

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.

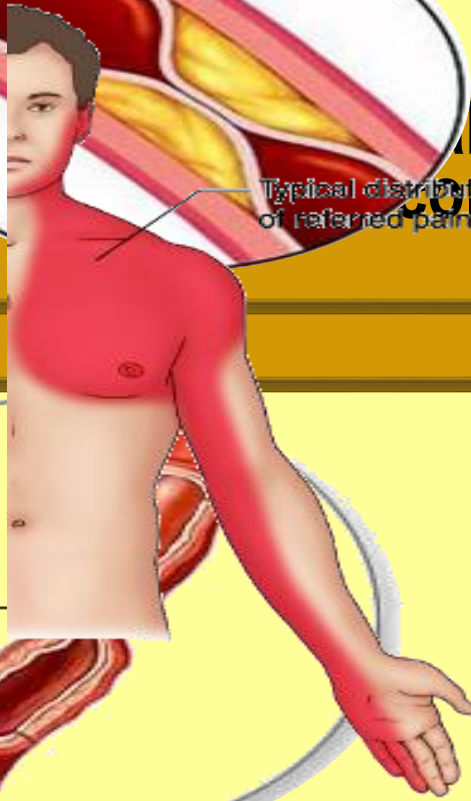
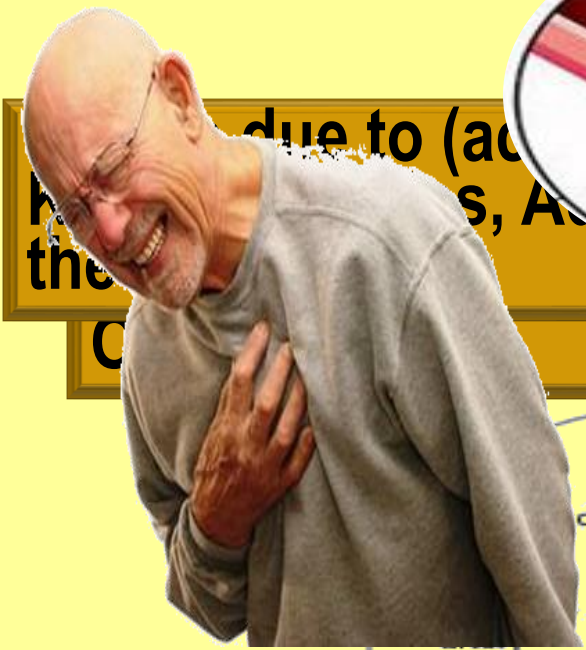
MINICASE



**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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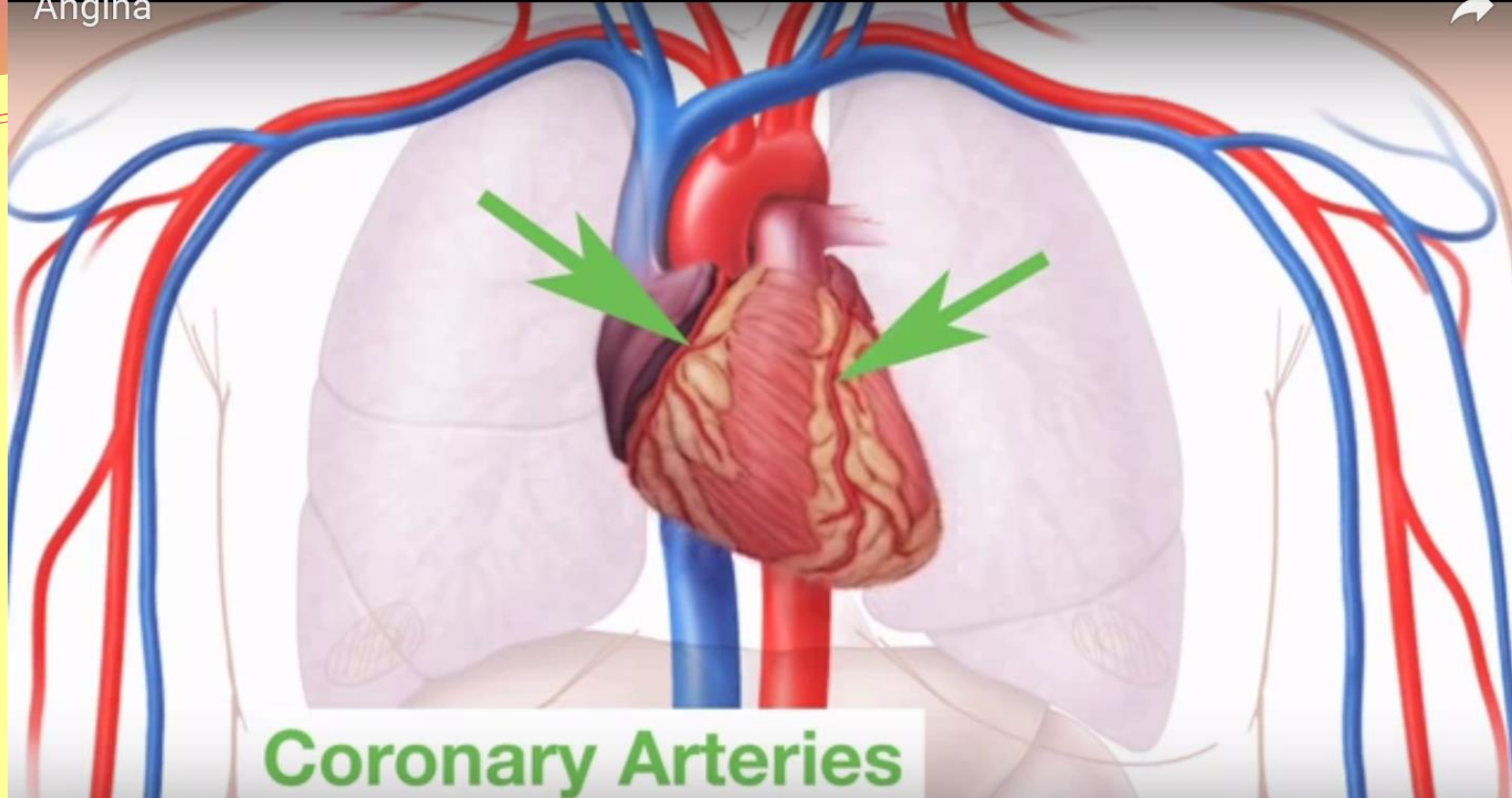


"You say it's a sharp, stabbing pain. Hmmm ... sharp ... stabbing pain."

MINICASE



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

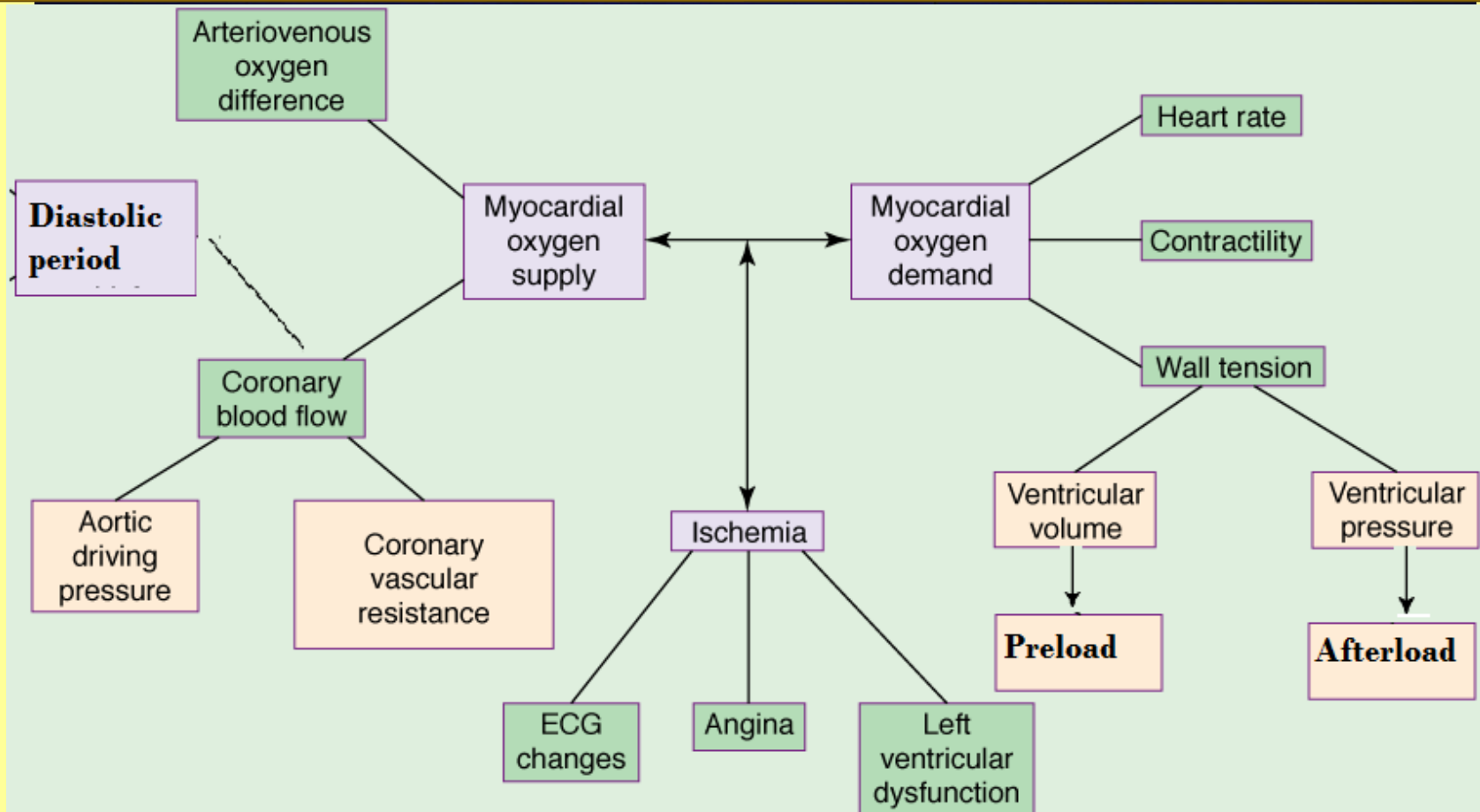


In Exercise

- 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 ↑.

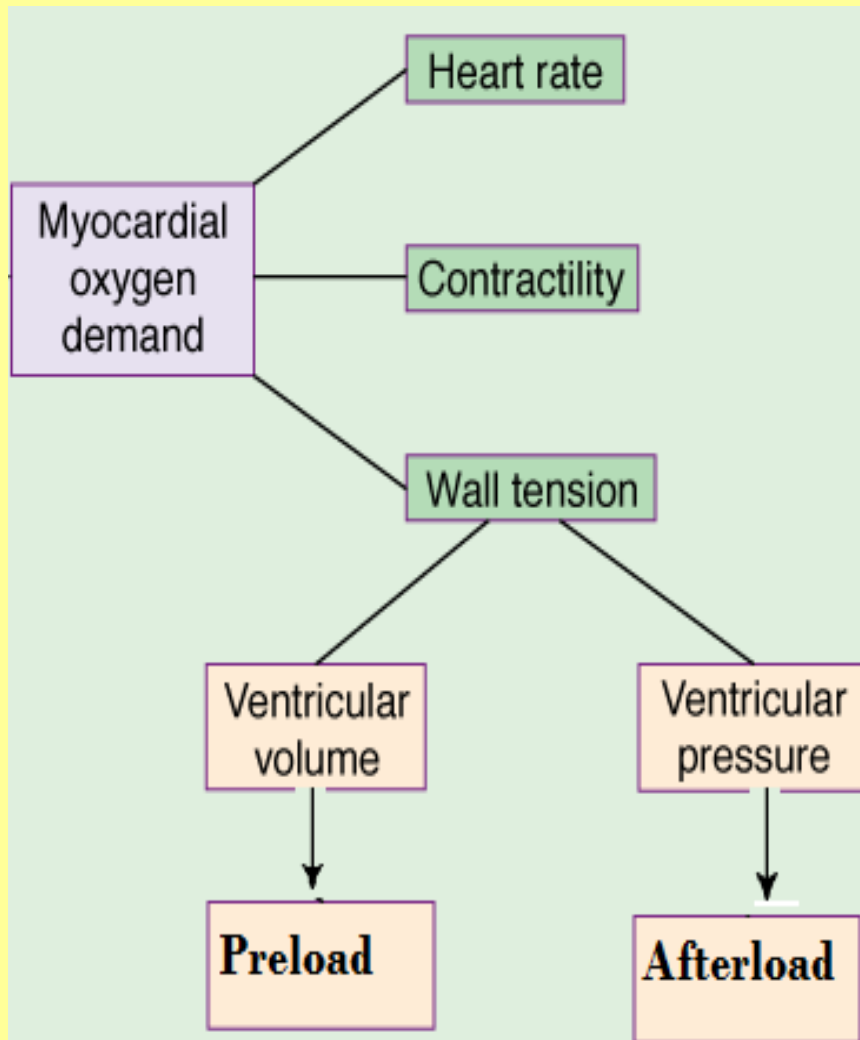
WHAT IS BASIC MECHANISM OF ANGINA PECTORIS?

WHAT ARE THE DETERMINANTS OF OXYGEN DEMAND & SUPPLY?



MYOCARDIAL OXYGEN
DEMAND IS DETERMINED BY:-

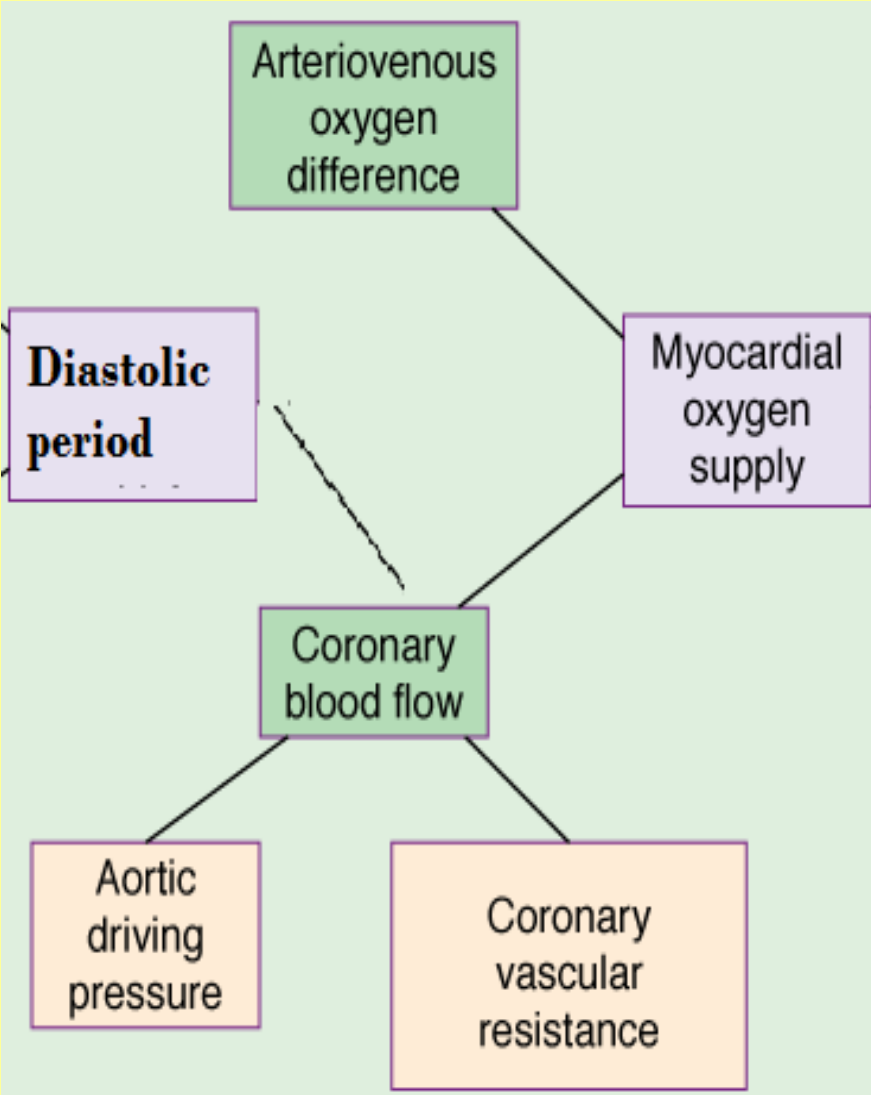
MYOCARDIAL OXYGEN
DEMAND IS DIMINISHED BY:-



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 WORSEEN THE SYMPTOMS IN CASE OF HELMI?

WHAT IS THE POSSIBLE UNDERLYING CAUSE OF ANGINA IN HELMI?

Types of Angina Pectoris

Stable Angina

**Effort ,
Typical.**

Atherosclerosis.

**Exercise,
Emotion,
Heavy meal.**

Pain

Variant Angina

Prinzmetal.

**α - receptor
mediated V.C.**

With or without
atherosclerosis.

Pain even at rest

Unstable Angina

Accelerated.

Severe type.

change in pattern.

**↑ frequency & or
duration of pain.**

TREATMENT OF ANGINA PECTORIS

1-Agents that improve symptoms & ischemia

Traditional Approach

New approaches

Metabolic modulation
(Trimetazidine)

K⁺ channel opener
(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

MECHANISM OF ACTION

LONG ACTING

ISOSORBIDE MONONITRATE

SHORT ACTING

NITROGLYCERINE

Sodium Nitrate

Organic Nitrates



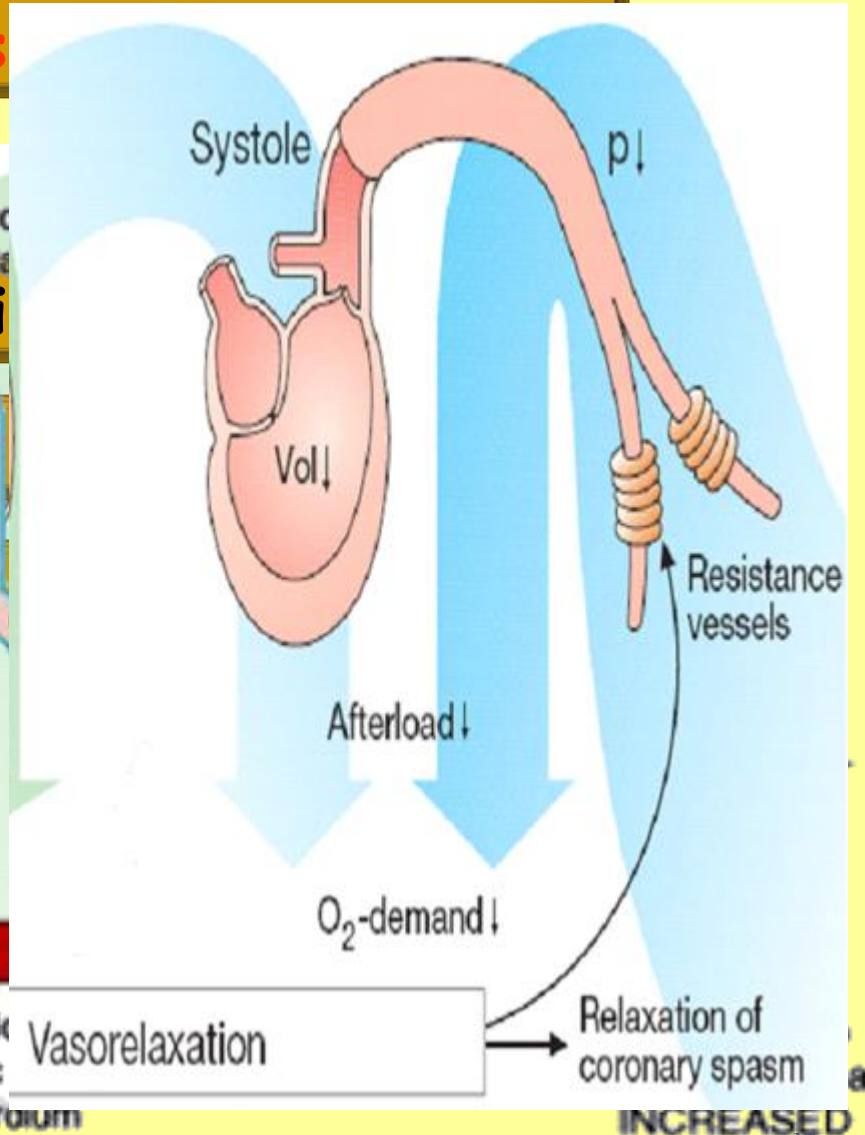
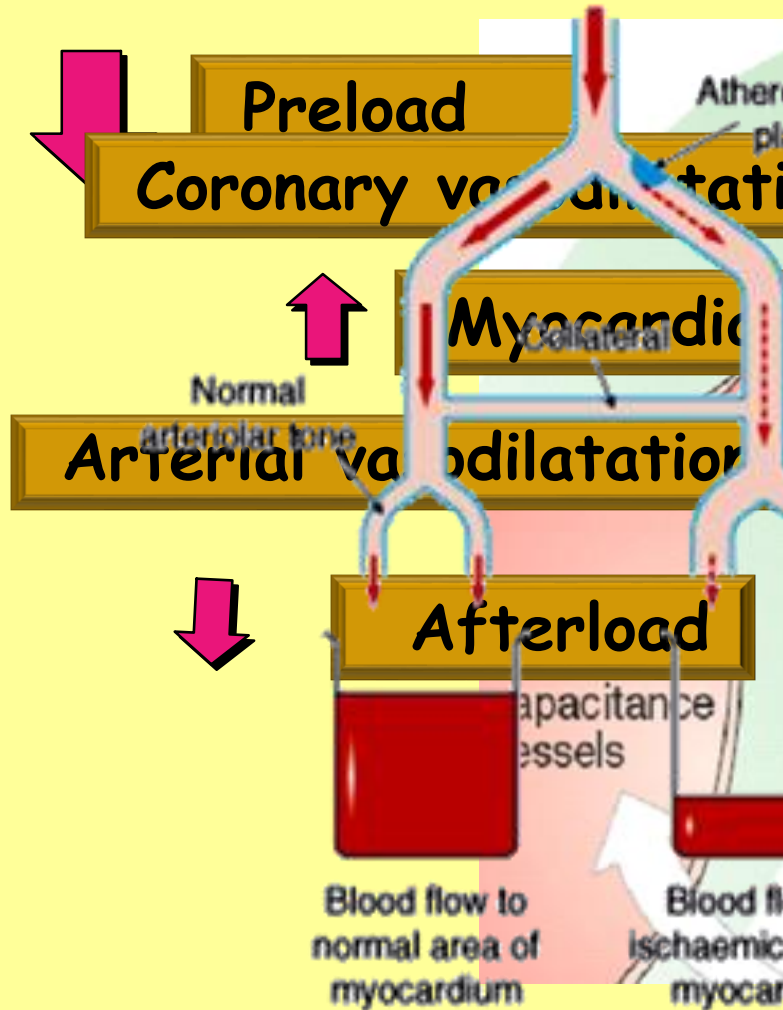
Nitric
vasc

ate
ell t

cGM. activates cGMP to produce relaxation

HEMODYNAMIC EFFECTS OF NITRATES

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



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

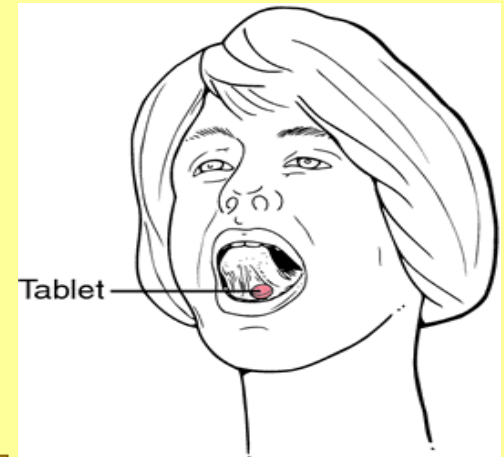
Oral isosorbide dinitrate & mononitrate

Very well absorbed & 100% bioavailability
the liver (10-20%) bioavailability

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

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

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



nteral

INDICATIONS

IN STABLE ANGINA;

IN VARIANT ANGINA → **sublingual GTN**

Prevention; Persistent 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 PDE₅ Inhibitors

Known sensitive to organic nitrates

Sexual stimulation

Organic nitrates

Glaucoma; nitrates → ↑ aqueous humor formation

Nitric oxide formation

Headache, cerebral hyperemia, hypotension, priapism

Sildenafil

GTP

Activates

cGMP

GMP

Guanylate cyclase

PDE

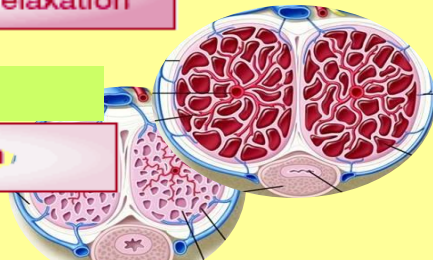
Uncorrected hypovolemia

Corpus cavernosum smooth muscle relaxation

Vascular smooth muscle relaxation

Erection

Vasodilation



Sildenafil + nitrates → Severe hypotension & death

ADVERSE DRUG REACTIONS

THROBBING HEADACHE



FLUSHING IN BLUSH AREA



TACHYCARDIA & PALPITATION



POSTURAL HYPOTENSION, DIZZINESS & SYNCOPE



RARELY METHEMOGLOBINEMIA

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

PREPARATIONS

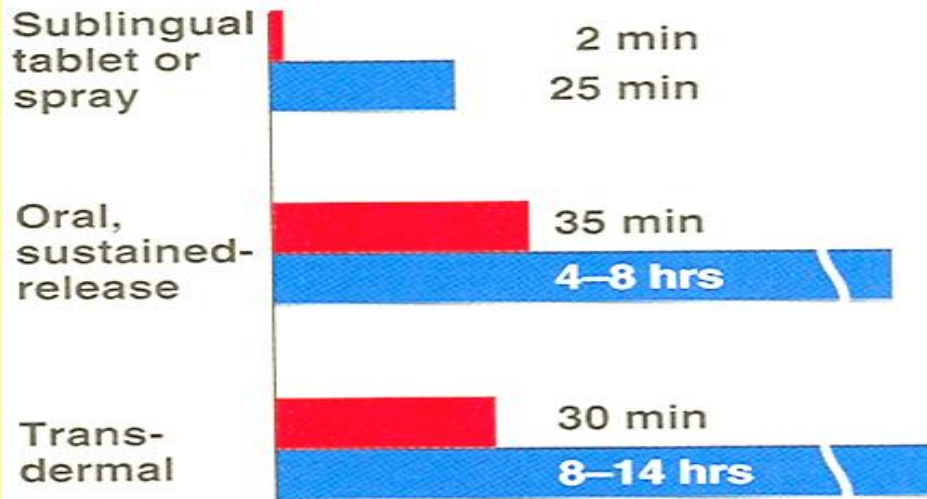
Nitroglycerine

Sublingual t

Transderma

Key:  Onset of action
 Duration of action

Nitroglycerin

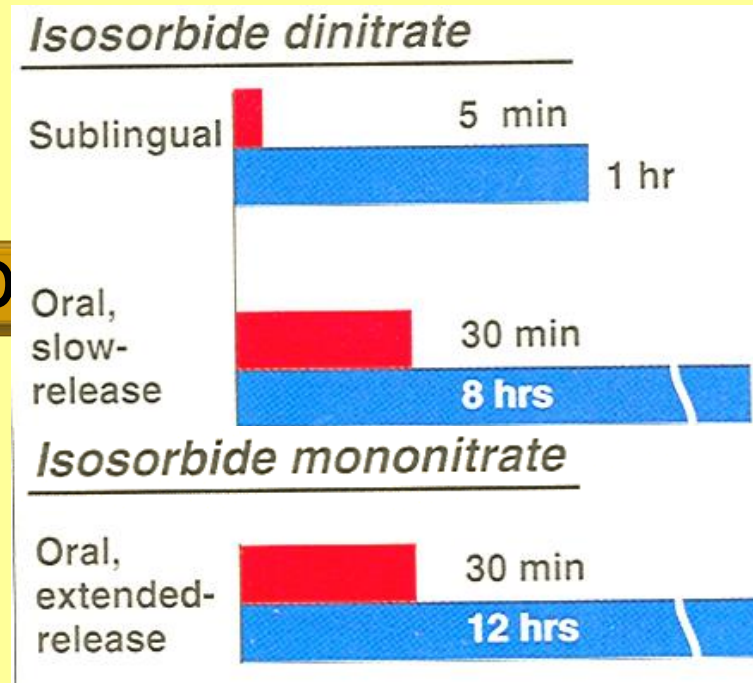


Oral or bucal sustained release
I.V. Preparations

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.

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.