ANTIANGINAL AGENTS AND VASODILATORS \(^{(1)}\)

**Context**

Heart diseases are grouped into three major disorders:

- Cardiac failure or contractile dysfunction.
- Ischemic heart disease (with angina as its primary symptom)
- And cardiac arrhythmia.

Most coronary artery disease conditions are due to deposits of atheromas in the intima of large and medium-sized arteries serving the heart.

The process is characterized by an insidious onset of episodes of cardiac discomfort caused by ischemia from inadequate blood supply to the tissues. Angina pectoris (angina), the principal symptom of ischemic heart disease, is characterized by a severe constricting pain in the chest, often radiating from the pericardium to the left shoulder and down the arm.

The syndrome has been described since 1772 but not until 1867 was amyl nitrite introduced for the symptomatic relief of angina pectoris.

It was believed at that time that anginal pain was precipitated by an increase in blood pressure and that the use of amyl nitrite reduced both blood pressure and, concomitantly the work required of the heart. Later, it was generally accepted that nitrites relieved angina pectoris by dilating the coronary arteries and that changes in the work of the heart were of only secondary importance.

“We now know that the coronary blood vessels in the atherosclerotic heart already are dilated and that ordinary doses of dilator drugs do not significantly increase blood supply to the heart; instead, anginal pain is relieved by a reduction of cardiac consumption of oxygen.”

Although vasodilators are used in the treatment of angina, a more sophisticated understanding of the hemodynamic response to these agents has broadened their clinical usefulness to other cardiovascular conditions.

Because of their ability to reduce peripheral vascular resistance, vasodilators, including organonitrates, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor—blocking agents are used to improve cardiac output in some patients with heart failure (CHF).
"The coronary circulation supplies blood to the myocardial tissues to maintain cardiac function. It can react to the changing demands of the heart by dilating its blood vessels to provide sufficient oxygen and other nutrients and to remove metabolites.”

Myocardial metabolism is almost exclusively aerobic, which makes blood flow critical to the support of metabolic processes of the heart. This demand is met effectively by the normal heart because it extracts a large proportion of the oxygen delivered to it by the circulation.

The coronary blood flow depends strongly on myocardial metabolism, which in turn is affected by work done by the heart and the efficiency of the heart. The coronary system normally has a reserve capacity that to respond by vasodilation to satisfy the needs of the heart during strenuous activity by the body.

**Coronary atherosclerosis**, one of the more prevalent cardiovascular diseases, develops with increasing age and may lead to a reduction of the reserve capacity of the coronary system. It most often results in multiple stenoses and makes it difficult for the coronary system to meet adequately the oxygen needs of the heart that occur during physical exercise or emotional stress.

**Insufficient coronary blood flow (cardial ischemia) in the face of increased oxygen demand produces angina pectoris.**

**The principal goal in the prevention and relief of is to limit the oxygen requirement of the heart so that the amount of blood supplied by the stenosed arteries is adequate.**

   Nitrate esters, such as nitroglycerin, lower arterial blood pressure and, in turn, reduce the work of the left ventricle. This action is produced by the powerful vasodilating effect of the nitrates on the arterial system and, to an even greater extent, on the venous system. The result is reduced cardiac filling pressure and ventricular size.

   This reduces the work required of the ventricle and decreases the oxygen requirements, allowing the coronary system to satisfy the oxygen demands of myocardial tissue and relieve anginal pain.

**Intermediary Myocardial Metabolism**

Energy metabolism by heart tissue provides an adequate supply of high-energy phosphate compounds to replace the adenosine triphosphate (ATP) that is continually being consumed in contraction, ion exchange across membrane and other energy-demanding processes. Because of the high turnover rate of ATP in heart muscle, a correspondingly high rate of ATP production in the mitochondria is requested. Normal myocardial metabolism is aerobic, and the rate of oxygen use parallels the amount of ATP synthesized by the cells. Free fatty acids (FFAs) are the principal fuel for myocardial tissue, but lactate, acetate, acetoacetate, and glucose are also oxidized to CO₂ and water. A large volume of the cell consists of mitochondria in which two-carbon fragments from FFA breakdown are metabolized through the Krebs cycle.
Flavin and nicotinamide-dinucleotides formed by this metabolism are reoxidized by the electron-transport chain because of the presence of oxygen (Fig 19-1). In the hypoxic or ischemic heart, the lack of oxygen inhibits the electron-transport chain function an accumulation of reduced flavin and nicotinamide-dinucleotide, as a result, fatty acids are converted to lipids rather than being oxidized to compensate for this. Glucose is used and glycogenolysis increases, but the resulting pyruvate cannot be oxidized, instead, it is converted to lactic acid. A great loss of efficiency occurs as a result of the change of metabolism from aerobic to anaerobic pathway.

Normally 36 moles of ATP are formed from the oxidation of 1 mole of glucose, but only 2 moles are formed from its glycolysis. This great loss of high-energy stores during hypoxia thus limits the functional capacity of the heart during stressful conditions and is reflected by the production anginal pain.

Figure 19-1 Normal and ischemic myocardial metabolism of glucose. A total production of 36 moles of ATP results from the aerobic catabolism of 1 mole of glucose and use of NADH and FADH₂ in the oxidative phosphorylation process in mitochondria. When oxygen is not available, NADH and FADH₂ levels rise and shut off the tricarboxylic acid (TCA) cycle. Pyruvate is converted to lactic. Only 2 moles of ATP are formed from anaerobic catabolism of 1 mole of glucose. (Adapted from Guyton, A. C., et al.: Cardioiology: Fundamentals and Practice, 2nd ed. By permission of the Mayo Foundation, Rochester, MN.)
Nitro-vasodilators

SMOOTH MUSCLE RELAXATION
The contractile activity of all types of muscle (smooth, skeletal) is regulated primarily by the reversible phosphorylation of myosin. Myosin of smooth muscle consists of two heavy chains (MW 200,000 each) that are coiled to produce a filamentous tail. Each heavy chain is associated with two pairs of light chains (MW 20,000 and 16,000) that serve as substrates for calcium- and calmodulin-dependent protein kinases in the contraction process. Together with actin (MW 43,000) they participate in a cascade of biochemical events that are part of the processes of muscle contraction and relaxation (Fig. 19-2). Cyclic nucleotides; cyclic adenosine monophosphate (cAMP), and, especially cyclic guanosine monophosphate (cGMP) play important roles in the regulation of smooth muscle tension, cAMP is the mediator associated with the smooth muscle relaxant properties of drugs such as α-adrenergic agonists. It activates the protein kinases that phosphorylate myosin light-chain kinase (MLCK). Phosphorylation of MLCK inactivates this kinase and prevents its action with Ca²⁺ and calmodulin to phosphorylate myosin, which interacts with actin to cause contraction of smooth muscle. The activity of cGMP in smooth muscle relaxation is affected by exogenous and endogenous agents.

It is suggested that nitrovasodilators undergo metabolic transformation in vascular smooth muscle cells to form nitric oxide (NO). NO mediates smooth muscle relaxation by activating guanylate cyclase to increase intracellular concentrations of cGMP. cGMP activates protein kinases that can regulate free Ca²⁺ levels in the muscle cell and cause relaxation of smooth muscle by phosphorylating MLCK.

A short-lived free radical gas NO is widely distributed in the body and plays an important role by its effect through cGMP on the smooth muscle vasculature. It is synthesized in the vascular endothelial cell from the semi-essential amino acid L-arginine by NO synthase. After production in the cell, it diffuses to the smooth muscle cell, where it...
activates the enzyme guanylate cyclase, which leads to an increase in cGMP and then muscle relaxation (Fig.)

![Mechanism of nitrovasodilators](image)

**Endothelium derived relaxing factor (EDRF), released from the endothelial cell to mediate its smooth muscle—relaxing properties through cGMP, is identical with NO. Inhibitors of phosphodiesterase of cAMP and cGMP also cause smooth muscle relaxation. These inhibitors increase cellular levels of cAMP and cGMP by preventing their hydrolysis to AMP and GMP, respectively. Drugs such Papaverine and theophylline, do so in part by inhibiting phosphodiesterases.**

**Pharmaceutical preparations and dosage forms**

Organic nitrates are administered by inhalation; by infusion; as sublingual, chewable, and sustained release tablets; as capsules; as transdermal disks; and as ointments.
Absorption, metabolism, and therapeutic effects
Organic nitrates are used for both treatment and prevention of painful anginal attacks. The therapeutic approaches to achieve these two goals, however, are distinctly different. For the treatment of acute anginal attacks (i.e. attacks that have already begun), a rapid-acting preparation is required. In contrast, preventative therapy requires a long-acting preparation with more emphasis on duration and less emphasis on onset. The onset of organic nitrate action is influenced not only by the specific agent chosen but also by the route of administration. Sublingual administration is used predominantly for a rapid onset of action. The duration of nitrate action is strongly influenced by rate of metabolism. All of the organic nitrates are subject to rapid first-pass metabolism not only by the action of glutathione-nitrate reductase in the liver, but also in extra hepatic tissues, such as the blood vessel walls themselves. In addition, rapid uptake into the vessel walls plays a significant role in the rapid disappearance of organic nitrates from the bloodstream. Sublingual, transdermal, and buccal administration routes have been used in an attempt to avoid at least some of the hepatic metabolism.

Acute angina most frequently is treated with sublingual glyceryl trinitrate. This sublingual preparation is rapidly absorbed from the sublingual, lingual, and buccal mucosa and usually provides relief within 2 minutes. The duration of action also is short (~30 minutes). Other treatments include amyl nitrite by inhalation and sublingual isosorbide dinitrate. Amyl nitrite is by far the fastest-acting preparation, with an onset of action in approximately 15 to 30 seconds, but the duration of action is only approximately 1 minute. Isosorbide dinitrate, although usually used as a long-acting agent, may be used to treat acute angina. Sublingually administered isosorbide dinitrate has a somewhat slower onset than glyceryl trinitrate (~3 minutes), but its action may last for 4 to 6 hours. Although the onset appears to be almost as rapid as that of glyceryl trinitrate, waiting an additional minute for relief may be deemed unacceptable by some patients.

To prevent recurring angina, long-acting organic nitrate preparations are used. Several agents fall into this category, such as orally administered isosorbide dinitrate, pentaerythritol tetranitrate, and erythritol tetranitrate. In addition, a number of long-acting glyceryl trinitrate preparations are available. These include oral sustained-release forms, glyceryl trinitrate ointment, transdermal Patches, and buccal tablets. Of these therapeutic options, isosorbide dinitrate and glyceryl trinitrate preparations are by far the most frequently used.

At first, the whole concept of prophylactic nitrate use was met with skepticism by many physicians, both because early studies indicated that oral nitrates were almost completely broken down by first-pass metabolism and because blood levels of the parent drug appeared to be virtually nil. These findings, in conjunction with several clinical studies showing equivocal efficacy, led Needleman et al. to conclude, “There is no rational basis for the use of ‘long-acting’ nitrates (administered orally) in the prophylactic therapy of angina pectoris.” More recent studies, however, suggest that oral prophylactic nitrates may be effective if appropriate doses are used. Moreover, some metabolites of long-acting nitrates are active as venodilators, albeit less potent
than the parent drug. An example of this is isosorbide dinitrate, which is metabolized primarily in the liver by glutathione-nitrate reductase, which also participates in the metabolism of other organic nit rates, catalyzing the denitrification of the parent drug to yield two metabolites, 2- and 5- isosorbidemononitrate. Of these, the 5-isomer is still a potent vasodilator, and its plasma half-life of approximately 4.5 hours is much longer than that of isosorbide dinitrate itself. The extended half-life, because of the metabolite's resistance to further metabolism, indicates that it may be contributing to the prolonged duration of act ion associated with use of isosorbide dinitrate.

**Calcium Antagonists**

**ION CHANNELS AND CALCIUM**

Calcium ions play an important role in the regulation of many cellular processes, such as synaptic transmission and muscle contraction. The role of calcium in these cellular functions is as a second messenger, for example regulating enzymes and ion channels. The entry of extracellular Ca\(^{2+}\) into the cytosol of myocardial cells and the release of Ca\(^{2+}\) from intracellular storage Sites is important for initiating contractions of the myocardium. Normally, the concentration of Ca\(^{2+}\) in the extracellular fluid is in the millimolar range, whereas the intracellular concentration of free Ca\(^{2+}\) is less than 10\(^{-7}\)M, even though the total cellular concentration may be 10\(^{-3}\)M or higher. Most of the Ca\(^{2+}\) is stored within intracellular organelles or tightly bound to intracellular proteins. The free Ca\(^{2+}\) needed to satisfy the requirements of a contraction resulting from a stimulus may result from activation of calcium channels on the cell membrane and/or the release of calcium from bound internal stores. Each of these methods of increasing free cytosolic Ca\(^{2+}\) involves channels that are selective for the calcium ion. Calcium channel blockers reduce or prevent the increase of free cytosolic calcium ions by interfering with the transport of calcium ions through these pores.

Four types of calcium channels, differing in location and function, have been identified:

(a) L type, located in skeletal, cardiac, and smooth muscles, causing contraction of muscle cells.

(b) T type, found in pacemaker cells, causing entry, inactivated at more negative potentials and more rapidly than the L type.

(c) N type, found in neurons and acting in transmitter release.

(d) P type, located in Purkinje cells but whose function is unknown at this time.

**Calcium antagonists act only on the L-type channel to produce their pharmacological effects.**

The L channels are so called because once the membrane has been depolarized their action is long lasting. Once the membrane has been depolarized, L channels must be phosphorylated to open. Although (here are similarities between L-type calcium channels that exist in cardiac and smooth muscle) there are distinct differences between the two. Cardiac L channels are activated through stimulation via a cAMP dependent phosphorylation process, while L channels in smooth muscle may be
regulated by the inositol phosphale system linked to G-protein—coupled receptor-linked phospholipase C activation.

**CALCIUM CHANNEL BLOCKERS**

The L-type calcium channel, acted on by calcium channel blockers, consists of five different subunits, designated \( \alpha_1, \alpha_2, \beta, \gamma \) and \( \delta \). The \( \alpha_1 \) subunit provides the central pore of the channel (Fig. 19-6).

Calcium channel blockers can be divided conveniently into the three different chemical classes of the prototype drugs that have been used:

- Phenylalkylamines (verapamil).
- 1,4-dihydropyridines (Nifidipine)
- Benzothiazepines (diltiazem).
These prototype compounds sometimes are termed the "first generation" of calcium channel blockers because two of the groups of drug classes have been expanded by the introduction of a "second" generation of more potent analogues. The specific Ca\textsuperscript{2+} channel antagonists verapamil, nifidipine, and diltiazem interact at specific sites on the calcium channel protein. These blockers do not occlude the channel physically but bind to sites in the channel, as they can promote both channel activation and antagonism. Affinity binding sites on the channel varies, depending on the status of the channel. The channel can exist in either an open (0) or resting (R) or inactivated state, and the equilibrium between them is determined by stimulus frequency and membrane potential. Verapamil and diltiazem do not bind to a channel in the resting state, but only after the channel has been opened. They are ionized, water-soluble Ca\textsuperscript{2+} entry blockers that reach their binding sites by the
hydrophilic pathway when the channel is open. Verapamil and diltiazem are use dependent (i.e. their Ca\textsuperscript{2+}-blocking activity is a function of the frequency of contractions). An increase in contraction frequency causes a reduction, rather than an augmentation of contractions. Nifedipine is a neutral molecule at physiological pH and can cause interference with the Ca\textsuperscript{2+} in the open or closed state. In the closed state, nifedipine can traverse the phospholipid bilayer to reach its binding Site because of its lipid solubility.

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**CARDIOVASCULAR EFFECTS OF CALCIUM ION CHANNEL BLOCKERS**

All Ca\textsuperscript{2+} antagonists yet developed are vasodilators. Vasodilation is due to the uncoupling of the contractile mechanism of vascular smooth muscle, which requires Ca. Coronary artery muscle tone is reduced in healthy humans but it is particularly pronounced in a condition of coronary spasm. Peripheral arteriole resistance is reduced more than venous beds. The vasodilatory effect of these drugs is the basis for their use in the control of angina and hypertension.

Although verapamil, nifedipine and diltiazem can cause vasodilatation, they are not equally effective at blocking the Ca channels found in various tissues. The phenylalkylamine verapamil and the benzothiazepine diltiazem have both cardiac and vascular actions. These drugs have antiarrhythmic, Antianginal, and antihypertensive activity. They depress the cardiac neural network, and so slow sinus node automaticity prolong atrioventricular (AV) nodal conductance, and depress myocardial contractility, as well as reduce peripheral vascular resistance to prevent a coronary vascular spasm. Nifedipine and other 1,4-dihydropyridines are more effective at causing vasodilation than affecting pacemaker and tension responses in the heart. This is especially important because selectivity occurs as a consequence of disease states. Hypertensive smooth muscle is more sensitive to channel blockers than is normotensive tissue. This makes verapamil and diltiazem more useful in ischemic conditions as they have a more profound effect on cardiac muscle calcium channels.

The inhibition of Ca\textsuperscript{2+} influx into cardiac tissue by Ca\textsuperscript{2+} antagonists is also the basis for the use of these drugs as antiarrhythmic agents. The channel blockers dampen Ca\textsuperscript{2+}
dependent automaticity in the regular pacemaker cells in the sinoatrial (SA) node and depress the origination of ectopic foci. Calcium antagonists can block reentry pathways in myocardial tissue, an integral component of arrhythmias. Numerous side effects in the heart, such as bradycardia, decreased cardiac contractility, and reduced AV conductance, are traced to Ca2 channel—blocking activity.

The General SAR for 1,4-Dihydropyridine derivatives.

- 1,4-dihydropyridine ring is essential for the activity.
- Phenyl ring at 4-position optimizes the activity, Although hetero-aromatic rings (e.g. pyridine) show similar therapeutic activity but not used due to toxicity
- Position 2,6 are substituted with alkyl groups that play a role in the drug duration of action.
- Phenyl ring substitution (X): compounds with O- or m-substitutions with electron withdrawing group (Cl, NO2) possess optimal activity, while those which are unsubstituted or contain p-substitution show a significant decrease in activity.