17 Antianginal Drugs

Garrett J. Gross

DRUG LIST

Angina pectoris is a clinical manifestation that results from coronary atherosclerotic heart disease. An acute anginal attack (secondary angina) is thought to occur because of an imbalance between myocardial oxygen supply and demand owing to the inability of coronary blood flow to increase in proportion to increases in myocardial oxygen requirements. This is generally the result of severe coronary artery atherosclerosis. Angina pectoris (variant, primary angina) may also occur as a result of vasospasm of large epicardial coronary vessels or one of their major branches. In addition, angina in certain patients may result from a combination of coronary vasoconstriction, platelet aggregation, plaque rupture, and an increase in myocardial oxygen demand (crescendo or unstable angina).

Antianginal drugs may relieve attacks of acute myocardial ischemia by increasing myocardial oxygen supply or by decreasing myocardial oxygen demand or both. Three groups of pharmacological agents have been shown to be effective in reducing the frequency, severity, or both of primary or secondary angina. These agents include the nitrates, β-adrenoceptor antagonists, and calcium entry blockers. To understand the beneficial actions of these agents, it is important to be familiar with the major factors regulating the balance between myocardial oxygen supply and demand. These factors are summarized in Table 17.1.

THE THERAPEUTIC OBJECTIVES IN THE USE OF ANTIANGINAL DRUGS

The major therapeutic objectives in the treatment of angina are aimed at terminating or preventing an acute attack and increasing the patient's exercise capacity. These objectives can be achieved by reducing overall myocardial oxygen demand or by increasing oxygen supply to ischemic areas. A decrease in myocardial oxygen demand can be attained through use of the organic nitrates, calcium entry blockers, and β-adrenoceptor blocking agents. Increases in myocardial oxygen supply are more difficult to achieve, especially when coronary blood vessels are partially or totally obstructed. However, redistribution of blood flow to the subendocardium of

T A B L E 17.1	Major Determinants of Myocardial Oxygen Supply and Demand

Oxygen Supply	Oxygen Demand
Coronary blood flow	Wall tension
Aortic diastolic pressure	Ventricular volume
Endocardial–epicardial flow	Radius or heart size
Coronary collateral blood flow	Systolic pressure (afterload)
Large coronary artery diameter	Diastolic pressure (preload)
	Heart rate
	Contractility

ischemic areas has been documented in experimental animals following nifedipine (*Adalat, Procardia*), diltiazem (*Cardizem*),verapamil (*Calan*), amlodipine (*Norvasc*), nitroglycerin (*Nitrostat, Tridil, Nitro-Dur*), or propranolol (*Inderal*) administration. Increases in collateral flow to ischemic areas also have been observed in experimental animals and humans after treatment with certain calcium entry blockers and organic nitrates.

When coronary vasospasm occurs, the balance between oxygen supply and demand can be restored by relieving the spasm, thereby restoring normal coronary blood flow. Acute vasospasm has been successfully aborted through the use of nitroglycerin. In contrast, calcium entry blockers and long-acting nitrates have proved effective in the chronic therapy of coronary vasospasm.

SPECIFIC ANTIANGINAL DRUGS

Organic Nitrates

Organic nitrates have been used in the therapy of angina pectoris routinely for more than 140 years, and their use is increasingly favored in a variety of other cardiac conditions, such as decompensated congestive heart failure and acute myocardial infarction. The prototype of these agents is nitroglycerin. Other common organic nitrates are isosorbide mononitrate (*Ismo*), isosorbide dinitrate (*Isordil, Sorbitrate*) and pentaerythritol tetranitrate (*Peritrate*). With the exception of nitroglycerin, which is a liquid having a high vapor pressure, these compounds are solid at room temperature. All organic nitrates are very lipid soluble.

Mechanism of Vasodilator Action

The mechanism of action of nitroglycerin and other organic nitrates is thought to involve an interaction with nitrate receptors that are present in vascular smooth muscle. Intact vascular endothelium is not necessary for the vasodilator action of the nitrates to be produced. The nitrate receptor possesses sulfhydryl groups, which reduce nitrate to inorganic nitrite and nitric oxide (NO). The formation of nitrosothiols, and possibly free NO, has been proposed to stimulate intracellular soluble guanylate cyclase, which leads to an increase in intracellular cyclic guanosine monophosphate (GMP) formation (Fig. 17.1). The increase in GMP results in vascular smooth muscle relaxation, possibly through inhibition of calcium entry via L-type calcium channels, decreased calcium release from the sarcoplasmic reticulum, or via an increase in calcium extrusion via a sarcolemmal Ca^{++}-adenosine triphosphatase (ATPase).

Absorption, Metabolism, and Excretion

Nitroglycerin is a lipid-soluble substance that is rapidly absorbed across the sublingual or buccal mucosa. Its onset of action occurs within 2 to 5 minutes, with maximal effects observed at 3 to 10 minutes. Little residual activity remains 20 to 30 minutes after sublingual administration. The plasma half-life of nitroglycerin, given
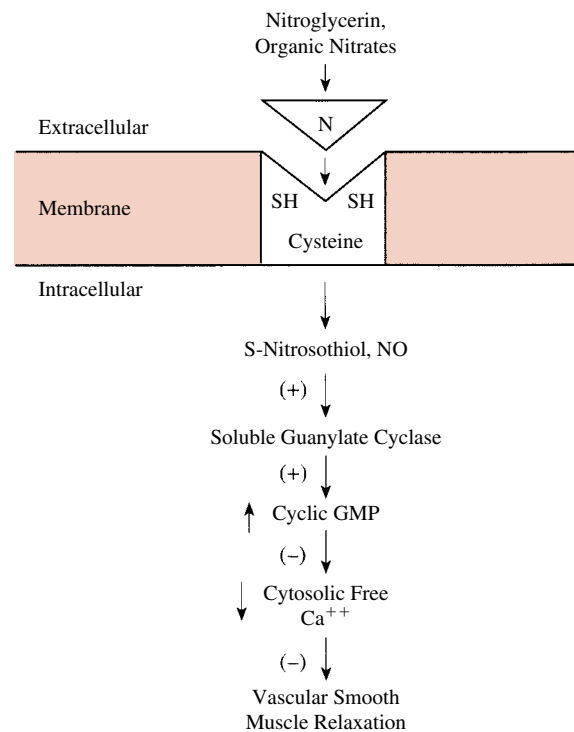
FIGURE 17.1

Proposed mechanism by which nitroglycerin and the organic nitrates produce relaxation in vascular smooth muscle. Nitrates induce endothelial cells to release NO or a nitrosothiol (endothelium-derived releasing factor, or EDRF). EDRF activates the enzyme guanylate cyclase, which causes the generation of cyclic guanosine monophosphate (GMP), producing a decrease in cytosolic free calcium. The end result is vascular smooth muscle relaxation. SH, sulfhydryl.

sublingually or by spray, is estimated to be 1 to 3 minutes. Isosorbide dinitrate and pentaerythritol tetranitrate also can be administered sublingually or buccally. These compounds have a slower onset and slightly longer duration of action than sublingually or buccally administered nitroglycerin.

Nitroglycerin and other organic nitrate esters undergo first-pass metabolism and are rapidly metabolized in the liver by the enzyme glutathione organic nitrate reductase. Although the metabolites of nitroglycerin are virtually inactive as vasodilators, two metabolites of isosorbide dinitrate, isosorbide 2-mononitrate and isosorbide 5-mononitrate, do retain some vasodilator and antianginal activity. Isosorbide mononitrate can be administered orally and does not undergo any first-pass metabolism. The latter esters and their metabolites are water soluble and are readily excreted by the kidney.

Pharmacological Actions

There is little doubt concerning the effectiveness of nitroglycerin in the treatment of angina pectoris.

However, the exact mechanism by which the drug acts to reduce myocardial ischemia is still controversial (Fig. 17.2). Although nitroglycerin dilates both peripheral capacitance and resistance vessels, the effect on the venous capacitance system predominates. Dilation of the capacitance vessels leads to pooling of blood in the veins and to diminished venous return to the heart (decreased preload). This reduces ventricular diastolic volume and pressure and shifts blood from the central to the peripheral compartments of the cardiovascular system. These effects of nitroglycerin and other organic nitrates are similar to those of mild phlebotomy, which has been shown clinically to relieve acute anginal attacks by decreasing circulating blood volume.

According to Laplace's law, a reduction in ventricular pressure and heart size results in a decrease in the myocardial wall tension that is required to develop a given intraventricular pressure and therefore decreases oxygen requirement. Since blood flow to the subendocardium occurs primarily in diastole, the reduction in left ventricular end diastolic pressure induced by nitroglycerin reduces extravascular compression around the subendocardial vessels and favors redistribution of
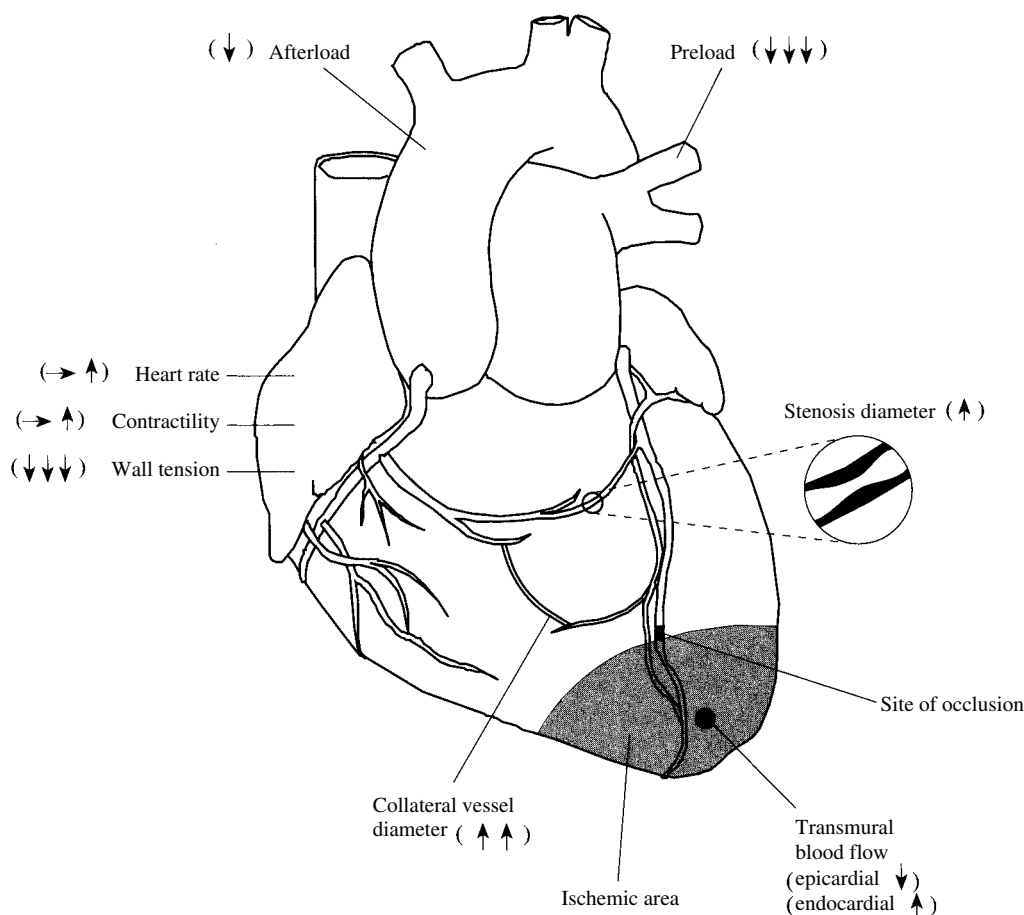
FIGURE 17.2

Major actions of the nitrates on the ischemic heart and peripheral circulation. ↓, decrease; ↑, increase; →, unchanged; ↑↓, variable effect.

coronary blood flow to this area. This effect of nitroglycerin on the distribution of coronary flow is important because the subendocardium is particularly vulnerable to ischemia during acute anginal attacks.

At higher concentrations, nitroglycerin also relaxes arteriolar smooth muscle, which leads to a decrease in both peripheral vascular resistance and aortic impedance to left ventricular ejection (decreased afterload). The decreased resistance to ventricular ejection may also reduce myocardial wall tension and oxygen requirements.

Thus, nitroglycerin relieves the symptoms of angina by restoring the balance between myocardial oxygen supply and demand. Oxygen demand is lowered as a consequence of the reduction in cardiac preload and afterload, and this results in a decrease in myocardial wall tension. Oxygen supply to the subendocardium of ischemic areas is increased because extravascular compression around the subendocardial vessels is reduced. In addition, nitroglycerin may increase blood flow to ischemic areas by its direct vasodilator effect on eccentric epicardial coronary artery stenoses and collateral blood vessels and by its action to inhibit platelet aggregation. Other organic nitrates are thought to exert the same beneficial actions as nitroglycerin.

Nitrate-induced Late Preconditioning

Recent findings suggest a potential new action of nitrates in the treatment of patients with ischemic heart disease. Administration of intravenous (IV) or transdermal nitroglycerin to conscious rabbits exerts a protective effect against myocardial infarction that persists for 72 hours; this effect has been termed late preconditioning. The magnitude of this effect was also found to persist in animals that displayed tolerance to the vascular effects of nitroglycerin. Although this effect of nitroglycerin has not been demonstrated unequivocally in patients receiving long-term nitrate therapy, these results are provocative and may support new uses of nitrates in patients or benefits that have until now remained unrecognized.

Clinical Uses

Sublingual or buccal nitroglycerin is used either to terminate an acute attack of angina or for short-term prevention of angina. Nitroglycerin is also the mainstay of therapy for relieving acute coronary vasospasm because of its rapid onset of action. When taken at the onset of chest pain, the effects of nitroglycerin appear within 2 to 5 minutes; however, the true duration of action is difficult to establish in patients with secondary angina, since the onset of pain causes patients to reduce their physical activity, and this alone can ameliorate the symptoms. Isosorbide dinitrate and pentaerythritol tetranitrate also can be taken sublingually, shortly before antici-

pated physical or emotional stress, to prevent anginal attacks.

Nitroglycerin ointment applied to the skin acts within 15 minutes and may produce its effects for 2 to 6 hours. Sustained-release transdermal nitroglycerin has been shown to deliver an antianginal effect for 2 to 4 hours following small doses and up to 24 hours after larger doses.

Orally administered long-acting nitrates, including nitroglycerin and various nitrate esters, nitroglycerin ointment, and transdermal nitroglycerin, were developed with the goal of providing a nitrate preparation that would have prolonged pharmacological activity for prophylactic therapy of angina pectoris. Considerable controversy surrounds the therapeutic use of the orally active agents because of their extensive first-pass metabolism, and many clinicians consider them to be ineffective. More recently, however, numerous clinical investigations have demonstrated the efficacy of transdermal nitroglycerin, although tolerance can be a problem with prolonged transdermal exposure to nitroglycerin. The drugs and dosage forms of organic nitrates available for therapeutic use, their usual dose, onset of action, and duration of action are summarized in Table 17.2.

Tolerance and Dependence

Repeated and frequent exposure to organic nitrates is accompanied by the development of tissue tolerance to the drug's vasodilating effects. When nitroglycerin formulations (e.g., transdermal patches, sustained-release oral dosing, or ointments) that produce sustained plasma and tissue levels are used, tolerance may occur within 24 hours. The mechanism underlying the phenomenon of nitrate tolerance is not as yet completely understood but may be related to a nitrate-induced oxidation of sulfhydryl groups via the formation of free radicals, a decrease in the sensitivity of vascular smooth muscle soluble guanylate cyclase, or activation of the renin–angiotensin system.

To help avoid nitrate tolerance, clinicians should employ the smallest effective dose and administer the compound infrequently. A daily nitrate-free period is also recommended, particularly with use of the transdermal patches or ointment. A better understanding of the pharmacokinetic profile achieved with these sustained-release formulations should result in more effective dosing regimens.

Since depletion of tissue stores of sulfhydryl groups has been proposed to play an important role in nitrate tolerance, some investigators have administered sulfhydryl-containing compounds in an attempt to reverse or prevent the development of tolerance. The most commonly used agent is N-acetylcysteine (NAC), which is hydrolyzed in vivo to cysteine. Although some

TABLE 17.2 Dosage Forms and Pharmacokinetics of Nitrates Most Commonly Used in Angina Pectoris

Drug and Dosage Form	Usual Dose (mg)	Onset of Action (min)	Duration of Action (hr)
Nitroglycerin			
Sublingual	0.3–0.6	2–5	0.16–0.50
Transmucosal (buccal)	1–3	2–5	3–6
Oral	3–20	20–45	2–8
Ointment (2%)	1–5 (0.5–2 inches)	15–60	3–8
Transdermal	5–30 (per 24 hr)	30–60	12–24
Intravenous	5–300 mEq/min	Immediate	Transient
Isosorbide dinitrate			
Sublingual	2.5–10	3–20	1–2
Oral, chewable	5–60	30–60	2–10
Oral, sustained release	40	30–60	6–10
Isosorbide mononitrate			
Oral	20	15–30	6–12
Erythrityl tetranitrate			
Sublingual	5–10	5–15	2–3
Oral, chewable	10–30	30	2–6
Pentaerythritol tetranitrate			
Oral	10–20	30	2–6
Oral, sustained release	30–80	30–60	4–12

investigators have shown a positive effect with NAC, the antinitrate tolerance effect of this compound has not been universally confirmed. Thus, further well-controlled clinical studies are necessary to establish the effectiveness of sulfhydryl-containing compounds at preventing or reversing nitrate tolerance.

Industrial exposure to organic nitrates induces both tolerance and physical dependence. The state of dependence becomes manifest when exposure to nitrates is withdrawn suddenly. For example, munitions workers who have become dependent on nitroglycerin have been reported to undergo angina, myocardial infarction, or even sudden death following removal from contact with nitroglycerin. Some of these patients showed symptoms of ischemic heart disease, even though their coronary arteriography was judged to be normal. Since it is possible that coronary vasospasm plays a role in the pathogenesis of angina that occurs in nitrate-dependent individuals, these patients should be cautioned to watch for increased chest pain when they withdraw from medication or discontinue their exposure.

Adverse Effects

Vascular headache, postural hypotension, and reflex tachycardia are common side effects of organic nitrate therapy. Fortunately, tolerance to nitrate-induced headache develops after a few days of therapy. Postural hypotension and tachycardia can be minimized by proper dosage adjustment and by instructing the patient to sit down when taking rapidly acting preparations. An effective dose of nitrate usually produces a fall in upright systolic blood pressure of 10 mm Hg and a reflex rise in heart rate of 10 beats per minute. Larger changes than these should be avoided, because a reduction in myocardial perfusion and an increase in cardiac oxygen requirements may actually exacerbate the angina.

Since nitrite ions oxidize the iron atoms of hemoglobin and convert it to methemoglobin, there may be a loss in oxygen delivery to tissues. While methemoglobinemia does not follow therapeutic doses of organic nitrates, it can be observed after overdosage or accidental poisoning.

Cautions

Chest pain that is not relieved by two or three tablets within 30 minutes may be due to an acute myocardial infarction. In addition, nitrate administration may result in an increase in intracranial pressure, and therefore, these drugs should be used cautiously in patients with cerebral bleeding and head trauma.

β-Adrenoceptor Blocking Agents

β-Adrenoceptor blockade is a rational approach to the treatment of angina pectoris, since an increase in sympathetic nervous system activity is a common feature in acute anginal attacks. Based on their ability to reduce oxygen demand, all β-blockers tested so far have also been shown to be effective in the treatment of second-

ary angina. Administration of these compounds results in a decrease in frequency of anginal attacks, a reduction in nitroglycerin consumption, an increased exercise tolerance on the treadmill, and a decreased magnitude of ST segment depression on the electrocardiogram during exercise. Propranolol is the prototype of this class of compounds

β-Blockers approved for clinical use in secondary angina in the United States include propranolol and nadolol (*Corgard*), compounds that block both β_1- and β_2-adrenoceptors equally, while atenolol (*Tenormin*) and metoprolol (*Lopressor*) are cardioselective β_1-receptor antagonists.

Mechanism of Action

The myocardial response to exercise includes an increase in heart rate and myocardial contractility. These effects are mediated in part by the sympathetic nervous system. Propranolol and other β-adrenoceptor blockers antagonize the actions of catecholamines on the heart and thereby attenuate the myocardial response to stress or exercise (Fig. 17.3). The resting heart rate is reduced by propranolol, but not to the same extent as is the decrease in exercise-induced tachycardia. Overall, propranolol reduces myocardial oxygen consumption for a given degree of physical activity.

Arterial blood pressure (afterload) is also reduced by propranolol. Although the mechanisms responsible for this antihypertensive effect are not completely understood, they are thought to involve (1) a reduction in cardiac output, (2) a decrease in plasma renin activity, (3) an action in the central nervous system, and (4) a resetting of the baroreceptors . Thus, propranolol may exert a part of its beneficial effects in secondary angina by decreasing three of the major determinants of myocardial oxygen demand, that is, heart rate, contractility, and systolic wall tension.

Propranolol and other β-blockers also have been shown to produce an increase in oxygen supply to the subendocardium of ischemic areas. The mechanism responsible for this effect is most likely related to the
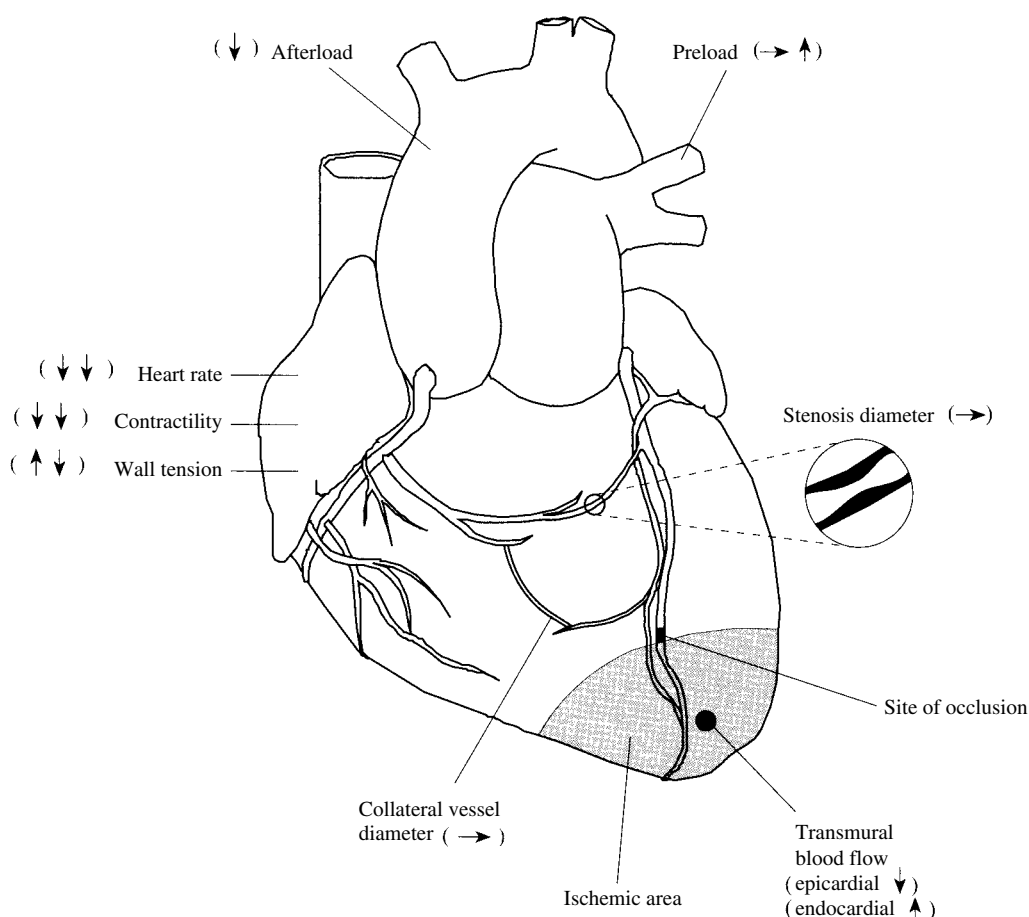
FIGURE 17.3

A schematic drawing indicating the major actions of the β-blockers on the ischemic heart and peripheral circulation. ↓, decrease; ↑, increase; →, unchanged; ↑↓, variable effect.

TABLE 17.3 Doses and Pharmacokinetics of β-Receptor Antagonists Used in the Treatment of Angina Pectoris

Compound	Usual Daily Dose (mg)	Oral Bioavailability (%)	Plasma $t_{1/2}$ (hr)	First-pass Metabolism (%)
Propranolol	40–80	25–30	3–6	90
Nadolol	40	30–40	12–24	0
Metoprolol	50–100	40–45	3–4	50
Atenolol	50	50–55	5–10	0

ability of β-blockers to reduce resting heart rate and increase diastolic perfusion time. Because subendocardial blood flow and flow distal to severe coronary artery stenosis occur primarily during diastole, this increase in diastolic perfusion time, due to the bradycardiac effect of propranolol and other β-blockers, would be expected to increase subendocardial blood flow to ischemic regions. β-Blockers have no significant effect on coronary collateral blood flow. Finally, there is evidence that β-blockers can inhibit platelet aggregation.

Absorption, Metabolism, and Excretion

Propranolol is well absorbed from the gastrointestinal tract, but it is avidly extracted by the liver as the drug passes to the systemic circulation (first-pass effect). This effect explains the large variation in plasma levels of propranolol seen after oral drug administration.

Because of these interindividual variations in the kinetics of propranolol, the therapeutic dose of this drug is best determined by titration. End points of titration include relief of anginal symptoms, increases in exercise tolerance, and plasma concentration of propranolol between 15 and 100 ng/mL. For additional details on the pharmacokinetics of propranolol and other β-receptor antagonists approved for clinical use in the treatment of angina pectoris, see Table 17.3 and Chapter 11.

Clinical Uses

By attenuating the cardiac response to exercise, propranolol and other β-blockers increase the amount of exercise that can be performed before angina develops. Although propranolol does not change the point of imbalance between oxygen supply and demand at which angina occurs, it does slow the rate at which the imbalance point is reached.

Propranolol is particularly indicated in the management of patients whose angina attacks are frequent and unpredictable despite the use of organic nitrates. Propranolol may be combined with the use of nitroglycerin, the latter drug being used to control acute attacks of angina. The combined use of propranolol and organic nitrates theoretically should enhance the therapeutic effects of each and minimize their adverse effects (Table 17.4).

Propranolol and nadolol also have been used successfully in combination with certain calcium entry blockers, particularly nifedipine, for the treatment of secondary angina. Caution should be used, however, when combining a β-blocker and a calcium channel blocker, such as verapamil or diltiazem, since the negative inotropic and chronotropic effects of this combination may lead to severe bradycardia, arteriovenous nodal block, or decompensated congestive heart failure.

TABLE 17.4 Effects of Nitrates, β-Receptor Antagonists, and Calcium Entry Blockers on Determinants of Cardiac Oxygen Supply and Demand

Determinant	Nitrates	β-Receptor Blockers	Calcium Entry Blockers
Wall tension	↓	±	↓
Ventricular volume	↓	↑	±
Ventricular pressure	↓	↓	↓
Heart size	↓	↑	±
Heart rate	↑ (reflex)	↓	±
Contractility	↑ (reflex)	↓	±
Endocardial-epicardial blood flow ratio	↑	↑	↑
Collateral blood flow	↑	→	↑

Table 17.3 and Chapter 11 provide additional details concerning the most commonly used β-blockers (i.e., propranolol, nadolol, atenolol, and metoprolol) in the treatment of angina pectoris.

Adverse Effects

Abrupt interruption of propranolol therapy in individuals with angina pectoris has been associated with reappearance of angina, acute myocardial infarction, or death due to a sudden increase in sympathetic nervous system tone to the heart. The mechanisms underlying these reactions are unknown, but they may be the result of an increase in the number of β-receptors that occur following chronic β-adrenoceptor blockade (up-regulation of receptors). When it is advisable to discontinue propranolol administration, such as before coronary bypass surgery, the dosage should be tapered over 2 to 3 days.

Calcium Entry or Calcium Channel Blockers

The calcium entry blockers or calcium channel blockers are a group of orally active drugs that have been approved for use in the treatment of vasospastic and ef- fort-induced angina. These compounds block L-type voltage-dependent calcium channels in vascular smooth muscle and the heart, block platelet aggregation, and are particularly effective in the prophylaxis of coronary vasospasm or variant angina. In addition, these compounds are used in the chronic treatment of secondary angina. Two members of this group, verapamil (*Calan*) and diltiazem (*Cardiazem*), also have been approved for use in the therapy of certain supraventricular tachyarrhythmias (see Chapter 16). Other potential clinical uses of these compounds include systemic and pulmonary hypertension and Raynaud's syndrome

A detailed discussion of the pharmacology of this important class of drugs can be found in Chapter 19. Their major hemodynamic effects on the primary determinants of myocardial oxygen supply and demand are summarized in Figure 17.4. A comparison of the effects of all three classes of antianginal drugs on these important parameters is summarized in Table 17.4.
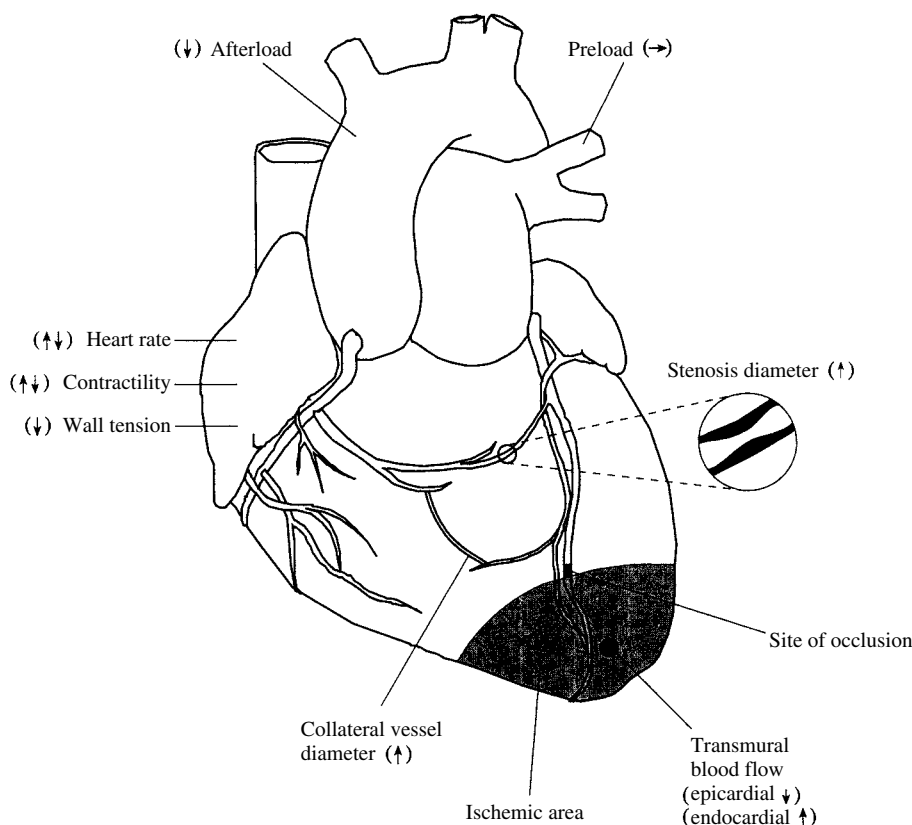
FIGURE 17.4

Major actions of the calcium antagonists on the ischemic heart and coronary circulation. ↓, decrease; ↑, increase; →, unchanged; ↑↓, variable effect.

Study QUESTIONS

1. A patient comes to your office with effort-induced angina and resting tachycardia. You choose the following drug to treat the patient because it slows heart rate by blocking L-type calcium channels in the SA node:
   (A) Verapamil
   (B) Propranolol
   (C) Nitroglycerin
   (D) Isosorbide dinitrate
   (E) Metoprolol

2. Which of the following hemodynamic effects of nitroglycerin are primarily responsible for the beneficial results observed in patients with secondary angina?
   (A) Reduction in the force of myocardial contraction
   (B) Reduction in systemic vascular resistance (afterload)
   (C) Increased heart rate
   (D) Reduction in venous capacitance (preload)
   (E) Increased blood flow to the subepicardium

3. A woman is prescribed a combination of drugs consisting of a nitroglycerin patch and a β-blocker, such as propranolol, to treat her attacks of secondary angina. Which effect of propranolol would counteract an adverse effect of nitroglycerin?
   (A) A decrease in preload
   (B) A decrease in afterload
   (C) A decrease in heart rate
   (D) An increase in myocardial contractile force
   (E) A reduction in coronary vasospasm

4. A patient who has been taking propranolol for a long period for secondary angina comes to your office complaining of increased frequency of chest pains on exertion. You decide to stop the propranolol and give him diltiazem because you suspect he has a mixture of secondary and primary angina. Why would diltiazem be more likely to relieve the angina if your new diagnosis is accurate?
   (A) Diltiazem produces a decrease in heart rate.
   (B) Diltiazem dilates coronary blood vessels in spasm.
   (C) Diltiazem produces AV blockade.
   (D) Diltiazem reduces myocardial contractility.
   (E) Diltiazem reduces afterload.

5. Metoprolol would produce which beneficial effect in a patient with secondary angina?
   (A) A decrease in preload
   (B) An increase in collateral blood flow
   (C) An increase in afterload
   (D) An increase in diastolic filling time

(E) An increase in blood flow through a concentric stenosis

ANSWERS

1. **A.** Verapamil is an L-type calcium channel blocker. Nitroglycerin and isosorbide are both organic nitrates and have no direct effect on L-type calcium channels at the SA node, while propranolol and metoprolol are β-adrenoceptor blockers and will slow heart rate by blocking the actions of norepinephrine and epinephrine on β-receptors at the SA node.

2. **D.** Nitroglycerin can reduce preload, which in turn reduces wall tension and increases subendocardial blood flow. Nitroglycerin also reduces afterload, but this is a small effect compared to the reduction in preload. Its effects on heart rate and contractility are minimal, and if anything reflex tachycardia and increase in contractility would be detrimental effects of too much nitroglycerin.

3. **C.** Nitroglycerin can increase heart rate via an increase in sympathetic tone to the heart due to an excessive decrease in blood pressure; propranolol would block the β-receptors responsible for the tachycardia. Propranolol does not decrease preload, and its effect to decrease afterload would exacerbate the decrease in afterload produced by nitroglycerin. Propranolol does not increase myocardial contractile force and could actually increase the incidence of vasospasm by unmasking α-adrenoceptors in the coronary blood vessels.

4. **B.** Both diltiazem and propranolol would produce the effects listed in A, C, D, and E. Only diltiazem would dilate vessels in spasm. Propranolol would tend to produce vasoconstriction, not vasodilation.

5. **D.** An increase in time spent in diastole would increase subendocardial blood flow. Metoprolol does not decrease preload or increase afterload; in fact the opposite is likely to occur. Metoprolol does not affect collateral blood flow or flow through a concentric stenosis.

SUPPLEMENTAL READING

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C A S E **Study** **Treatment of Coronary Vasospasm**

A 60-year-old man comes into the office complaining of chest pains that primarily occur in the early morning and do not appear to be associated with stress or exercise. Following coronary angiography and a positive ergonovine test you determine that this patient has angina pectoris as a result of coronary artery spasm. How would you (1) treat the patient to alleviate the acute attacks when they occur and (2) treat chronically to prevent their reoccurrence?

ANSWER: Treat the patient with sublingual nitroglycerin for the acute attacks because of its rapid onset of action and its powerful vasodilating effect on the large epicardial conductance coronary arteries, which are normally the primary site of the spasm. For the chronic treatment there are two possibilities, an oral calcium channel blocker, such as amlodipine or verapamil, or a long-acting nitrate preparation, such as the transdermal form of nitroglycerin given once a day at bedtime to prevent the early morning episodes. β-Adrenoceptor blockers are not used for patients with coronary vasospasm, as they may worsen the condition.