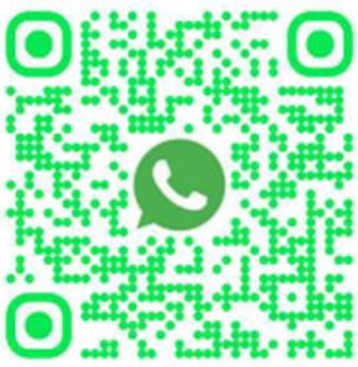
Unit-1
Pharmacology- II

B.Pharma 5th Sem Notes

Unit: 1

Pharmacology of drugs acting on cardio vascular system

- **Introduction to hemodynamic and electrophysiology**
- **Drugs used in congestive heart failure**
- **Anti-hypertensive drugs.**
- **Anti-anginal drugs.**
- **Anti-arrhythmic drugs.**
- **Anti-hyperlipidemic**



Introduction to hemodynamic and electrophysiology:

Hemodynamics The study of blood flow and the factors that influence its circulation is known as hemodynamics.

It encompasses various factors such as blood pressure, blood vessel resistance, and cardiac output, which is the amount of blood pumped by the heart per minute.

Electrophysiology focuses on the electrical activity of cells, particularly the heart.

The heart muscle generates electrical signals that trigger its rhythmic contractions. Electrophysiology studies the generation, conduction, and interpretation of these electrical signals.

Heart:

- The heart is a muscular organ responsible for pumping blood throughout the body.
- It is located in the thoracic cavity, slightly to the left of the midline, and is enclosed within the pericardium.
- The heart consists of four chambers: two atria (upper chambers) and two ventricles (lower chambers).
- It has the property of auto-rhythmicity which means it generates all electrical impulse.
- Ex: SA node, also known as Pacemaker.

Function:

- Delivery of Blood.
- Delivery of O2 and nutrient.

Factors affecting heart rate:

- Autonomic activity
- Circulating hormone
- Physical Activity
- Age
- Emotions
- Baroreceptors

Electrophysiology of Heart:

Cardiac muscles have property of

- Excitability
- Contractility
- Automaticity

Congestive Heart Failure:

Heart Failure is the complex progress disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.

Its symptoms are-

- Shortness of breath
- Fatigue or fluid retention
- Heart Failure is due to an impaired availability of the heart to the adequetly filled with and or the blood.
- Heart failure may primarily be due to systolic dysfunction of diastolic dysfunction.
- Other cause is
    - Arterioschloretic heart disease.
    - Myocardial infraction
    - Hypertension
    - Valbular heart disease

Systolic Dysfunction:

- Ventricles or dilated an enable to develop sufficient wall tension.
- This occurs in ischemic heart disease valbular heart disease.

Diastolic Dysfunction:

- Ventricular wall are thicker and unable to relax during diastole, ventricular filling is impaired because of its output low.

Compensatory Physiological Response in CHF:

The failing heart evokes 3 major compensatory mechanism to enhance cardiac output-

1. **Increase sympathetic activity:**
    - Baroreceptor sense a decrease in BP. And activates the sympathetic nervous system.
    - The stimulation of β-adrenergic receptors results in increase heart rate. And a greater force of contraction of the heart muscle which in turn increase cardiac output.
    - These compensatory mechanic or response increase the work of the heart which in the long term contributes to further decline in cardiac function.
2. **Activation of rennin Angiotensin aldosterone system:**
    - Fall in cardiac output decreases blood flow to the kidney promoting the release of renin, resulting in increase formation of angiotensin-2.
    - This results in increase peripheral resistance (after load) and retention of Na and H_2O.
    - Blood volume increase and more blood is return to the heart.
    - If the heart is unable to pump this extra vol pulmonary edema occurs.
    - Which in the long term contribute to further decline in cardiac function.

3. **Myocardial hypertrophy:**
    - The heart increase in size and the chambered dilated.
    - Stretching in the heart muscles leads to a stronger contraction of the heart.
    - However in weaker contraction and reduces the ability to eject the blood.

Drugs used in CHF:

- **Angiotensin-Converting Enzyme (ACE) Inhibitors:** These reduce afterload and improve cardiac output by relaxing blood vessels. Examples include enalapril and lisinopril.
- **Angiotensin II Receptor Blockers (ARBs):** Used as an alternative to ACE inhibitors for patients intolerant to them. Examples include losartan and valsartan.
- **Beta-Blockers:** These decrease heart rate and myocardial oxygen demand, improving heart function over time. Common examples are carvedilol and metoprolol
- **Diuretics:** Used to manage fluid retention and reduce symptoms like swelling and shortness of breath. Loop diuretics (e.g., furosemide) are commonly used.
- **Mineralocorticoid Receptor Antagonists (MRAs):** Spironolactone and eplerenone help reduce mortality and hospitalization by blocking aldosterone effects.
- **SGLT2 Inhibitors:** Drugs like dapagliflozin and empagliflozin have shown benefits in improving outcomes in heart failure with reduced ejection fraction.
- **Digoxin:** Sometimes used for symptomatic relief and to manage atrial fibrillation in CHF patients.
- **Vasodilators:** Combination therapy with hydralazine and isosorbide dinitrate is particularly effective in specific populations, such as African Americans.

Antihypertensive Drugs:

- Hypertension is defined as either a sustained systolic BP of greater than 140mm Hg or a sustained diastolic BP of greater than 90 mm Hg.
- Hypertension, commonly known as high blood pressure, is a chronic medical condition in which the force of blood against the walls of the arteries is consistently elevated.
- It is a major risk factor for cardiovascular diseases, stroke, kidney damage, and other health complications.

Types of Hypertension:

1. **Primary (Essential) Hypertension**: No identifiable cause; influenced by genetic and lifestyle factors.
2. **Secondary Hypertension**: Caused by an underlying condition such as kidney disease, endocrine disorders, or medication side effects.

Risk Factors:

- **Modifiable**: Obesity, high salt intake, sedentary lifestyle, excessive alcohol consumption, smoking, and stress.
- **Non-Modifiable**: Age, family history, gender, and ethnicity.

Symptoms:

Often called the "silent killer," hypertension usually has no symptoms. In severe cases, it may present with:

- Headaches
- Dizziness
- Blurred vision
- Nosebleeds

Diagnosis:

- Blood pressure readings of **≥140/90 mmHg** on multiple occasions confirm hypertension.

Classification Of Drugs:

Antihypertensive Drug Classes

	Classes	Drug Names	Examples	Mechanism of Action	Main Effect on BP
A	ACE Inhibitors	"pril"	Lisinopril Enalapril	Inhibit ACE	↓ SVR, SV
A	ARBs	"sartan"	Losartan Valsartan	Block Angiotensin II Receptors	↓ SVR, SV
A	Alpha Blockers	"osin"	Doxazosin Terazosin	Block Alpha Receptors	↓ SVR
B	Beta Blockers	"lol"	Metoprolol Labetalol	Block Beta Receptors	↓ HR, SV
C	Calcium Channel Blockers (CCBs)	"dipine"	Amlodipine Nicardipine	Block Calcium Channels	↓ SVR
D	Diuretics	"ide"	Furosemide Hydrochlorothiazide	Facilitate Diuresis	↓ SV

**Alpha blockers refer to selective alpha-1 blockers, and calcium channel blockers refer to dihydropyridines

- **Diuretics:** Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide High ceiling: Furosemide, etc. K + Sparing: Spironolactone, Amiloride
- **ACE inhibitors:** Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.
- **Angiotensin (AT1 receptor) blockers:** Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan
- **Direct renin inhibitor:** Aliskiren
- **Calcium channel blockers:** Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
- **β Adrenergic blockers:** Propranolol, Metoprolol, Atenolol, etc.
- **α Adrenergic blockers:** Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
- **Central sympatholytics:** Clonidine, Methyldopa
- **Vasodilators Arteriolar:** Hydralazine, Minoxidil, Diazoxide Arteriolar + venous: Sodium nitroprusside

Anti-anginal drugs:

- Anti-anginal drugs are used to manage angina pectoris, a condition characterized by chest pain or discomfort caused by insufficient blood flow to the heart (myocardial ischemia).
- These drugs aim to reduce myocardial oxygen demand or improve oxygen supply to the heart.

Classification of Anti-Anginal Drugs:

1. **Nitrates**
    - Dilate coronary and systemic blood vessels, reducing preload and afterload, and improving oxygen delivery.
    - **Examples**: Nitroglycerin, Isosorbide dinitrate, Isosorbide mononitrate
2. **Beta-Blockers**
    - Decrease heart rate, myocardial contractility, and blood pressure, reducing oxygen demand.
    - **Examples**: Metoprolol, Atenolol, Propranolol
3. **Calcium Channel Blockers (CCBs)**
    - Prevent calcium entry into vascular smooth muscle and myocardial cells, reducing afterload and improving coronary artery perfusion.
    - **Examples**:
        - Dihydropyridines: Amlodipine, Nifedipine
        - Non-dihydropyridines: Verapamil, Diltiazem
4. **Potassium Channel Openers**
    - Cause vasodilation by activating potassium channels in vascular smooth muscle.
    - **Example**: Nicorandil

Mechanism of Action:

- **Reduction in Oxygen Demand**: By lowering heart rate, myocardial contractility, or ventricular wall stress.
- **Improvement in Oxygen Supply**: Through coronary vasodilation or reducing vascular resistance.

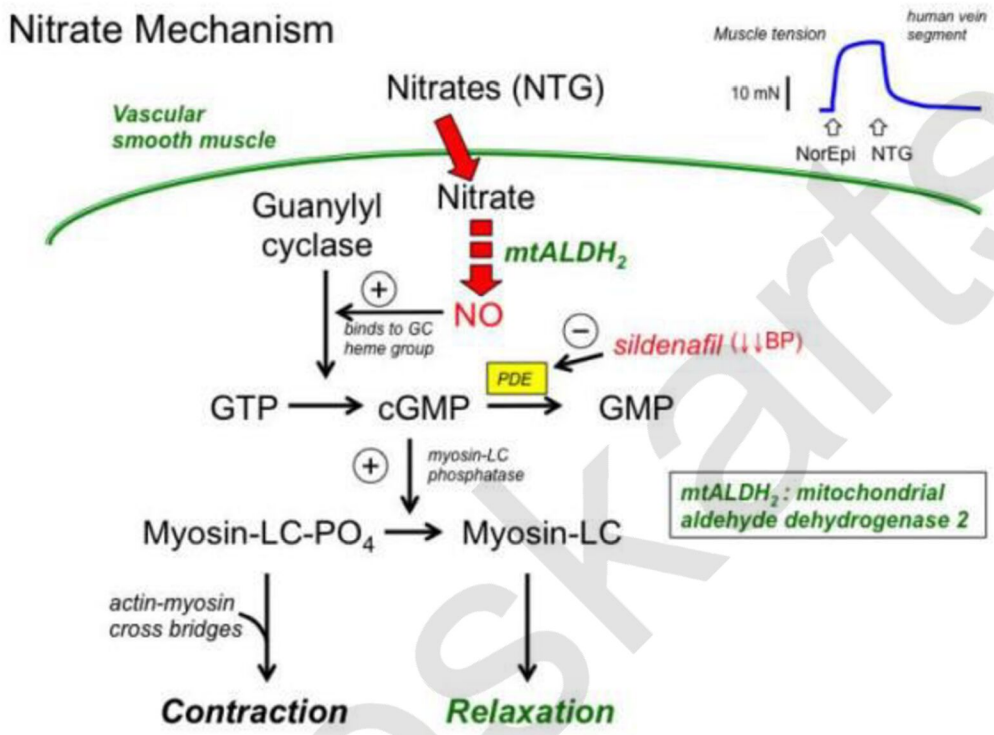
Indications:

- Stable angina
- Unstable angina (as part of combination therapy)

- Variant (Prinzmetal's) angina

1. Nitrates:

Mechanism of action:



- Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical nitric oxide (NO) which activates cytosolic guanylylcyclase which converts Guanosine triphosphate (GTP) to Cyclic guanosine monophosphate (cGMP), that causes dephosphorylation of myosin light chain kinase (MLCK) through a cGMP dependent protein kinase.
- Reduced availability of phosphorylated (active) MLCK interferes with activation of myosin, which fails to interact (Coupling) with actin need for contraction. Consequently relaxation occurs.
- Raised intracellular cGMP may also reduce $Ca2^{+}$ entry which is also contributing to relaxation.

2. Beta-Blockers

- **Mechanism**: Beta-blockers block beta-adrenergic receptors, primarily beta-1 receptors in the heart, reducing the effects of adrenaline and noradrenaline.
- **Effect**: Decreases heart rate (negative chronotropic effect), myocardial contractility (negative inotropic effect), and blood pressure, which reduces myocardial oxygen consumption.

3. Calcium Channel Blockers (CCBs)

- **Dihydropyridines**:

- **Mechanism**: Inhibit L-type calcium channels in vascular smooth muscle, leading to vasodilation.
- **Effect**: Reduces afterload, lowering blood pressure and improving coronary blood flow.

- **Non-Dihydropyridines**:
  - **Mechanism**: Inhibit L-type calcium channels in both the heart and vascular smooth muscle.
  - **Effect**: Reduces heart rate and myocardial contractility (negative chronotropic and inotropic effects), as well as vasodilation.

4. Ranolazine

- **Mechanism**: Inhibits the late sodium current (INa) in myocardial cells, reducing intracellular sodium accumulation, which leads to decreased calcium overload.
- **Effect**: Improves myocardial relaxation and reduces diastolic tension, thereby reducing oxygen demand without affecting heart rate or blood pressure significantly.

5. Potassium Channel Openers (Nicorandil)

- **Mechanism**: Opens ATP-sensitive potassium channels in vascular smooth muscle, causing hyperpolarization and relaxation of the muscle.

Antiarrhythmic drugs:

- A class of medications known as antiarrhythmic drugs is used to treat irregular cardiac rhythms, including ventricular fibrillation, ventricular tachycardia, atrial fibrillation, and atrial flutter.
- Arrhythmias, another name for these irregular rhythms, can cause palpitations, lightheadedness, fainting, and even abrupt heart death, among other problems.

Mechanisms of Action

- Antiarrhythmic drugs work by modifying the electrophysiological properties of cardiac cells.
- They primarily target ion channels and adrenergic receptors, which play important roles in the generation and conduction of electrical impulses in the heart.
- Based on their primary mechanisms of action, antiarrhythmic drugs are classified into four main classes according to the **Vaughan Williams classification**:

Class I: Sodium Channel Blockers

These drugs block the fast sodium channels in cardiac cells, which are responsible for the rapid depolarization phase of the action potential. By blocking these channels, they slow down the rate of depolarization and conduction velocity in the heart. Class I antiarrhythmics are further subdivided into three subclasses based on their effects on action potential duration and conduction:

- **Class IA:** These drugs moderately block sodium channels and prolong repolarization. Examples include quinidine, procainamide, and disopyramide.
- **Class IB:** These drugs weakly block sodium channels and shorten repolarization. Examples include lidocaine and mexiletine.
- **Class IC:** These drugs strongly block sodium channels with minimal effects on repolarization. Examples include flecainide and propafenone.

Class II: Beta-Adrenergic Blockers

- These drugs block the beta-adrenergic receptors in the heart, which are responsible for the stimulatory effects of the sympathetic nervous system on heart rate and contractility.
- By blocking these receptors, they slow down the heart rate, prolong AV nodal conduction, and reduce myocardial contractility. **Examples include propranolol, metoprolol, and esmolol**.

Class III: Potassium Channel Blockers

- These drugs block the potassium channels in cardiac cells, which are responsible for the repolarization phase of the action potential.
- By blocking these channels, they prolong the action potential duration and refractoriness of cardiac cells. **Examples include amiodarone, sotalol, and dofetilide.**

Class IV: Calcium Channel Blockers

- These drugs block the L-type calcium channels in cardiac cells, which are responsible for the slow inward current during the plateau phase of the action potential. By blocking these channels, they slow down AV nodal conduction and reduce myocardial contractility. **Examples include verapamil and diltiazem.**

Examples of Antiarrhythmic Drugs and Their Clinical Uses

- **Amiodarone:** A Class III antiarrhythmic drug used to treat various supraventricular and ventricular arrhythmias, including atrial fibrillation, ventricular tachycardia, and ventricular fibrillation.
- **Lidocaine:** A Class IB antiarrhythmic drug used to treat ventricular arrhythmias, particularly in the acute setting of myocardial infarction.
- **Metoprolol:** A Class II antiarrhythmic drug used to treat supraventricular arrhythmias, such as atrial fibrillation and atrial flutter, as well as to control ventricular rate.
- **Verapamil:** A Class IV antiarrhythmic drug used to treat supraventricular arrhythmias, such as atrial fibrillation and paroxysmal supraventricular tachycardia.

Anti-hyperlipidemic:

- Anti-hyperlipidemic drugs, also known as lipid-lowering agents, are used to manage elevated levels of lipids (cholesterol and triglycerides) in the blood, reducing the risk of cardiovascular diseases such as atherosclerosis, heart attack, and stroke.
- These are drugs which lower the levels of lipids and lipoproteins in blood.

Classification:

1. **HMG-CoA reductase inhibitors (Statins):** Ex. Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Pitavastatin
2. **Bile acid sequestrants (Resins):** Ex . Cholestyramine, Colestipol
3. **Lipoprotein lipase activators (PPARα activators, Fibrates):** Ex. Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate.
4. **Lipolysis and triglyceride synthesis inhibitor:** Ex. Nicotinic acid.
5. **Sterol absorption inhibitor:** Ex. Ezetimibe.

1. HMG-CoA Reductase Inhibitors (Statins)

- **Mechanism:** Inhibit HMG-CoA reductase, a key enzyme in cholesterol synthesis in the liver. This leads to decreased cholesterol production, which in turn causes the liver to pull more LDL cholesterol from the bloodstream.
- **Effects:** Primarily lower LDL cholesterol, but also modestly lower triglycerides and raise HDL cholesterol.
- **Examples:** Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Pitavastatin, Fluvastatin

2. Bile Acid Sequestrants (Resins)

- **Mechanism:** Bind to bile acids in the intestine, preventing their reabsorption. This increases the demand for bile acid production, which uses up cholesterol and lowers LDL levels.
- **Effects:** Primarily lower LDL cholesterol. May increase triglycerides in some individuals.
- **Examples:** Cholestyramine, Colestipol, Colesevelam

3. Lipoprotein Lipase Activators (PPARα activators, Fibrates)

- **Mechanism:** Activate peroxisome proliferator-activated receptor alpha (PPARα), which increases the activity of lipoprotein lipase. This enzyme breaks down triglycerides in lipoproteins, leading to lower triglyceride levels.
- **Effects:** Primarily lower triglycerides, but also raise HDL cholesterol and have a variable effect on LDL cholesterol.
- **Examples:** Clofibrate (less commonly used now), Gemfibrozil, Bezafibrate, Fenofibrate

4. Lipolysis and Triglyceride Synthesis Inhibitor (Nicotinic Acid)

- **Mechanism:** Inhibits lipolysis in adipose tissue, which reduces the availability of free fatty acids for triglyceride synthesis in the liver. This leads to lower triglyceride levels. It also has complex effects on cholesterol metabolism, leading to lower LDL and higher HDL.
- **Effects:** Lowers LDL cholesterol, triglycerides, and raises HDL cholesterol.
- **Example:** Niacin (Nicotinic acid)

5. Sterol Absorption Inhibitor

- **Mechanism:** Selectively inhibits the absorption of cholesterol in the small intestine, leading to lower LDL cholesterol levels.
- **Effects:** Primarily lowers LDL cholesterol. Can be used in combination with statins for greater LDL reduction.
- **Example:** Ezetimibe