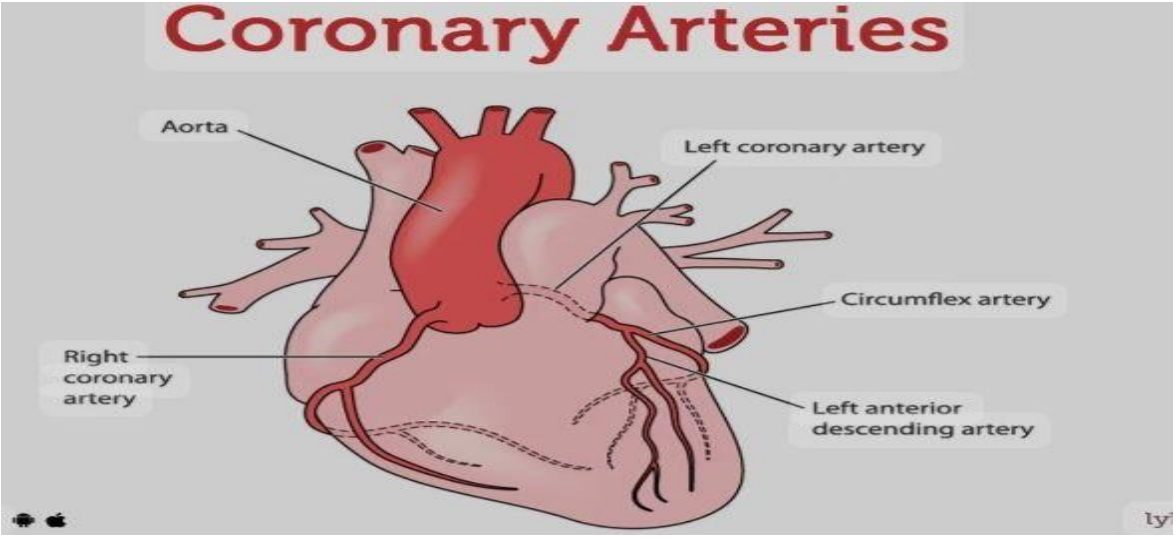
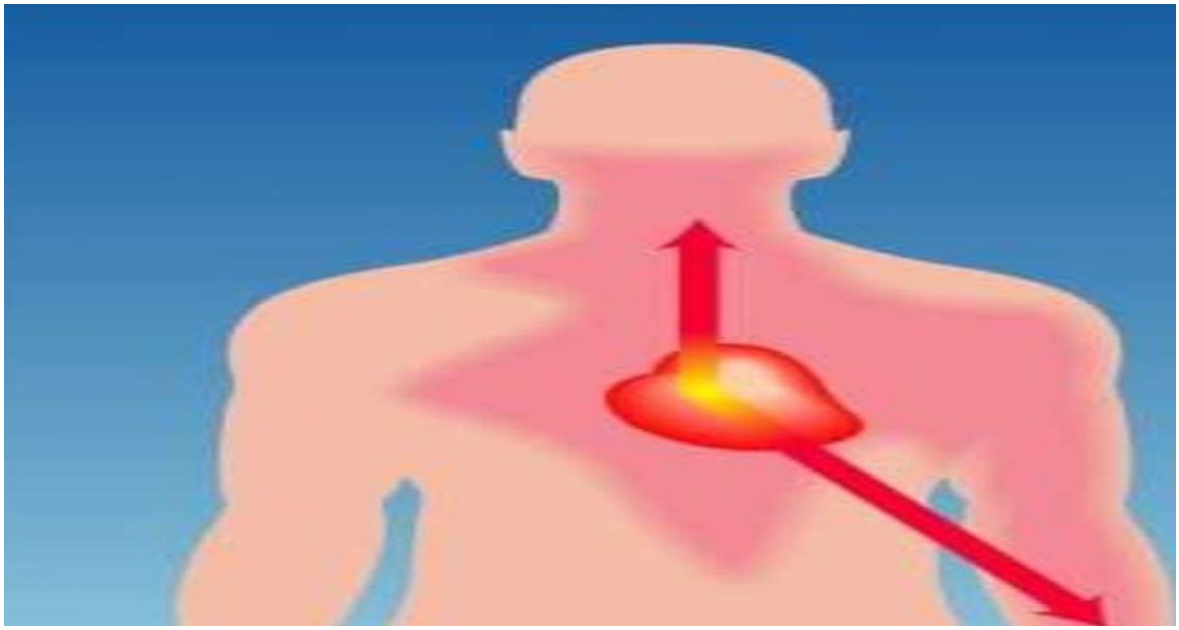
❖ Introduction



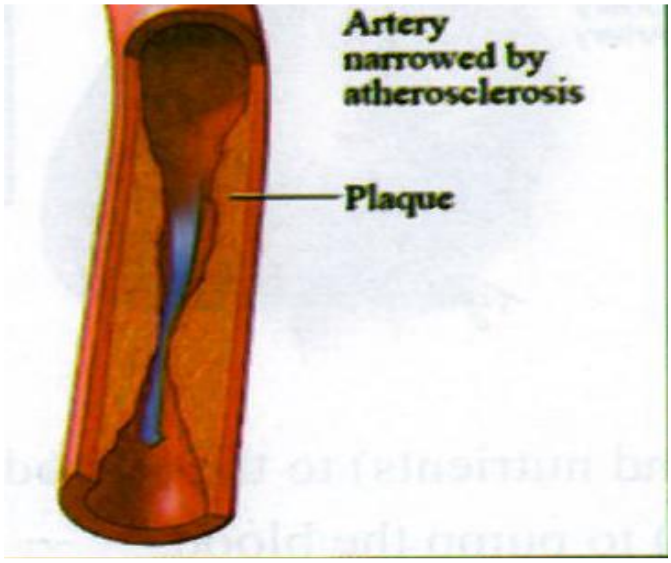
- ❖ Heart pump blood which carry oxygen and nutrient to the all body tissue.
- ❖ Heart need oxygen and nutrient to pump the blood.
- ❖ Blood which carry oxygen and nutrient pumbed from the heart to heart through coronary arteries.
- ❖ Coronary artery narrowing cause small amount of blood reached to the heart and lead to decrease heart work ⟶ Angina pain.
- ❖ Angina pain is chest pain caused by transient myocardial ischemia due to an imbalance between myocardial oxygen supply and oxygen demand .This pain characterize by sudden, severe, crushing pain that may radiate to the neck, jaw, back, and arms.
- ❖ Angina pectoris imbalance between oxygen supply and oxygen demand



❖ Types of Angina

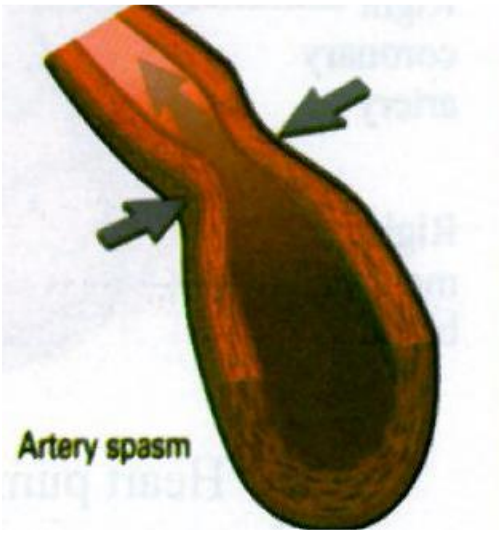
1-Stable angina, effort-induced angina, classic or typical angina

Classic or typical angina pectoris is the most common form of angina caused by the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis. Angina attack induced by event such as physical activity, emotional stress or excitement, or any other cause of increased cardiac workload and this attack is promptly relieved by rest or *nitroglycerin*



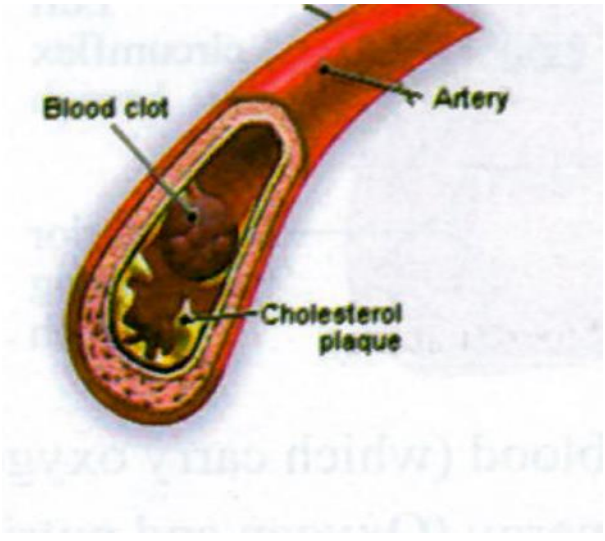
2-Vasospastic angina

Vasospastic angina, also known as rest angina, variant angina, or Prinzmetal's angina, is responsible for less than 10% of cases. It involves reversible spasm of coronaries, usually at the site of an atherosclerotic plaque. Spasm may occur at any time, even during sleep. Vasospastic angina may deteriorate into unstable angina.



3-Unstable angina

Unstable angina also called per infarction angina or crescendo angina, also known as **acute coronary syndrome** −is characterized by increased frequency and severity of attacks that result from a combination of atherosclerotic plaques, platelet aggregation at fractured plaques, and vasospasm. Unstable angina is thought to be the immediate precursor of myocardial infarction and is treated as a medical emergency.



❖ Therapeutic strategies

The defect that causes anginal pain is inadequate coronary oxygen delivery relative to the myocardial oxygen requirement. This defect can be corrected—at present—in 2 ways: by **increasing oxygen delivery** and by **reducing oxygen requirement.** Traditional pharmacologic therapies include the **nitrates**, the **calcium channel blockers**, and the **β blockers.**

1-Nitrate

These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms. They are effective in stable, unstable, and variant angina.

A. Mechanism of action

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which in turn activates guanylate cyclase and increases synthesis of cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation .

Effect on CVS and other organs

Cardiovascular—Smooth muscle relaxation by nitrates leads to an important degree of venodilation, which results in reduced cardiac size and cardiac output through reduced preload. Relaxation of arterial smooth muscle may increase flow through partially occluded epicardial coronary vessels.

Other organs—Nitrates relax the smooth muscle of the bronchi, gastrointestinal tract, and genitourinary tract, but these effects are too small to be clinically useful.

B- Pharmacokinetic

-Well absorbed from buccal mucosa, intestine, skin and alveoli.

-Low oral bioavailability [Excessive first pass effect].

-Excreted in urine after conjugation with the glucuronic acid.

C-Adverse Effect

Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.

Nitrates interact with **sildenafil** and similar drugs promoted for erectile dysfunction. These agents inhibit a phosphodiesterase isoform (PDE5) that metabolizes cGMP in smooth muscle. The increased cGMP in erectile smooth muscle relaxes it, allowing for greater inflow of blood and more effective and prolonged erection. This effect also occurs in vascular smooth muscle. As a result, the combination of nitrates (through increased production of cGMP) and a PDE5 inhibitor (through decreased breakdown of cGMP) causes a synergistic relaxation of vascular smooth muscle with potentially dangerous hypotension and inadequate perfusion of critical organs.

Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. The nitrate-free interval of 10 to 12 hours is usually taken at night when myocardial oxygen demand is decreased. However, variant angina worsens

early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in patients with variant angina should occur in the late afternoon. *Nitroglycerin* patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free interval.

2-Calcium channel blocker

Effective in all type of angina

A-Mechanism of action

Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance**.**

B-Classification and Pharmacokinetics

-Dihydropyridine calcium channel blockers

Amlodipine an oral dihydropyridine, has minimal effect on cardiac conduction and functions mainly as an arteriolar vasodilator. The vasodilatory effect of *amlodipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm. ***Nifedipine*** is another agent in this class; it is usually administered as an extended-release oral formulation. [Note: Shortacting dihydropyridines should be avoided in CAD because of evidence of increased mortality after an Ml and an increase in acute Ml in hypertensive patients.]

- Nondihydropyridine calcium channel blockers

Verapamil slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. *Verapamil* has greater negative inotropic effects than *amlodipine*, but it is a weaker vasodilator. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. ***Diltiazem*** also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator. *Diltiazem* can relieve coronary artery spasm and is particularly useful in patients with variant angina. Nondihydropyridine calcium channel blockers can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

C-Adverse Effect

The calcium channel blockers cause constipation, pretibial edema, nausea, flushing, and dizziness. More serious adverse effects include heart failure, AV blockade, and sinus node depression; these are most common with verapamil and least common with the dihydropyridines**.**

3-B-blocker

Because they reduce cardiac work (and oxygen demand), all β blockers are effective in the prophylaxis of atherosclerotic angina attacks.

A. Effects and Clinical Use

The B-adrenergic blockers decrease the oxygen demands of the myocardium by blocking B1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure. These agents reduce myocardial oxygen demand during exertion and at rest. As such, they can reduce both the frequency and severity of angina attacks.

B-Blockers can be used to increase exercise duration and tolerance in patients with effort-induced angina. B-blockers are recommended as initial antianginal therapy in all patients unless contraindicated. [Note: The exception to this rule is vasospastic angina, in which B-blockers are ineffective and may actually worsen symptoms.].

Agents with intrinsic sympathomimetic activity (ISA) such as *pindolol* should be avoided in patients with angina and those with a history of MI.

Propranolol is the prototype for this class of compounds, but it is not cardioselective Thus, other B-blockers, such as *metoprolol* and *atenolol*, are preferred. [Note: All B-blockers are nonselective at high doses and can inhibit B2 receptors.] B-blockers should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely. Nonselective B-blockers should be avoided in patients with asthma.

[Note: It is important not to discontinue B-blocker therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, Ml, and hypertension.]

B-**Adverse effect**

Brady cardia, worsening peripheral vascular disease, blunt hypoglycemia awareness, inhibit B2-mediated bronchodilation in asthmatics.

4- *Ranolazine*

Has no effect on heart rate and used in combination with antianginal drug .

A-Mechanism of action and pharmacokinetic

inhibits the late phase of the sodium current (late INa , improving the oxygen supply and demand equation. Inhibition of late INa reduces intracellular sodium and calcium overload, thereby improving diastolic function. ***Ranolazine*** has antianginal as well as antiarrhythmic properties. It is most often used in patients who have failed other antianginal therapies. The antianginal effects of ***ranolazine*** are considerably less in women than in men. The reason for this difference in effect is unknown.

Ranolazine is extensively metabolized in the liver, mainly by the CYP3A family and also by CYP2D6. It is also a substrate of P-glycoprotein. As such, ***ranolazine*** is subject to numerous drug interactions. In addition, ***ranolazine*** can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

B-Adverse effect

Constipation, edema and QT interval prolongation