UNIT – I

DRUG ACTING ON CVS

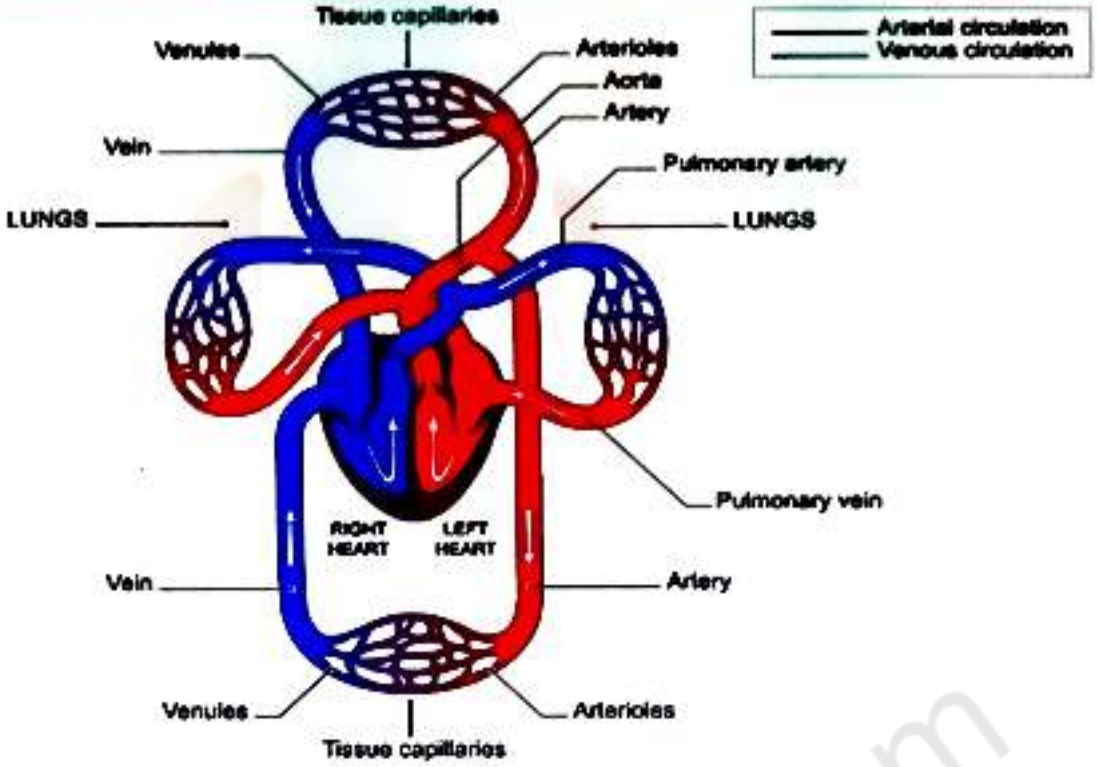
PART –(a) INTRODUCTION TO HEMODYNAMICS & ELECTROPHYSIOLOGY OF HEART

Points to be covered in this topic

1. INTRODUCTION TO HEMODYNAMICS
2. CORONARY BLOOD FLOW
3. BLOOD PRESSURE
4. ELECTROPHYSIOLOGY OF HEART
5. AUTONOMIC INFLUENCE ON CARDIAC SYSTEM

❑ INTRODUCTION TO HEMODYNAMICS

- Dynamics means study of motion. Hemodynamics refers to the study of movement of blood through circulatory system.
- Hemodynamics is a physical and physiological principle of blood flow (circulatory system) in the body.
- The cardiovascular system is concerned with the circulation of the blood.
- Essentially it consists of heart, which works as pump, and the blood vessels, which carry the blood.
- The blood carries oxygen and nutrients and circulates through various tissue of the body.



❖ **The main functions of blood are**

- ✓ Transportation of blood gases, nutrients, wastes
- ✓ Homeostasis (regulation) of pH, body temperature, water content
- ✓ Protection

❖ **The forces involved with the movement of blood throughout the human circulatory system include:**

- **Kinetic** and **potential energy** provided by the cardiac pump.
  - ✓ Kinetic Energy: Active energy, of motion as **forward movement of blood.** It is transformed in to potential energy when it produces a lateral pressure or stretching of vessel walls during systole.
  - ✓ Potential energy: Stored energy, it is converted back in to kinetic energy when the arterial walls rebound during diastole
- **Gravitational force**
- Hydrostatic Pressure (weight of the liquid acting on a unit area at that depth plus any pressure acting on the surface of the liquid).
- **Pressure gradients** or differences between two any points.

❖ **Properties of blood that affect its flow:**

- Viscosity
- Inertial mass (mass of an object measured by its resistance to acceleration)
- Volume of blood to be moved

❖ **Factors affecting motion of blood in vascular channels:**

i. Size of the blood vessel

ii. Condition of blood vessel

iii. Smoothness of lumen

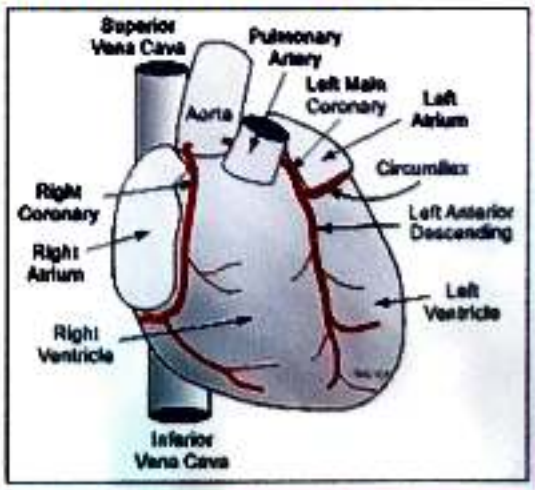
iv. Elasticity of muscular layer (*tunica* media)

v. Destination of blood (vascular bed)

Note - Cardiovascular hemodynamics comprises of **blood circulation to the heart** and in turn the **blood circulation regulated by the heart.**

❑ CORONARY BLOOD FLOW

- Coronary circulation is **the circulation of blood in the blood vessels that supply the heart muscle (myocardium).**
- Coronary arteries **supply oxygenated blood to the heart muscle.** Cardiac veins then **drain away the blood after it has been deoxygenated.**
- Resting coronary blood flow in human average is approximately **225ml/minute**, which is **0.7 to 0.8 ml per gram of the heart muscle.**
- During the diastole, **cardiac muscle relaxes completely** and no longer obstructs the blood flow through left ventricular capillaries.
- This is **phasic changes in coronary blood flow** during cardiac muscle compression.

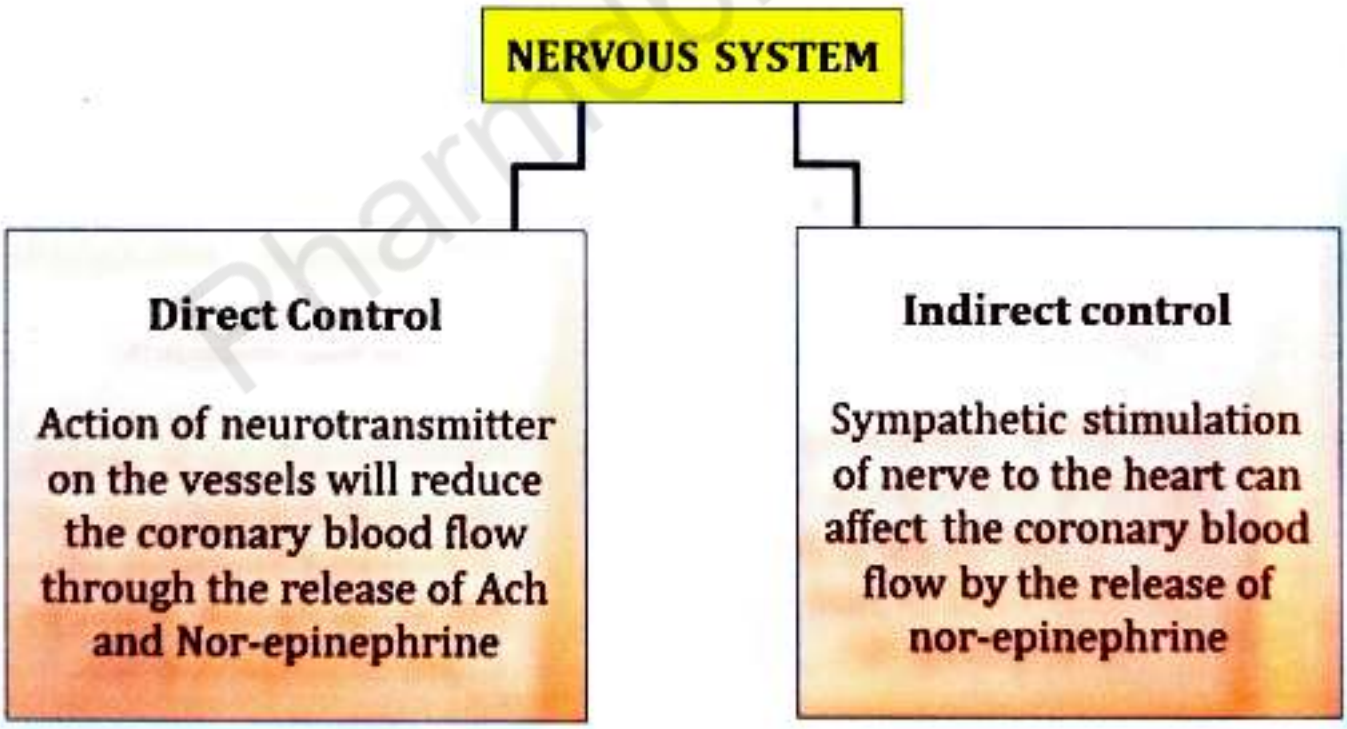


- During **cardiac contraction** – Intra myocardial pressure in the inner layer of the heart muscle is so much greater than the outer layer.
- It **compresses the sub endocardial blood vessels** far more than it compresses the outer vessel.

➢ **Control of Coronary Blood Flow:**

- **Oxygen demand** is a major factor in local blood flow regulation.
- Determinants of **oxygen consumption.**
- Importance of increase in coronary blood flow in response to **myocardial oxygen usage.**
- **Reactive hyperemia** in coronary system.

❖ **Nervous Control** - Stimulation of autonomic nerves of the heart can affect coronary blood flow in two ways.



❖ **Stroke Volume** - The **amount of blood pumped by the left ventricle** of the heart in one contraction. Normally only about 2/3rd of the blood in the ventricle is expelled with each beat.

❖ **Cardiac Output:** It is defined as the **amount of blood flowing from the heart** (from the left ventricle in to aorta) over a given period of time (or in single heart beat). Flow of blood is usually measured in L/min

Cardiac Output = Stroke volume x Heart rate

= 70 ml x 72/min = 5040 ml/min

= About 5 liter/min

Where, **Stroke volume** = Volume of blood pumped by heart/heart beat

Heart rate = Ventricular systole/min

❑ Blood pressure

- Blood pressure is the **pressure of circulating blood against the walls of blood vessels** (particularly arteries). Driving force for blood flow is pressure created by ventricular contraction.
  - ✓ Elastic **arterial walls expand and recoil** to allow continuous blood flow.
  - ✓ Blood pressure is **highest in the arteries** and falls continuously –

Systolic pressure in Aorta → 120 mm Hg

Diastolic pressure in Aorta → 80 mm Hg

❖ Blood Pressure Regulation

- Blood pressure is **determined by vascular resistance and cardiac output.**
- Vascular resistance is **regulated at the level of the arterioles**, influenced by neural and hormonal inputs.
- Cardiac output is determined by **heart rate and stroke volume**, which is **strongly influenced by blood volume.**
- Blood volume in turn is **regulated mainly by renal sodium excretion or resorption.**
- Renin, a major regulator of blood pressure, is **secreted by the kidneys** in **response to decreased blood pressure** in afferent arterioles. This secretion activates the most complex cardiovascular mechanism called **RAAS system** i.e., Renin-Angiotensin-Aldosterone System.

❑ ELECTROPHYSIOLOGY OF HEART

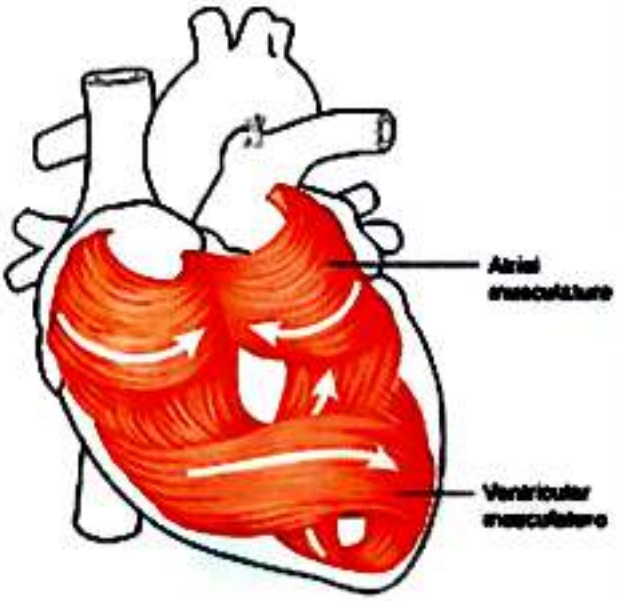
❖ Physiology of Cardiac Muscle :-

➢ **Three major types of cardiac muscle fiber –**

- **Atrial muscle**
- **Ventricular muscle**

} **Atrial and ventricular muscle contract in a same way as skeletal muscle but the duration of contraction is longer**

- **Specialized excitatory and conductive muscle fibers** – They contract feebly because they **contain few contractile fibrils.**
- Exhibit **automatic rhythmical electrical discharge** in the form of action potentials.



❖ Action Potential in Cardiac Muscle –

The cardiac action potential is a **brief change in voltage** (membrane potential) across the cell membrane of heart cells. This is caused by the **movement of charged atoms** (called ions) between the inside and outside of the cell, through proteins called ion channels.

❖ Phases of the cardiac action potential :-

The action potential in typical cardiomyocytes is **composed of 5 phases** → **(0-4) is beginning** of AP and **ending with phase 4**.

1. Phase 0: Rapid Depolarization –

External stimulus to excitable tissue

⬇

Opens the voltage gated sodium ion channels

⬇

Sodium ions enter the cells decreases their electrochemical gradient

⬇

Intracellular movement of sodium ion depolarizes the membrane

⬇

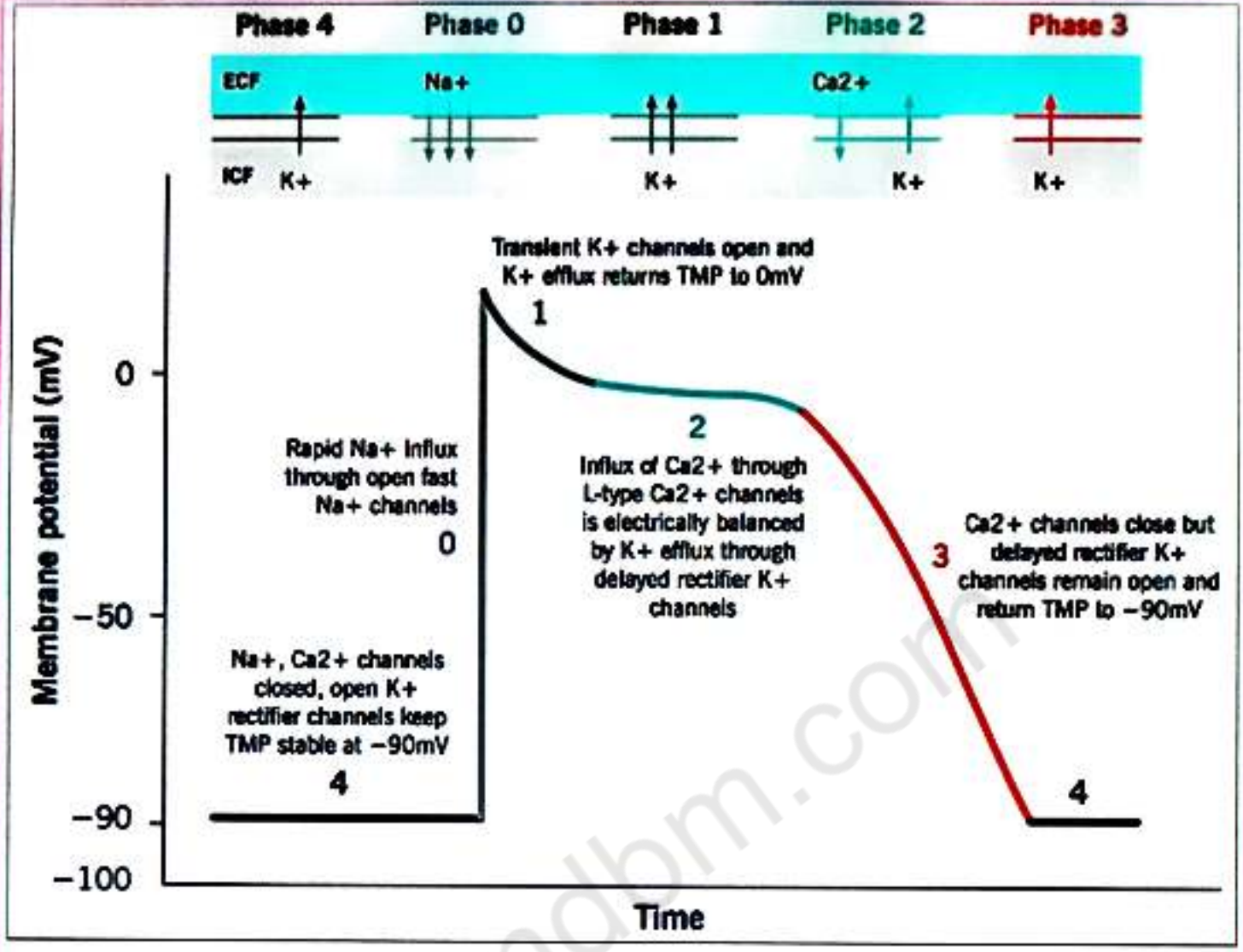
Increases the membrane conductance to sodium ion displaces the membrane potential to +30mv

2. Phase 1 (Early Repolarization) –

- Following phase 0, **membrane repolarizes rapidly** and transiently to almost 0 mV because of the **inactivation of sodium ion channel** and simultaneous transient **increases in outward potassium currents.**

3. Phase 2: The plateau phase –

- Membrane potential **remains approximately 0mV** for a relatively prolonged duration.
- A balance between **slow inward Ca^{2+} and outward K^{+} currents** mediate the plateau phase of the action potential.



4. Phase 3 (Repolarization)

- Inactivation of Ca^{2+} channels and a simultaneous increase in outward K^+ current through K^+ channels produces a net outward movement of positive charge and repolarization of the membrane.

5. Phase 4 (Resting Membrane Potential)

- The membrane potential of ventricular myocytes remains at the resting membrane potential until the cell is stimulated again.
- The types of action potential in heart can be separated into two categories:
  - ✓ **Fast-response action potentials**, which are found in the His-Purkinje system and atrial or ventricular cardio-myocytes.
  - ✓ **Slow- response action potentials**, which are found in the pacemaker cells in the SA and AV nodes.

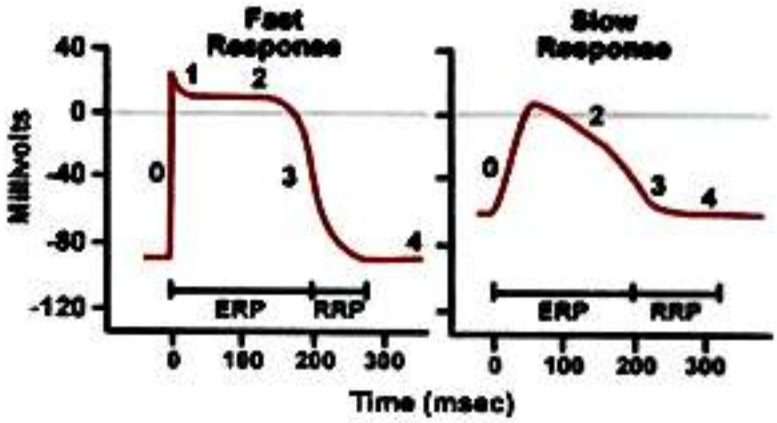
❖ Types of action potential :-

- There are two types of action potential (AP) possible as shown below in figure –

Fast- and Slow Response Action Potentials

i. **Slow action potential**

ii. **Fast action potential**



➢ **The slow channel AP is characterized by :-**

(a) Initiation at a higher threshold **(less negative level).**

(b) **Slower depolarization** during 0 phase.

(c) Less overshoot, **low amplitude.**

(d) Very **slow propagation, decremental conduction and a low safety factor** for conduction.

(e) Can arise and propagate in fibers **too that depolarized to support fast channel** responses.

The characteristics of both action potential are given in table below :-

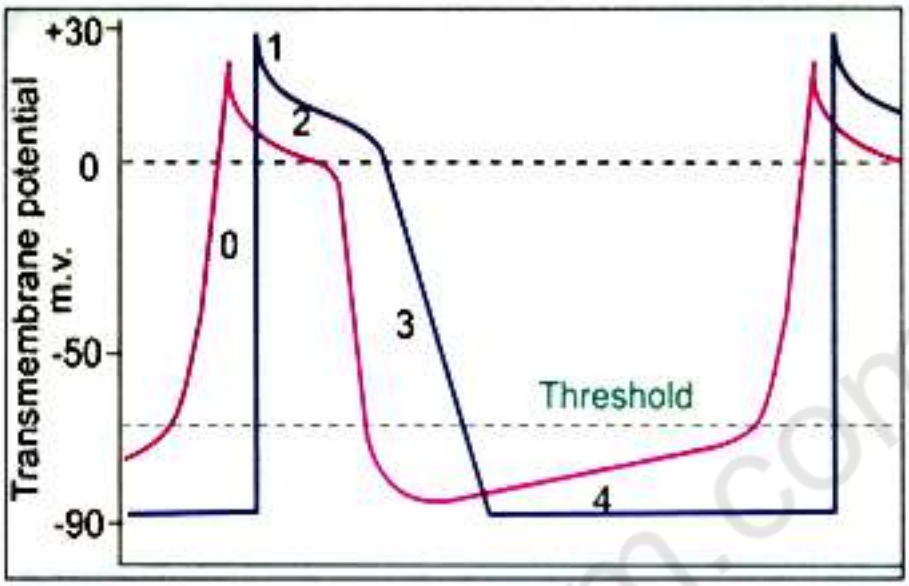
	Fast channel AP	Slow channel AP
1. Sites of occurrence	Atria, ventricles, Purkinje fibres	SA and A-V nodes, round A-V ring, coronary sinus opening
2. Predominant ion moving in 0 phase	Na^+	Ca^{2+}
3. Activation-inactivation kinetics	Fast	Slow
4. Channel reactivation	Voltage-dependent	Time-dependent
5. Activation potential (threshold voltage)	-60 to -70 mv	-45 to -55 mv
6. Conduction velocity	0.5–5 m/sec	0.01–0.1 m/sec
7. ERP–APD* relationship	ERP < APD	ERP > APD
8. Selective channel blocker	Tetrodotoxin, Local anaesthetics	Verapamil, Diltiazem, Mn^{2+}

***ERP**—Effective refractory period; **APD**—Action potential duration.

❖ Cardiac Electrophysiology and drug action on heart :-

The properties which are especially important for understanding drug action on heart are:

1. **Impulse generation** - Electrophysiologically, **two types of myocardial fibers** can be distinguished



Transmembrane potential of automatic (red) and non-automatic (purple) myocardial fibers recorded through intracellular electrodes

i. Non-automatic fibres –

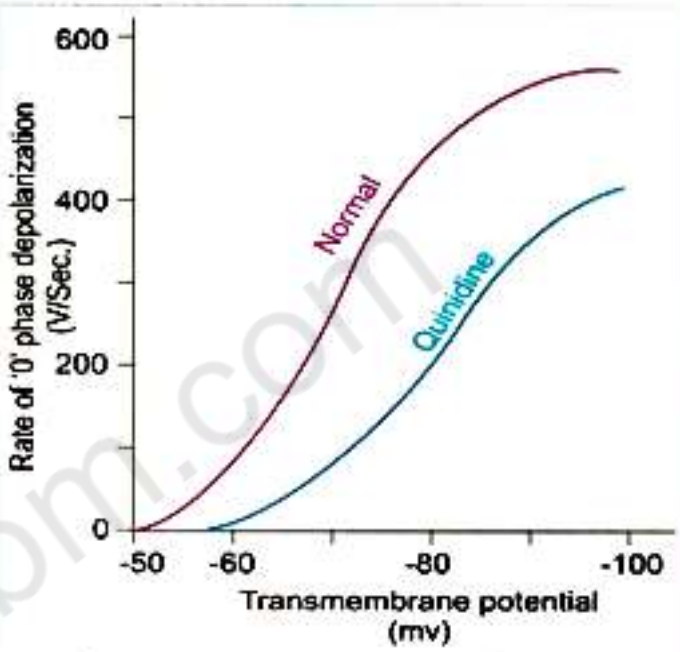
- ✓ These are ordinary working myocardial fibres; **cannot generate an impulse of their own**. During diastole, **resting membrane potential remains stable** (approximately 90mV negative).
- ✓ When stimulated, they follows action potential as explained earlier (**i.e., Phase 0 – 4**).
- ✓ Resting membrane potential, once attained, does not decay (stable phase-4).

ii. Automatic fibers –

- ✓ These are present in the **sinoatrial (SA), atrioventricular (A-V) nodes**, and in **His-Purkinje system**, i.e. especialized conducting tissue.
- ✓ The most **characteristic feature** of these fibers is phase-4 or slow diastolic depolarization, i.e. after repolarizing to the maximum value, **the membrane potential decays spontaneously.**

2. **Conduction –**

- The rate of conduction through a fiber is a **function of its membrane responsiveness**, which is defined by **rate of rise of AP (dv/dt) as a function of membrane potential** at which activation occurs.
- A **completely polarized membrane depolarizes faster** because more Na^+ channels have recovered (voltage dependent reactivation).
- This type of relationship is seen in **atrial, ventricular and Purkinje fibers** (fast channel fibers which depolarize by Na^+ current), but **not in SA and A-V nodal cells** which remain refractory for some time even after attainment of maximal resting potential (Ca^{2+} channel reactivation is time-dependent).



Membrane responsiveness curve of a myocardial fiber showing the relationship between membrane polarization & dv/dt of 0 phase.

3. **Excitability –**

- This property of a fiber is defined by the **strength of stimulus required to elicit a response or to produce an AP.**
- **Hyperpolarization decreases excitability** while **small reductions in resting membrane potential increase excitability** by respectively increasing and decreasing the gap between it and the threshold potential.

4. **Refractory period –**

- Pharmacologically, the effective refractory period (ERP) which is the **minimum interval between two propagating APs**, is the most important. It is **closely related to the AP duration** (APD).

❖ Autonomic influences on cardiac system:-

It would be profitable to study the influence of sympathetic and parasympathetic stimulation on variables of cardiac function, because many cardiovascular drugs have indirect/secondary autonomic effects.

Autonomic influences on cardiac electrophysiology and contractility

Parameter	Effect of stimulation	
	Parasympathetic (ACh)	Sympathetic (Adr)
1. Automaticity		
SA node	Bradycardia	Tachycardia
Ectopic ventricular	—	Enhanced
2. Refractory period		
Atria	Shortened (inhomogeneous)	Shortened
Conducting tissue	Prolonged	Shortened
3. Conductivity	Depressed	Enhanced
4. Contractility	Decreased (little effect on ventricle)	Increased

UNIT – I

DRUG ACTING ON CVS

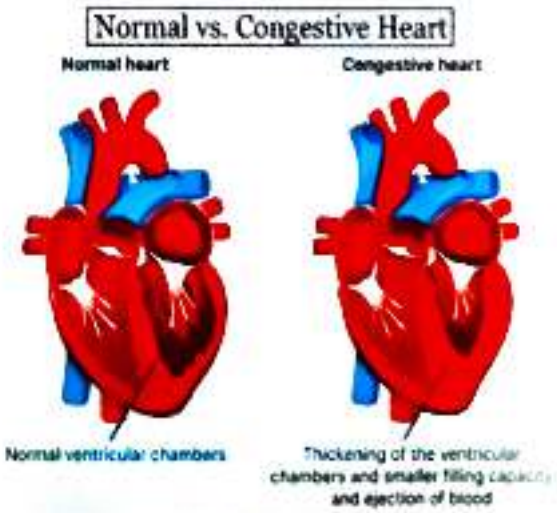
PART-(b) CONGESTIVE HEART FAILURE

Points to be covered in this topic

1. WHAT IS CONGESTIVE HEART FAILURE ??
2. EPIDEMOLOGY
3. CLASSIFICATION OF CHF
4. PATHOPHYSIOLOGY OF C.H.F
5. COMPENSATORY MECHANISMS OF CHF
6. TREATMENT OF CHF

❑ WHAT IS CONGESTIVE HEART FAILURE ??

- Congestive heart failure (CHF) is a clinical syndrome during which the **cardiac center is unable to pump ample blood to fulfill the metabolic necessities** of the body or will do thus solely at an elevated filling pressure.
- The **pumping ability of the heart is reduced** & cardiac output decreases.
- Thus **ventricles are not completely emptied** resulting in **increased venous pressure** in the pulmonary and systemic circulation.
- The **ejection fraction (EF) decreases** — the normal EF of the left ventricle is 55 –65% while in chronic heart failure it falls to less than 40%.



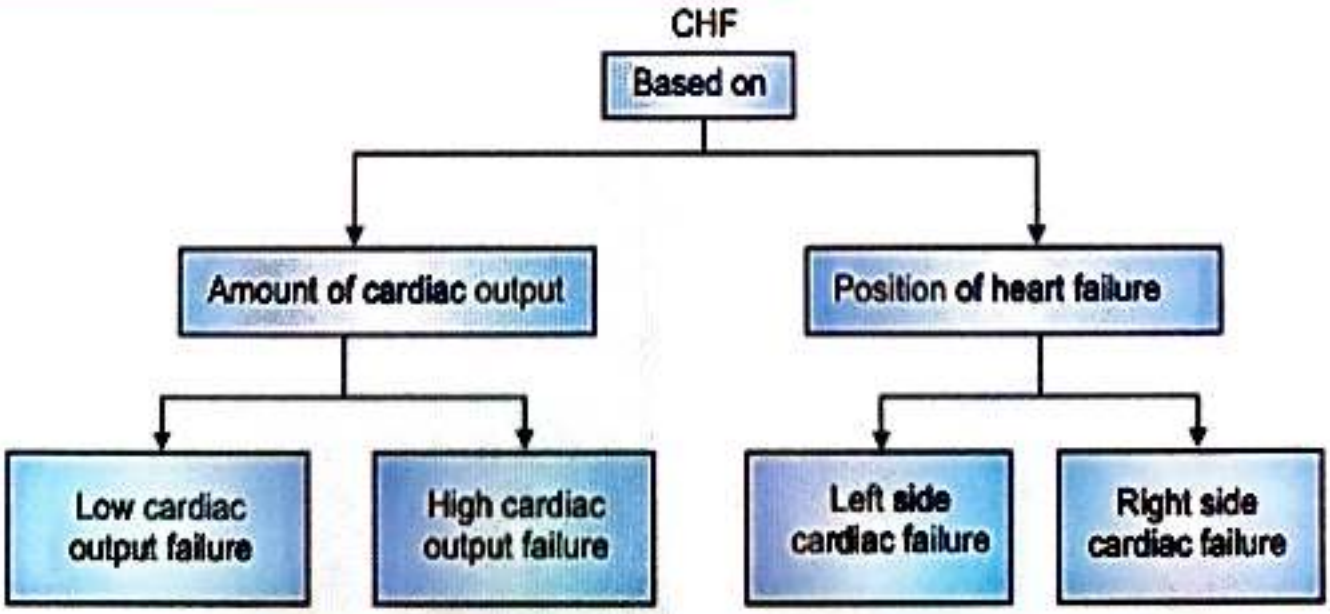
❑ EPIDEMIOLOGY

- Congestive cardiac failure is **one of the common causes of morbidity and mortality** with almost 50% mortality at 5 years.
- The overall **prevalence of HF** within the adult population **in developed countries is 2%.**
- HF prevalence **follow an exponential pattern**, rising with age, and affects 6-10% of people over age 65.
- The **incidence of HF is lower in women** than in men.
- Although HF once was through to arise primarily within the setting of a **depressed left chamber (LV) ejection fraction (EF)**, medical specialty studies have shown that around simple fraction of patients WHO develop HF have a standard or preserved EF (EF 40-50%).
- Accordingly, **HF patients are now broadly categorized into one of two groups:**

(1) HF with a depressed EF (systolic failure) or

(2) HF with a preserved EF (diastolic failure).

❑ CLASSIFICATION OF CHF



I. Based on amount of Cardiac Output :-

1. Low cardiac Output Failure

- **Most frequent**
- Metabolic **demands of the body organs for oxygen are normal** and within limits
- **Myocardial fraction** is major factor for the **failure of systolic and diastolic function** of the ventricles, ultimately results in low cardiac output failure.

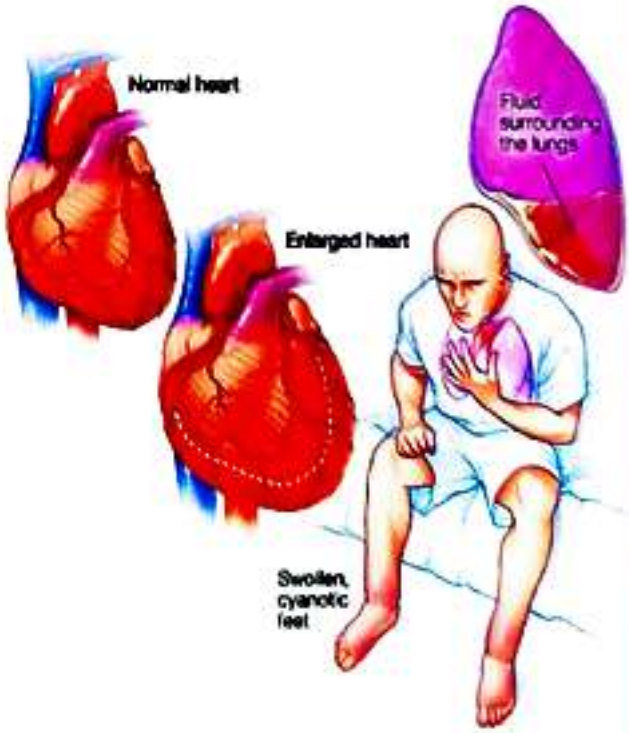
2. High cardiac Output Failure

- **Very rarely**
- Metabolic **demands of the body for oxygen is very high.**
- **Hyperthyroidism, anaemia, arteriovenous shunt** causes high cardiac output failure.

II. Based on the position of Heart Failure

1. Left side Cardiac Failure

- ✓ Is the result of **right side cardiac failure.**
- ✓ **Inefficient pumping** action of left ventricle is responsible for the **accumulation of blood in the ventricles.**
- ✓ **Left ventricle fails** to accept OR collect the blood from lungs due to back pressure.
- ✓ **Pulmonary congestion/oedema** is the final result.



2. Right side Cardiac Failure

- Is the result of **left side cardiac failure.**
- **Inefficient pumping action of right ventricle** is responsible for the **accumulation of blood in right ventricle.**
- **Right ventricle fails to accept/collect the blood** from peripheral organs.
- Peripheral generalized oedema is the final result.

❖ Other parameters that are leading to CHF :-

1. Systolic failure (systolic dysfunction) or ejection failure –

- It is the **inability of the ventricles** to pump and empty adequately.
- Contractility and ejection fraction are reduced as in ischemic heart diseases and myocarditis.
- The ventricles are dilated and, therefore, need to develop higher tension in its walls to eject the blood efficiently.

Laplace's Law

Wall tension = Intraventricular pressure × Ventricular radius

2. Diastolic failure –

- It is **filling failure** and occurs when the **ventricles are not filled adequately during diastole** because of **both stiffening and inadequate relaxation** during diastole.
- As the filling is reduced, cardiac output is reduced. However, ejection fraction may be normal.
- In patients with **ventricular hypertrophy** as in prolonged hypertension, aortic stenosis, hypertrophic cardiomyopathy and congenital heart diseases, diastolic failure is seen.
- Some patients may have both systolic as well as diastolic dysfunction.

❑ PATHOPHYSIOLOGY OF CONGESTIVE CARDIAC FAILURE (C.C.F)

- Cardiac membrane is lipoproteinous in nature. Normally Na^+ ion are concentrated extracellularly.

When Na^+ levels falls

⬇

Sarcoplasmic reticulum remains inactive

⬇

Causes low level of Ca^{++}

⬇

Leads to weak myocardial systole

⬇

This causes accumulation of blood in ventricles

⬇

Leads to ventricular distension

⬇

Heart tries to expel this accumulated blood volume

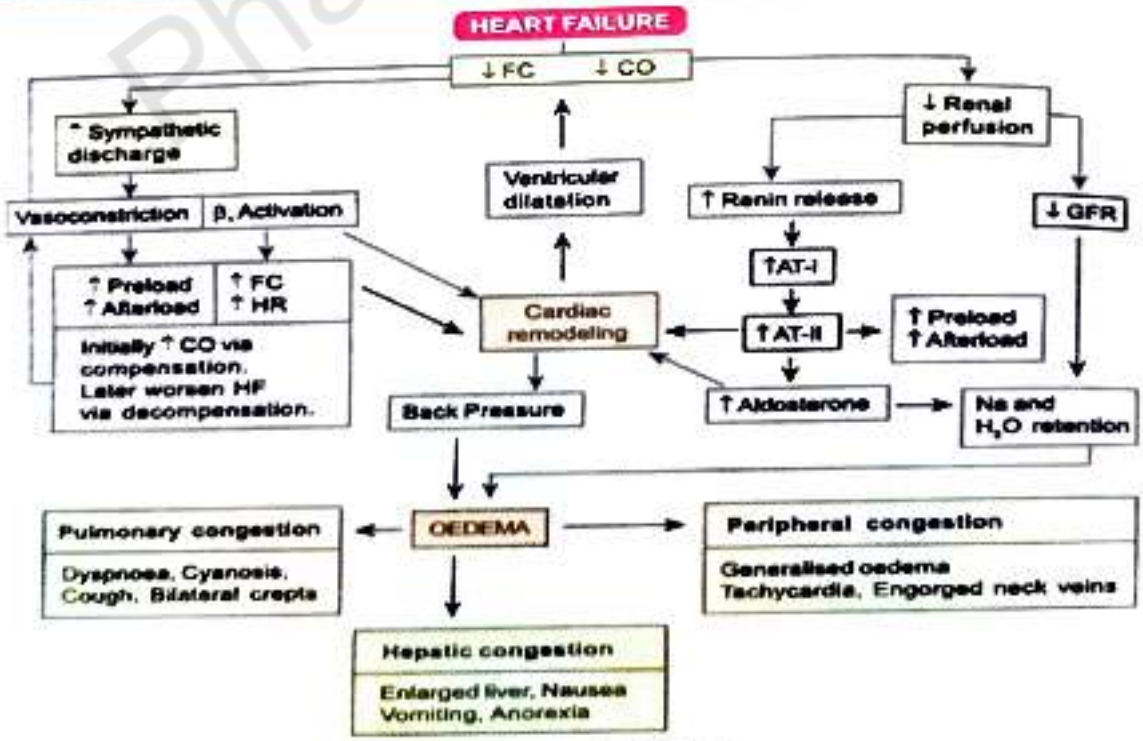
⬇

Gets exhausted and fails to work

⬇

This failure due to accumulation of blood volume is defined as Congestive Heart Failure

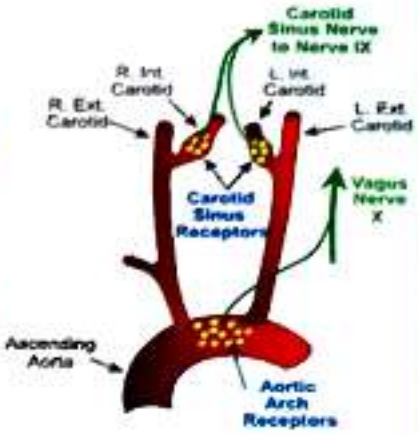
❖ PHYSIOLOGICAL MANIFESTATION OF CHF



Key: FC—Force of contraction; CO—Cardiac output; AT-I and AT-II—Angiotensin I and II, respectively

❑ COMPENSATORY MECHANISMS OF CHF

I. <u>To enhances cardiac output</u>, body compensates for intrinsic cardiac effects in the following manner :-

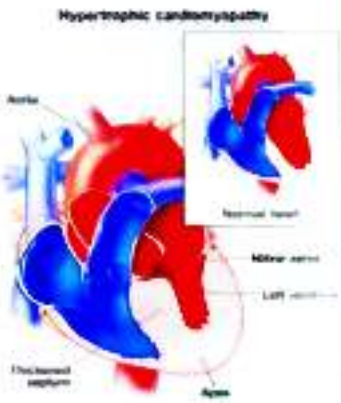


1. Increased sympathetic discharge.
2. To complete the remittent B.P., **baroreceptors** present in **arch of aorta** at sinuses arterial blood vessel and walls of center get excited & **causes activation of β-adrenergic receptors** resulting in an increase in rate and force of contraction of heart.
3. An increase in blood vessel comes back (**preload**) is additionally seen because of the activation of alpha adrenergic receptors.
4. Increased **rate associated force of contraction** at the side of the enhanced preload ends up in an initial increase within the flow.
5. Vasoconstriction of the arteries due to **alpha stimulation** also causes an increase in after load, leading to fall in ejection fraction.

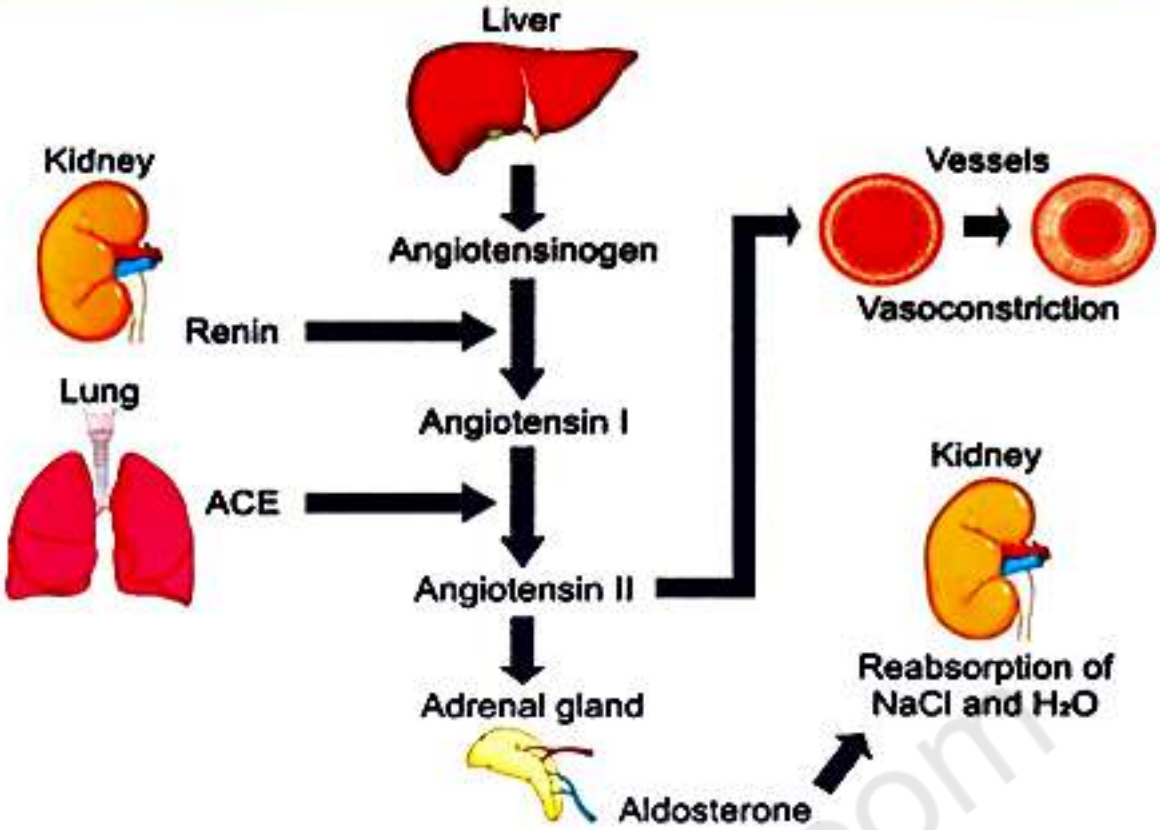
II. <u>Activation of Renin Angiotensin Aldosterone (RAA)</u>

- Fall within the **flow decreases the urinary organ** perfusion rate; as a result the RAA system gets activated.
- Angiotensin II may cause **atrophic response in vascular smooth muscle (with vasoconstriction) and myocardial hypertrophy**, attempting to restore wall stress to normal.

III. <u>Cardiac Remodeling</u>: It is most vital mechanism by that ody stipendiary for the intrinsic internal organ effects.



- It involves changes within the form of the center (from traditional to spherical) because of **cardiac muscle hypertrophy**.



- During cardiac remodeling, the connective tissue cells as well as the abnormal myocardial cells **undergo proliferation and dilation instead of stretching** under the influences of angiotensin-2.
- In the early stages, the remodeled heart **maintains cardiac performances**.
- But later on, **hypertrophy may exert certain adverse effects like ischemic changes**, decrease in the rate and force of contraction of heart.
- After certain period of time the **antagonistic mechanisms get exhausted** and worsen the cardiac performances.
- The **stress on heart increases** and at certain stage mechanisms fails to maintain the adequate cardiac output.

❖ **Clinical manifestations/signs and symptoms**

- Fluid retention
- Pulmonary congestion
- Dyspnoea & orthopnoea

❖ **CVS Manifestations**

- Resting tachycardia
- Ventricular arrhythmias
- Enlargement of heart

❖ **Renal Manifestations** • Nocturia • Oliguria

❖ **Other Manifestations**

- **Reduced cardiac output** lead to poor perfusion of skeletal muscle resulting in fatigue.
- **Reduced flow** cause poor perfusion of muscle leading to fatigue.
- **Reduced perfusion to brain** results in altered mental states and confusion.
- Reduced perfusion might also **cause the patient to seem pale with cold and perspiring hands.**

❑ TREATMENT OF CHF

I. Non drug treatment/ non pharmacological approach :-

- **Physical exercise** - Regular exercise should be encouraged
- **Salt intake** - Advise patients to **avoid high salt content foods** and not to add salt (particularly in severe cases of congestive heart failure)
- **Fluid intake** - Urge overloaded patients and those with severe congestive heart failure to **restrict their fluid intake.**
- **Moderate alcohol consumption** advised (abstinence in alcohol related cardiomyopathy)
- **Diet** - **ensure adequate general nutrition** and, in obese patients, weight reduction
- **Smoking** - **Avoid smoking** (adverse effects on coronary disease, adverse hemodynamic effects).

II. Drug therapy

➢ There are two distinct goals of drug therapy in CHF:

[A] Relief of congestive/low output symptoms and restoration of cardiac performance. This can be achieved by:

a. **Inotropic drugs:** Digoxin, Dobutamine/Dopamine, Amrinone/Milrinone

b. **Diuretics:** Furosemide, Thiazides

c. **RAS inhibitors:** ACE inhibitors/ARBs

d. **Vasodilators:** Hydralazine, Nitrate, Nitroprusside

e. **β-blocker:** Metoprolol, Bisoprolol, Carvedilol, Nebivolol

f. **Synthetic BNP** — Nesiritide

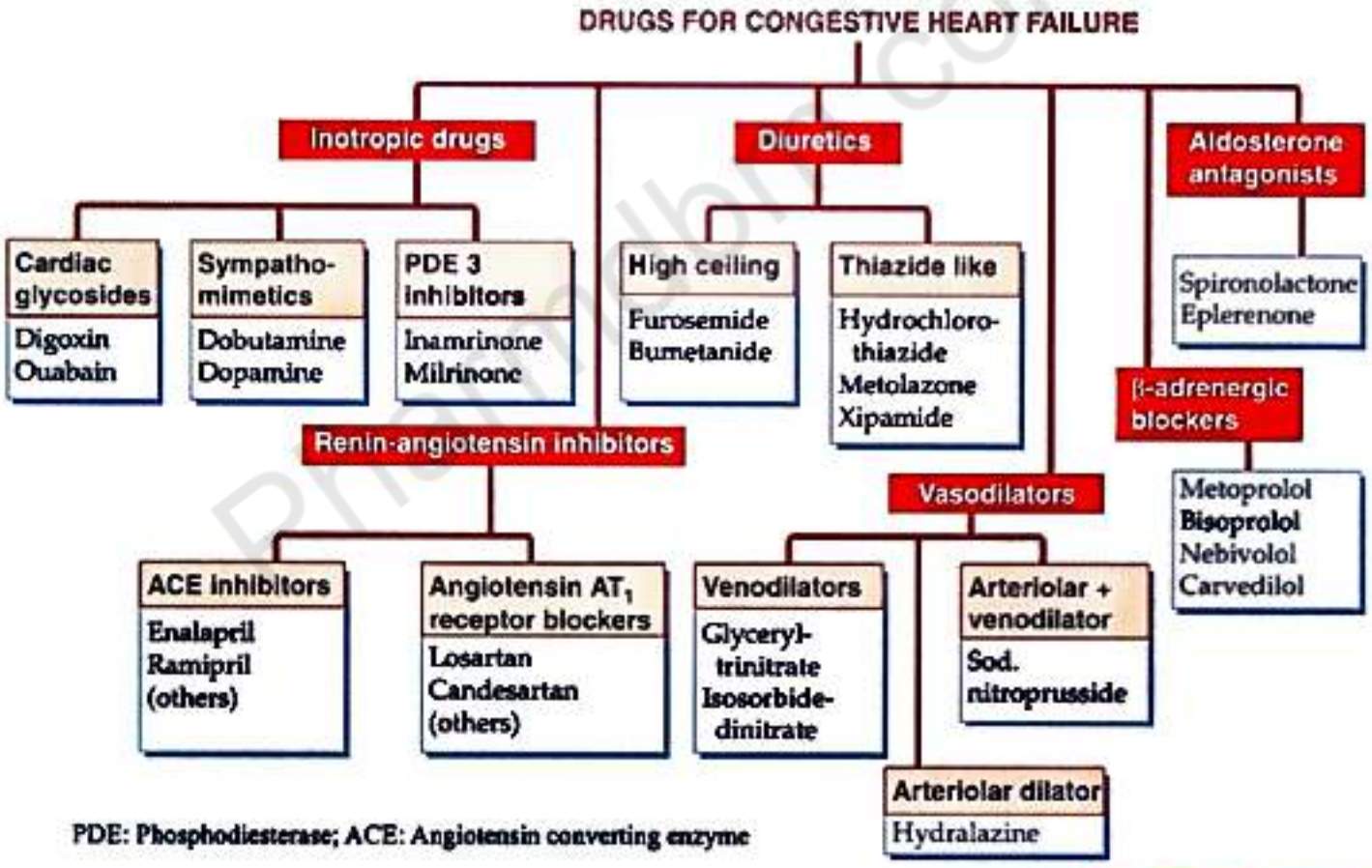
B. <u>Arrest/reversal of disease progression and prolongation of survival, possible with</u>:

a. **ACE inhibitors/ARBs,**

b. **β-blockers**

c. **Aldosterone antagonist:** Spironolactone, Eplerenone

d. **Neprilysin inhibitor** — Sacubitril



PDE: Phosphodiesterase; ACE: Angiotensin converting enzyme

❖ <u>CLASSIFICATION OF DRUG FOR CHF</u>

A. Inotropic Drugs

1. <u>Cardiac glycoside</u> – Digitalis (Digoxin)

MOA – "Effect on cardio vascular function in CHF".