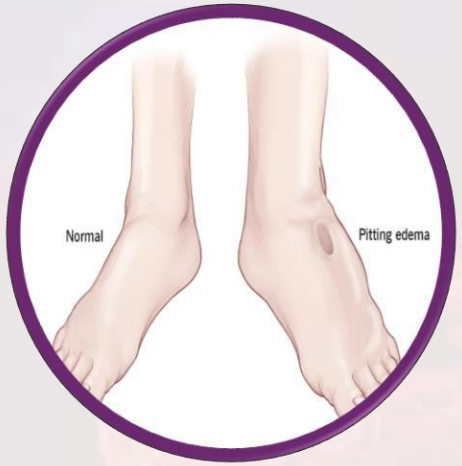
Abnormal relaxation: Stiff or scarred

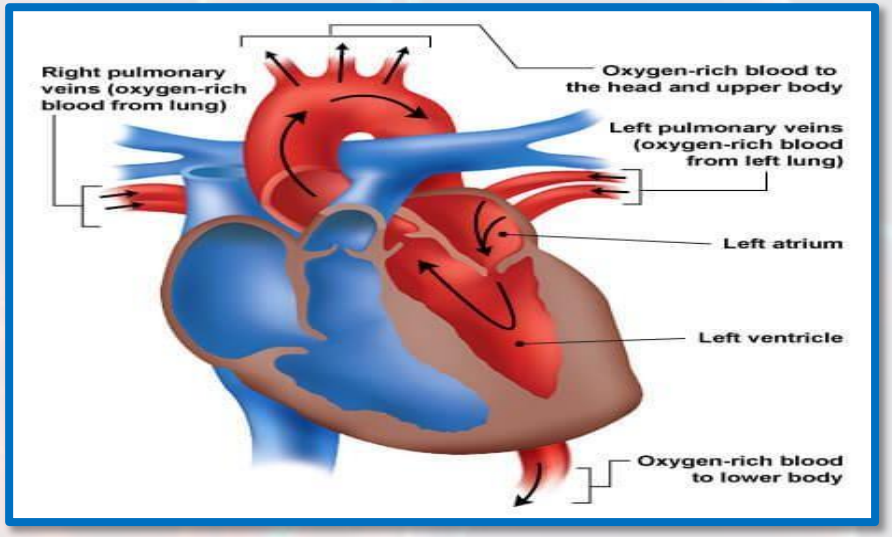
→Won't allow enough blood to fill the heart before it squeezes

Heart Failure types

(Acc. to **side of failure**)

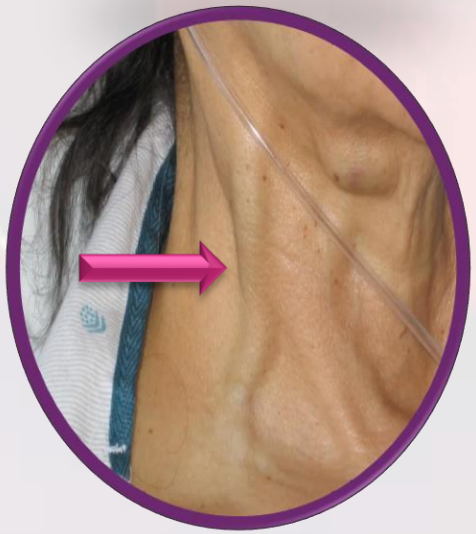






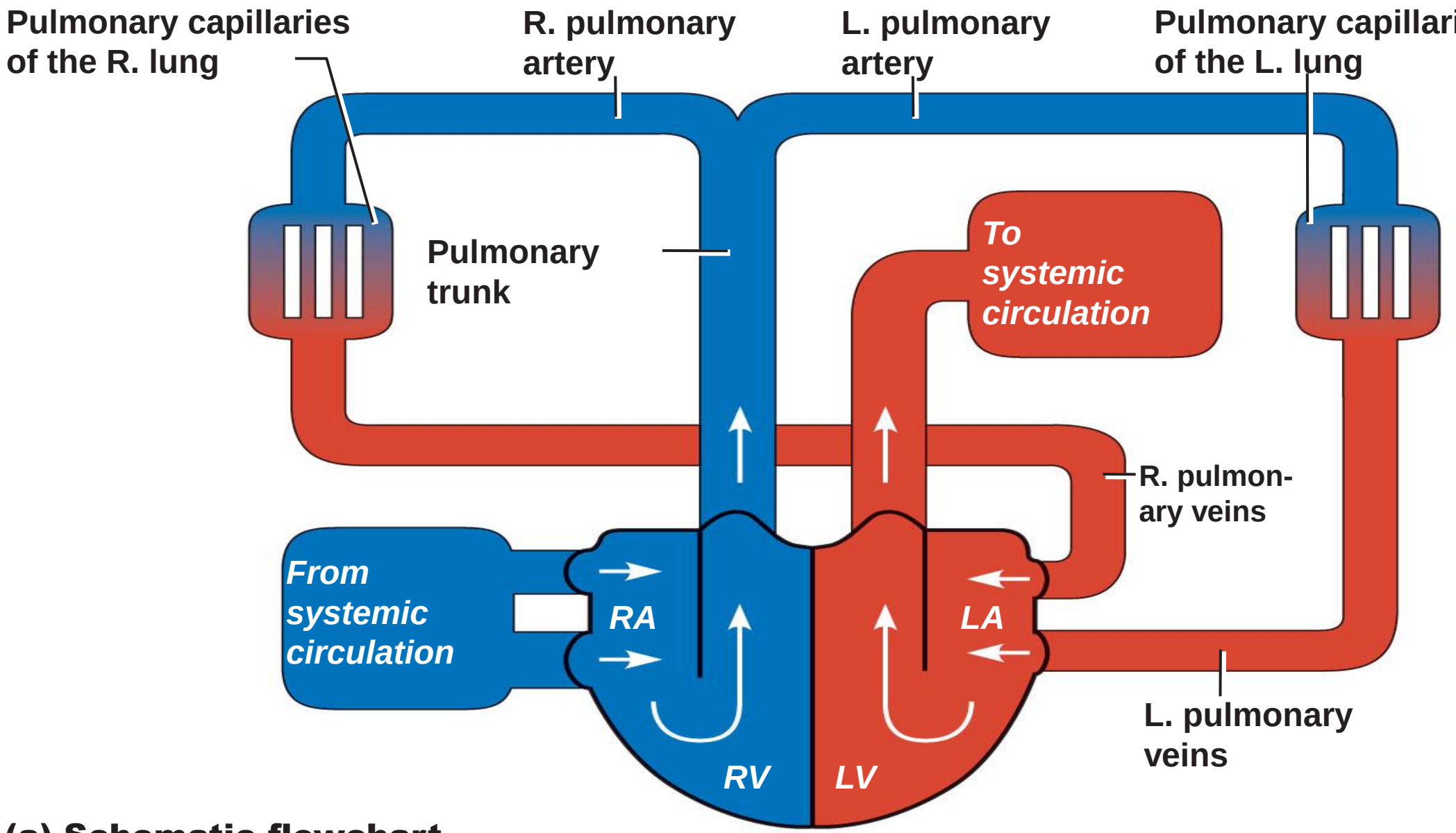
Right sided HF

- ✓ Venous congestion and distention (JVD)
- ✓ Peripheral edema (ankles edema)
- ✓ Hepatomegaly , splenomegaly



Left sided HF

- ➢ **Decreased stroke volume (C.O.P)**
- ✓ Poor perfusion of systemic circulation
- ✓ Generalized fatigue and muscle weakness
- ➢ **Pulmonary edema (pulmonary congestion)**
- ✓ Dyspnea, cough, frothy sputum, crackling sounds and Orthopnea.



(a) Schematic flowchart.

Figure 19.19a

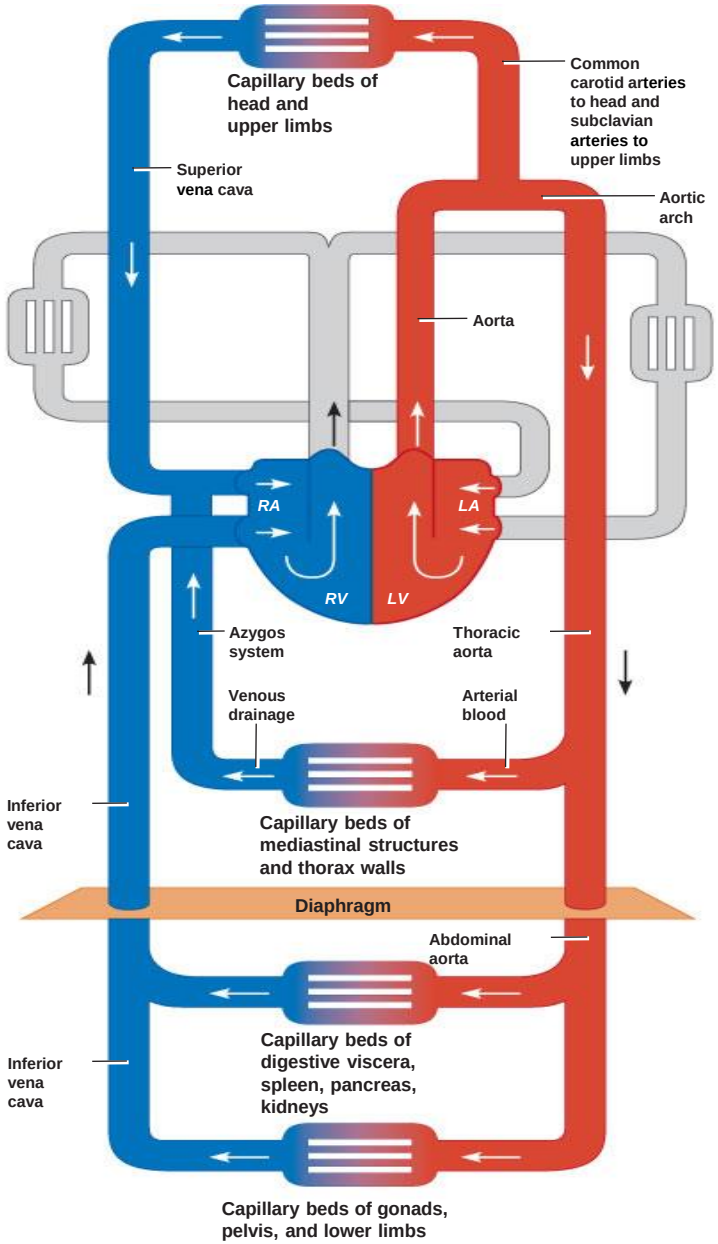
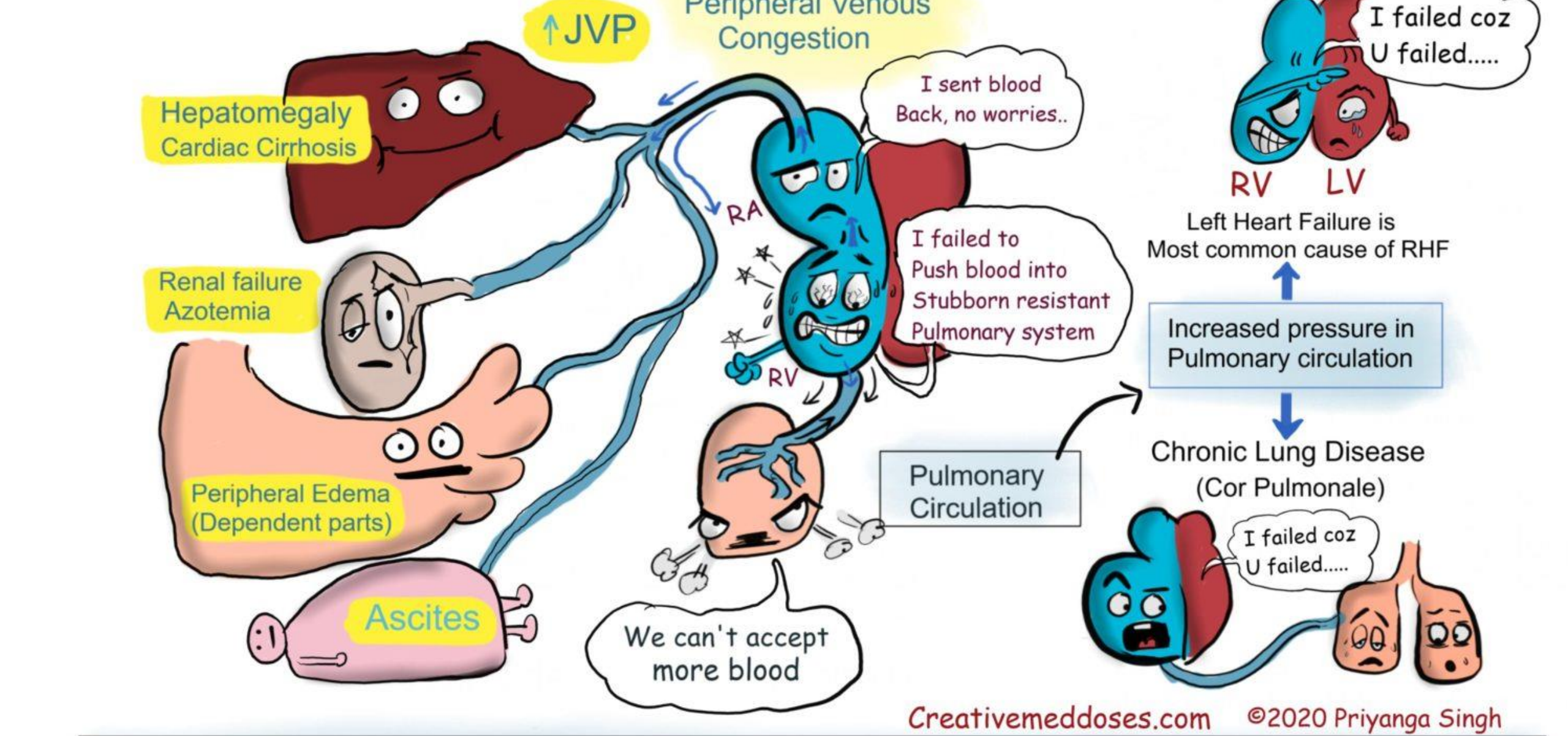

Capillary beds of head and upper limbs
Common carotid arteries to head and subclavian arteries to upper limbs
Superior vena cava
Aortic arch
Aorta
RA
LA
RV
LV
Azygos system
Thoracic aorta
Venous drainage
Arterial blood
Inferior vena cava
Capillary beds of mediastinal structures and thorax walls
Diaphragm
Abdominal aorta
Capillary beds of digestive viscera, spleen, pancreas, kidneys
Inferior vena cava
Capillary beds of gonads, pelvis, and lower limbs

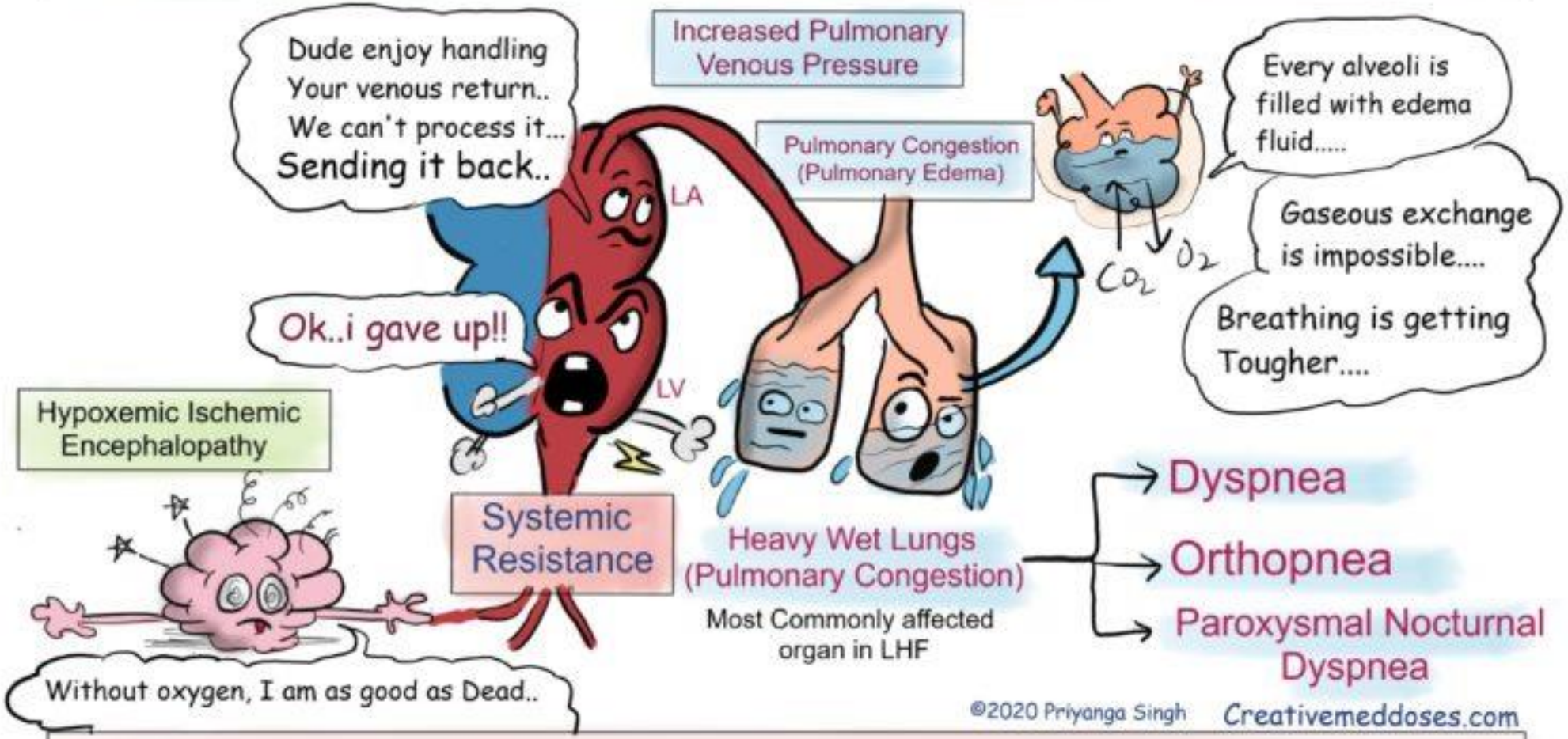
Figure 19.20



Right side ⟶ Pumps blood into Lungs ⟶ Failure happens because of- Increased pulmonary vascular pressure

Left-sided Heart Failure

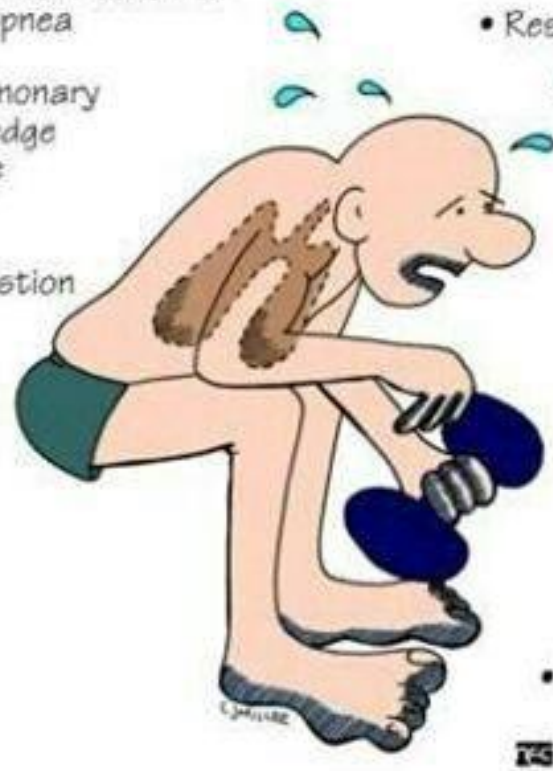
Left side ⟶ Venous Return from Lungs ⟶ Failure leads to Pulmonary Congestion & Pressure



Left side ⟶ Supply Body Organs ⟶ Failure leads to low organ perfusion and hypoxia

LEFT SIDED ♥ FAILURE

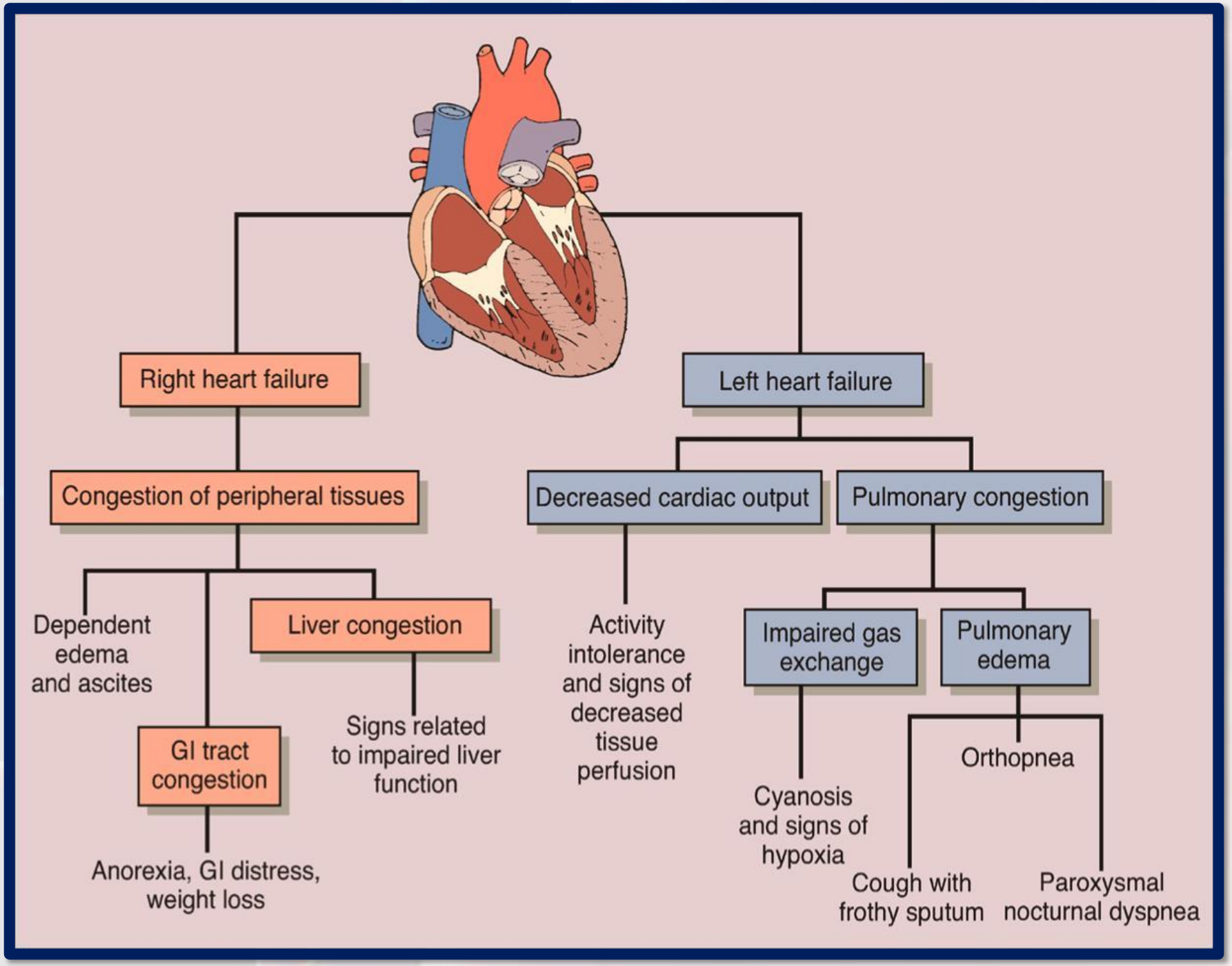
- Paroxysmal Nocturnal Dyspnea
- Elevated Pulmonary Capillary Wedge Pressure
- Pulmonary Congestion
  - Cough
  - Crackles
  - Wheezes
  - Blood-Tinged Sputum
  - Tachypnea
- Restlessness
- Confusion
- Orthopnea
- Tachycardia
- Exertional Dyspnea
- Fatigue
- Cyanosis



RIGHT SIDED ♥ FAILURE

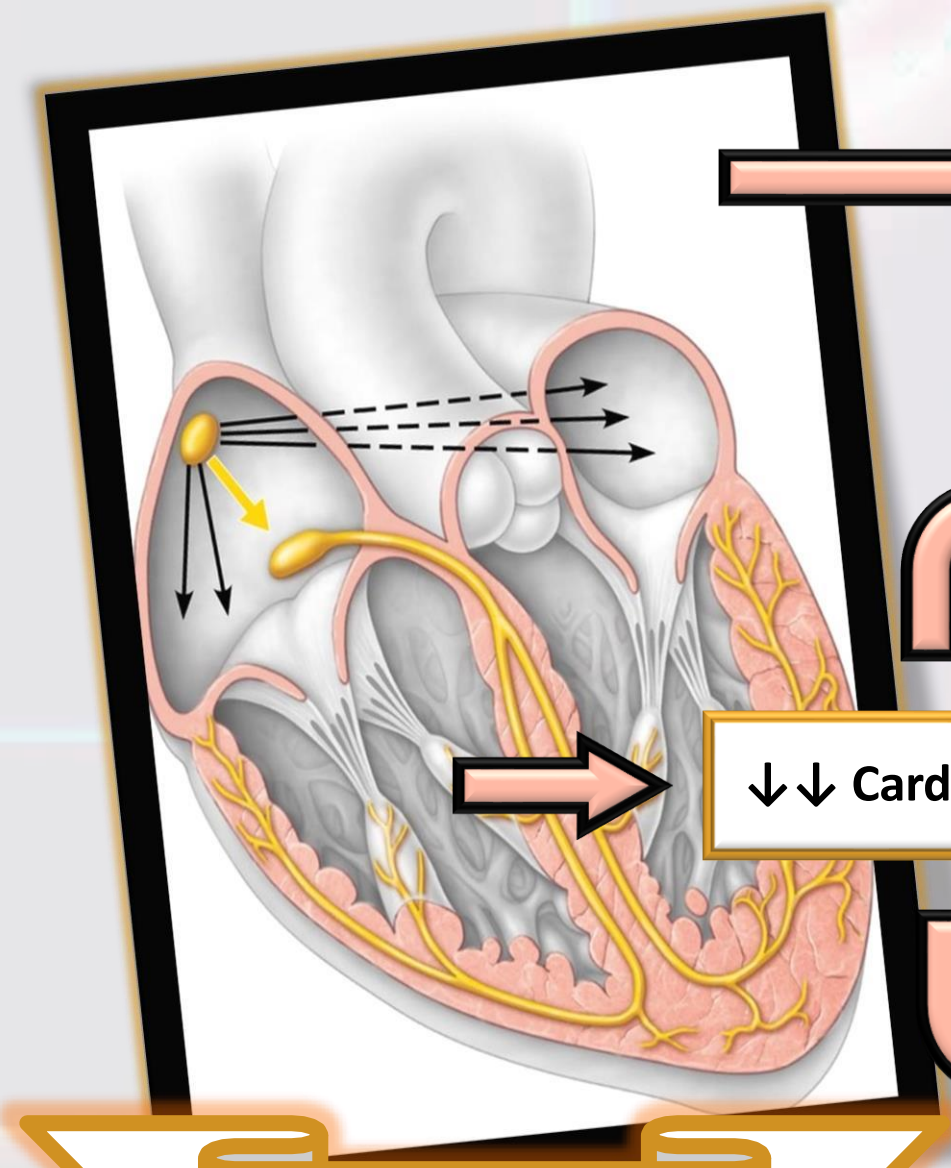
(Cor Pulmonale)

- Fatigue
- ↑ Peripheral Venous Pressure
- Ascites
- Enlarged Liver & Spleen
- May be secondary to chronic pulmonary problems
- Distended Jugular Veins
- Anorexia & Complaints of GI Distress
- Weight Gain
- Dependent Edema



The primary **goal** of **drug therapy** in heart failure is to

* **improve cardiac function** and
* **reduce the clinical symptoms associated with heart failure** (e.g., **edema**, **shortness of breath**, exercise intolerance).



Blood congestion (edema)
Congestive heart failure

↓↓ Perfusion to kidney
→ Activation of RAAS

↑ Blood volume

V.C

↓↓ Cardiac output

Neuro-hormonal system activation

Activation of sympathetic nervous system (SNS)

↑ heart rate

↑ force of contraction

Worsening of heart failure with time

Classification of heart failure according to severity of symptoms?

The New York Heart Association (NYHA) **classification** is a well-accepted classification of heart failure **based on the severity of symptoms**:

- **Class I –** No symptoms with normal physical activity.
- **Class II –** Slight limitation and shortness of breath on moderate to severe exertion.
- **Class III –** **Marked** limitation of activity, less than ordinary activity causes shortness of breath.
- **Class IV –** **Severe disability**, **dyspnea at rest**, **no physical activity** possible without discomfort.

NEW YORK HEART ASSOCIATION (NYHA) HEART FAILURE CLASSIFICATION

CLASS I

NO LIMITATION OF PHYSICAL ACTIVITY; ORDINARY PHYSICAL ACTIVITY DOES NOT CAUSE SYMPTOMS

CLASS II

SLIGHT LIMITATION OF PHYSICAL ACTIVITY; COMFORTABLE AT REST; ORDINARY PHYSICAL ACTIVITY CAUSES SYMPTOMS

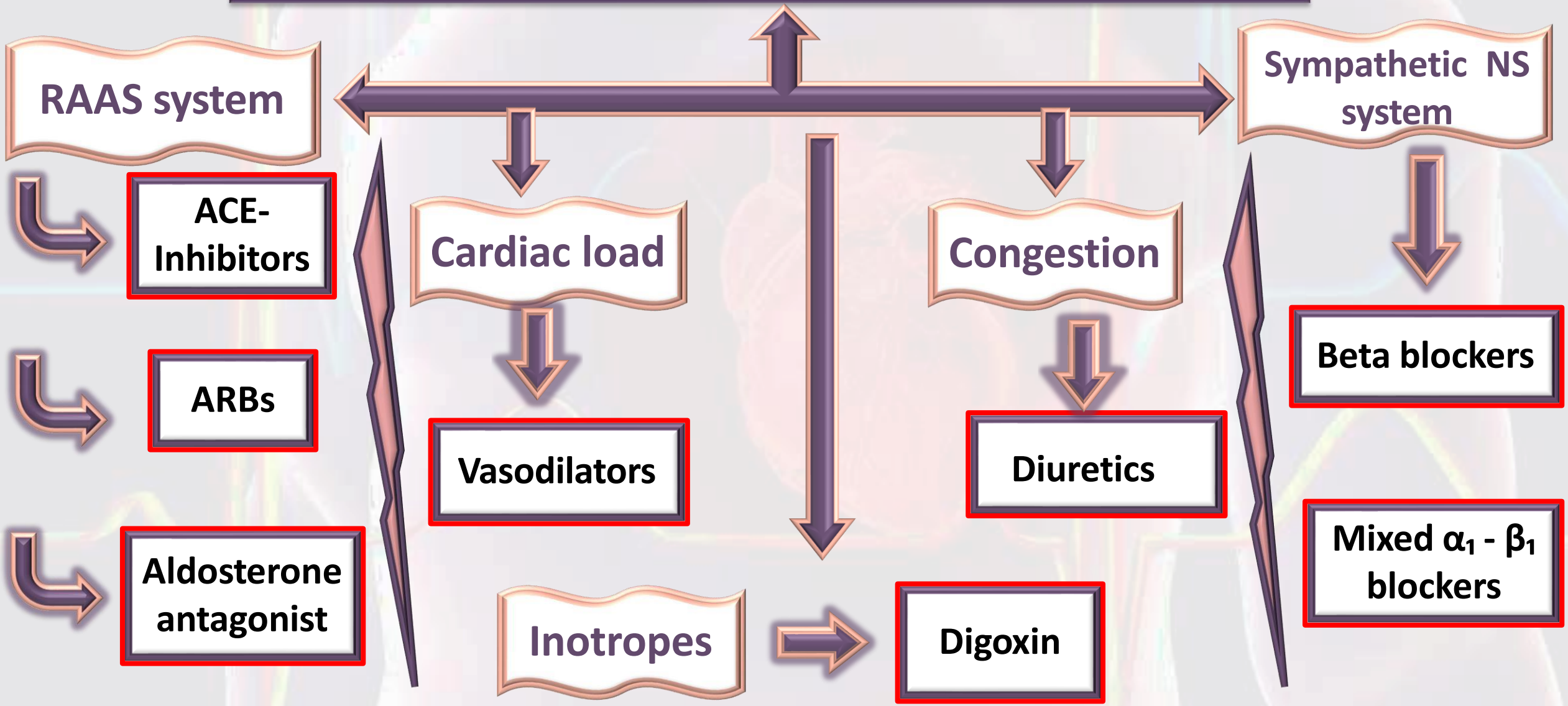
CLASS III

MARKED LIMITATION OF PHYSICAL ACTIVITY; COMFORTABLE AT REST, BUT LESS THAN ORDINARY ACTIVITY CAUSES SYMPTOMS

CLASS IV

SEVERE LIMITATION AND DISCOMFORT WITH ANY PHYSICAL ACTIVITY; SYMPTOMS PRESENT EVEN AT REST

Treatment of heart failure



1) Diuretics

- They ↓ Na/water retention → ↓ preload → improve cardiac function
- They ↓ pulmonary congestion → improve Lung function
- Loop diuretic (furosemide)
- Thiazide
- **Spironolactone** is used for two reasons:

1) **It antagonizes the effect of aldosterone that increased in CHF due to secondary stimulation of RAAS system**
2) **Recent evidence showed that it reduces hypertrophy, remodeling and mortality rate in patient with advanced HF (NYHA class III and IV).**

Disadvantages:

1. High dose → hypovolemia → ⬇ COP
2. Diuretic-induced **acid-base imbalance** may impair cardiac function.
2. Diuretic induce Hypokalemia can increase digitalis toxicity and cardiac arrhythmia

SO

Combination of diuretics to increase efficacy and/or to counteract K^+ imbalance is preferred

These adverse effects could be minimized by **diuretic combination** (**loop diuretics/or Thiazide** + **K^+ sparing** diuretics) to minimize hypokalemia and acid-base imbalance.

2) ACE inhibitors - ARBs

They ↓ arterial VC → ↓ afterload

They ↓ aldosterone → ↓ Na/ water retention → ↓ preload

They prevent myocardial wall thickening and remodeling

3) Vasodilators

- Used ***if diuretic and ACE inhibitors are not sufficient***
- **Hydralazine and nitrate** → they have **complementary** hemodynamic actions:
  1. **Hydralazine**: is a direct **arterio-dilator** → ↓ resistance and after load
  2. **Nitrate**: are primary **veno-odilators** **(mainly at small dose)** → ↓ preload.

- Recent evidences showed that **combination** of nitrate and hydralazine ↓ **mortality** and **hospitalization** for HF patient
- Guidelines recommend this combination to **moderate to sever** HF
- The combination **is first line** therapy in patient **unable to tolerate ACE inhibitors or ARBs** due to any contraindications

4) B-Blockers

Bisoprolol, **Metoprolol** and **Carvedilol**

Advantages

1. ⬇ tachycardia and sympathetic over activity
2. ⬇ renin release → ⬇ cardiac remodeling caused by Ang II (RAAS)
3. ⬇ BP → ⬇ ventricular strain (effort)

Disadvantages

1. -ve inotropic activity
2. Worsen cardiac effect

- High doses of B blockers are generally not recommended in heart failure due its adverse effect
- **Small doses** only **used** for its benefits and not used for AHF
- According to currently evidence, **Bisoprolol, Metoprolol** and **Carvedilol** have **shown the most useful effects** in patients with **chronic HF**

✓ **Carvedilol =** Additional **VD + antioxidant**

5) +ve Inotropic

- Group of drugs that aim to ↑ ventricular contractility ↑ COP → ↑ ejection fraction to 50 - 60% as normal
- ↑ COP cause:
  1. ↑ blood supply to brain → ↓ sympathetic overstimulation
  2. ↑ renal blood supply →↓ Renin → ↓ RAAS system →
     a. ↓ VC (Ang II)
     b. ↓ Na /water retention
     c. ↓ cardiac remodeling

But remember, we never start treatment of HF with digoxin because it may worsen the case

- **They are divided into:**

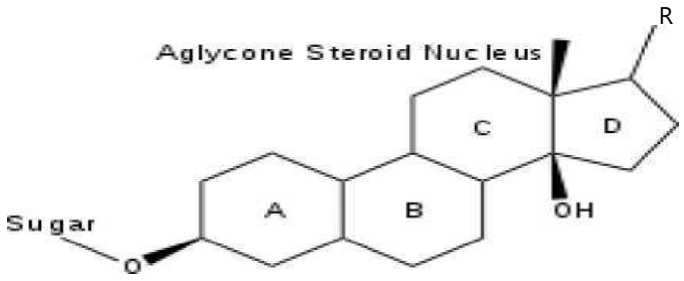
1. Short acting: Dopamine and Dobutamine - PDE_3 inhibitors
2. Long acting: (Cardiac glycoside digitalis)

A) Cardiac glycosides

- Natural plant derivatives extracted from (Digitalis Purpurea)

They include different compounds but the most widely used is **digoxin**

Cardiac glycoside consisted of a lactone ring and a steroid moiety attached to sugar molecules



Dosage and administration

1 - Initial digitalization (maintenance dose):

- Giving (**1*1*5**) one tablet / day for 5 days /week and 2 days as drug free interval (drug holiday)
- Drug will reach to steady state after 5 $t_{1/2}$ that mean after one week

2- Loading dose

- In emergency condition only follow the role **(2*2*2) or (2*3*1)**

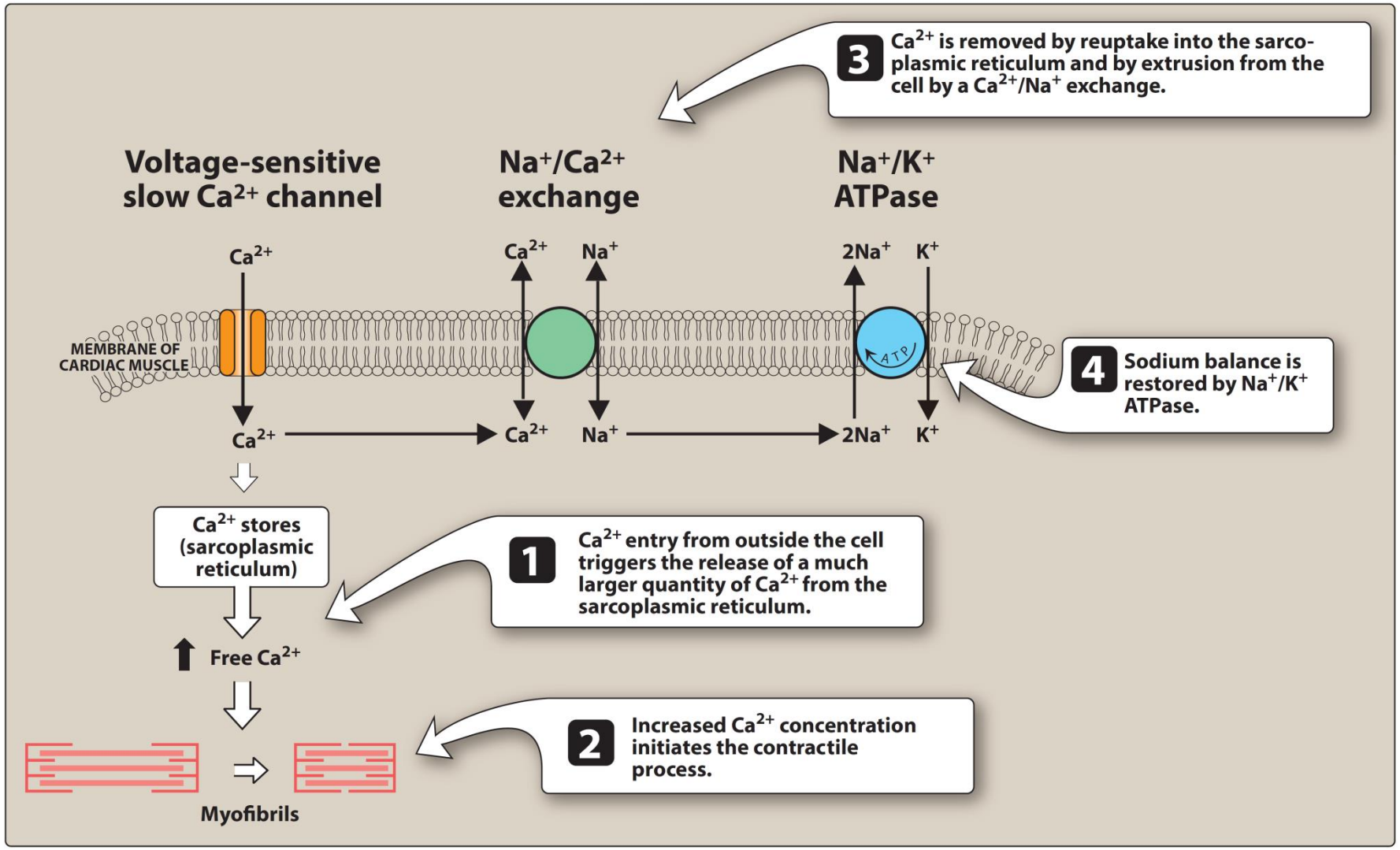
It means:

- **(2*2*2)** 2 tablet twice a day for 2 days
- **(2*3*1)** 2 tablets 3time daily or one day

then complete with normal maintenance dose

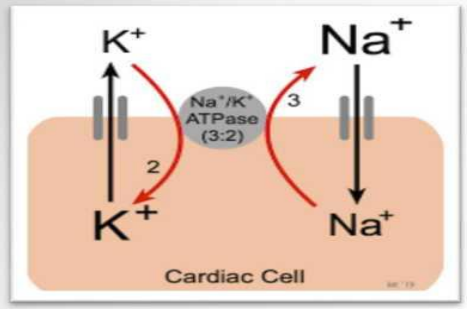
Mechanism of action

1. +Ve inotropic effect:- Mechanism of Positive Inotropic Action:



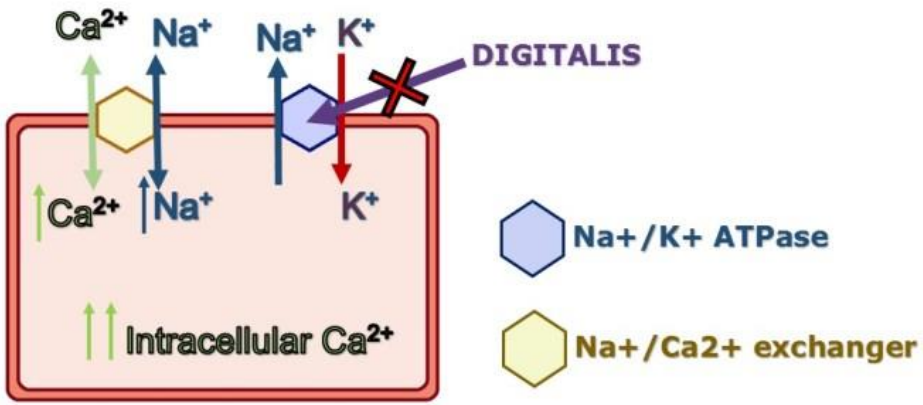
***Note:** drugs that reduce Na influx or Ca influx will be **negative** inotropic*

NOTE: Hypokalemia increases Dig effect



Digoxin inhibits Na^+/K^+ ATPase

inhibit Na^+/K^+ pump



accumulation Na^+ inside cell

Exchange Ca^{+2} with Na^+ through Na^+/Ca^{+2} Exchanger

↑ in the intracellular Ca^{+2}

↑ Ca^{+2} release from the SR → +ve inotropic effect

- Direct inhibition of membrane bound Na^+/K^+ ATPase, which normally pump 3 Na+ outside the cell in exchange with 2 K+ inside the cell which is responsible for maintenance of resting membrane potential in most excitable cells
- Inhibition of Na^+/K^+ ATPase causes an ↑ intracellular Na^+ ions.
- ↑ intracellular Na^+ → stimulates Na^+ and Ca^{+2} exchange through Na^+/Ca^{+2} pump/exchanger → ↑ in the intracellular $Ca+^2$.
- The ↑ in intracellular $Ca+^2$ mobilizes more $Ca+^2$ from the sarcoplasmic reticulum, and increases its effect on the contractile proteins.

→ → +ve inotropic effect

- Cardiac glycosides (Digoxin) and K+ compete for this ATPase enzyme. This could explain the antagonistic effects of low serum potassium towards digitalis toxicity.

2- Autonomic effect

- **Stimulate valgus** nerve → activate M2 receptor →
  - **Inhibit SA node** → ↓ HR
  - **Inhibit AV node** → ↓ heart Conduction velocity
- ↓ Atrium refractory period

Pharmacological effects

1. inhibition of SA node due to vagal stimulation → Decrease HR (bradycardia)
2. ↓ atrial refractory period → ↑ atrial contractility
3. inhibition of AV node → ↓ conduction velocity → ↑ ventricular refractory period.
4. ↑ ventricular contractility and C.OP.
5. ↑ excitability and automaticity leading to → ectopic foci and ***arrhythmia***

Therapeutic use

1- In chronic treatment of heart failure but it is not the first line therapy

2- Chronic **CHF associated with atrial fibrillation** (AF) because it ↑ ventricular contractility and ↓ AV conduction velocity at the same time.

3- in case of **atrial fibrillation (**AF**)** alone other drugs like **verapamil** or **B blockers** are preferred

Contraindication

1. All causes of Bradycardia.
2. Heart block: because it inhibits AV conduction
3. Ventricular arrhythmia
4. Cardiac disease (Acute MI) ^ increase infract size and aggravates arrhythmia
5. Systemic hypertension
6. Pulmonary hypertension
7. Acute rheumatic carditis

Digoxin should also be used with caution with other drugs that slow AV conduction, such as β-blockers, verapamil, and diltiazem.

Drug interaction

- Digoxin normally competes with K^+ for the same binding site on the Na^+/K^+-ATPase pump → so all drugs cause **Hypokalemia** increase its binding to Na^+/K^+ ATPase enzyme causing toxicity ex: **loop diuretic** & **thiazide**
- **Hypercalemia increase** toxicity of digoxin ex some **thiazide**
- Quinidine , verapamil, amiodarone → **increase** digoxin levels
  - **Quinidine** → **displace** Digoxin from its plasma protein binding site + **reduce** its **renal clearance** → ↑ serum Digoxin
  - Digoxin is a substrate of P-gp, and inhibitors of P-gp, such as **clarithromycin**, **verapamil**, and **amiodarone**, can significantly **increase digoxin levels**, necessitating a reduced dose of digoxin.
- Antacid gels, kaolin, and cholestyramine → bind with digoxin in the gut → Decreased bioavailability of digoxin (absorption).
- Metoclopramide→ increase gut motility → reduce Digoxin absorption.
- Atropine → reduce gut motility → increase Digoxin absorption.
- Beta blockers (causing increase in bradycardia and heart block).
- Calcium channel blockers (causing bradycardia)

Digitalis Toxicity

1) predisposing factors

1 Hypokalemia : increase digoxin binding and effect

2- Hypercalcemia

3- Hypomagnesaemia

3- presence of renal impairment

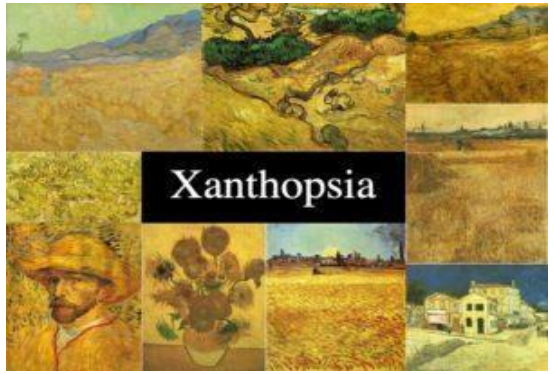
2) Manifestation

a. Cardiac: bradycardia, heart block and arrhythmia

b. Extra cardiac:

- **GIT** is the most common side effect of digitalis toxicity Effects include anorexia, nausea, vomiting and diarrhea)
  - This toxicity may be caused by direct effect on GIT or due to chemoreceptor trigger zone stimulation.

- **CNS**: Headache, hallucination and convulsion
- **Endocrine**: Gynecomastia (chronic uses)
- **Eye/Vision** → xanthopsia (yellow-colored vision))



3) Management

A. **Stop digitalis** administration.
B. Correct **hypokalemia** -> K+ i.v or oral (2 mg/4hh)
C. Treat digitalis **arrhythmia** :
   - **Atropine** for bradycardia and heart block
   - **Lidocaine** for ventricular arrhythmia
D. Specific digitalis **antibodies** (**Fab fragment**) to bind to digitalis and promote its **clearance**


Thank you. . .