Drug Therapy of Angina

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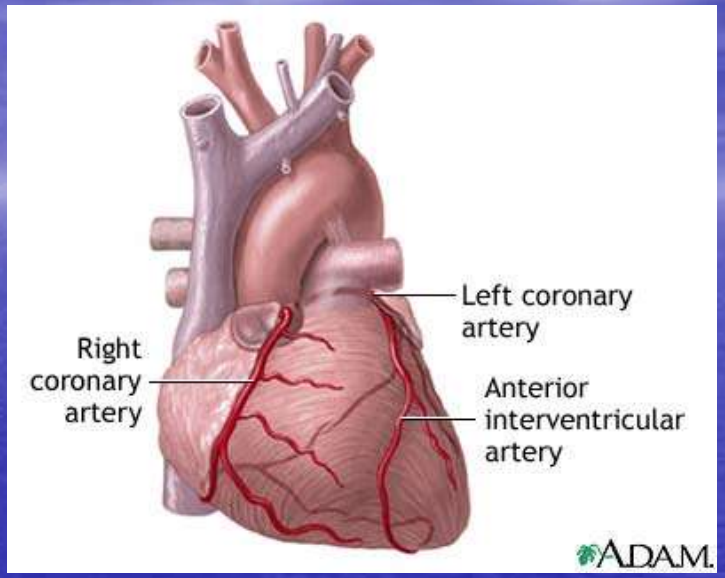
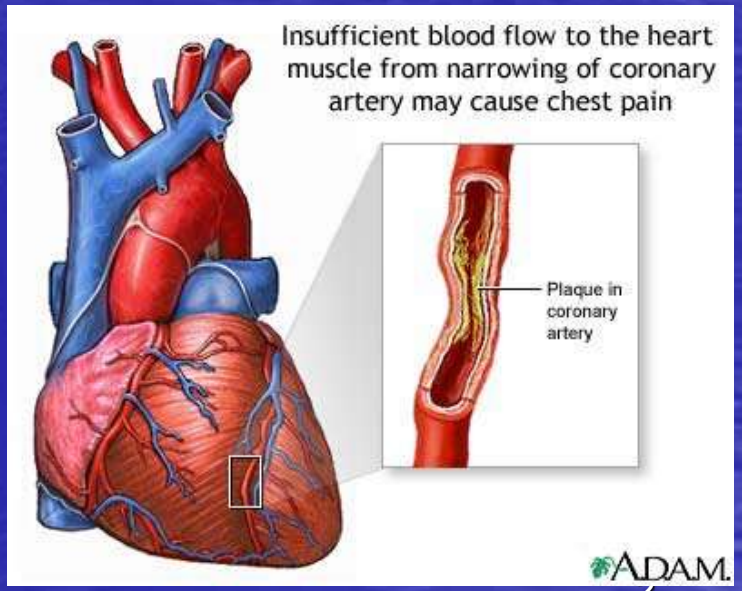
Angina Pectoris

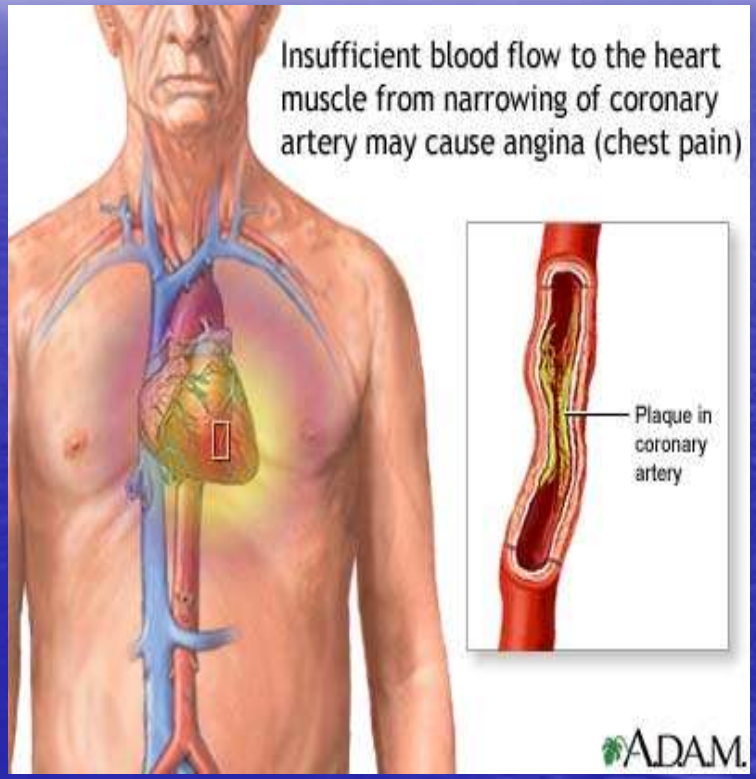
- **Angina** is **a specific type of pain in chest** caused by **inadequate blood flow through blood vessels (coronary vessels)** of **heart muscle (myocardium)**





Angina pectoris

- Angina pectoris is characterized by **retrosternal chest pain** precipitated by **stress (physical or emotional)** & **relieved by rest** or **sublingual nitrate**



Pathophysiology of angina pectoris

- Angina occurs due to **imbalance between myocardial oxygen demand** & **myocardial oxygen supply**

Pathophysiology of angina pectoris

- **Myocardial oxygen demand depends on:**
- **Preload** (volume & pressure of ventricles at end diastole; related to venous return)
- **Afterload** (pressure at ventricles at end systole; related to vascular resistance)
- **Myocardial contractility**
- **Heart rate**

Pathophysiology of angina pectoris

- Myocardial oxygen **supply** is determined by **blood flow in coronary circulation**
- **The most frequent cause of angina** is **atherosclerosis of a large coronary artery (classic angina)**
- **Transient spasm of a coronary artery** can also produce ischemia **(variant angina)**

- **Stress**, whether physical or emotional, **increases sympathetic tone** resulting in **increase in oxygen demand** without proportional concomitant increase in coronary blood flow due to atherosclerosis. This imbalance will result in **ischaemia & anginal attacks on effort**
- **In variant angina**, oxygen supply to heart decreases as a result of **spasm in coronary vessels (Prinzmetal's angina)**

Types of Angina

Stable angina	Unstable angina	Prinzmetal's angina
Precipitated by stress (emotional, exercise)	At rest (or with less effort)	At rest Due to coronary artery spasm
Pain is relieved by rest or nitroglycerin	Is not relieved by rest or nitroglycerin	Relieved by nitroglycerin, CCBs

Lines of Treatment

1. General measures

- **Risk factors** control as diabetes, obesity, hypertension, hyperlipidaemia, smoking
- **Associated conditions** as anaemia, valvular heart disease should be corrected

2. Drug therapy

- Organic nitrates
- Beta-blockers
- Calcium channel blockers (CCBs)

3. Other measures

- **PCA** (Percutaneous coronary angioplasty)
- **Grafting** (Aorto-coronary bypass grafting)
- **Aspirin 75 mg daily**

- **Angina can be relieved by:**
  - **Decreasing oxygen demand** or by
  - **increasing coronary blood flow**

- **Oxygen demand can be reduced** by **decreasing cardiac work**
- **Coronary blood flow** may be increased by **vasodilation**

- The available useful drugs in angina, **nitrates, beta-blockers & CCBs decrease myocardial oxygen demand**

- **In variant angina, nitrates & CCBs** may also **increase oxygen supply** by reversing coronary artery spasm

Organic nitrates

- They cause rapid reduction in myocardial oxygen demands, followed by rapid relief of symptoms
- These include:
- **Glyceryl trinitrate** (GTN, nitroglycerin; **Angesid**) **($t_{1/2}$ 3 min)**
- **Isosorbide dinitrate (Isoket) ($t_{1/2}$ 20 min)**
- **Isosorbide mononitrate (Isotard) ($t_{1/2}$ 4 hr)**

Pharmacodynamics of Organic Nitrates

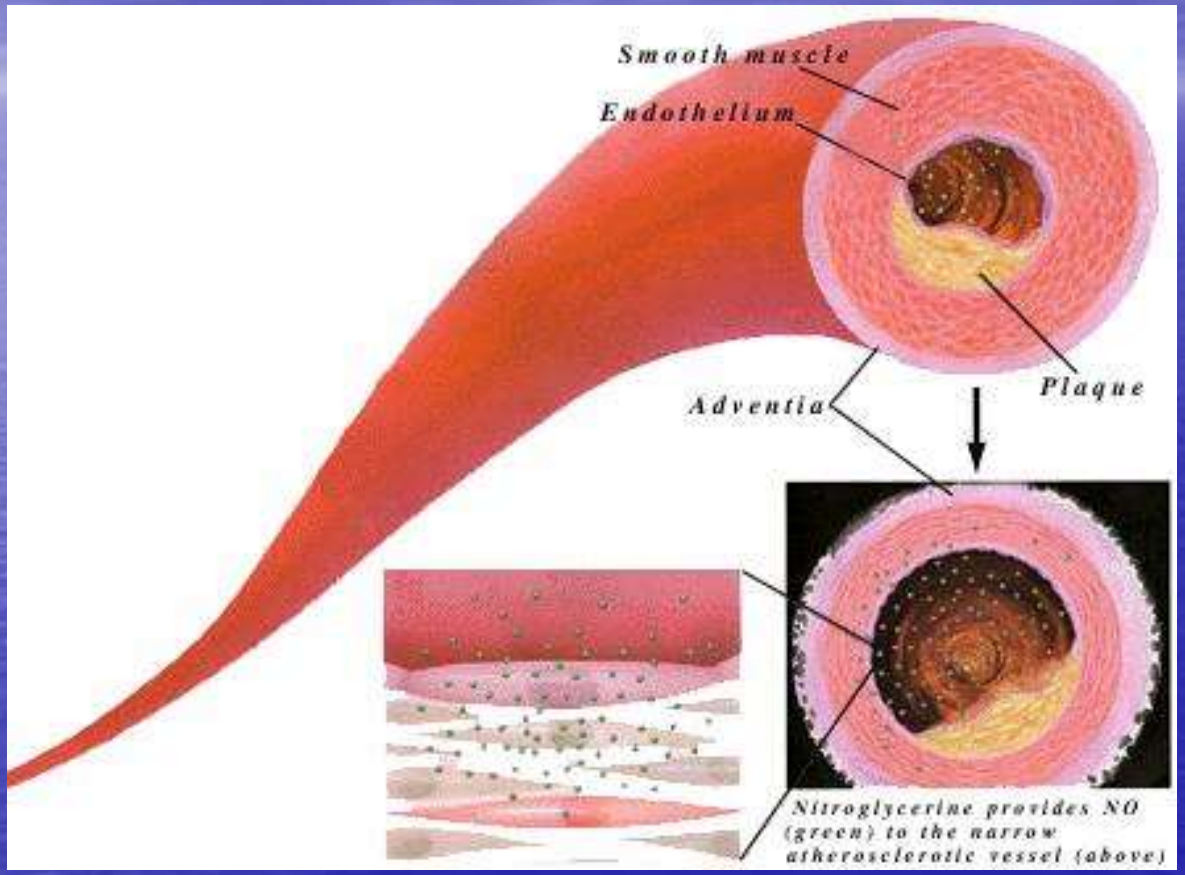
- **Organic nitrates relieve anginal chest** pain by **reducing cardiac work**

They reduce cardiac work by following mechanisms:

- **Venodilatation** resulting in:
  - **Venous pooling** & **decrease end-diastolic volume** & pressure (**preload**)
  - Leading to **decrease in cardiac output** resulting in
  - **Decrease O2 demand**
- **Arteriolar dilatation** resulting in**:**
  - Decrease **afterload** (Peripheral vascular resistance) & **decrease ABP**
  - **Decreasing O2 demand**

- **Organic nitrates** have **vasodilator action** due to their ability to **release nitric oxide (NO) in vascular smooth muscles**
- This **endothelial derived relaxing factor (EDRF) activates guanylate cyclase & increases cGMP** resulting **in vascular smooth muscle relaxation**
- **A reflex sympathetic** stimulation occurs that will **increase heart rate & contractility**

- **Organic nitrates relax all types of smooth muscles, vascular & non-vascular**
- including bronchial, GIT & GUT muscles. They also inhibit platelet aggregation


Smooth muscle
Endothelium
Plaque
Adventia
Nitroglycerine provides NO (green) to the narrow atherosclerotic vessel (above)

Routes of administration

- GTN is usually given **sublingual** to **relieve acute attacks** & **for prophylaxis against possible attacks**
- Nitrates are **highly lipid-soluble** with high 1st pass hepatic metabolism
- **When given sublingually**, produce rapidly its useful effects

- GTN can also be given **transdermally** as an **ointment** or **skin patch** to provide long term **prophylaxis against anginal attacks**
- They are **applied on skin during day** & **avoided during night**. **The application-free periods during the night are recommended to avoid tolerance to the drug**

- **Isosorbide dinitrate** can be used **orally** & **sublingually**
- **Isosorbide mononitrate** is given **orally** as it has high bioavalability

Duration of action

- **Sublingual GTN** — **30 min**
- **Transdermal GTN** — **10 hrs**
- **Sublingual isosorbide** — **60 min**
- **Oral isosorbide** — **6 hrs**

- **Tolerance** & cross tolerance may occur

Adverse effects of nitrates

- Headache
- Postural hypotension
- Tachycardia
- Flushing

Beta-blockers

- **Atenolol (Tenormin, Hypoten), metoprolol**
- **These agents have cardioprotective effects through their:**
  - **Negative inotropic effect**
  - **Negative chronotropic effect**
- **Decrease ABP**
- They will lead to **decrease O2 demand at rest & during exercise**

Beta-blockers

- **Beta-blockers** should be given **daily** for **prophylaxis against anginal attacks**
- **Sudden withdrawal of therapy should be avoided** because of risk of **precipitation of severe chest pains or even myocardial infarction** due to **upregulation of receptors** (increase number of receptors following continuous inhibition by the antagonist)

Beta-blockers are contraindicated:

- Asthma
- Diabetes
- Severe bradycardia
- Peripheral vascular disease
- Chronic obstructive pulmonary disease (COPD)

Calcium channel blockers

- **Verapamil** (mainly affects myocardium)
- **Nifedipine** (mainly affects vascular smooth muscle)
- **Diltiazem** (intermediate in its action)

Calcium channel blockers

- **These vasodilator drugs prevent influx of calcium through slow Ca channels** during **phase 2** of action potential:
  - **This will reduce intracellular calcium**
  - **Leading to vasodilatation & direct –ve inotropic & chronotropic effects**
  - **These effects will reduce O2 demand & afterload**

Calcium channel blockers

- Calcium channel blockers are useful in **prophylaxis of classic angina pectoris** & **treatment of acute variant angina attacks**

Indications of Ca channel blockers in angina

- **Alternative** to **beta-blockers** in presence of **contraindications** to them
- **With beta-blockers in resistant angina using nifedipine**
- **Prinzmetal's angina due to acute coronary spasm**

General Remarks

- **Classic effort angina** is associated with **ST segment depression & T-wave inversion**
- **Prinzmetal's angina** manifests as severe chest pain associated with transient reversible **ST segment elevation**

Myocardial Infarction

- **Initial management:**
  - Oxygen
  - Morphine or diamorphine (slow i.v)
  - Metoclopramide
  - Aspirin 300mg
  - Clopidogrel (Plavix)
  - Percutaneous coronary angioplasty
  - Thrombolytic drugs: Streptokinase, or alteplase

- Heparin
- Nitrate
- Beta-blockers
- ACE inhibitors or angiotensin-II receptors antagonists

- **Long-term management:**
  - Aspirin 75mg daily
  - Clopidogrel
  - Aspirin plus warfarin (cannot tolerate clopidogrel)
  - Beta blockers (acebutol, metoprolol, propranolol)
  - Diltiazem or verapamil (cannot use B-blockers)
  - ACE inhibitors or angiotensin II receptor antagonist
  - Statins