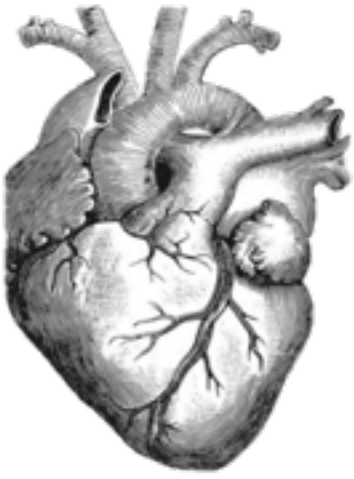
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



Anti-Anginal Drugs

Objectives:

- 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

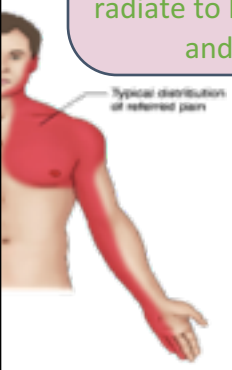
Special thanks to 436's Pharmacology Team!

Important Notes Extra

Introduction

Signs and Symptoms of Angina Pectoris:

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



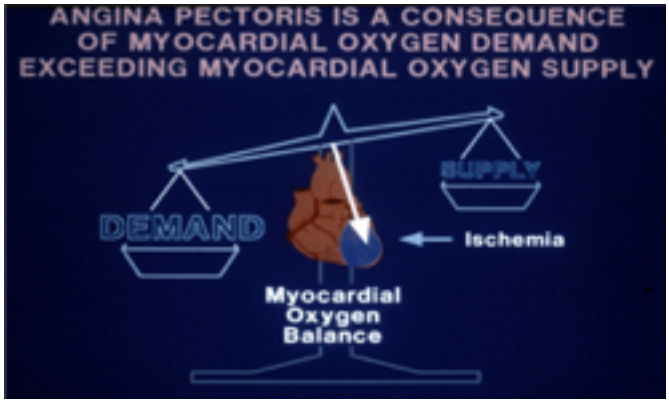
Coronary Arteries in Exercise

-During exercise respiration in skeletal muscles increase → the demand for O_2 & glucose also increases which means Cardiac Output must increase.
-Greater amount of blood to be delivered to skeletal muscle so we need perfusion to increase, therefore we need to increase the amount of blood that goes into the heart and increase the cardiac output.

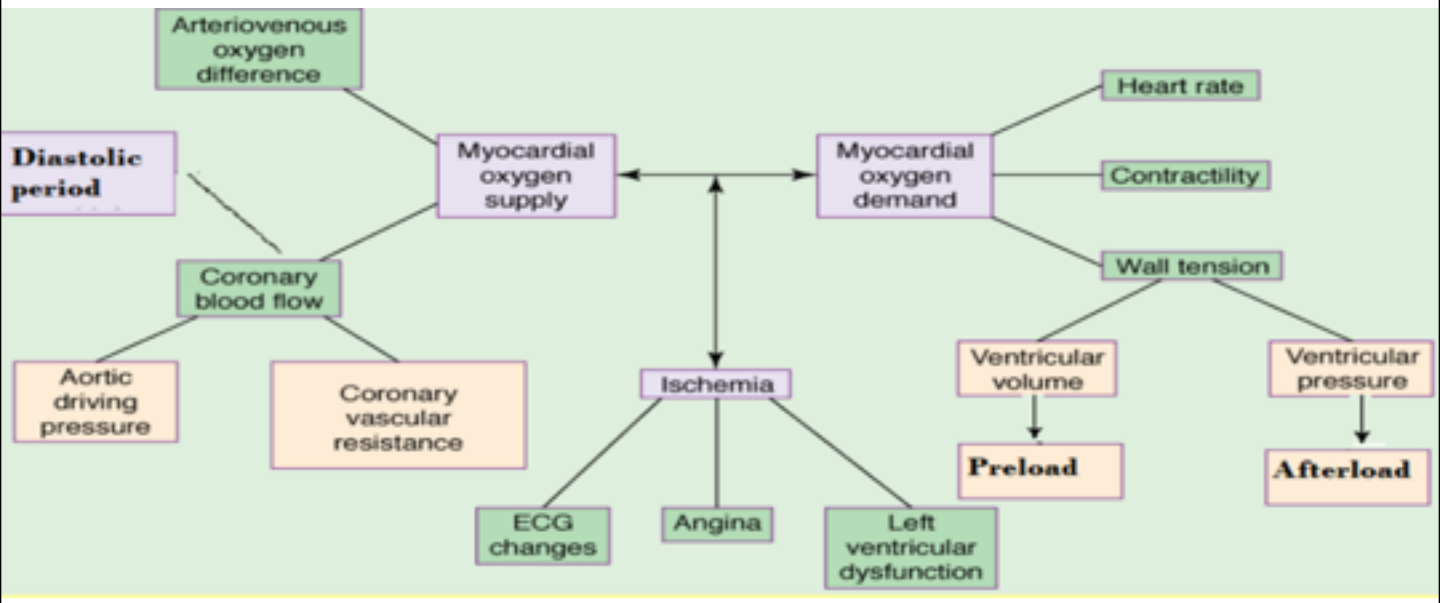
What is the mechanism of Angina Pectoris?

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).

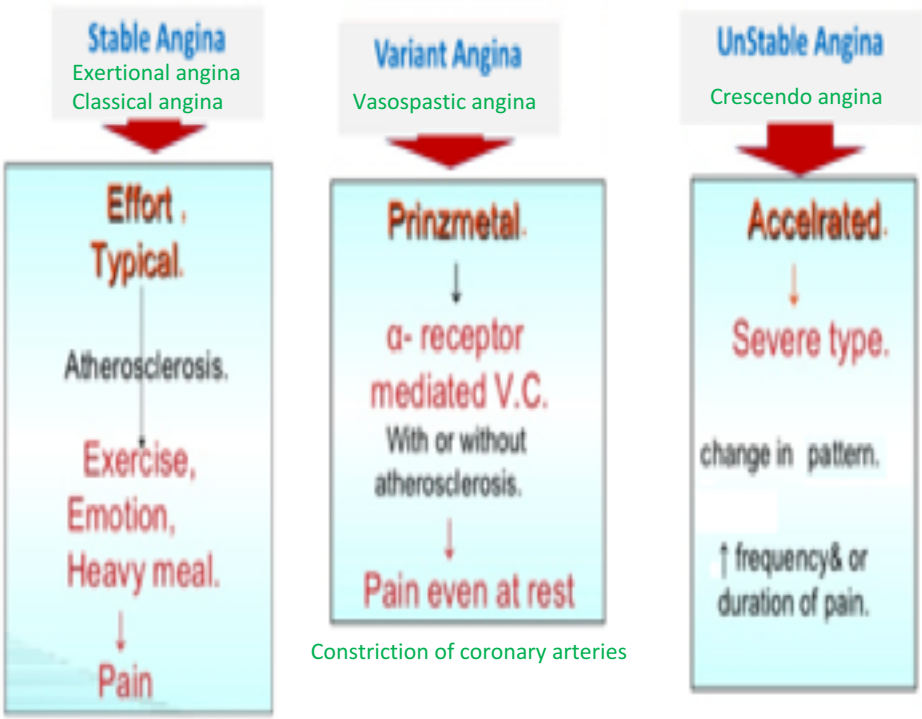
There is an imbalance between oxygen demand and oxygen supply



Determinants of Oxygen Demand & Supply

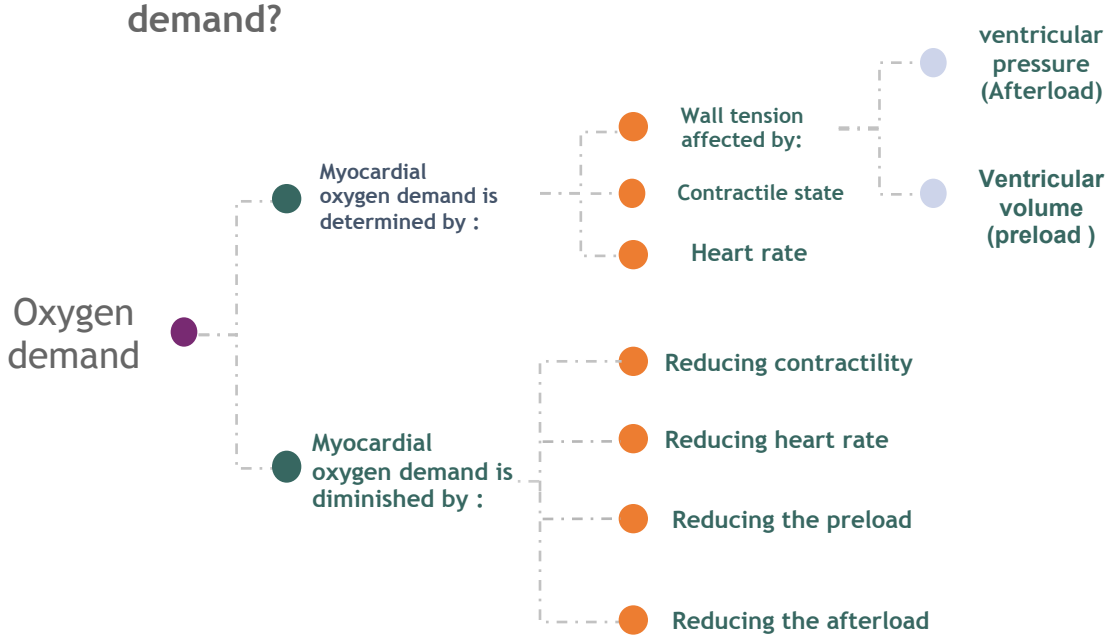


Types of Angina Pectoris

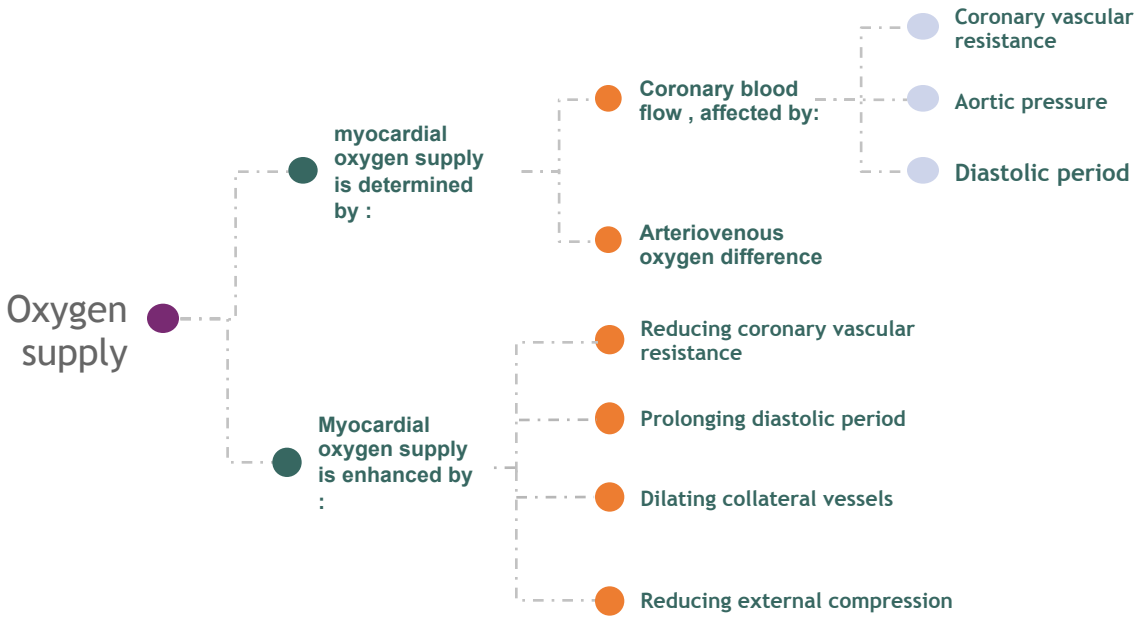


Cont.

What are the determinants of oxygen demand?



What are the determinants of oxygen supply?



Treatment of Angina

1.Agents that improve symptoms & ischemia

Traditional Approach

- Nitrates
- Beta Blocker
- Calcium Channel Blocker (CCB)

New Approaches

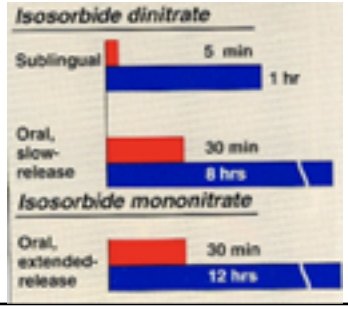
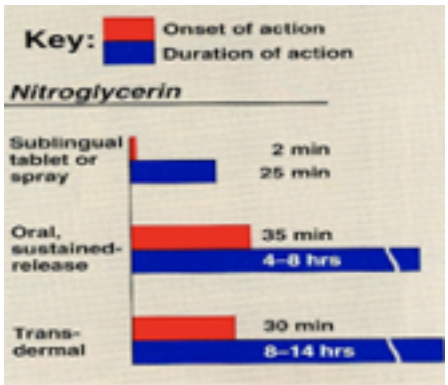
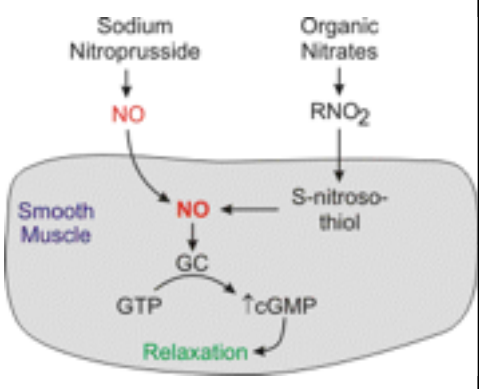
- Metabolic Modulation, eg. Trimetazidine
- Potassium channels openers, eg. Nicorandil
- Late Na+ current inhibition, eg. Ranolazine.
- Sinus Node inhibition, eg. Ivabradine

2.Agents that improve prognosis

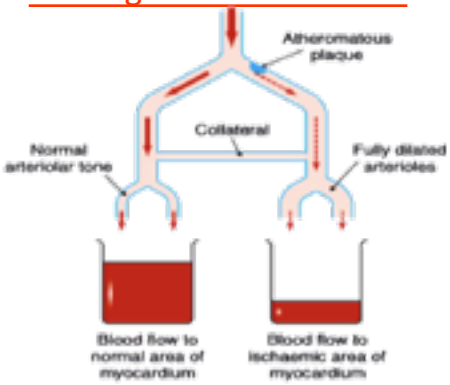
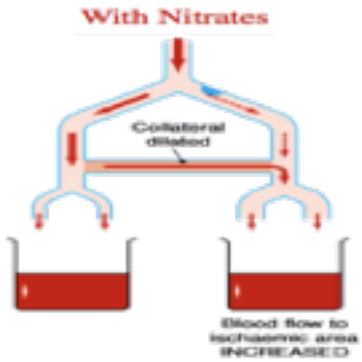
Halt progression, prevent acute insult, improve survival.

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

Organic Nitrates

Classification	Long acting	Short acting
Drug	• Isosorbide mononitrate • Isosorbide dinitrate	• Nitroglycerin (GTN) or glyceride dinitrate
Preparations	• Isosorbide mononitrate -Oral sustained release • Isosorbide Dinitrate -Sublingual tablets (fastest onset of action) -Oral sustained (extended) release(delayed onset, longer duration) -Infusion Preparations	-Sublingual tablets -Spray -Transdermal patch -Oral or buccal (between cheek and teeth) sustained release chronic or nocturnal angina -I.V. Preparations
P.K.	-Oral isosorbide -Very well absorbed & 100% bioavailability -The dinitrate undergoes denitration to two mononitrates → both possess antianginal activity (mono and dinitrate both work) -(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%) low bioavailability So giving it orally is not first choice -Given sublingual or via transdermal patch, or parenteral (routes of administration which bypass portal circulation) 
MOA	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)	

Organic Nitrates Cont.

Classification	Long acting	Short acting
Hemo-dynamic effects	• Venous vasodilation (Decrease the preload) and decrease diastolic pressure • Coronary vasodilation (Increase the myocardial perfusion) • Arterial vasodilation (decrease afterload) • Shunting (diverting) of flow from normal area to ischemic area by dilating collateral vessels  	
Indications	**In stable angina:** -Prevention: Persistent prophylaxis for chronic or nocturnal angina (most likely he will use transdermal patch preparation) -Congestive Heart Failure: Second line treatment is isosorbide mononitrate + hydralazine (When there is ACE inhibitor contraindications)	**In stable angina:** -Acute symptom relief (sublingual/spray) - Situational prophylaxis: sublingual for example before climbing mountain,before doing عمرة 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 Methemoglobinema (iron is in ferric state instead of ferrous, hemoglobin is unable to carry oxygen.)	

Organic Nitrates Cont.

Classification	Long acting	Short acting
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)(Sildenafil this is viagra) why? because the nitrate and sildenafil will have a synergistic effect on CGMP and cause severe hypotension • 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. If tolerance occurs the patient will start feeling the pain again. • **The Mechanism:** 1-Compensatory neurohormonal counter-regulation (body response which causes vasoconstriction) 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

Some explanation

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.

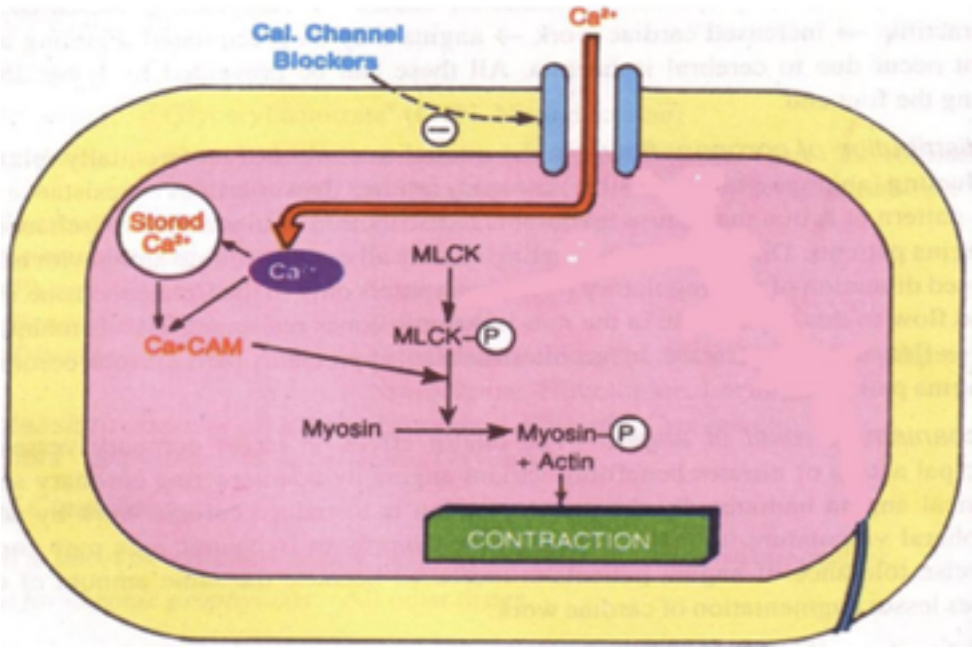
Effect	Mechanism and Result
Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased work and myocardial oxygen requirement
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion 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

Calcium Channel Blockers

	Classifications:	Selectivity:
Drug:	Dihydropyridines: • **Nifedipine, Nicardipine** (short acting) • **Amlodepine** (long acting)	**Nifedipine**: Vascular smooth muscle
	Phenylalkylamines e.g. **Verapamil**	Cardiomyocytes
	Benzthiazepines e.g. **Diltiazem**	Intermediate ON BOTH BUT NOT AS STRONG AS THE PREVIOUS
Mechanism:	• Binding of calcium channel blockers [CCBs] to the **L-type Ca channels** (most important in the heart) ↓ their frequency of opening in response to depolarization • **↓ entry of Ca** → ↓ Ca release from internal stores (sarcoplasmic reticulum) → No Stimulus-Contraction Coupling → **RELAXATION**	
Antianginal actions:	↓ Cardiomyocyte Contraction → ↓ cardiac work through their –ve inotropic & chronotropic action (verapamil strongest & diltiazem) → **↓ myocardial oxygen demand**	
	↓ VSMC Contraction → ↓ **Afterload** → ↓ cardiac work → **↓ myocardial oxygen demand**	
	Coronary dilatation → **↑myocardial oxygen supply**	
Therapeutic uses:	• In **variant** (vasospastic) angina: → Attacks prevented (>60%) / sometimes variably aborted • In **unstable** angina: Seldom (rarely) added in refractory cases. • In **stable** angina: useful regular prophylaxis if with CHF	

Calcium Channel Blockers

M.O.A



- Short acting dihydropyridine should be avoided?
  -Yes,it can precipitate anginal attack and cause reflex tachycardia

- Can be combined to b-AR blockers?
  - Yes, we can use dihydropyrdine. But we can not combine Phenylalkylamines such as Verapamil which work on the heart because beta blocker works on the heart also but we can give something that works on the blood vessel like dihydropyrdnes.

- Can be combined with nitrates?
  -Yes, because nitrates can cause reflex tachycardia and CCB like verapamil will decrease it.

- Dihydropyridenes useful antianginal if with CHF?
  - Yes, especially dihydropyridine which **reduce the preload and the afterload** by vasodilation and thus decreasing the workload of the heart and decrease in demand.

β Adrenergic Blockers

Type:	**Selective β1 blocker**	
Examples:	Atenolol, Bisoprolol, Metoprolol	
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. (Because we don't want to block B2) • First choice for chronic use. • Can be combined with nitrates. • Can be combined with dihydropyridine CCB. But not with 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, if not withdrawn gradually severe tachycardia could occur.
- Given to diabetics with ischemic heart disease?
  -With caution can be given because it interferes with insulin release and covers the symptoms of hypoglycemic state.

- In stable angina

cardioselective b-blockers are prefered.
Prolong use reduces incidence 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

Potassium Channel Openers

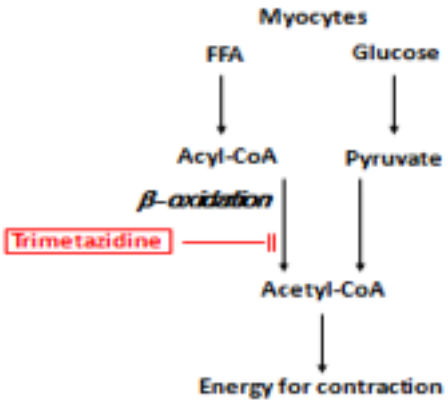
Drug	Nicorandil
MOA	has dual mechanism of action : 1.Opens potassium K-ATP channels(arteriolar dilator) 2.NO donor as it has a nitrate moiety (venular dilator)
P.K	• **As K channel opener** 1. On vascular smooth muscles: opening K channels > hyperpolarization > vasodilation. 2. On cardiomyocytes:opening K channels>repolarization>decrease cardiac work. • **As NO donor** Increase in cGMP/PKG which leads to vasodilation.
Indication	-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

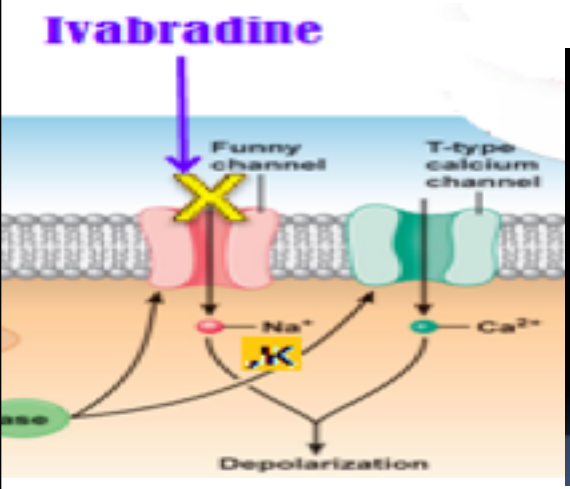
Drug	Trimetazidine Trimetazidine= Triacylglycerol(FA)	Ranolazine	Ivabradine
P.K.	Oxygen requirement of glucose pathway is lower than Free Fatty Acids (FFA), so during ischemia oxidized FFA levels rise=blunting the glucose pathway = reduces oxygen demand without altering hemodynamics. no effect on pre or after load.	Inhibits late sodium current which increase during ischemia	-selectively blocks I_f, I_f current is an inward Na/K current that activates pacemaker cells of the SA node funny channel allow the passage of both Na and K. funny current = mixed Na/K current
MOA	shifts oxidation to glucose instead of FFA to reduce oxygen demand of heart.(save energy)	look at next slide.	↓ slope of depolarization, ↓ HR, ↓ myocardial work, ↓ oxygen demand.
Indication	add-on therapy. can't be used alone.	chronic angina patients concomitantly with other drugs	-Treatment of chronic stable angina in patients with normal sinus rhythm who can't take b-blockers. -in combination with b-blockers in heart failure with LVEF < 35% inadequately controlled by b-blocker alone and whose HR > 70/min
ADRs	GIT disturbances	dizziness,constipation	luminous phenomena
Contra-indication	-hypersensitivity - pregnancy & lactation	Prolongs QT intervals = contraindicated in class Ia & III antiarrhythmics -Toxicity develop due to interaction with CYT 450 inhibitor eg. diltiazem,verapamil, ketoconzole macrolideant	-

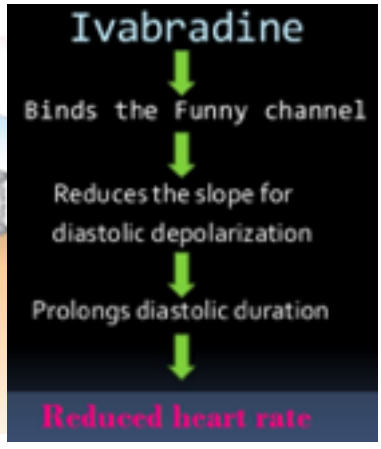
Cont.

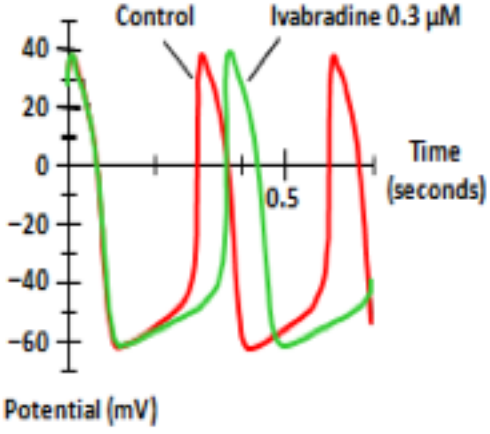
M.O.A of Trimetazidine



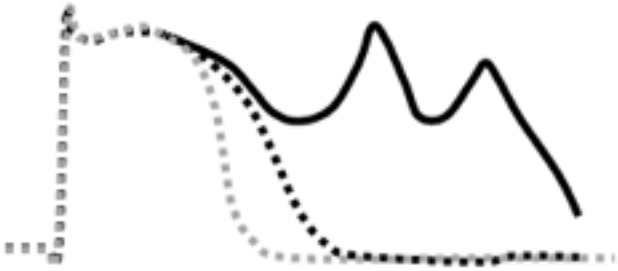
M.O.A of Ivabradine

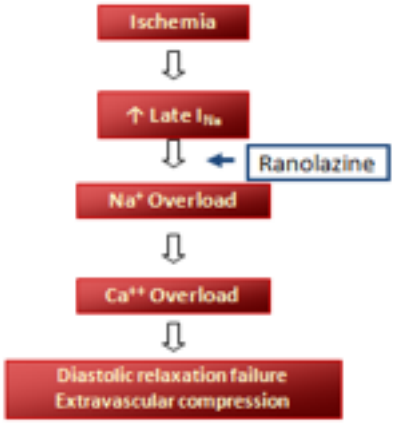






M.O.A of Ranolazine





Helmi's Case

From Pharmacology Team 435

Helmi, a 62-year-old male smoker with Type 2 Diabetes Mellitus & 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.

1. **Which signs or symptoms of Helmi suggest diagnosis of angina pectoris?**

Exercise induce, chest pain and depression of ST segment*. *sign of ischemia

1. **What life style modifications should Helmi carry out?**

Quit smoking, control of diabetes, diet control and moderate exercise.

1. **What triggers the onset of symptoms in helmi?**

Exercise

1. **What factors worsen the symptoms in case of Helmi?**

Smoking, hypertension, diabetes and enhanced LDL.

1. **What is the possible underlying cause of angina in Helmi?**

Atherosclerotic plaque

1. **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. Captoril.

1. **Which antianginal drug is the best choice for the case of Helmi? And Why?**

Nitroglycerine, if became tolerant to nitrates choose Ca channel blockers or beta blockers.

1. **If Helmi dose not respond to monotherapy, what other drug should be added to his regimen?**

Ca channel blockers (selective to blood vessels e.g. Amlodepine) + beta blockers

1. **Which antihyperlipidemic drug should be prescribed to Helmi?**

Statins, to decrease LDL levels.

Questions

MCQs:

1- A 52 year old man with stable Angina is participating in a race. Which of the following is the drug/administration method of choice:

A) Isosorbide dinitrate, orally
B) Isosorbide dinitrate, transdermal patch
C) Nitroglycerin, subcutaneously
D) Nitroglycerin, orally

2- Side effects of nitrates and nitrite drugs are, EXCEPT:

A) Orthostatic hypotension
B) Tachycardia and palpitation
C) GI disturbance
D) Throbbing Headache

3- A 47-year-old man recently diagnosed with stable angina started a treatment with sublingual nitroglycerin, as needed, and oral isosorbide mononitrate. Which of the following is a potential detrimental effect of nitrates in the prophylactic treatment of stable angina?

A) Decreased ejection time
B) Increased cardiac rate
C) Increased capacitance of systemic veins
D) Decreased arterial pressure

Questions

MCQs:

4- A 54-year-old man complained to his physician of palpitations, flushing of the face and vertigo. The man had been suffering for gastroesophageal reflux disease for three years. Two weeks ago he was diagnosed with exertional angina and started the prescribed therapy. Which of the following drugs most likely caused the patient's symptoms?

A) Propranolol
B) Verapamil
C) Nifedipine
D) Nitroglycerin

5- A 71-year-old man with congestive heart failure (treated with carvedilol) also suffers from angina. Which of the following is the drug of choice?

A) Amlodipine
B) Diltiazem
C) Verapamil
D) Nifedipine

6- Which of the following is contraindicated in variant angina?

A) Nicorandil
B) Nicardipine
C) Metoprolol
D) Verapamil

4-D 5-A 6-C

Questions

SAQ:

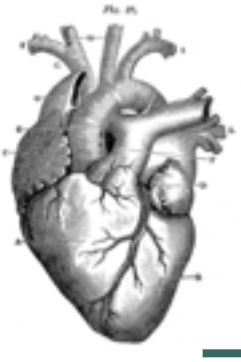
An 80-year-old woman suffers from stable angina and was prescribed medication. Name the drug and describe its hemodynamics:

Isosorbide mononitrate and dinitrate

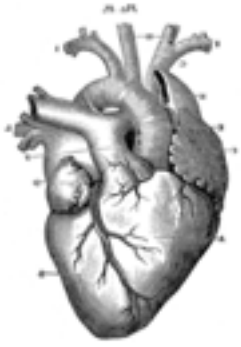
- Venous vasodilation (Decrease the preload) and decrease diastolic pressure
- Coronary vasodilation (Increase the myocardial perfusion)
- Arterial vasodilation (decrease afterload)
- Shunting of flow from normal area to ischemic area by dilating collateral vessels

Name the metabolically acting agent used as add-on therapy to Nitrates, Calcium Channel Blockers, and β blockers and describe its pharmacological effect:

1) Trimetazidine.
2) Metabolism shifts during ischemia to FFA oxidation to provide more energy, but this requires more O2. This drug shifts oxidation to glucose instead of FFA to reduce oxygen demand of heart.



"It is not hard, you just made it to the end!"



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References:

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