Part 3: Ischemic heart disease and antianginal drugs

Basic information

Ischemic heart disease includes:

- **Chronic stable angina (Classic; exertional angina):**
  - It is due to atheromatous narrowing of the coronary artery.
  - Pain is induced by effort and disappears with rest.

- **Acute coronary syndromes (ACS):**
  - ***Unstable angina:*** It is due to rupture of atheromatous plaque and formation of thrombus. The patient experiences acceleration in the frequency or severity of chest pain, or new-onset angina pain.
  - ***Myocardial infarction:*** An intraluminal thrombus completely occludes the epicardial coronary artery at the site of plaque rupture leading to irreversible coagulative necrosis.

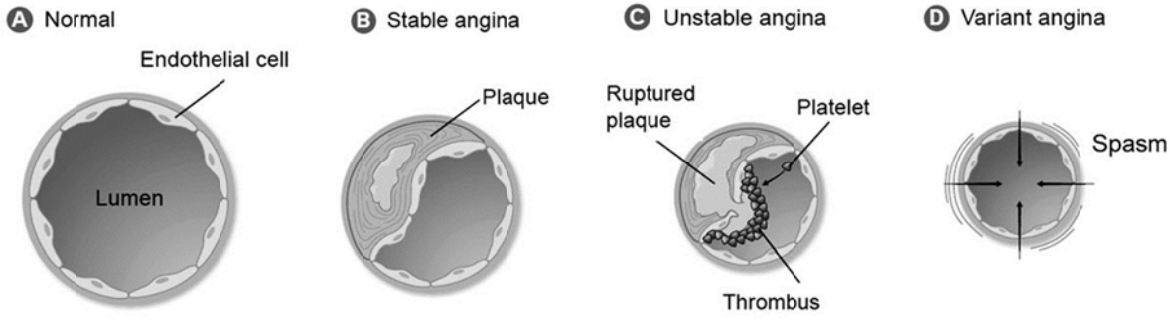
Afterload: it is the resistance that the ventricles must overcome to eject blood during systole. It is mainly determined by the resistance of the arterial side.

Preload: the stress (stretch) of the ventricular wall caused by venous filling just before contraction (also known as end-diastolic pressure). It is mainly determined by the amount of venous return (VR).

N.B. veins are capacitance vessels; venodilatation leads to decrease VR and preload.

- **Prinzmetal's angina (Variant angina; angina of rest; α-mediated angina):**

  The coronary artery undergoes severe spasm due to overactivity of α_1 receptors. The patient develops pain at rest.



Chronic stable angina

Definition: retrosternal pain due to ischemia of the myocardium as a result of imbalance between heart work *(O_2 demand)* and coronary blood flow *(O_2 supply)*.

Clinical picture:

Central chest pain is the cardinal symptom:

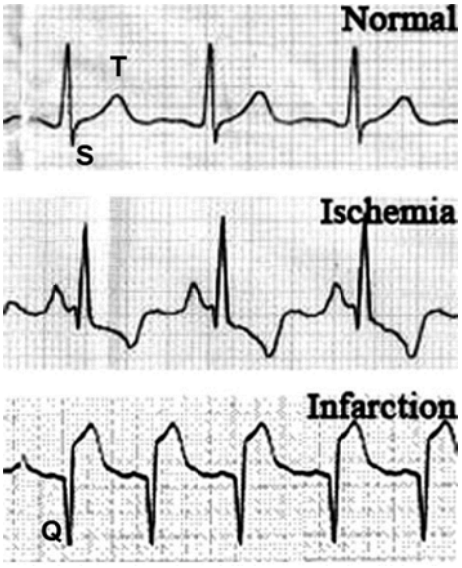
- Site and radiation: retrosternal, radiating to the left shoulder and the left arm.
- Character: any character *(usually sense of chest tightness)*.
- Precipitated by 3E: **e**xertion, **e**motion, **e**ating, and relieved by rest and nitrates.
- Duration: usually < 10-15 min. If longer than 15 min → suspect ACS.

Diagnosis:

- **ECG:**
  - Resting 12-lead ECG: this is often normal *and does not exclude ischemic heart disease.*
  - During attack: there is ST segment depression and T-wave inversion.
  - In myocardial infarction: ST elevation and deep Q-wave.
- **Exercise ECG:** recording ECG under controlled physical effort to record ischemic changes.
- **Nuclear isotope stress imaging.**
- **Coronary angiography.**

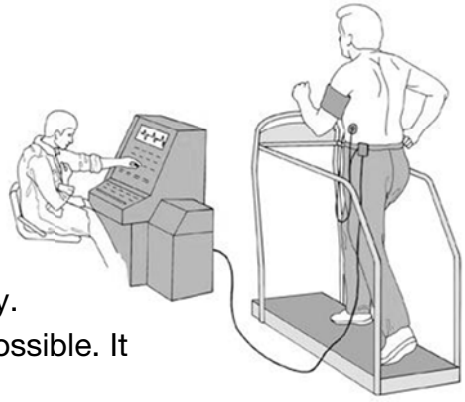
Guidlines

- Do not use people's response to glyceryl trinitrate (GTN) to make a diagnosis.
- Refer people to hospital as an emergency if an ACS is suspected.
- Do not exclude an ACS when people have a normal resting 12-lead ECG.
- Do not routinely administer oxygen. Only offer oxygen to:
  - People with arterial oxygen saturation (SaO2) < 92%.
  - People with COPD.



Management of stable angina

- **Non-drug therapy = life style modification:**
  - The same as hypertension (see before).
- **Pharmacological therapy:**
  - **Immediate treatment of acute chest pain:**
    - Glyceryl trinitrate (GTN): sublingual or spray.
    - Aspirin 300 mg loading dose as soon as possible. It reduces the risk of progression to MI.
    - Refer the patient to hospital if an ACS is suspected.
  - **Long-term therapy:**



- Beta-blockers: the first-line agents for chronic stable (exertional) angina.
- CCBs: the second-line agents for chronic stable angina
- Long and intermediate acting nitrates.
- pFOX inhibitors: trimetazidine
- Newer antianginal drugs: ranolazine and nicorandil
- Lipid lowering drugs: statins (see chapter 6).
- Antiplatelet drugs: e.g. aspirin, clopidogrel (see pharmacology of blood).

- **Surgical treatment (myocardial revascularization).**

Organic nitrates and nitrites

Classification

	Dose	Onset	Duration
Short-acting nitrates:			
Amyl nitrite crushable ampoules	0.3 ml inhalation	1-2 min	5-10 min
Glyceryl trinitrate tablets or spray	0.5 mg SL	1-5 min	10-20 min
Isosorbide dinitrate	5 mg SL	3-5 min	60 min
Glyceryl trinitrate (Tridil®)	5 µg/min i.v.i.		
Intermediate-acting nitrates:			
Isosorbide dinitrate	10 mg oral	15 min	3-6 hrs
	40 mg oral SR	30 min	6-10 hrs
Long-acting nitrates:			
Isosorbide mononitrate	20 mg oral	30 min	6-8 hrs
	60 mg oral SR	30 min	6-10 hrs
Transdermal patches		30 min	12-18 hrs

Pharmacokinetics

Absorption: nitrates are rapidly absorbed from all sites of administration.
Metabolism: in the liver:

- If given oral → **extensive first-pass** metabolism (oral bioavailability <10%)
- If given sublingual → **no first-pass** metabolism → high bioavailability.
- Mononitrate: has **no hepatic metabolism** → long duration of action.

Excretion: via the kidney.

Mechanism of action

- Nitrates cause formation of the free radical **nitric oxide (NO)** which is identical to the endothelial derived relaxing factor **(EDRF)** → ↑ cGMP → VD (more on veins than arteries).
- They also ↑ formation of vasodilator PGE2 and PGI_2.

Pharmacological effects

CVS: Blood vessels:

- VD of the venous (and to lesser extent the arterial) side leading to ↓ preload and ↓ afterload → ↓ cardiac work.
- VD of coronary arteries leading to increased coronary blood flow.
- VD of arteries in the face and neck leading to *flushing of the face.*
- VD of meningeal arteries leading to *throbbing headache*.

Heart: Reflex tachycardia (in high dose) 2ry to ↓ BP.
BP: High doses cause ↓↓ in both systolic and diastolic BP.

Smooth ms: Relaxation of all smooth ms (bronchial, GIT, uterine, and biliary).

Respiration: Reflex tachypnea due to hypotension in **high** doses.

Blood: Methemoglobinemia in **high** doses due to oxidation of Hb into met-Hb.

Therapeutic uses

- **Angina pectoris**

  Nitrates are used for treatment of all types of angina both for relieving the **acute** attack and for prophylaxis. The **mechanism** is due to:

  - Nitrates cause formation of the free radical **nitric oxide (NO)** which is identical to the endothelial derived relaxing factor **(EDRF)** → ↑ cGMP → VD (more on veins).
  - They also ↑ formation of vasodilator PGE_2 and PGI_2.

  These effects lead to:

  - Decrease cardiac work & myocardial O_2 demand through:
    - Venodilatation → ↓ venous return (preload = ↓ end-diastolic pressure).
    - Arteriolodilatation → ↓ peripheral resistance (afterload).
  - Enhancement of coronary blood flow (perfusion) through:
    - Coronary VD.
    - Redistribution of blood from large epicordial vessels to ischemic subendocardial vessels.

- **Myocardial infarction:** to ↓ the area of myocardial damage.
- **Acute heart failure:** to ↓ preload and afterload.
- **Treatment of cyanide poisoning:** see box

Adverse effects

- **Hypotension** and **reflex tachycardia:** may aggravate angina.
- **Throbbing headache:** due to VD of meningeal arteries.
- **Flushing** of the face.
- **Nitrate tolerance:** means diminished response to nitrates with continuous administration which cannot be corrected by increasing the dose. The exact mechanism is unclear but there are 2 theories to explain this:
  - Recent studies showed that continuous administration of nitrates leads to formation of **free radicals** of the reactive oxygen species (ROS) leading to oxidation and inhibition of the enzyme MALDH2 responsible for bioactivation of nitrites into the vasoactive NO.
  - Prolonged VD by nitrates leads to reflex sympathetic stimulation and activation of renin-angiotensin system → VC and salt & water retention.
  - Prevention of nitrate tolerance: make a daily **nitrate-free interval** (10–12 h) to give chance for bioactivating enzymes to regenerate. During this period, give another anti-anginal drug e.g. beta-blocker or CCBs.
- **Methemoglobinemia:** rare and require high doses.

Treatment of cyanide poisoning

Principle: cyanide has high affinity for metHb more than normal Hb.

- **Sodium nitrite** (300 mg i.v.) is given to convert part of Hb to metHb to attract cyanide ions and form cyan-metHb.
- **Sodium thiosulphate** (25 gm i.v.) is given to convert cyan-metHb to thiocyanate (non-toxic) → renal excretion.

Precautions during nitrate therapy

- Use the **smallest effective dose** to avoid hypotension and reflex tachycardia.
- The patient should **consult his doctor** if anginal pain does not improve after taking 3 SL tablets of GTN during 15 min (the pain may be due to MI).
- Nitroglycerine tablets should not be put in **direct sunlight** (light sensitive) or with **cotton** (to avoid formation of the explosive *nitrocellulose*).
- The **expiry date** should be checked (active tablets have **burning** taste).
- Nitrates should not be used with **sildenafil.** Why?

Beta-blockers

- Beta-blockers are considered first-line in **chronic exertional** (classic) angina *(note that short acting nitrates are the first line during the **acute** attack)*.
- Treatment objectives include lowering the resting HR to 50-60 beats/min and limiting maximal exercise HR to ~ 100 beats/min or less.

- There is little evidence to suggest superiority of any particular β-blocker, but β-blockers with ISA should be avoided because the reduction in HR and O2 consumption would be minimal.
- They are contraindicated in **Prinzmetal's (variant) angina** because they block the β_2-mediated coronary dilatation leaving the α_1 receptors unopposed → ↑ coronary spasm.

Mechanism of β-blockers in exertional angina

- They ↓ contractility, HR, and systolic BP → ↓ myocardial work and O_2 demand.
- They ↑ diastolic (coronary) filling time.
- Cause redistribution of blood from normal to ischemic (subendocardial) regions
- Cytoprotective effect: they produce metabolic switch from myocardial *fat* utilization to *carbohydrates* utilization (i.e. improves myocardial metabolism).

Combination of BBs and nitrates ↑ their efficiency & ↓ their side effects**:**

	β-blockers	Nitrates	Combination
– **HR**	↓	↑ (Reflex)	↓ or no effect
– **Contractility**	↓	↑ (Reflex)	↓ or no effect
– **Diastolic filling time**	↑	↓	↑ or no effect
– **Blood pressure**	↓	↓	↓↓

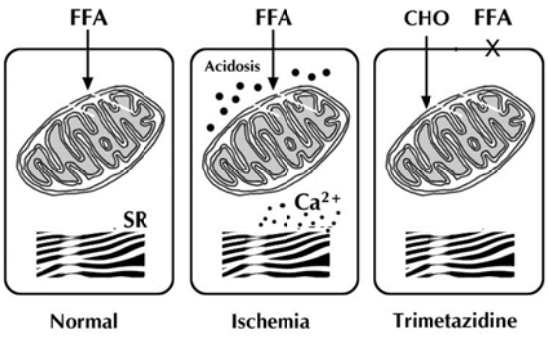
Calcium channel blockers (CCBs)

- They are considered first-line treatment for **Prinzmetal's** (variant) angina.
- They are considered second-line alternative after beta-blockers in chronic stable angina in whom beta-blockers are contraindicated.
- Short acting dihydropyridines are associated with increased risk of ACS and should be avoided. Long acting dihydropyridines (e.g. amlodipine) and non-dihydropyridines (verapamil and diltiazem) are more preferred.
- **Amlodipine** is the CCB of best choice for symptomatic treatment of angina and/or hypertension in patients with chronic heart failure.

Newer options for treatment of chronic angina

- **pFOX inhibitors, potassium channel openers,** and **ranolazine** are examples of new anti-anginal drugs. These drugs alter the balance between myocardial work and O2 supply by novel mechanism(s) of action.
- Their efficacy in treatment of angina is controversial; however they are approved for treatment of chronic stable angina **in combination** with β-blockers, CCBs, and nitrates.

pFOX inhibitors (metabolic modifiers): Trimetazidine



- They are termed pFOX inhibitors because they partially **inhibit fatty acid oxidation** in the myocardium.
- This "metabolic switch" from fats to carbohydrate utilization requires less O_2 consumption.
- By inhibition of fatty acid oxidation, they ↓ intracellular lactic acidosis leading to ↓ intracellular Ca^{2+} & Na^{+} accumulation and ion disturbance, so they prevent cell necrosis and preserve contractile function.
- It does not affect HR, blood pressure or coronary blood flow.

Potassium channel openers: Nicorandil

- Nicorandil is a new antianginal drug with 2 proposed mechanisms of action:
  - It opens ATP-dependent K^{+} channels in the vascular wall leading to VD of peripheral and coronary arteries.
  - Nitrate-like activity: it has a nitrate component and ↑ cGMP like nitrates but tolerance to its effects is less marked.
- Like nitrates, it should **not** be used with **sildenafil**.

Ranolazine

- It ↓ intracellular Ca^{2+} indirectly by reducing the late Na^{+} current that facilitates Ca^{2+} entry into myocardial cells. The reduction in intracellular Na^{+} and Ca^{2+} load reduces cardiac contractility and work.
- It does not affect HR, blood pressure or coronary blood flow.

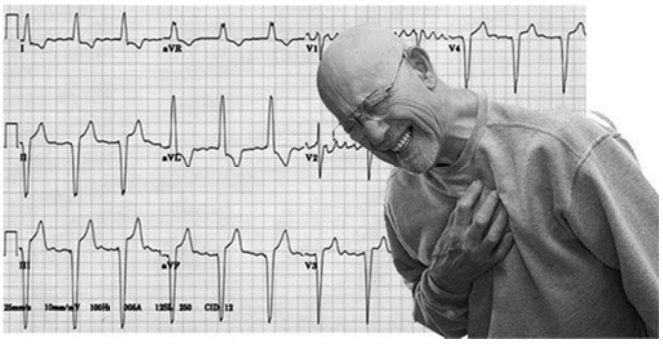
Antiplatelets and cholesterol lowering drugs: see pharmacology of blood.

Choice of antianginal drugs in patients with another disease:

Angina with….	Most preferred	Least preferred
Bronchial asthma	Nitrates, CCBs	Beta-blockers
Heart failure	Amlodipine	Beta-blockers, Verapamil
Hypertension	Beta-blockers, CCBs	Nitrates
Diabetes mellitus	Nitrates, Nifedipine	Beta-blockers, Verapamil

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION (AMI)

Manifestations: persistent central crushing chest pain + ST segment elevation or depression + pathological Q wave + raised biochemical markers of myocardial cell death (troponin enzyme).
All cases must be **hospitalized** in a specialized coronary care unit.



■ Non-pharmacologic therapy:

Patients presenting within 12 hours of symptom onset, the treatment of choice is percutaneous coronary intervention (PCI, or coronary angioplasty). A balloon catheter, guided by x-ray imaging, is introduced into the occluded artery to open it.

■ Pharmacologic therapy:

- **Morphine sulfate (5 mg i.v.):**
  - To produce analgesia and ↓ stress of the patient → ↓ sympathetic discharge and heart work.
  - Morphine causes venodilatation → ↓ venous return and cardiac work.
- **Oxygen:** recent evidence suggests that routine O2 administration has doubtful significance and did not reduce mortality.
- **Nitroglycerine** and **beta-blockers:** to limit the infarct size.
- **Anticoagulant drugs: heparin** 10,000 IU i.v. then 5000 IU/8h s.c. especially when the patient is obese or if there is history of previous MI.
- **Thrombolytic (fibrinolytic) therapy:** streptokinase, urokinase, or t-PA as early as possible (see blood).
- **Sedatives:** diazepam 5 mg i.v.
- **Treatment of Complications:**
  - Cardiogenic shock → dobutamine i.v.i
  - Arrhythmia → lidocaine i.v.

Morphine and AMI

Morphine is usually given s.c. but in AMI it is given **5 mg i.v.**

Morphine is contraindicated in cases of MI involving the inferior wall of the heart **(inferior MI)** because in this case, the patient has bradycardia and morphine causes **vagal stimulation** and aggravates bradycardia.

Meperidine is a good alternat-ive in cases of inferior MI because it has **atropine-like action** and counteract bradycardia.

What other opioid analgesics are contraindicated in AMI?

Pentazocin and **butorphanol** because they *increase pulmonary and systemic vascular resistance with more strain on the heart* (see CNS).