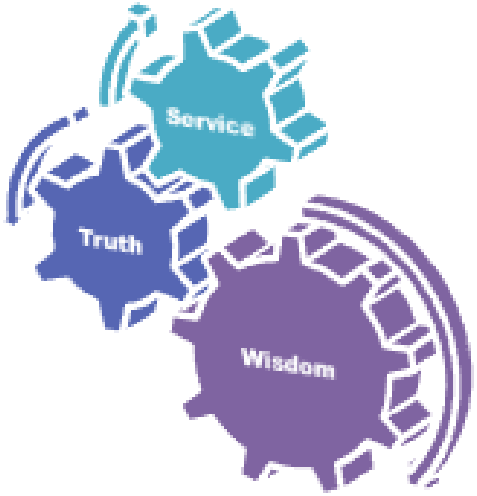
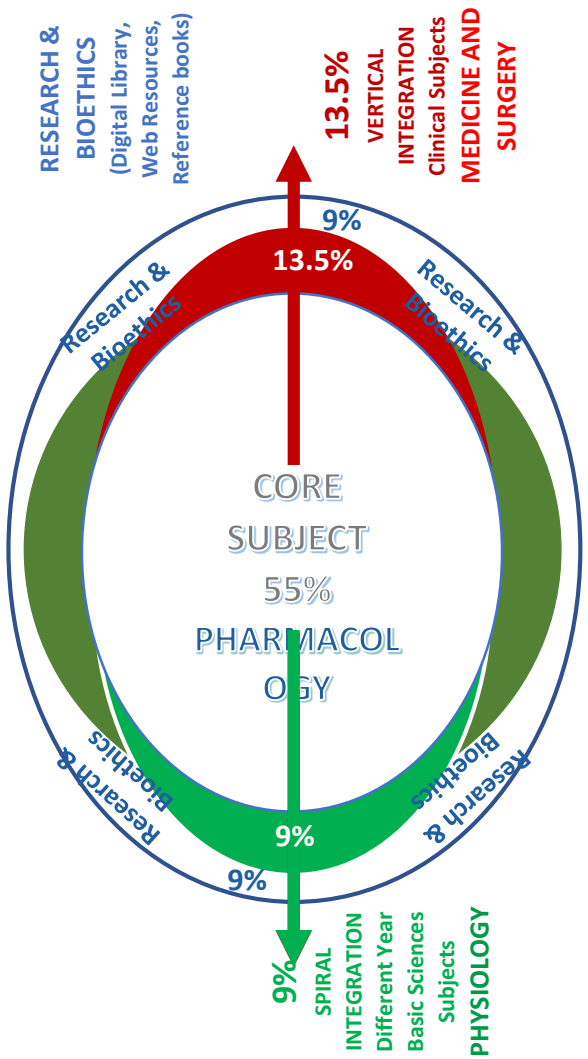

بسم الله الرحمن الرحيم

MOTTO AND VISION



- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology LGIS (slides)	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine (10 %)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

Anti-Anginal Drugs

LEARNING OBJECTIVES

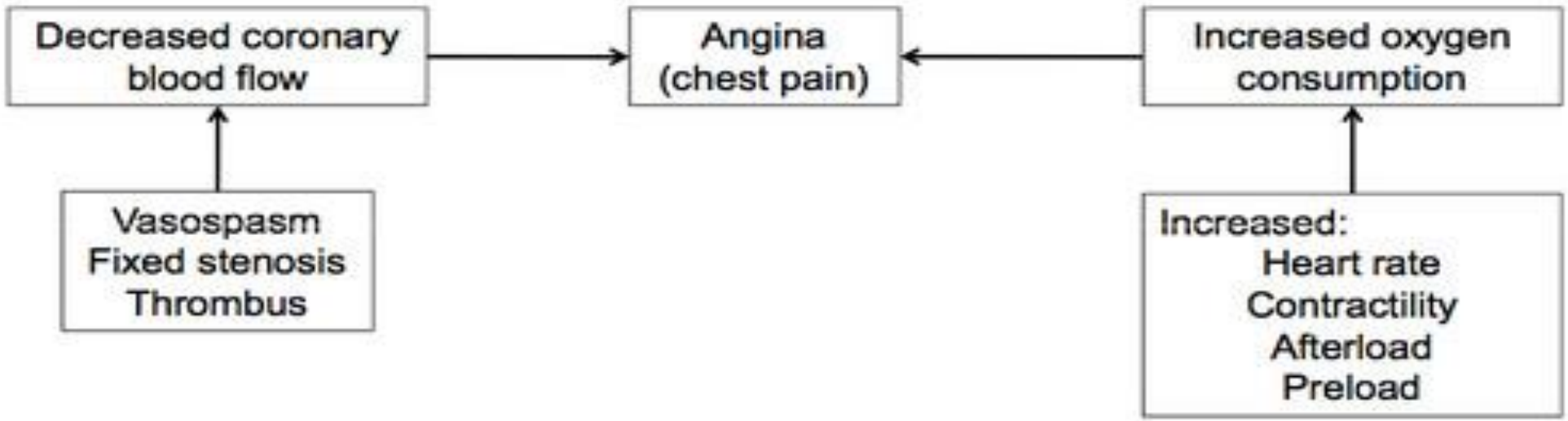
At the end of the lecture, students should know about

- Classification of anti-anginal drugs
- Mechanism of action and adverse effects of anti-anginal drugs

- SPIRAL INTEGRATION ANATOMY/ PHYSIOLOGY

Angina Pectoris

When myocardium becomes hypoxic pain receptors within heart are triggered → classical presentation of chest pain



Vasospasm (transient constriction of coronary arteries)

Fixed stenosis (chronic narrowing of a coronary artery)

Coronary thrombosis (formation of blood clot within the vessel)

TYPES OF ANGINA

1. <u>Stable Angina (exertional angina)</u>

Caused by atherosclerosis

- This leads to reduced blood flow, especially during exertion or stress when the heart's demand for oxygen increases. Symptoms typically resolve with rest or nitroglycerin.

2. <u>Unstable Angina</u>

Caused by plaque rupture and thrombosis.

- Represents a more severe form of ischemia causing pain at rest or with minimal exertion.

3. <u>Variant Angina</u> (Prinz metal's/ Variant Angina)

Caused by coronary artery spasm, leading to transient narrowing of the arteries and reduced blood flow.

- This type can occur at rest, often during sleep, and is not necessarily related to exertion. It may be associated with certain triggers, such as stress or smoking.

Core subject – Pharmacology

Drug Treatment of Angina / IHD

1. Organic Nitrates

- Nitroglycerine (Glyceryl Trinitrate)
- Isosorbide Dinitrate
- Isosorbide Mononitrate
- Pentaerythritol Tetranitrate
- Amyl Nitrite

2. β Blockers

- Propranolol
- Metoprolol
- Atenolol
- Carvedilol
- Bisoprolol
- Nebivolol

3. Calcium Channel Blockers

- Verapamil
- Diltiazem
- Dihydropyridine derivatives
  - *Nifedipine*
  - *Amlodipine*
  - *Felodipine*
  - *Nicardipine*

NEW ANTI ANGINAL AGENTS

4. Potassium Channel Opener

- Nicorandil

5. pFOX Inhibitors

- Trimetazidine

6. Direct Bradycardiac Agents

- Ivabradine

7. Inhibitors of Late Sodium Current

- Ranolazine

8. Rho kinase (ROCK) Inhibitor

- Fasudil

Organic Nitrates

Nitroglycerin… prototype

Explosive in nature

- (Glyceryl trinitrate)….. used in
  - Dynamite industry
  - As fertilizer

- Loose potency….. Due to Volatilization
- Should be kept in tightly closed glass containers

PHARMACOKINETICS

Low oral bioavailability (10-20%)

- Liver contains organic nitrate reductase……. Removes nitrate group…….inactivation

Sublingual route……(fast onset and brief effect…15-30mins)

For longer effect……. Long acting oral agents

Transdermal and buccal route for slow release preparations

- Excretion mainly by glucuronide conjugation by kidneys

Nitrates

GIT availability	Route	Onset	Duration
Glyceryl trinitrate			
poor	sublingual (tablet, spray)	<5 minutes	<1 hour
	patch	30–60 minutes	prolonged
	IV infusion	<10 minutes	
Isosorbide dinitrate			
20–25%	oral tablet	15–40 minutes	4–6 hours
	sublingual tablet	<10 minutes	1–2 hours
Isosorbide mononitrate			
100%	controlled release tablet	1–2 hours	prolonged

Australian Medicines Handbook

Organic Nitrates

Mechanism of action

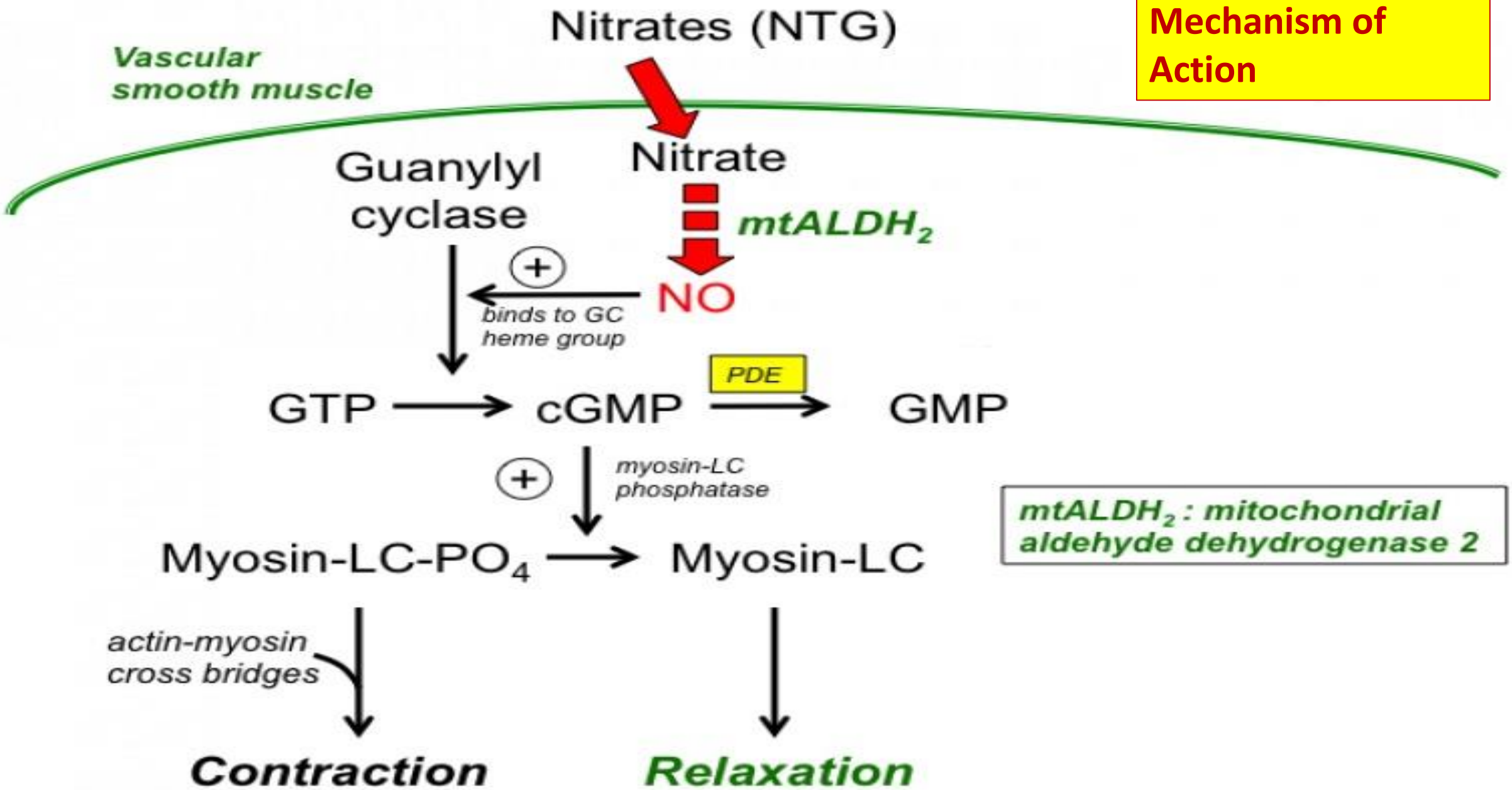
- **Vascular Smooth muscle cells**

❖ **Cellular Mechanism of Action of Nitrates**

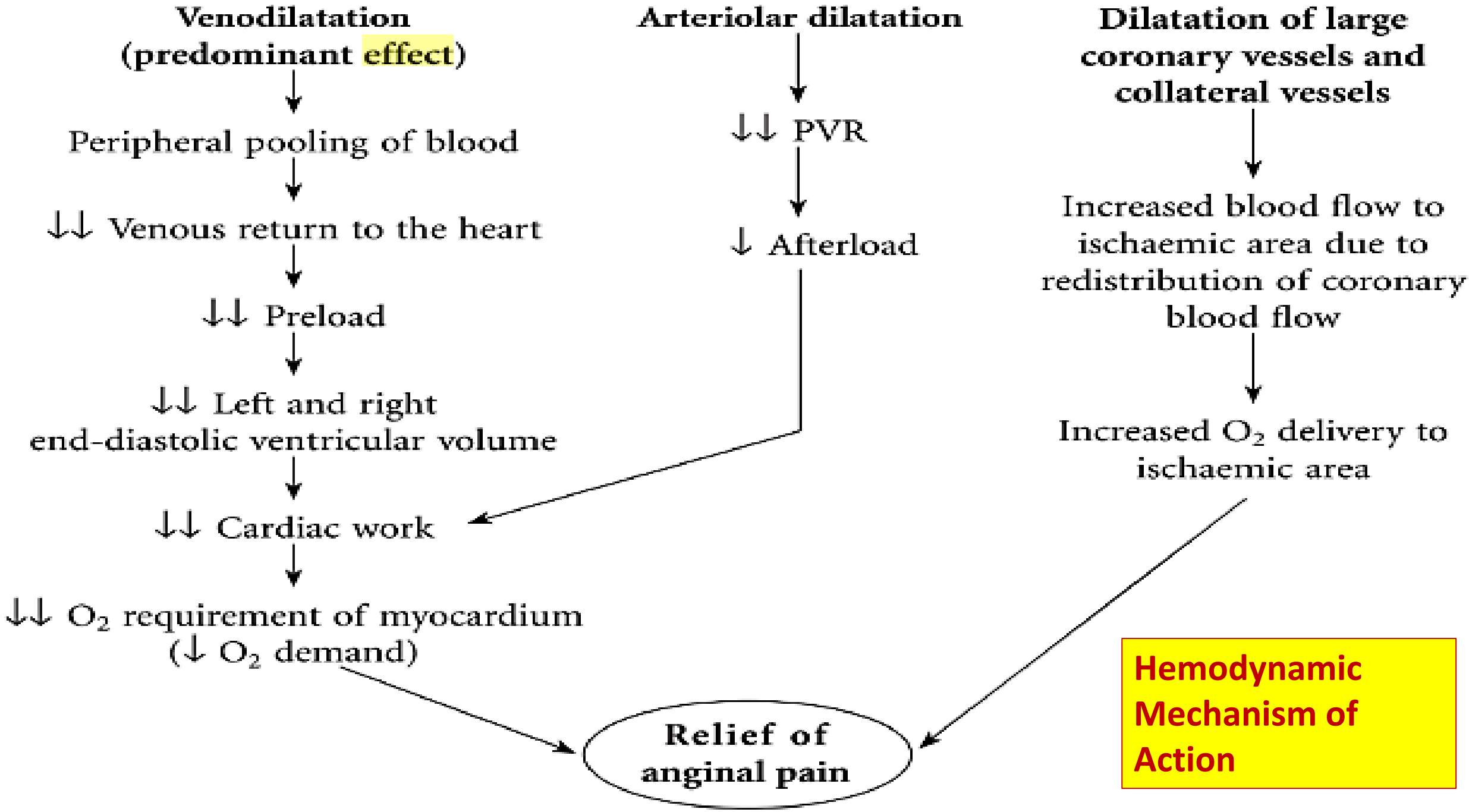
❖ **Hemodynamic Mechanism of Action of Nitrates**

Nitrate Mechanism

Cellular Mechanism of Action



$mtALDH_2$: mitochondrial aldehyde dehydrogenase 2


Venodilatation
(predominant effect)
Peripheral pooling of blood
↓↓ Venous return to the heart
↓↓ Preload
↓↓ Left and right
end-diastolic ventricular volume
↓↓ Cardiac work
↓↓ O2 requirement of myocardium
(↓ O2 demand)
Arteriolar dilatation
↓↓ PVR
↓ Afterload
Dilatation of large
coronary vessels and
collateral vessels
Increased blood flow to
ischaemic area due to
redistribution of coronary
blood flow
Increased O2 delivery to
ischaemic area
Relief of
anginal pain
Hemodynamic
Mechanism of
Action

Organic Nitrates

Pharmacological Actions or Organ System Effects

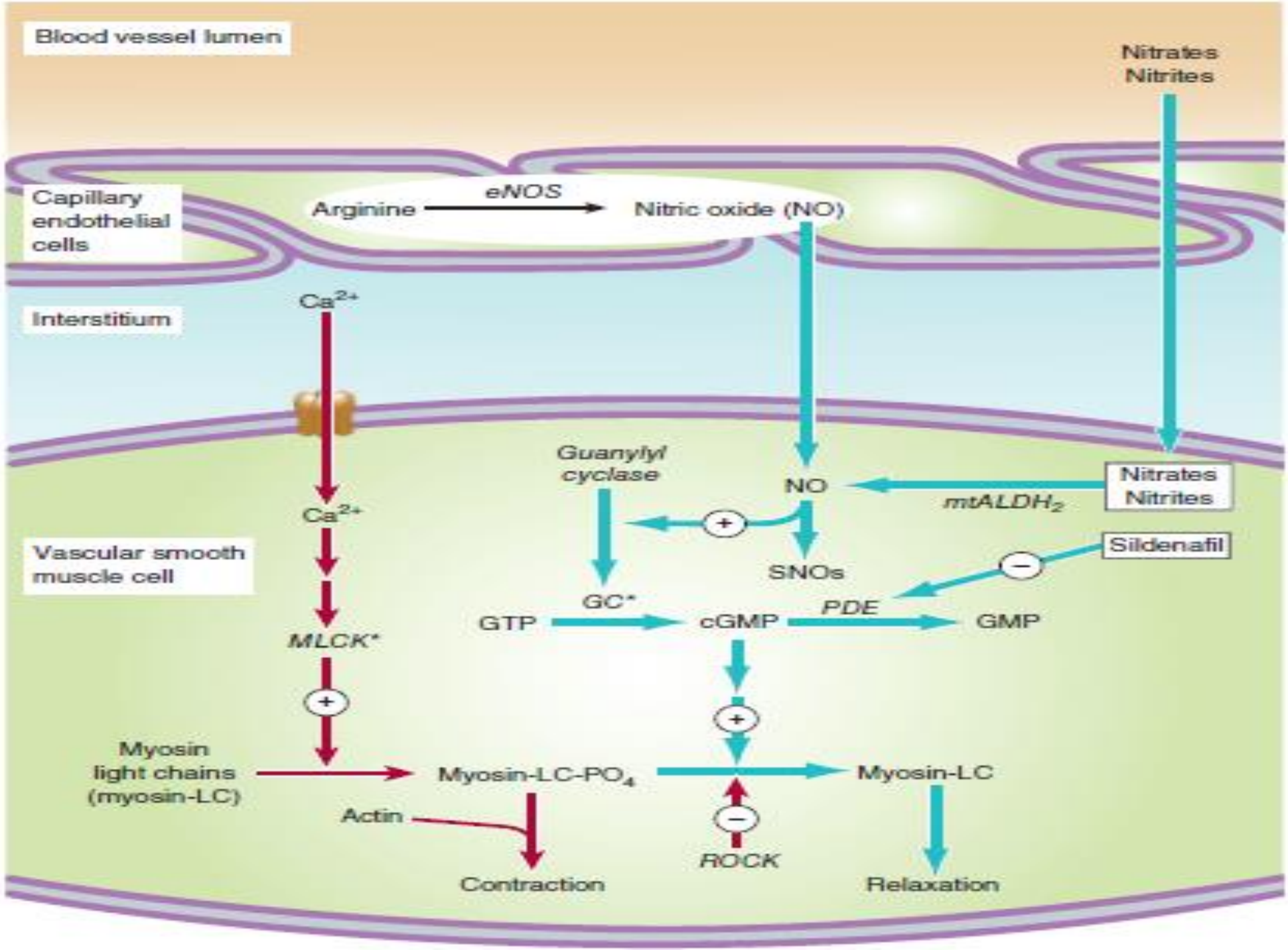
- **Vascular Smooth Muscle**
  - **Sensitivity of vessels**
    - **Veins > Arteries > Arterioles & precapillary sphincters**

► **Action on Platelets**

- **Increase cGMP in platelets…….Decrease Aggregation**

► **Relaxation of Other Smooth Muscle Organs**

- **Bronchi**
- **Genito-urinary**
- **Erectile tissue (prolongs erection…misuse as recreational drug)**


Blood vessel lumen
Nitrates
Nitrites
Capillary endothelial cells
Arginine
eNOS
Nitric oxide (NO)
Interstitium
Ca^{2+}
Guanylyl cyclase
NO
Nitrates
Nitrites
$mtALDH_2$
Ca^{2+}
Vascular smooth muscle cell
Sildenafil
SNOs
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin light chains (myosin-LC)
Myosin-LC-PO_4
Myosin-LC
Actin
ROCK
Contraction
Relaxation

- VERTICLE INTEGRATION MEDICINE/ SURGERY

Therapeutic Uses

1. Angina Pectoris or Ischemic Heart Disease
    - Effect in Variant or Vasospastic Angina
        - Relieve coronary vasospasm
        - Improve coronary blood supply
    - Effects in Unstable Angina
        - Decrease O_2 requirement……pre- & after-load
        - Improve coronary blood supply
        - Decrease platelet aggregation
2. Myocardial Infarction
        - Relieve Pain / Pulmonary Congestion
        - Limit Infarct Area

3. Congestive Cardiac Failure
    - Decrease Preload…… Decrease end diastolic volume
    - Improve LV function in Acute LVF
    - Relieve Pulmonary Congestion

4. Cyanide poisoning

Cyanide Poisoning

Cyanide primarily inhibits cytochrome c oxidase in the mitochondrial electron transport chain required for the final step of aerobic respiration

•Prevents oxygen from being utilized in cellular metabolism causing a cellular "asphyxia" despite adequate oxygen levels in the blood.

- **Cyanide antidote kit**

  (Amyl nitrite + Sodium nitrite+ Sodium thiosulphate)

- Nitrites converts hemoglobin into methemoglobin.
- This methemoglobin has a higher affinity for cyanide, binding to it and reducing its free concentration in the blood.
- This process mitigates the toxic effects of cyanide on cellular respiration.
- **Methylene Blue… if severe methaemoglobinemia**
  - **Hydroxocobalamin…… now preferred**

Treatment of cyanide poisoning

Haemoglobin

↓ **(after inhaling amyl nitrite)**

sodium nitrite (10ml of 3% sol. IV)

↓

Methaemoglobin

↓ **cyanide**

Cyanomethaemoglobin

↓ **sodium thiosulphate (50ml of 25%sol. IV)**

Methaemoglobin + sodium thiocyanate

↓

excrited in urine

Organic Nitrates

Adverse Effects

- **Acute Adverse Effects**
  - **Extension of pharmacological effects**
    - **Throbbing Headache, Hypotension, Tachycardia**
  - **Transdermal patch ignited…….Defibrillator electroshock…….superficial burns**

Tolerance

Chronic exposure to nitrates can lead to increased oxidative stress. Elevated ROS levels can impair endothelial function and reduce the bioavailability of NO.

Mechanism

1. **Reduced bio-activation…reduced NO release**
2. **SH groups depletion**
3. **Soluble GC responsiveness**
4. **Oxygen free radicals**

Treatment:

- **Nitrate free periods**
- **Anti- oxidant supplementation**

Monday Disease

A phenomenon commonly experienced by workers who are exposed to certain hazardous substances in industrial settings.

Symptoms often arise after a weekend away from exposure to these substances on return to work.

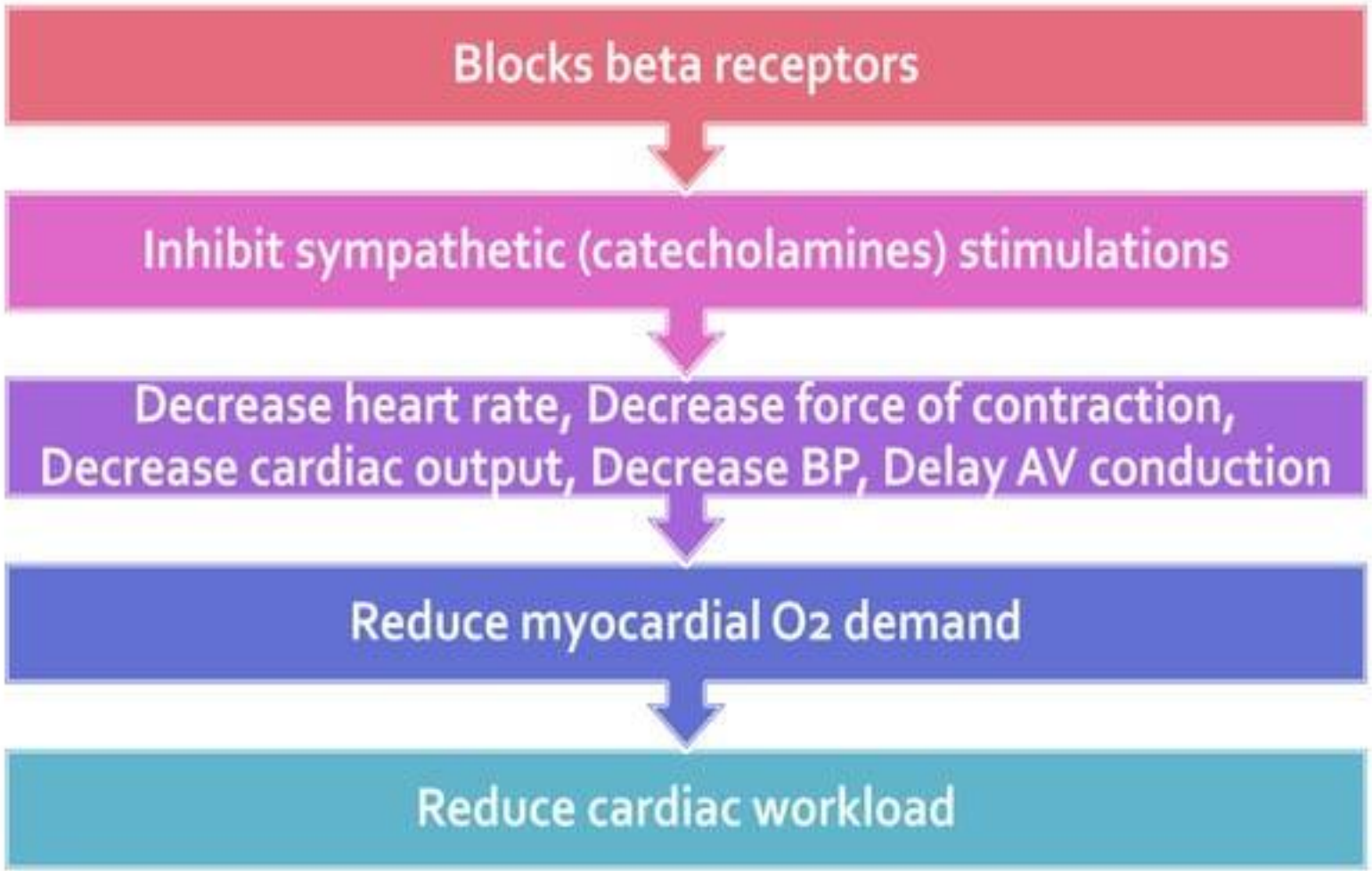
- **Mechanism**:
- Body adjusts to the absence of exposure over the weekend. Upon re-exposure, the body reacts more vigorously due to a buildup of sensitivity or tolerance to the substance.

DRUG INTERACTIONS

- **Sildenafil and Other PDE5 Inhibitors**
- **Other Blood Pressure Medications**
- **Alcohol**
- **Antidepressants**

Beta adrenergic blockers

Mechanism of action



- VERTICLE INTEGRATION MEDICINE/ SURGERY

Uses

- **Hypertension**
  - As first line drugs in mild to moderate hypertension
  - Used alone or with other antihypertensives.
- **Angina pectoris**
  - Long term prophylaxis of exertional angina and classical angina.
  - Cardioselective drugs are preferred than non selective drugs.
  - Have to take on regular basis.
- **Cardiac arrnythmias**
  - For both supraventricular & ventricular arrhythmias

- **Myocardial infarction**
  - Given IV infusion in acute MI to limit the size of infarct.
  - Long-term treatment prolongs survival.
- **Congestive cardiac failure**
- **Obstructive cardiomyopathy**
- **Pheochromocytoma**
  - Propranolol is given before surgery to control hypertension.

Calcium channel blockers

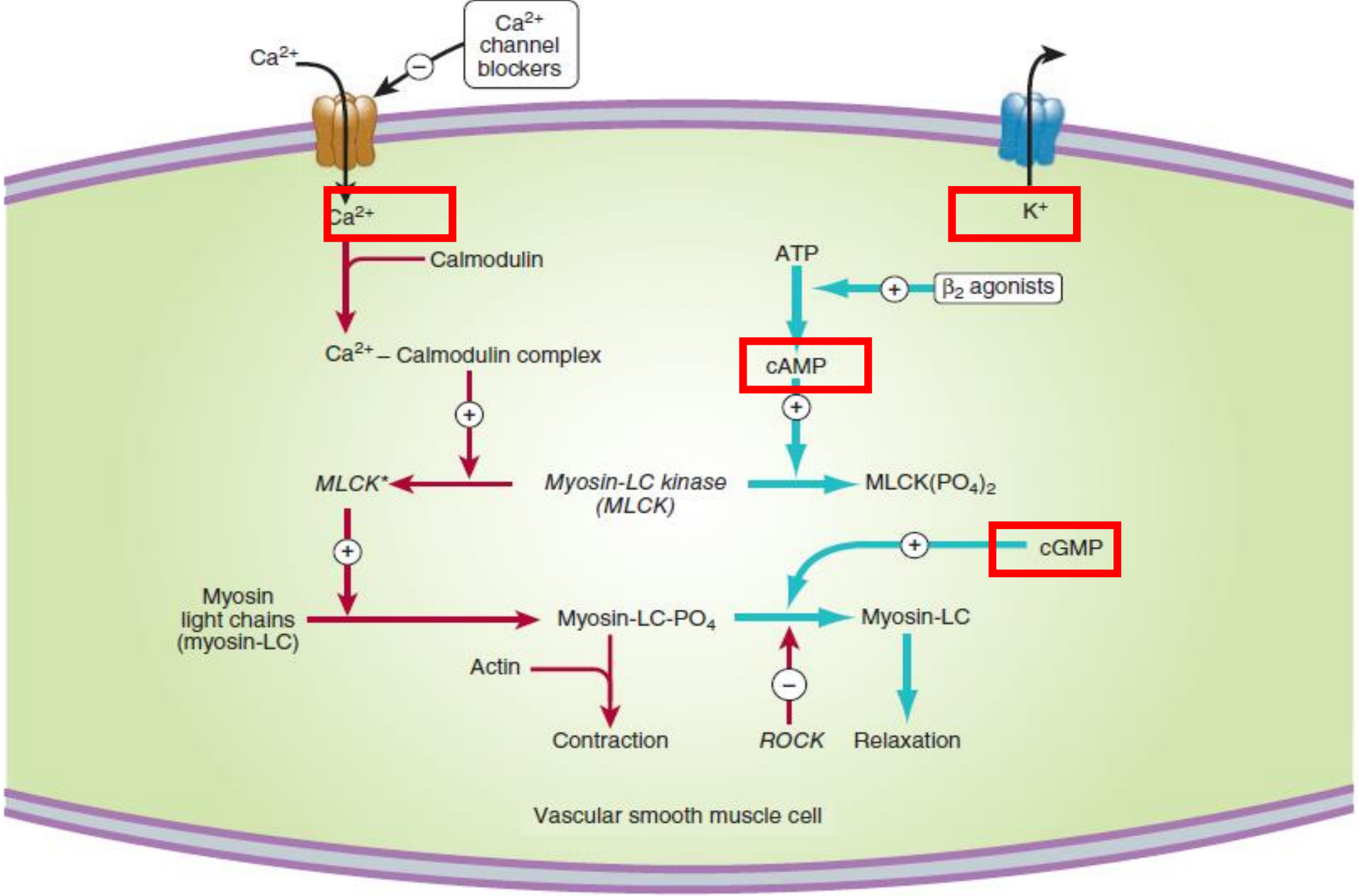
Core subject – Pharmacology

CALCIUM CHANNEL BLOCKERS
Mechanism of action

- Voltage sensitive Calcium channels are of 3 types:

  L-Type, T-Type and N-Type

- Normally, L-Type of channels admit Ca+ and cause depolarization → excitation-contraction coupling through phosphorylation of myosin light chain →contraction of vascular smooth muscle → elevation of BP
- CCBs block L-Type channel leading to:
  - Smooth Muscle relaxation
  - Negative chronotropic and ionotropic effects in heart


Ca^{2+}
Ca^{2+} channel blockers
Ca^{2+}
Calmodulin
Ca^{2+} – Calmodulin complex
MLCK*
Myosin light chains (myosin-LC)
Actin
Contraction
K^+
ATP
β_2 agonists
cAMP
Myosin-LC kinase (MLCK)
$MLCK(PO_4)_2$
cGMP
$Myosin\text{-}LC\text{-}PO_4$
Myosin-LC
ROCK
Relaxation
Vascular smooth muscle cell

Calcium Channel blockers

Phenylalkylamines:

Verapamil

Benzothiazepines:

Diltiazem

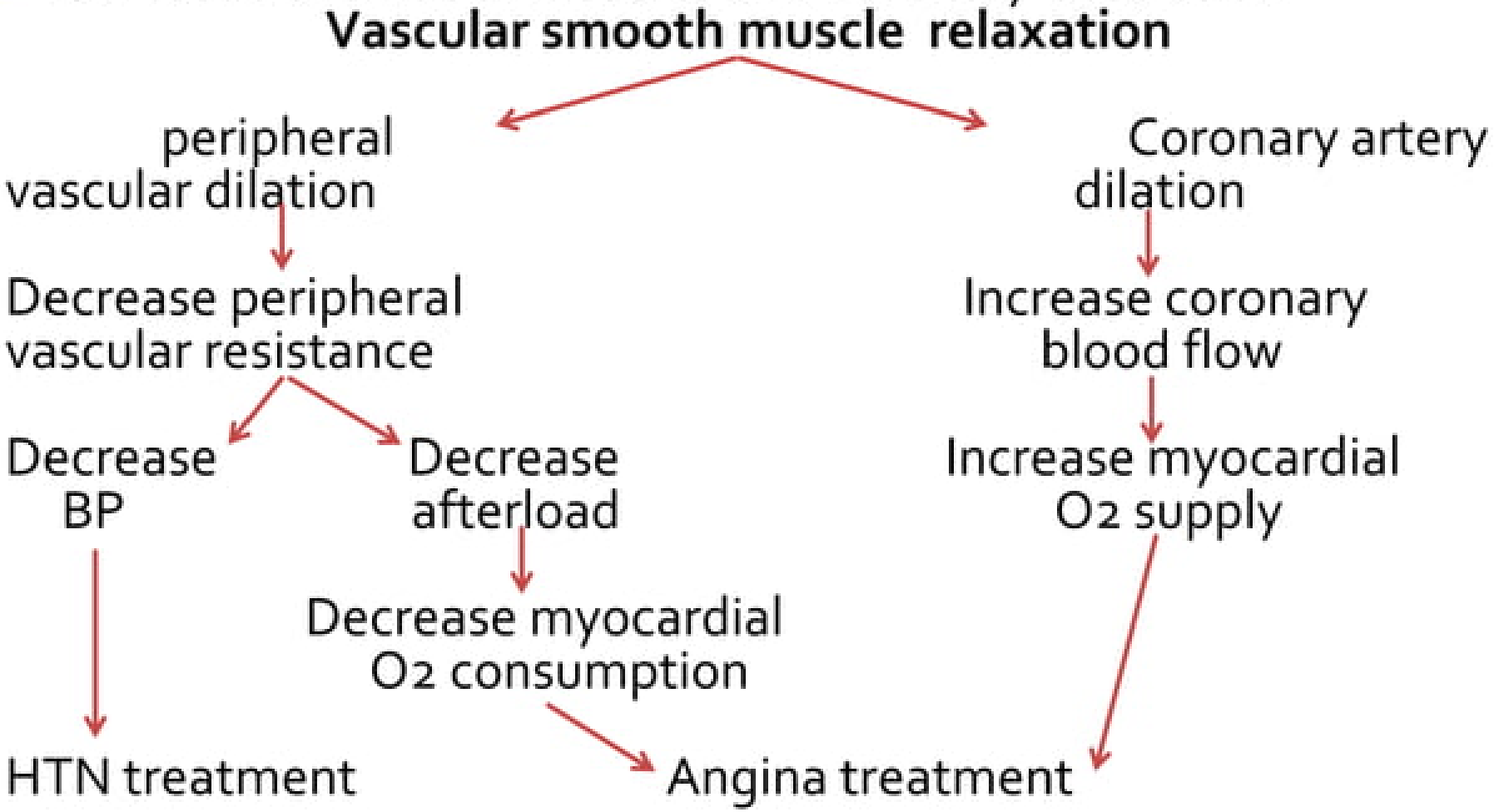
Dihydropyridines:

Nifedipine,Nicardapine,Isradapine, Fenoldopine,Amlodipine

Pharmacological action

- On vascular smooth muscles and Coronary circulation
- On other smooth muscles
- On heart

- On vascular smooth muscles and Coronary circulation



- Dihydropyridine CCBs have prominent effect on blood vessels.
- Nimodipine crosses the blood brain barrier and relaxes the cerebral blood vessels.

On other smooth muscles

- Relax GI and bronchial smooth muscles
- Relax uterus, so used in premature labor.

- **On heart**

Decrease myocardial Contraction

↓

Decrease heart Rate

↓

Reduce myocardial workload

↓

Decrease myocardial O_2 Consumption

↓

Angina treatment

Decrease AV conduction velocity

↓

Bradycardia

↓

Arrhythmia treatment

Pharmacokinetics

- CCBs are well-absorbed orally but undergo extensive first pass metabolism.
- They are metabolized in the liver.
- Excreted through kidneys.
- Onset of action is in 30-60 minutes after oral administration while on IV use the action is quick.

Individual CCBs

1. **Verapamil**

- Decrease heart rate (negative chronotropic effect)
- Decrease force of myocardial contraction (negative ionotropic effect)
- Decrease AV conduction
- Vasodilator effect of verapamil is less potent.
- Used in arrhythmia and angina.
- Dose: 40-160 mg TDS orally and 5 mg by slow IV inj.
- Adverse effects
  - Nausea
  - Constipation
  - Bradycardia
  - Heart block
  - Hypotension
  - Skin rashes

2. **Diltiazem**

- Decrease heart rate (negative chronotropic effect)
- Decrease force of myocardial contraction (negative ionotropic effect)
- Vasodilator effect is less potent.
- Dose: 30-60 mg TDS orally.
- Adverse effects –same as verapamil.

3. **Nifedipine**

- Potent vasodilator and causes a significant fall in BP and evokes reflex tachycardia.
- Myocardiac depressant effect is weak
- It can be given orally or sublingually. Patches also
- Dose: 5-20 mg BD
- Adverse effects
  - Headache
  - Flushing
  - Palpitation
  - Dizziness
  - Fatigue
  - Hypotension
  - Leg cramps
  - Ankle edema
  - Long-term use : gum hypertrophy

3. **Nimodipine**

- Crosses the blood brain barrier and relaxes the cerebral blood vessels.
- Used in haemorrhagic stroke and subarachnoid haemorrhage.
- Dose: 30-60 mg QID.

- VERTICLE INTEGRATION MEDICINE/ SURGERY

CONTRAINDICATIONS OF CCBs

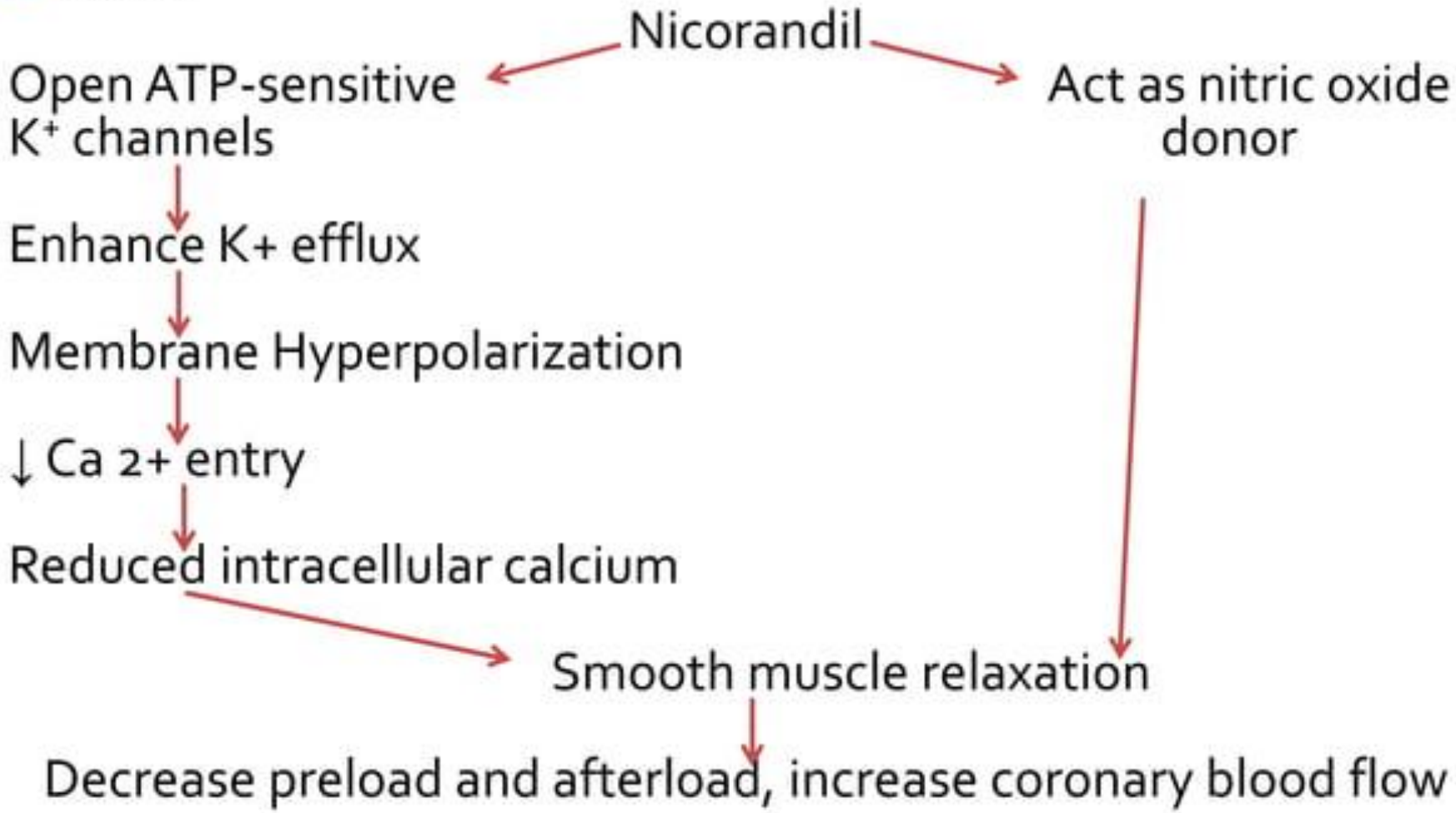
- Hypotension
- Wolf-Parkinson white syndrome (WPWS)…….. VFIB
- Heart block (dec. conduction)
- Decompensated heart failure (dec. contractility)
- Aortic stenosis (syncope)

CLASSIFICATION AND ACTIONS OF ANTIANGINAL DRUGS	
Drug class	**Antianginal actions**
Nitrates and Nitrites	- Decrease in cardiac O_2 demand by ***reducing preload*** (the main action) - Increase in cardiac O_2 delivery by relieving coronary spasm.
Calcium-channel blocking drugs	- Decrease in cardiac O_2 demand by: a) ***reducing afterload*** (the main action) b) ***reducing cardiac contractility and rate*** - Increase in cardiac O_2 delivery by relieving coronary spasm.
Beta adrenoceptor blocking drugs	- Decrease in cardiac O_2 demand **by *reducing cardiac contractility and rate***

Potassium channel openers

Nicorandil

- Nicorandil is an arterial and venous dilator.
- **MOA**



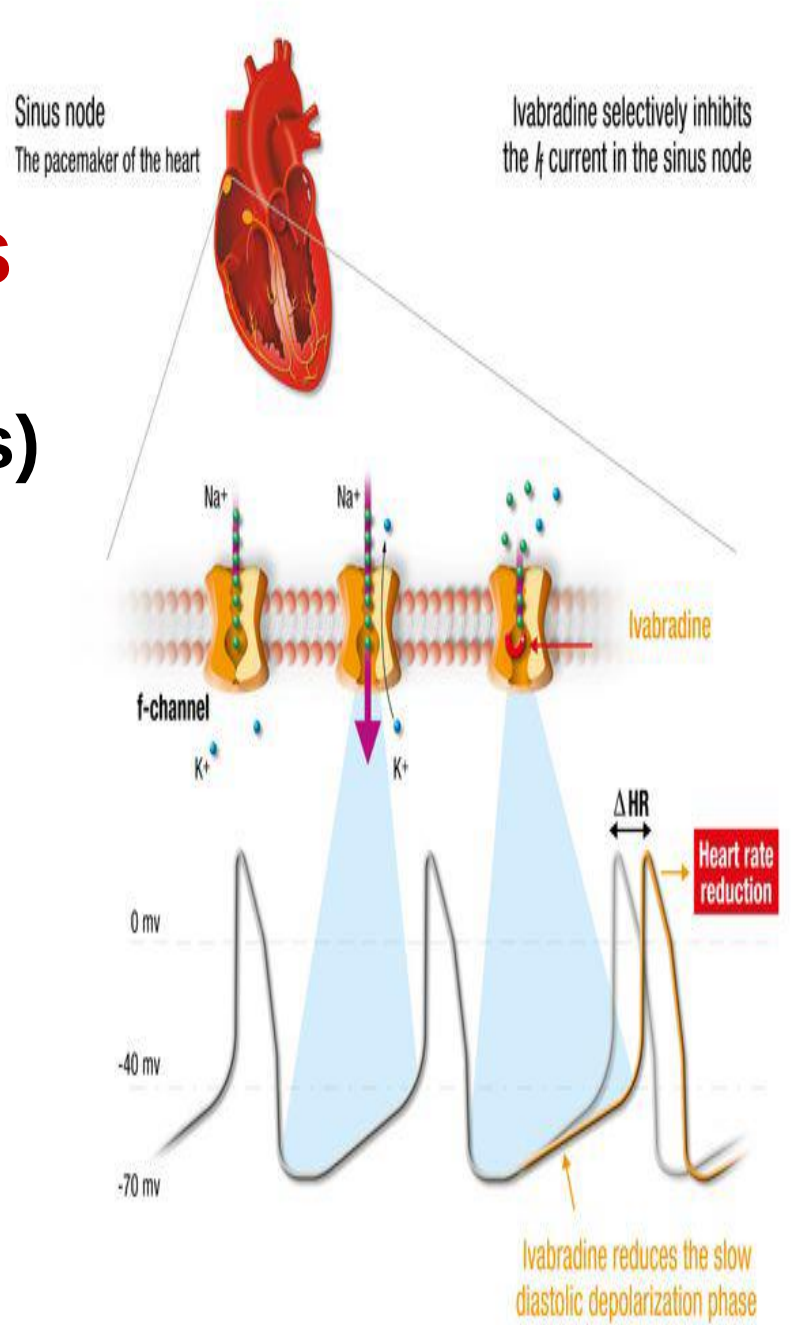
- Use
  - Resistant angina
  - In combination with other drugs
- Dose: 10-20 mg twice daily.
- Adverse effects
  - Headache
  - Flushing
  - Palpitation
  - Dizziness
  - Hypotension

Miscellaneous drugs

Direct acting Bradycardiac Agents

- Ivabradine
- Inhibits funny Na+ channels (I*f*- channels)
- SA node
- Pacemaker activity
- Reduce heart rate
- Uses
  - Angina
  - Heart failure

  Adverse effect
  - Visual disturbances



Trimetazidine

- Anti-anginal action through inhibition of fatty acid metabolism, also known as fatty acid oxidation inhibitor.
- Used in post MI patients.
- Dose: 20 mg TID.

pFOX Inhibitors

- **Trimetazidine**
- **In myodarcial Ischemia, metabolism shifts to Fatty Acid oxidation…..Oxygen requirement and ATP utilization increases**

- **It Inhibits Fatty Acid oxidation Pathway by inhibiting enzyme LC-3KAT(long-chain 3-ketoacyl thiolase)**

RANOLAZINE

Pharmacology	Ranolazine is a piperazine derivative. In 2006 ranolazine received FDA approval for the treatment of chronic angina. Ranolazine is metabolized mainly by the CYP3A system
Mechanism of action	It inhibits the late Na current in cardiac muscle thus preventing calcium overloading of heart muscle, which in turn reduces the tension and oxygen consumption in heart muscle
Common use	Chronic stable angina
Side effects	Dizziness, constipation, headache, nausea, syncope
Promising role	Stable ischemic heart disease with diabetes mellitus, postcardio version and post-CABG atrial fibrillation

FDA: Food and Drug Administration, CABG: Coronary artery bypass grafting

Rho kinase (ROCK) Inhibitor

Fasudil

► ROCK…. Family of enzymes that inhibit vascular relaxation

► Inhibit ROCK…..vasodilation…. reduces Coronary vasospasm

Research Article

- https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-12/Novel-agents-in-the-treatment-of-stable-angina

- https://www.brainkart.com/article/Newer-Antianginal-Drugs_24521

The Four Key Principles of Bioethics

Non-Maleficence

"Do no harm." Minimize any possible risks to the patient.

Autonomy

The patient family retains the right to make treatment decisions with all relevant information presented to them.

Beneficence

The overall needs of the individual must be taken into account with the benefits balanced against the risks.

Justice

Access to treatment and care should be fair and equitable.

How To Access Digital Library

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6. Journals and Researches will appear
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Thank you

Thank you