"Pharmacology ÷ 5th Semester"

Unit - 1st

÷ Drug Acting On Heart ÷

Hemodynamics & Electrophysiology of heart ÷

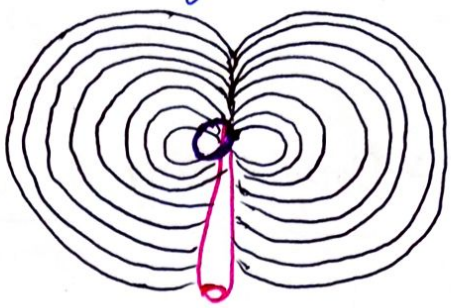
- **Hemodynamics ÷** The term Hemodynamics is derived from two word. Hemo & dynamics.
- → The hemo means "Blood" and the term dynamics means Flow rate and Mechanism or Physiology.
- → The branch of pharmacology in which we study about the flow rate, mechanism and physiology of blood and heart this is called the hemodynamic.

÷ Physiology & Structure of heart ÷

- → Heart is situated in the mediastenam space of thoracic cage
- → Heart is situated in middle but it is slightly left.
- → The structure of heart is conical shape. Pulsatile organ and red in color.
- → The average weight of heart is 250-350g
- → The outer covering of heart is called Pericardium
- → It is divided into two layer.

i) Exocardium
ii) Endocardium.

The fluid is filled in between both layer is called pericardium fluid.



→ The structure of heart is devide into two types of chamber

i) Atrium or Auricle → Upper Side.

(ii) Ventricle. → Lower Side.

Heart is devide into four type of chamber.

1) Left Auricle (LA)
2) Right Auricle (RA)
3) Left Ventricle (LV)
4) Right ventricle. (RV)

Each chamber of heart is seprated with each other by sepfum.

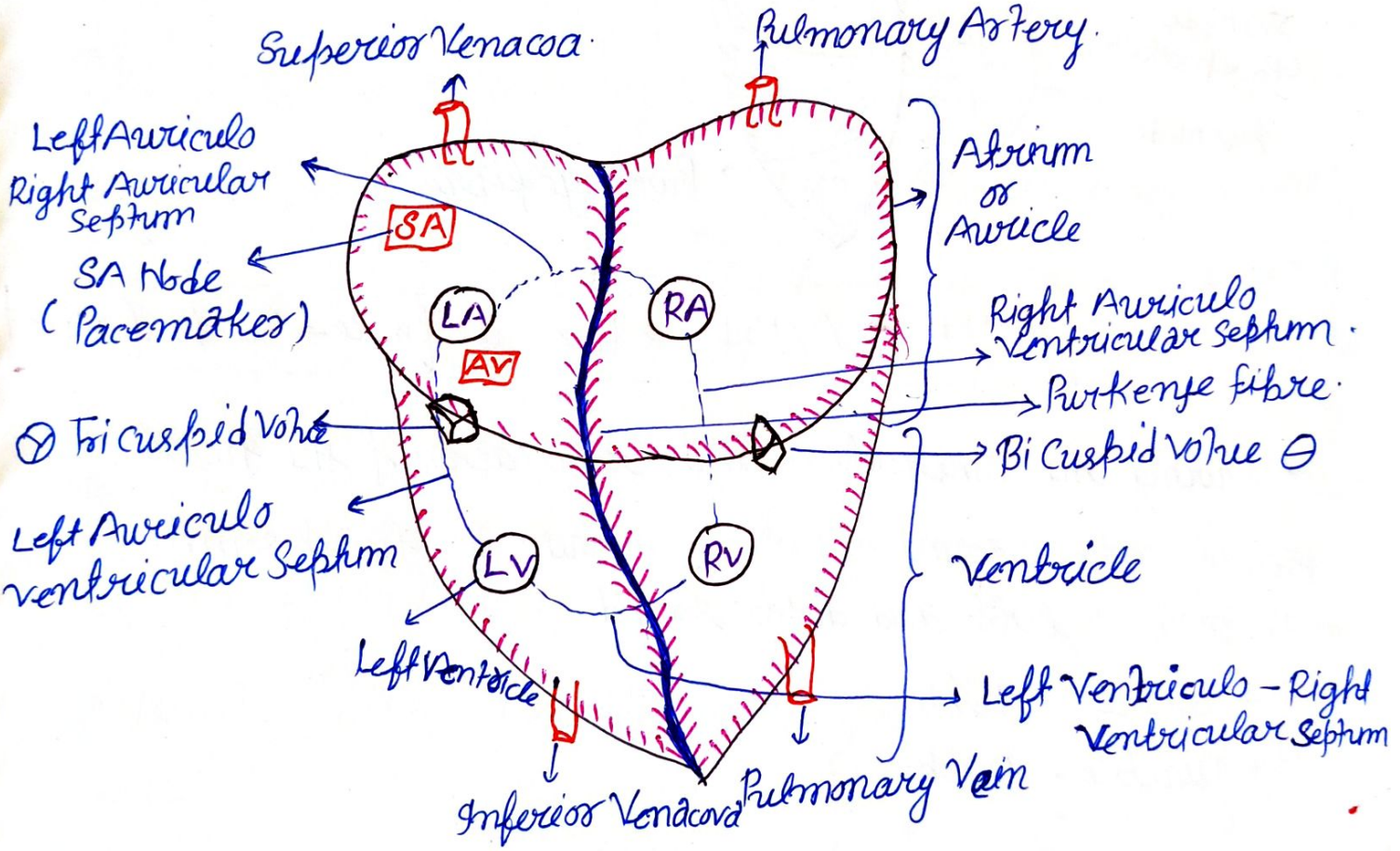
Sepfum	In b/w
Left Auricule Right Auricular Sepfum.	LA ↔ RA
Left Ventricule Right ventricular Sepfum	LV ↔ RV
Left Auricule Ventricular Sepfum	LA ↔ LV
Right Auricule Ventricular Sepfum	RA ↔ RV

→ The flow of blood from LA to LV is controlled by tricuspid valve

→ From RA to RV is controlled by bi cuspid valve.

→ SA Node or AV Node are present in left Auricle which generate the Impulse.

→ Cardiac fibre are present in the inner wall of heart which is known as Purkenje Fibre.



÷ Conduction System of heart ÷

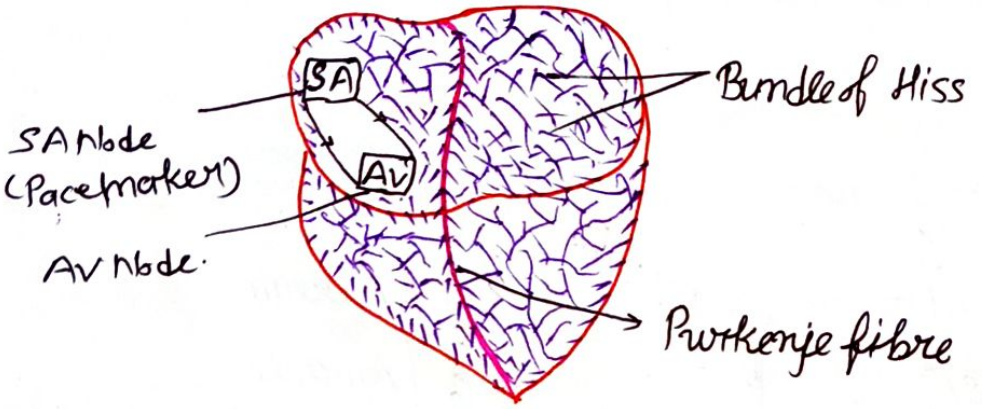
→ In heart SA Node is present which is known as pacemaker of heart.

→ It produced electric Impulse of 0.75 mV which transfer to AV node.

Impulse transfer from AV Node to purkenje fibre to bundle of Hiss.

→ Bundle of hiss are present in the inner wall of the heart.

→ And so current is reaches in all over heart so contraction and relaxation is start.



SA Node → AV Node → Purkenje fibre → Bundle of Hiss

→ During the contraction and relaxation of the heart, Heart produce sound which is known as heart sound.

→ It produce Lubb and dubb sound.

- → Systale → Lubb
- → Diastale → Dubb.

÷ Myocardium ÷

→ The muscle which are present in the heart is called myocardium or cardiac Muscle.

→ They have a single nucleus in thecentral and they contain some number of Mitochondria.

→ The myocardium muscle contraction relaxation is controlled by three mechanism -

1) Na^+ (Sodium) K^+ (Potassium) ATPase pump mechanism.
2) Ca^{++} (Calcium) Ion Channel mechanism.
3) Acting Myosin protein mechanism

∴ CardioVascular Disease ∴

(i) Angina Pectoris :- Due to ischemic condition of heart pain is started in heart, left hand and slowely-2 in all over organ is called Angina Pectoris.

ii) CHF - Cardiac Heart Faliure :- Due to Athroma, Ischemia and myocardial infraction. The heart becomes fail to pump blood and it cause death. This is called CHF.

∴ Frank Starling law :-

According to Frank Starling law, the force of contraction of cardiac muscles is depends upon the stretching of Ventricular muscles. How the Ventricular muscle will stretch the FOC of Heart will be increased.

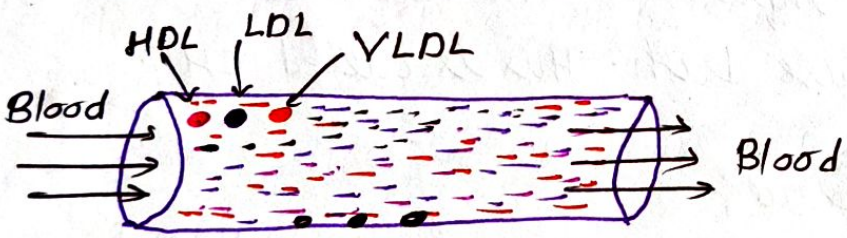
And as per Frank Starling law, when the stretching of Ventricular muscles are crossed the critical length, then the capacity of Heart muscles to contract is decreased. And this decrease in FOC is caused CHF.

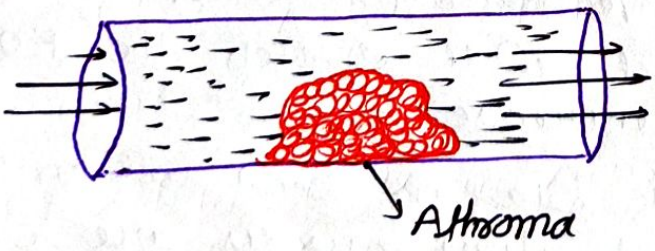
÷ Thromboembolic disease or Atheroschlerosis or Athroma ÷

Three types of liquid are flow in our blood -

i) High density liquid
ii) Low density liquid
iii) Very low density liquid.

- LDL & VLDL are bad liquids they stick on the blood vessels value.
- Slowly-2 they form Athroma of blood vessel and decrease the lumen size.
- Due to Athroma formation insufficient amount of blood reach in to heart and may cause heart Attack.





← Arrhythemia →

When the conduction system of heart is disturbed and the normal rhythm is change this condition is ~~change~~ called Arrhythemia

- The normal rate of rhythm is 72 per min.

÷ Drug Used in CHF ÷

Congestive Heart failure ÷ The ability of heart to pump the blood into all over organ its called its ionotropic nature or Force of contraction nature

→ The condition of heart in which the heart unable to pump the blood to all over organ and the blood accumulate in the ventriculars and the size of ventriculars is increase this is called congestive heart failure.

→ According to the Frank starling law. The force of contraction of cardiac muscle is directly proportional to the ventricular muscle stretching.

→ As much as or How much the ventricle muscle are stretch the force of contraction is increase

→ And the force of contraction is increase the blood pump in to the all over of organ.

→ According to the Frank starling second statements. if the ventricular muscle is increase beyond the critical length (Max Power) then the cardic muscle force of contraction is decrease this is called -ve Ionotropic condition.

→ And in the condition of -ve ionotropic condition the blood accumulates in the ventricle and the size of ventricle wall is increase And unable to pump the blood

→ And this condition is called congestive heart faliure.

Mechanism of Action of Cardiac Glycoside

→ In the condition of CHF the inotropic action of cardiac muscle is decrease.

→ In the cardiac muscle sodium, Potassium ATPase pump is present which is regulated by the ATP.

→ When Na^+, K^+ pump is regulated in normal condition then took two K^+ ion from ECf to ICf and three Na^+ ion goes outside from ICf to ECf

→ And due to this sodium Potassium ATPase pump Negative potential is develope which is essential for the depolarisation.

→ Beside the Na^+, K^+ ATPase pump, Na^{++}, Ca^{++} exchanger is present.

→ Which exchange the Ca^{++}, Na^{++} ion from ICf to ECf and ECf to ICf for balancing the ion.

→ Now when the cardiac glycoside given then it bind with the Na^{2+}, K^+ ATPase pump and block the Na^{2+}, K^+ ATPase pump.

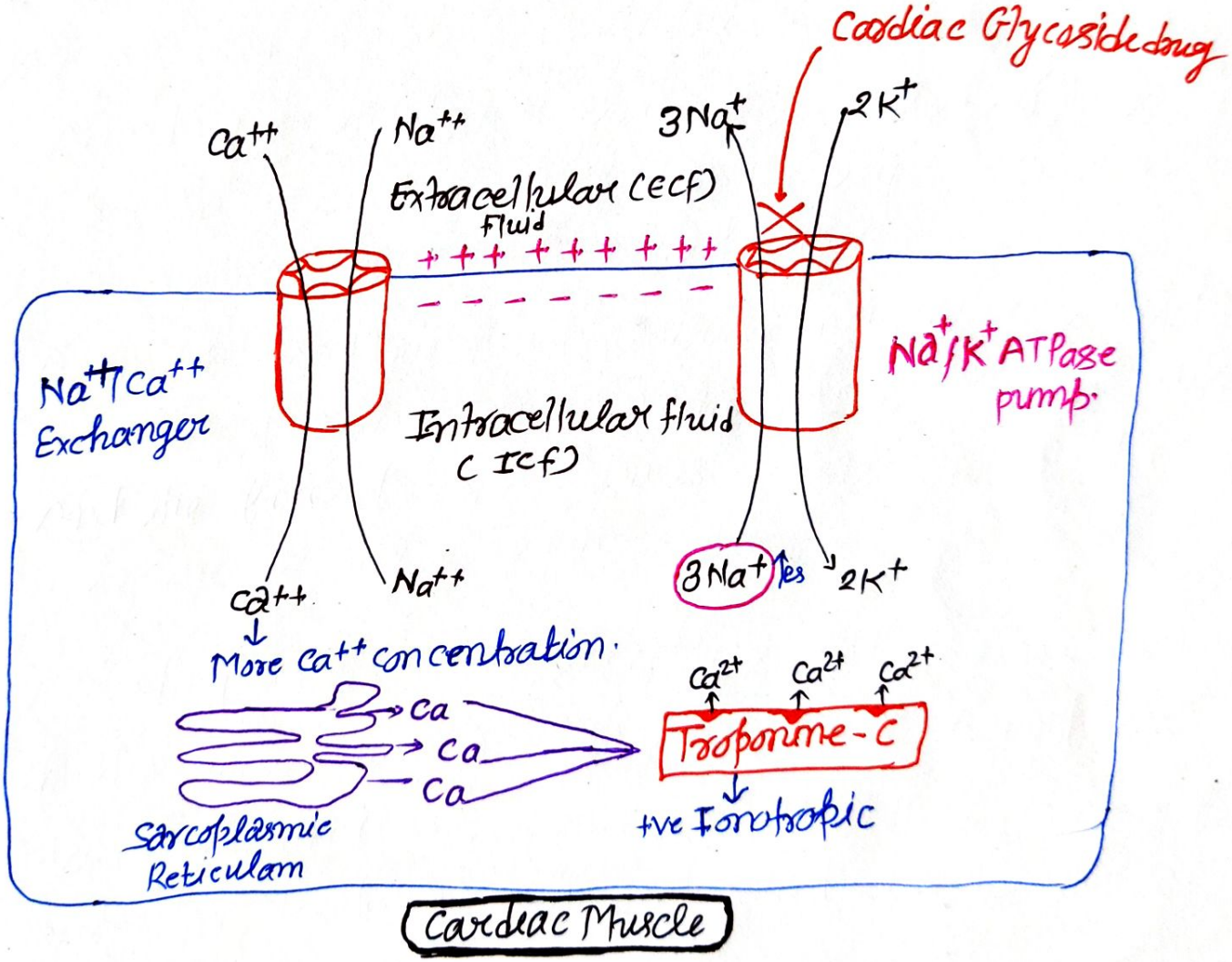
→ When the sodium potassium ATPase pump is block then the concentration of Na^{2+} ion in ICf is increase.

→ For maintaining the increase concentration of Na ion Na, Ca exchanger is on and it expell the Na ion into the ECf and Ca^{++} ion comes inside the Intracellular.

→ When the concentration of Ca^{++} ion is increases into the Cardiac Cell it Activate the sarcoplasmic Reticulam to release

More Ca^{++} ion.

- And when the calcium ion is increase then it bind the Troponine-C receptar.
- When Ca^{+} bind with the troponine-c receptar then it activate the Actin and myosine.
- Due to this Actin and Myosine (FOC) force of contraction start and this is +ve ionotropic.



Cardiac Muscle

L-5

Pharmacokinetics of Cardiac Glycoside:-

→ The absorption of Digitoxin is greater than the digoxin. because the digoxin of the reaction inside the body. convert into the 2-Hydroxy digoxin which is inactive form.
- So there absorption and bioavailability is less.
→ And this is bioavailability and absorption is about to 20 to 25%
→ But in the case of Digitoxin there bioavailability is very much effective.
→ It is 90 to 92% percent.
→ So Digoxin is canbe given in the form of Injection (Injectible.)
→ And Digitoxin can be give in the form of oral (Tab. Cap.
→ The plasma protein binding of digitoxin is greater than the Digoxin.
→ And its half life 35–40 hr. in our body.
→ Both Digitoxin and Digoxin cardio glycoside drug are metabolites into the liver.
→ And it is excreated through kidney in the form of catabolic product. in the Hydrolised form, catabolites form; oxydised form, from the kidney.

:- Therapeutic Use:-

(1) CHF:- When the congestive heart failure occurs the force of contraction of heart is reduce then the Digitoxin and Digoxin drugs are given which increase the force of contraction and relief the patient from cardiac heart failure.

→ Arrhythemia: When the conduction system of heart is change or disturbed and the normal Rhythm is change this condition is called Arrhythemia.

→ The normal rate of Rhythm is 72 per min.
→ Cardiac glycoside induce the SA Node to induce the electricle Impulse.

Adverse Effect: → Cardiac Glycoside produces some Adverse effect. due to three reasons -

→ Because it over activate the parasympathetic system.
→ Because it increase the Ca^{++} ion concentration in Icf
→ It decrease the K^+ ion concentration in Ecf.

- GIT: Diarrhoea, Hausia, Vomiting, GIT Gramp, Abdominal Pain.

Eye: · Blurred Vission, Photophobia, Object appear to be green & yellow.

Nervous: Headache, Drowsiness, Fatique. Delirium

Cardiac Effect: → Force of contraction increase more.
⇒ Increase Heartload.
→ Increase Blood pressure.

Hypertension: The persistant and Prolonged increase in blood pressure in body is called blood pressure

⇒ Hypertension is a condition in which the blood pressure is acting on the endothelial wall is increase 120/80 for persistant and prolong period.

⇒ Hypertension is a condition of body it is a persistant and prolonged increase blood pressure.

⇒ When blood flow on blood vessel then they create pressure on endothelial layer this is called blood pressure

⇒ The pressure exerted by blood on endothelial layer is called blood pressure.

⇒ The normal blood pressure of human being 120/80 in which 120 mmhg is systolic pressure and 80 mmhg is diastolic pressure.

Types of hypertension:

Hypertension	Systolic	Diastolic
Type-1	120 - 129	80 - 89
Type-2	130 - 139	90 - 99
Type-3	140 - 149	100 - 110
Type-4	> 150	> 110

Etiology:- There are following reasons for hypertension.

(i) Genetics
(ii) ANS
(iii) RAS
(iv) Endothelial Dysfunction
(v) Sodium / Potassium Ratio

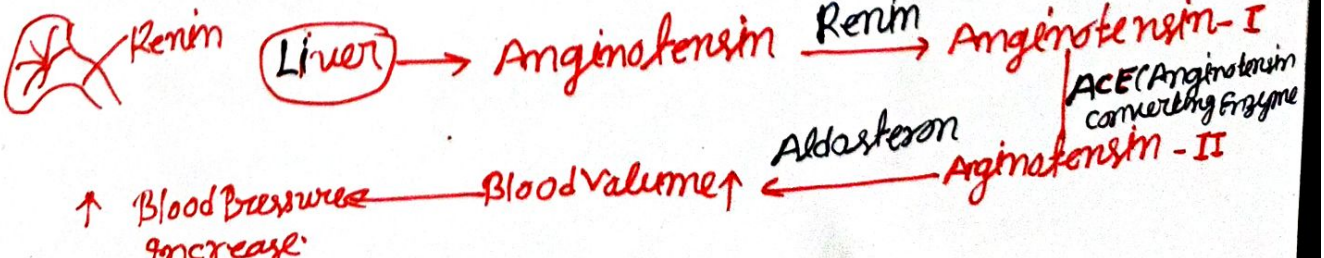
(i) **Genetics:-** There are some genes which are identified who is responsible for increasing blood pressure.

(ii) **ANS:-** From sympathetic and parasympathetic neurons neuro transmeter are release like acetylcholine, Adrenaline, they are responsible for the blood vessel contraction by blood pressure is increase.

(iii) **RAS (Renin Angiotensin System):-** When the blood pressure of body is reduce then kidney release an enzyme called Renin, Renin converts Angiotensin into angiotensin-I which was released by the liver.

⇒ Angiotensin-I is convert into Angiotensin-II by the enzyme ACE (Angiotensin Converting Enzyme)

⇒ Angiotensin-II stimulate the secretion of Aldosteron which increase the blood volume so the blood pressure is increase.

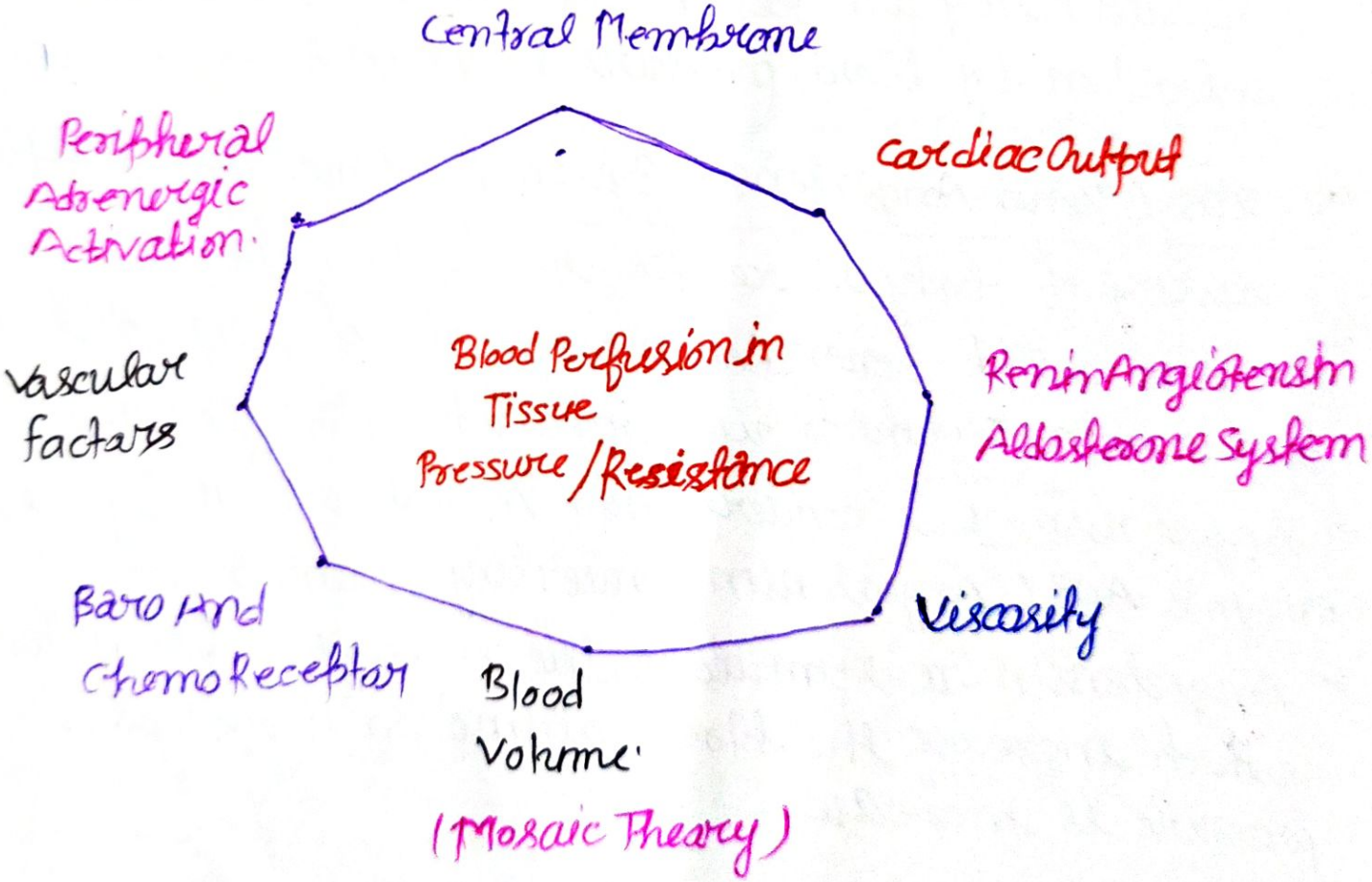


Sign Symptom:-

- Increased Heart Rate
- Severe headache
- Shortness of breath
- Nose bleeding.

Complication:-

- Cardiac failure
- Renal damage
- Heart Attack
- Metabolic Syndrome
- Problem in memory and understanding.



(Mosaic Theory)

÷ Classification of Anti Hypertensive Drugs ÷

(A) Drugs Affecting Sympathetic Tone ÷

(i) Drugs that alter central Sympathetic Activity.
Ex- Methyl dopa, Clonidene.

(ii) Drugs that act as adrenergic Neuron blockers.
Ex- Guanethidine, Reserpine

(iii) Ganglionic blocking drugs Ex- Trimethaphan.

(iv) α - Adrenoceptor blocking agent.
Ex- Prazosin, Phentolamine.

(v) β - Adrenoceptor blocking agent.
Ex. Propranolol, Atenolol.

(2) Vasodilators ÷

(a) Direct Vasodilators -
(i) Arterial dilaters Ex- Hydralazene.
(ii) Balanced Vasodilators. Ex- Minoxidil.

(B) Calcium channel blocking Agent.
Ex- Nifedipine.

(c) Agent Acting on Renin Angiotensin System.

(i) Renin Inhibitors.
(ii) Angiotensin Antagonists.
Ex- Saralasin.
(iii) Angiotensin converting Enzyme inhibitors.
Ex. Captopril, Enalapril.

(2) Diuretics :-

(i) Thiazides Ex- Hydrochlorothiazide.
(ii) Loop diuretics Ex - Furosemide.
(iii) Potassium Sparing diuretics
Ex - Triamterene.

÷ Antihypertensive Drugs ÷

÷ Diuretics Drugs ÷

Ex ÷ Thiazides ÷ Hydrochlorothiazide, Chlorthalidone, Indapamide.

High Ceiling ÷ Furosemide.

K + Sparing ÷ Spironolactone, Triamterene, Amiloride.

← Mechanism of Antihypertensive Action (High ceiling diuretics)

Fall in BP is dependent only on reduction in plasma volume & Cardiac output (similar to the initial fall in BP due to thiazides) but unlike thiazides the Na deficit is not persistant due to short action of high ceiling diuretics. Hence no fall in t.p.r and no subsistenance of BP fall

→ Basically diuretics drug reduce the cardiac outfput of the heart so the blood pressure is decrease.

→ When the diuretics drug is given then it reduce the blood volume by increase the urine volume.

→ When the blood volume is decrease. then the cardiac output is decrease and the blood flow in the blood vessel is decrease so the blood pressure is decrease.

← Desirable Properties of Diuretics As Antihypertensives ⇒

→ Once a day dosing
→ No fluid retention
→ No tolerance development to Antihypertensive action.
→ Low incidence of postural hypotension.
→ Effective in isolated systemic hypertension.
→ Less risk of fractures in elderly (Hypocalciuric Action of Thiazides
→ Low cost.

÷ Drawbacks of Diuretics as Antihypertensive ÷

→ Hypokalaemia → Muscle Pain and Fatigue.
→ Hyperglycemia.
→ Hyperlipidemia.
→ Hyperuricaemia.
→ Sudden cardia death — Torsades de pointes due to Hypokalemia.
→ All the above adverse effects occur at higher doses of thiazides (50-100 mg per day)
→ These Adverse effects are minimum with low doses (12.5 to 25mg)
→ So low doses of thiazides are used as Antihypertensive now.

÷ Current Status ÷

→ Thiazides are mild Antihypertensive, causes fall of Abt 10mmHg in BP.

→ Alone they are used only in (Mild HTN (Stage 1 HTN).

→ Low dose of thiazides therapy is used preferably with a potassium sparing diuretics as first choice in elderly.

→ They prevent tolerance to other Antihypertensives. can be used as combination in any grade of HTN.

÷ Indapamide ÷ Modified thiazides with minimal side effects It has very mild diuretic Action and is used mainly as Antihypertensive and not as diuretics.

÷ Loop diuretics ÷ Cause more fluid & electrolyte imbalance. They are indicated in HTN only if it is complicated by-

→ Chronic Renal failure

→ Refractory CHF

→ Resistance to thiazides

→ Marked fluid retention.

÷ K+ Sparing diuretics ÷ used only in conjunction with Thiazides to prevent K+ loss & to supplement their antihypertensive action.

← RAAS - System (Renin Angiotensin System) →

→ Renin is produced by JG cells of kidney in response to -
  → Fall in BP or blood volume.
  → Decrease Na^+ in macula densa.
→ Renin acts on a plasma protein Angiotensinogen to convert it to Angiotensin-I.
→ Angiotensin-I is rapidly converted to Angiotensin-II by ACE (Present in luminal surface of vascular endothelium)
→ Angiotensin-II is degraded by peptidases to produce Angiotensin-III
→ Angiotensin-II causes Vasoconstriction (Increased TPR) leading to rise in diastolic BP
→ Both Angiotensin-II and Angiotensin-II stimulates Aldosterone secretion from Adrenal cortex.
→ Aldosterone promotes Na^+ & water reabsorption by the kidneys leading to increased blood volume & Increased COP & Systolic BP.

← ACE inhibitors →

MOA: Inhibit synthesis of Angiotensin II by Inhibiting ACE → Decrease in (TPR) and blood volume → Fall in diastolic and systolic BP.

Drawbacks/ Adverse Effects :-

- Cough - Persistent brassy cough due to inhibition of bradykinin breakdown in lungs.
- Hyperkalemia (in renal failure patients, those with K+ sparing diuretics, NSAID and beta blockers (routine check of K+ level.
- First dose Hypotension - Sharp fall may occur.
- Angioedema: Swelling of lips, mouth nose etc.
- Rashes urticaria
- Dysgeusia : loss or Alteration of taste
- Foetopathic Hypoplasia of organs groum retardation Etc.
- Neutropenia.
- Acute renal failure (Occurs in patients with bilateral renal artery stenosis.

Current Status :- - 1st line antihypertensive drug.

- Used in relatively young patients.
- Most Appropriate Antihypertensive in patients with Diabetes.
- Chronic Kidney disease.
- CHF
- Left Ventricular Hypertrophy.
- Angina, Post MI, Stroke
- Dyslipidemia
- Gout.

- **Avoid in :-** Pregnancy, Bilateral, renal Artery stenosis hypersensitivity, Hyperkalaemia, Preexisting dry cough.

Captopril:- ⇒ Sulfhydryl containing dipeptide.

⇒ Not a prodrug. Has drawbacks mentioned earlier.

⇒ Half life: 2 Hrs multiple doses.

Enalapril:- Prodrug - Converted to enalaprilate.

⇒ Advantages over captopril.

⇒ More Potent

⇒ Longer duration of Action - once daily dose.

⇒ Absorption not affected by food.

⇒ Rash and loss of taste are less frequent.

⇒ Slower onset of Action, Hence First dose, Hypotension less marked.

ACE Inhibitors - Other Uses (to be discussed under ACE Inhibitors)

⇒ Congestive Heart failure.

⇒ Myocardial Infraction.

⇒ Prophylaxis of high CVS Risk subjects.

⇒ Diabetic Nephropathy.

⇒ Scleroderma Crisis.

Angiotensin Receptor blockers (ARBs)

Example:- Losartan, Candesartan, Telmisartan.

:- Mechanism of Antihypertensive Action:-

Angiotensin Receptors (AT_1 & AT_2) are present on Target cells. Most of the Physiological actions of angiotensin are mediated via AT_1 receptor.

→ ARBs are competitive antagonists and inverse agonist of AT_1 receptor.

→ Blocks all the action of A-II mediated by AT_1 like Vasoconstriction, Aldosterone release and renal actions of salt & water reabsorption.

Direct renin Inhibitor - Aliskiren :- (Aliskiren)

→ Inhibits production of Angiotensin I & II.

→ Equally effective as ACEI & ARBs

→ Since Experience with it is limited, so it is used only as a second line Antihypertensive when more established ACEI & ARBs cannot be used.

Beta blockers :- Ex- Non selective Propranolol.
→ Cardioselective - Metaprolol, Atenolol.

Mechanism of Antihypertensive Action :-

Decrease heart rate, contractility, conduction velocity cardiac output (Inverse Agonist on B1) Total Peripheral resistance increase initially.

→ Initial Phase - CO decreases (Systolic BP decreases) T.P.R increase (diastolic BP increases) → overall little BP change

→ With prolonged use resistance vessels adapt to decreased CO so that T.P.R decreases) → Both systolic & Diastolic BP decrease.

÷ Desirable Properties as Antihypertensive ÷

- No postural hypotension.
- No salt and water retention.
- Low incidence of side effect.
- Low cost.
- Once a day regime.

Drawbacks of Non Selective beta blockers ÷

- Fatigue, lethagy (low CO?) decreased work capacity.
- Bradycardia.
- Loss of libido - impotence.
- Cognitive defects forgetfulness.
- Warsening of carbohydrate tolerance, lipid profile PVD asthma
- Sudden withdrawal - chance of rebound HTN precipitation of MI or Anaina.

Advantages of Cardio - Selective beta blockers over non selective beta blockers ÷ ÷

- Safer in Asthmatics (No bronchoconstriction).
- Safer in diabetes (No interference with hypoglycemia.
- Induced glycogenolysis.
- Less warsening of PVD.
- Lipid profile less deterioration

Current Status - As first line drugs cardioselective beta blockers alone in mild/Moderate HTN
→ Action maintained over 24 hrs.
→ Preferred in :-
- young non-obese hypertensives those with coexisting anxiety, migraine, tachycardia & Those with IHD
→ For preventing sudden cardiac death in past MI patients
→ In stable heart failure along with ACEI.
→ Not perferred in old.

÷ Alpha blockers ÷

Ex :- Non selective alpha blockers (Phenoxybenzamine) Phentolamine) Not used in chronic essential hypertension. but used in Pheochromocyloma.
→ Specific Alpha-1 blocker like prazosin, Terazosin and doxazosine are used in HTN treatment.

→ Mechanism of Antihypertensive Action.

Blockade of vasoconstrictor α receptors ÷.

→ Pooling of blood in capacitance vessels → decreased Venous return & decreased Cop → Fall in BP.

Adverse Effects ÷ → Postural hypotension.
→ Salt and water retention.
→ Nasal stuffiness.
→ Miosis.
→ Failure of ejaculation in males.

Current Status :- But Not used as first line agent
- May be added to diuretics + Beta blockers if target bp is not achieved with their use alone.

:- Alpha + Beta blockers :-

- Labetalol used IV for rapid BP reduction. Orally used for severe HTN.
- Carvedilol used as Antihypertensive as well as in CHF.

:- Calcium Channel Blockers :-

:- Mechanism of Antihypertensive Action :-

- Three types of Ca^+ channels is smooth muscle- Voltage sensitive, receptor operated and leak channel.
- Voltage sensitive are again 3 types - L-Type, T-Type and N-Type.
- Normally - L-Type of channels admit Ca^+ and causes depolarization - Excitation Constraction Coupling trough Phosphorylation of myosin light chain constraction of Vascular smooth muscle - Vasoconstriction - elevation of BP.

:- CCBs block L-Type channel resulting in :-

- Smooth muscle relaxation
- Negative chronotropic, inotropic effects on heart.

DHPs :- DHPs have highest smooth muscle relaxation and vasodilator action followed by verapamil and Diltiazem Hence DHPs are the CCBs used in HTN.

÷ Vasodilators ÷

Hydralazine ÷ Directly acting vasodilator.

→ **MOA ÷** Hydralazine causes No release - relaxation of vascular smooth muscle → fall in BP.

- **Uses ÷** (i) Moderate hypertension when 1st line fails.
  (ii) Hypertension in Pregnancy

Minoxidil ÷ Relaxes smooth muscle & relaxes arterioles used only in life threatening HTN & Topically in Alopecia

÷ Centrally Acting Drugs ÷

→ Alpha-Methyl Dopa (Alpha methyl Analogue of DOPA) - a prodrug.

→ **MOA ÷** Gets converted to Alpha Methyl Noradrenaline which acts on alpha-2 receptors in brain and causes inhibition of Adrenergic discharge - Fall in BP.

→ Only used therapeutically now in Hypertension during pregnancy.

Clonidine ÷ Agonist of Central Alpha-2 receptor.

→ Not frequently used now because of tolerance and withdrawal hypertension.

Some Important Points ÷ Antihypertensive preferred in a patient with coexisting DM - ACEI, ARBs, CCBs, Diuretics (Less preferred as compared to other 3 due to hyperglycemia)

→ Antihypertensive preferred in a patient with coexisting asthma / COPD - CCBs, ARBs

→ Antihypertensives preferred in a patient with coexisting CAD - Diuretics, ACEI, ARBs Cardioselective beta blockers.

→ Antihypertensives preferred in a patient with coexisting stroke - Diuretics ACEI, ARBs, CCBs

Drugs for hypertension in pregnancy :-

Drugs found safe for treating HTN in Pregnancy :-

Alpha methyl dopa.

- CCBs like Nifedipine (But they should be stopped before labour as they weaken uterine contractions.

→ Cardioselective beta blockers & Those with ISA (Atenolol Metrolol) used only if no other choice available.

→ Prazosin, Clonidine.

→ Hydralazine.

Drugs to be Avoided :-

ACEI :- Fetopathic.

Diuretics Reduce uteroplacental circulation → increased risk of fetal death.

Non Selective Beta blockers :- cause low birth weight neonatal bradycardia and hypoglycemia.

Sodium Nitroprusside -

÷ Drugs for Hyperctensive Emergencies ÷

(Parenteral Therapy :-) ÷

→ **Sodium Nitroprasside ÷** DOC for emergencies due to its instantaneous, balanced, Arteriovenous, vasodilatary action & lack of development of tolerance.

GTN ÷ Acts in 2-5 min and has brief titrable action but is a less patent hypotension. Its predominant venodilator action makes it particularly suitable for lowering BP in acute LVF, MI Unstable Angina.

Hydralazine ÷ Hydralazine is less predictable and not a first line drug used in eclampsia.

→ **Esmolol ÷** Esmolol useful when cardiac contractility and work is to be reduced, such as in aortic dissection.

÷ Anti Anginal drugs ÷

Angina Pectoris ÷ • Main symptom of IHD

→ Occurs due to imbalance b/w oxygen supply and oxygen demand of myocardium.

→ **Clinical type ÷** → Stable Angina

→ Prinzmetals Angia.

→ Unstable Angina.

÷ Pathophysiology ÷

↓ O_2 Supply

- → Coronary.
- → Atherosclerosis.
- → Vasospasm.
- → Thrombosis.

↑ O_2 demand

- → ↑ Heart Rate
- → Ventricular
  - Hypertrophy
- ↑ Wall contraction.
- ↑ Contractility.

÷ Classification of drugs ÷

→ For treatment of Acute Anginal Attack ÷

→ Nitroglycerine, Isosorbide dinitrate (SL)

→ For chronic Prophylaxis ÷

→ Nitrates -: Nitroglycerine, Isosorbide di nitrate, Isosorbide mononitrate, Penta erythritol tetranitrate.

- Beta blockers ÷

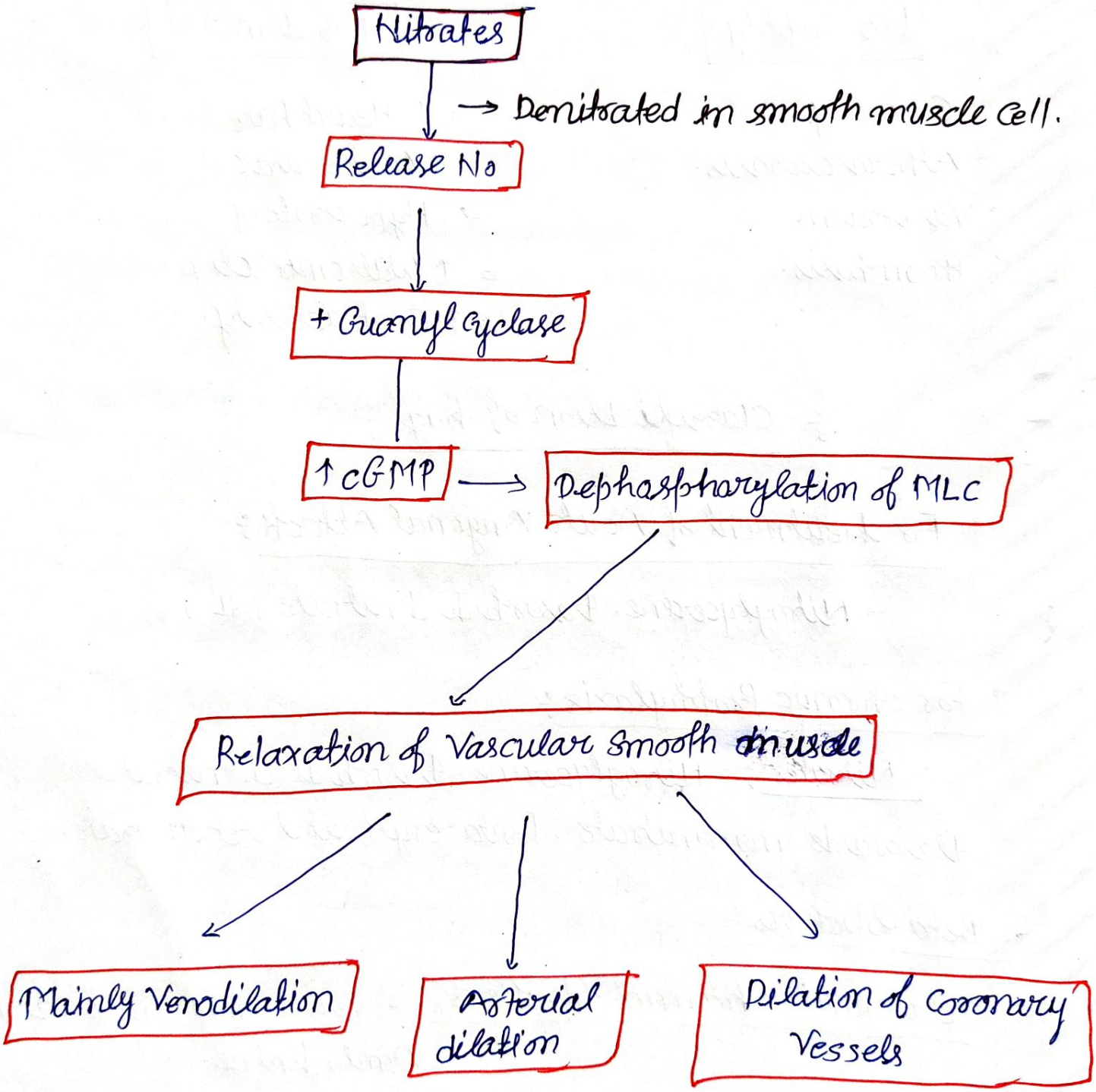
- Calcium Channel blockers ÷ • Verapamil, Diltiazem Amlodipine.

→ Potassium Channel Opener ÷ • Nicorandil, Pinacidil.

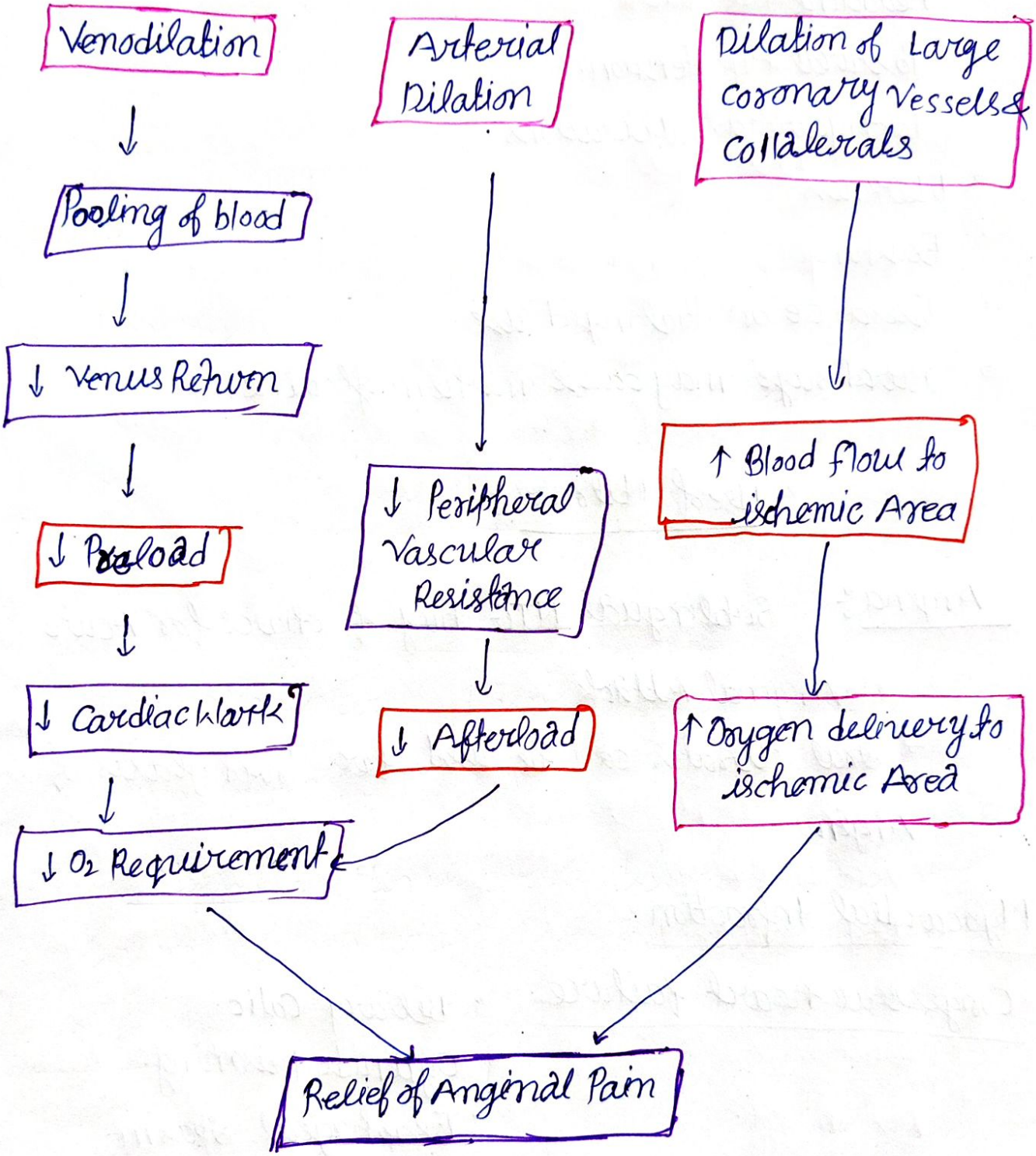
→ Miscellaneous ÷ • Dipyridamole.

Nitrates

(Mechanism of Action)



÷ Pharmacological Action ÷



Pharmacokinetics ÷

- Absorbed through buccal mucosa, skin & GIT.
- All except "Isosorbide "mononitrate" undergo extensive first pass metabolism
- Sub lingual route produces rapid onset 2 to 5 min but shorter Duration of Action.
- Absorption through skin is slow.

Adverse Effects

- Headache
- Postural Hypotension.
- Tachycardia, Palpitations.
- Weakness.
- Flushing
- Tolerance on Prolonged use.
- Overdosage may cause methemoglobinemia.

Use of Nitrates

Angina: Sublingual NTG drug of choice for Acute Anginal Attack

- Oral Nitrates can be used for Prophylaxis of Angina

Myocardial Infraction:-

Congestive heart failure.

- Biliary Colic.
- Cyanide poisoning.
- Esophageal Spasm.

β- Blockers

- Reduce frequency and severity of Anginal Attacks of exertional Angia.
- Used for long term Prophylaxis of Classical Angina, may be combined with nitrates.

MOA:- ↓ Oxygen Consumption by ↓ Contractility & HR

⇒ Selective Beta blockers are preferred.

∴ Calcium channel Blockers ∴

Block Voltage sensitive L-type of Ca^{2+} channels

⇓

Prevent Entry of Calcium into the cell.

⇓

No excitation contraction coupling in the heart and Vascular smooth muscle.

- Relaxation of vascular Smooth muscle ↓ PVR & After load
- Myocardial Contractility cardiac work & oxygen consumption
- Coronary vasodilation

∴ Calcium Channel Blockers ∴

Verapamil:- Predominant Action on heart.

- ⇒ ↓ Force of Contraction & Heart rate
- ⇒ Cause Bradycardia so not given with β-Blockers.
- ⇒ Less Potent Vasodilator

Nifedipine:-

- ⇒ Potent Vasodilator causes significant fall in BP
- ⇒ Evokes reflex tachycardia.
- ⇒ Weak Myocardial Depressant
- ⇒ Can be given sublingually.

∴ Other calcium Channel Blockers ∴

- Amlodipine
- Nimodipine
- Diltiazem.
- Nitrendipine.

Phamacokinetics ∴

- All CCBS well absorbed through GIT
- Undergo varying degree of first pass metabolism
- Highly bound to plasma proteins.

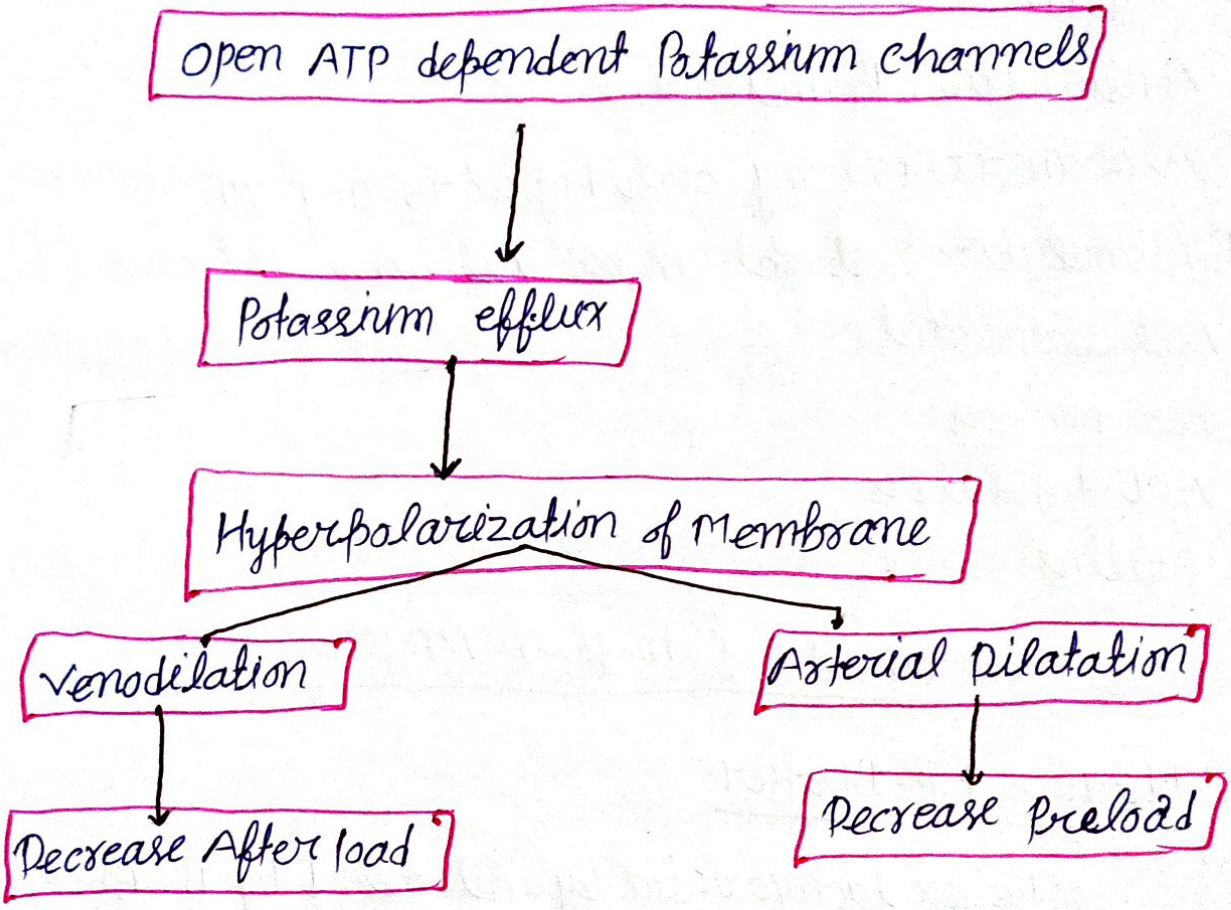
∴ Adverse Effects ∴

- Headache, Flushing.
- Reflex Tachycardia, Palpitations.
- Postural Hypotension.
- Ankle Edema.
- Leg Cramps.
- Dizziness
- Verapamil can cause constipation, Sinus bradycardia Av, block.

∴ Uses ∴

- Angina Pectaris
- Hypertension.
- Paroxysmal supraventricular tachycardia.
- Peripheral Vascular disease
- Migraine Verapamil

Potassium channel Openers
[Nicorandil]



÷ Pharmacotherapy of Angina ÷

→ **Acute Anginal Attack ÷** → Tab Nitroglycerine 0.5 mg sublingually, if pain is not relieved within 5 min, repeat dose but not more than 3 tablets in 15 min.

→ **Prophylaxis/Prevention of Further attacks ÷** → Long Acting nitrates, Beta blockers, calcium channel blockers.

∴ Treatment of Myocardial Infraction ∴

- Injection morphine Sulphate 10 mg IV.
- Oxygen.
- Antiemetic : Promethazine.
- Aspirin 75-150 mg clopidogrel 75 mg OD.
- Fibrinolytics : Streptokinase, Alteplase
- Anticoagulants
- Beta blockers.
- ACE Inhibitors
- Statins

∴ Combination of drugs in Angina ∴

- **Nitrates + β-Blocker.**
  - Reflex tachycardia by nitrates ↓ by β-Blockers.
- **Nifedipine + β-Blocker ∴**
  - Reflex tachycardia countered by β-Blockers.
- **Nitrates + calcium channel blockers ∴**
  - Nitrates ↓ Preload, calcium channel blockers ↓ Afterload.
- **Calcium channel blockers + β-Blocker + Nitrates.**
  - If not controlled by 2 drugs.

∴ Anti-Arrhythmic drugs ∴

Cause of Arrhythmia ∴ Basically there are three causes of Arrhythmia which may occurs in our body.

(1) Automaticity (Impulse Generation)
(2) Conduction System Block
(3) Refractory Period of mypcardium.

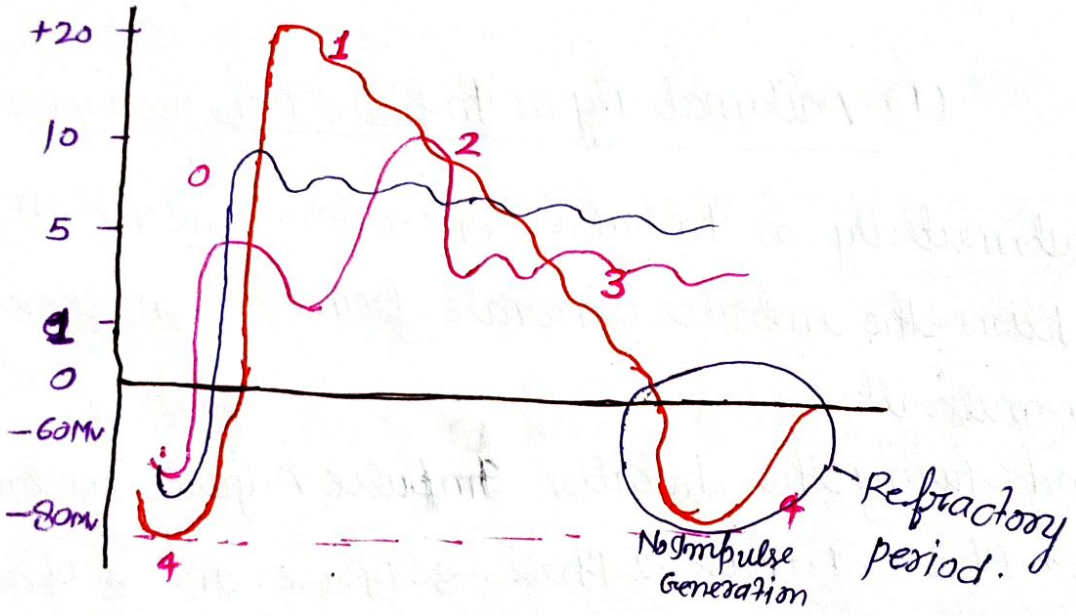
(1) Automaticity or Impulse Generation

Automaticity or Impulse Generation means at normal condition the impulse Generate from -80 milivalt to the +20 milivalt

- And during this duration Impulse Adjusts in four stages 0, 4 Phase, 1, Phase, 2 Phase, 3-Phase, and 4 Phase.
- In 4-Phase impulse start and in 0-Phase Impulse sudden increases. Up to +20 mv.
- And in Phase 1, 2 and 3 the article and Ventricles are depolarised. and the contract.
- But due to the wrong Impulse generation or Any Problem in Impulse generation. when Reenby and circus Moment are start in the impulse generation then it causes the Arrhythmia.

⇒ When the impulse start from -55 to 60 mv. and it goes up to 10 to 15 mv. and shows small small impulse generation. They are called reentry impulse generation.

⇒ And when impulse create a circle it means they reaches that point where from start. they are called circus moment. And due to this circus and reentry moment the impulse generation is effected so this process the Arrhthemia.



(2) Conduction System block :

⇒ Basically SA Node are the Pacemaker & AV Node which are responsible for the impulse generation.

⇒ But when the SA Node is unable to produce the proper conduction system or Proper impulse generation this is called conduction system block.

⇒ Conduction System is block of three category.

(A) 1° Block
(B) 2° Block
(C) 3° Block.

(A) → 1°-Block :- In primary block only the impulse generation is delayed.

(B) 2°-Block :- In this block the conduction is partialy Affected.

(C) 3°-Block :- In this block the conduction system is completely block. when the completely block this condition is called heart attack. and Patient will be died.

(3) Refractory Period of Myocardium :-

⇒ The situation of 4th stage of impulse generation. -where is no conduction system. and no depalarization. this is called Refractory Period of Myocardium :-

⇒ And when the Refractary Period of myocardium is increase or decrease in both cases they can cause the Arrhythemia.

⇒ The 4th stage of impulse generation when there is no thresold value. there, is no conduction in heart this is called Refractary period.

÷ Classification of Anti Arrhythmic drugs ÷

(i) **Class-1** Membrane Steblizing Agent ÷

Class-1(a) ÷ ↑ EPR (Increase Effective Refractary Period) → Quinidine, Procainamide, Disopyramide.

Class-1(b) ÷ Repolerisation More quickly → Lidocain, Phenytain, Mexiletine, Tocainine.

Class-1-c) ↓ Conduction Velocity ÷ Propafenone, Encainide. Flecainide.

(2) Class-2 → β-Adrenergic Blocker ÷ Alperenolal, Metoprolal, Propenalal, Pindolal.

(3) Class-3 Increase Refractory Period. Amiodarone, Brethylinm, Satalal, Clafilinm.

(4) Class-4 ÷ Ca^{++} channel blocker ÷ Verapamil. Diltiazem.

Quinidine

→ Historically first Antiarrhythmic drug used.
- In 18th century, the bark of the cinchona plant was used to treat "rebellious palpitations.

Pharmacological Effects: ↑ Threshold for excitability.
- → ↓ Automaticity.
- Prolong Action Potential.

Clinical Pharmacokinetics: - Well Absorbed.
- → 80% bound to plasma proteins (Albumin)
- → Extensive hepatic oxidative Metabolism
- 3-Hydroxyquinidine.
- Is nearly as potent as quinidine in blocking cardiac Na^+ channels and Prolonging Cardiac Action Potentials.

Uses: To maintain sinus rhythm in Patients with artial flutter or Atrial Fibrillation.
→ To prevent recurrence of ventricular tachycardia or Ventricular Failure.

Adverse Effect:

Non Cardiac: → Diarrhoea, Thrombocytopenia.
- Cinchonism & Skin Rashes.

Cardiac:- Marked QT- Interval Prolongation & Torsades de-Pointes (2-8%)

- Hypotension.
- Tachycardia.

Disopyramide

- Exerts electrophysiologic effects very similar to those of quinidine.
- Better tolerated than quinidine.
- Exert prominent Anticholinergic Actions.
- Negative Ionotropic Action.

Adverse Effect:- - Precipitation of Glaucoma.
- Constipation, dry mouth.
- Urinary retention.

Procainamide

- Lesser Vagolytic Action, depression of Contractility & Fall in Blood Pressure.
- Metabolized by acetylation to N-Acetyl procainamide which can block K^+ channels.
- Doesn't alter plasma digoxin levels.
- Cardiac adverse effects like quinidine.
- can cause SLE not recommended >6 Months.

Use:- Monomorphic VT, WPW Syndrome.

÷ Lignocaine ÷

- Blocks inactivated Sodium channels more than open state.
- Relatively selective for partially depolarized cell.
- Selectively acts on diseased myocardium.
- Rapid onset & Shorter duration of Action.
- Useful only in ventricular Arrhythmias Digitalis induced ventricular ~~Arrhythmias~~.
- Lidocaine is not useful in atrial Arrhythmias ??
- Atrial action potentials are so short that the Na^+ channel is in the inactivated state only briefly compared with diastolic (Recovery) times, which are relatively long:

÷ Pharmacokinetics ÷

- High first pass metabolism.
- Metabolism dependent on hepatic blood flow.
- $T_{1/2}$ = 8 min - distributive, 2 hours - Elimination.
- Propranolol decreases half life of Lignocaine.
- Dose = 50-100 mg bolus followed by 20-40 mg every 10-20 min. I.V (Intravenous)

Adverse Effects ÷ Relatively safe in recommended doses.

- Drowsiness, disorientation, Muscle twitchings.
- Rarely convulsions, Blurred vision, Nystagmus.
- Least cardiotoxic Antiarrhythmic.

Mexiletine

- Oral Analogue of lignocain.
- No first pass metabolism in liver.

use: → Chronic treatment of ventricular Arrhythmias associated with previous MI.
- Unlabelled use in diabetic neuropathy

Adverse Effect: Tremor is early sign of mexiletine toxicity.
- Hypotension, Bradycardia, Widened QRS dizziness, Nystagmus may occur.

Tocainide

- Structurally similar to lignocaine but can be Administered orally
- Serious non cardiac side effects like pulmonary fibrosis, Agranulocytosis, thrombocytopenia limit its use.

Propafenone Class-1c

- Structural similiarity with propranalol & has β-Blocking action.
- Undergoes variable first pass metabolism.
- Reverse drugs for ventricular Arrhythmias, reentrat tachycardia involving accesory pathway.

Adverse Effects:- Metallic taste. Constipation and is proarrhythmic.

:- Flecainide Class 1c :-

→ Patent blocker of Na & K channels with slow unblocking kinetics.

→ Blocks K channels but does not prolong APD & QT Interval

→ Maintain sinus rhythm in supraventricular Arrhythmias

Cardiac Arrhythmia Suppression Test (Cast Trial):- When Flecainide & other class 1c ~~again~~ given prophylactically to patients convalescing from Myocardial Infraction it increased mortality by 2½ fold. Therefore the trial had to be prematurely terminated.

:- Class-11 Beta Blockers :-

→ β- receptor stimulation
- → ↑ Automaticity
- → ↑ AV conduction velocity.
- → ↓ Refractory period

→ β- Adrenergic blockers competitively block catecholamine induced stimulation of cardiac β- receptors.

→ Depress phase 4 - Depolarization of Pacemaker Cells.

→ Slow sinus as well as AV Nodal Conduction decrease Heartrate increase PR

⇒ ↑ ERP, prolong AP Duration by ↓ AV conduction.
→ Reduce myocardial oxygen demand.
→ Well tolerated, Safer.

÷ Esmolol ÷

→ β_1 Selective agent.
→ Very short elimination $t_{1/2}$ 9mins.
→ Metabolised by RBC Esterases.
→ Rate control of rapidly conducted AF

Use: Arrythmia associated with Anaesthesia.
→ Supraventricular tachycardia.

← Amiodarone ÷

→ Iodine containing long acting drug.
→ **Mechanism of Action:** (Multiple Actions)
→ Prolongs APD by blocking K^+ channels.
→ Blocks inactivated sodium channels.
→ β blocking action, Blocks Ca^{2+} channels
→ Decrease Conduction, Decrease Ectopic Automaticity

Pharmacokinetics: Variable absorption 35-36%.
→ Slow onset 2 days to several weeks.

DOA: Weeks to months.

Dose: Loading dose: 150 mg over 10 min.

→ Then maintenance infusion of 0.5 mg/min for 24 hr.

Uses: Can be used for both supraventricular and ventricular tachycardia.

Adverse Effects: Cardiac: Heart block, QT Prolongation, bradycardia, Cardiac failure, Hypotension.

→ Pulmonary: Pneumonitis leading to pulmonary fibrosis.

→ Bluish discoloration of skin, corneal microdeposits

→ GIT Disturbances: Hepatotoxicity.

→ Blocks peripheral conversion of T_4 to T_3 can cause hypothyroidism or Hyperthyroidism.

→ Antiarrhythmic
Multiple Action
Iodine containing
Orally used mainly
Duration of Action is very long ($t_{1/2}$ = 3-8 weeks)
APD & ERP increases.
Resistant AF, V tach, Recurrent Vf are indication.
On prolonged use - Pulmonary fibrosis
Neuropathy may occur
Eye - corneal microdeposits may occur.

Bretylium

→ Adrenergic Neuron blocker used in resistant ventricular Arrhythmias.

Sotalol

→ Beta blocker.

Dofetilide Ibutilide:

→ Selective K^+ Channel blocker, less Adverse events
→ Use in AF to convert or maintain sinus rhythm
→ May cause QT Prolongation.

Calcium Channel Blocker:

→ Inhibit the inward movement of calcium ↓ Contractility, automaticity, and AV conduction.
→ Verapamil and diltiazem.

Antihyperlipidemic drug

Hyperlipidemia: Hyperlipidemia is a broad term also called hyperlipoproteinemia is a common disorder in developed countries and in the major cause of coronary heart disease

→ It results from abnormalities in lipid metabolism or plasma degradation of plasma lipoproteins.
→ "When conc. of lipid, lipoprotein, Triglyceride, Phasphoglyceride is increase in the blood beyond the normal level this is called Hyperlipidemia!"

Hyperlipidemics → ↑ Plasma lipid
↑ Plasma Tri Glyceride
↑ Plasma cholesterol

÷ Plasma lipid ÷

→ Lipids are the heterogenous mixtures of fatty acids and alcohal that are present in the body.

→ The major lipids in the bloodstream are cholesteral and it's esters triglycerides and phospolipids.

Lipid < Fatty Acid
Adicohal

When, lipoprotein, Fatty Acid and lipid are circulated in body in the form of globule they are called Chylomicron

→ Chylomicron.

÷ Lipoproteins ÷

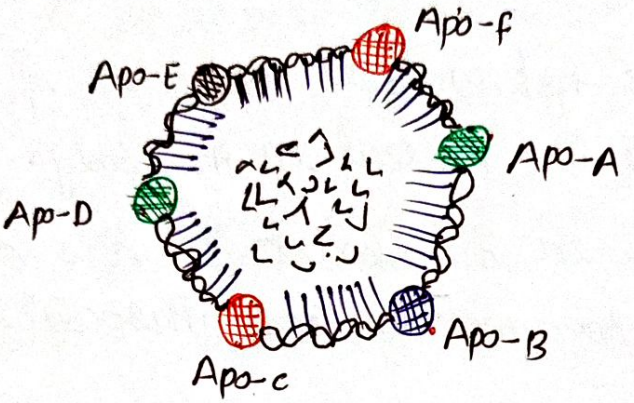
→ Since blood and other body fluids are watery, so fats need a special transport system to travel around the body.

→ They are carried from one place to another mixing with protein particles, called lipoproteins.

→ There are four or five types of lipoproteins each having very distinct job

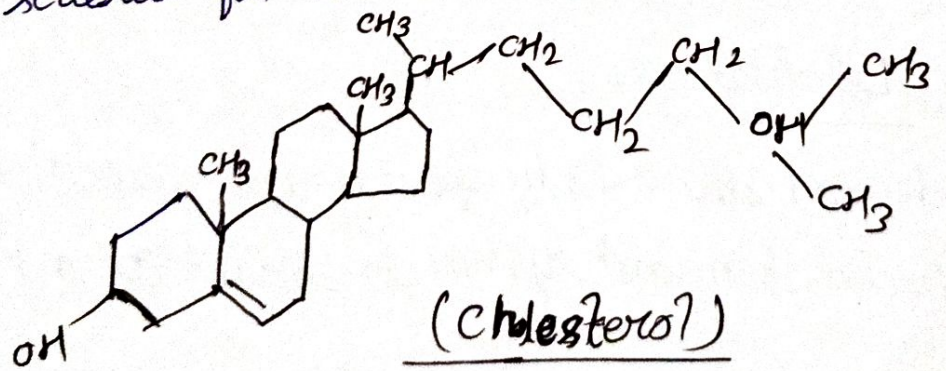
⇒ A lipoprotein contains both proteins and lipid, bound to another proteine which is called apalipoproteins, which allow fats to move through the water inside and outside cells.

⇒ Provide structural support and stability binds to receptors.



Cholesteral:- Chalesteral is produced by the liver and we consume it from meat and dairy products.

⇒ Is C27 steraid that serves as an important component of all cell membranes and important precursor molecule for the biosynthesis of bile acids steraid harmones and several fat soluble vitamins.



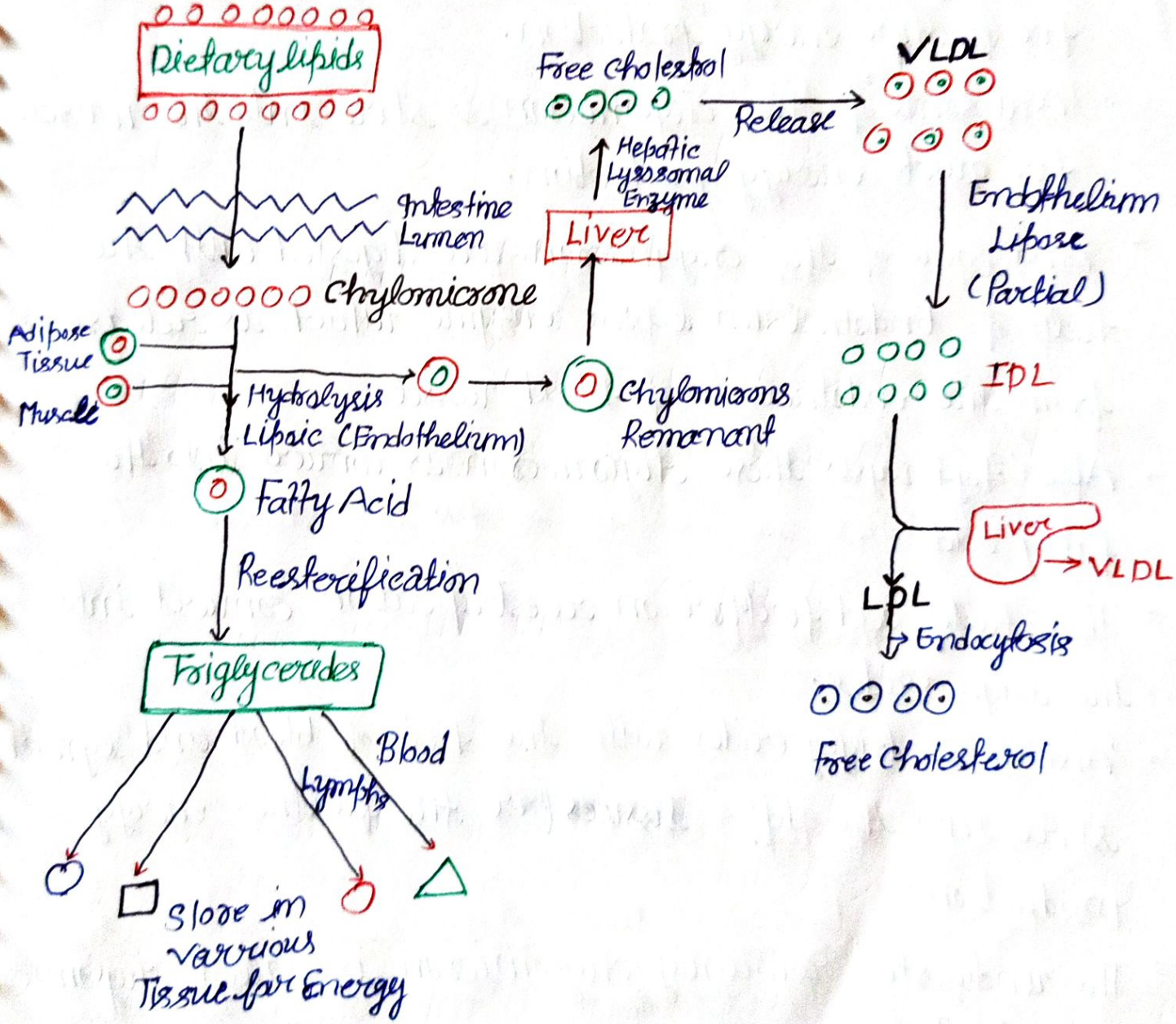
(Cholesterol)

Function of Cholesteral in body:- It is necessary for new cell to form and for older cells to repair themselves after injury.

⇒ Cholesteral is also used by the Adrenal glands to form harmones such as cortisal, by the testicles to form testosterone, and by the ovaries to form estrogen and progesterone.

Antihyperlipidemic drug: The drug which are given to reduce the level of bad cholesterol, bad lipids in our body they are called Antihyperlipidemic drug.

:- Lipoprotein Transport Mechanism :-



→ When we intake the food then the dietary lipid comes inside our intestine and stomach.

→ And from the intestine wall it absorb and comes inside the blood in the form of chylomicron.

⇒ When the chylomicron reaches in to the blood then it goes into four diff-2 direction.

→ Some of the chylomicron is store into the adipose tissue for further energy production.

⇒ And some of the chylomicron is store into the muscle for quick energy production.

⇒ And some of the chylomicron are digested with the help of Endothelium lipase enzyme which is release from the endothelium of blood vessel.

→ After hydrolysis these chylomicron is convert into the fatty acid.

⇒ This fatty acid further on reestrification convert into the triglycerides.

→ And these triglycerides with the help of blood and lymph store into the diff-2 tissues for the further energy production.

⇒ The undigested remainig chylomicron is called chylomicron remanant

→ This chylomicron remanant is store into the liver and inside the liver with the help of hepatic lysosomal enzyme these chylomicron is convert into the free cholestral.

→ And this free cholestrol is reason for the obesity and reason for the cardiac and heart problem.

→ These free cholestrol release VLDL.

→ And then further VLDL with the help of Endothelial lipase enzyme is convert into the IDL.

→ And some part of IDL is goes inside the liver and convert into again VLDL.

→ And some part of LDL by the help of Endocytosis of cell convert into the free cholestrol.

→ And these free cholestrol is very harmful for the body.

Hyperlipoproteinemia

→ That disease condition in which the concentration of LDL VLDL is increases in our blood this is called hyperlipoproteinema.

→ The hyperlipoproteinema disease can be devide into two types.

(i) Primary Hyperlipoproteinemia.

(ii) Secondry Hyperlipoproteinemia.

HLP (Hyperlipoproteinemia)

Primary Hyperlipoproteinemia → Genetic

Secondry Hyperlipoproteinemia → Dietary

(1) :- Primary Hyperlipoproteinemia :-

→ Actually this is the genetic reason because some of the chromosome, and genes are responsible for the increasing the no of the bad cholestrol and lipid they are called Primary hyperlipoproteinemia.

- On the basis of no of gene Primary hyperlipoproteinemia is devide into two type.

(a) Monogenic HLP

(b) Polygenic HLP

(a) **Monogenic HLP :-** For this disease only one type of gene is responsible

(b) **Polygenic HLP :-** More than one type of gene or Multiple no of genes are responsible for this disease

Example of Primary HLP :-

(1) **Abetalipoproteinemia :-** In this type of condition the body is absence of chylomicron.

(2) **Familial Lipoprotein Lipase difficiency desorder :-** This is the genetic desorder there is the enzyme Lipoprotein lipase is absent in the person so the bad cholesteral is increase.

(3) ÷ Familial Type -III Hyperlipoproteinemia ÷ When in any person there is E_3 and E_4 isomer of Apolipoprotein E is absent then this disease is called Familial Type -III Hyperlipoproteinemia.

(4) Familial Hypercholesteremia ÷ Difficiency of LDL Receptar site.

(ii) Secondry Hyperlipoproteinemia ÷

⇒ The secondry Hyperlipoproteinemia is based on the dietary and desease condition.

- If any person consume more diet, fatty diet then it may be cause hyperlipoproteinemia.
- And they are suffering from the various disease

for Ex ÷

(i) Diabetes Mellites
(ii) Uremia.
(iii) Cardicosteraid Excess.
(iv) Hypothyroidism
(v) Chronic Alcohalism
(vi) Nephrosis.
(vii) Glycogen Storage disease.

÷ Classification of Anti Hyperlipidemic Drugs ÷

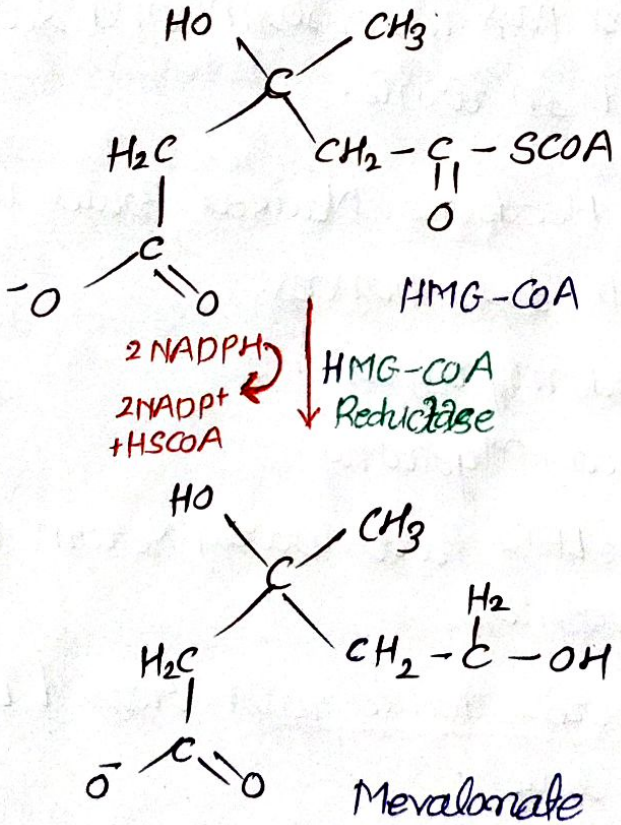
S. No	Class	Example
1)	HMG CoA Reductase Inhibitors	Lovastatin, Simvastain, Metastain Bravastatin, Flevastatin, Atorvastatin Pitavastatin, Rosuvastatin
2)	Fibric Acid Derivatives	Clofibrate, Fenofibrate, Gemfibrozil Ciprofibrate, Benzaffibrate Fluvestatin
3)	Bile Acid Sequestrants	Cholestyramine, Colestipal
4)	LDL oxidation Inhibitor	Probucal
5)	Pyridine Derivatives	Nicotinic Acid, Nicotinamide
6)	Cholesteral Absorption Inhibitors	Ezetimibe
7)	Miscellaneous Agent	β-Sitosteral, Dextrothyroxine.

HMG-CoA Reductase Inhibitor (statin)

→ The enzyme that catalyzes the conversion of HMG-CoA to mevanolate.

→ This reaction is the rate determining step in the synthetic pathway of ~~cholesteral~~.

→ 3-Hydroxy-3-Methylglutaryl-Co-enzyme A (HMG-CoA)



Mevalonate

Mechanism of Action:- The de novo synthesis of cholesteral involve a pathway in which mevalonic acid is formed and by the enzyme hydroxymethylglutaryl Co-Enzyme reductase (HMG-CoA reductase), The statine inhibits this step resulting in decrease hepatic cholesteral synthesis.

Resultantly Synthesis of high affinity LDL receptors on the liver occurs and increased clearance of plasma LDL

→ Decrease liver Cholesteral
→ Increase LDL Gene Expression.
→ Decrease Plasma LDL
→ Decrease VLDL Synthesis.
→ Decrease TGLS

Pharmacokinetics: → Given orally except fluvastatin
→ Upto 90% available
→ Undergoes first pass metabolism and secreted in bile
→ 5-10% excreted in urine.

Adverse Effect: → Headache, Nausea, Bowel Upsets rashes
→ Sleep disturbances.
→ Rhabdomyalysis.
→ Myalgia, Myopathy
→ Rise in LFTs Particularly Serum transminases
→ Muscle Weakness

Indications: Hyperlipidemia with raised LDL and cholesteral level.
→ Progression of Atherosclerotic lesion.
→ Ischemic heart disease of elderly.

← Cholestyramine →

→ Cholestyramine also known as bile acid binding resin.

→ Bile acid binding resins are cholesteral lowering drugs that are man made resins.

- They are gritty, insoluble granules which are available in the form of a bar that has to be chewed throughly or comes in the form of a powder and needs to be mixed with a liquid.

→ These prevent re-absorption of cholesteral into the body when they bind with the cholesteral-rich the acids secreted by the liver.

→ Resulting in decreased enterohepatic circulation of causing the liver to increase production of bile acids utilizing cholesteral.

→ Decrease LDL Levels.

⇒ Increase LDL receptor gene expression.

→ It significant effect on LDL levels by utilizing the LDL receptors but no effect on the HDL levels.

Pharmacokinetics: → Orally (chewed)

→ No systemic effect as it is retained the GI Tract.

→ Usual dose of 12-36 g of resin per day in divided doses with meals

Side effect: - Increased VLDL and triglycerides
→ Usually causes GI symptoms like constipation and flatulence.
→ May interfere with the absorption of fat-soluble vitamin and may bind with other drugs if taken concurrently.

Drug Interactions: Orally administered drugs.

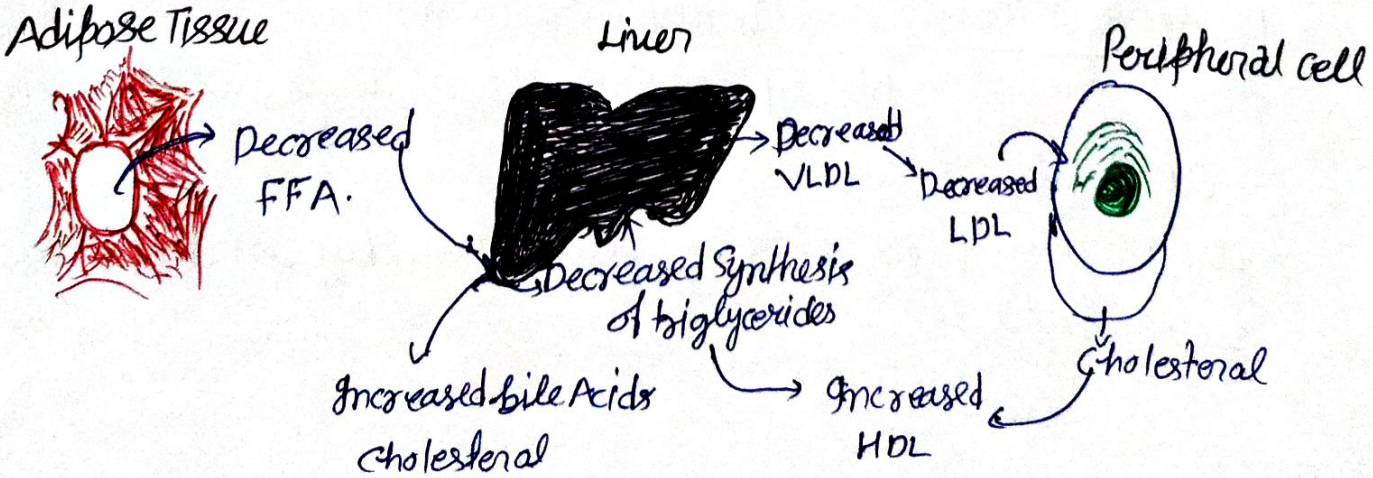
Contraindication: → Hypertriglyceridemia.

Nicotinic Acid

→ Inhibition of VLDL synthesis (Inhibiting)
(APO-B100 gene expression and resulting in.
→ Decreased Plasma VLDL
→ Decreased Plasma LDL
→ Increased Plasma HDL

Side-Effects: → Flushing, Pruritus, Rashes.
→ Hepatotoxicity.

Mechanism of Action of Nicotinic Acid:



Fibric Acid Derivatives

→ Prototype :- Gemfibrozil.

→ Others :- Clofibrate / Benzafibrate.

Mechanism of Action :- → Induction of lipoprotein lipase

→ Activation of the nuclear transcription receptor

(Activation of the nuclear transcription receptor)

"Peroxisome proliferator-Activated receptor alpha "(PPAR-α)

→ Mediate effects of insulin.

→ Class of intracellular receptors that modulate carbohydrate and fat metabolism and adipose tissue differentiation.

→ PPAR-α Activation by fibrates results in numerous changes in lipid metabolism that act together to decrease plasma triglyceride levels and increase plasma HDL

→ Decrease VLDL and IDL

Indication :- → Hypertriglyceridemias :- In which VLDL predominate and in dysbetalipoproteinemia.

→ Treatment of hypertriglyceridemia resulting from treatment with viral protease inhibitors.

Contraindication Hypercholesterolemia.

Pharmacokinetics:- → Absorbed from the GI Tract & Undergoes enterohepatic circulation.

→ Most (70%) is eliminated unchanged through the kidneys.

→ Half life 1.5 hours.

Side effects

→ Rare cases of Rash

→ GI Symptoms

→ Gall Stones

→ Myositis

→ Myopathy

→ Arrhythmias

→ Hypokalemia &

→ High aminotransferase or Alkaline Phosphatase levels risk of cholesteral Gallstones.