!! JAY AMBE !!

1. ANGINA PECTORIS

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ANGINA PECTORIS

Definition: "Angina pectoris is a syndrome characterized by chest pain resulting from an imbalance between oxygen supply and demand"

Epidemiology:

- Angina affects about 1% of the population, the prevalence increasing with age.
- In a survey of British civil servants angina was diagnosed in:
- 3% of 40-49 year old men
- 8% of 60-64 year old men

Types of angina

- There are six main anginal syndromes:
- Chronic stable angina
- Nocturnal angina
- Unstable angina
- Variant angina (Prinzmetal's)
- Decubitus angina
- Syndrome X

1. Chronic stable angina

- Pain is provoked by physical exertion, especially after a meal, in cold weather or walking against the wind. The pain is often also aggravated by anger or excitement.
- The pain is relieved within 2-10 min by rest. Occasionally the pain will disappear even though exertion continues.
- Often angina will be precipitated by a predictable degree of exertion in a particular patient; the threshold for pain varies widely between patient.
- The severity of the symptoms is not closely related to the extent of coronary artery disease, indeed periods of ischaemia and myocardial infarction may be entirely painless.
- The pain is often more easily provoked in the morning.

2. Nocturnal angina

- Nocturnal angina wakes a patient from sleep and may be provoked by vivid dreams. Symptoms are commonest in the early hours of the morning when coronary artery tone is maximal.
- The patient often has critical coronary artery disease and hence usually suffers from exertional angina.
- Nocturnal angina may be associated with coronary artery spasm - Prinzmetal's angina.

3. Unstable angina

- Unstable angina is defined as recurrent episodes of angina on minimal effort or at rest. It may be the initial presentation of ischaemic heart disease, or it may represent the abrupt deterioration of a previously stable anginal syndrome.
- Unstable angina is also described as crescendo angina, preinfarction angina, and intermediate chest pain syndrome.

- Unstable angina is provoked more easily and persists for longer than stable angina. It may fail to respond to therapy. Pain is often associated with reversible ST segment depression on the ECG.
- Unless vigorously treated, 30% of patients will progress to myocardial infarction or death within 3 months.

4. Prinzmetal's angina or Variant Angina Pectoris

- This type of angina results from transmural myocardial ischemia caused by coronary artery spasm and may occur in patients with or without coronary atherosclerosis. Pain occurs principally at rest, usually unprovoked, but since coronary artery disease may coexist, pain may also be provoked by exercise.
- The pain may occur in a circadian manner, often in the early morning hours. The pain is associated with ST-segment elevation, in contrast to typical angina pectoris.
- Often sub clinical (painless) episodes occur with ST- segment elevations, often associated with arrhythmias, or bundle branch block.
- This is angina caused by focal spasm of angiographically normal coronary arteries.
- In about 75% of patients there is also atherosclerotic coronary artery obstruction. In cases where there is atherosclerotic obstruction the vasospasm occurs near the stenotic lesion.

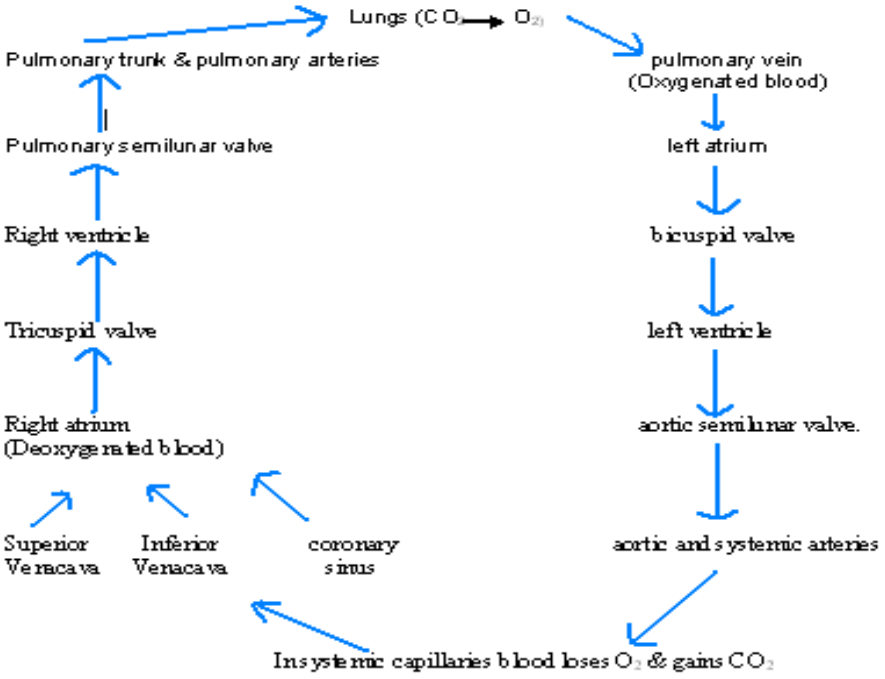
5. Decubitus angina

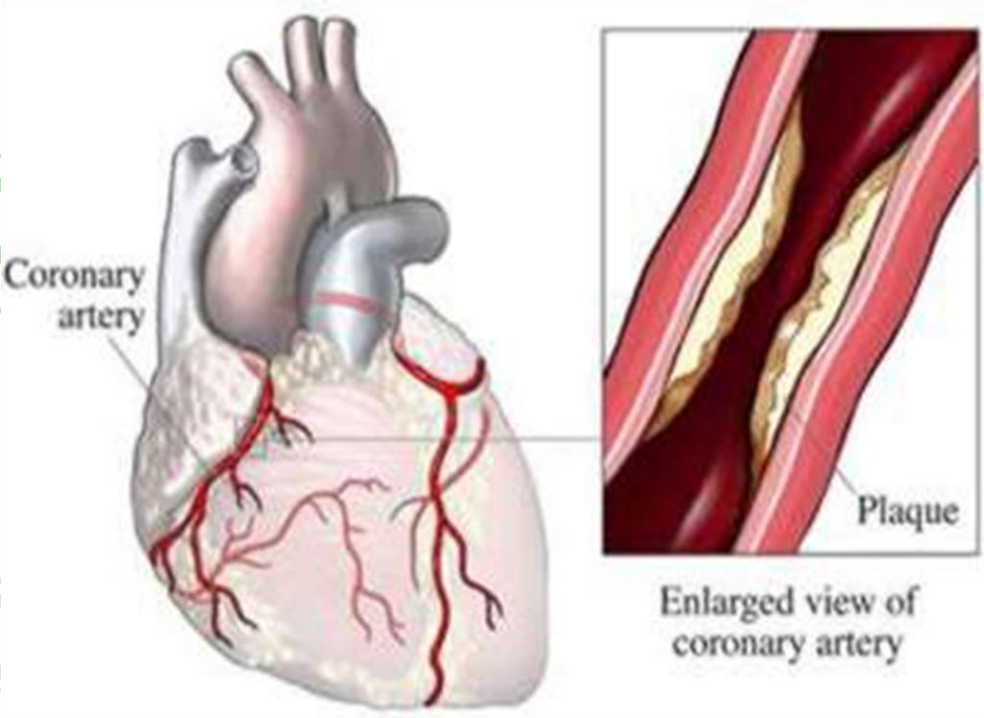
- Decubitus angina occurs when the patient lies down.
- It is usually a complication of cardiac failure due to the strain on the heart resulting from the increased intravascular volume.
- Patients usually have severe coronary artery disease.

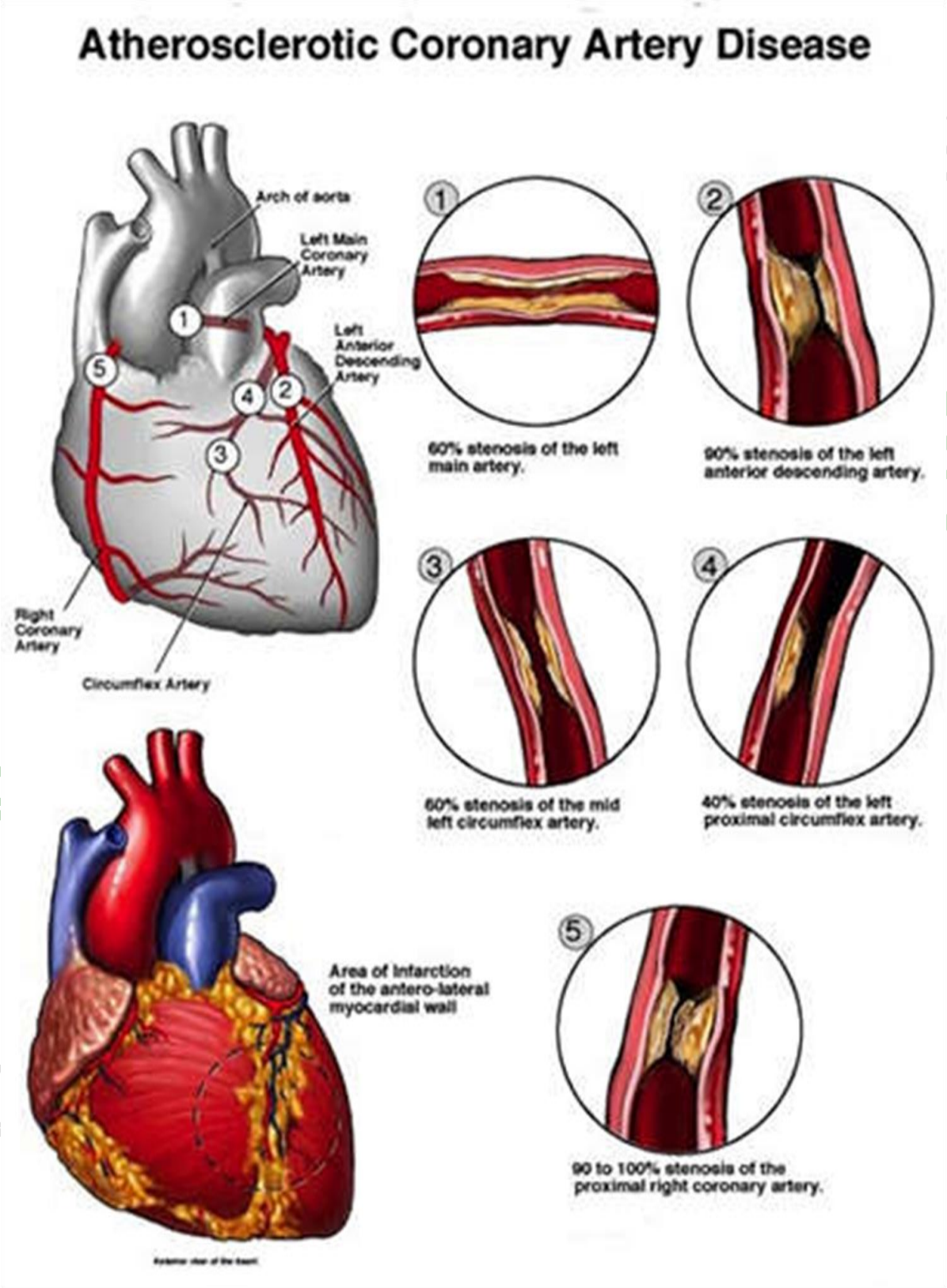
6. Syndrome X (angina)

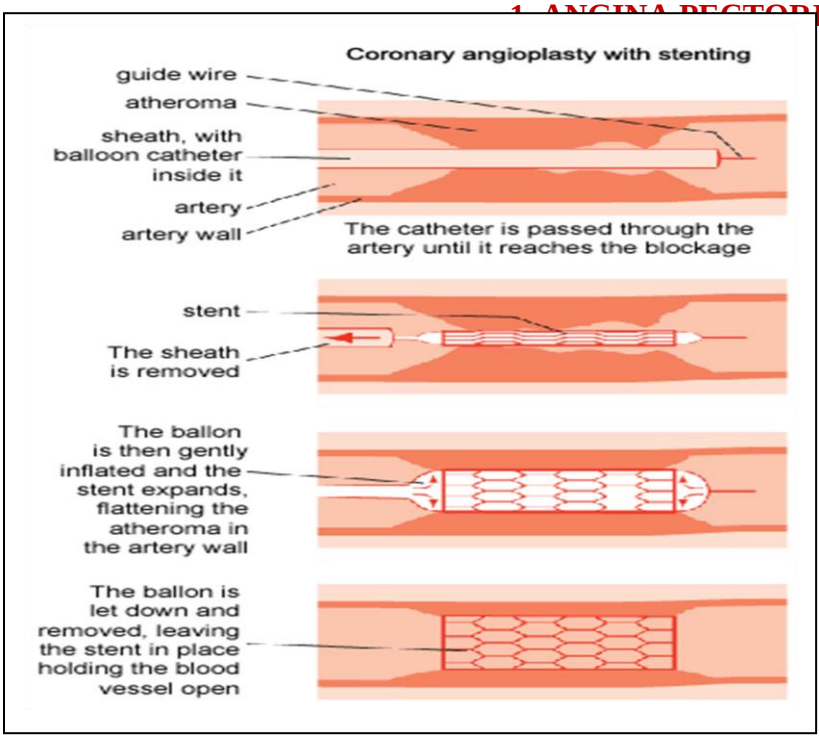
- Syndrome X comprises:
- Symptoms and signs of angina
- Radiologically normal coronary arteries
- Positive exercise test
- Syndrome X may be due to microvascular disease.

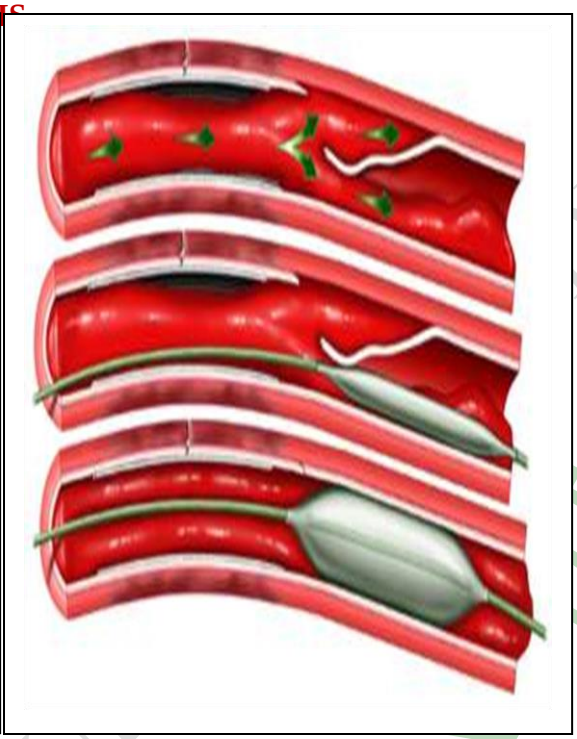
1. ANGINA PECTORIS






Atherosclerotic Coronary Artery Disease
Arch of aorta
Left Main Coronary Artery
Left Anterior Descending Artery
Right Coronary Artery
Circumflex Artery
1
2
3
4
5
60% stenosis of the left main artery.
90% stenosis of the left anterior descending artery.
60% stenosis of the mid left circumflex artery.
40% stenosis of the left proximal circumflex artery.
Area of infarction of the antero-lateral myocardial wall
90 to 100% stenosis of the proximal right coronary artery.





CLASSIFICATION OF DRUGS:

1) Nitrates:-

a) Rapid on set of action, short acting: -

- E.g. Glyceryl trinitrate (nitroglycerine), amyl nitrite.

b) Slow on set, long acting: -

- E.g. Isobarbide dinitrate, Isobarbide mononitrate, pentaerythritol tetra nitrate.

2) B- blockers:

Eg.: Propranolol, Atenolol, Meteprolol

3) Ca^+ channel blockers:

a) Phenyl alkylamine: Verapamil

b) Benzothiazepine: Deltiazem

c) Dihydropyridine: Nifedipine, Felodipine, amlodipine, nimodipine, lacidipine

4) K^+ channel opener:

Eg.: Nicorandil

5) Anti platelets drug:

Eg.: Aspirin, Dipyidamol

6) Antilipidemic: (See hypolipidemic agents)

PHARMACOLOGIC MANAGEMENT/NON INVASIVE MANAGEMENT

1) Nitroglycerin

- Reduces preload
- Reduces afterload
- Dilates collaterals

2) Beta Blocker

- Reduces Heart Rate
- Reduces afterload
- Decreases cardiac contractility
- Contraindications
- Decompensate Congestive Heart Failure (CHF)

3) Calcium Channel Blocker

- Reduces afterload
- Prevents vasoconstriction
- No significant effect on vasodilatation

4) Aspirin

a) Inhibit Platelet aggregation

5) Combination: Beta Blocker with:

a) Dihydropyridine Calcium Channel Blocker OR
b) Nitroglycerin

6) Ranolazine

- Used in combination with other agents above
- Reduces angina frequency and Nitroglycerin use

7) Lipid lowering agents

a) Decrease morbid events significantly
   I) Myocardial Infarction
   II) Angina

b) Do not significantly affect coronary lesions size

c) Do probably change composition of Plaques
   I) Decreases risk of Plaque rupture

➢ NITRATES:

Mechanism of action:

Organic nitrate after entering smooth cells

↓

Release inorganic nitrite (NO_2^-)

↓

Converted in to nitric oxide (NO)

↓

NO its self converted in to a reactive nirosothiol intermediate (R-SNO)

↓

Activates guanylate cyclase

↓

Stimulate formation of CGmp

↓

Cause the dephosphorylation of myosin light chain kinase (MLCK)

↓

Reduce activation of myosin

↓

Reduce actin myosin complex

↓

Reduce the contraction of smooth muscles.

Reduce the Ca^+ influx in cell.

So above both effects gives the relaxation of blood vessels and produce,

1) **Dilation of veins:**
   - Decrease venous return and decrease filling of heart and decrease pre load of heart.
   - So decrease the less energy required to pump so decrease the oxygen demand of heart.
2) **Dilation of large arteries:**
   - Decrease peripheral action or resistance and decrease after load.
   - So blood is pumped against the resistance.
   - So decrease the O_2 demand of heart.
3) **Dilation of coronaries:**
   - Favorable redistribute the blood in coronary artery and improvement in blood supply to heart.

Pharmacokinetics:

- Organic nitrates are lipid soluble substance and absorbed well from GIT. Glyceryl trinitrate however under goes first pass metabolism and is ineffective orally.
- It is given sublingually or as skin patch. Its metabolites (di, and mono nitrates) are active.
- Other organic nitrates are given orally.

Pharmacological action:

a) Action on the smooth muscle:

- Nitrates have a direct relaxant action on the smooth muscle (bronchi, ureter, and sphincter of oddi) and blood vessels which is independent of innervations.
- They do not alter the response to electrical stimulation or spasmogens.

b) Action on cardio vascular system: -

- Nitrates dilate both arterioles and venuls, but in low dose venodilation is more marked than arteriolar dilation.
- As a result of generalized venodilation, there is pooling of blood in the veins decrease the preload.

With large dose, nitrates cause arteriolar dilation with following effect:

- Cutaneous vessels are dilated causing flushing of face, neck and neck and clavicular areas.
- Meningeal vessels are dilated causing stretching of pain-sensitive tissue around meningeal arterials causing headache and throbbing as very common symptoms.
- Retinal vessels are dilated which may cause rise in intra ocular tension and splanchnic vessels are dilated cause increase in organ volume and decrease the after load.

c) Action on heart :-

- The beneficial effect on heart is secondary to the vascular action of nitrates.
- Reduction of preload, after load and dilation of coronary artries produce relief of the anginal pain.
- In very large doses, nitrates depress myocardium.

d) Action on platelets: -

- Decrease platelets aggregation.

Therapeutic application or uses:

a) Angina pectoris: -

- The primary use of organic nitrates is for the prophylaxis and treatment of attack of angina pectoris.

b) Spasmolytic:

- As spasmolytic nitroglycerine may be tried in biliary colic.

c) Intractable congestive cardiac failure: -

- In patients not responding to diuretic therapy, Isobarbide dinitrate is being increasingly used to reduce the preload.

d) Cyanide poisoning:

- The lethal action of cyanide is due to anoxia caused by chelation of ferric part of the respiratory enzyme, cytochrome oxidase.
- So here, Amyl nitrate inhalation or sod. Nitrate i.v converts hemoglobin to methaemoglobin which competes with cytochrome oxidase for CN^- ion and forms cyanohaemoglobin which is unstable.
- Subsequently administration of sod.thiosulphate (25%, 50ml) i.v reacts with cyanamethaemoglobin and form sod.thiocynate which gets excrete in urine.

➢ β- ADRENOCEPTOR BLOCKER BLOCKERS:

Mechanism of action:

β – Agonist
↓
Protein kinase-C
↓
Adenyl cyclase (AC)
↓
Increase the level of Camp
↓
Phosphorylates to MLCK
↓
Cause contraction

- β - Agonist activates adenyl cyclase (AC) to raise level of Camp. It activates the kinase that phosphorylates to MLCK and cause contradiction.

- **While B-blocker** gives **opposite effect** to the agonist, it prevents the muscle contraction.
- Also these drugs diminish the cardiac response to sympathoadrenal activity, decrease the emotional or exercise induce increase in heart rate and force of contraction, thus increase exercise tolerance.
- They cause bradycardia and reduction in cardiac contractility thereby decreasing work load on the heart.
- All these process decrease myocardial oxygen requirement, reducing frequency and severity of anginal attack.

Therapeutic uses:

1) In anginal attack.
2) Combination with nitroglycerine with is able to prevent the attack of anginal in nearly 85% of patient.

Contraindication:

- In asthma, diabetes mellitus.
- A.V block, heart failure.

Adverse effect:

- Bradycardia and hypotension can occur.
- Renal plasma flow and glomerular filtration rate may be reduced.
- Tachyarrhythmia may occur when blocker are suddenly withdrawn.

➢ **Ca^{+2} - CHANNEL BLOCKERS:**

Ca^{+2} influxes in cells are essential for contraction of cardiac and vascular cells. Ca^{+2} channels have three type of classification;

1) Voltage (Gated) sensitive channel:

- Activate when membrane potential drop around -40mv.

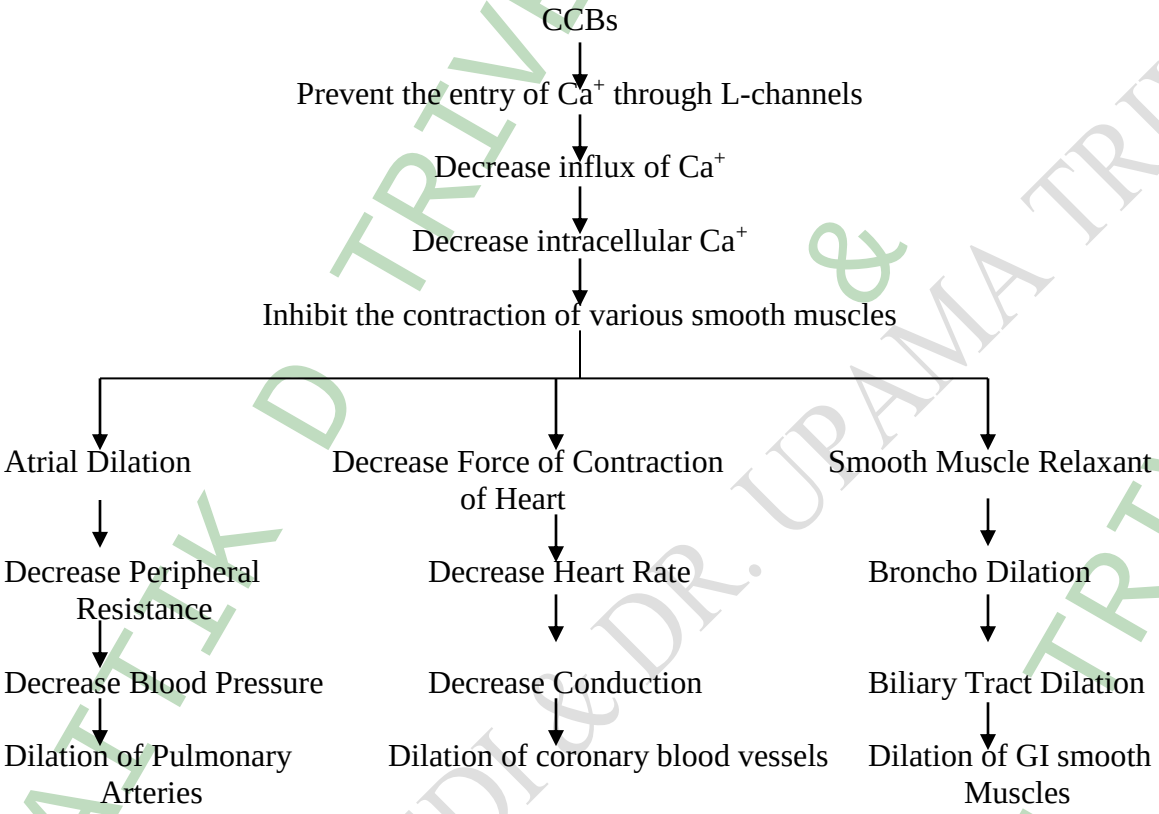
It is further sub divided in to;

a) L-type---Long lasting current
b) T-type---Transient current
c) N-type---Neuronal current.

Note:-

Only L-type channels are blocked by calcium channel blockers (CCBs)

Mechanism of action:



CCBs produce their action by,

1) Verapamil, diltiazem and bepridil decrease myocardial contractile force and decrease oxygen demand.
2) Nifedipine inhibit atrial spasm, dilates arterioles and increase oxygen supply to myocardium in patients at variant angina.

Note: -

Nifedipine mainly act on arterials and does not decrease AV conduction so can be used safely in AV conduction defects and also in combination with B-blocker, for which verapamil and diltiazem can not be used due to their negative ionotropic effect on heart

Pharmacological action:

- Decrease force of contraction of heart so decrease heart rate and conduction and dilation of coronary decrease the blood pressure.

- It has antihypertensive as well as anti arrhythmetic action.
- It has smooth muscle relaxant properties.

Pharmacokinetics:

a) All are orally well absorbed except amlodipine.

b) Peak blood level: -

1) Nifedipine: - 30 min.
2) Diltiazem: - 1hr.
3) Verapamil: - 1-2hr
4) Nicordipine: - 8-9hr.
5) Amlodipine: - 6-12hr

c) All five drugs are highly bounded by serum protein.

d) Verapamil metabolize by first pass effects.

Therapeutic use:

a) use in angina: -

- Treatment of both prinzmetal's and classic exert ional angina

b) other use: -

- Use in hyper tension.
- Verapamil-arrhythmias.
- In migraine treatment.

Adverse effect:

a) When used with B-adrenergic blocking.

2) Hypotension.
3) A.V block.
4) CHF.
5) Asystole.

b) Mild dizziness and peripheral edema.

c) Nicordipine-negative effect-intravenous to patient with CHF.

➢ **RATIONAL DRUG COMBINATION:**

Three major classes of anti anginal drug described above, generally one agent is used initially. When it is unable to provide adequate relief in tolerated doses, concurrent use of 2 or 3 drugs may try.

1) B-blocker + long acting nitrate combination is rational in classical angina because: -

a) Tachycardia is blocked by B-blocker.

b) The tendency of B-blocker to cause ventricular dilation is counteracted by nitrate.

c) The tendency of B-blocker to reduce total coronary is opposed by nitrate.

2) The above advantage also be obtained by combining a slow acting DHP (in place of nitrate) with B-blocker. However, verapamil or deltiazem should not be used with B-blocker since their depressant effects on SA and A-V may add up.

3) Nitrates primarily decrease preload, while CCBs have a grater effect on after load. Their concurrent use may decrase cardiac work to an extent not possible with either drug alone. This combination may be especially valuable in severe variant angina.

4) In the most severe and resistant cases of classical angina, combined drug of all three classes is indicated. As their primary mechanism of benefit is different, super additive results may be obtained.

Notes: -

- Nitrates primarily decrease preload.
- CCBs mainly reduce after load + increase coronary flow.
- B-blocker decrease cardiac work primarily by direct action on heart.
- Verapamil/deltiazem should be avoided in such combinations.

➢ **POTASSIUM CHANNEL OPENERS:**

Mechanism of action:

- Intracellular of K^+ is much higher (150mM) compaired to extacellular (4-5), K^+ channel opening result in outflow of K^+ ions and hyper polarization.

There are multiple types of K^+ channels;

- Voltage dependent,
- Ca++ activated, receptor operated,
- ATP sensitive,
- Na+ activated and
- Cell volume sensitive

Which serve diverse functions and exhibit different sensitivity to drugs. As such, K+ openers exhibit considerable diversity in action. The most prominent action of K^+ channel openers is smooth muscle relaxation-vascular as well as visceral.

Nicorandil (K^+ opener drug):

- This novel anti anginal drug activates ATP sensitive K^+ channels produce hyperpolarizing smooth muscle.
- The vasodilator action is partly antagonized by glibenclamide. Its also act as a NO donor-relaxes blood vessels by increasing CGmp. Thus arterial dilation is coupled with venodilation. Coronary flow is increased; dilation of epicardial conducting vessels and deeper resistance vessels has been demonstrated.
- Beneficial effects comparable to nitrates, B-blocker and CCBs have been obtained in stable as well as vasospastic angina.

Side effects:

Flushing, palpitation, weakness, headache, dizziness, nausea and vomiting.

➢ **ANTI PLATELETS DRUG:**

Mechanism of action:

It activate irreversibly Cyclo-oxygenase in platelets and in vascular endothelium

↓

Inhibit platelets aggregation

↓

So its act as thrombolytic agents

- It may reduce thromboembolism in arterial fibrillation.
- It is used to decrease incidences of early graft closure after bypass surgery

Side Effects:

Dyspepsia, nausea, vomiting, aggravation of prinzmetal's variant angina by promotion of coronary artery spasm.

IMPORTANT QUESTIONS:

1. **Write down the classification of anti anginal drug and explain the detail mechanism of action of B- Blocker drugs.**
2. **Explain the pharmacological action of B-blocker.**
3. **Write short note on calcium channel blocker.**
4. **Explain the drug spirenolactone.**

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