Angina pectoris: is the principle symptom of ischemic heart disease which is characterized by sudden, severe substernal pain or pressure.

The primary cause of angina is imbalance between myocardial O$_2$ demand and O$_2$ supplied by coronary vessels. This imbalance may be due to:

1. A decrease in myocardial Oxygen delivery
2. An increase in myocardial Oxygen demand
3. Both.

Peculiarities of coronary circulation:

1. End arteries.
2. Max. Oxygen extraction.

Risk factors:

- Hypotension.
- Smoking.
- Dyslipidemia.
- DM or impaired glucose tolerance.
- Obesity.
- Sedentary lifestyle.

Classification of angina:

There are 3 types of angina:

1. Stable (Effort or Classic) angina.
2. Variant (Printzmetals or Vasospastic) angina.
3. Unstable angina.

Stable angina is due to fixed stenosis of the coronary arteries, and is brought on by exercise and stress.

Unstable angina can occur suddenly at rest, and becomes progressively worse, with an increase in the number and severity of attacks.

Variant angina occurs at rest, at the same time each day and usually due to coronary artery spasm.

Anti-angina Drugs:

- Nitrates.
- Beta Blockers.
- Calcium channel blockers (CCBs)
- Potassium channel openers.
- Other. Trimetazidine.
**Nitrates: Pharmacological mechanism**

Organic nitrates

- NO
- Guanylyl cyclase
- cGMP
- cGMP dependent protein kinase
- Intracellular Ca++

Vascular smooth muscle relaxation.

**Nitrates: Pharmacological mechanism**

- Nitrates provide an exogenous source of vasodilator nitric oxide (NO), thereby inducing vasodilation. They vasodilate whether or not the endothelium is intact.
- Nitrates, after entering the vessel wall, are converted to NO, which stimulates guanylate cyclase to produce cyclic GMP (cGMP). Thus intracellular Calcium (in the vascular myocyte) falls, and vasodilation results. Sulfhydryl (SH) groups are required for such formation of NO and the stimulation of Guanylate cyclase.
- Nitrates relax all types of smooth muscle irrespective of the preexisting muscle tone. They have no direct effect on cardiac and skeletal muscles.

**Nitrates: Pharmacological Effects**

1. **Increase myocardial blood and O2 supply:**
   Nitrates increase blood flow. They dilate large coronary arteries and arterioles to redistribute blood flow along collateral channels and from epicardial to endocardial regions. Further, they relieve coronary spasm and dynamic stenosis, especially at epicardial sites.

2. **Decrease myocardial oxygen consumption:**
   - **Reduce Preload:** Venodilation, predominates at therapeutic dosage, which increase the venous capacitance, causing pooling of the blood in the peripheral veins and a reduction in the venous return and in ventricular end-distolic volume and pressure.
   - **Reduce afterload:** Arteriodilation (at high dose) reduce peripheral resistance, causing a fall in systolic pressure.

3. **Antiplatelet effect:** Possibly through release PGI₂.

**Nitrates Uses:**

1. All types of angina.
2. MI.
3. CHF & LVF.
5. Cyanide poisoning.

**Short Acting nitrates for acute effort angina:**

- GTN (Sublingual or spray).
  *GTN (glyceryl trinitrates) or (Nitroglycerin).
- ISDN (sublingually) is alternative option.
  *ISDN (Isosorbide dinitrate).
**Long Acting nitrates for angina prophylaxis:**
- ISDN and MNT (oral preparations).
- GTN (transdermal patches and ointment).

**Nitrates for Unstable Angina:**
- Intravenous GTN.
- Intracoronary nitroglycerin is often used to avoid coronary spasm during PTCA.  
  * PTCA (Percutaneous transluminal coronary angioplasty).

**Nitrates for MI:**
- Intravenous GTN for selected cases.

**Contraindications in MI:**
1. Right Ventricular involvement.
2. Hypotension (BP 90mmHg).
3. Recent use of Sildenafil.

**Nitrates for CHF:**
Combination of high dose ISDN plus hydralazine.

**Nitrates for Acute Pulmonary Edema:**
GTN is effective with some risk of precipitous falls in BP. Intravenous GTN is usually the best method, as the dose can be rapidly adjusted upward or downward depending on the clinical and hemodynamic response. However, repeated sublingual doses of GTN can relieve dyspnea within 15 to 20 minutes, with a fall of LV filling pressure and a rise in cardiac output.

**Nitrates: Side Effects:**
1. **Severe throbbing headache (most common).** Headaches frequently limit dose and often respond to aspirin.
2. **Syncopy and hypotension (serious).** Alcohol or cotherapy with other vasodilators may augment hypotension. Treat by recumbency.
3. **Tachycardia (frequent),** but unexplained bradycardia occasionally occurs in MI.
4. **Facial flushing, dizziness, halitosis (sublingual).**
5. **Methemoglobinemia** treat by IV methylene blue (1-2mg/kg).

**Nitrates: Drug-Drug interaction:**
The chief drug interaction of nitrates are PDE5.

- Hypotensive interaction.
- Heparin resistance.
- Beneficial interaction with hydralazine.
**Hypotensive interaction:**

1- Interaction with PDE-5 inhibitors (Sildenafil, Tadalafil, and Vardenafil). ED is often treated by one of these drugs, which are also systemic vasodilators, and can all cause serious hypotension when combined with nitrates because they inhibit the breakdown of cGMP.

2- Triple therapy of angina (Nitrate, B-Blocker, and CCB) each drug can predispose to excess hypotension.

3- ACEIs and nitrates in early phase (MI).

**Heparin Resistance:**
Nitroglycerin can produce heparin resistance with relatively high dose infusions. With lower doses, or with ISDN, no resistance will found.

**Beneficial interaction with hydralazine:**
Hydralazine helps to lessen nitrate tolerance, probably acting through inhibition of free radicals. This may explain why the combination of nitrates and hydralazine is effective in heart failure.

**Nicorandil:**
Nicorandil is acting chiefly by dilation of the large coronary arteries, as well as by reduction of pre- and afterload. It has a double cellular mechanism of action, acting both as a potassium channel activator and having a nitrate-like effect.

**Others:**

1- pFox inhibitors.
2- Ranolazine.
3- Trimetazidine.

**Ivabradine:**
An inhibitor of the sinus node pace making current owes to heart rate reduction avoiding drawbacks of b-blockers therapy such as depressed contractility and bronchoconstriction.

**B-Blockers: Mechanism of action**

1. Decrease myocardial O₂ consumption (inhibit myocardial contractility and heart rate).
2. Improve blood and O₂ supply to ischemia area (lower heart rate, prolong diastolic perfusion time, and increase endocardium flow).
3. Promote O₂ to dissociate from HbO₂.

**Partial Fatty Acid Oxidation (pFox) Inhibitors:**
Ranolazine (Ranexa).

- For chronic angina, acute coronary syndromes (ACS). And long term prevention of ACS.
- Acts by partially inhibiting fatty acid oxidation in the myocardium, thus shifting metabolism to glucose that requires less oxygen to metabolism.
- No hemodynamic effects.
- QT prolongation and testicular toxicity are possible toxicities.