

**Vasodilators,  
Treatment of Angina Pectoris  
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<ul style="list-style-type: none"><li>• <b>Nitrates and nitrites</b></li></ul>	<ol style="list-style-type: none"><li>1. Amyl nitrite (<i>Aspirols</i>)</li><li>2. Isosorbide dinitrate (Isordil, Cardioket)</li><li>3. Isosorbide mononitrate (Monoket)</li><li>4. Nitroglycerine (Nitroderm TTS, Perlinganit, Nitrolingual)</li><li>5. Pentaerytritol tetranitrate (Danitrin)</li></ol>
<ul style="list-style-type: none"><li>• <b><math>\beta</math>-blockers</b></li></ul>	<ol style="list-style-type: none"><li>1. Propranolol (Dideral) and others</li></ol>
<ul style="list-style-type: none"><li>• <b>L-type voltage dependent calcium channel blockers</b></li></ul>	<ol style="list-style-type: none"><li>1. Amlodipine (Norvasc)</li><li>2. Bepridil (<i>Vasacor</i>)</li><li>3. Diltiazem (Diltizem)</li><li>4. Mibefranil (preparatı yok)</li><li>5. Nifedipine (Adalat Crono)</li><li>6. Verapamil (Isoptin)</li></ol>
<ul style="list-style-type: none"><li>• <b>Other antianginal drugs</b></li></ul>	<ol style="list-style-type: none"><li>1. Flunarizine (Sibelium)</li><li>2. Cromakalime (no preparation)</li><li>3. Pinacidil (<i>Pindac</i>)</li><li>4. Ranolarizine (<i>Ranexa</i>)</li><li>5. Trimetazidine (Vastarel)</li></ol>

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## Angina pectoris I

- Angina pectoris is the most common condition involving tissue ischemia in which vasodilator drugs are used.
- The name denotes chest pain caused by accumulation of metabolites resulting from myocardial ischemia.
- The organic nitrates, eg, **nitroglycerin**, are the mainstay of therapy for the immediate relief of angina.
- Another group of vasodilators, the **calcium channel blockers**, is also important, especially for prophylaxis, and the  **$\beta$  blockers**, which are *not* vasodilators, are also useful in prophylaxis.
- New groups of drugs under investigation include fatty acid oxidation inhibitors and selective cardiac rate inhibitors.

## Angina pectoris II

- Ischemic heart disease is the most common serious health problem in many Western societies.
- By far the most frequent cause of angina is atheromatous obstruction of the large coronary vessels (**atherosclerotic angina, classic angina**).
- However, transient spasm of localized portions of these vessels, which is usually associated with underlying atheromas, can also cause significant myocardial ischemia and pain (**vasospastic or variant angina**).

### *Angina pectoris III*

- The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels.
- In classic angina, the imbalance occurs when the myocardial oxygen requirement increases, as during exercise, and coronary blood flow does not increase proportionately.
- The resulting ischemia usually leads to pain.
- Classic angina is therefore "angina of effort".  
(In some individuals, the ischemia is not always accompanied by pain, resulting in "silent" or "ambulatory" ischemia.)
- In variant angina, oxygen delivery decreases as a result of reversible coronary vasospasm. Variant angina is also called **Prinzmetal's** angina.

### *Angina pectoris IV*

- In theory, the imbalance between oxygen delivery and myocardial oxygen demand can be corrected by **decreasing oxygen demand** or by **increasing delivery** (by increasing coronary flow).
- In effort angina, oxygen demand can be reduced by decreasing cardiac work or, according to recent studies, by shifting myocardial metabolism to substrates that require less oxygen per unit of ATP produced.
- In variant angina, on the other hand, spasm of coronary vessels can be reversed by nitrates or calcium channel blockers. Lipid-lowering drugs, especially the "**statins**" have become extremely important in the long-term treatment of atherosclerotic disease.

## **Angina pectoris V**

- **Unstable angina**, an acute coronary syndrome, is said to be present when there are episodes of angina at rest and when there is a change in the character, frequency, and duration of chest pain as well as precipitating factors in patients with previously stable angina.
- Unstable angina is caused by episodes of increased epicardial coronary artery tone or small platelet clots occurring in the vicinity of an atherosclerotic plaque. Low dose **aspirin** can reduce the incidence of myocardial infarction in these patients.
- In most cases, formation of labile nonocclusive thrombi at the site of a fissured or ulcerated plaque is the mechanism for reduction in flow.
- The course and the prognosis of unstable angina are variable, but this subset of acute coronary syndrome is associated with a high risk of myocardial infarction and death.

## **Determinants of Myocardial Oxygen Consumption**

Wall stress  
  **Intraventricular pressure**  
  **Ventricular radius (volume)**  
  **Wall thickness**  
Heart rate  
Contractility

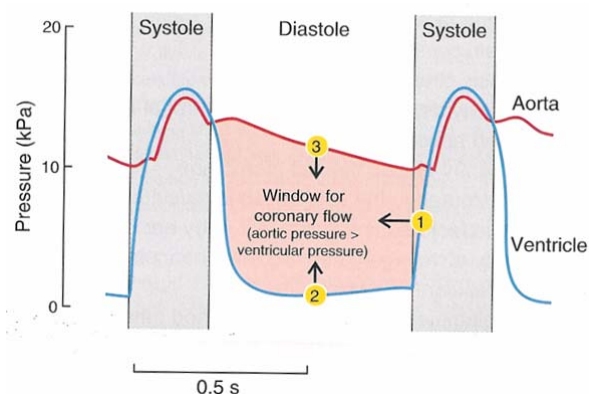
## Determinants of Coronary Blood Flow & Myocardial Oxygen Supply

- Increased myocardial demands for oxygen in the normal heart are met by augmenting coronary blood flow. Coronary blood flow is directly related to the perfusion pressure (aortic diastolic pressure) and the duration of diastole. Because coronary flow drops to negligible values during systole, the duration of diastole becomes a limiting factor for myocardial perfusion during tachycardia.
- Coronary blood flow is inversely proportional to coronary vascular bed resistance. Resistance is determined mainly by intrinsic factors—including metabolic products and autonomic activity—and by various pharmacologic agents.
- **Damage to the endothelium** of coronary vessels has been shown to alter their ability to dilate and to increase coronary vascular resistance.

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## Mechanical Factors as Determinants of Coronary Blood Flow



The 'window' for coronary flow may be encroached upon by: (1) shortening diastole, when heart rate increases; (2) increased ventricular end-diastolic pressure; and (3) reduced diastolic arterial pressure.

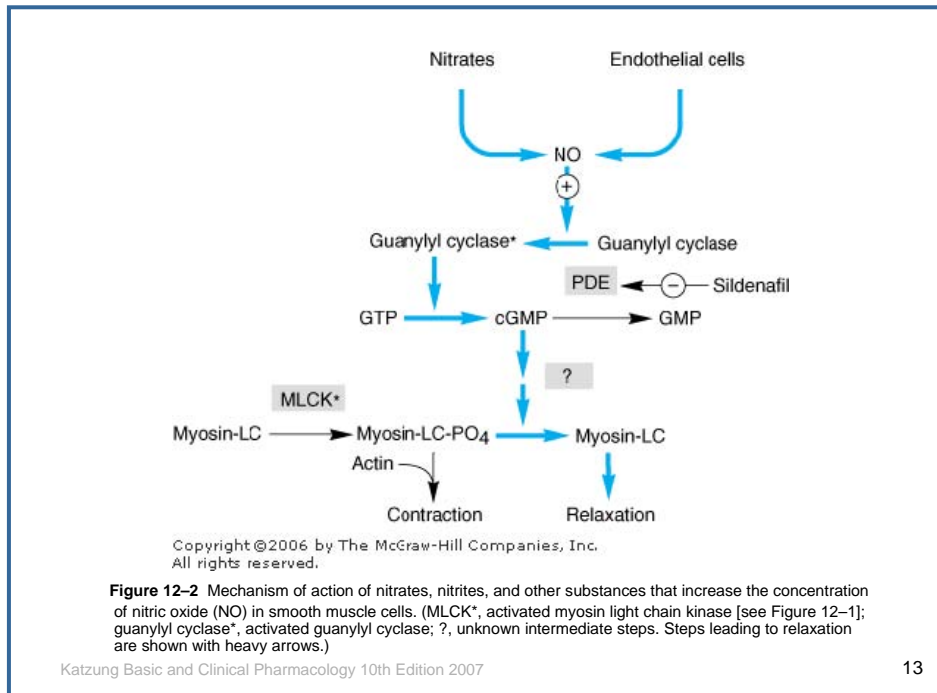
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## ***Determinants of Vascular Tone***

- Arteriolar and venous tone (smooth muscle tension) both play a role in determining myocardial wall stress.
- **Arteriolar tone** directly controls peripheral vascular resistance and thus arterial blood pressure. In systole, intraventricular pressure must exceed aortic pressure to eject blood; arterial blood pressure thus determines the **systolic wall stress** in an important way.
- **Venous tone** determines the capacity of the venous circulation and controls the amount of blood sequestered in the venous system versus the amount returned to the heart. Venous tone thereby determines the **diastolic wall stress**.

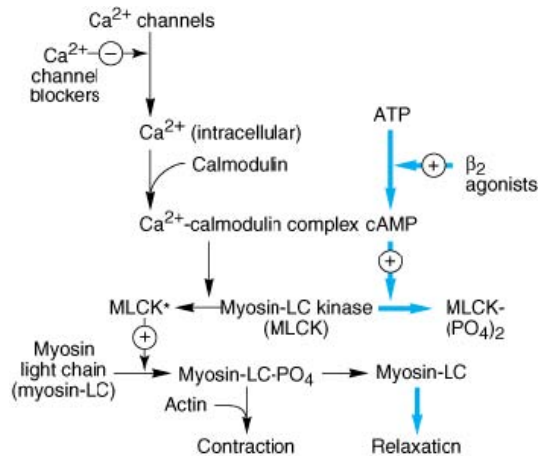
## ***Mechanisms of vascular smooth muscle relaxation I***

- **Increasing cGMP**  
cGMP facilitates the dephosphorylation of myosin light chains, preventing the interaction of myosin with actin.
- Nitric oxide is an effective activator of soluble guanylyl cyclase and acts mainly through this mechanism.
- Important molecular donors of nitric oxide include nitroprusside and the organic nitrates used in angina.



## ***Mechanisms of vascular smooth muscle relaxation II***

- **Decreasing intracellular Ca<sup>2+</sup>:**  
Calcium channel blockers predictably cause vasodilation because they reduce intracellular Ca<sup>2+</sup>, a major modulator of the activation of myosin light chain kinase.
- Beta blockers and calcium channel blockers reduce Ca<sup>2+</sup> influx in cardiac muscle, thereby reducing rate, contractility, and oxygen requirement unless reversed by compensatory responses.



**Figure 12-1** Control of smooth muscle contraction and site of action of calcium channel-blocking drugs. Contraction is triggered by influx of calcium (which can be blocked by calcium channel blockers) through transmembrane calcium channels. The calcium combines with calmodulin to form a complex that converts the enzyme myosin light chain kinase to its active form (MLCK\*). The latter phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin. Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK (heavy arrows) and by facilitating the expulsion of calcium from the cell (not shown).

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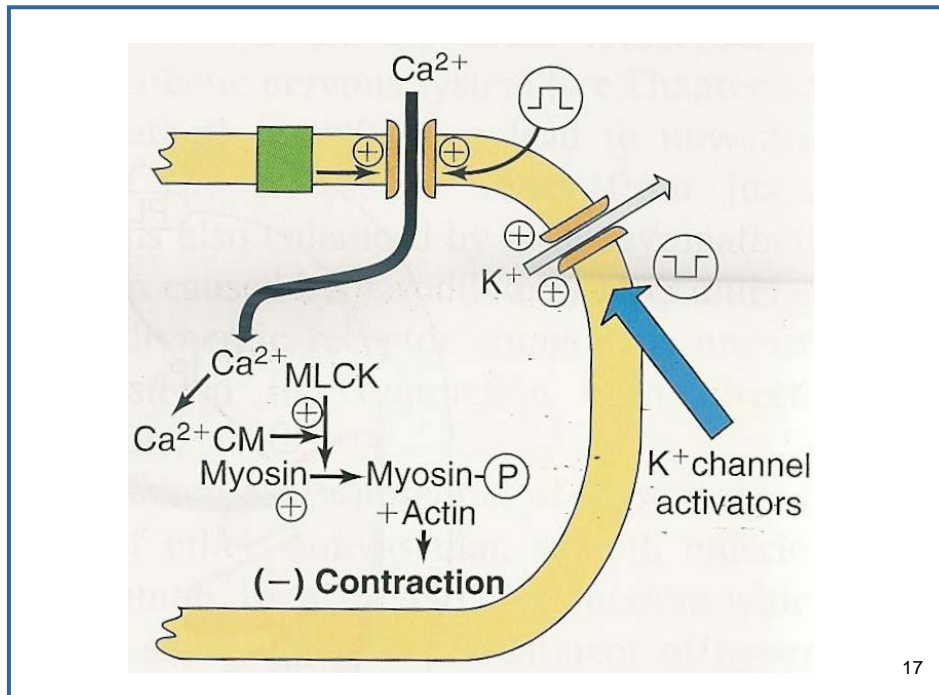
### **Mechanisms of vascular smooth muscle relaxation III**

- **Stabilizing or preventing depolarization of the vascular smooth muscle cell membrane:** The membrane potential of excitable cells is stabilized near the resting potential by increasing potassium permeability.
- Potassium channel openers, such as minoxidil sulfate, increase the permeability of  $\text{K}^+$  channels, probably ATP-dependent  $\text{K}^+$  channels.
- Certain newer agents under investigation for use in angina (eg, nicorandil) may act, in part, by this mechanism.

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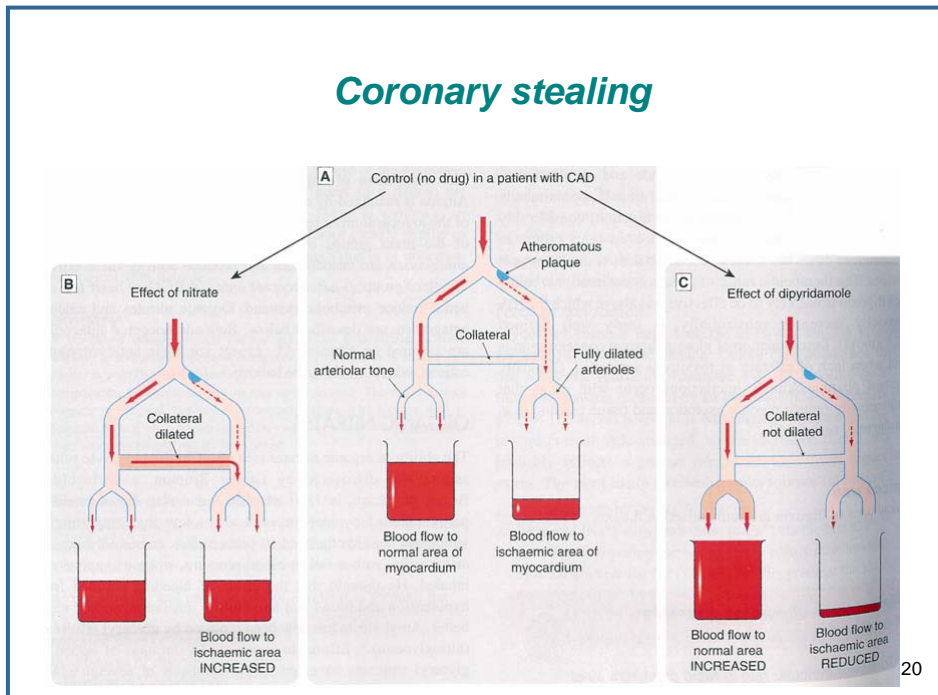
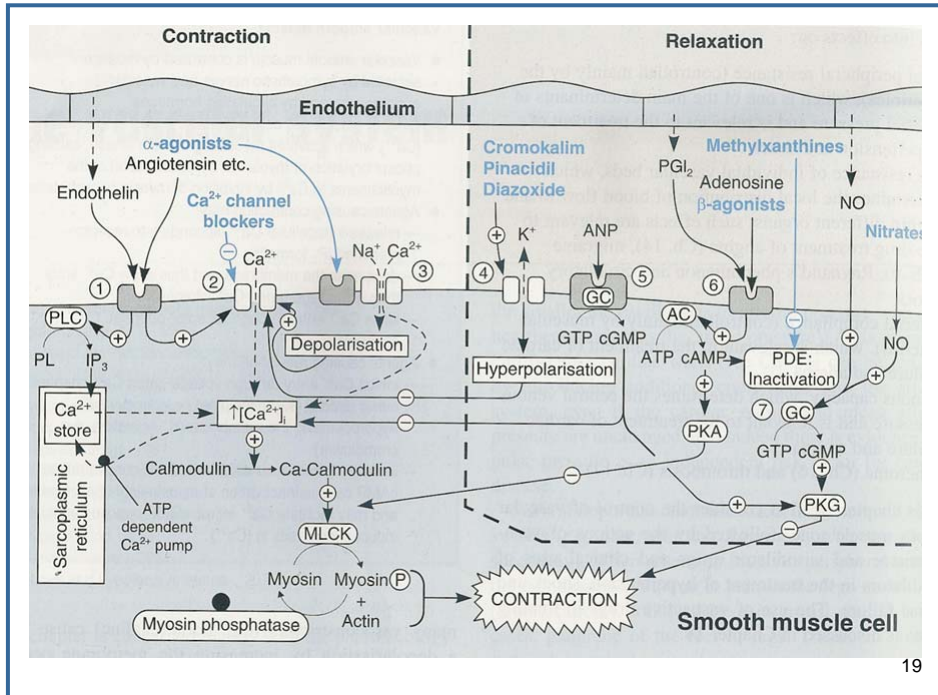




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### **Mechanisms of vascular smooth muscle relaxation IV**

- Increasing cAMP in vascular smooth muscle cells:**  
 An increase in cAMP increases the rate of inactivation of myosin light chain kinase, the enzyme responsible for triggering the interaction of actin with myosin in these cells.
- This appears to be the mechanism of vasodilation caused by  $\beta_2$  agonists, drugs that are *not* used in angina.



## Nitrates & Nitrites

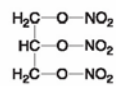
- These agents are simple nitric and nitrous acid esters of polyalcohols. **Nitroglycerin** may be considered the prototype of the group. Although nitroglycerin is used in the manufacture of dynamite, the formulations used in medicine are not explosive. The conventional sublingual tablet form of nitroglycerin 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. It is not sensitive to light.
- All therapeutically active agents in the nitrate group have identical mechanisms of action and similar toxicities. Therefore, pharmacokinetic factors govern the choice of agent and mode of therapy when using the nitrates.

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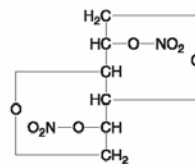
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NONPROPRIETARY NAMES AND TRADE NAMES	CHEMICAL STRUCTURE
Nitroglycerin (glyceryl trinitrate; NITRO-BID, NITROSTAT, NITROL, NITRO-DUR, others)	$\begin{array}{c} \text{H}_2\text{C}-\text{O}-\text{NO}_2 \\   \\ \text{HC}-\text{O}-\text{NO}_2 \\   \\ \text{H}_2\text{C}-\text{O}-\text{NO}_2 \end{array}$
Isosorbide dinitrate (ISORDIL, SORBITRATE, DILATRATE-SR, others)	
Isosorbide-5-mononitrate (IMDUR, ISMO, others)	

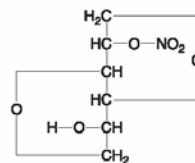
Nitroglycerin  
(glyceryl trinitrate;  
NITRO-BID, NITROSTAT,  
NITROL, NITRO-DUR,  
others)



Isosorbide dinitrate  
(ISORDIL, SORBITRATE,  
DILATRATE-SR, others)



Isosorbide-5-mononitrate  
(IMDUR, ISMO, others)



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## Pharmacokinetics

- The liver contains a high-capacity organic nitrate reductase that removes nitrate groups in a stepwise fashion from the parent molecule and ultimately inactivates the drug.
- Therefore, oral bioavailability of the traditional organic nitrates (eg, nitroglycerin and **isosorbide dinitrate**) is very low (typically < 10–20%).
- For this reason, the sublingual route, which avoids the first-pass effect, is preferred for achieving a therapeutic blood level rapidly. Nitroglycerin and isosorbide dinitrate are both absorbed efficiently by this route and reach therapeutic blood levels within a few minutes.
- However, the total dose administered by this route must be limited to avoid excessive effect; therefore, the total duration of effect is brief (15–30 minutes).
- When much longer duration of action is needed, oral preparations can be given that contain an amount of drug sufficient to result in sustained systemic blood levels of the parent drug plus active metabolites.
- Other routes of administration available for nitroglycerin include transdermal and buccal absorption from slow-release preparations; these are described below.

## Mechanism of Action in Smooth Muscle

- Nitroglycerin is denitrated by glutathione S-transferase. Free nitrite ion is released, which is then converted to **nitric oxide**.
- A different unknown enzymatic reaction releases nitric oxide directly from the parent drug molecule. Nitric oxide (or an S-nitrosothiol derivative) causes activation of guanylyl cyclase and an increase in cGMP, which are the first steps toward smooth muscle relaxation.
- The production of prostaglandin E or prostacyclin (PGI<sub>2</sub>) and membrane hyperpolarization may also be involved. There is no evidence that autonomic receptors are involved in the primary nitrate response (although autonomic *reflex* responses are evoked when hypotensive doses are given).
- **Tolerance** is an important consideration in the use of nitrates. While tolerance may be caused in part by a decrease in tissue sulfhydryl groups, it can be only partially prevented or reversed with a **sulfhydryl-regenerating agent**. Increased generation of oxygen free radicals during nitrate therapy may be another important mechanism of tolerance.
- Nicorandil and several other investigational antianginal agents appear to combine the activity of nitric oxide release with potassium channel-opening action, thus providing an additional mechanism for causing vasodilation.

## ***Beneficial and Deleterious Effects of Nitrates in the Treatment of Angina***

<b>Effect</b>	<b>Result</b>
<b>Potential beneficial effects</b>	
Decreased ventricular volume	Decreased myocardial oxygen requirement
Decreased arterial pressure	
Decreased ejection time	
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
<b>Potential deleterious effects</b>	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

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## ***Nitrate and Nitrite Drugs Used in the Treatment of Angina***

<b>Drug</b>	<b>Dose</b>	<b>Duration of Action</b>
<b>"Short-acting"</b>		
Nitroglycerin, sublingual	0.15–1.2 mg	10–30 minutes
Isosorbide dinitrate, sublingual	2.5–5 mg	10–60 minutes
Amyl nitrite, inhalant	0.18–0.3 mL	3–5 minutes
<b>"Long-acting"</b>		
Nitroglycerin, oral sustained-action	6.5–13 mg per 6–8 hours	6–8 hours
Nitroglycerin, 2% ointment, transdermal	1–1.5 inches per 4 hours	3–6 hours
Nitroglycerin, slow-release, buccal	1–2 mg per 4 hours	3–6 hours
Nitroglycerin, slow-release patch, transdermal	10–25 mg per 24 hours (one patch per day)	8–10 hours
Isosorbide dinitrate, sublingual	2.5–10 mg per 2 hours	1.5–2 hours
Isosorbide dinitrate, oral	10–60 mg per 4–6 hours	4–6 hours
Isosorbide dinitrate, chewable oral	5–10 mg per 2–4 hours	2–3 hours
Isosorbide mononitrate, oral	20 mg per 12 hours	6–10 hours

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## Other Effects I

- Nitric oxide released from nitroglycerin stimulates guanylyl cyclase in platelets as in smooth muscle.
- The increase in cGMP that results is responsible for a decrease in platelet aggregation.
- Unfortunately, recent prospective trials have established no survival benefit when nitroglycerin is used in acute myocardial infarction.

## Other Effects II

- **Nitrite ion** reacts with hemoglobin (which contains ferrous iron) to produce **methemoglobin** (which contains ferric iron). Because methemoglobin has a very low affinity for oxygen, large doses of nitrites can result in pseudocyanosis, tissue hypoxia, and death.
- Fortunately, the plasma level of **nitrite** resulting from even large doses of organic and inorganic **nitrates** is too low to cause significant methemoglobinemia in adults.
- However, sodium nitrite is used as a curing agent for meats. In nursing infants, the intestinal flora is capable of converting significant amounts of inorganic nitrate, eg, from well water, to nitrite ion.
- Thus, inadvertent exposure to large amounts of nitrite ion can occur and may produce serious toxicity.

### **Other Effects III**

- One therapeutic application of this otherwise toxic effect of nitrite (i.e. methemoglobinemia) has been discovered.
- Cyanide poisoning results from complexing of cytochrome iron by the  $\text{CN}^-$  ion. Methemoglobin iron has a very high affinity for  $\text{CN}^-$ ; thus, administration of sodium nitrite ( $\text{NaNO}_2$ ) soon after cyanide exposure will regenerate active cytochrome.
- The cyanmethemoglobin produced can be further detoxified by the intravenous administration of sodium thiosulfate ( $\text{Na}_2\text{S}_2\text{O}_3$ ); this results in formation of thiocyanate ion ( $\text{SCN}^-$ ), a less toxic ion that is readily excreted.
- Methemoglobinemia, if excessive, can be treated by giving methylene blue intravenously.

### **Clinical Use of Nitrates**

- Because of its rapid onset of action (1–3 minutes), sublingual nitroglycerin is the most frequently used agent for the immediate treatment of angina. Because its duration of action is short (not exceeding 20–30 minutes), it is not suitable for maintenance therapy.
- The onset of action of intravenous nitroglycerin is also rapid (minutes), but its hemodynamic effects are quickly reversed by stopping its infusion. Clinical application of intravenous nitroglycerin, therefore, is restricted to the treatment of severe, recurrent rest angina.
- Slowly absorbed preparations of nitroglycerin include a buccal form, oral preparations, and several transdermal forms. These formulations have been shown to provide blood concentrations for long periods but, as noted above, this leads to the development of tolerance.

## ***Adverse effects***

- The major acute toxicities of organic nitrates are direct extensions of therapeutic vasodilation: orthostatic hypotension, tachycardia, and throbbing headache.
- Glaucoma, once thought to be a contraindication, does not worsen, and nitrates can be used safely in the presence of increased intraocular pressure.
- Nitrates are contraindicated, however, if intracranial pressure is elevated.

## ***Calcium Channel-Blocking Drugs***

- Calcium influx is necessary for the contraction of smooth and cardiac muscle.
- The discovery of a calcium channel in cardiac muscle was followed by the finding of several different types of calcium channels in different tissues.
- The discovery of these channels made possible the development of clinically useful blocking drugs.
- Although the successful therapeutic blockers developed to date have been exclusively L-type channel blockers, selective blockers of other types of calcium channels are under intensive investigation.

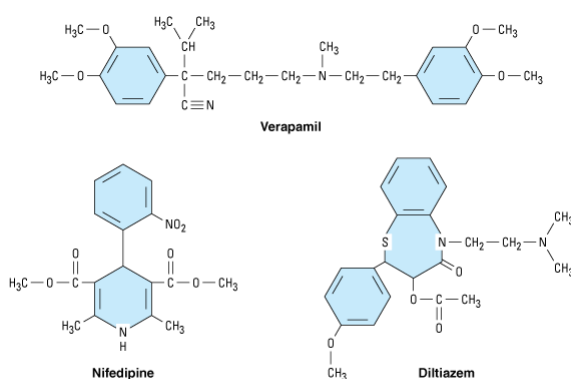


## Chemistry & Pharmacokinetics

- **Verapamil**, the first clinically useful member of this group, was the result of attempts to synthesize more active analogs of papaverine, a vasodilator alkaloid found in the opium poppy.
- Since then, dozens of agents of varying structure have been found to have the same fundamental pharmacologic action.
- **Nifedipine** is the prototype of the dihydropyridine family of calcium channel blockers; dozens of molecules in this family have been investigated, and seven are currently approved in the USA for angina and other indications. Nifedipine is the most extensively studied of this group, but the properties of the other dihydropyridines can be assumed to be similar to it unless otherwise noted.
- The calcium channel blockers are orally active agents and are characterized by high first-pass effect, high plasma protein binding, and extensive metabolism. Verapamil and diltiazem are also used by the intravenous route.

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## **Mechanism of Action I**

- The L-type calcium channel is the dominant type in cardiac and smooth muscle and is known to contain several drug receptors. It has been demonstrated that nifedipine and other dihydropyridines bind to one site, while verapamil and diltiazem appear to bind to closely related but not identical receptors in another region.
- Binding of a drug to the verapamil or diltiazem receptors also affects dihydropyridine binding.
- These receptor regions are stereoselective, since marked differences in both stereoisomer-binding affinity and pharmacologic potency are observed for enantiomers of verapamil, diltiazem, and optically active nifedipine congeners.

## **Properties of Several Recognized Voltage-Activated Calcium Channels**

<b>Type</b>	<b>Channel Name</b>	<b>Where Found</b>	<b>Properties of the Calcium Current</b>	<b>Blocked By</b>
L	CaV1.1– CaV1.3	Muscle, neurons (CaV1.4 is found in retina)	Long, large, high threshold	Verapamil, DHPs, Cd <sup>2+</sup>
T	CaV3.1– CaV3.3	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni <sup>2+</sup>
N	CaV2.2	Neurons	Short, high threshold	-CTX-GVIA, Cd <sup>2+</sup>
P/Q	CaV2.1	Cerebellar Purkinje neurons	Long, high threshold	-Aga-IVA
R	CaV2.3	Neurons	Pacemaking	SNX-482

## ***Mechanism of Action II***

- Blockade by these drugs resembles that of sodium channel blockade by local anesthetics.
- The drugs act from the inner side of the membrane and bind more effectively to channels in depolarized membranes. Binding of the drug reduces the frequency of opening in response to depolarization.
- The result is a marked decrease in transmembrane calcium current, resulting in smooth muscle with a long-lasting relaxation, and in cardiac muscle with a reduction in contractility throughout the heart and decreases in sinus node pacemaker rate and in atrioventricular node conduction velocity.

## ***Mechanism of Action III***

- Smooth muscle responses to calcium influx through *receptor*-operated calcium channels are also reduced by these drugs but not as markedly.
- The block can be partially reversed by elevating the concentration of calcium, although the levels of calcium required are not easily attainable.
- Block can also be partially reversed by the use of drugs that increase the transmembrane flux of calcium, such as sympathomimetics.

## ***Effects on Smooth Muscle I***

- Most types of smooth muscle are dependent on transmembrane calcium influx for normal resting tone and contractile responses. These cells are relaxed by the calcium channel blockers.
- Vascular smooth muscle appears to be the most sensitive, but similar relaxation can be shown for bronchiolar, gastrointestinal, and uterine smooth muscle.

## ***Effects on Smooth Muscle II***

- In the vascular system, arterioles appear to be more sensitive than veins; orthostatic hypotension is not a common adverse effect. Blood pressure is reduced with all calcium channel blockers. Women may be more sensitive than men to the hypotensive action of diltiazem. The reduction in peripheral vascular resistance is one mechanism by which these agents may benefit the patient with angina of effort. Reduction of coronary arterial tone has been demonstrated in patients with variant angina.
- Important differences in vascular selectivity exist among the calcium channel blockers. In general, the dihydropyridines have a greater ratio of vascular smooth muscle effects relative to cardiac effects than do diltiazem and verapamil. Furthermore, the dihydropyridines may differ in their potency in different vascular beds. For example, nimodipine is claimed to be particularly selective for cerebral blood vessels.

## ***Effects on Cardiac Muscle I***

- Cardiac muscle is highly dependent upon calcium influx for normal function. Impulse generation in the sinoatrial node and conduction in the atrioventricular node—so-called slow response, or calcium-dependent, action potentials—may be reduced or blocked by all of the calcium channel blockers.
- Excitation-contraction coupling in all cardiac cells requires calcium influx, so these drugs reduce cardiac contractility in a dose-dependent fashion. In some cases, cardiac output may also decrease.
- This reduction in cardiac mechanical function is another mechanism by which the calcium channel blockers can reduce the oxygen requirement in patients with angina.

## ***Effects on Cardiac Muscle II***

- Important differences between the available calcium channel blockers arise from the details of their interactions with cardiac ion channels and, differences in their relative smooth muscle versus cardiac effects.
- Sodium channel block is modest with verapamil and still less marked with diltiazem. It is negligible with nifedipine and other dihydropyridines. Verapamil and diltiazem interact kinetically with the calcium channel receptor in a different manner than the dihydropyridines; they block tachycardias in calcium-dependent cells, eg, the atrioventricular node, more selectively than do the dihydropyridines.
- On the other hand, the dihydropyridines appear to block smooth muscle calcium channels at concentrations below those required for significant cardiac effects; they are therefore less depressant on the heart than verapamil or diltiazem.

## ***Toxicity of Calcium Channel-Blocking Drugs***

- The most important toxic effects reported for the calcium channel blockers are direct extensions of their therapeutic action. Excessive inhibition of calcium influx can cause serious cardiac depression, including cardiac arrest, bradycardia, atrioventricular block, and heart failure. These effects have been rare in clinical use.
- Retrospective case control studies reported that immediate-acting nifedipine increased the risk of myocardial infarction in patients with hypertension. Slow-release and long-acting vasoselective calcium channel blockers are usually well tolerated. However, dihydropyridines, compared with angiotensin-converting enzyme inhibitors, have been reported to increase the risk of adverse cardiac events in patients with hypertension with or without diabetes. These results suggest that relatively short-acting calcium channel blockers have the potential to enhance the risk of adverse cardiac events and should be avoided. Patients receiving  $\beta$ -adrenoceptor-blocking drugs are more sensitive to the cardiodepressant effects of calcium channel blockers.
- Minor toxicity (troublesome but not usually requiring discontinuance of therapy) includes flushing, dizziness, nausea, constipation, and peripheral edema.

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## ***Mechanisms of Clinical Effects I***

- Calcium channel blockers decrease myocardial contractile force, which reduces myocardial oxygen requirements.
- Inhibition of calcium entry into arterial smooth muscle is associated with decreased arteriolar tone and systemic vascular resistance, resulting in decreased arterial and intraventricular pressure.
- Some of these drugs (eg, verapamil, diltiazem) also possess a nonspecific antiadrenergic effect, which may contribute to peripheral vasodilation.
- As a result of all of these effects, left ventricular wall stress declines, which reduces myocardial oxygen requirements.
- Decreased heart rate with the use of verapamil or diltiazem causes a further decrease in myocardial oxygen demand.
- Calcium channel-blocking agents also relieve and prevent the primary cause of variant angina—focal coronary artery spasm. Use of these agents has thus emerged as the most effective prophylactic treatment for this form of angina pectoris (in this form  $\beta$ -blockers may enhance angina via vasoconstriction).

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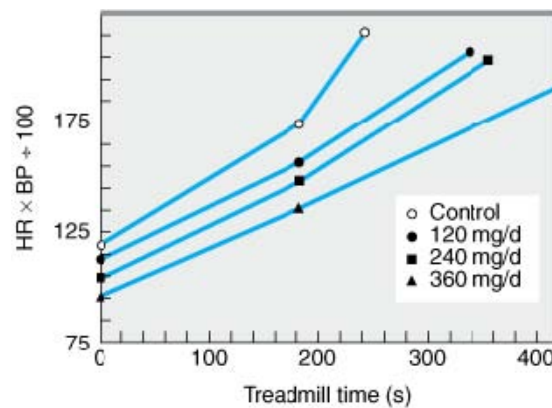
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## Mechanisms of Clinical Effects

- Sinoatrial and atrioventricular nodal tissues, which are mainly composed of calcium-dependent, slow response cells, are affected markedly by verapamil, moderately by diltiazem, and much less by dihydropyridines.
- Thus, verapamil and diltiazem decrease atrioventricular nodal conduction and are effective in the management of supraventricular reentry tachycardia and in decreasing ventricular responses in atrial fibrillation or flutter.
- Nifedipine does not affect atrioventricular conduction. Nonspecific sympathetic antagonism is most marked with diltiazem and much less with verapamil. Nifedipine does not appear to have this effect.
- Thus, significant reflex tachycardia in response to hypotension occurs most frequently with nifedipine and less so with diltiazem and verapamil.
- These differences in pharmacologic effects should be considered in selecting calcium channel-blocking agents for the management of angina.

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- **Figure 12-5** Effects of diltiazem on the double product (heart rate times systolic blood pressure) in a group of 20 patients with angina of effort. In a double-blind study using a standard protocol, patients were tested on a treadmill during treatment with placebo and three doses of the drug. Heart rate (HR) and systolic blood pressure (BP) were recorded at 180 seconds of exercise (midpoints of lines) and at the time of onset of anginal symptoms (rightmost points). Note that the drug treatment decreased the double product at all times during exercise and prolonged the time to appearance of symptoms. (Data from Lindenberg BS et al: Efficacy and safety of incremental doses of diltiazem for the treatment of angina. *J Am Coll Cardiol* 1983;2:1129. Used with permission of the American College of Cardiology.)

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## ***Clinical Uses of Calcium Channel–Blocking Drugs***

- Angina pectoris
- Hypertension
- Supraventricular tachyarrhythmias
- Hypertrophic cardiomyopathy
- Migraine
- Raynaud's phenomenon

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## ***Beta-Adrenoreceptor–Blocking Drugs I***

- Although they are not vasodilators,  $\beta$ -blocking drugs are extremely useful in the management of angina pectoris associated with effort.
- The beneficial effects of  $\beta$ -blocking agents are related primarily to their hemodynamic effects—decreased heart rate, blood pressure, and contractility—which decrease myocardial oxygen requirements at rest and during exercise.
- Lower heart rate is also associated with an increase in diastolic perfusion time that may increase coronary perfusion. However, reduction of heart rate and blood pressure and consequently decreased myocardial oxygen consumption appear to be the most important mechanisms for relief of angina and improved exercise tolerance.

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## ***Beta-Adrenoreceptor–Blocking Drugs II***

- Beta blockers may also be valuable in treating silent or ambulatory ischemia. Because this condition causes no pain, it is usually detected by the appearance of typical electrocardiographic signs of ischemia.
- The total amount of "ischemic time" per day is reduced by long-term therapy with a  $\beta$ -blocker. Beta-blocking agents decrease mortality of patients with recent myocardial infarction and improve survival and prevent stroke in patients with hypertension. Randomized trials in patients with stable angina have shown better outcome and symptomatic improvement with  $\beta$ -blockers compared with calcium channel blockers.

## ***Beta-Adrenoreceptor–Blocking Drugs III***

- Undesirable effects of  $\beta$ -blocking agents in angina include an increase in end-diastolic volume and an increase in ejection time. Increased myocardial oxygen requirements associated with increased diastolic volume partially offset the beneficial effects of  $\beta$ -blocking agents. These potentially deleterious effects of  $\beta$ -blocking agents can be balanced by the concomitant use of nitrates.
- The contraindications to the use of  $\beta$ -blockers are asthma and other bronchospastic conditions, severe bradycardia, atrioventricular blockade, bradycardia-tachycardia syndrome, and severe unstable left ventricular failure.
- Potential complications include fatigue, impaired exercise tolerance, insomnia, unpleasant dreams, worsening of claudication, and erectile dysfunction.

### Effects of Nitrates Alone and with $\beta$ Blockers or Calcium Channel Blockers in Angina Pectoris

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	<i>Reflex increase</i>	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	<i>Increase</i>	None or decrease
Contractility	<i>Reflex increase</i>	Decrease	None
Ejection time	Decrease	<i>Increase</i>	None

**Table 13-4. Therapeutic Classification of Subsets in Acute Myocardial Infarction.**

Subset	Systolic Arterial Pressure (mm Hg)	Left Ventricular Filling Pressure (mm Hg)	Cardiac Index (L/min/m <sup>2</sup> )	Therapy
1. Hypovolemia	< 100	< 10	< 2.5	Volume replacement
2. Pulmonary congestion	100-150	> 20	> 2.5	Diuretics
3. Peripheral vasodilation	< 100	10-20	> 2.5	None or vasoactive drugs
4. Power failure	< 100	> 20	< 2.5	Vasodilators, inotropic drugs
5. Severe shock	< 90	> 20	< 2.0	Vasoactive drugs, inotropic drugs, circulatory assist devices
6. Right ventricular infarct	< 100	RVFP > 10 LVFP < 15	< 2.5	Volume replacement for LVFP, inotropic drugs. Avoid diuretics.
7. Mitral regurgitation, ventricular septal defect	< 100	> 20	< 2.5	Vasodilators, inotropic drugs, circulatory assist, surgery

***Drugs or Drug Groups under Investigation for Use in Angina***

Metabolic modulators, eg, ranolazine

Direct bradycardic agents, eg, ivabradine

Potassium channel activators, eg, nicorandil

Rho-kinase inhibitors, eg, fasudil

Sulfonylureas, eg, glibenclamide

Thiazolidinediones

Vasopeptidase inhibitors

Nitric oxide donors, eg, L-arginine

Capsaicin

Amiloride

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***Thank you...***

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