Coronary and arterial vasodilation = increased oxygen supply and decreased demand

- Volatile liquid
- Inhalant, onset of 15-30 s, lasts about 1 min

- Volatile but retains potency 3-4 months when properly stored
- Sublingual, onset ~3 min, lasts 4 - 6 h
- Used at onset of angina or better just before
- Efficacy strongly related to patient’s psychology

- Less volatile formulations, can be used sublingual
- Slow release and chewable formulations
- Often much longer lifetime or duration
Metabolism:
Rapid, first-pass reduction by glutathione-nitrate reductase in the liver and in extra-hepatic tissues such as blood vessels themselves. Sublingual and transdermal formulations reduce hepatic clearance. Long-acting nitrate activity achieved with nitroglycerin ointments and isosorbide dinitrate (oral formulation):

![Chemical structures](image)

Plasma half-life 4.5 h

Adverse effects:

Most common is headache and postural hypotension. Dizziness, nausea, vomiting, rapid pulse are less common symptoms. Many of these are not present when first experience with nitrate is in the presence of a health practitioner; thus, these effects are not considered clinical. Similarly, tolerance in the form of shorter duration of action is not thought to be clinically relevant.

Drug interactions:

Significant interactions w/ other agents that cause hypotension such as other vasodilators, alcohol and tricyclic antidepressants. Efficacy inhibited by sympathomimetics amines (e.g., ephedrine, norepinephrine).
nicorandil

A mixed-action nitrate. It opens potassium channels in addition to exhibiting nitrate activity

- Potassium channel opener - vasodilation of arterioles and large coronary arteries
- Nitrate activity - venous dilation via guanylate cyclase
- Thought to induce myocardial preconditioning, which is cardioprotective
- Metabolism is de-nitration followed by urinary excretion ($t_{1/2} = 1$ h)
- Adverse effects same as other nitrates but also may cause ulcers
- NOT to be used with sildenafil

Myocardial Bioenergetics

The heart obtains 65% of its energy from the oxidation of fatty acids and most of the remaining energy is from oxidation of glucose.

Fatty acid oxidation is more oxygen demanding than is glucose oxidation.

Fatty acid oxidation inactivates pyruvate dehydrogenase (PDH), which is essential for glucose oxidation.

Drugs that activate PDH (insulin, dichloro acetic acid) or inhibit fatty acid uptake (CPT-1,2 inhibitors) or inhibit $\beta$-oxidation (trimetazidine) have been shown to relieve angina and protect against ischemic damage.

Trimetazidine is the only approved pFOX inhibitor.
Members of a new class of drugs known as pFOX inhibitors

Trimetazidine

Ranolazine

- Thought to inhibit a 3-ketoacyl thiolase involved in β-oxidation
- Metabolism not well characterized
- Peak serum level achieved in 2-3 h but relief from angina not apparent for 2-6 week
- Very well tolerated, slight bp increase and some gastric burning
**Smooth muscle contraction**

- Calcium channel blockers

**Calcium Channel Blockers**

- Target is the L-type potential-dependent channel found in skeletal, smooth and cardiac muscle.

- Pentameric transmembrane protein with a core α1-subunit that is the binding site for calcium channel blockers.

- Differences in genes encoding the α1-subunit are responsible for differences in the L-calcium channels in different tissues.

- Inhibition of calcium ion influx via blocking L-channels causes vasodilation and reduced sensitivity to contractile stimuli.

- Thus, calcium channel blockers are commonly used to treat angina and hypertension.

- Depolarization of cardiac muscle involves calcium ion influx via L-channels. Thus, calcium channel blockers produce a negative inotropic effect and decreased AV node conduction.
- Substituted aromatic ring at C4 optimizes activity but size and position of the substituent are the only important factor (ortho or meta active).
- Esters at the C3 and C5 positions are optimal for blocking activity (antagonism) and replacement with EWG’s produce agonist activity.
- The C3 and C5 positions are non-equivalent and asymmetrical substitutions at these positions produce drugs with tissue selectivity.
- Oxidation to pyridine or reduction to piperidine abolishes activity.
- The N1 nitrogen is not basic (i.e., it is not ionized at neutral pH)

Molecular models of nifedipine show the C4-aromatic ring orthogonal to the dihydropyridine, which is thought to be the active conformation. The ortho-nitro group provides steric bulk that stabilizes this conformation.

The dihydropyridines are actually classified as calcium channel "modulators" because they can also be agonists.
Verapamil (a phenylalkylamine)

- Reactivity similar to DHP's and inhibits their action
- Has a pKa of 8.9 (+ charge at neutral pH)
- 1st-pass metabolism gives nor-verapamil, which is still active

Diltiazem (a benzothiazazapine)

- Reactivity is similar to DHP's and inhibits their action
- Enhances activity of verapamil
- Has a pKa of 7.7 (mostly + charge)
- Less effective at treating hypertension or as a vasodilator

Bepridil (a diaminopropyl ether)

- Also blocks fast sodium channels, which alters cardiac conduction and slows heart rate. Thus, contraindicated for patients with arrhythmias, hypotension, AV block
- Generally only used when patients are intolerant to other calcium blockers

Calcium blocker metabolism and adverse effects:
- All first pass but otherwise poorly characterized- probably CYP 3A4
- DHP's oxidized to inactive pyridine analogs
- Can cause hypotension and palpitations
- Many adverse effects of DHP's are eliminated with simultaneous administration of beta-blockers
- Verapamil, Diltiazem and Bepridil are not to be used w/ beta blockers
- Initially edema and weakness are common but resolved after dosage adjustments