Antianginal drugs

Revised by
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OBJECTIVES:

-Recognize variables contributing to a balanced myocardial supply versus demand.
-Differentiate between drugs used to alleviate acute anginal attacks and those meant for prophylaxis & improvement of survival.
-Detail the pharmacology of nitrates and other drugs used as antianginal therapy.

- Titles
- Very important
- Extra information
- Doctor’s notes

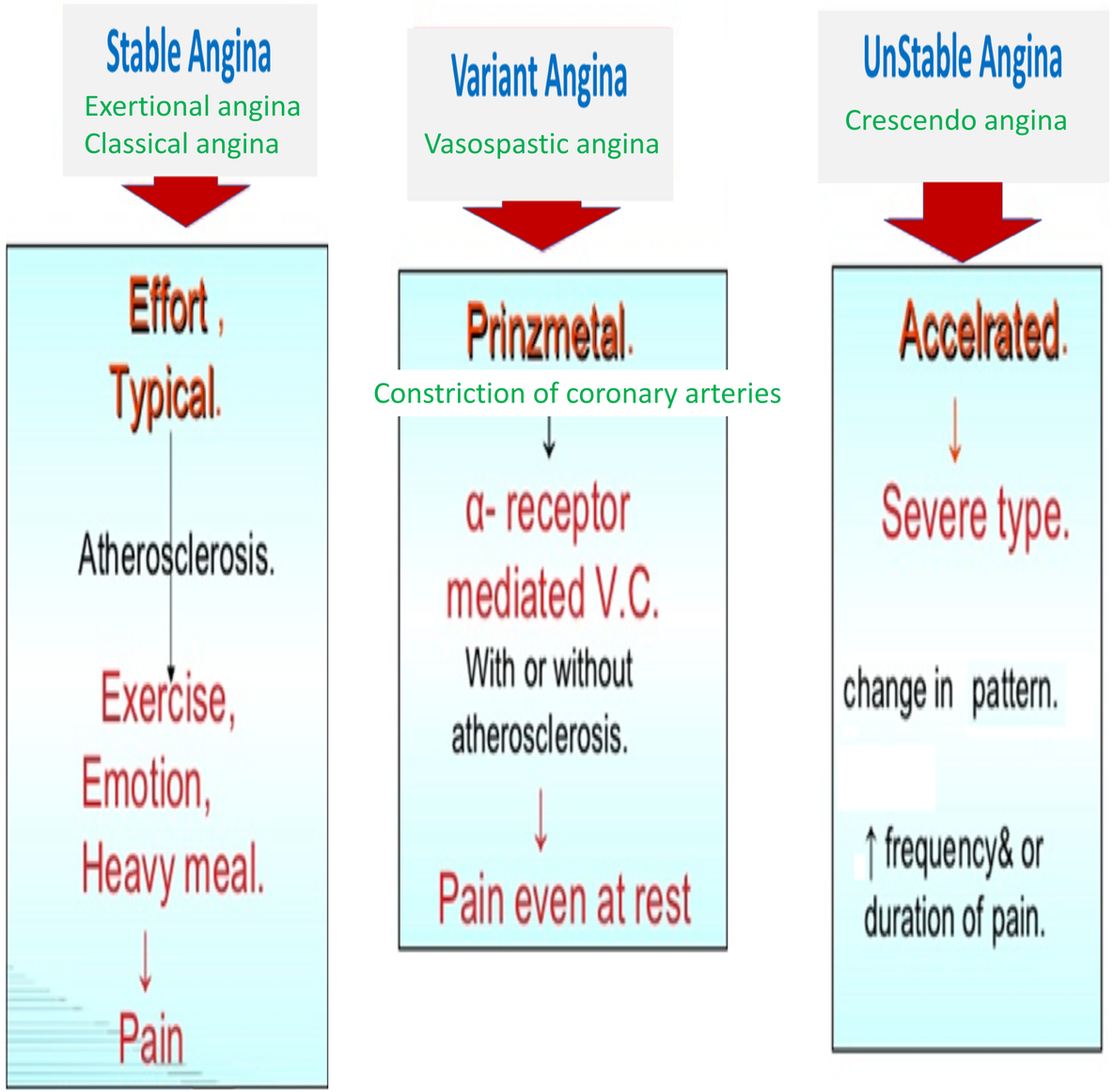
Signs and symptoms of angina pectoris:

1-A clinical syndrome of chest pain (varying in severity) caused by ischemia of heart muscle. (the pain can radiate to left shoulder and arm)
2-pain due to the accumulation of metabolites (K+,PGs, kinins, adenosine) secondary to ischemia
3-pain due to either obstruction or spasm.

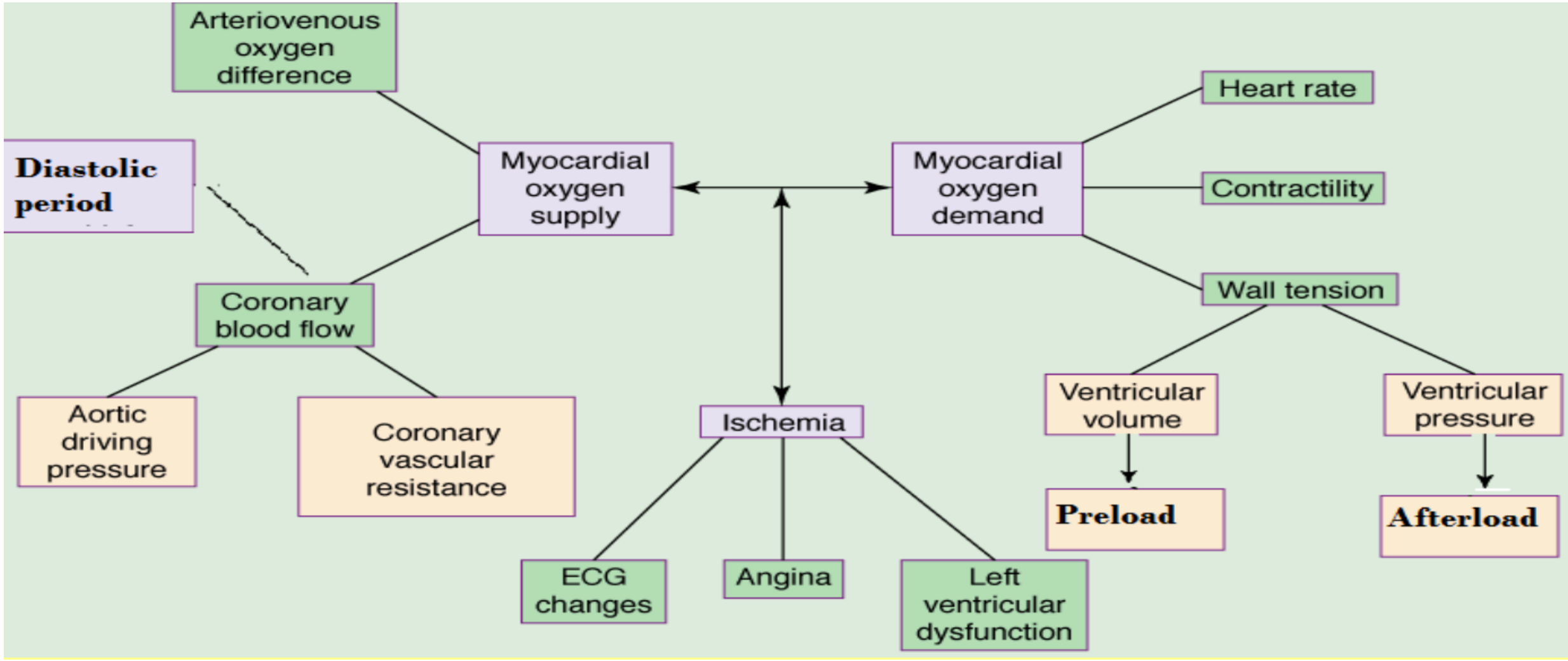
What is the mechanism of angina pectoris?

Is a consequence of myocardial oxygen demand exceeding myocardial oxygen supply (that means that the blood supply of oxygen is less than what body needs)
(obstruction lead to ischemia).
There is an imbalance between oxygen demand and oxygen supply

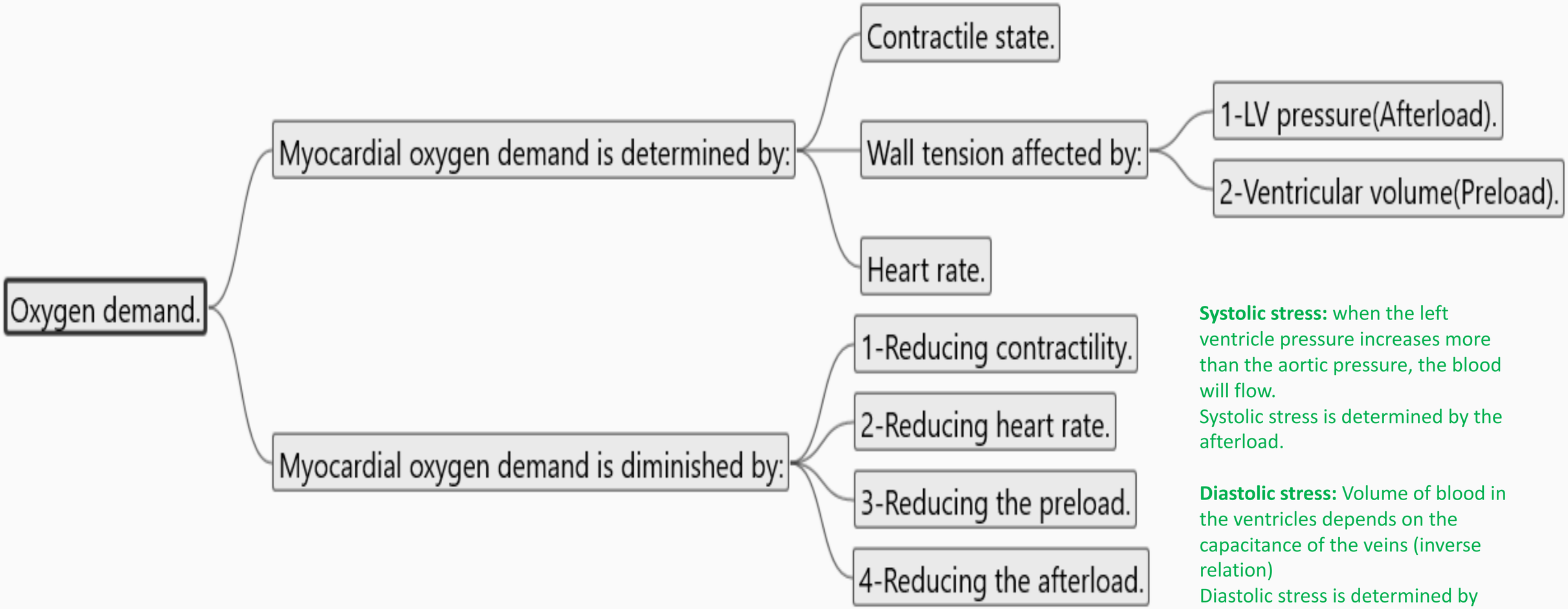
Types of angina pectoris:



What are the determinants of oxygen demand and supply?



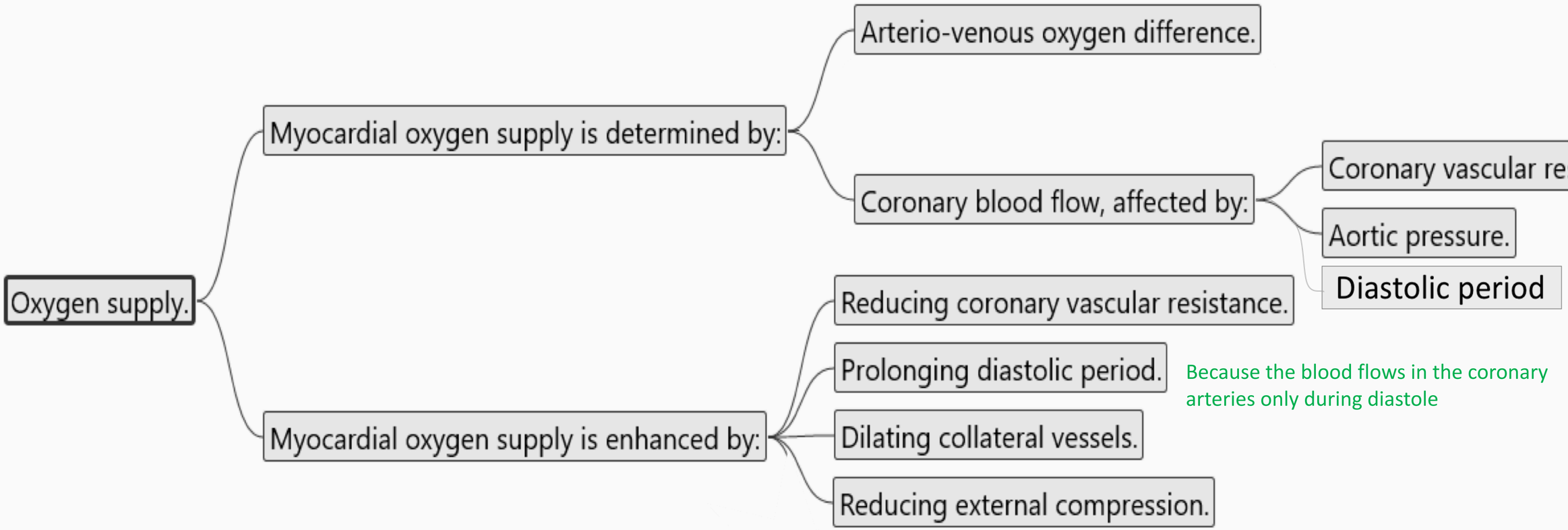
What are the determinants of oxygen *demand*?



Systolic stress: when the left ventricle pressure increases more than the aortic pressure, the blood will flow.
Systolic stress is determined by the afterload.

Diastolic stress: Volume of blood in the ventricles depends on the capacitance of the veins (inverse relation)
Diastolic stress is determined by preload.

What are the determinants of oxygen *supply* ?



Because the blood flows in the coronary arteries only during diastole

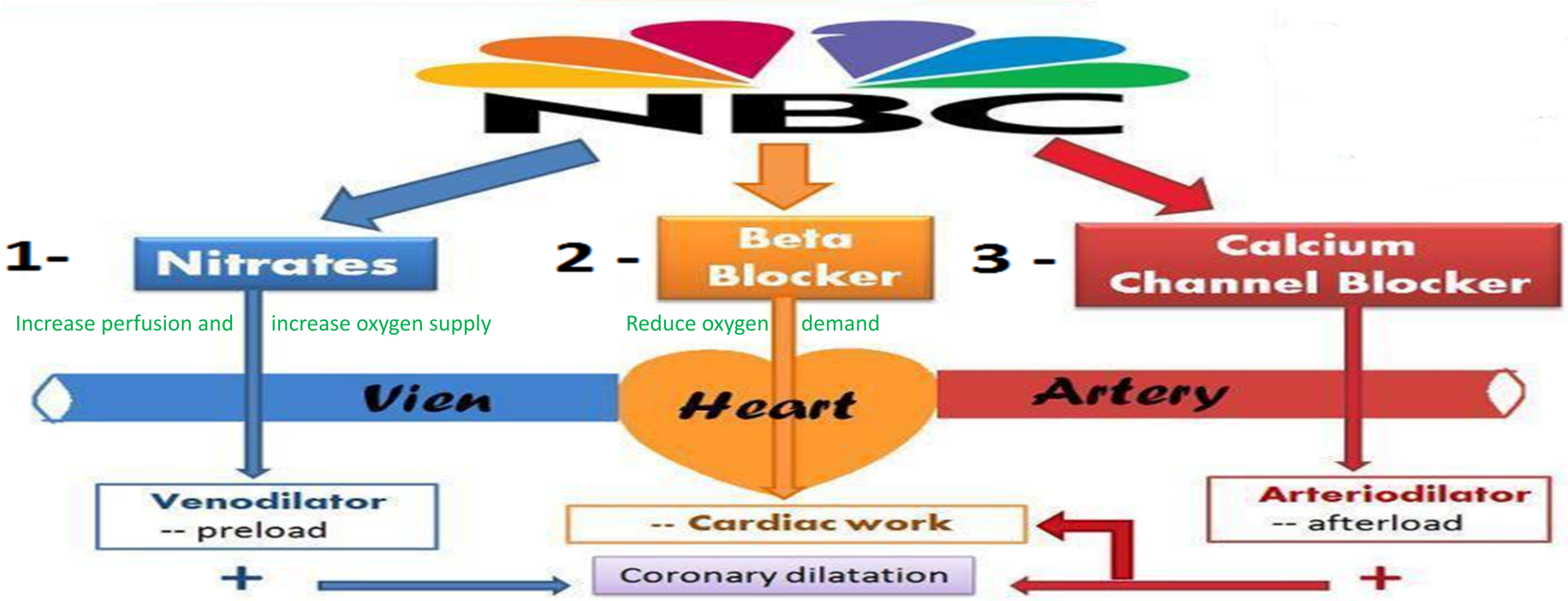
Treatment of angina pectoris

1-agents that improve symptoms and ischemia:

- NBC
- Potassium channels openers.
- Late Na+ current inhibition :ranolazine.
- Sinus node inhibition. ex: Ivibradine.

Reduction of afterload
Reduction of force of contraction and heart rate

They are fatty acid oxidation inhibitors
So they decrease oxygen demand



1) Decreasing afterload by dilating arteries
2) increasing oxygen supply by dilation coronary arteries
3) Decreasing contractility and heart rate, therefore decreasing the workload, therefor decreasing demand

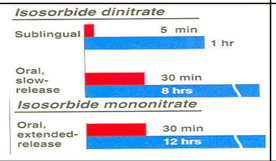
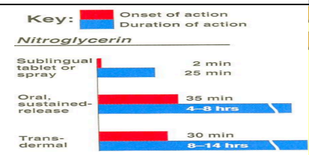
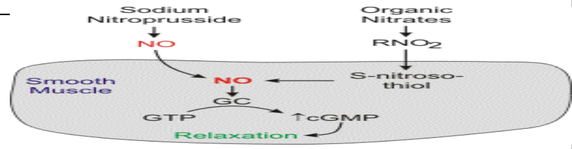
Treatment of angina pectoris

2- Agents that Improve Prognosis:

Halt progression, prevent acute insult, improve survival

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

Organic nitrates

Classification	Long acting	Short acting
Drug	Isosorbide mononitate and dinitrate	Nitroglycerine or glyceride dinitrate
Preparations	**Isosorbide Dinitrate** Sublingual tablets (fastest onset of action) Oral sustained (extended) release (delayed onset, longer duration) Infusion Preparations **Isosorbide mononitate** Mononitrate Oral sustained release 	Sublingual tablets spray Transdermal patch Oral or bucal sustained release I.V. Preparations 
pharmacokinetics	Oral isosorbide Very well absorbed & 100% bioavailability The dinitrate undergoes denitration to two mononitrates➔ both possess antianginal activity (both pharmacologically active) (t1/2 1-3 hours) Further denitrated metabolites conjugate to glucuronic acid in liver. Excreted in urine.	Significant (high) first pass metabolism occurs in the liver (10-20%) bioavailability Given sublingual or via transdermal patch, or parenteral (routes of administration which bypass portal circulation)
Mechanism of action	By enzymes: Organic nitrase is reduced into nitride into nitrosothiol which will release nitric oxide. Nitric oxide binds to guanylate cyclase in vascular smooth muscle cell to form cGMP. cGMP activates PKG to produce relaxation. Difference between organic nitrates and sodium nitroprusside: nitroprusside doesn't need enzymes to release Nitric oxide. (spontaneously)	
Hemodynamic effects	Venous vasodilatation (Decrease the preload) at low dose Coronary vasodilatation (Increase the myocardial perfusion) Arterial vasodilatation (decrease afterload) at high dose Shunting (diverting) of flow from normal area to ischemic area by dilating collateral vessels	
Indications	In stable angina: Persistant prophylaxis Chronic Heart Failure: Second line treatment is isosorbide mononitrate + hydralazine When there is ACE inhibitor contraindications	In stable angina: Acute symptom relief (sublingual) Situational prophylaxis: for example before climbing mountain, before physical stress IN VARIANT ANGINA (sublingual) IN UNSTABLE ANGINA (IV) Acute Heart Failure Refractory AHF and AMI (IV)
ADRs Mostly due to vasodilation	Throbbing headache Flushing in blush area Postural hypotension, dizziness & syncope Tachycardia & palpitation Rarely Met-hemoglobinema (iron is in ferric state instead of ferrous)	
contraindications	Known sensitivity to organic nitrates Glaucoma. nitrates increase synthesis of aqueous humor formation. Head trauma or cerebral haemorrhage = Increase intracranial pressure. Uncorrected hypovolemia Concomitant administration of PDE5 Inhibitors (phosphodiesterase type 5 inhibitor)(Slidenafil) Sildenafil + nitrates → Severe hypotension & death	
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. The Mechanism: 1-Compensatory neurohormonal counter-regulation 2-Depletion of free-SH (sulfahydrate) groups which is required for activation of nitrates. To decrease tolerance, the patient can take the drug but with a drug free period. 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.	

Effects of nitrates in treatment of angina and their results	
Effects	**Results**
↓Arterial pressure	↓ O2 demand " By decreasing the afterload"
Reflex ↑ in contractility	↑ O2 demand "due stimulation of sympathetic activity after high dose which dilate arteries"
↑Collateral flow	Improved perfusion to ischemic myocardium
↓Ventricular volume	↓ O2 demand "By decreasing the preload"
Reflex tachycardia	↑ O2 demand "due stimulation of sympathetic activity after high dose which dilate arteries"
↓Left ventricular diastolic pressure	Improve subendocardial perfusion
↓Diastolic perfusion time due to tachycardia	↓ myocardial perfusion
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm

CALCIUM CHANNEL BLOCKER

	Classifications:	Selectivity :
Drug	Dihydropyridines: Nifedipine ,Nicardipine (short acting) نايف نكر بسرعة Amlodepine (long acting) بالمصري .. أمل أعدي"اقعدي" باين حنطول	Nifedipine :Vascular smooth muscle نايف دا باني عضل
	Phenylalkylamines e.g. Verapamil	Cardiomyocytes فيه رابر اسمها أمل قلبها رهيف
	Benzthiazepines e.g. Diltiazem دليتي عازم	Intermediate "action on both but less degree " دليتي عازم؟ دايم ضايع يشتغل هنا و هناك
Mechanism	كلهم يحبوا يشربوا حليب Binding of calcium channel blockers [CCBs] to the L-type Ca channels ↓their frequency of opening in response to depolarization ↓entry of Ca → ↓Ca release from internal stores → No Stimulus-Contraction Coupling →RELAXATION	
Pharmacodynamics Antianginal actions	↓Cardiomyocyte Contraction →↓cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem) →↓myocardial oxygen demand	
	↓VSMC Contraction →↓Afterload →↓cardiac work →↓myocardial oxygen demand	
	Coronary dilatation → ↑myocardial oxygen supply	
Therapeutic Uses	IN VARIANT ANGINA : →Attacks prevented (> 60%) / sometimes variably aborted IN UNSTABLE ANGINA: Seldom added in refractory cases IN STABLE ANGINA: useful regular prophylaxis if with CHF	

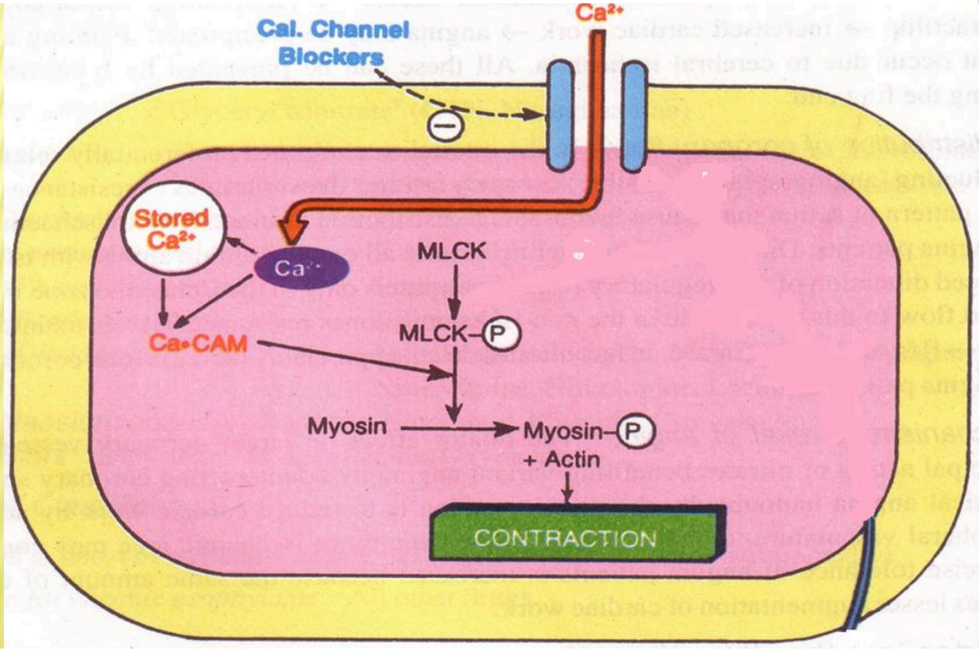
- Short acting dihydropyridine should be avoided ?
- Can be combined to b-AR blockers ?

Yes, we can use dihydropyrdine. But we can not combine Phenylalkylamines such as Verapamil which is work on the heart because beta blocker works on the heart also but we can give something works on the blood vessel like the dihydropyrdnes

- Can be combined with nitrates?
- Dihydropyridenes useful antianginal if with CHF ?

Yes especially dihydropyrdine which reduce the afterload by vasodialtation and thus decreasing the workload of the heart and decrease in demand .

verapmil and diltizam useful as antianinal in case of hypotension?



β Adrenergic Blockers			
	Type	Selective β1 blocker	
	Examples	Atenolol, Bisoprolol , Metoprolol I Met Biso At Ten	
	Antianginal Mechanism	Decrease heart rate & contractility thus: -Increase duration of diastole > increase coronary blood flow > increase oxygen supply -Decrease workload > Decrease O2 consumption > Decrease oxygen demand	
	Indications in angina	Stable	Regular prophylaxis, selective are prefered. First choice for chronic use? Can be combined with nitrates? Can be combined with dihydropyridine CCB? Verapamil ?
		variant	Contraindicated
		Unstable	Halts progression to MI, improve survival
		Myocardial infarction	Reduce infarct size Reduce morbidity & mortality →reduce O2 demand →reduce arrhythmias

- b- blockers should be withdrawn gradually?
  - Because of the upregulation of the receptors.
- Given to diabetics with ischemic heart disease?
  - Because it covers the symptoms of hypoglycemic state.

POTASSIUM CHANNEL Openners

Drug	Nicorandil	
Mechanism	has dual mechanism of action: 1. Opens potassium ATP channels (arteriolar dilator) 2. NO donor as it has a nitrate moiety (venular dilator)	
Pharmacodynamics Antianginal actions	As K channel opener	1. On vascular smooth muscles: opening K channels> hyperpolarization>vasodilation. 2. On cardiomyocytes: opening K channels> repolarization> decrease cardiac work.
	As NO donor	Increase in cGMP/PKG which leads to vasodilation.
Therapeutic Uses	1.Prophylactic 2nd line therapy in stable angina 2.Refractory variant angina	
Adverse Reactions	Flushing, headache, Hypotension, palpitation, weakness Mouth & peri-anal ulcers, nausea and vomiting.	

In stable angina

cardioselective are prefered?

Prolong use reduces incidince of sudden death?

In Unstable angina

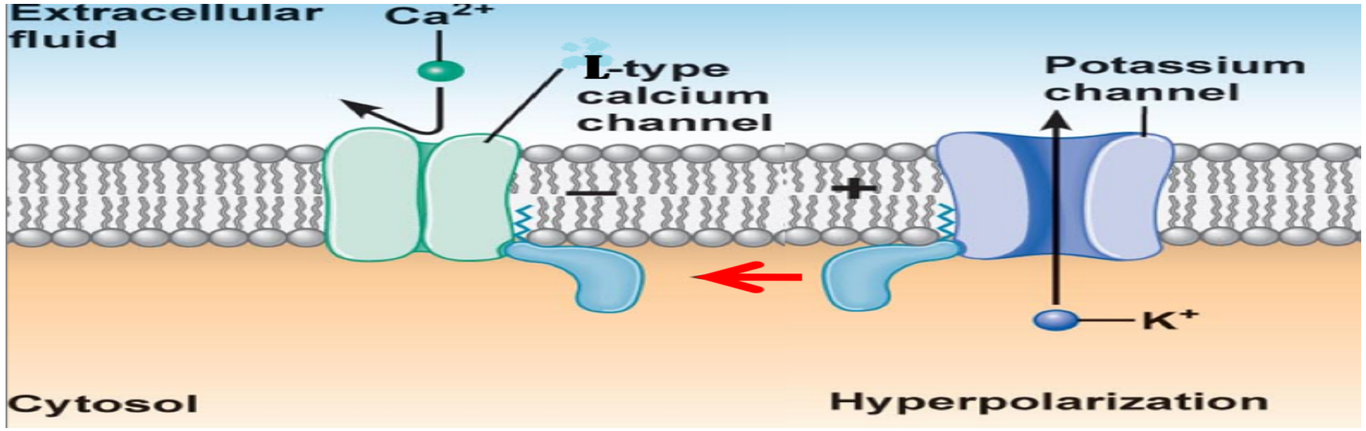
Halts progression to AMI, improve survival

In Variant Angina

contraindicated ?

IN AMI

Reduce infarct size, reduce morbidity and mortality



Metabolically acting agents:

Trimetazidine

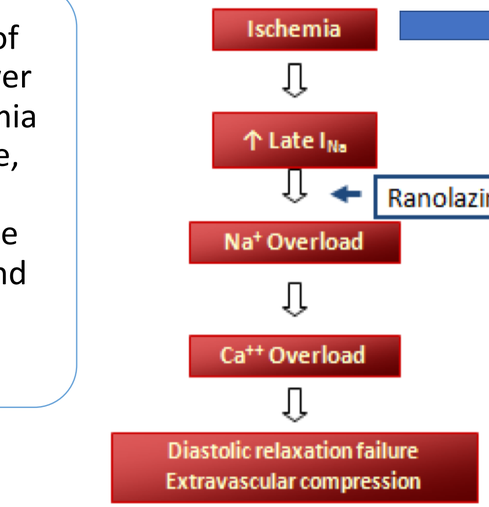
Trimetazidine = Triacylglycerol (FA)

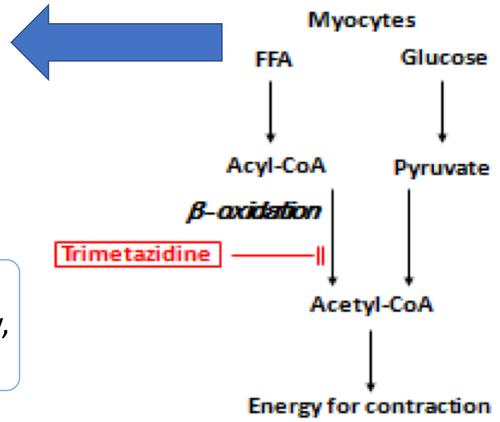
Oxygen requirement of glucose pathway is lower than FFA, during ischemia oxidized FFA levels rise, blunting the glucose pathway. Trimetazidine reduces oxygen demand without altering hemodynamics

Indications: as add on therapy

Adverse Reactions: GIT disturbances

contraindications: hypersensitivity , pregnancy, and lactationرضاعة





Ranolazine

Ranolazine → No=Na
قالوا رنا لزين قالت لا

Inhibits late sodium current which increases during ischemia

Prolongs QT intervals so contraindicated with class Ia and III antiarrhymatics

Toxicity develops due to interaction with CYT 450 inhibitors as diltiazem, verapamil, ketoconzole, macrolides, antibiotics, and grapefruit juice

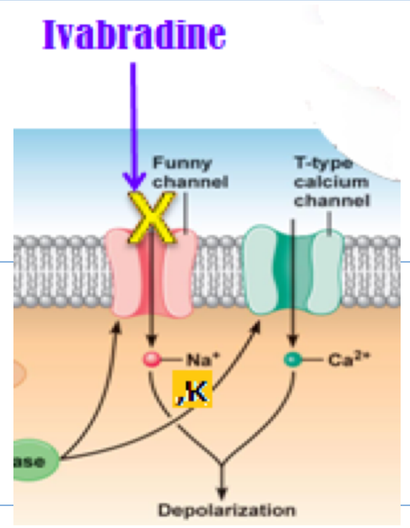
ADRs:- dizziness , constipation

Used in chronic angina concommitanly with other drugs

Ivabradine

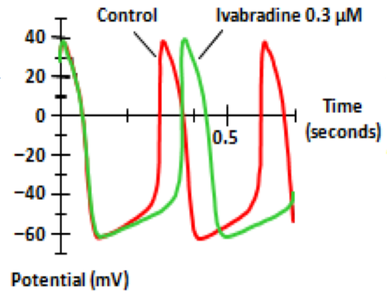
Ivabradine → $I_v = I_f$

reduces slope of depolarization, slowing HR, reducing myocardial work, and oxygen demand



I_f current is an inward Na/K current that activates pacemaker cells of the SA node, ivabradine selectively blocks it

ADR:- luminous phenomena



Used in treatment of chronic stable angina in Patients with normal sinus rhythm who cannot take b-blockers

Used in combination with beta blockers in people with heart failure with LVEF lower than 35% inadequately controlled by beta block whose heart rate exceeds 70/min

Pharmacology
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436
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