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CVS
PHARMACOLOGY

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Recap:

- **many drugs are named in ways that refer to their mechanism of action or their class, here are some examples that could help you memorize:**

- ARtAN= Angiotensin Recepetor ANtagonist.

Calcium channel blockers:

- di**P**henylalkyl**AM**ine: vara**PAM**il

- benz**THIAZE**pines: dil**TIAZE**m

- **DI**hydro**P**yrid**INE**s: nife**DIPINE**

Types of angina

- Angina has three overlapping patterns, which are caused by varying combination of increased myocardial demand and decreased myocardial perfusion.

A. Stable angina, the most common form, and characterized by a burning heavy or squeezing feeling in the chest.

Caused by reduction of coronary perfusion due to coronary atherosclerosis. So the heart become susceptible to ischemia whenever there is demand, such as exercise, emotional excitement.

Thus this type is also called effort-induced, excerise-based angina.

This type is rapidly relieved by rest or nitroglycerin.

Types of angina

B. Unstable angina, lies between stable angina and myocardial infarction, Often unrelated to exercise.

The symptoms are not relieved by rest or nitroglycerin.

unstable angina require more aggressive therapy, for example treatments of dyslipidemias, hypertension, anti-platelets.

C. Variant angina, occurs at rest and caused by coronary artery spasm (i.e. caused by contraction of the smooth muscle tissue in the vessel walls rather than directly by atherosclerosis)

Generally, this type rapidly responds to nitroglycerin and calcium channel blockers.

NOTES FOR THE PREIVOUS SLIDE:-

Unstable angina:

Unstable angina occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort, this is because it is related to severe atherosclerotic disease and vascular obstruction, and thus it starts to appear in a fashion that is less exercise-based or effort-dependent , this description of unstable angina makes it clearer why it is harder to treat and requires more aggressive therapy that targets dyslipidemia, hypertension, and may need anti-platelet drugs.

Sometimes it occurs due to rupture of an atherosclerotic plaque, which forms a flap that may completely obstruct the coronary artery or promote thrombus formation in that artery.

Variant angina:

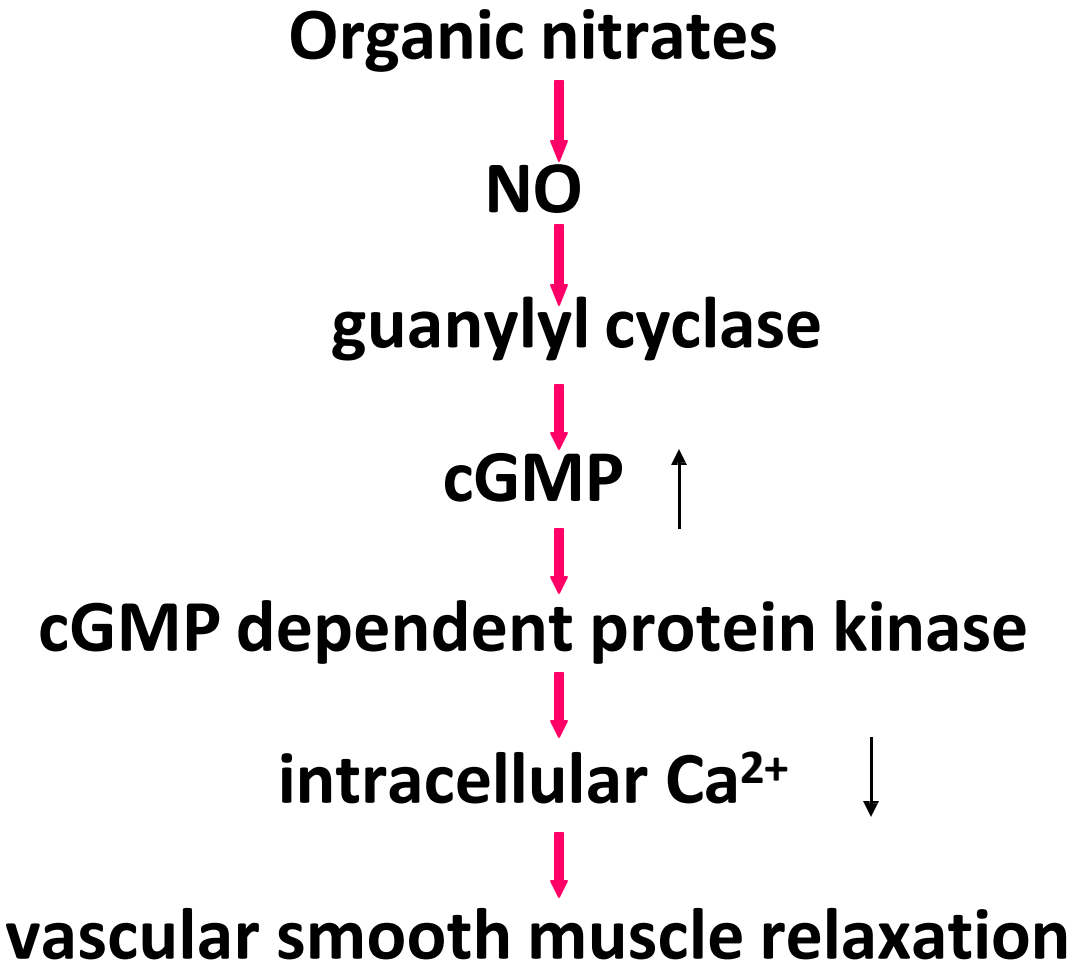
Also called vasospastic angina or Prinzemetal angina, occurs at rest and is due to decreased blood flow to the heart muscle caused by spasm of the coronary arteries that is usually related to calcium, thus it responds rapidly to calcium channel blockers or nitroglycerine.

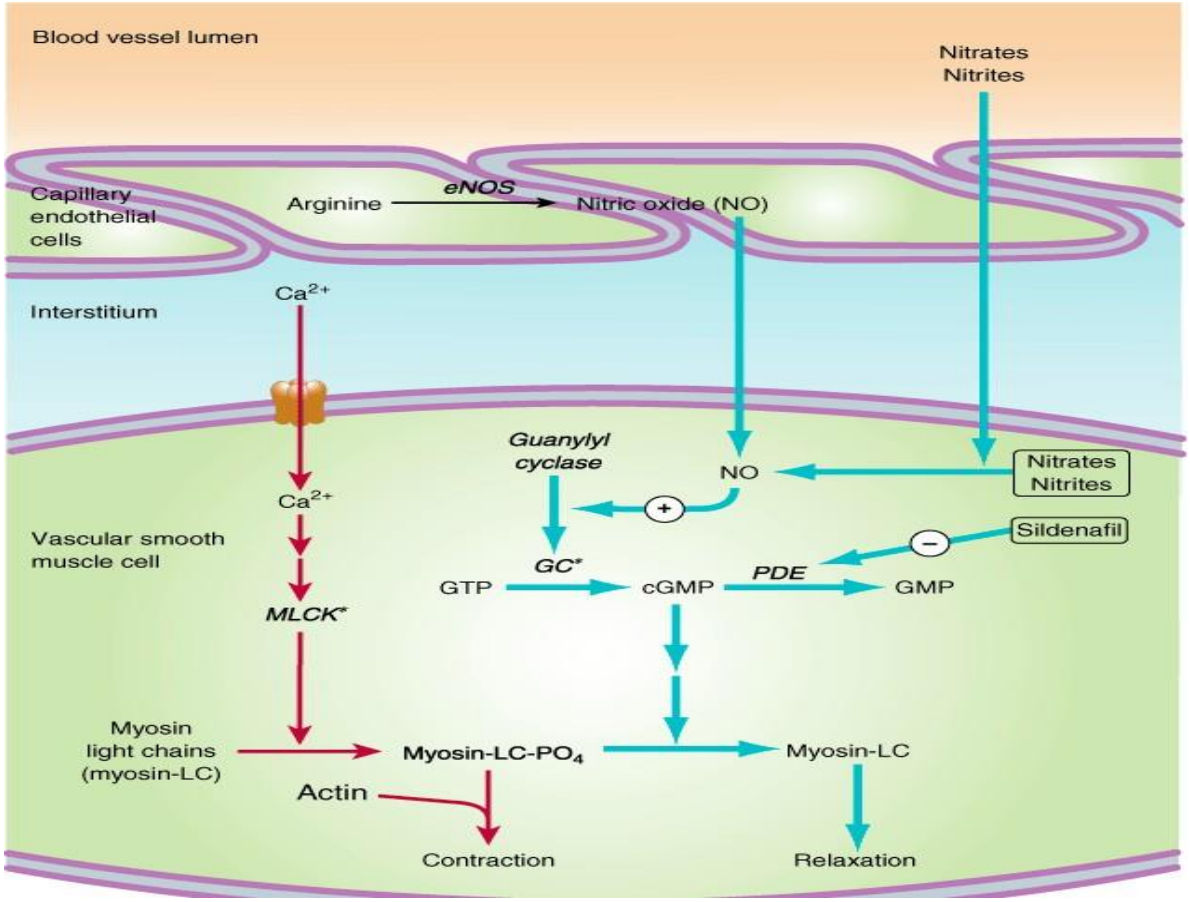
the clinical management of all types of angina focuses mainly on stopping the recurrence of the attacks

Organic nitrates

- These compounds cause a rapid reduction in the myocardial oxygen demand, and so provide a rapid relief for the angina symptoms.(which basically puts less work on the heart, thus relieving the angina)
- Their mechanism of action summarized in a decrease coronary spasm or vasoconstriction and in an increase perfusion of the myocardial by relaxing the coronary arteries.
- Members of this group include: isosorbide dinitrate, isosorbide mononitrate, and Nitroglycerine.

2.Pharmacological mechanism





GC:guanylyl cyclase
LC: light chain
PDE: phosphodiesterase

PDE is an enzyme with multiple isoforms that breaks the phosphodiester bond in cGMP,cAMP, and other cyclic mononucleotides, thus it lowers cGMP levels inside smooth muscle cells, diminishing cGMP mediated vasodilation.

Sildenafil (Viagra), is a PDE inhibitor and thus it results in the same effect as organic nitrates which is vasodilation.

Nitrates should never be used with Sildenafil (Viagra) because they synergize and cause excessively high vasodilation leading to shock and circulatory collapse, accompanied by reflex tachycardia and increased cardiac output.
Both of them, in addition to other vasodilators (Ca2+ channel blockers for ex) cause headache as an adverse effect, which is a general and expected side effect of vasodialtors.

Organic nitrates:

- All of the three agents are effective but they differ in the onset and duration of action.

- For rapid relief of an ongoing attack that precipitate by exercise and emotional stress, sublingual nitroglycerine is the drug of choice.

- At therapeutic doses nitroglycerine has two major effects:

  a. dilation of the large veins, resulting in pooling of blood in the veins (diminish preload and reduce the work of heart).

  orthostatic hypotension and syncope.

  b. dilates the coronary arteries.

All organic nitrates undergo significant first pass metabolism, but nitroglycerine undergoes near 100% first pass metabolism making it nearly ineffective orally, so instead it administered sublingually, or as a transdermal patch (not available in Jordan).
Other nitrates can be given orally but with adjustment according to the degree of first pass metabolism.

Beneficial and Deleterious Effects of Nitrates in the Treatment of Angina

	Result
1. Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased myocardial oxygen requirement
Vasodilation of epicardial coronary arteries: especially useful in the context of vasospastic angina.	Relief of coronary artery spasm
Increased collateral flow: Collaterals are newly formed blood vessels that serve as a new path for blood after obstruction or stenosis has occurred, they are formed by the complex process of angiogensis.	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
2. Potential deleterious effects	
Reflex tachycardia	Both lead to Increased myocardial oxygen requirement
Reflex increase in contractility	
Decreased diastolic perfusion time due to tachycardia: so there is less time for the blood to perfuse into the ischemic tissue during diastole.	Decreased coronary perfusion

All these beneficial effects are wanted in all types of angina, but to a lesser degree in usntable angina because of the effect of the atherosclerotic plaque and dyslipidemia.

- All the subsequnelty mentioned potentially deleterious effects of nitrates can be prevented or decreased by beta blockers, they will reduce tachycardia (reducing chronotropic activity) by blocking beta 1 receptors on SA and AV nodes, reduce contractility (reducing inotropic activity), and increase diatsolic perfusion times.

- Thus high dose beta blockers with nitrates are a mainstay in treatement of every angina patient (stable and unstable).

- However, by our understanding of vasopsatic angina, we conclude that beta blockers are contraindicated in Prinzemetal, vasospastic angina, but why?

- Beta 2 receptors mediate vasodilation, thus using a beta blocker, even if it is cardioselective such as atenolol, it can block these beta 2 receptors, which would increase the spasm and vasocontsriction that are mediating this type of angina in the first place.

Organic nitrates

- The time to onset the action varies from 1 min for nitroglycerine to 1 hr for isosorbide mononitrate .
- Significant first pass metabolism of nitroglycerine occurs so it administrated sublingually or transdermally (patch).
- Isosorbide mononitrate has long duration of action due to its ability to avoid first pass effect (so it is administrated orally).

Very important subtle differences between nitroglycerine and the other nitrates: 1) Nitroglycerine at low doses adminstered sublingually is more selective for veins than arterioles, other nitrates lack this selectivity, however nitroglycerine at high doses loses this selectivity for veins.

Thus low dose sublingual nitroglycerine will case venodilation more than arteriolodilation, decreasing the preload (venous return) on the heart, and decreasing the chance and severity of sympathetic reflexes such as tachycardia and increased contractiliy, which are all potentially bad effects.

If the patient doesn't respond to low dose sublingual nitroglycerine in an emergency angina situation, repeat and adminster sublingual nitroglycerine again, however repeat after 10-15 minutes from the previous dose.

Organic nitrates

- Adverse effect:

  a. headache (throbbing headach) is a common early side effect of nitrates, which is usually decrease after the first few days (patient develop tolerance).

b. high doses can cause postural hypotension syncope, also can result and tachycardia.

- Sildinafil (Viagra) potentiates the action of nitrates, and to avoid the dangerous hypotension, an interval of six hour between the two agents is recommended.

Tolerance

- Tolerance to the action of the nitrates develops rapidly, the blood vessels become desensitized to the vasodilation.
- Why????? diminished release of nitric oxide resulting from depletion of tissue thiol compounds may be partly responsible for tolerance to nitroglycerin.
- The tolerance can be overcame by providing a daily “nitrate free intervals” to restore sensitivity to the drug (this interval are usually 10 – 12 hr at night)
- These intervals help by giving smooth muscle cells time to reform thiol compounds which are needed for the conversion of nitrates into nitric oxide (NO).

Important notes to your patient

- The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light.

- spray is equally effective; it has a shelf life of two to three years and does not require refrigeration

β-adrenergic blocking agents

- They suppress the heart by blocking β1 receptors, and so reduce the work of the heart by decreasing the cardiac output and blood pressure.
- They reduce the frequency and the severity of angina attack.
- The cardioselective β1 agents, such as acebutolol and atenolol and metoprolol are preferred.
- They combined with nitrates to increase exercise duration and tolerance.

Beta-Blockers

- Decrease myocardial oxygen consumption
- Blunt exercise response
- Try to avoid drugs with intrinsic sympathomimetic activity
- First line therapy in all patients with stable angina

Undesirable effects

- **An increase in end-diastolic volume and an increase in ejection time, both of which tend to increase myocardial oxygen requirement.(blocking b1 receptors relaxes the heart,which in turn increases the time needed to eject blood, thus increasing the volume of the end diastolic volume, so now the heart needs more power to pump the blood,thus requiring more oxygen)**

- **These deleterious effects of beta -blocking agents can be balanced by the concomitant use of nitrates.**

β-adrenergic blocking agents

2.clinical uses

stable and unstable angina myocardiac infarction

3.contraindication

variant angina, bronchial asthma (especially non-selectives), bradycardia,

Calcium channel blockers

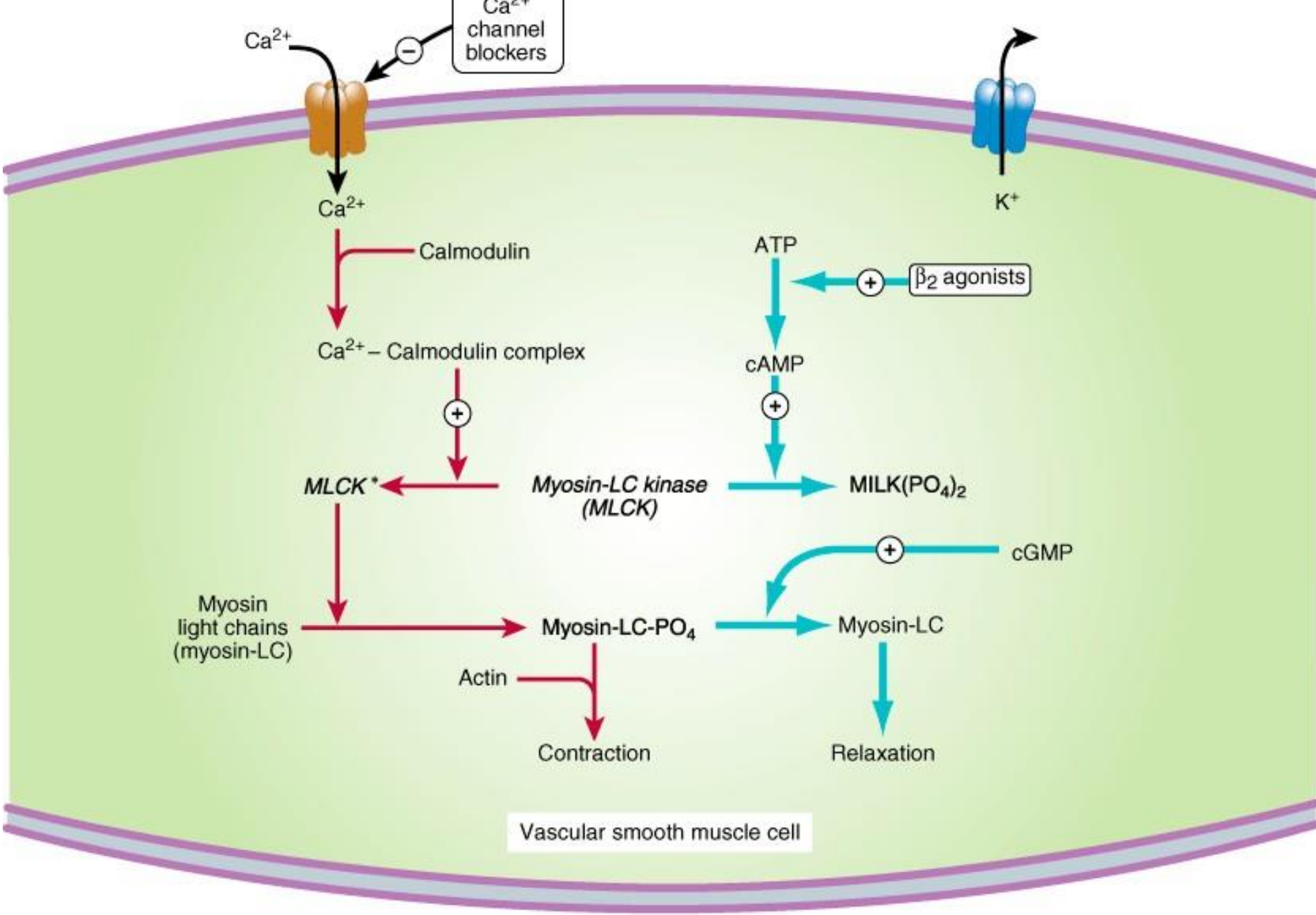
- Inhibiting the entrance of calcium into cardiac and smooth muscles cells of the coronary arteries and so they lower blood pressure.

A. Nifidipine, arterioles vasodilation effect with minimal effect on the heart, and is useful in the treatments of angina caused by spontaneous coronary spasm (Variant angina).

Since beta blockers are contraindicated in variant angina, you cannot use them with nitrates,because this raises the fear of reflex sympathitic stimulation on the heart, and thus it usually best to use –dipines in these patients.

B. Verapamil, slow cardiac conduction directly, and thus decrease oxygen demand, so should be avoided in a patient with a congestive heart failure due to its negative inotropic effect on the heart.

C. Diltiazem has similar effect on the heart to Verapamil.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Calcium Channel Blockers
Mechanisms of Action

- Arterial dilation/after-load reduction
- Coronary arterial vasodilation
- Prevention of coronary vasoconstriction
- Enhancement of coronary collateral flow
- Improved subendocardial perfusion
- Slowing of heart rate with diltiazem, verapamil

Calcium channel blockers

- Long-acting CCB's (e.g. amlodipine) or sustained release formulations of short-acting CCB's (e.g. nifedipine, felodipine, verapamil and diltiazem) are preferred,

to minimize fluctuations of plasma concentrations and cardiovascular effects.

- Side-effects are also concentration-dependent, and mainly related to the arterial vasodilator responses

  (headache, flushing and ankle oedema);

  these effects are more pronounced with dihydropyridine CCB's.

Verapamil and Diltiazem

- **In patients with relatively low blood pressure, dihydropyridines can cause further deleterious lowering of pressure.**

Verapamil and diltiazem appear to produce less hypotension and may be better tolerated in these circumstances.

- **In patients with a history of atrial tachycardia, flutter, and fibrillation, verapamil and diltiazem provide a distinct advantage because of their antiarrhythmic effects.**

Remember Verapamil and Diltiazem are less selective for L-type calcium channels of the vascular smooth muscle when compared to dihydropyridines, thus they have a negative inotropic and chronotropic effect on the heart which is beneficial for patients with arrhythmias and fibrillation.

Comparison

- Meta-analyses comparing effects of beta-blockers and CCB's in stable angina pectoris indicate that:

beta-blockers are more effective than CCB's in reducing anginal episodes,

but that effects on exercise tolerance and ischemia of the two drug classes are similar

- However, CCB's are especially effective in patients with vasospastic (Prinzmetal) angina

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

Recommendations for pharmacological therapy of vasospastic angina

- Treatment with calcium antagonists and if necessary nitrates in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.

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

اللهم انصرهم وثبت اقداهم وسدد رميهم
يارب العالمين إنك على كل شيء قدير، اللهم
غزة وأهل غزة وأراضى وأطفال ورجال
ونساء غزة .. اللهم احمهم بعينك التى لا
تنام.

Thank You