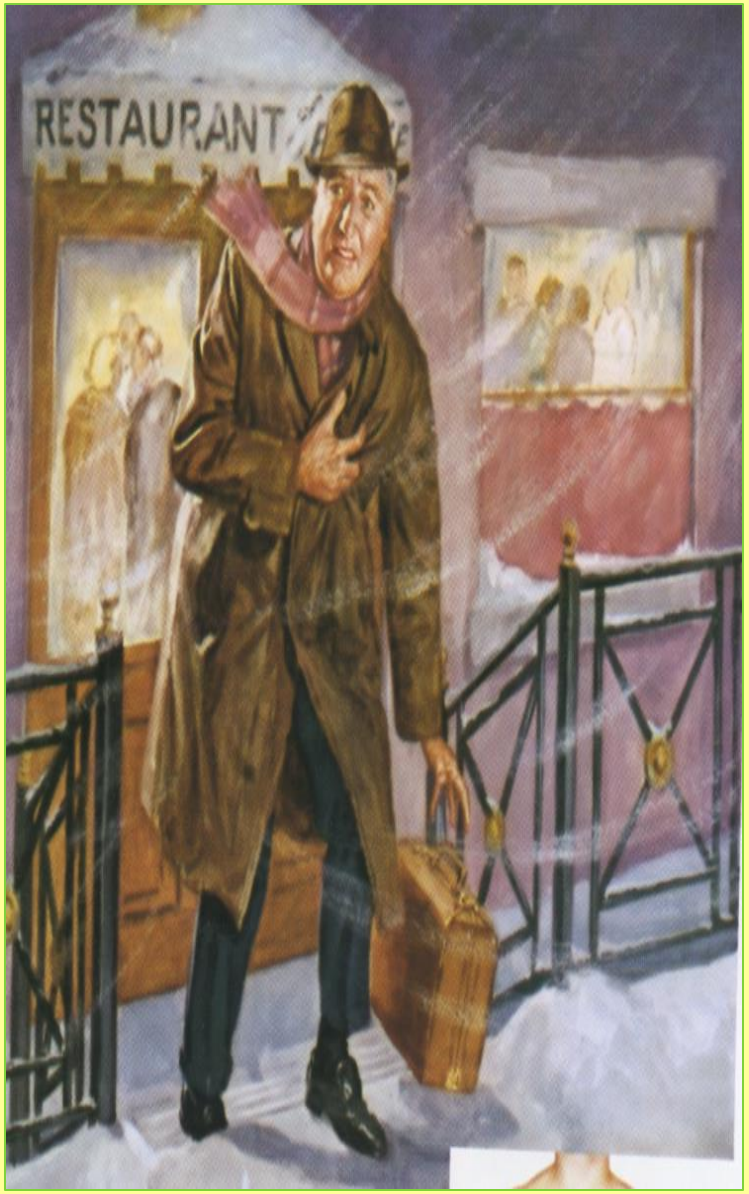
ANTIANGINAL DRUGS

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, and other drugs used as antianginal therapy



What is Angina Pectoris?

A Pain is caused either by obstruction

severity) due to ischemia of heart muscle

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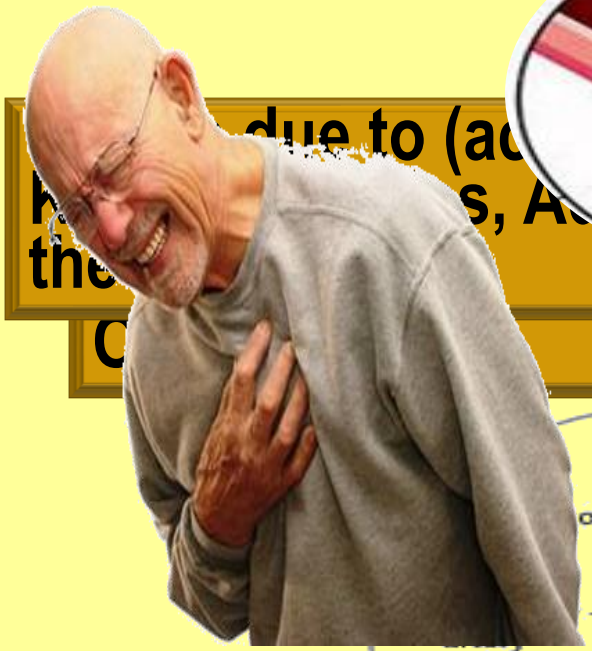
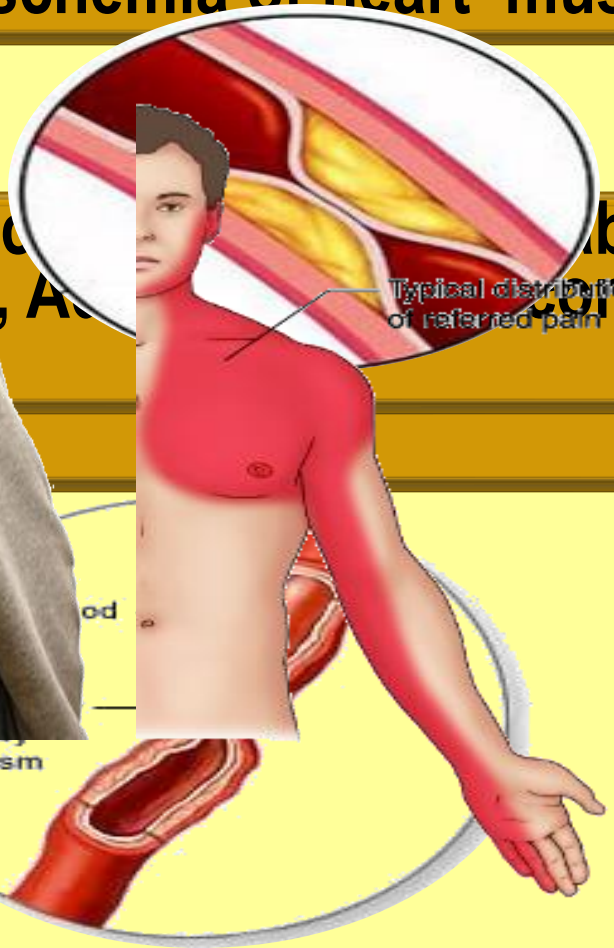
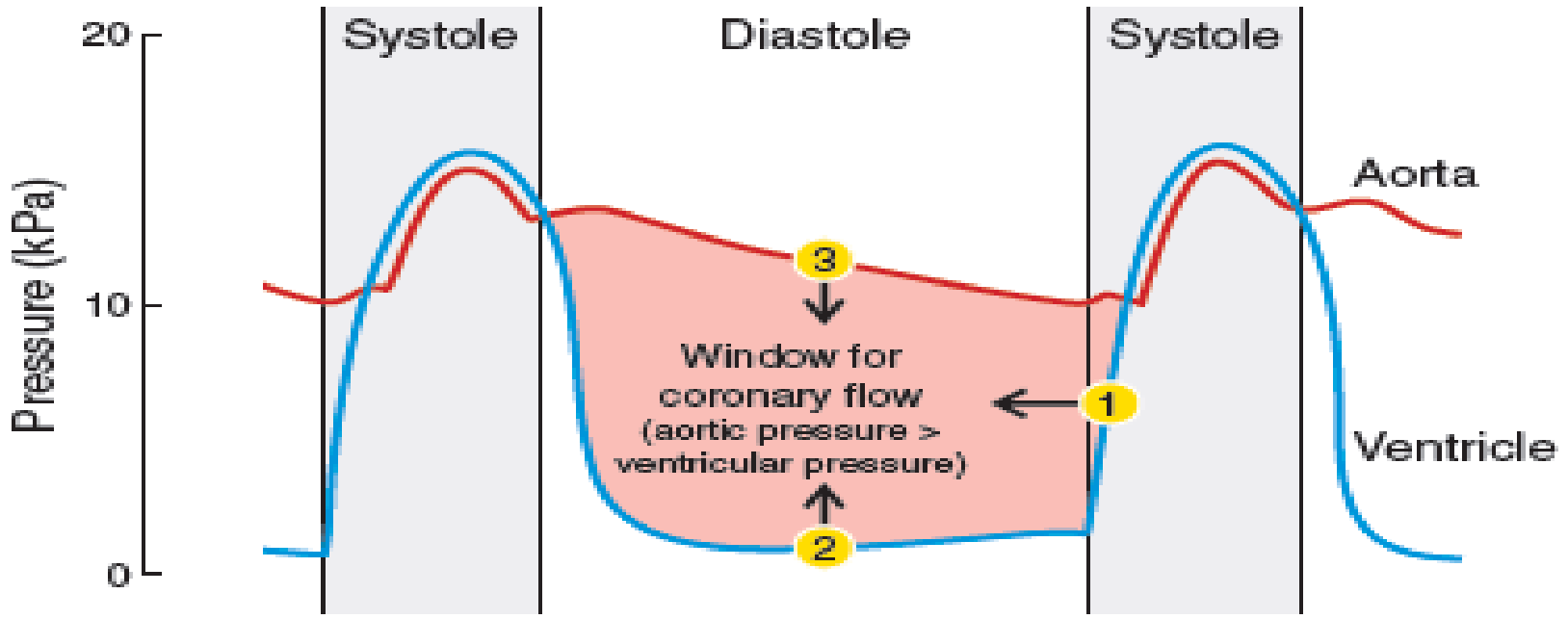




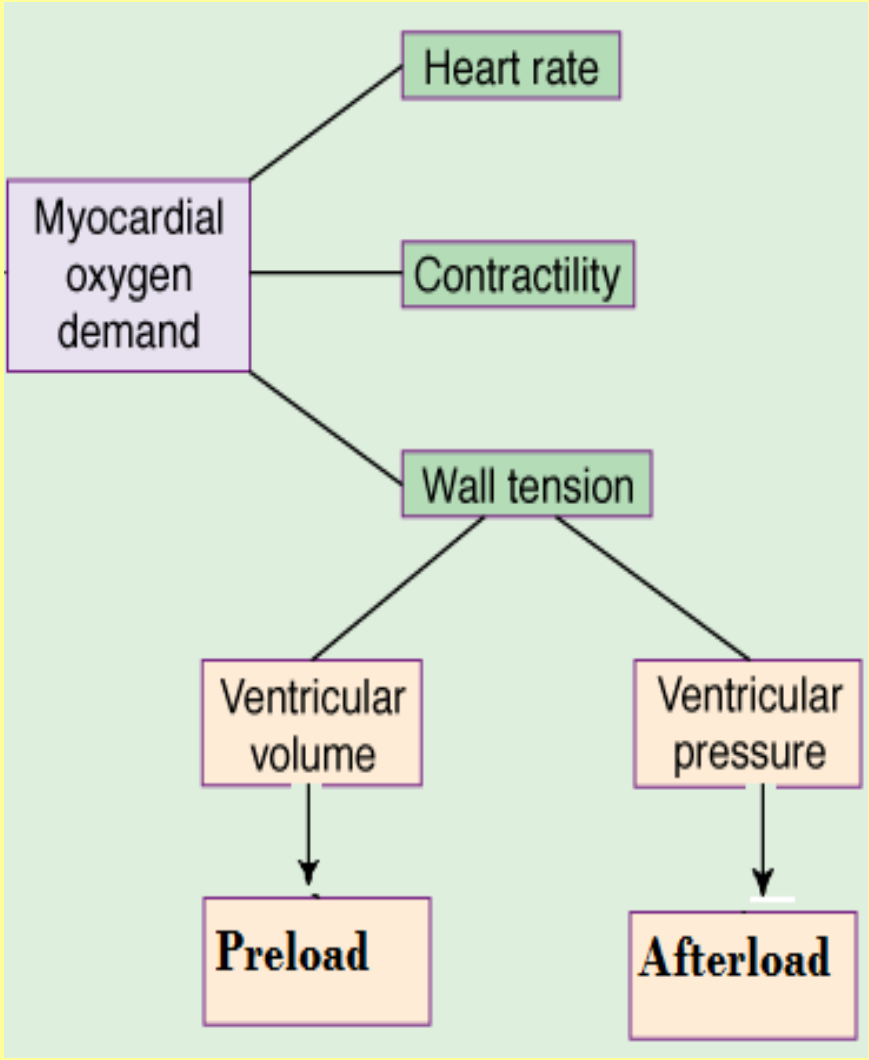
WHAT IS BASIC MECHANISM OF ANGIA PECTORIS?

WHAT ARE THE DETERMINANTS OF OXYGEN DEMAND AND SUPPLY?



Coronary Perfusion Pressure = Aortic Pressure - Left Ventricular End diastolic Pressure

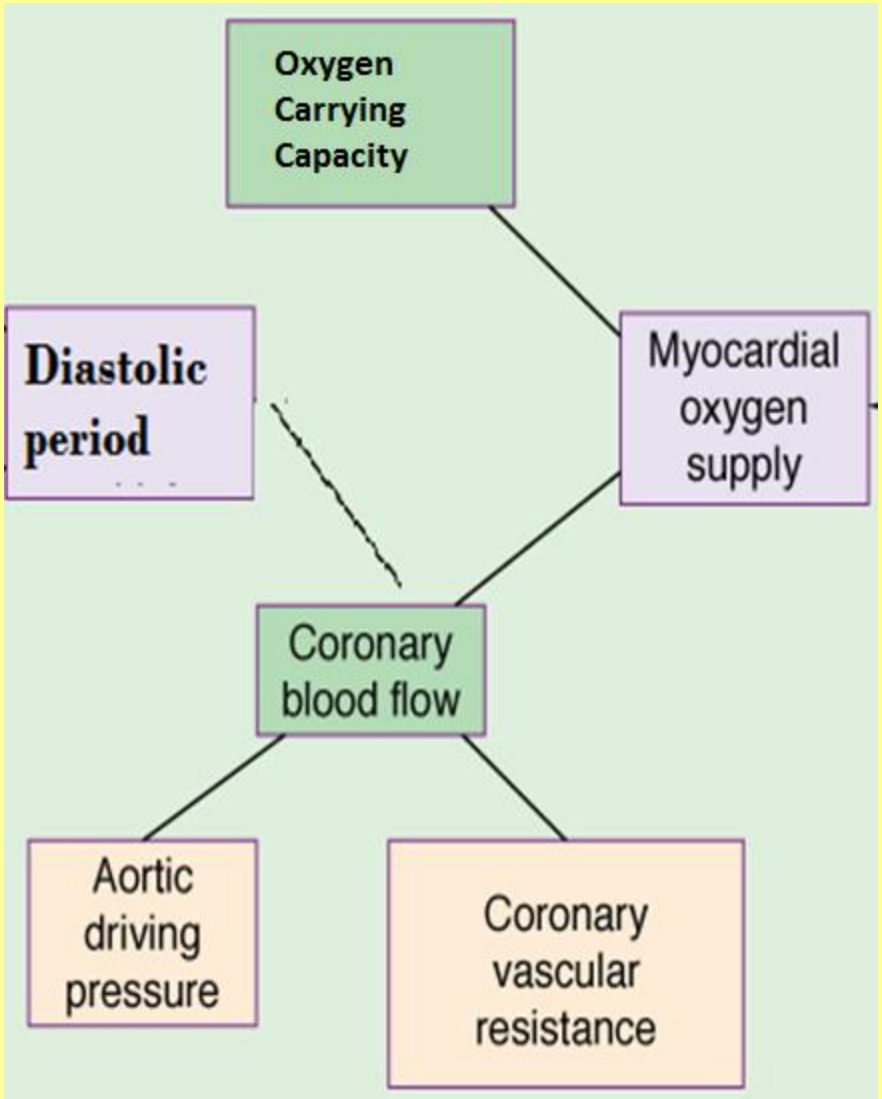
MYOCARDIAL OXYGEN DEMAND IS DETERMINED BY:-



MYOCARDIAL OXYGEN DEMAND IS DIMINISHED BY:-

Reducing contractility
Reducing heart rate
Reducing the preload
Reducing the afterload

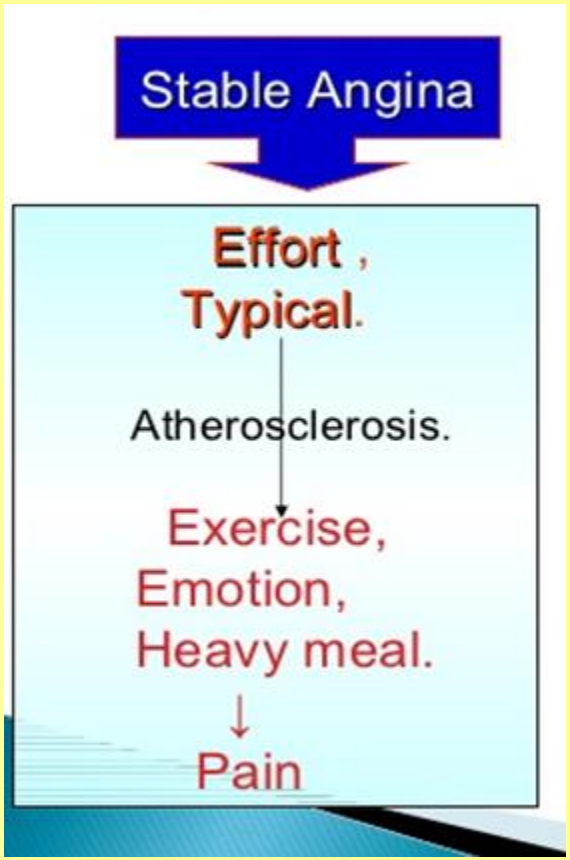
MYOCARDIAL OXYGEN SUPPLY IS DETERMINED BY:-

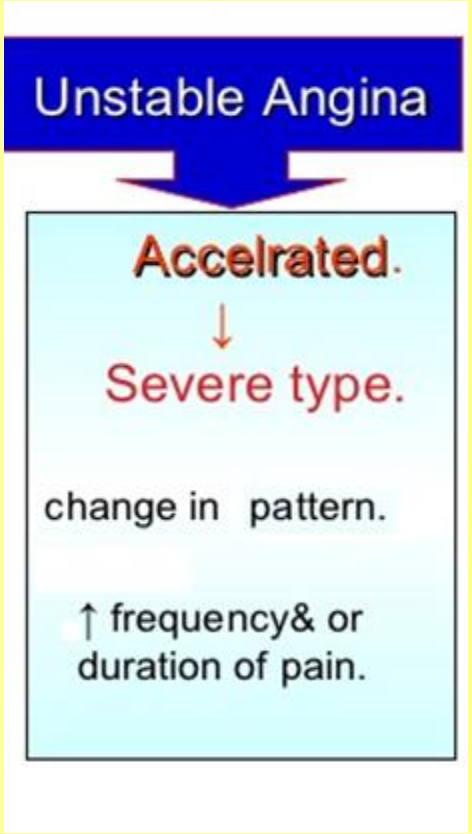


MYOCARDIAL OXYGEN SUPPLY IS ENHANCED BY:-

Reducing coronary vascular resistance
Prolonging diastolic period
Reducing external compression
Dilating collateral vessels
Optimizing hemoglobin & RBCs

Types of Angina Pectoris

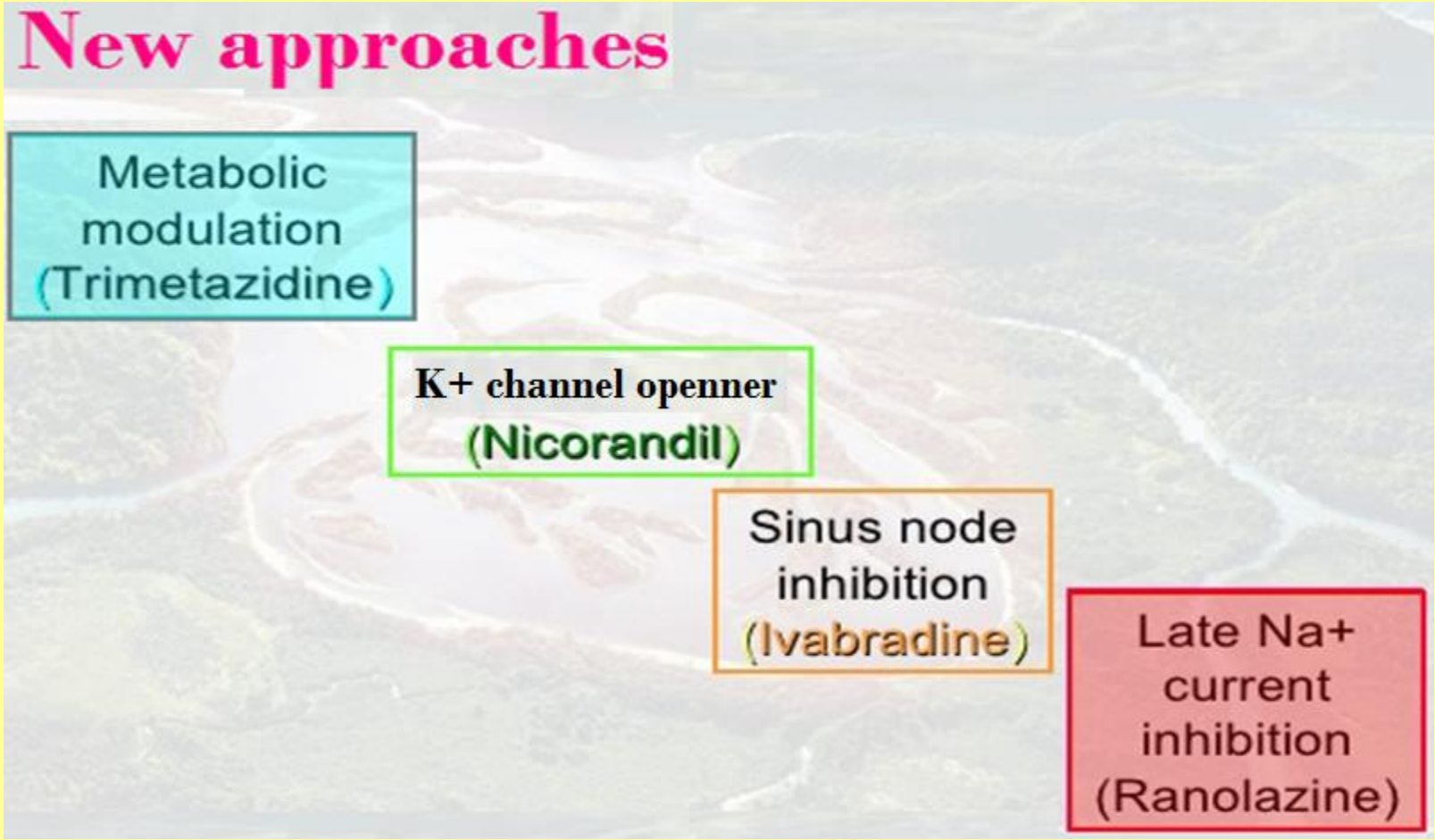




TREATMENT OF ANGIA PECTORS

1-Agents that improve symptoms & ischemia

Traditional Approach



TREATMENT OF ANGIA PECTORS

2-Agents that improve prognosis

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

ORGANIC NITRATES

MECHANISM OF ACTION

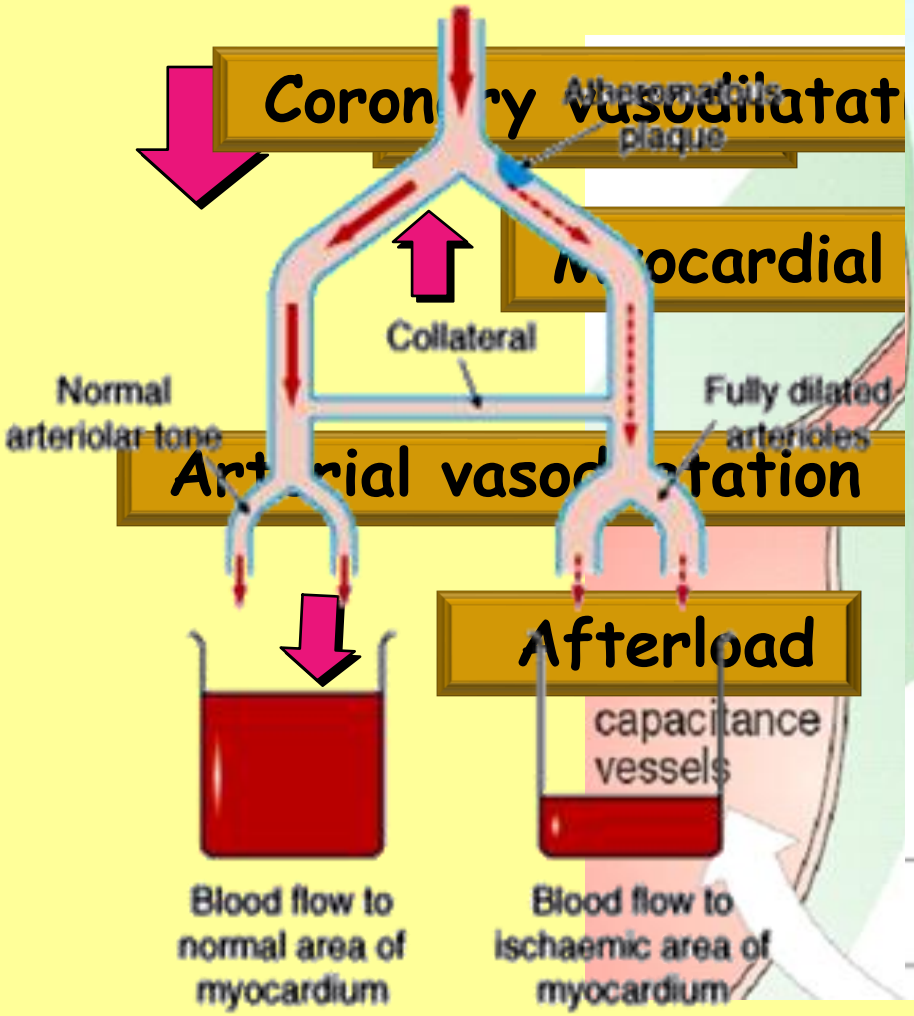
- LONG ACTING
  - ISOSORBIDE MONONITATE
- SHORT ACTING
  - NITROGLYCERIN

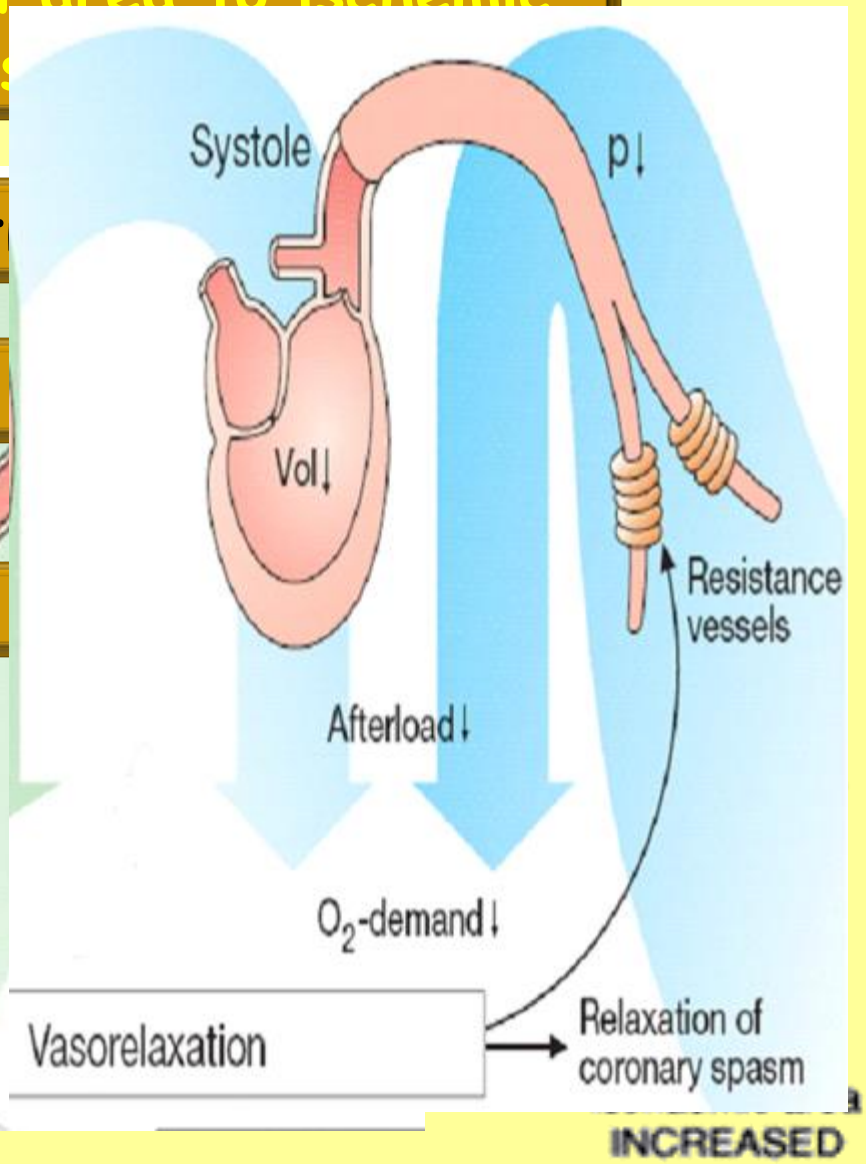
Nitric … ate
vasc … ell t…

cGM… …duce relaxation

HEMODYNAMIC EFFECTS OF NITRATES

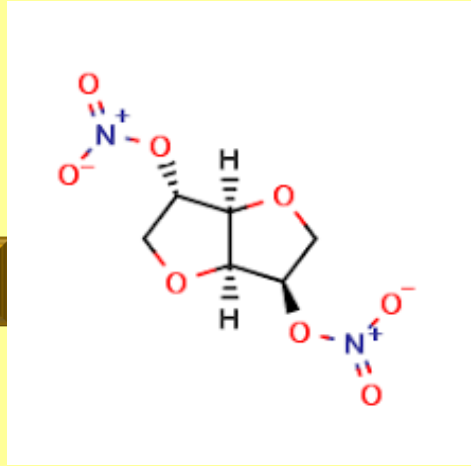
Shunting of flow from normal area to ischemic area by dilating collateral ves





INCREASED

PHARMACOKINETICS



Oral isosorbide dinitrate & mononitrate

Very well absorbed . Mononitrate, 100% bioavailability

the liver (10-20%) bioavailability

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

enteral

($t_{1/2}$ 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 ACE Is]

AMI → IV GTN

CONTRAINDICATIONS

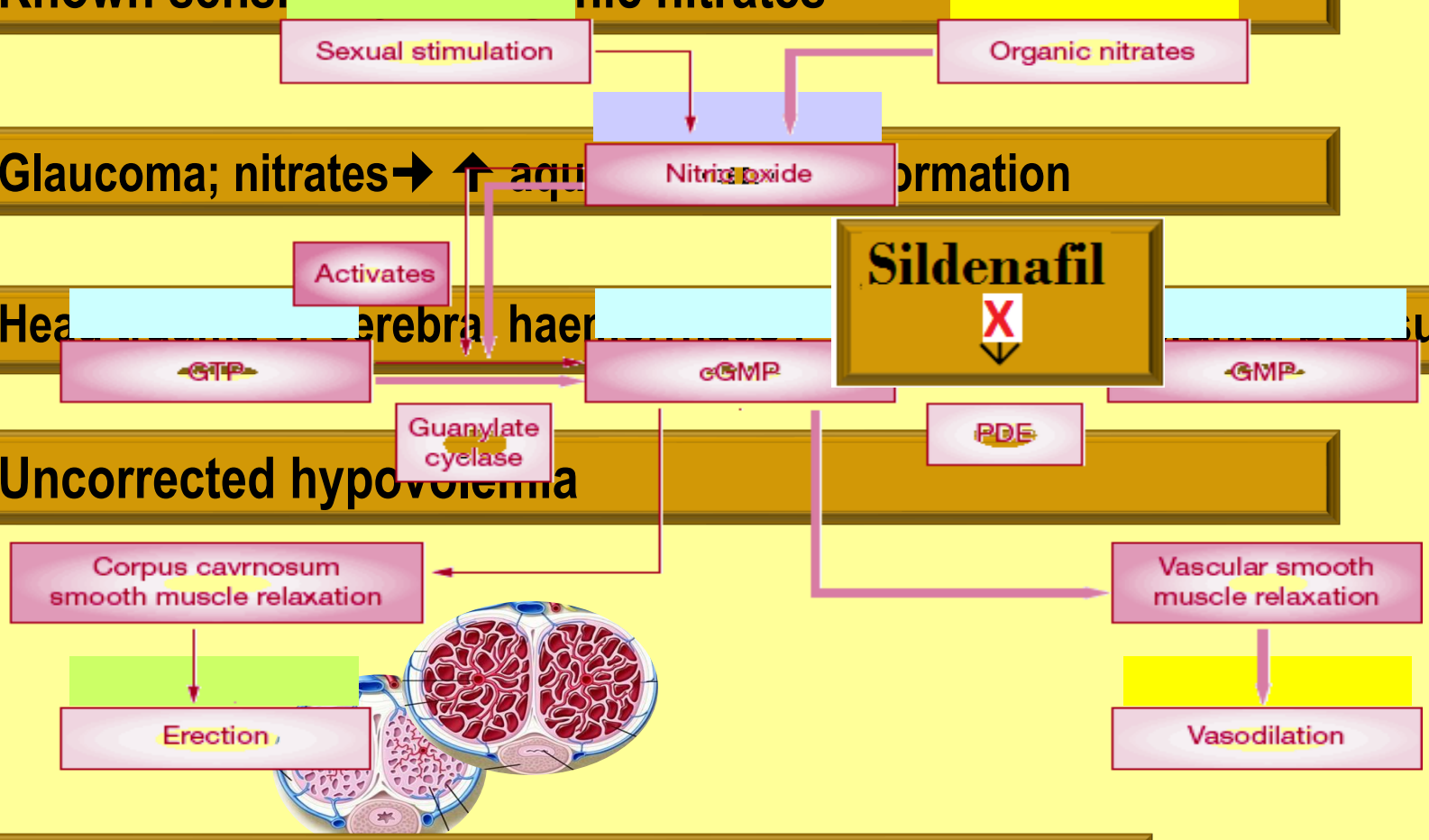
Concomitant administration of PDE_5 Inhibitors

Known sensi nic nitrates

Glaucoma; nitrates → ↑ aqu ormation

Hea erebra haem sure.

Uncorrected hypovolemia



Sildenafil + nitrates → Severe hypotension & death

ADVERSE DRUG REACTIONS

THROBING HEADACHE

FLUSHING IN BLUSH AREA

TACHYCARDIA & PALPITATION

POSTURAL HYPOTENSION, DIZZINESS & SYNCOPE

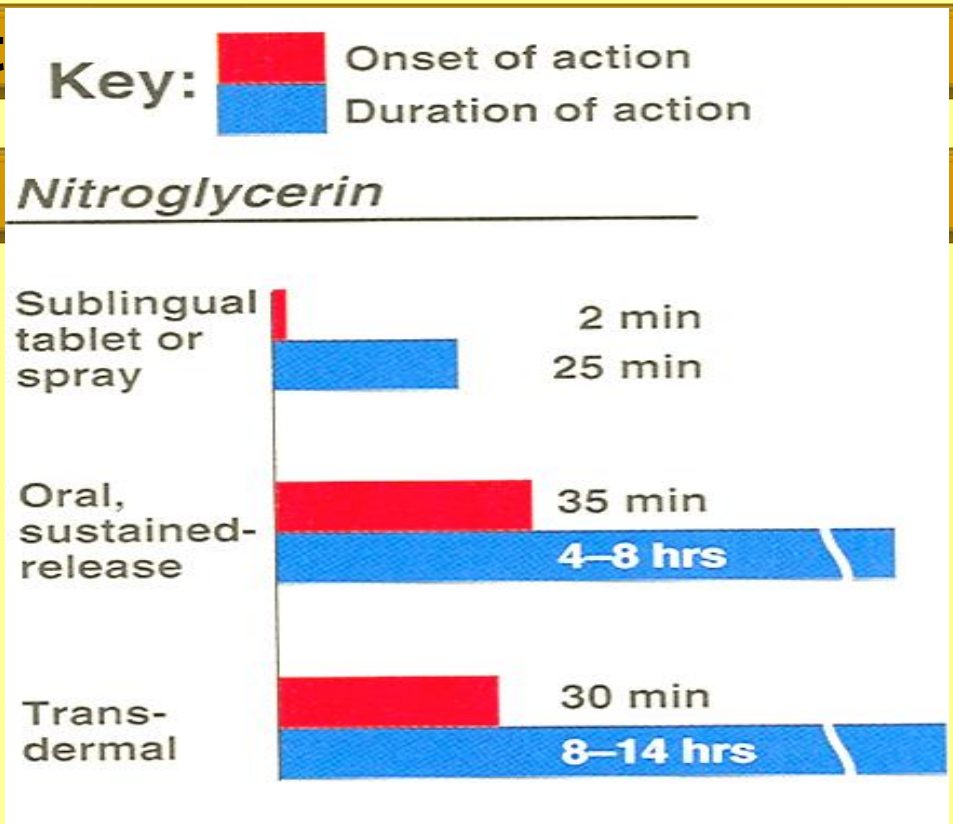
RARELY METHEMOGLOBINEMA

PREPARATIONS

Nitroglycerin

Sublingual t

Transderma



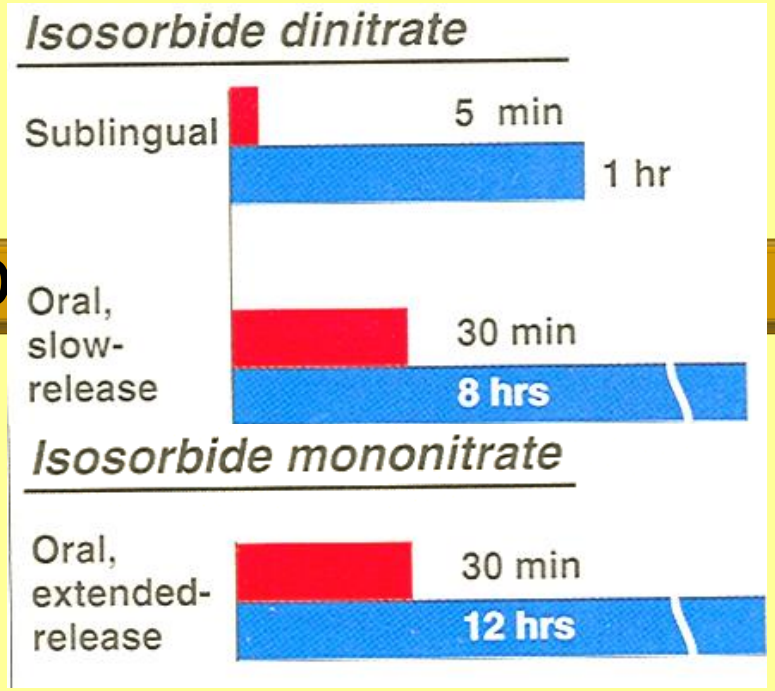
Oral or bucal sustained release
I.V. Preparations

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 intravenous infusions, for more than a few hours without interruption.

MECHANISM

1-Compensatory neurohormonal counter-regulation

2-Depletion of free-SH groups

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.

Calcium channel blockers

Classification

1-Chemecal structure

2-Selectivity

Dihydropyridines:-

Nifedipine , Nicardipine , Amlodepine

Nifedipine ,

Vascular smooth muscle

Verapamil

es:-

Cardiomyocytes

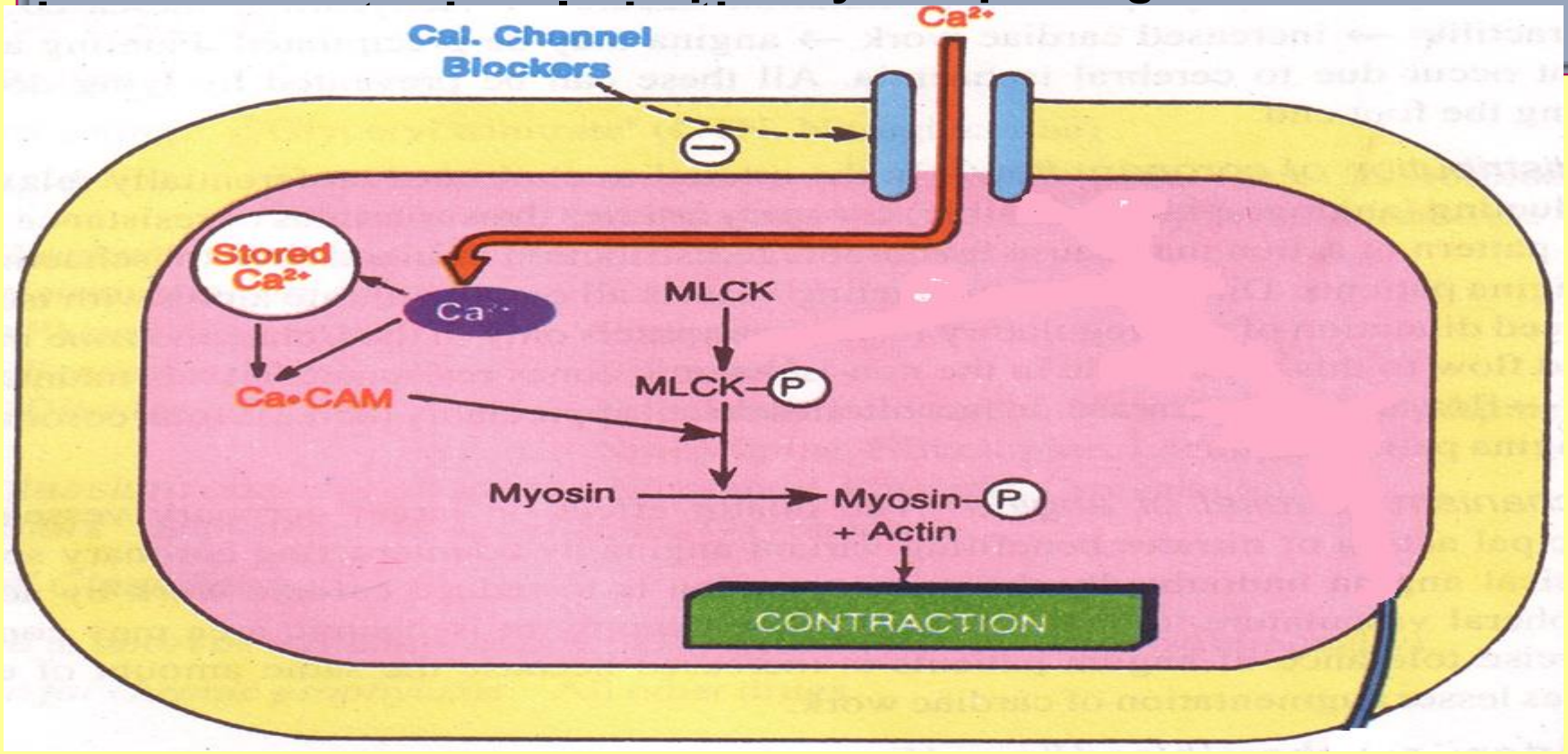
Diltiazem

:-

Intermediate

Mechanism of Action

Binding of calcium channel blockers [CCBs] to the L-type Ca channels ↓ their frequency of opening



Antianginal Action

↓ Cardiomyocyte Contraction → ↓cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem) → ↓myocardial oxygen demand

↓VSMC Contraction → ↓ After load → ↓cardiac work → ↓myocardial oxygen demand

Coronary dilatation → ↑myocardial oxygen supply

Therapeutic Uses

IN VARIANT ANGINA

- Attacks prevented (> 60%) / sometimes variably aborted

Short acting dihydropyridine should be avoided ??

Can be combined to β-AR blockers???

IN UNSTABLE ANGINA:

- Seldom added in refractory cases

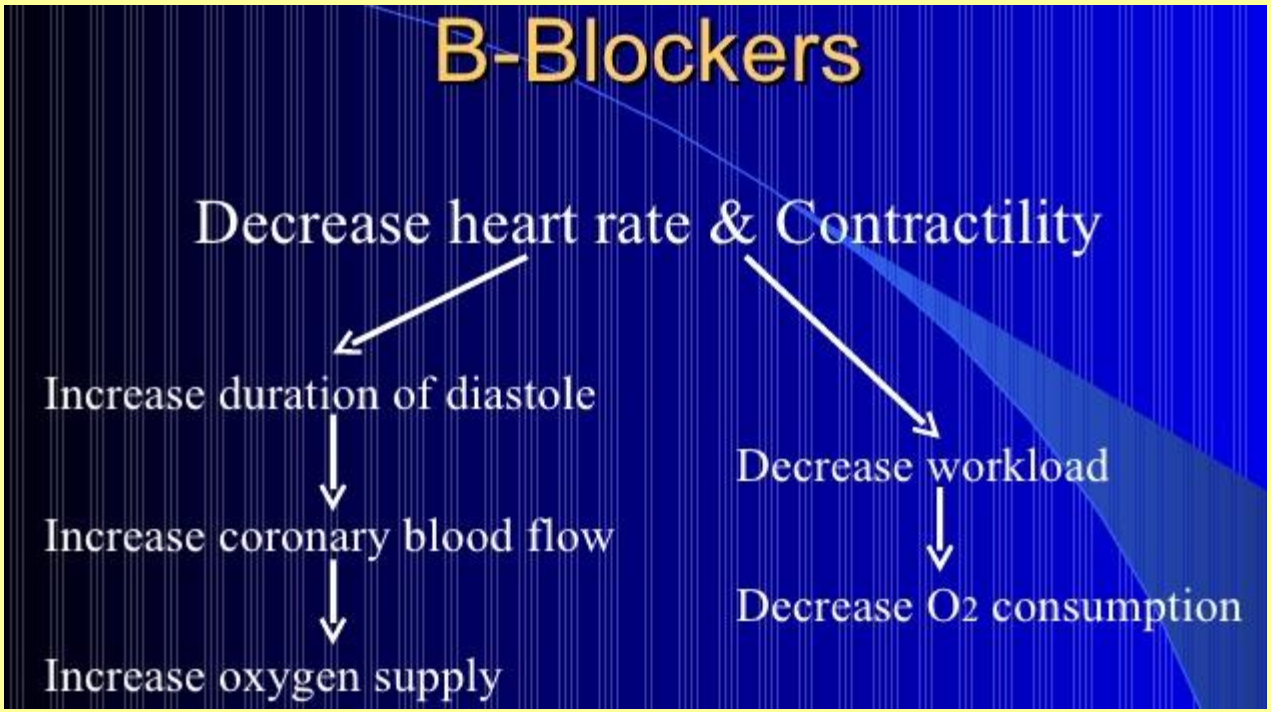
Can be combined with nitrates???

Dihydropyridenes useful antianginal if with CHF??

Beta Adrenoceptor Blockers

Examples Atenolol, Bisoprolol, Metoprolol (β_1 – Selective)

Antianginal Mechanism



Beta Adrenoceptor Blockers

Indications in angina

In stable angina

Regular prophylaxis, selective are prefered?

First choice for chronic use?

Can be combined with nitrates?

Can be combined with dihydropyridine CCB?

Verapamil?

In variant angina

Contraindicated?

Beta Adrenoceptor Blockers

Indications in angina

In Unstable angina

Halts progression to MI, improve survival

In Myocardial infarction

Reduce infarct size

Reduce morbidity & mortality

→reduce **O2 demand**

→reduce **arrhythmias**

Beta Adrenoceptor Blockers

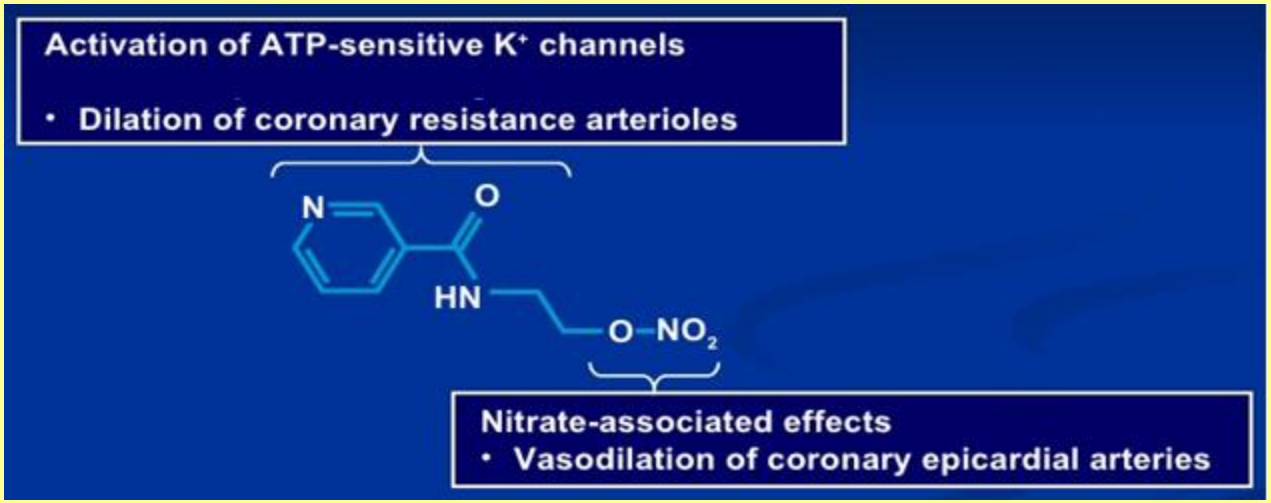
β- blockers should be withdrawn gradually?

Given to diabetics with ischemic heart disease?

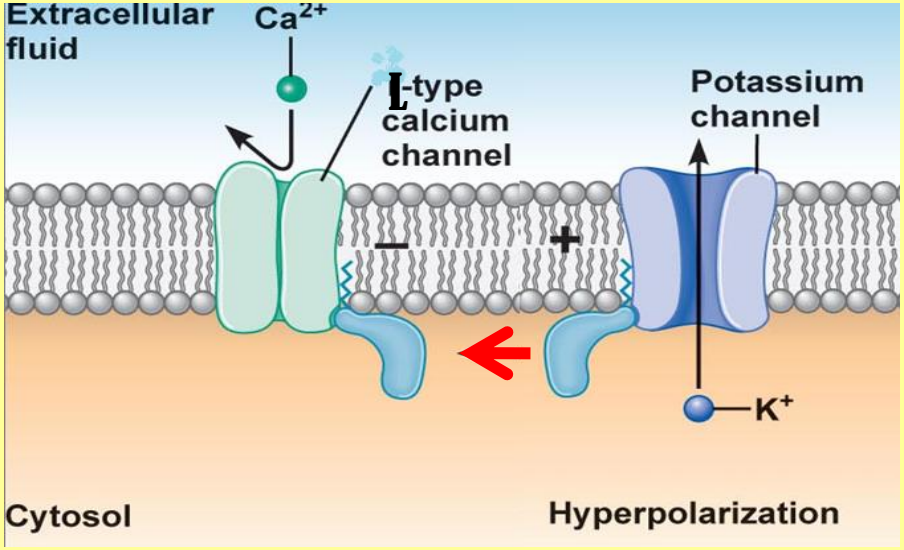
Potassium channel openners

Nicorandil

Mechanism



It has dual mechanism of action;
1. Opens K_{ATP} channels (> arteriolar dilator)
2. NO donner as it has a nitrate moiety (> venular dilator



Pharmacodynamic Effects

As K channel openner

As nitric oxide donor

s opening of K channels

➔hyperpolarization ➔ vasodilatation

NO ↑ cGMP/PKG ➔ vasoditation

On cardiomyocytes opening of K channels ➔repolarization

➔↓ cardiac work

Indications

Prophylactic 2nd line therapy in stable angina & refractory variant angina

ADRs

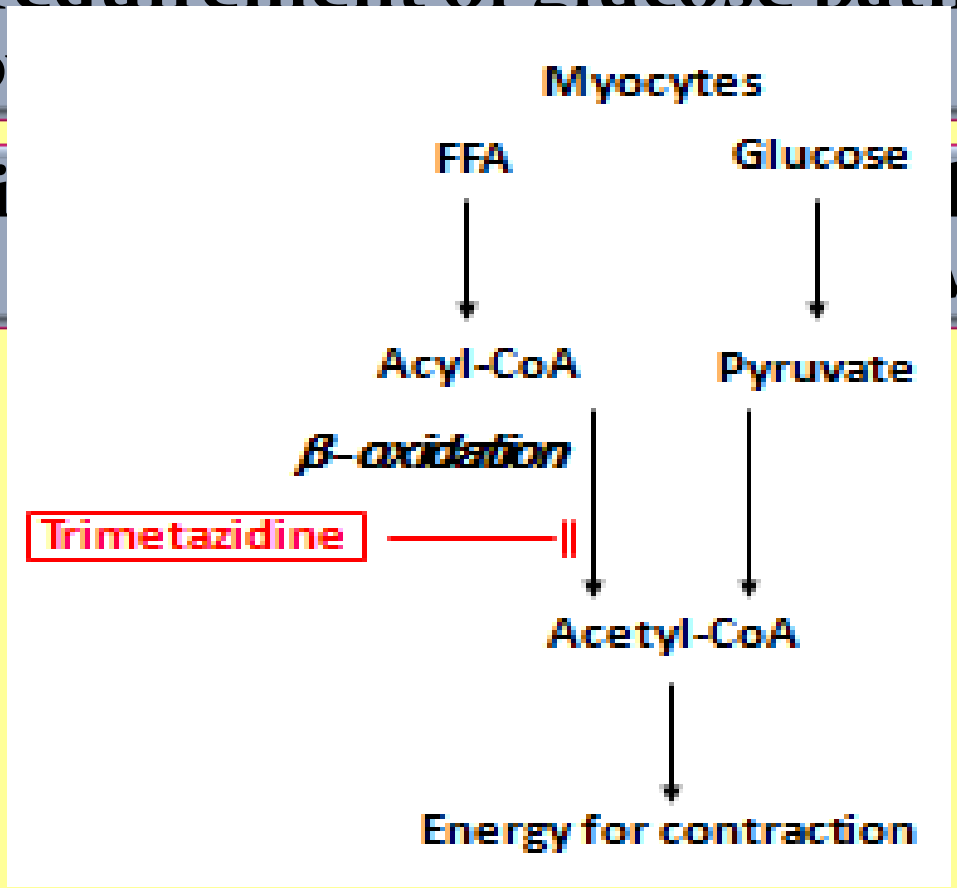
Flushing, headache,
Hypotension, palpitation, weakness
Mouth & peri-anal ulcers, nausea and vomiting.

Metabolically Acting Agents

e.g. Trimetazidine

O_2 requirement of glucose pathway is lo

Duri **levels rise,** **vay**



Reduces O_2 demand without altering hemodynamics

Trimetazidine

Indications

Used as an add on therapy

ADRs

GIT disturbances

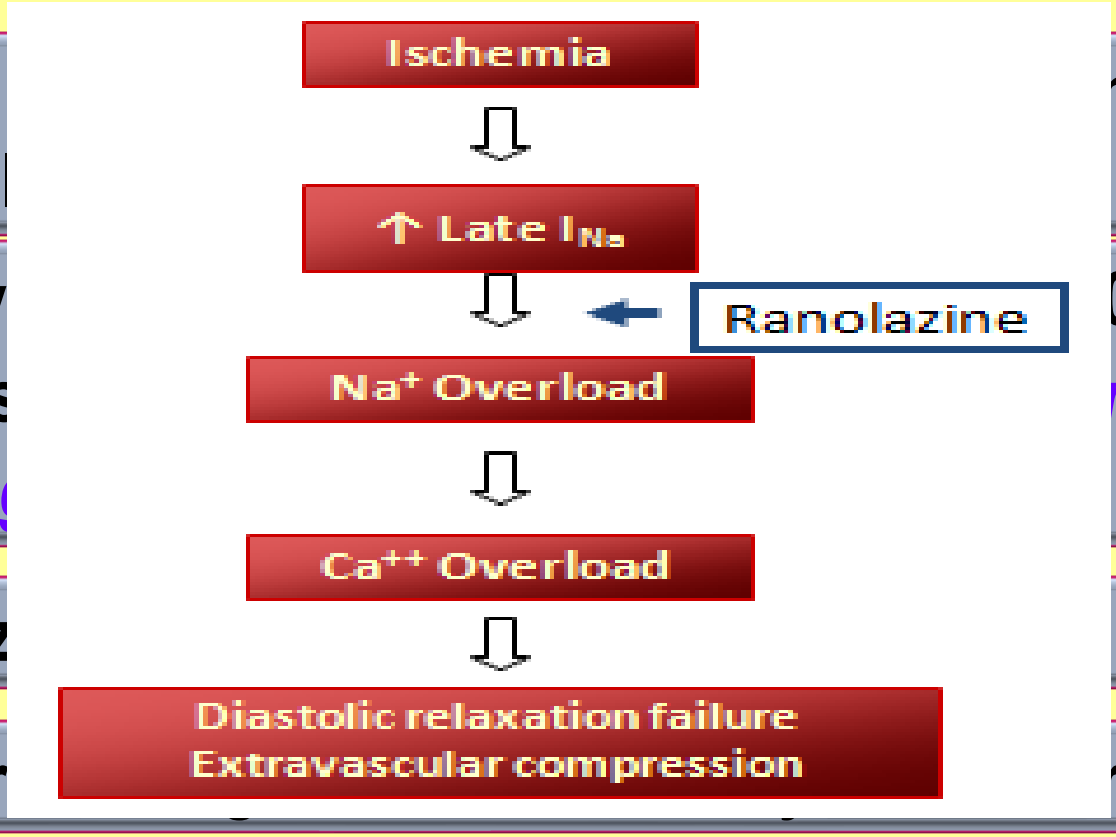
Contrindications

Hypersensitivity reaction

Pregnancy & lactation

Ranolazine

Inhibits the late sodium current which increases during ischemia



It prolongs
Class Ia & I
n;

Toxicity dev
inhibitors as
antibiotics,
0
macrolide

ADRs:- dizz

Used in chr
r drugs

Ivabradine

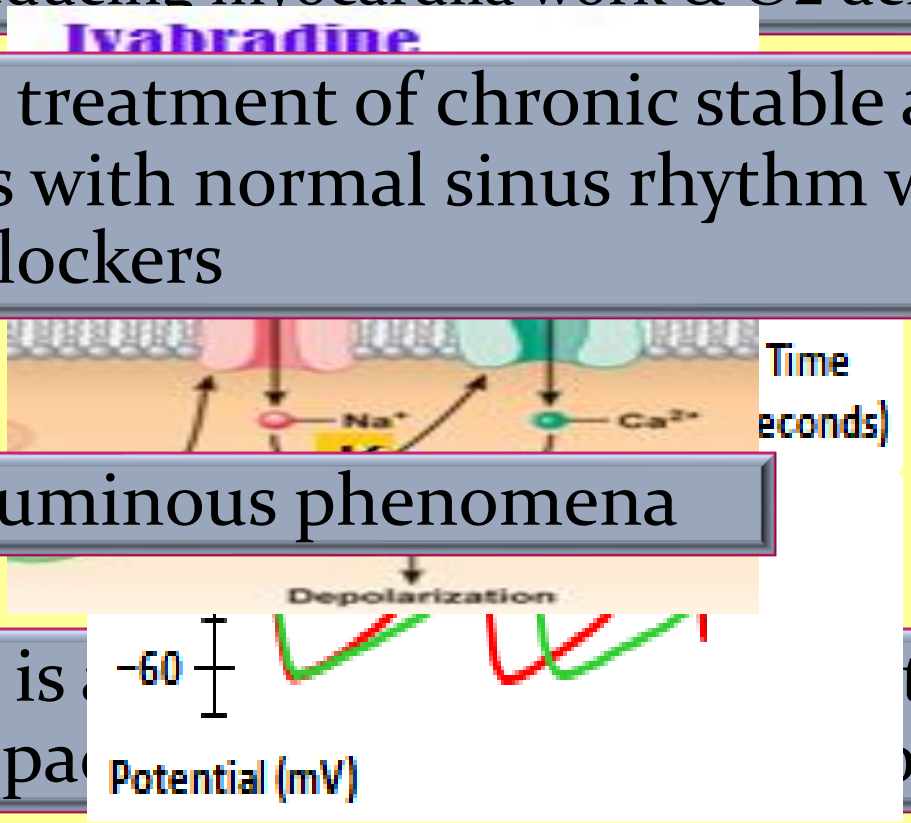
Ivabradine Selectively blocks I_f

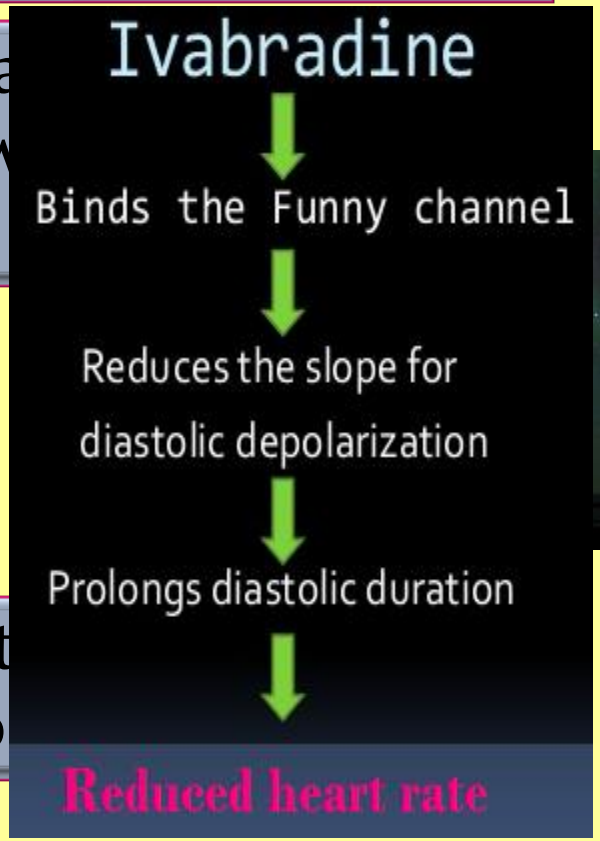
Ivabradine reduces slope of depolarization, slowing HR,reducing myocardila work & O2 demand

Used in treatment of chronic stable a patients with normal sinus rhythm w take ß-blockers

ADR:- luminous phenomena

I_f current is a activates pa





Agents that improve prognosis

- Aspirin / other antiplatelet agents
- ACE inhibitors
- Statins
- β - blockers

Halt progression
Prevent acute insult
Improve survival

New indication for an old drug

An average cost of developing a new drug is 2.6 billion dollars

It takes at least ten years for a drug to be developed

Computer- aided screening for existing drug activity is applied

The computer model will predict whether a given molecule will bind to a target and if so how strongly

Professor Didier Roult , infectios disease institute in Marseille, France

Hydroxy chloroquine can stop the virus from being contagious in just 6 days