Antianginal Drugs

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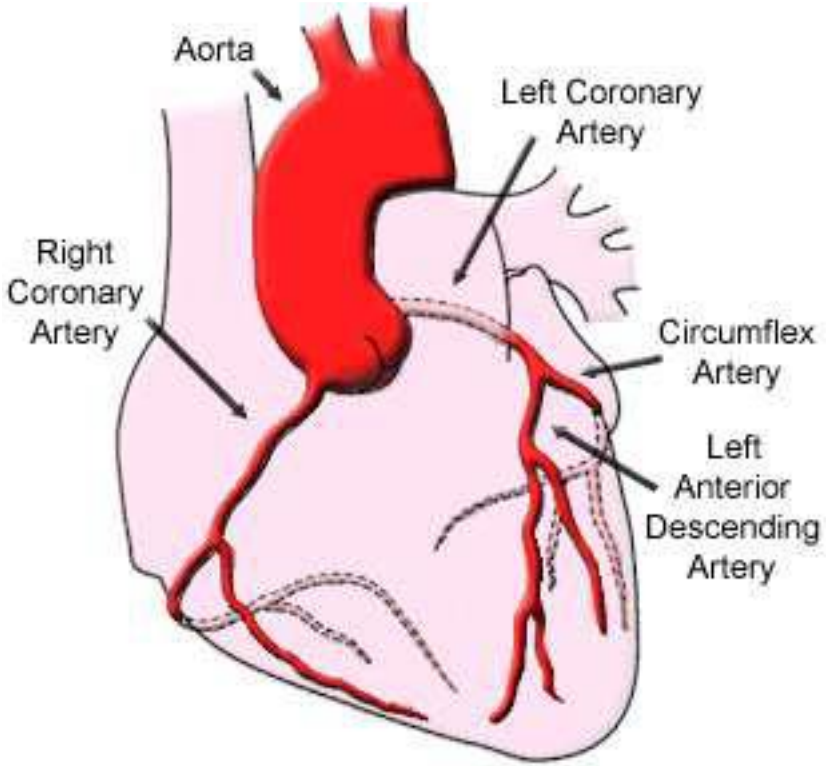
What is angina?

- Angina pectoris is a syndrome characterized by sudden severe pressing substernal chest pain or heaviness radiating to the neck, jaw, back and arms. It is often associated with diaphoresis, tachypnoea and nausea.
- Primary cause: imbalance between myocardial oxygen demand and oxygen supplied by coronary vessels.
- This imbalance may be due to:

1. decrease in myocardial oxygen delivery
2. an increase in myocardial oxygen demand, **or both**

- The discomfort abates when supply becomes adequate for demand. Typically angina lasts for seconds to minutes, up to 15 minutes

Factors affecting Myocardial Oxygen Delivery



- Coronary artery blood flow is the primary determinant of oxygen delivery to the myocardium.
- Myocardial oxygen extraction from the blood is nearly complete, even at rest.
- Coronary blood flow is essentially negligible during systole and is therefore determined by:
  - **Perfusion pressure** during diastole
  - Duration of diastole
  - Coronary vascular resistance: determined by numerous factors:
    - ✓Atherscelorosis
    - ✓Intracoronary thrombi
    - ✓Metabolic products that vasodilate coronary arterioles
    - ✓Autonomic activity
    - ✓Extravascular compression

Types of Angina

1. Classical angina(Stable)

2. Variant or Prinzmetal`s angina(Unstable)

Stable Angina

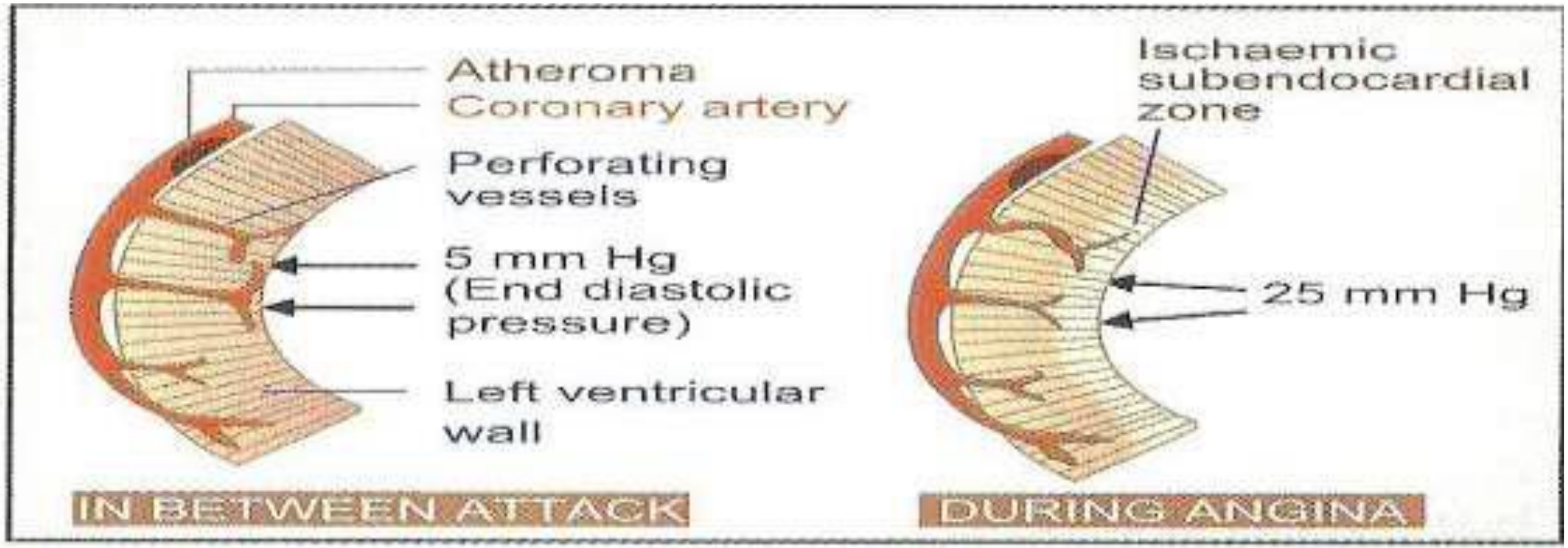


Fig. 39.1: Diagrammatic representation of subendocardial 'crunch' during an attack of angina

❖Common form and is also known as - exertional angina/typical or classic angina/angina of effort/atherosclerotic angina

– The underlying pathology is usually atherosclerosis (reduced oxygen delivery) giving rise to ischemia under conditions where the work load on the heart increases (increased oxygen demand)

– Anginal episodes can be precipitated by exercise, cold, stress, emotion, or eating

– Subendocardial crunch developes

❖Therapeutic goals:

– Increasing myocardial blood flow by dilating coronary arteries and arterioles (increase oxygen delivery)

– Decreasing cardiac load (preload and afterload: decrease oxygen demand)

– Decreasing heart rate (decrease oxygen demand)

Unstable Angina

- **Unstable angina** is also known as:

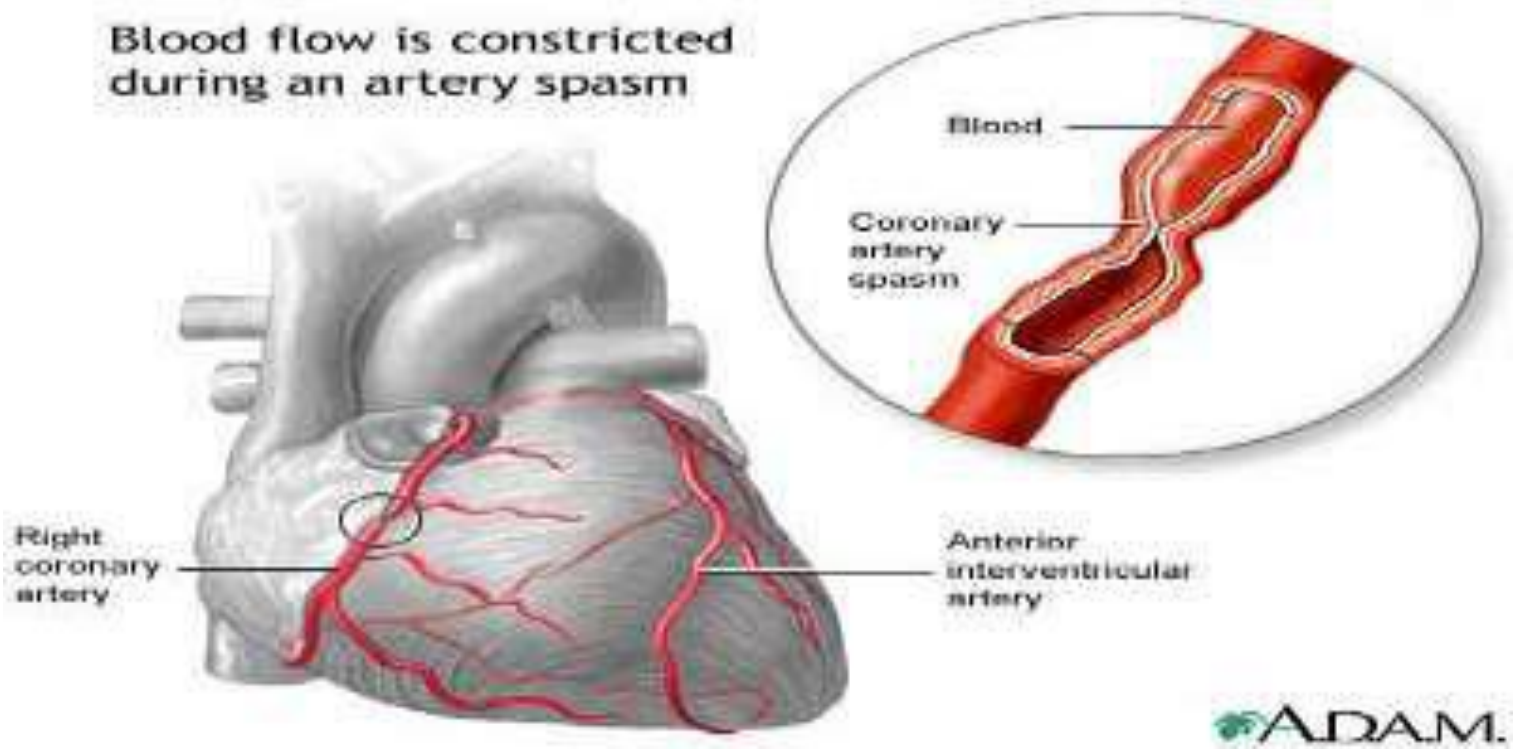
– Preinfarction angina/Crescendo angina/angina at rest

- Associated with a change in the character, frequency, and duration of angina in patients with stable angina, and episodes of angina at rest.
- Caused by recurrent episodes of small platelet clots at the site of a ruptured atherosclerotic plaque which can also precipitate local vasospasm.
- May be associated with myocardial infarction

Therapeutic Goal:

- Inhibiting platelet aggregation and thrombus formation (increase oxygen delivery), decreasing cardiac load (decrease oxygen demand), and vasodilate coronary arteries (increase oxygen delivery)

Vasospastic Angina



- **Vasospastic angina** (uncommon form) is also known as:
  - Variant angina/Prinzmetal's angina
- Caused by transient vasospasm of the coronary vessels
- Attack occurs even at rest or during sleep
- Usually associated with underlying atheromas, abnormally reactive or hypertrophied segments in coronary artery
- Chest pain may develop at rest.

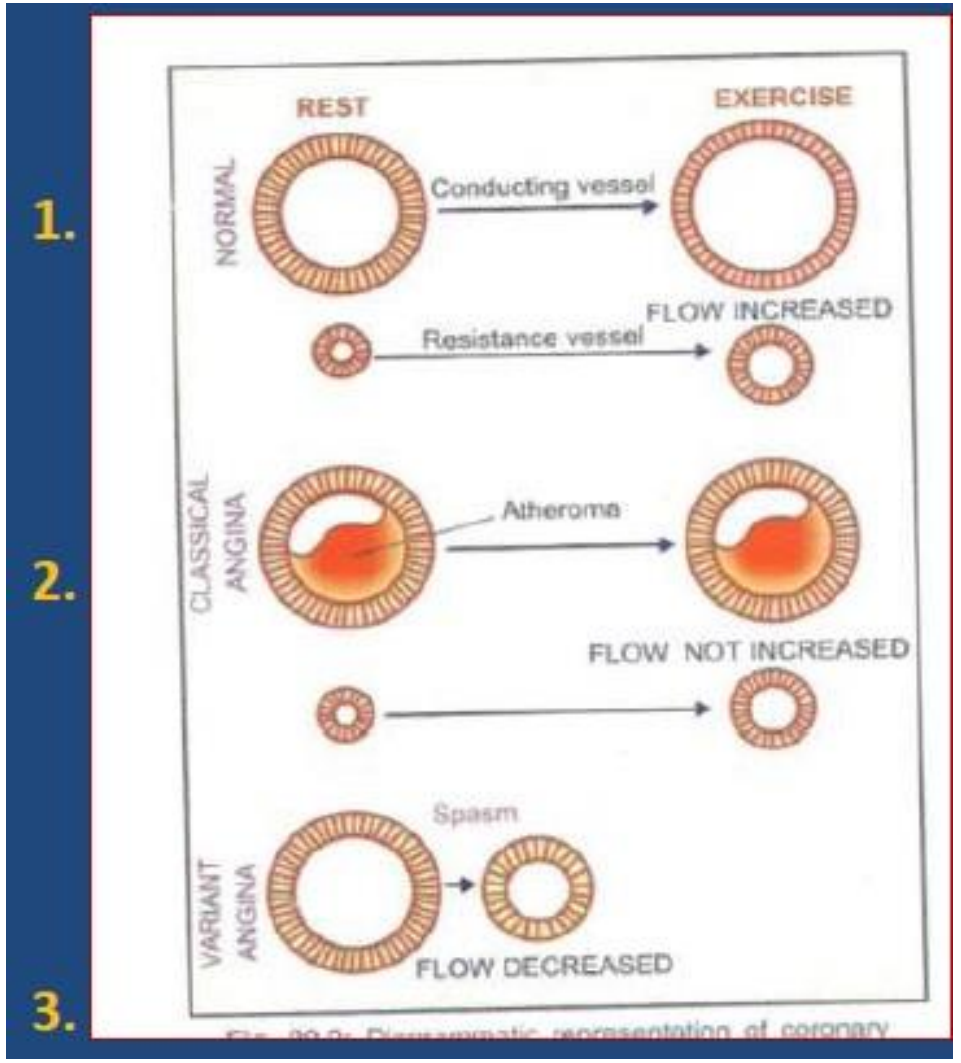
❖**Therapeutic rationale:** Decrease vasospasm of coronary vessels (calcium channel blockers are efficacious in >70% of patients; increase oxygen delivery)

Coronary artery image

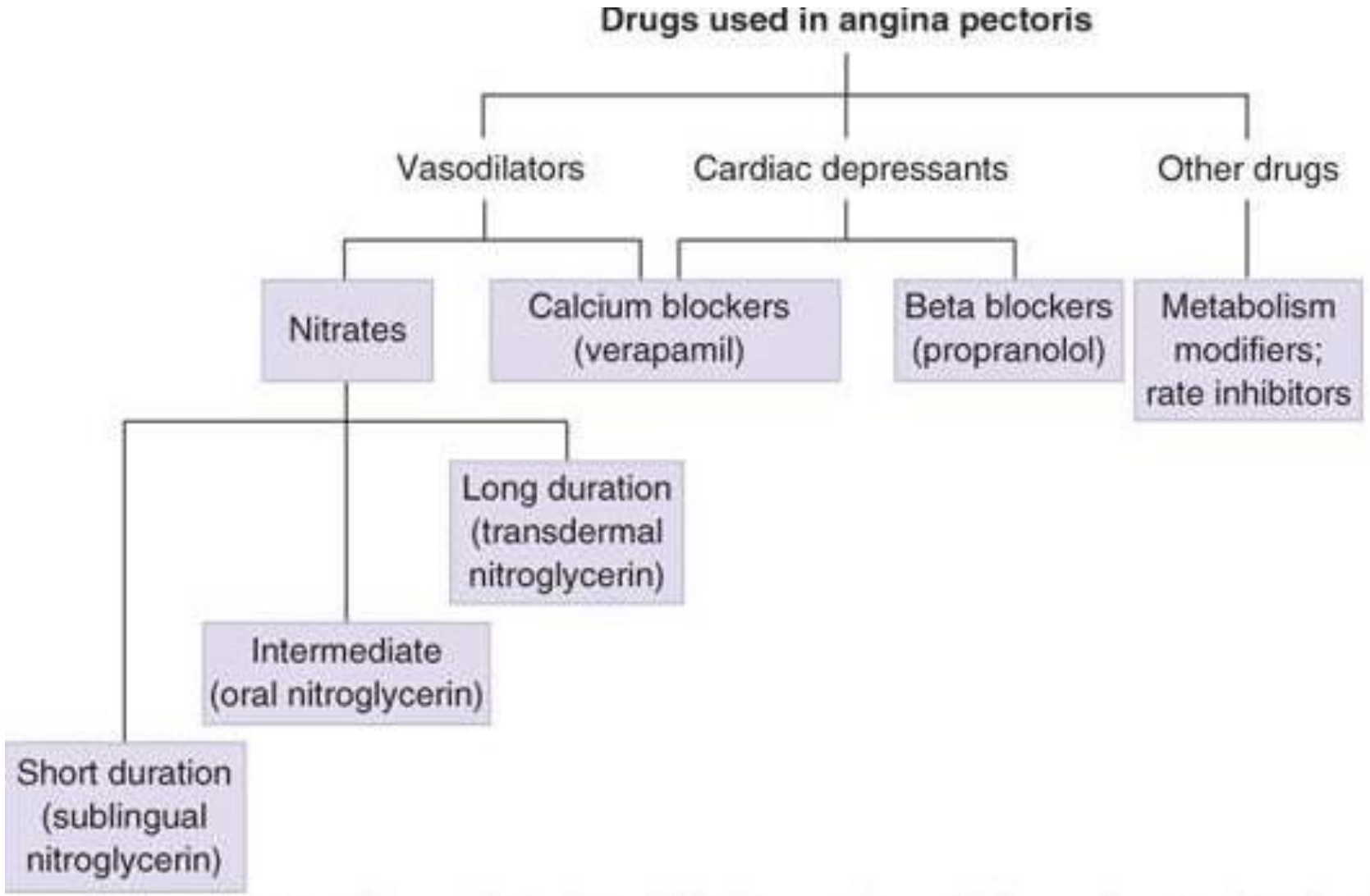
1. Normal

2. Classical angina

3. Variant angina



Classification of Antianginal Agents



1. Nitrates:

a) Short acting (10 minutes): Glyceryl trinitrate (GTN and Nitroglycerine) - **EMERGENCY**

b) Long acting (1 Hour): Isosorbide dinitrate, **Isosorbide mononitrate**, Erythrityl tetranitrate, Pentaerythritol tetranitrate

2. Calcium Channel Blockers:

a) Phenyl alkylamine:Verapamil

b) Benzothiazepin: Diltiazem

c) Dihydropyridines: Nifedipine, Felodipine, Amlodipine, Nitrendipine and Nimodipine

3. Beta—adrenergic Blockers: Propranolol, Metoprolol, Atenolol and others

4. Potassium Channel openers: Nicorandil

5. Others: Dipyridamole, Trimetazidine, Ranolazine and oxyphedrine

Actions of Nitrates

1. Preload reduction:

☐ Dilatation of veins more than arteries – peripheral pooling of Blood – decrease venous return

☐ Reduction in preload – decreased end diastolic size – decrease in fibre length

☐ Less wall tension to develop for ejection less oxygen consumption and reduction in ventricular wall pressure.

2-Afterload reduction:

- Some amount of arteriolar dilatation – Decrease in peripheral Resistance (afterload reduction) – reduction in Cardiac work (also fall in BP)
- Standing posture – pooling of Blood in legs – reflex tachycardia (prevented by lying down and foot end raising)
- However in large doses opposite happens – marked fall in BP – reflex tachycardia – increased cardiac work – precipitation of angina

3. Increased Myocardial Perfusion:

☐ Redistribution of coronary blood flow – facilitates entry of blood to Ischaemic area

☐ However, total blood flow in coronary vessels is almost unchanged with Nitrates

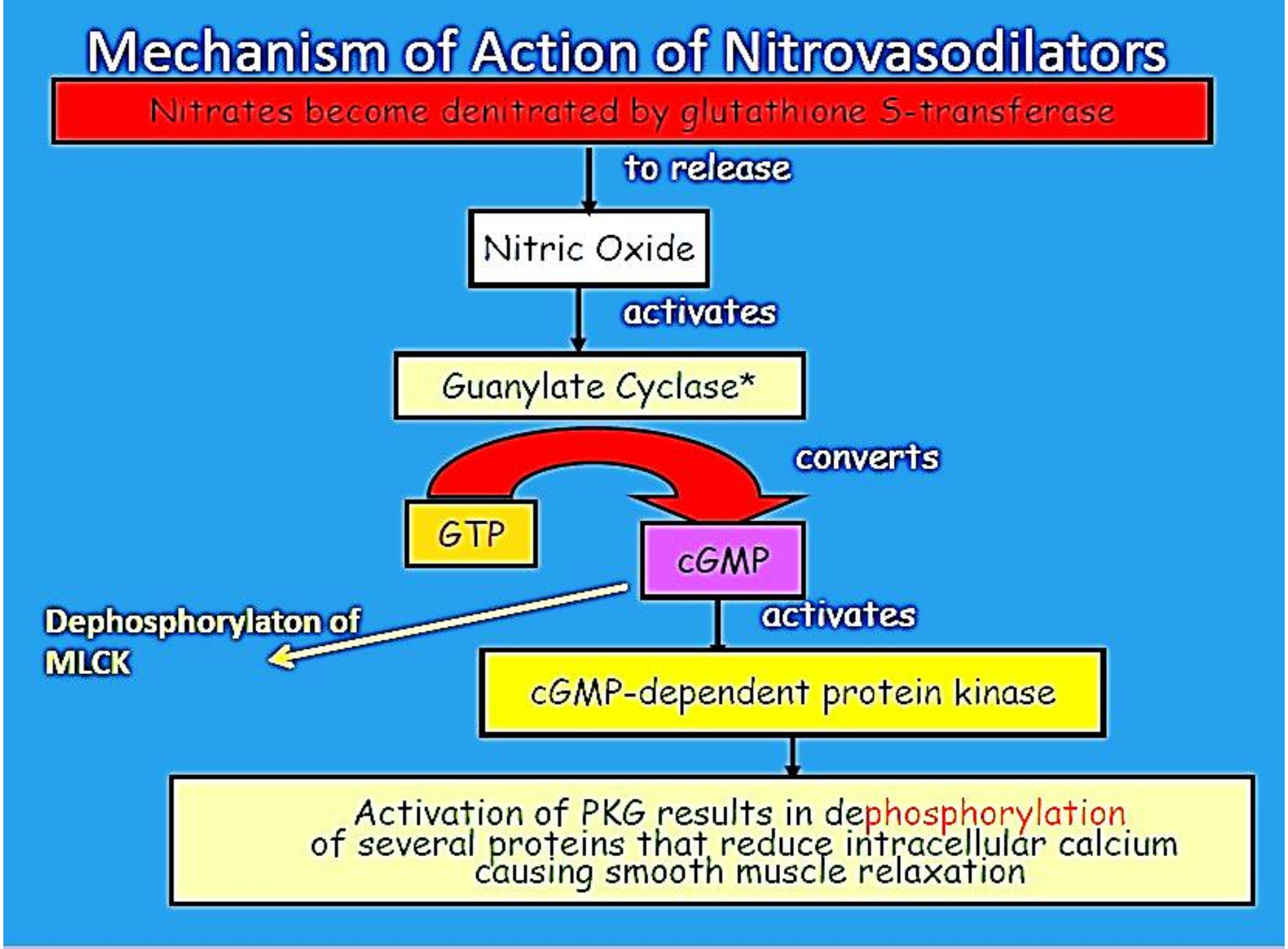
4. Mechanism of angina relief:

☐ Variant angina – coronary vasodilatation

☐ Classical angina – reduction in Cardiac load

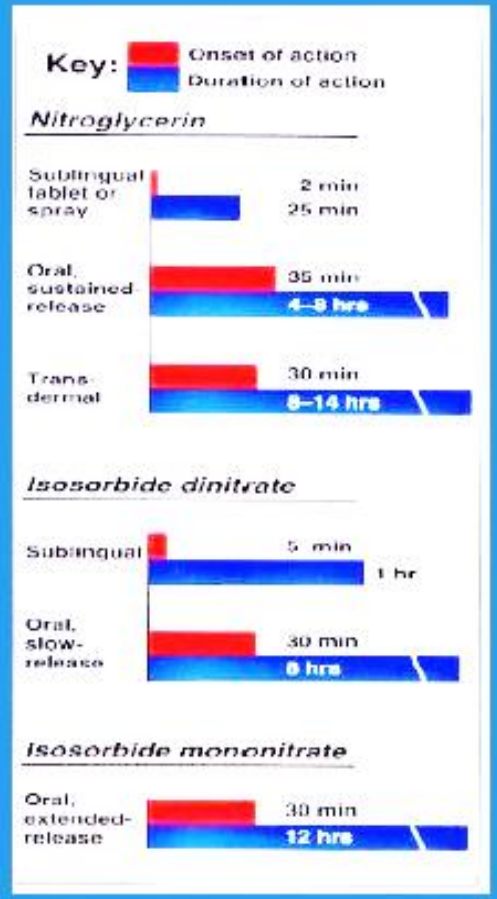
☐ Increased exercise tolerance

5. **Other actions:** Cutaneous vasodilatation (flushing), meningeal vessels dilatation (headache) and decreased splanchnic and Renal blood flow (compensatory)


Mechanism of Action of Nitrovasodilators
Nitrates become denitrated by glutathione S-transferase
to release
Nitric Oxide
activates
Guanylate Cyclase*
converts
GTP
cGMP
Dephosphorylaton of MLCK
activates
cGMP-dependent protein kinase
Activation of PKG results in dephosphorylation of several proteins that reduce intracellular calcium causing smooth muscle relaxation

Property	GTN	ISDN	5-ISMN
Half-life (min)	3	10	280
Plasma clearance (L/min)	50	4	0.1
Apparent volume of distribution (L/kg)	3	4	0.6
Oral bioavailability (%)	< 1	20	100

Comparison of Pharmacokinetic Properties of Nitrates



Nitrates – Therapeutic Uses

1.Angina pectoris: Classical and variant Types

2. Acute Coronary syndromes: Unstable angina and associated with MI (Combination Drugs)

3. Myocardial Infarction: In evolving MI : IV administration is useful in relieving – 3 things: chest pain, congestions of chest and reducing the infarct size favouring blood supply to ischemic zone

4. CHF and LVF: Pooling of blood

5. Biliary colic: Sl administration

6. Oesophageal spasm: Reduction in oesophageal tone (achalasia)

7. Cyanide Poisoning: Nitrates counter cyanide by producing Methaemoglobin – then **Cyanomethaemoglobin (Sod. Thiosulfate is given to form Sod. Thiocyanate)**

Role of Beta-blockers

- No coronary vasodilatation like the nitrovasodilators or calcium channel blockers - beta-blockers are important in the treatment of angina
- Instead coronary flow reduced – beta2 effect
- But, Coronary flow to ischaemic area not reduced:

– Redistribution and decrease in ventricular wall tension

- Improve myocardial perfusion by slowing heart rate (more time spent in diastole) less O2 consumption (decreased HR, Inotropy and mean BP)

- Benefits:
  - Decreased frequency and severity of attacks
  - Increased exercise tolerance (classical angina) – cardioselectives are preferred (coronary spasm due to alpha-blockade)
  - Lowers sudden cardiac death
  - Routinely used in UA and with MI – pretreatment with Nitrates or CCB
  - Avoid abrupt withdrawal

- ADRs and CI:
  - May exacerbate heart failure
  - Contraindicated in patients with asthma
  - Precaution in diabetes since hypoglycemia-induced tachycardia can be blunted or blocked
  - May depress contractility and heart rate and produce AV block in patients receiving non-dihydropyridine calcium channel blockers (i.e. verapamil and diltiazem)

Calcium Channel Blockers

1) **Phenylalkylamines:** Verapamil
2) **Dihydropyridines:**
   - **1st generation: Nifedepine**
   - **2nd generation:** Nicardipine, nimodipine, Felodipine, Isradipine
   - **3rd generation: Amlodipine**
3) **Benzothiazepines: Diltiazem**
4) **Diarylaminopropylamine *ethers:*** Bepridil
5) **Benzimidazole-substituted *tetralines: Mibefradil***

Pharmacological actions:

- **Smooth muscle:** The CCBs cause relaxation by decreasing intracellular availability of Ca2+. The dihydropyridines (DHPs) have the most marked smooth muscle relaxant and vasodilator action; verapamil is somewhat weaker followed by diltiazem.

Pharmacological actions:

- **Heart:** Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. The calcium channel blockers protect the tissue by **inhibiting the entrance of calcium** into cardiac and smooth muscle cells of the coronary and systemic arterial beds and **decreases smooth muscle tone and vascular resistance, afterload**.

CCBs – Therapeutic Uses

1. Angina Pectoris
2. Hypertension
3. Cardiac arrhythmia
4. Hypertrophic Cardiomyopathy: verapamil
5. Nifedipine – Preterm labour and Raynaud`s disease; Verapamil - migraine and nocturnal leg cramps

Adverse effects

Verapamil and Diltiazem:

- Nausea, constipation and bradycardia
- Headache, flushing and oedema – less common
- Hypotension and tachycardia - less common
- Precipitation of CHF in pre-existing patients
- Increase in plasma digoxin level
- Contraindicated in 2nd and 3rd degree heart block

- ❖DHP – immediate release forms e.g. Nifedepine:
  - ➢Palpitation, flushing ankle oedema, hypotension, headache
  - ➢Diuresis
  - ➢Higher incidence of frequency of angina
  - ➢Higer incidence of mortality
  - ➢Voiding difficulty (relaxed bladder Vs increased urine)
- ❖Nifedipine may increase mortality in patients with myocardial ischemia
  - ➢Cause increase in angina frequency (myocardial Ischaemia)
  - ➢Cerebral Ischaemia – rapid bringing down of BP
  - ➢Bladder relaxation
  - ➢Decrease in Insulin release

Combination Therapy of Angina

- Use of more than one class of antianginal agent can reduce specific undesirable effects of single agent therapy

Effect	Nitrates Alone	Beta-Blockers or Channel Blockers Alone	Nitrates Plus Beta-Blockers or Channel Blockers
Heart Rate	*Reflex Increase*	Decrease*	Decrease
Afterload	Decrease	Decrease	Decrease
Preload	Decrease	*Increase*	None or decrease
Contractility	*Reflex increase*	Decrease*	None
Ejection time	Decrease	*Increase*	None

Undesireable effects are shown in italics

* Dihydropyridines may cause the opposite effect due to a reflex increase in sympathetic tone

Potassium Channel Openers

Nicorandil Minoxidil and diazoxide

- MOA:
  - Activation of ATP sensitive K+ channel – hyperpolarization of vascular smooth muscle – relaxation of Smooth muscle
  - Also acts as NO donor and increases cGMP – Arterio-venous relaxation
  - Dilatation of all types of coronary vessels – epicardial and deep
- Benefits in angina (equipotent to nitrates, beta blockers and Ca++ channel blockers)
  - Reduced angina frequency
  - Increased exercise tolerance
- ADRs: Flushing, palpitation, nausea, vomiting, **aphthous ulcer**
- Dose: available as 5, 10 mg tabs and also injection

Other antianginal drugs

Dipyridamole	• Dipyridamole inhibits platelet aggregation • It is a powerful coronary dilator
Trimetazidine	• This antianginal drug acts by nonhaemodynamic mechanisms. • The mechanism of action of trimetazidine is uncertain, but it may improve cellular tolerance to ischaemia by inhibiting mitochondrial long chain 3-ketoacyl-CoAthiolase.
Ranolazine	• This **novel antianginal drug** primarily acts by inhibiting a late Na^+ current (late I_{Na}) in the myocardium.
Ivabradine	• This **'pure' heart rate lowering antianginal drug** has been introduced recently as an alternative to β blockers. • It blocks cardiac pacemaker (sino-atrial) cell 'f' channels.
Oxyphedrine	• Improve myocardial metabolism.


Thank You