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 **Pain is caused either by obstruction**

severity) due to ischemia of heart muscle

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the

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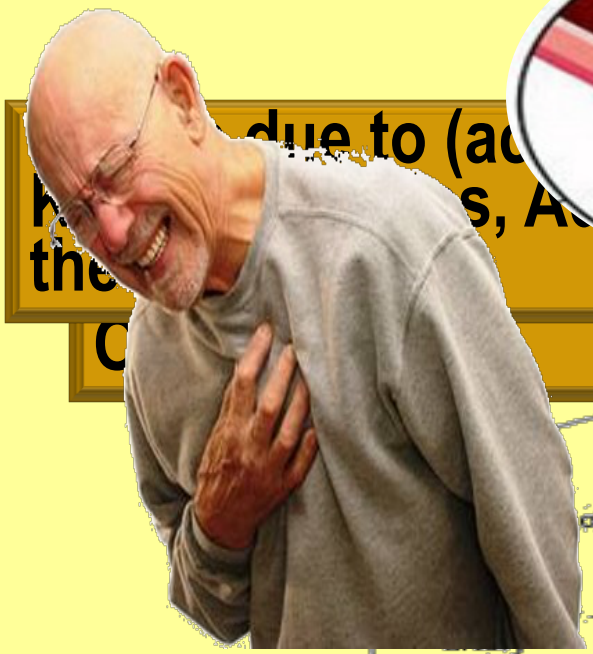
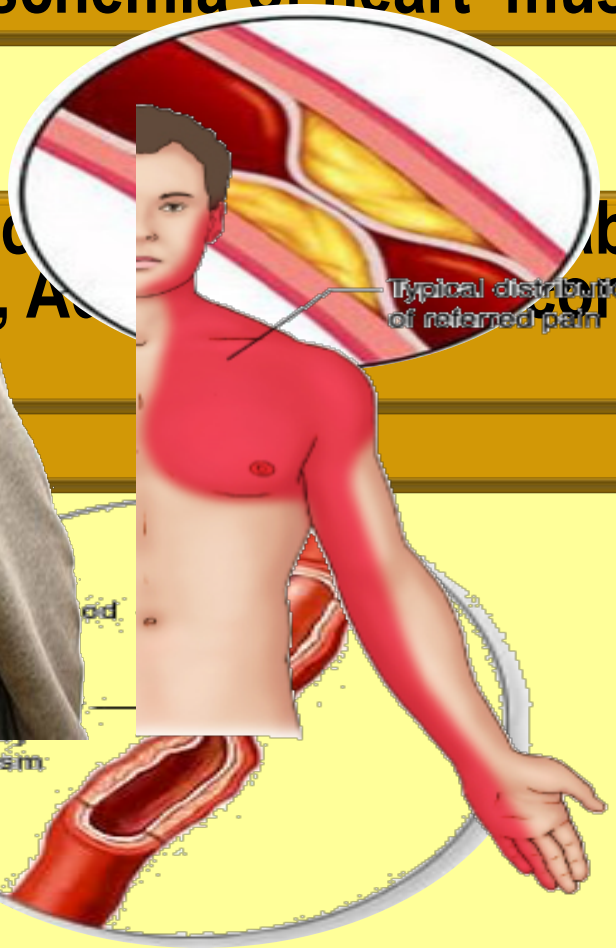
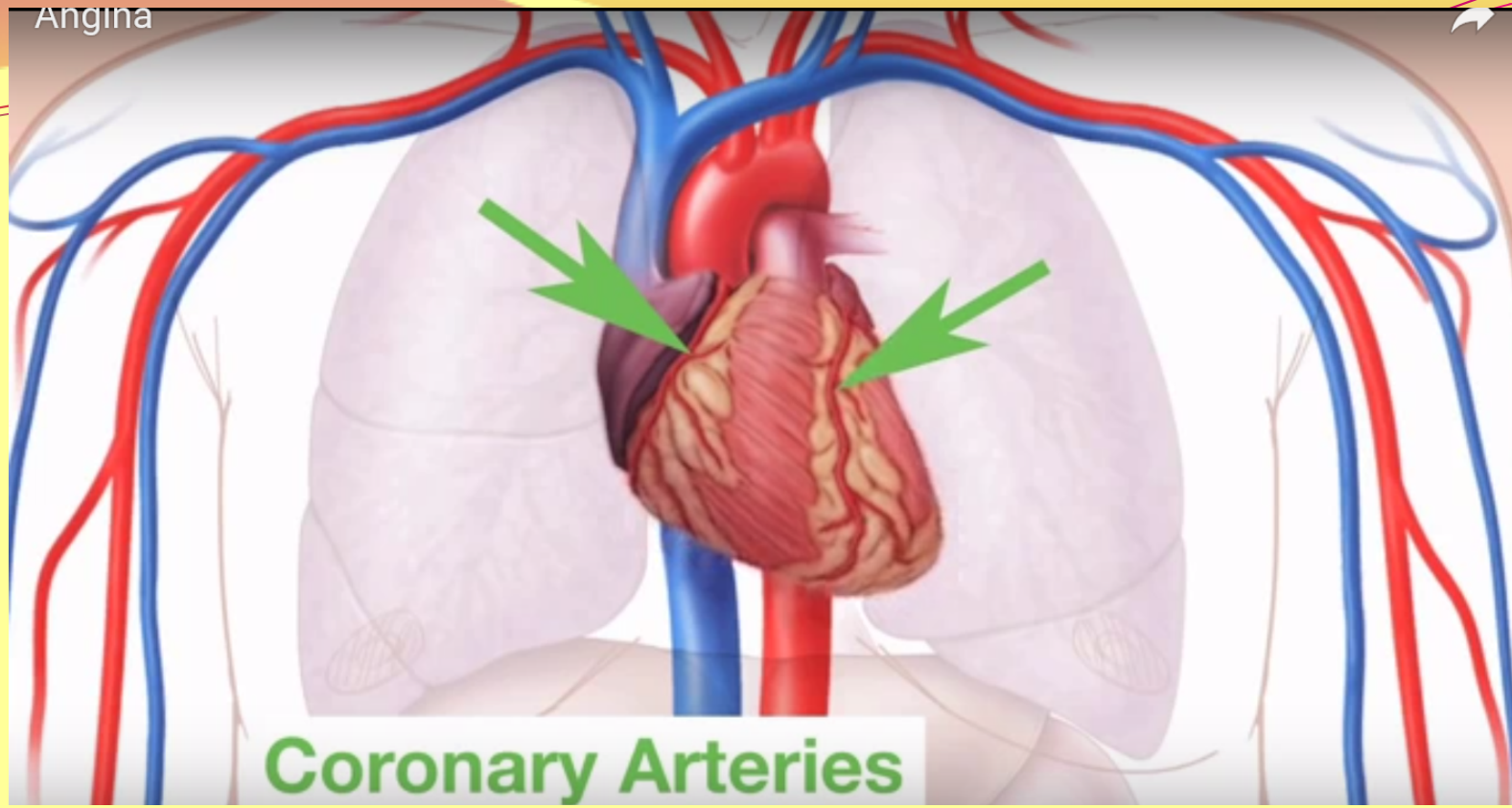




Minicase

What is the possible underlying cause of Helmi's exertional pain?



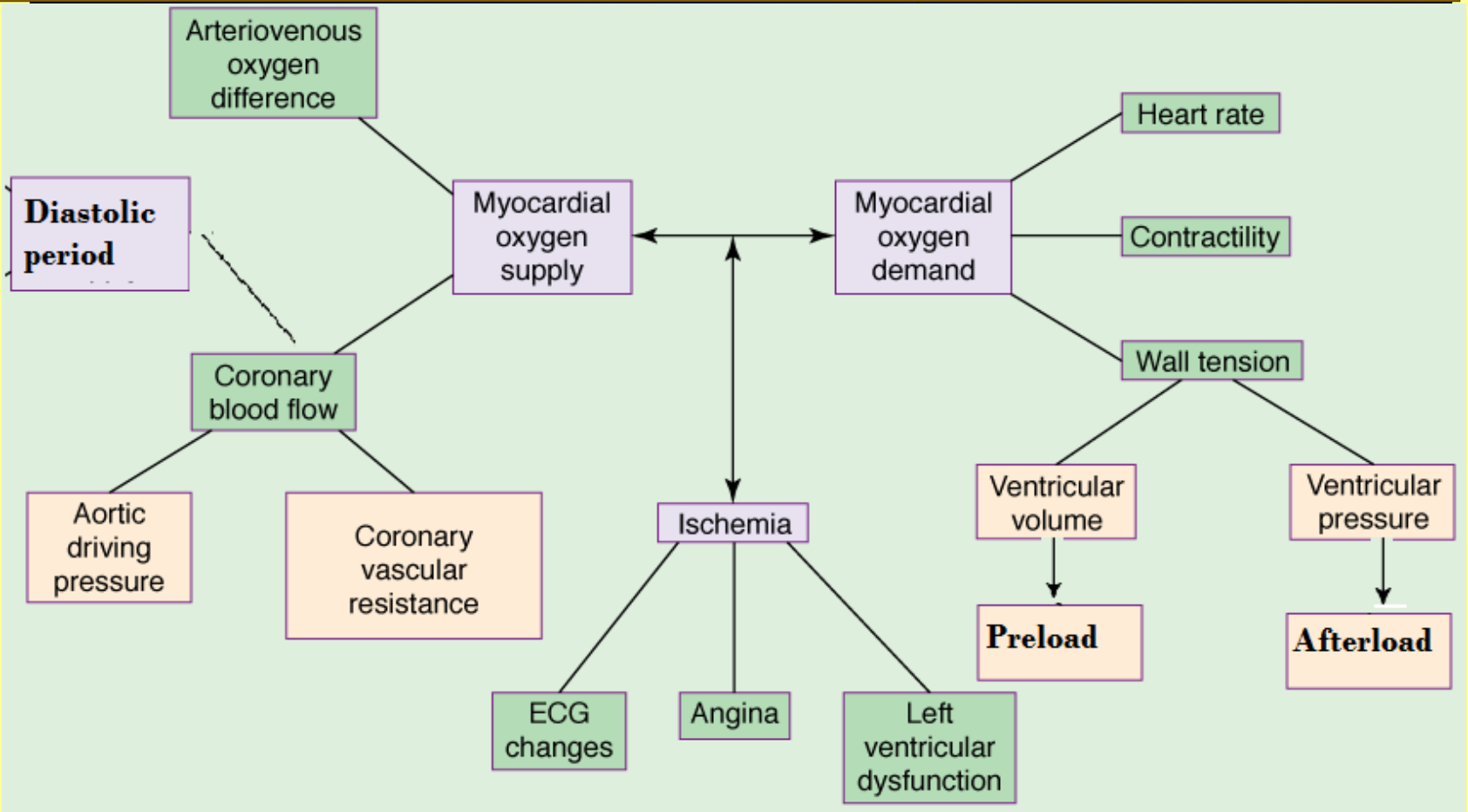
In Exercise

- 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 ↑)

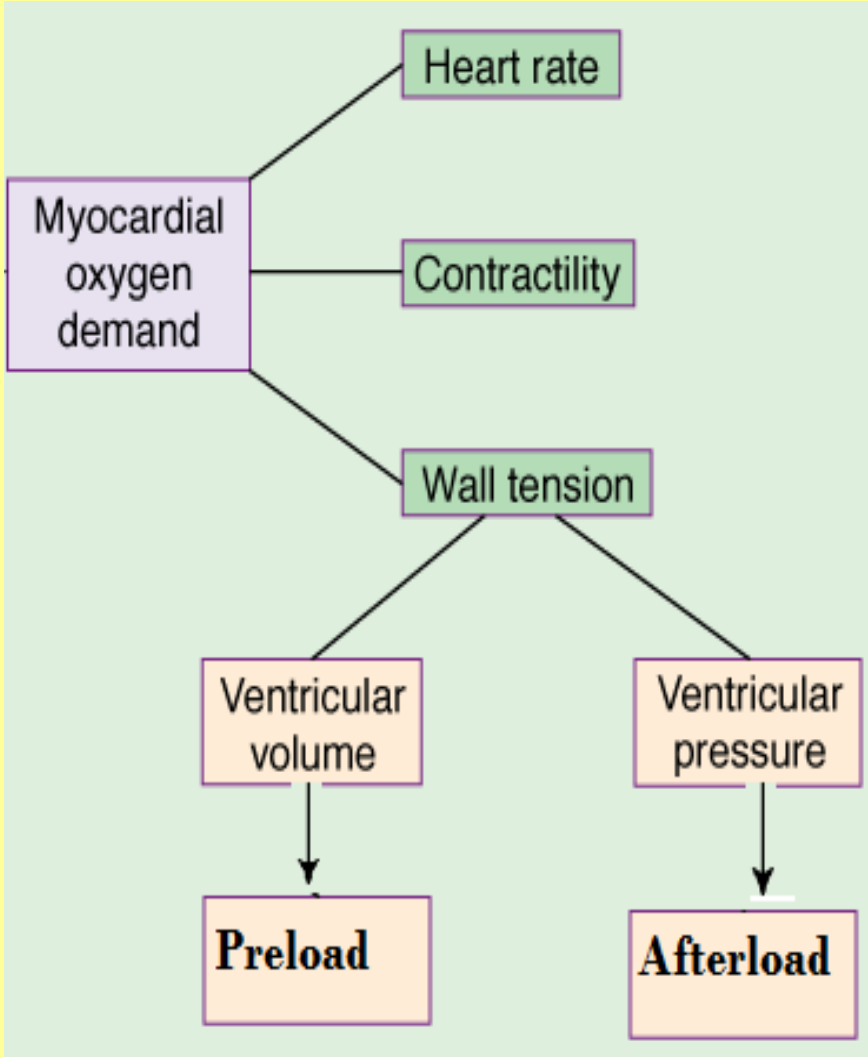
So we need to ↑ the amount of bld that go into the hrt (CO) to ↑ .

What is Basic mechanism of angia pectoris?

What are the determinants of oxygen demand & supply?



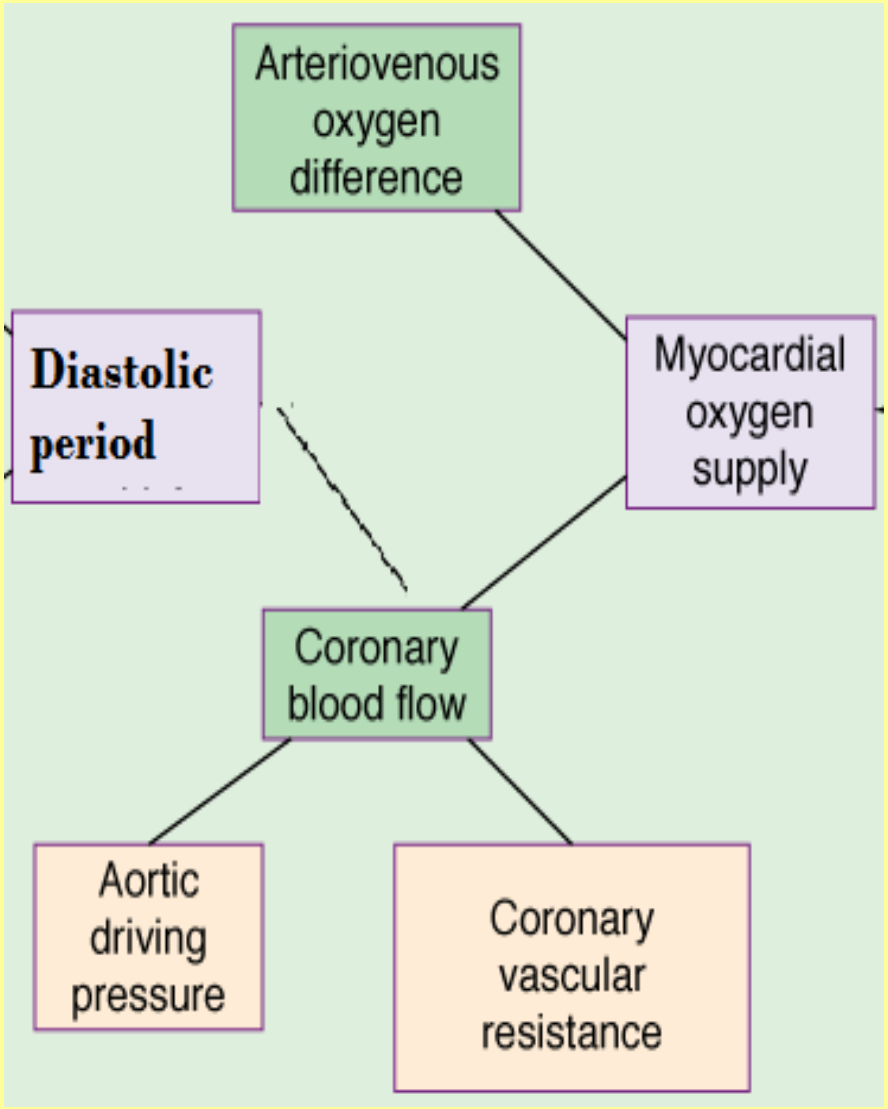
Myocardial oxygen demand is determined by:-



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

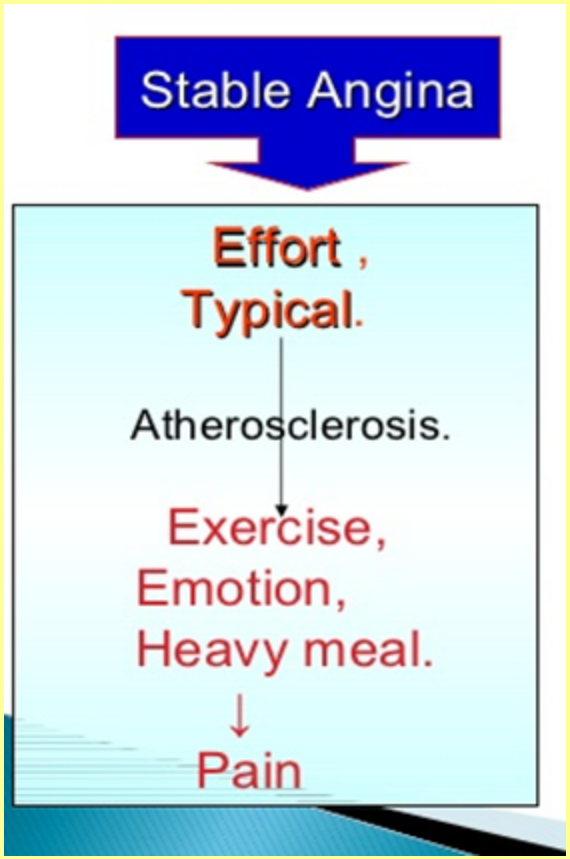
Minicase

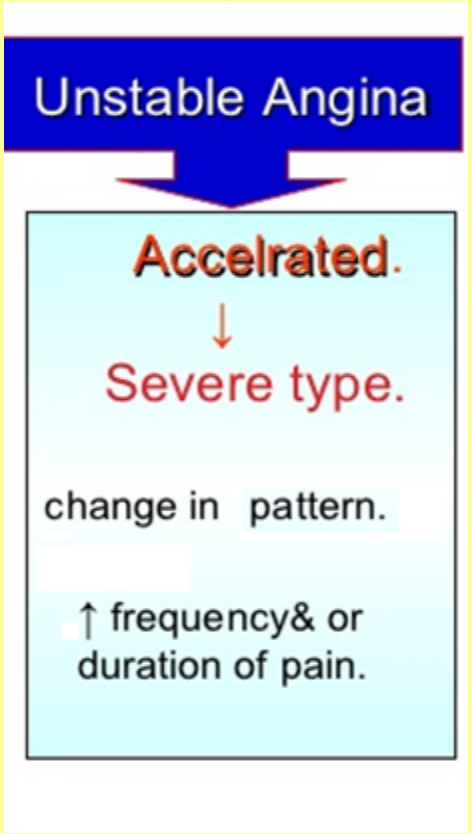
What triggers the onset of symptoms in helmi?

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

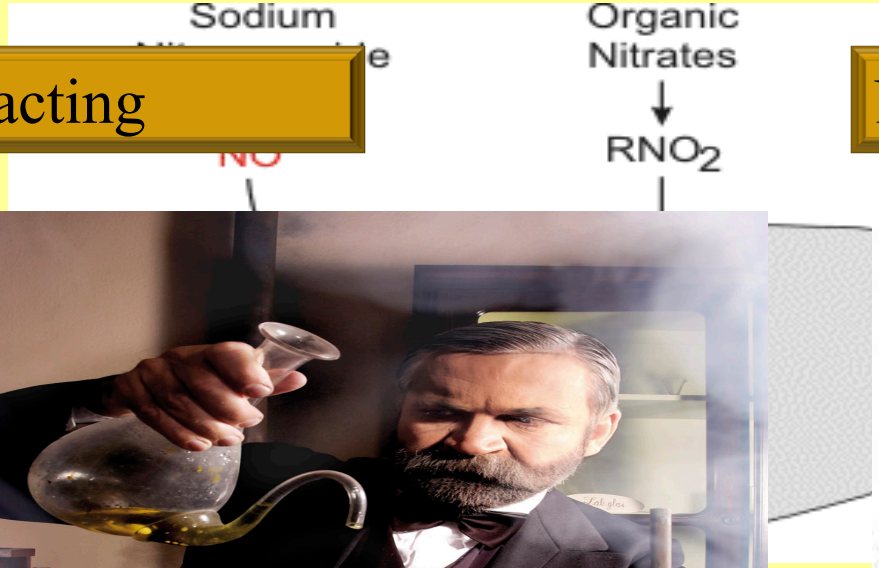
Organic nitrates

Long acting

Isosorbide mononitate

Short acting

Nitroglycerine



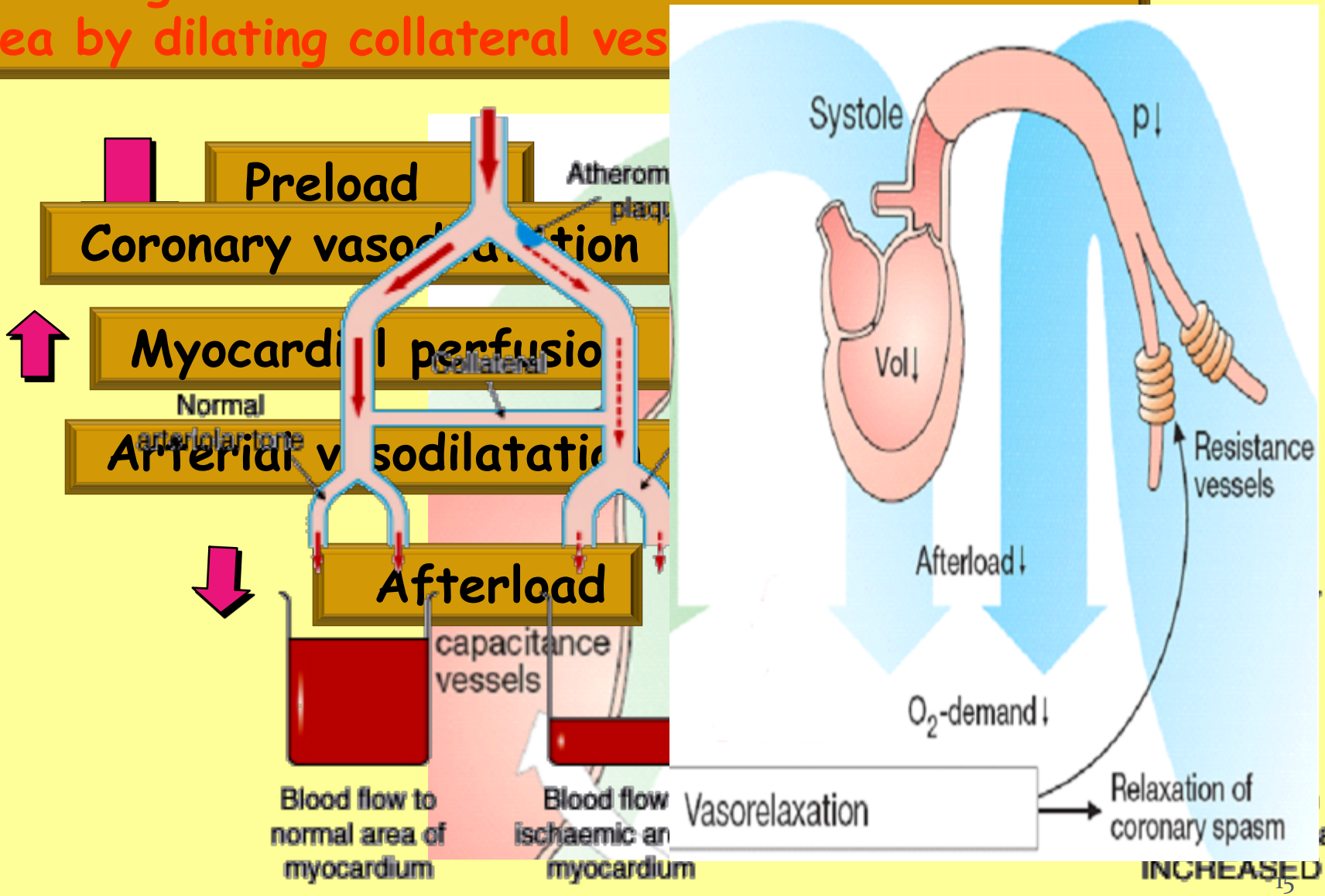
Nitri… …ate

vasc… …ll t…

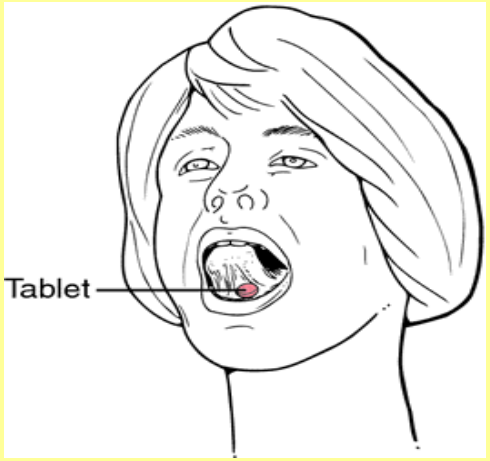
cGM… …duce relaxation

Hemodynamic effects of nitrates

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



pharmacokinetics



Oral isosorbide dinitrate & mononitrate

Very well absorbed & 100% bioavailability

the liver (10-20%) bioavailability

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

nteral

($t_{1/2}$ 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

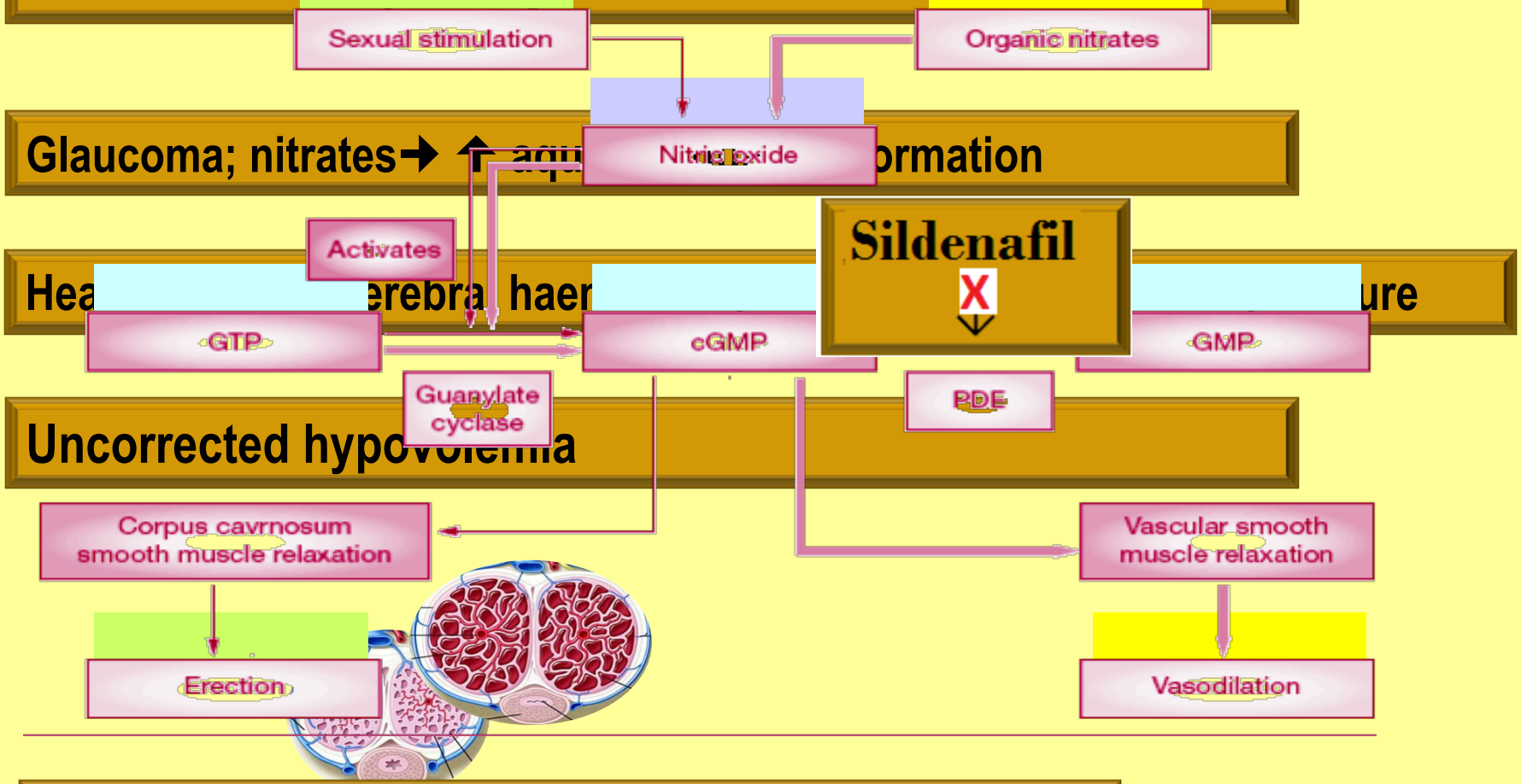
CHF ➔ Isosorbide mononitrate + hydralazine
[if contraindication to ACEIs]

AMI ➔ IV GTN

contraindications

Concomitant administration of PDE_5 Inhibitors

Known sensi nic nitrates



Glaucoma; nitrates → ↑ aqu ormation

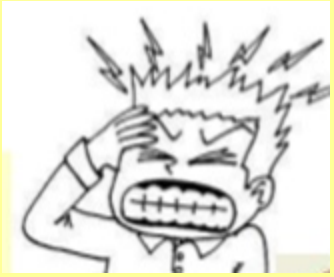
Hea erebra haer ure

Uncorrected hypovolemia

Sildenafil + nitrates → Severe hypotension & death

Adverse drug reactions

Throbbing headache



Flushing in blush area

Tachycardia & palpitation

Postural hypotension, dizziness & syncope

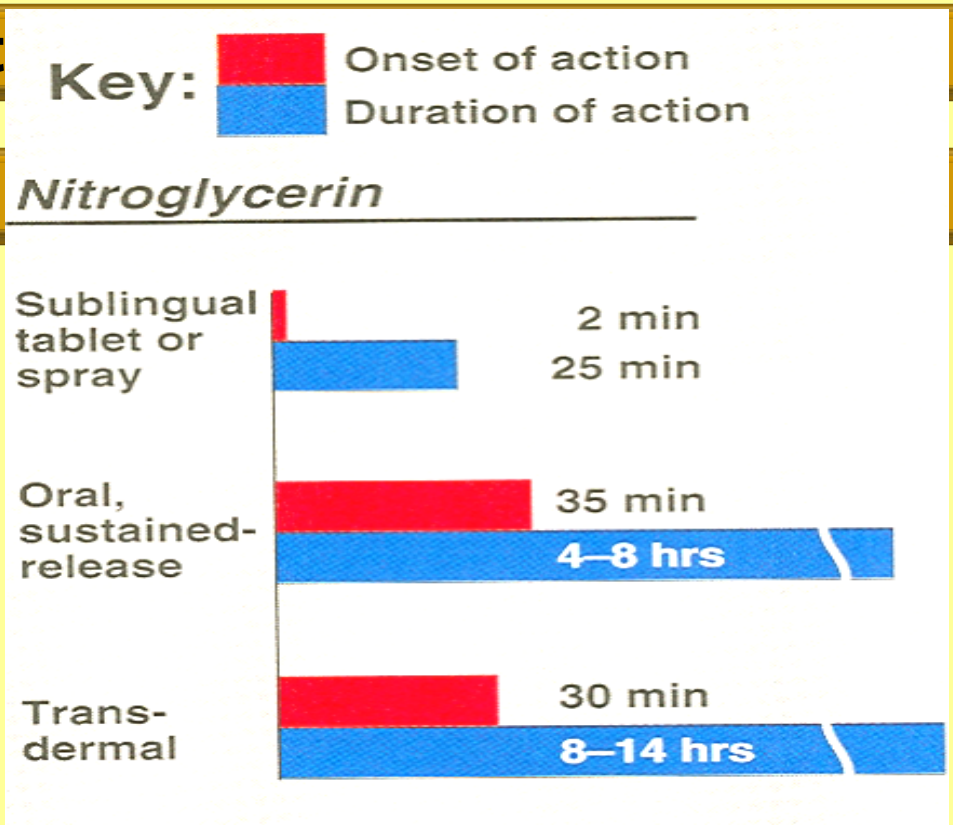
Rarely methemoglobinema

Preparations

Nitroglycerine

Sublingual t

Transderma



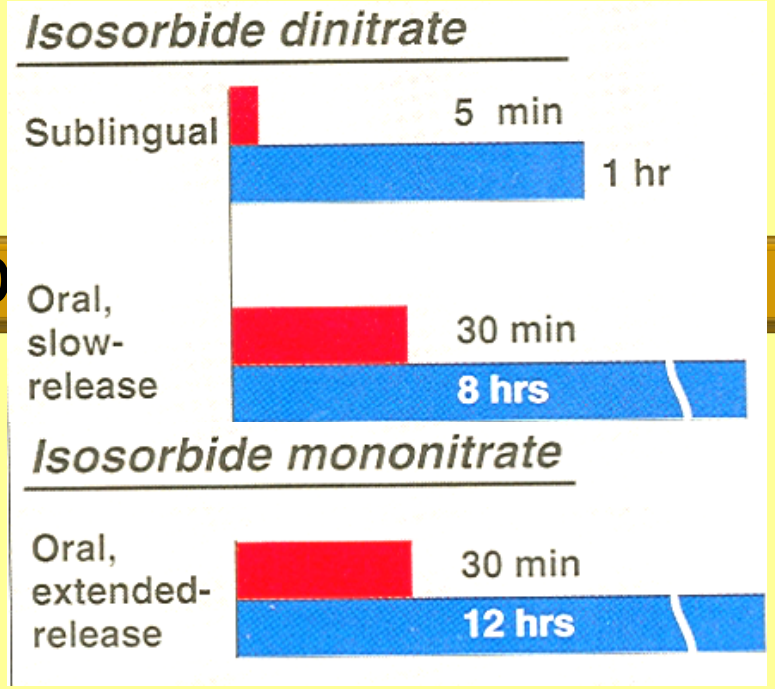
Oral or bucal sustained release
I.V. Preparations

Preparations

Isosorbide dinitrate

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

- Mononitrate O



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

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 Decreased arterial pressure 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