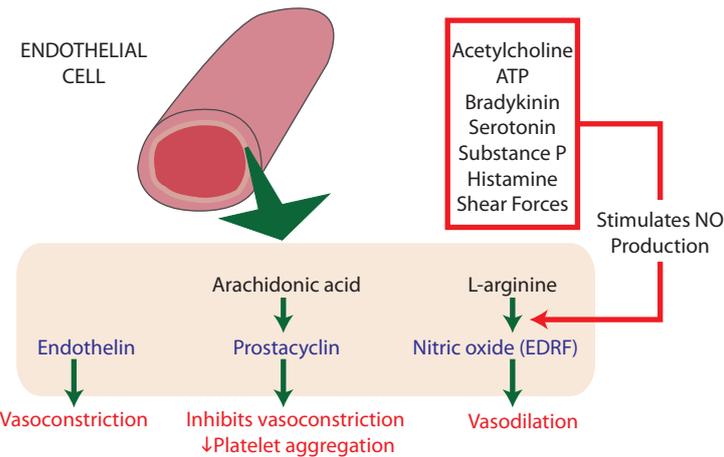


ANTIHYPERTENSIVE MEDICATIONS 2

Vasodilator medications This category includes those drugs who cause vasodilation. Ca²⁺ Channel blockers are considered separately in some classification schemes.

Ca²⁺ Channel Blockers Voltage-sensitive Ca²⁺ channels (**L-type or slow channels**) mediate the entry of extracellular Ca²⁺ into smooth muscle and cardiac myocytes and sinoatrial (SA) and atrioventricular (AV) nodal cells in response to electrical depolarization. In both smooth muscle and cardiac myocytes, Ca²⁺ is a trigger for contraction. All Ca²⁺ channel blockers relax arterial smooth muscle; they have **little effect on most venous beds** and hence **do not affect cardiac preload** significantly. In cardiac muscle, Ca²⁺ channel blockers can produce a **negative inotropic effect**. All bind to the alpha₁ subunit of the L-type Ca²⁺ channels and reduce Ca²⁺ flux through the channel; however, there are **fundamental differences amongst verapamil, diltiazem, and the dihydropyridines (including nifedipine)**, especially with respect to **pharmacokinetic** characteristics and pharmacodynamic aspects such as **electrical conduction** through the heart's conducting pathways and the **vasodilatory effects**.

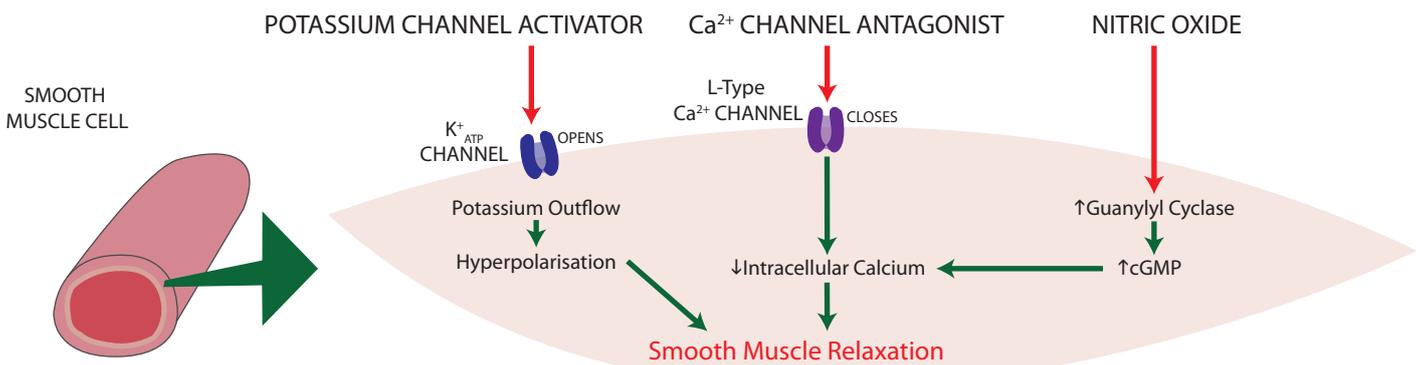
	Blood Pressure	Heart Rate	AV Conduction Time	Myocardial Contractility	Peripheral and Coronary vasodilatation
Verapamil	↓	↓	↑	↓↓	↑
Nifedipine	↓	↔ or ↓	↔ or ↓	↔ or ↓	↑↑↑
Diltiazem	↓	↓	↑	↓	↑↑



Vascular endothelium The whole of the cardiovascular system (heart and blood vessels) is lined with a **single layer of endothelial cells** forming the surface contact with blood. In addition to their capillary functions of nutrient and waste product diffusion and fluid filtration, endothelial cells **produce vasoactive substances** throughout the cardiovascular system. **Prostacyclin** is produced by the endothelium from arachidonic acid, and **inhibits platelet aggregation and vessel constriction**. Endothelial cells generate the **vasodilator nitric oxide** (also called endothelium derived relaxing factor) from L-arginine. NO increases smooth muscle cGMP, which decreases the intracellular Ca²⁺ producing muscle relaxation and vasodilation. Endothelial **NO production is stimulated by acetylcholine, ATP, bradykinin, serotonin, substance P and histamine**. NO production may also be enhanced by the shear forces caused by increased blood flow. Endothelial cells also **make the potent peptide vasoconstrictor endothelin** which increases the peripheral vascular resistance and therefore the blood pressure. Vascular endothelial cells will form new capillary networks under the influence of angiogenic factors.

Potassium Channel Activators act by **opening the normally closed potassium channels** causing leakage of potassium from myocardial cells and arterioles and subsequent hyperpolarisation. This hyperpolarisation results in **smooth muscle relaxation**. The most commonly used drug in this class is **nicorandil** which as the name suggests also has a nitrate moiety which augments its vasodilatory actions.

Direct acting vasodilators the mechanism of these drugs are not well understood. However they include minoxidil and hydralazine. **Hydralazine** is a **potent vasodilator of arterioles**. It has **little or no effect on venous smooth muscle** and its precise mode of action is unclear. It is endothelium dependent suggesting a role for nitric oxide. It also interferes with the mobilisation of calcium in the vascular smooth muscle. Its use is associated with a **baro-reflex mediated sympathetic increase in heart rate and an increase in renin production and fluid retention**; all of these effects counteract the antihypertensive effect of hydralazine. **Minoxidil** mechanism of action and principle effects are believed to be similar to hydralazine, although it should be noted that **in Goodman it is described as a Potassium Channel Activator**.



Nitrogen related antihypertensives The nitrogen related hypertensives primarily **dilate venous capacitance vessels to reduce BP**. Their effects are caused by the spontaneous or tissue mediated release of nitric oxide from the drugs. Nitric oxide stimulates guanylyl cyclase in vascular smooth muscle to increase cGMP levels, which in turn decreases intracellular calcium and cause arterial and venous dilation.

Sodium nitroprusside is used primarily to treat **hypertensive emergencies** but can also be used in many situations when short-term reduction of cardiac preload and/or afterload is desired. Nitroprusside **dilates both arterioles and venules equally**; the hemodynamic response results from a combination of venous pooling and reduced arterial impedance. In subjects with normal left ventricular function, venous pooling affects cardiac output more than does the reduction of afterload; cardiac output thus tends to fall. In patients with severely impaired left ventricular function and diastolic ventricular distention, the reduction of arterial impedance leads to a rise in cardiac output. **Tolerance does not develop to nitroprusside but it has a very short duration of action**, thus requiring constant infusion. The short term side effects are related to excessive vasodilation. Long term toxicity is a result of the **production of cyanomethemoglobin** which may interfere with oxidative phosphorylation and cause tissue hypoxia.

Glycerol trinitrate is used in the treatment of stable and unstable **angina**, as well as **acute pulmonary oedema**. The **dilation in venous system is more pronounced** than in the arterial system unlike SNP (where there is equal dilatation). The ability of nitrates to dilate epicardial coronary arteries is modest; the bulk of evidence favors a **reduction in myocardial work** and thus in myocardial oxygen demand as their primary effect in chronic stable angina. Unlike SNP repeated use of GTN **leads to tolerance** and decreased efficacy, regular interruptions in treatment are required. Side effects are related to the cardiovascular effects with headache being a common complaint. They should **never be used in conjunction with PDE inhibitors** such as sildenafil as this may lead to a profound peripheral dilation and associated hypotension.