# 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, & other drugs used as antianginal therapy.

# MINICASE

Helmi, a 62-year-old male smoker with T2DM & hypertension presents with a 4-month history of exertional chest pain.

Physical examination shows a BP of 152/90 mm Hg but is otherwise unremarkable.

The ECG is normal, & 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, & triglycerides 147 mg/dL.

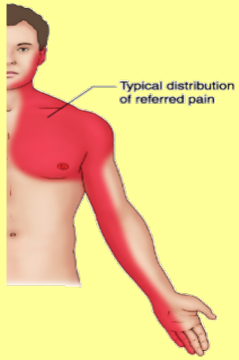
He exercises for 8 minutes, experiences chest pain, & is found to have a 2-mm ST-segment depression at the end of exercise.

# MINICASE

# WHAT LIFE STYLE MODIFICATIONS SHOULD HELMI CARRY OUT?

# Which signs or symptoms of Helmi suggest diagnosis of angina pectoris?

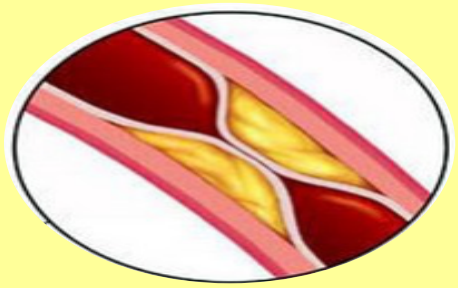
A clinical syndrome of chest pain (varying in severity) due to ischemia of heart muscle

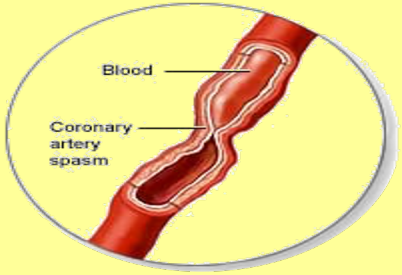



Pain is due to (accumulation of metabolites $K^+$, PGs, Kinins, Adenosine….) secondary to the ischemia

Pain is caused either by obstruction

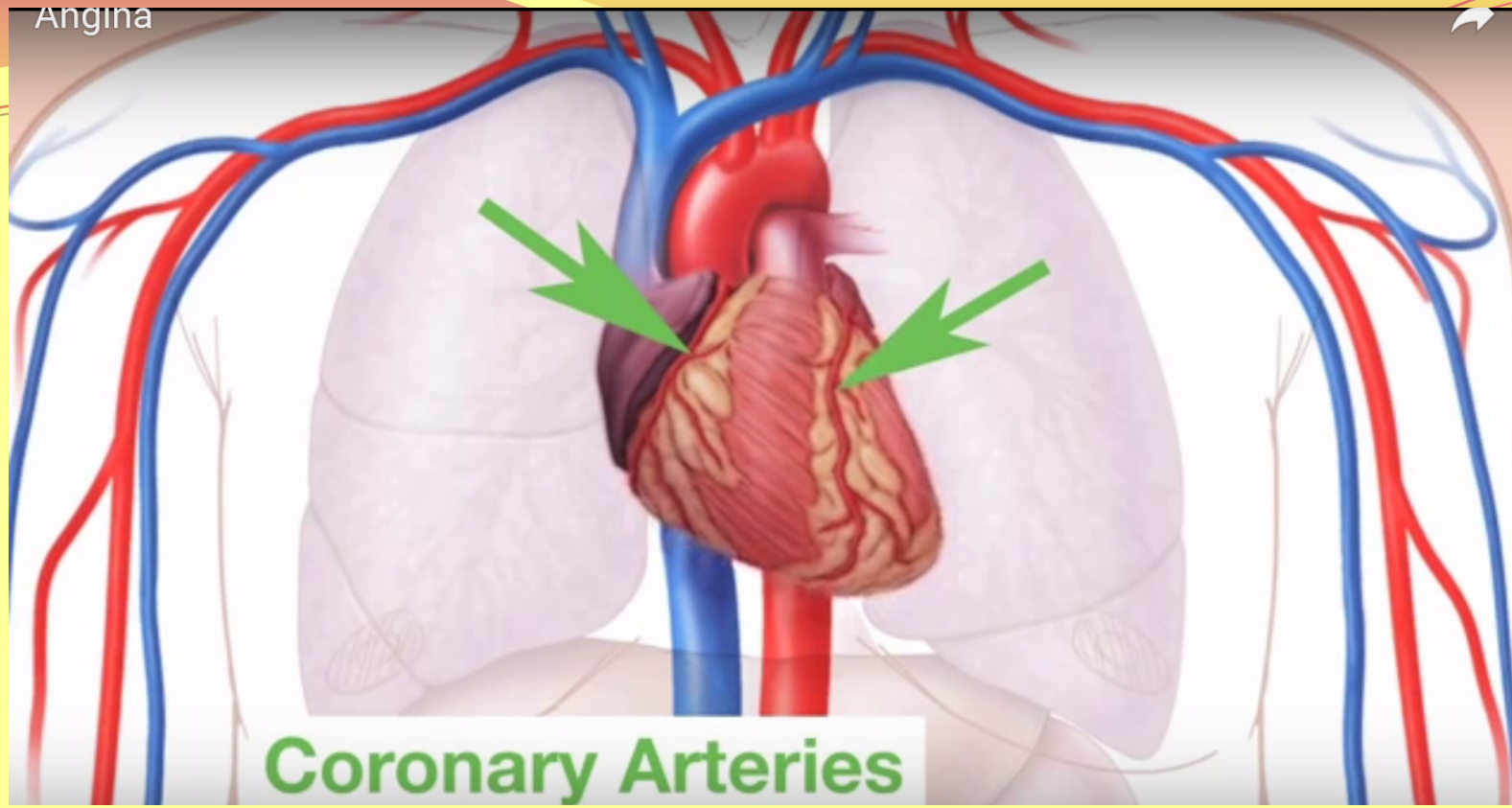
Or spasm






# MINICASE

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



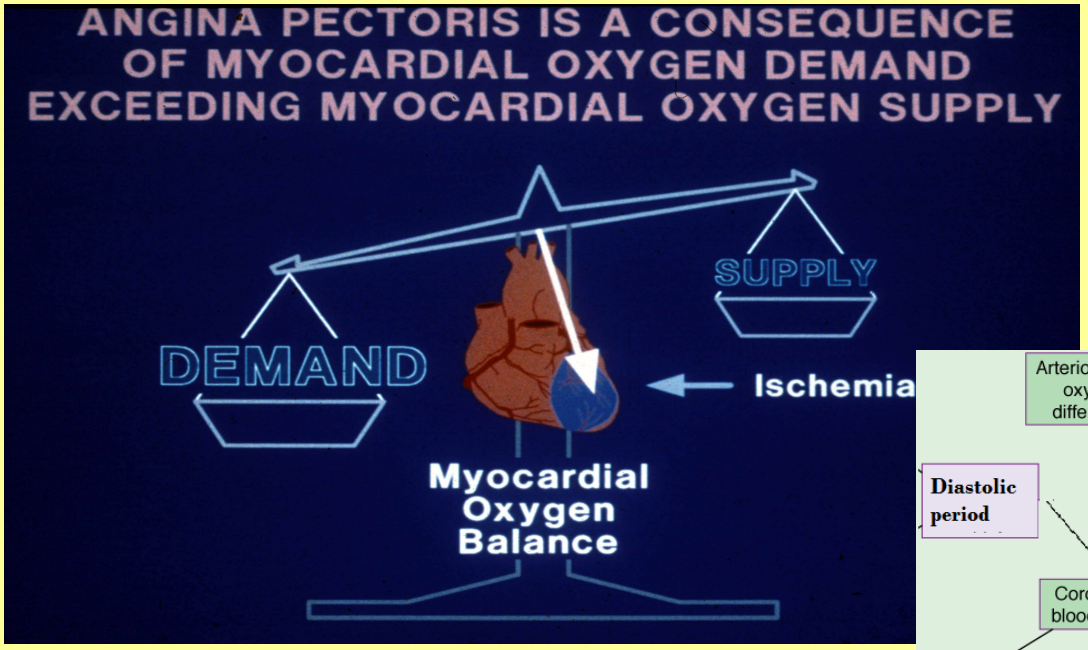

In Exercise

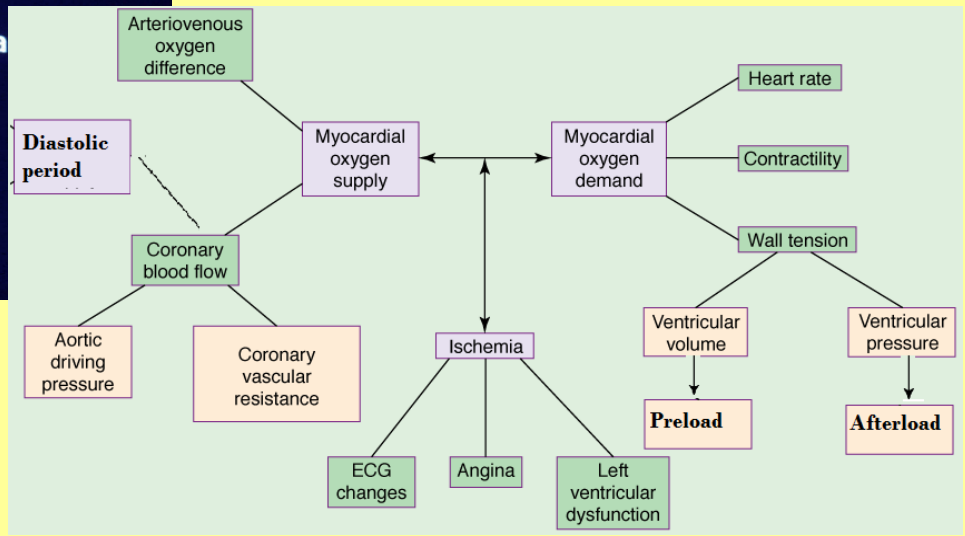
- Respiration in sk m ↑, Demand for O2 & glucose ↑, So CO has to ↑
- Greater amount of bld to be delivered to sk m (we need perfusion to ↑)

So we need to ↑ the amount of bld that go into the hrt (CO) to ↑ .

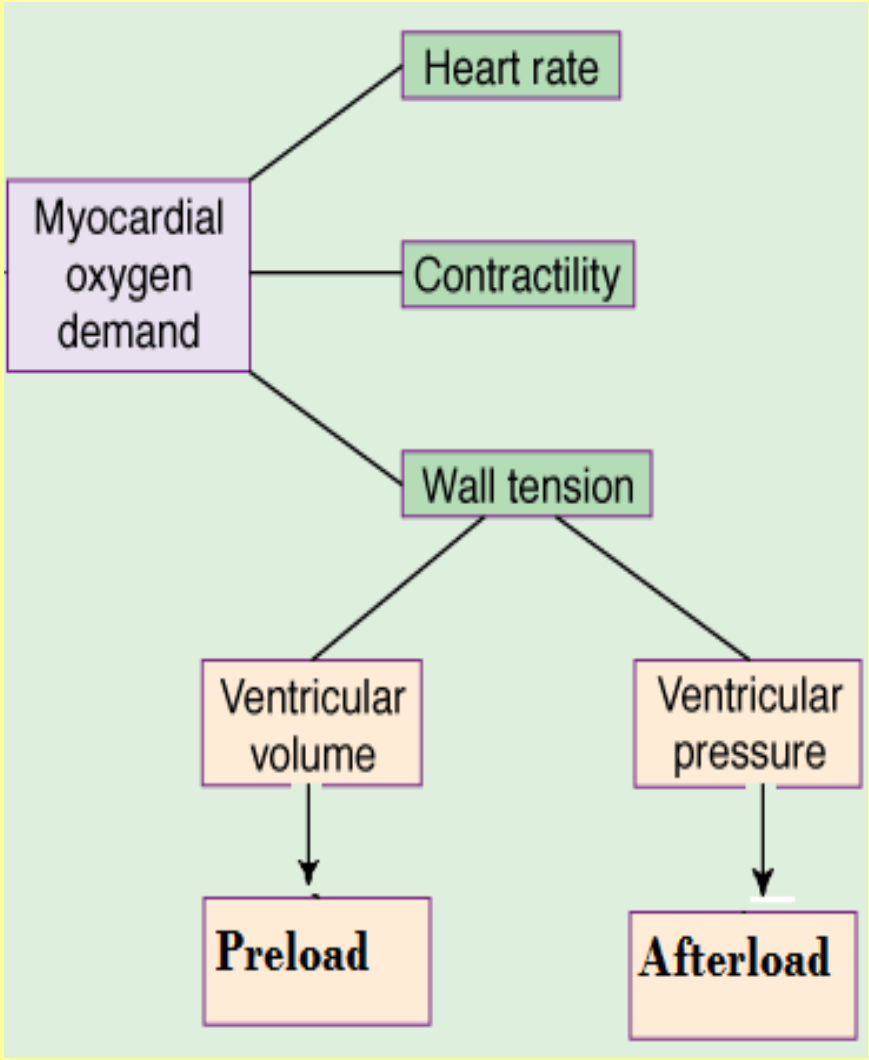
# WHAT IS BASIC MECHANISM OF ANGIA PECTORIS?

# WHAT ARE THE DETERMINANTS OF OXYGEN DEMAND & SUPPLY?



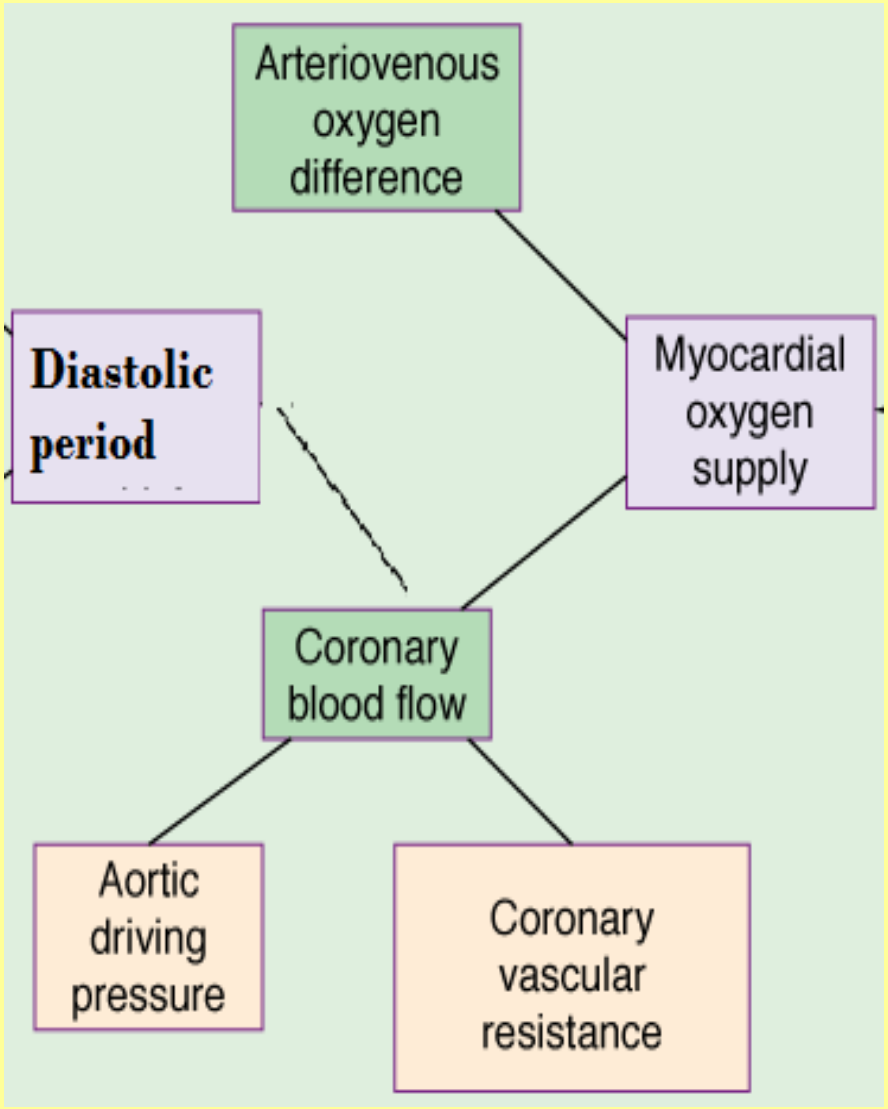
## MYOCARDIAL OXYGEN DEMAND IS DETERMINED BY:-




## 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

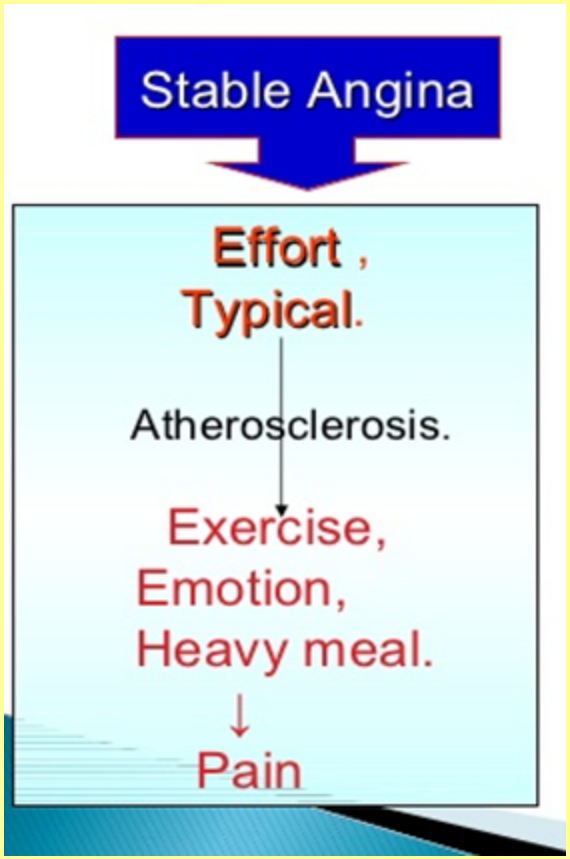
# MINICASE

WHAT TRIGGERS THE ONSET OF SYMPTOMS IN HELMI?

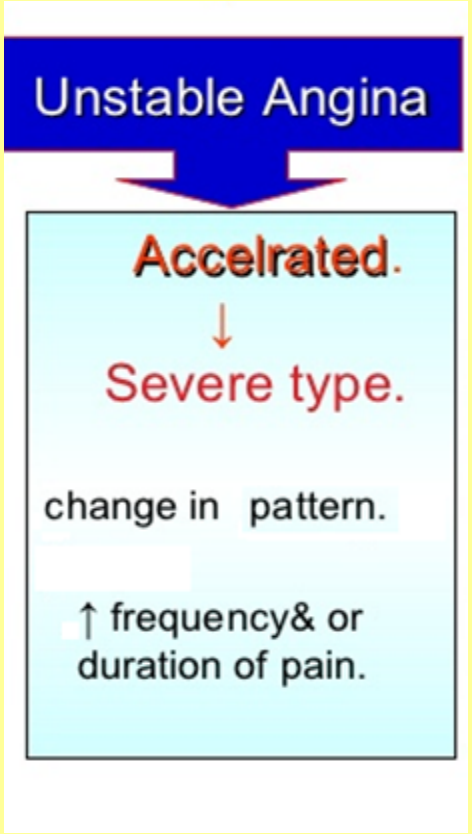
WHAT FACTORS WORSEN THE SYMPTOMS IN CASE OF HELMI?

WHAT IS THE POSSIBLE UNDERLYING CAUSE OF ANGINA IN HELMI?

# Types of Angina Pectoris







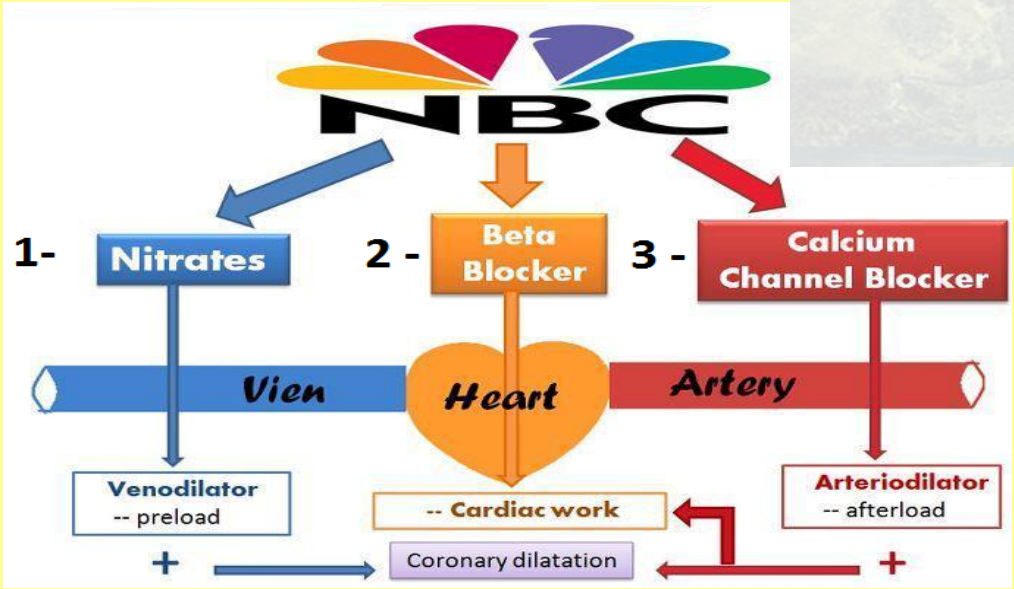
# TREATMENT OF ANGINA PECTORIS

## 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 ANGINA PECTORIS

## 2-Agents that improve prognosis

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

# ORGANIC NITRATES

## LONG ACTING

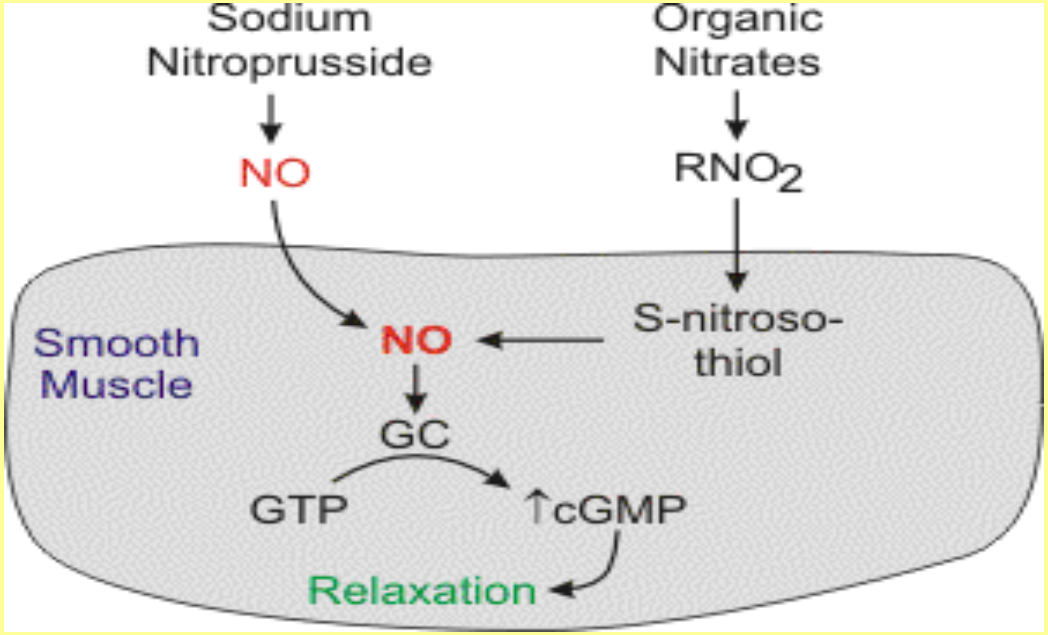
## ISOSORBIDE MONONITATE

## SHORT ACTING

## NITROGLYCERINE

# ORGANIC NITRATES

## MECHANISM OF ACTION



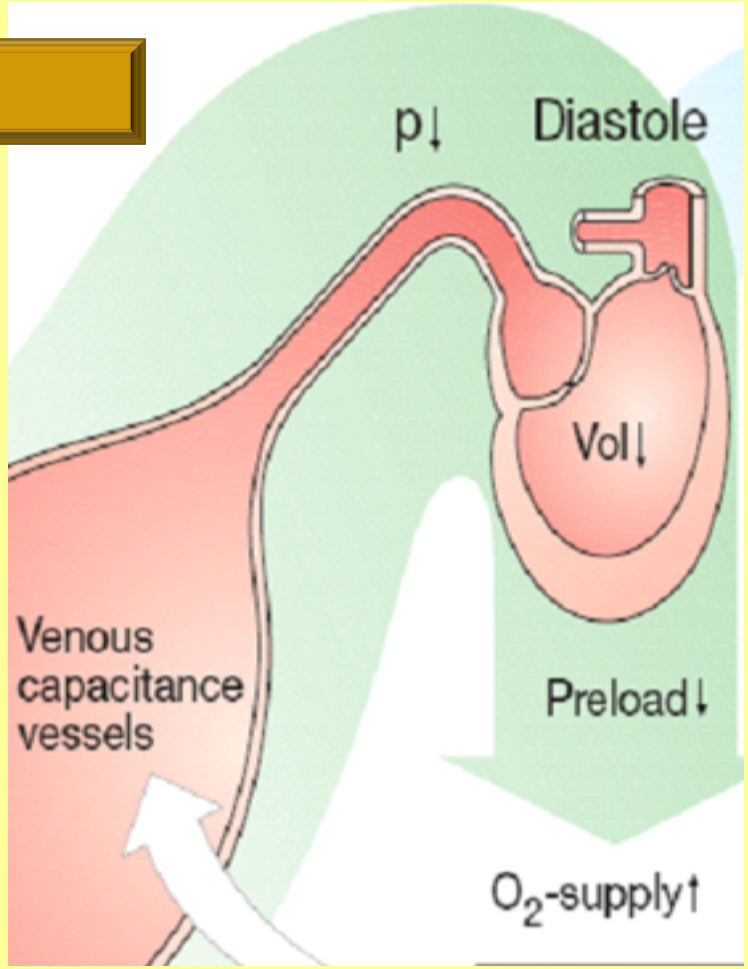

**Nitric oxide binds to guanylate cyclase in vascular smooth muscle cell to form cGMP.**

**cGMP activates PKG to produce relaxation**

# HEMODYNAMIC EFFECTS OF NITRATES

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

**Preload**



# HEMODYNAMIC EFFECTS OF NITRATES

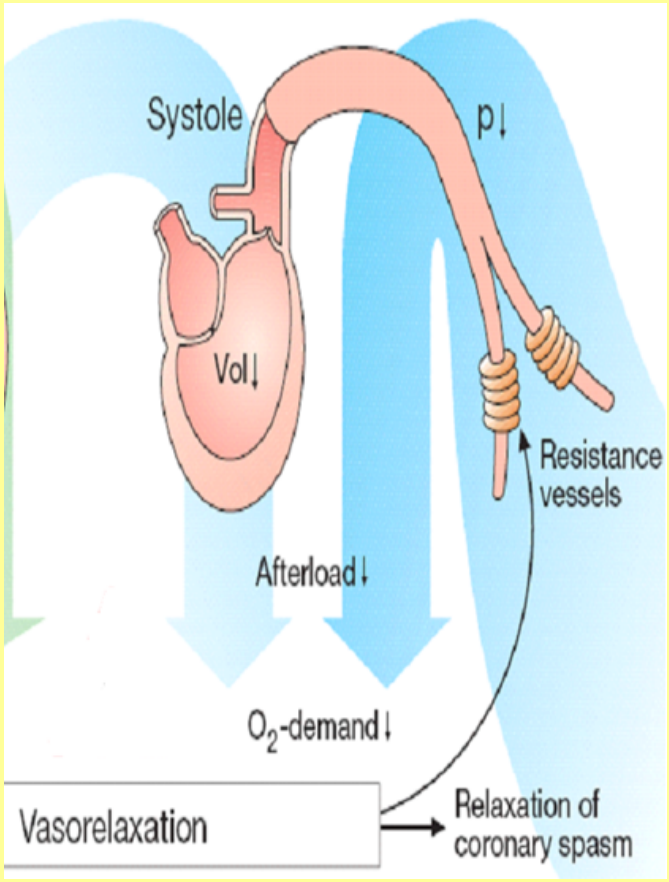
Shunting of flow from normal area to ischemic area by dilating collateral vessels

Coronary vasodilatation

↑ Myocardial perfusion

Arterial vasodilatation

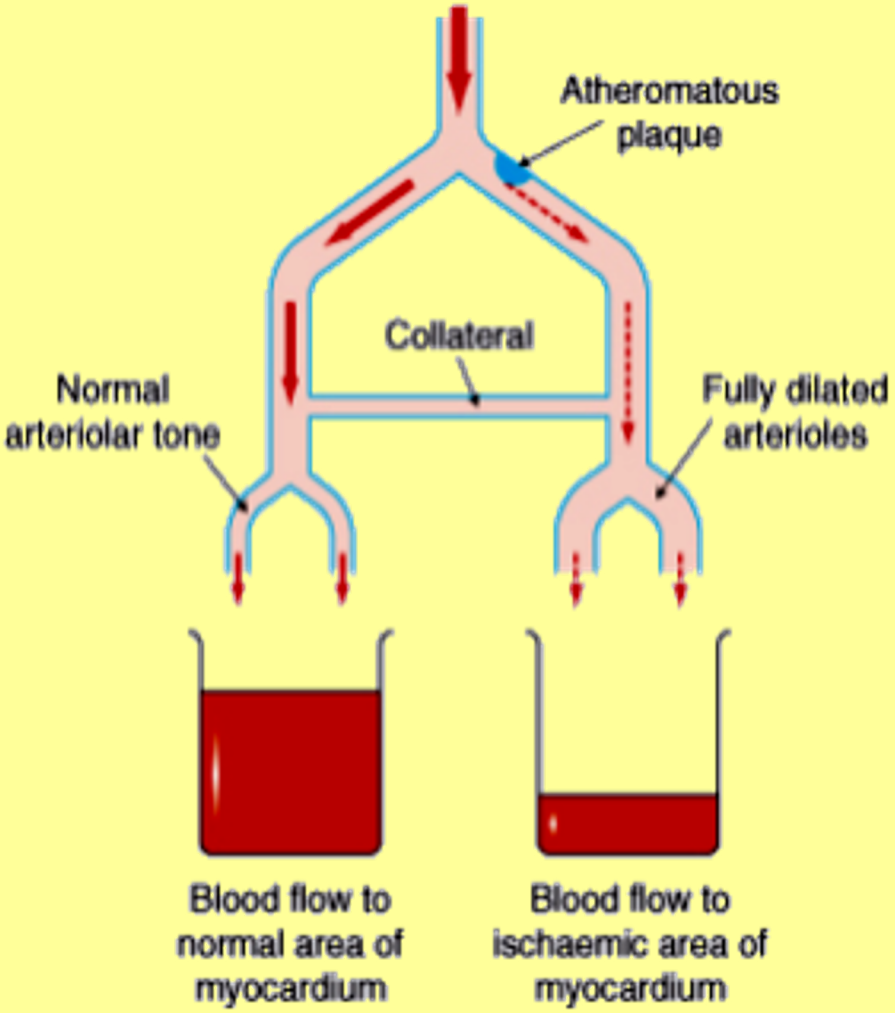
↓ Afterload

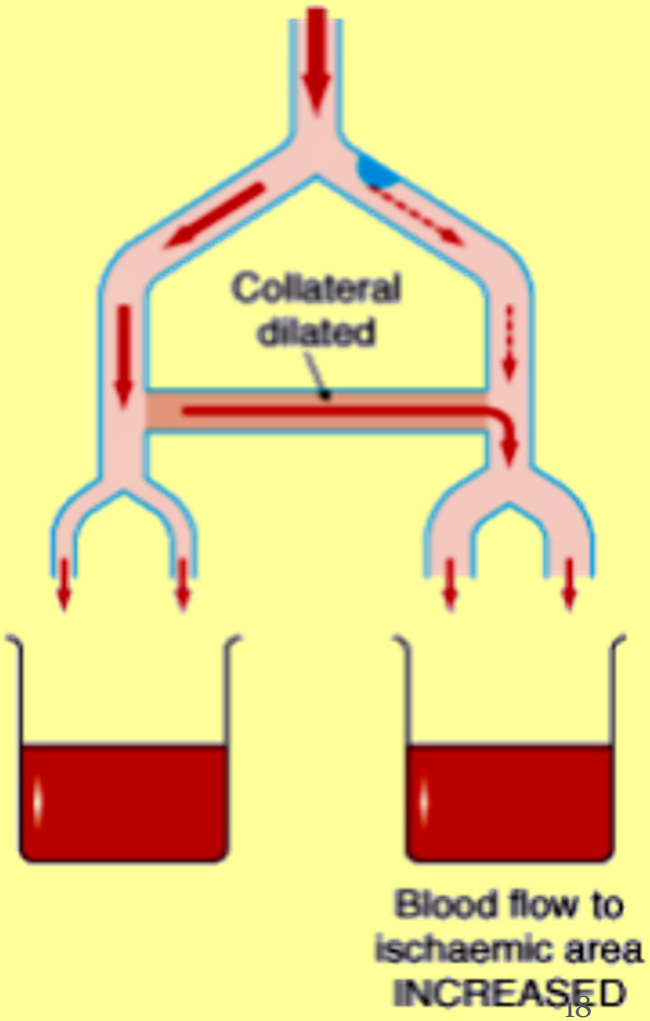


# HEMODYNAMIC EFFECTS OF NITRATES

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

**With Nitrates**

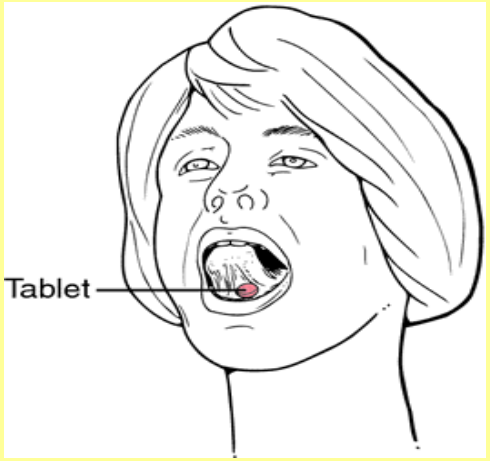


# PHARMACOKINETICS

**Nitroglycrine [GTN]**

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




**Given sublingual or via transdermal patch, or parenteral**

# PHARMACOKINETICS

**Oral isosorbide dinitrate & mononitrate**

**Very well absorbed & 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 ACEIs]***

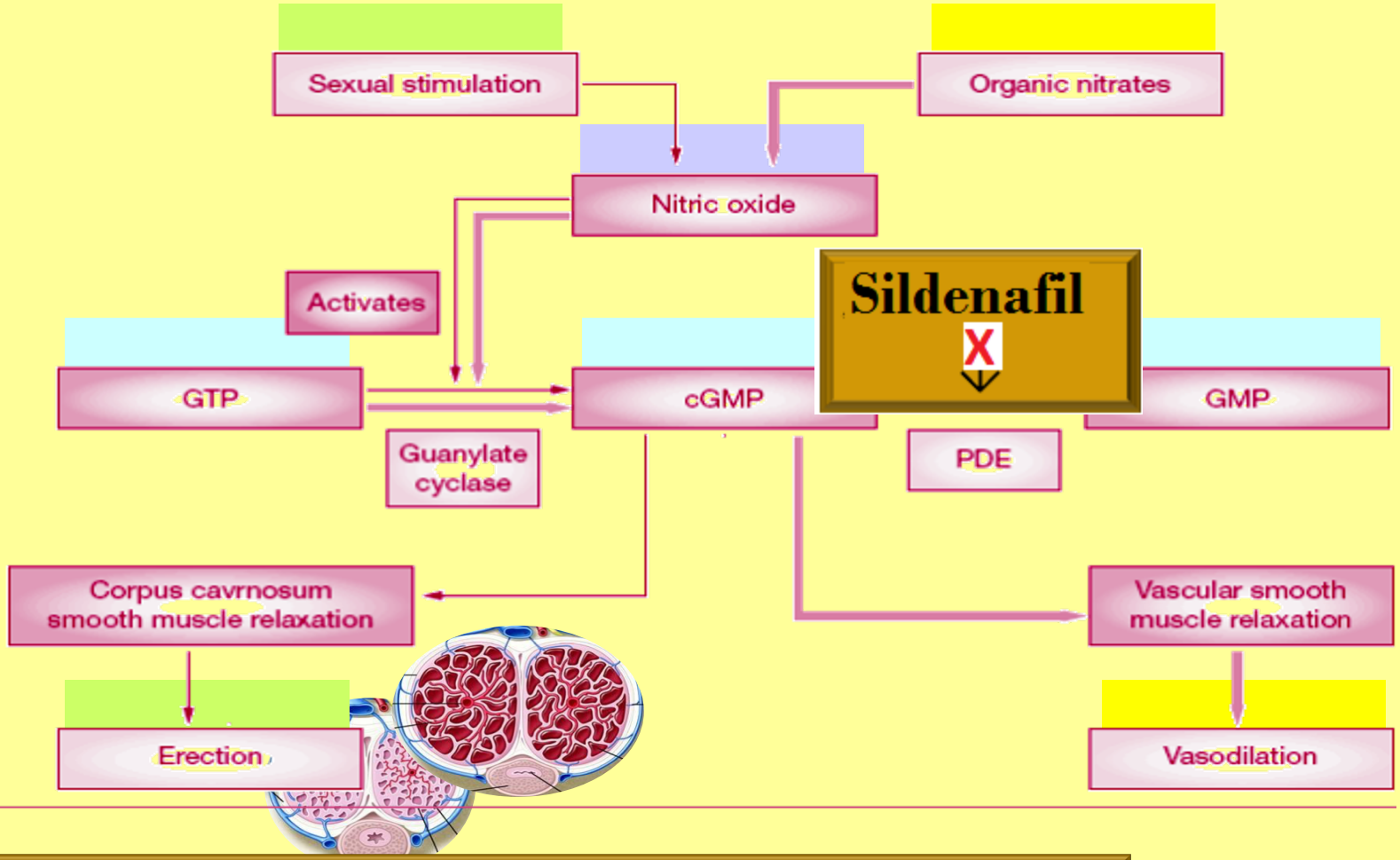
**AMI → IV GTN**

# 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

THROBBING HEADACHE

FLUSHING IN BLUSH AREA

TACHYCARDIA & PALPITATION


POSTURAL HYPOTENSION, DIZZINESS & SYNCOPE

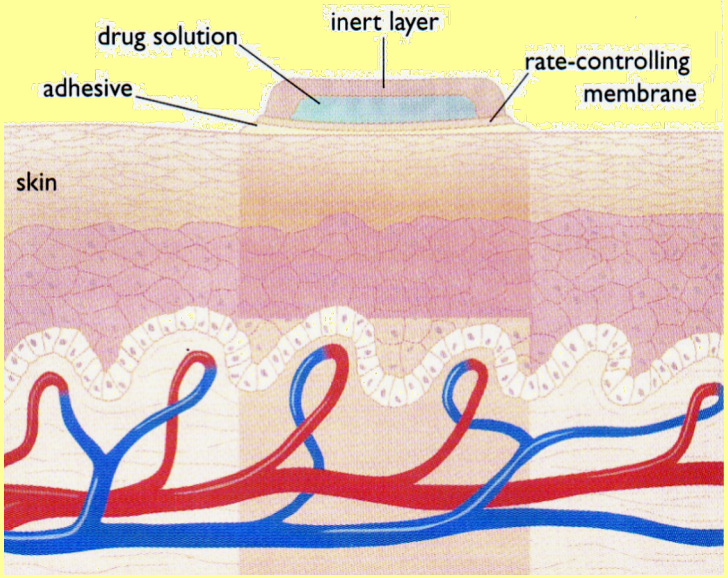
RARELY METHEMOGLOBINEMA

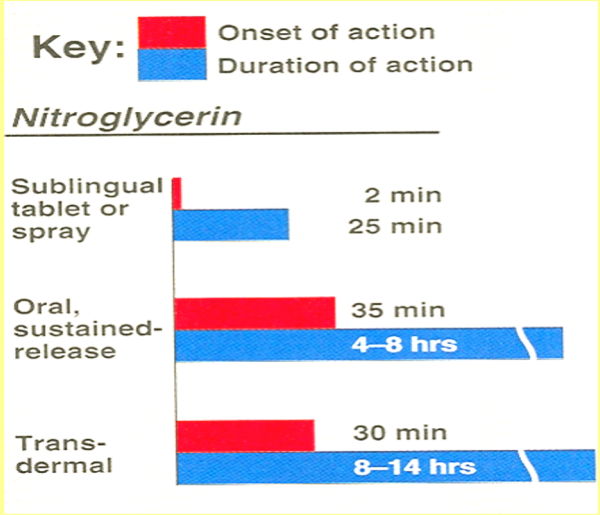
# PREPARATIONS

**Nitroglycerine**

**Sublingual tablets or spray**

**Transdermal patch**



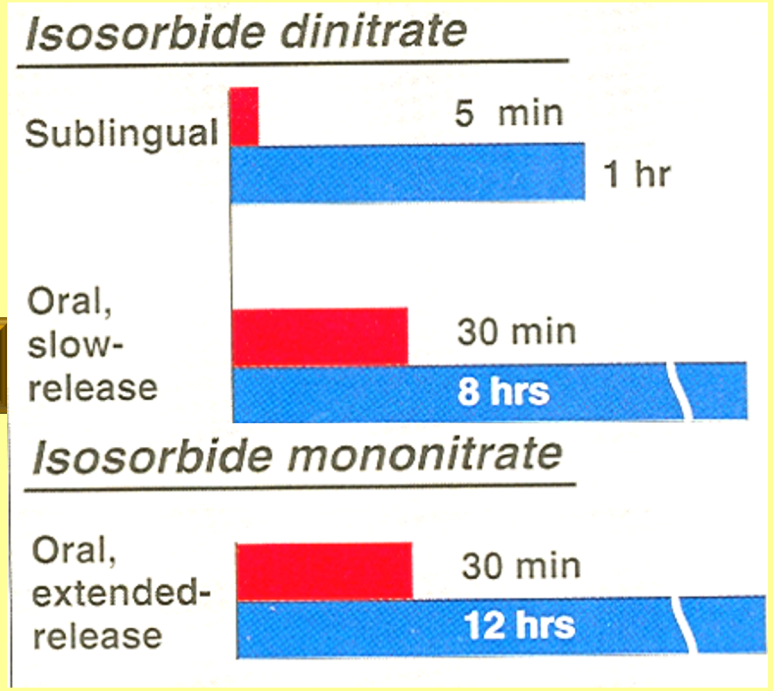

**Oral or bucal sustained release**
**I.V. Preparations**

# 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 IV 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.**

# THINK-PAIR-SHARE

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

| Effects | Results |
| --- | --- |
| 1-↓Ventricular volume | |
| 2-Reflex ↑ in contractility | A-↓ O2 demand |
| 3-↓Arterial pressure | B-↑ O2 demand |
| 4-↑Collateral flow | C-Relief of coronary artery spasm |
| 5-Reflex tachycardia | |
| 6-↓Left ventricular diastolic pressure | D-Improved perfusion to ischemic myocardium |
| 7-↓Diastolic perfusion time due to tachycardia | E-Improve subendocardial perfusion |
| 8-Vasodilation of epicardial coronary arteries | F-↓ myocardial perfusion |

# 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.

## Mechanisms of Clinical Effect

The beneficial and deleterious effects of nitrate-induced vasodilation are summarized in Table 12–2.

TABLE 12–2 Beneficial and deleterious effects of nitrates in the treatment of angina.

| Effect | Mechanism and Result |
|---|---|
| **Potential beneficial effects** | |
| Decreased ventricular volume<br>Decreased arterial pressure<br>Decreased ejection time | Decreased work and myocardial oxygen requirement |
| Vasodilation of epicardial coronary arteries | Relief of coronary artery spasm |
| Increased collateral flow | Improved perfusion of ischemic myocardium |
| Decreased left ventricular diastolic pressure | Improved subendocardial perfusion |
| **Potential deleterious effects** | |
| Reflex tachycardia | Increased myocardial oxygen requirement; decreased diastolic perfusion time and coronary perfusion |
| Reflex increase in contractility | Increased myocardial oxygen requirement |