ANTIANGINAL DRUGS

LEARNING OUTCOMES

Recognize variables contributing to a balanced myocardial supply versus demand

Expand on the drugs used to alleviate acute anginal attacks versus those meant for prophylaxis & improvement of survival

Detail the pharmacology of nitrates, other vasodilators, and other drugs used as antianginal therapy

MINICASE

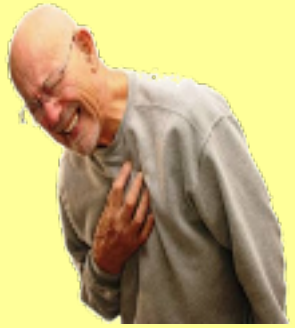
Helmi, a 62-year-old male smoker with type 2 diabetes mellitus and hypertension presents with a 4-month history of exertional chest pain. Physical examination shows a blood pressure of 152/90 mm Hg but is otherwise unremarkable. The ECG is normal, and laboratory tests show a fasting blood glucose value of 110 mg/dL, glycosylated hemoglobin 6.0%, creatinine 1.1 mg/dL, total cholesterol 160, LDL 120, HDL 38, and triglycerides 147 mg/dL. He exercises for 8 minutes, experiences chest pain, and is found to have a 2-mm ST-segment depression at the end of exercise.

MINICASE

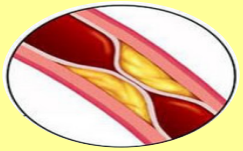
WHAT LIFE STYLE MODIFICATIONS SHOULD HELMI CARRY OUT?

Which signs or symptoms of Helmi suggest diagnosis of Angina Pectoris?

A clinical syndrome of chest pain (varying in severity) due to ischemia of heart muscle



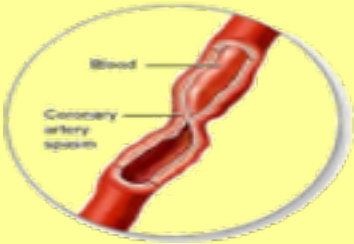
Pain is caused either by obstruction



Pain is due to (accumulation of metabolites K^+, PGs, Kinins, Adenosine….) secondary to the ischemia

"You say it's a sharp, stabbing pain. Hmmmm ... sharp ... stabbing pain."

Or spasm

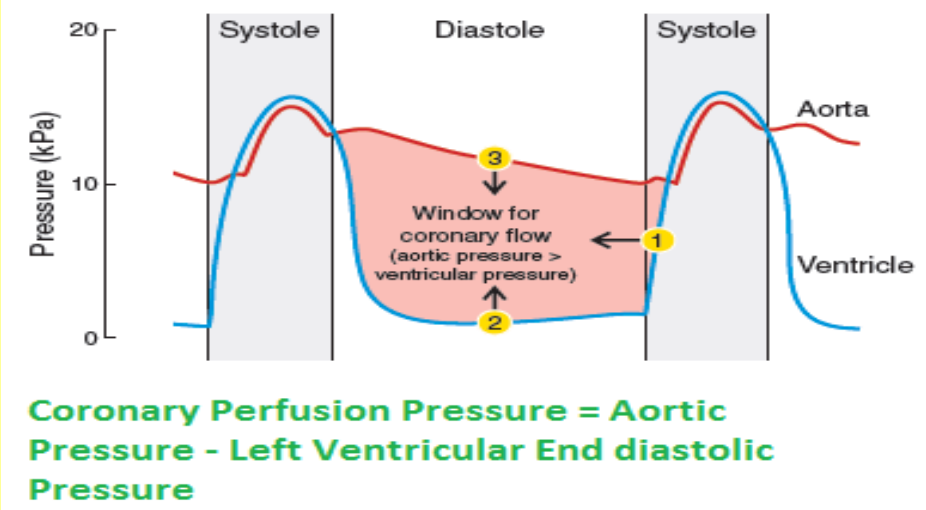


MINICASE

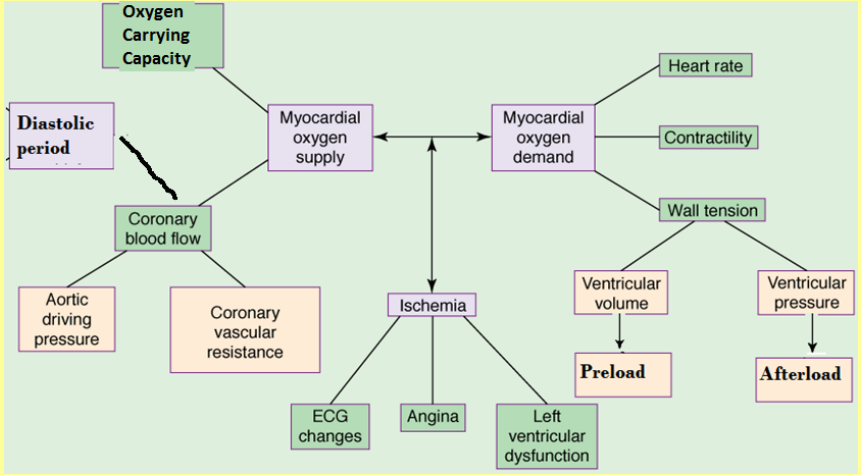
WHAT IS THE POSSIBLE UNDERLYING CAUSE OF HELMI'S EXERTIONAL PAIN?

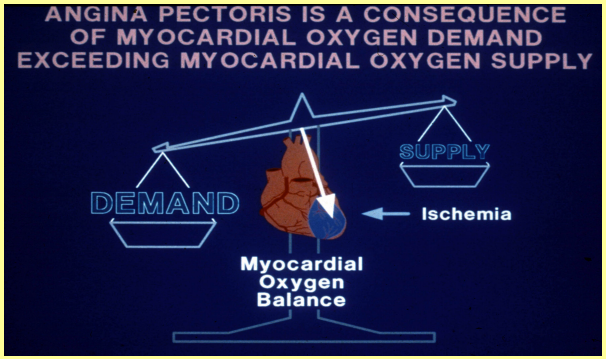
WHAT IS BASIC MECHANISM OF ANGIA PECTORIS?

WHAT ARE THE DETERMINANTS OF OXYGEN DEMAND AND SUPPLY?

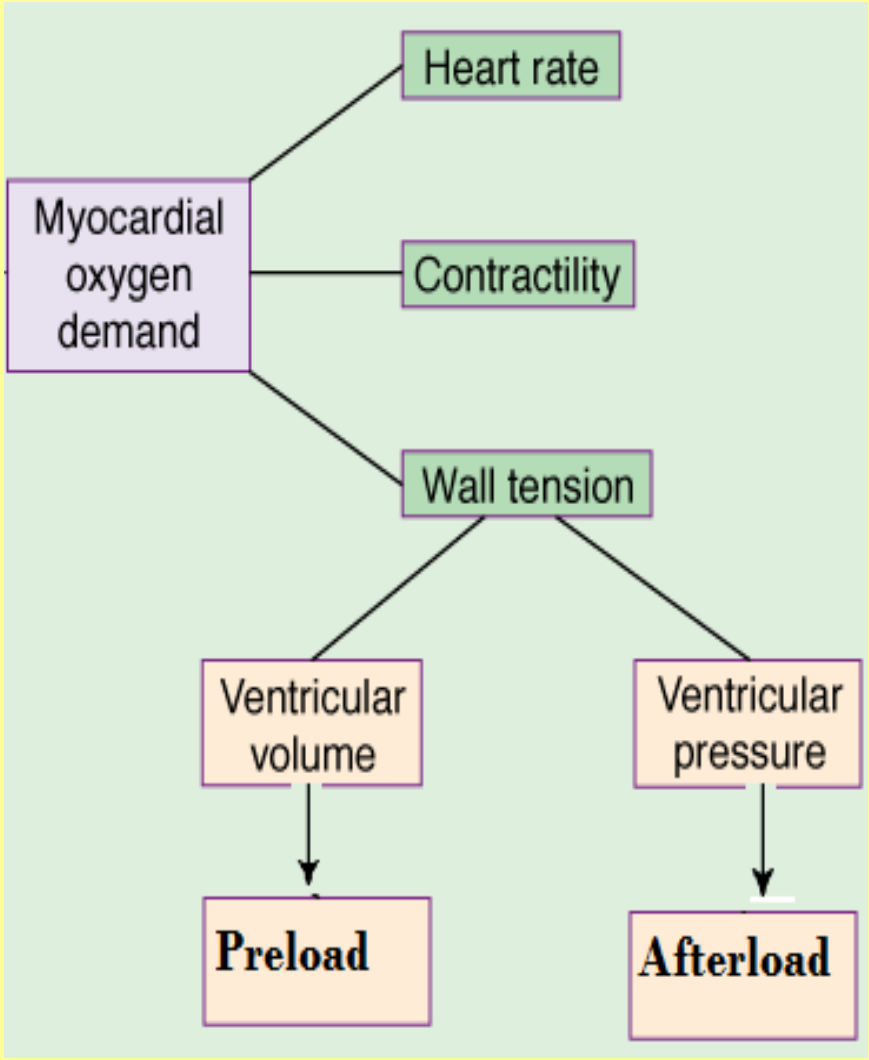


Coronary Perfusion Pressure = Aortic Pressure - Left Ventricular End diastolic Pressure





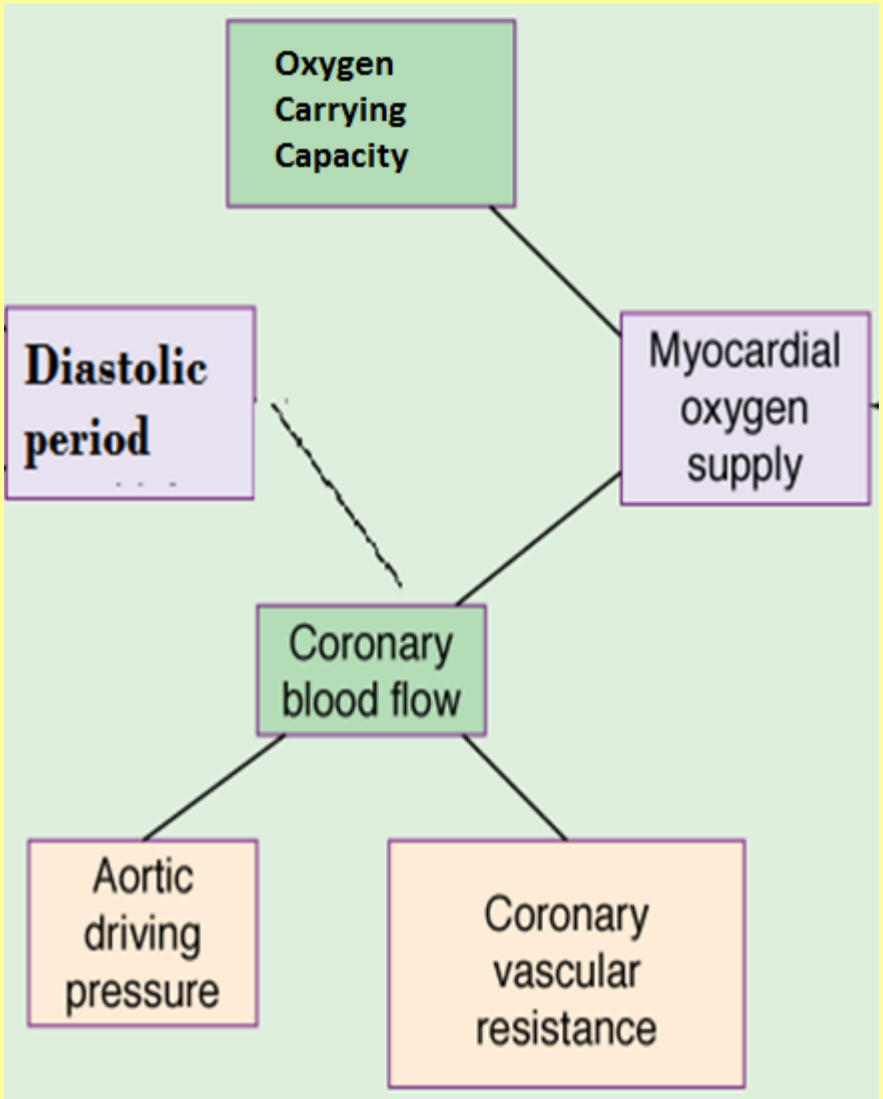
MYOCARDIAL OXYGEN DEMAND IS DETERMINED BY:-



MYOCARDIAL OXYGEN DEMAND IS DIMINISHED BY:-

Reducing contractility
Reducing heart rate
Reducing the preload
Reducing the afterload

MYOCARDIAL OXYGEN SUPPLY IS DETERMINED BY:-



MYOCARDIAL OXYGEN SUPPLY IS ENHANCED BY:-

Reducing coronary vascular resistance
Prolonging diastolic period
Reducing external compression
Dilating collateral vessels
Optimizing hemoglobin & RBCs

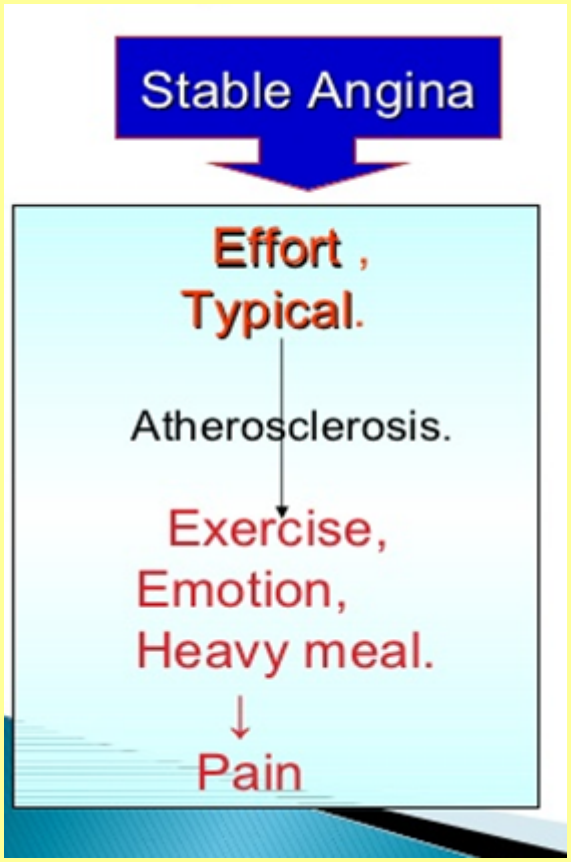
MINICASE

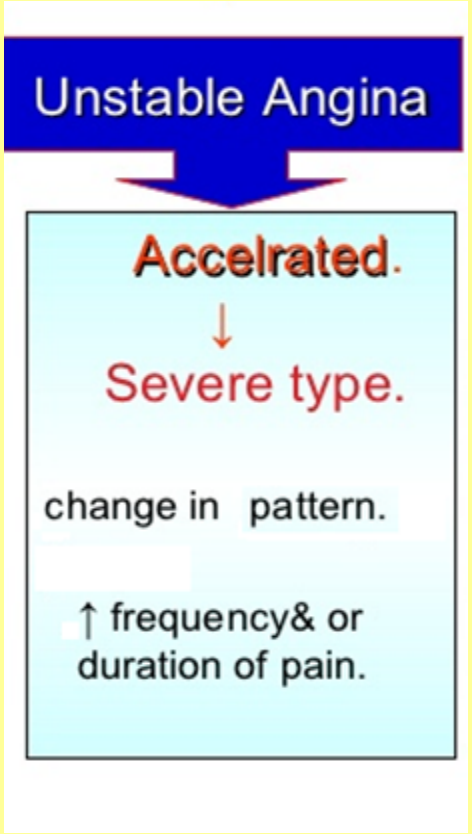
WHAT TRIGGERS THE ONSET OF SYMTOMS IN HELMI?

WHAT FACTORS WORSEN THE SYMPTOMS IN CASE OF HELMI?

WHAT IS THE POSSIBLE UNDERLYING CAUSE OF ANGINA IN HELMI?

Types of Angina Pectoris

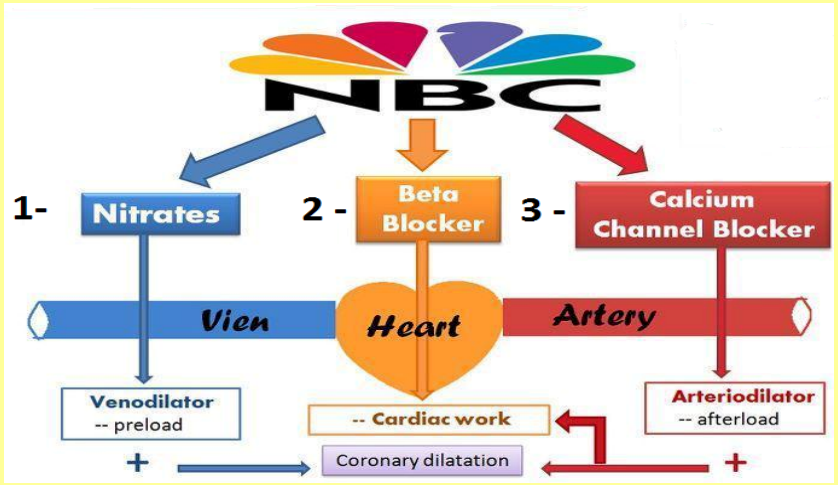




TREATMENT OF ANGIA PECTORS

1-Agents that improve symptoms & ischemia

Traditional Approach



New approaches

- Metabolic modulation (Trimetazidine)
- K+ channel openner (Nicorandil)
- Sinus node inhibition (Ivabradine)
- Late Na+ current inhibition (Ranolazine)

TREATMENT OF ANGIA PECTORS

2-Agents that improve prognosis

- Aspirin / Other antiplatelets
- Statins
- ACE Inhibitors
- β-AD blockers

ORGANIC NITRATES

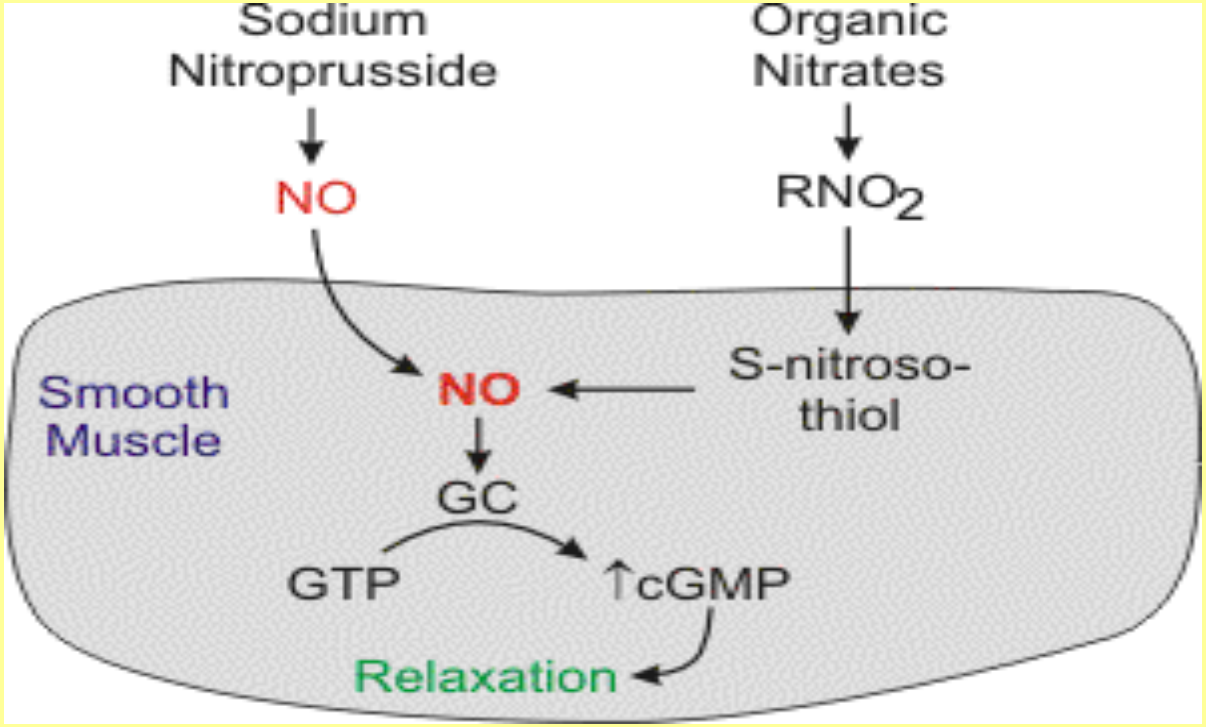
LONG ACTING

ISOSORBIDE MONONITATE

SHORT ACTING

NITROGLYCERIN

MECHANISM OF ACTION



Nitric oxide binds to guanylate cyclase in vascular smooth muscle cell to form cGMP.

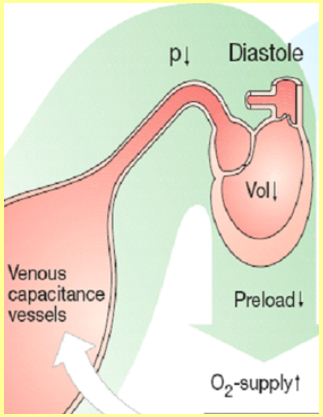
cGMP activates PKG to produce relaxation

HEMODYNAMIC EFFECTS OF NITRATES

Shunting of flow from normal area to ischemic area by dilating collateral vessels

Venous vasodilatation

↓ **Preload**

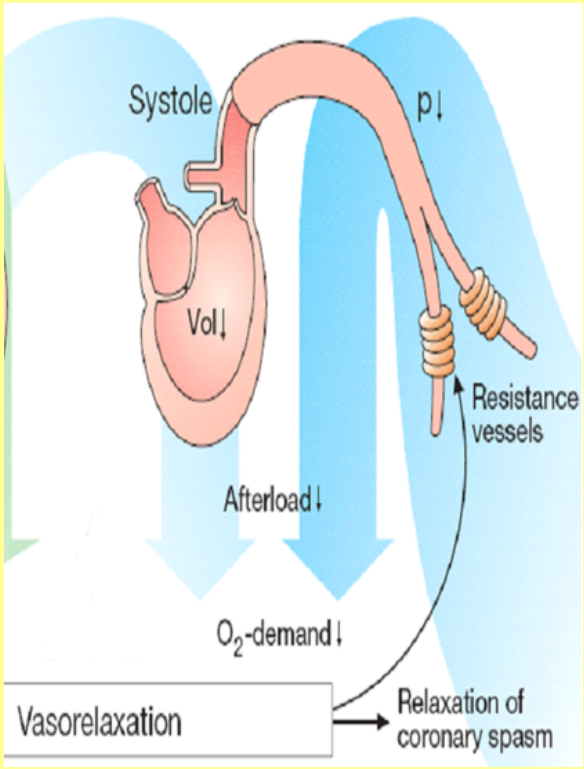


Coronary vasodilatation

↑ **Myocardial perfusion**

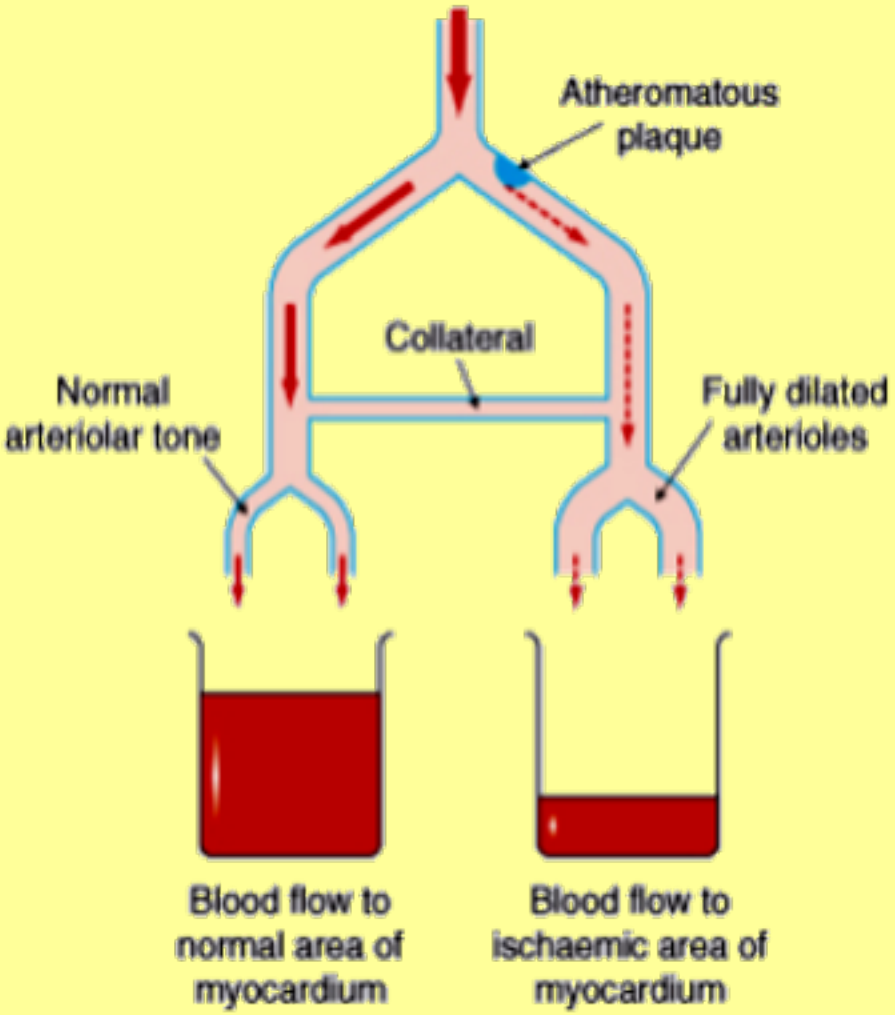
Arterial vasodilatation

↓ **Afterload**

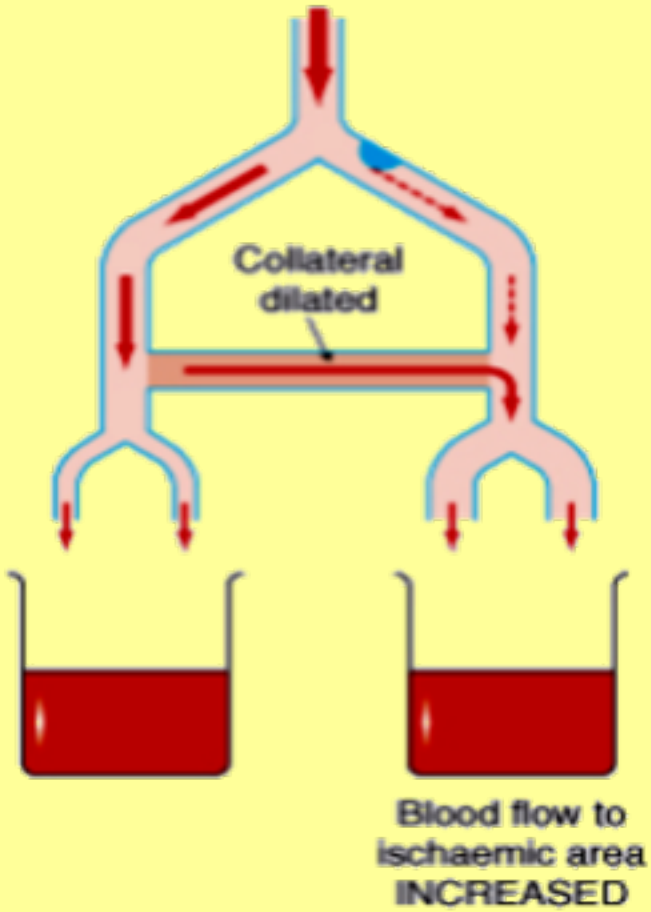


HEMODYNAMIC EFFECTS OF NITRATES

Shunting of flow from normal area to ischemic area by dilating collateral vessels



With Nitrates



THINK-PAIR-SHARE

Match the effects of nitrates in treatment of angina with their results

Effects

1-↓Ventricular volume

2-Reflex ↑ in contractility

3-↓Arterial pressure

4-↑Collateral flow

5-Reflex tachycardia

6-↓Left ventricular diastolic pressure

7-↓Diastolic perfusion time due to tachycardia

8-Vasodilation of epicardial coronary arteries

Results

A-↓ O2 demand

B-↑ O2 demand

C-Relief of coronary artery spasm

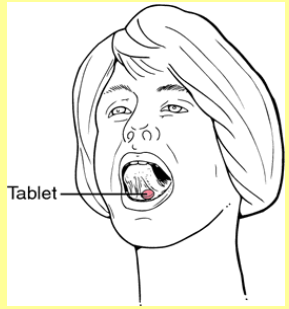
D-Improved perfusion to ischemic myocardium

E-Improve subendocardial perfusion

F-↓ myocardial perfusion

PHARMACOKINETICS

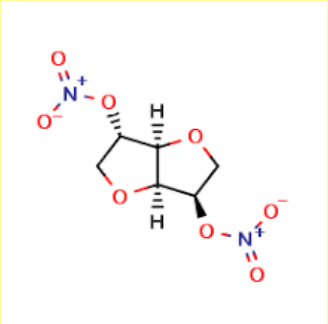
Nitroglycrin [GTN]



Significant first pass metabolism occurs in the liver (10-20%) bioavailability

Given sublingual or via transdermal patch, or parenteral

Oral isosorbide dinitrate & mononitrate



Very well absorbed . Mononitrate, 100% bioavailability

The dinitrate undergoes denitration to two mononitrates➔ both possess antianginal activity

($t_{1/2}$ 1-3 hours)

Further denitrated metabolites conjugate to glucuronic acid in liver. Excreted in urine.

INDICATIONS

IN STABLE ANGINA;

IN VARIANT ANGINA ➔ sublingual GTN

Prevention; Persistant prophylaxis ➔ Isosorbide mono or dinitrate

Heart Failure

Refractory AHF ➔ IV GTN

CHF ➔ Isosorbide mononitrate + hydralazine
[if contraindication to ACE Is]

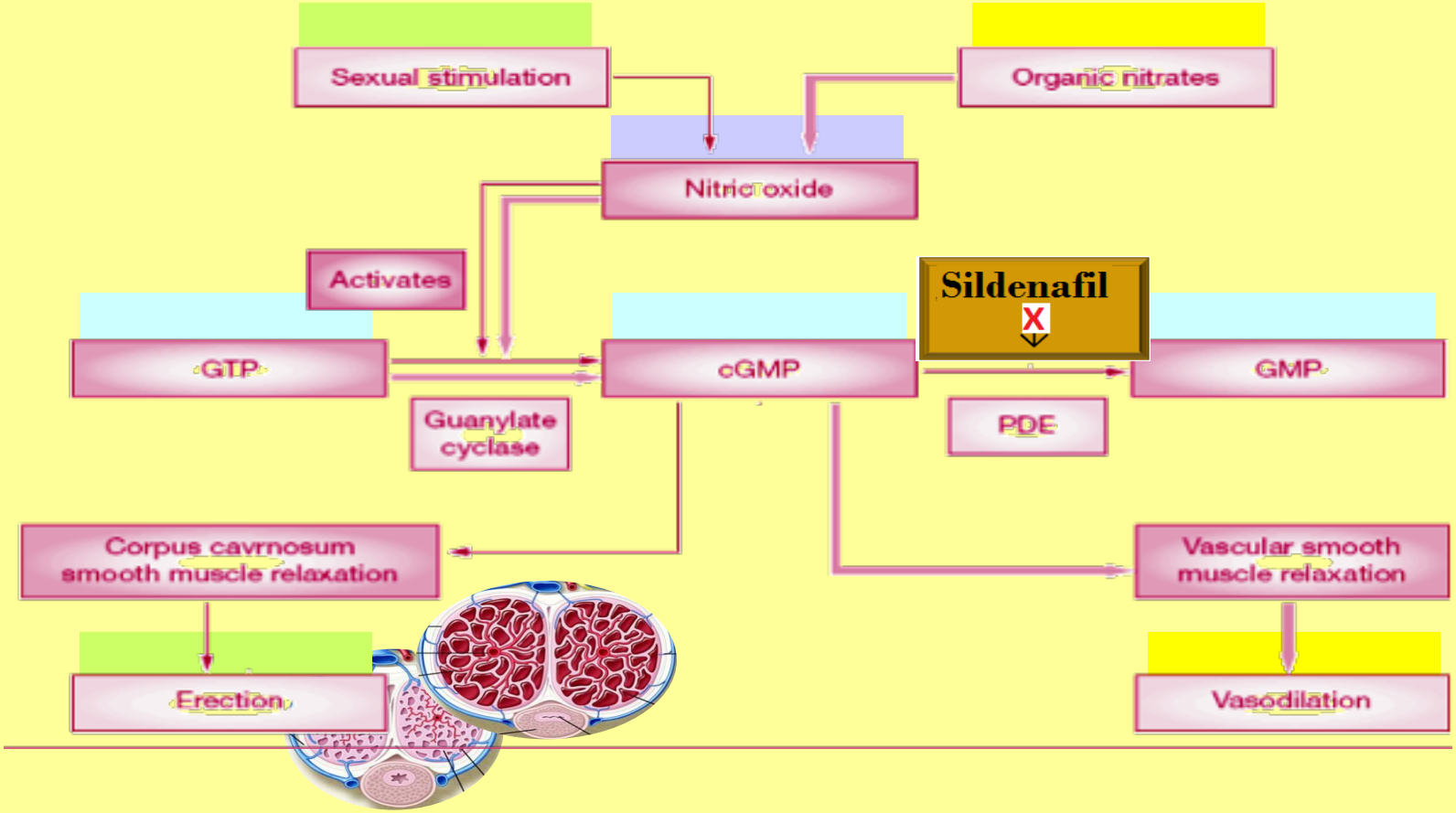
AMI ➔ IV GTN

CONTRAINDICATIONS

- Known sensitivity to organic nitrates
- Glaucoma; nitrates → ↑ aqueous humour formation
- Head trauma or cerebral haemorrhage , → Increase intracranial pressure.
- Uncorrected hypovolemia

CONTRAINDICATIONS

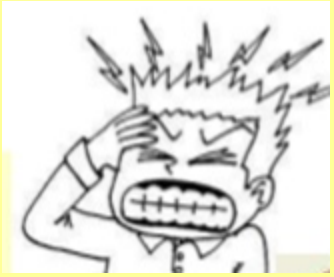
Concomitant administration of PDE_5 Inhibitors



Sildenafil + nitrates ➔Severe hypotension & death

ADVERSE DRUG REACTIONS

THROBING HEADACHE



FLUSHING IN BLUSH AREA

TACHYCARDIA & PALPITATION

POSTURAL HYPOTENSION, DIZZINESS & SYNCOPE

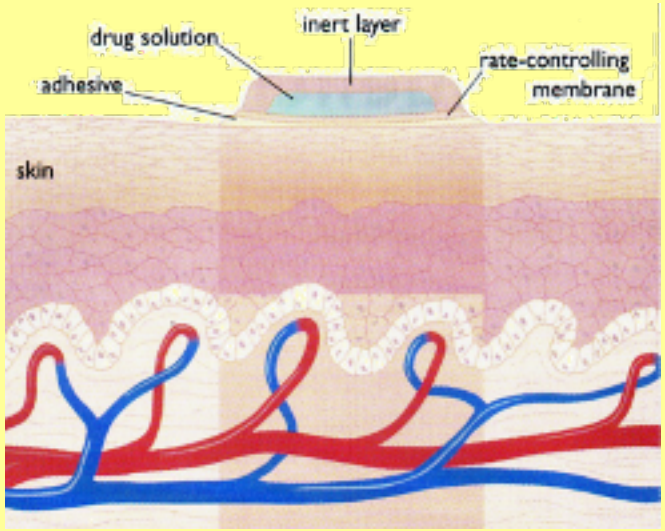
RARELY METHEMOGLOBINEMA

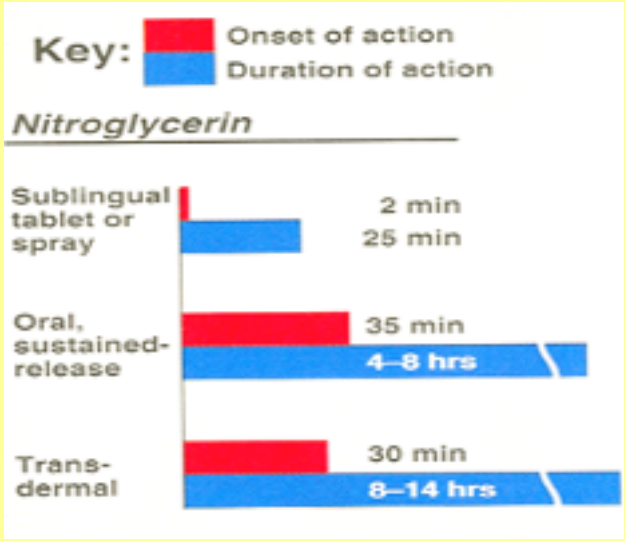
PREPARATIONS

Nitroglycerin

Sublingual tablets or spray

Transdermal patch





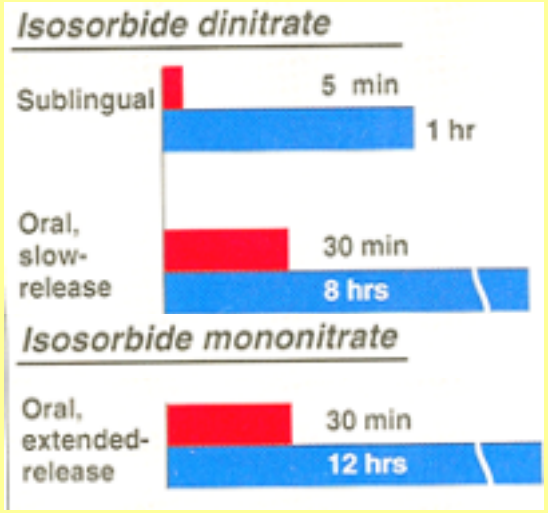
Oral or bucal sustained release
I.V. Preparations

PREPARATIONS

Isosorbide dinitrate

- Dinitrate Sublingual tablets
- Dinitrate Oral sustained release
- Infusion Preparations

- Mononitrate Oral sustained release



NITRATES TOLERANCE

Loss of vasodilator response of nitrates on use of long-acting preparations (oral, transdermal) or continuous intravenous infusions, for more than a few hours without interruption.

MECHANISM

1-Compensatory neurohormonal counter-regulation

2-Depletion of free-SH groups

MINICASE

If Helmi was prescribed nitrates & tolerance developed to its effect, how to overcome tolerance to nitrates?

Nitrate tolerance can be overcome by:

Smaller doses at increasing intervals (Nitrate free periods twice a day).

Giving drugs that maintain tissue SH group e.g. Captopril.

TASK- SELECTION OF A P-DRUG

Instructions:

1- Select a leader for your group

2- Discuss the case according to the steps shown in the sheet

3- Use your internet access to obtain evidence for efficacy, toxicity, convenience & cost.

4- Due to time constrains divide yourself into groups of five, each doing one search e.g. evidence for efficacy.

5- You have 10 minutes to do this and 1 minute to report to the class.