# CARDIOVASCULAR THERAPEUTICS IN CLINICAL PRACTICE

*Edited by*

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# PREFACE

Cardiovascular disease is the most common of the serious afflictions that affect the population of the industrialized world. Its management is crucial to the survival of millions of people, and significant new advances in therapeutic interventions have begun to have a major social and economic impact on society. The complexity of the treatment has made it more and more difficult for the practitioner alone to deliver a high standard of cardiovascular therapy without the contribution of those in other disciplines.

It has become clear that there must be a collaboration between basic and clinical scientists if sense and order are to be brought to the increasingly complex management of cardiovascular disease. This book grew out of such a collaboration between the Department of Pharmacology and the Division of Cardiology at The Medical College of Pennsylvania. A curriculum was devised by Drs. Frankl and Roberts that, with the combined efforts of staff pharmacologists and clinical cardiologists, could be used to educate cardiologists, medical and family practice house officers, cardiac fellows, third- and fourth-year students, pharmacologists, and candidates for an M.S. or a Ph.D. in cardiovascular pharmacology. The cross-fertilization of ideas arising during these sessions has proved to be valuable and has resulted in the writing of this book. Accordingly, the book provides a review for the postgraduate student, as well as an orientation toward the treatment of specific cardiovascular diseases. The book also provides the student as well as the practitioner with a single source covering the treatment of major cardiovascular diseases, including discussion of the pathophysiology, the clinical picture, the pharmacology of the therapeutic agents, and how they are used. The disease entities were selected on the basis of their clinical importance to cardiovascular medicine.

Over the past several decades, there has been an explosion of knowledge in such fields as biochemistry, biophysics, developmental biology, genetics, bioengineering, molecular biology, and experimental pathology, all of which have had a major impact on the field of cardiology. Although it is impossible to bring all of these developments into a book of this type, it must be emphasized that the understanding of cardiovascular therapy can no longer be based on clinical information alone. Therefore, we have attempted in this text to integrate basic science with clinical application.

In view of this approach, we have devised the concept of "core chapters" to avoid repetition of the basic pharmacology of drugs discussed in more than one chapter. For example, the "core chapter" for the pharmacology

of propranolol is Chapter 2, "Hypertension"; thus, this chapter includes the structure, mechanism of action, pharmacokinetics, and side effects associated with the use of propranolol. In other chapters in which propranolol is discussed, such as the chapters on antiarrhythmic and antianginal agents, pharmacological considerations are restricted to those that pertain directly to the use of the drug in the particular clinical condition. We have included in the table of contents reference to the "Core Pharmacology" to help the reader find this material; a table of contents listing classes of drugs and the various chapter(s) in which they appear is printed on the front end pages.

It has been a great pleasure for us to work with John Wiley & Sons, our publisher, who has been patient with us during the many months that it has taken to create this textbook. Our appreciation goes, of course, to our collaborators, without whom we could not have put together this work. We would also like to express our appreciation to our many students, whose penetrating questions and encouragement were, in part, responsible for the writing of this book. Finally, this book could not have been completed without the editorial assistance of Dr. Dorothy Greenhouse, whose perceptive and keen criticism kept us on track. Her dedication and incalculable hours of effort were the unifying force tht allowed us to finish our work.

*William S. Frankl*
*Jay Roberts*
*Claire M. Lathers*

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CHAPTER

# 1 ANGINA PECTORIS

Robert K. Dix
William S. Frankl



The treatment of angina pectoris is the most controversial area in modern cardiology. Although the purpose of this chapter is to discuss the pharmacologic management of angina, it is also necessary to review the controversy concerning medical versus surgical therapy, and to deal with the features of the disease that determine whether a patient is better treated medically or surgically. This controversy is well illustrated by several interesting claims and counterclaims that have appeared in the literature (1–16).

## Medical Versus Surgical Therapy

The primary goals of surgical and medical therapy are different. The objective of coronary bypass surgery is to increase myocardial blood flow, while the principal aim of medical therapy is to reduce myocardial oxygen demand. It may appear logical, considering coronary flow and cardiac hemodynamics, that significant coronary obstruction should best be treated by coronary bypass surgery, especially since most atherosclerotic obstructions occur in the proximal portions of large extramural coronary arteries. However, many factors may make bypass surgery impossible. For example, a vessel that appears suitable for surgery may, in fact, be diseased distally, perfuse infarcted muscle, or have developed an extensive system of

collaterals that provide satisfactory retrograde flow distal to the obstructed artery. In addition, bypass grafts may occlude, or the risk of the surgery itself may outweigh the potential benefits. Thus, the decision to use medical or surgical management must be highly individualized and depends on many factors (17, 18), including age, occupation, degree of disability, location and extent of the lesions, myocardial function, psychological status, presence of associated diseases (e.g., diabetes mellitus, hypertension, renal disease, pulmonary disease), and patient preference. Because of their aversion to surgery, some patients will prefer medical therapy, regardless of the extent, while other patients will prefer surgery to the use of multiple drugs and restriction of activity. Moreover, it is important to recognize that coronary artery disease is a chronic problem. Even if surgical therapy is elected, careful postoperative, medical management is required to prevent, as far as possible, further progression of the disease.

A common goal of medical and surgical therapy is the relief of symptoms; that is, reducing both the frequency and severity of pain, with a consequent increase in exercise tolerance. It has been suggested that many patients with angina pectoris can relieve their symptoms by eliminating tobacco, controlling hypertension, reducing blood cholesterol and triglycerides, and instituting a weight reduction and exercise program. When indicated, therapy with nitrates and propranolol can be initiated (19). However, patients will often require more extensive medical or surgical therapy.

There are several ways to determine clinically, with some degree of accuracy, those patients who will have a good or a poor prognosis. A history of stable angina* and an absence of signs of congestive heart failure suggest a good prognosis. A normal, resting electrocardiogram is a good prognostic sign in a patient with angina, whereas abnormal ST-T waves and/or evidence for previous myocardial infarction are poor prognostic signs (20–22). Mortality has a direct correlation to the extent of coronary disease, which can be roughly determined by analyzing ST-T wave abnormalities during exercise (stress testing) (23, 24). Sixty-seven percent of those patients with one ST-segment depression greater than 2 mm during, or after, exercise are likely to have significant disease of the right, left anterior descending, and left circumflex coronary arteries (triple-vessel disease). Coincidentally, ST segment depression that appears soon after exercise begins indicates extensive disease (23). Those patients with a good exercise tolerance have a very low risk of death 2 years post therapy; however, those who cease exercise shortly after beginning have a 54 percent, 2-year mortality rate (25). It has also been shown that the blood pressure response to exercise is extremely important. No rise or a

* Angina is defined as "stable" if chest pain has existed over a period of time without alteration in severity, frequency, or precipitating events; there is a consistent response to nitroglycerin, and there is no pain at rest or at night.

fall in systolic blood pressure during exercise indicates extensive coronary artery disease, often with significant stenosis of the left main coronary artery (26–28). A rise in diastolic pressure may also indicate extensive coronary disease.

The most solid evidence concerning prognosis, extent of disease, and the feasibility of coronary surgery is provided by cardiac catheterization and performance of left ventriculography and coronary arteriography. These studies are indicated for patients with symptoms that are not relieved by adequate medical therapy, a clinically determined poor prognosis, an uncertain diagnosis, or the presence of unstable angina.* The most significant indicators of survival in coronary artery disease are the extent of the lesions and abnormal ventricular function (29–34). Patients with significant, triple-vessel coronary artery disease appear to have a 10–15 percent yearly mortality rate. Patients with a disease that involves two of the coronary vessels (double-vessel disease) have a 5–6 percent yearly mortality rate, although the outlook appears to be worse if one of the vessels involved is the left anterior descending coronary artery (33). Significant single-vessel disease is associated with a low mortality of (*1*) 1–2 percent per year if either the right coronary or the circumflex branch of the left main coronary artery is involved (1, 29, 31, 35, 36), and (2) 4 percent or greater if the left anterior descending coronary artery is involved (35). These figures do not reflect the difference between isolated proximal versus isolated distal disease, since the latter has a better prognosis.

Abnormal ventricular function is an independent prognostic element (1, 30, 33). The mortality rate is high (whether the angina is managed medically or surgically) when cardiomegaly and/or signs of congestive heart failure are present and accompanied by either a reduced ejection fraction or significant abnormal contraction patterns, as demonstrated by left ventriculography. A very high mortality rate (an estimated 15–25 percent yearly) can also be expected with significant stenosis of the left main coronary artery (37–40); however, left ventricular function operates as an independent variable, even in this situation (39, 40). The sensitivity and specificity of assessment of left ventricular function is enhanced (*1*) by performing ventriculography both before and after administration of nitroglycerin, or assessing the ventriculogram before and after an ectopic ventricular beat (post-extrasystolic potentiation), and (2) by performing myocardial perfusion studies before and after exercise (41). Recently, the radioisotope angiogram has been used as a noninvasive method of estimating ventricular function. This test correlates well with left ventriculography (42–44).

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* Angina is defined as "unstable" if one or more of the following conditions exists: (*1*) new pain develops, (2) there is an increase in the frequency or severity of pain, (*3*) there is a change in the type of events that precipitate an attack, (*4*) there is a decreased response to nitroglycerin, and/or (*5*) pain is present at night or at rest.

After a patient has undergone careful clinical evaluation (including stress testing, cardiac catheterization, and isotope perfusion studies), and it has been determined whether the patient has stable or unstable angina, a decision on therapy can be developed. The following guidelines are offered for treatment of patients with stable angina and:

- *A normal coronary arteriogram.* Medical therapy is the only rational approach for controlling symptoms in these patients. Many patients have evidenced chest discomfort that is ischemic in nature; however, the medical outlook is excellent (45, 46). Some of these patients have exhibited coronary spasm (47–49), which may be difficult to control with drugs; however, there is no evidence that anginal pain associated with spasm is relieved by surgery, unless the spasm is engrafted upon a significantly fixed lesion. Coronary artery spasm will be discussed in a subsequent section.
- *Significant obstruction of the left main coronary artery.* A surgical approach is appropriate in these patients because mortality seems to be much higher among patients treated medically than among those treated with bypass surgery (1, 3, 37, 38, 40, 50). Mortality appears to be reduced from 15–25 percent per year with medical therapy, and to 5 percent or less with surgery (37, 38). Immediate surgical mortality is low (1–2 percent) and relief of symptoms is achieved among the vast majority of patients (3, 50, 51). Clinical recognition of these patients is not always reliable. However, as a generalization, they are more likely to demonstrate a positive exercise test, diffuse ST-T wave changes, and an exercise-related fall in systolic blood pressure than patients with other types of lesions (26–28, 30). An excellent prognosis applies to the patient with good distal runoff in the left anterior descending and circumflex branches, and with adequate ventricular function. If distal lesions are present, the distal vessels are small and diffusely diseased, ventricular function is poor (even after administration of nitroglycerin), prognosis with surgery becomes dismal, and the mortality rate can be expected to be high. Surgery has also been advocated by some physicians for asymptomatic patients with significant stenosis of the left main coronary artery discovered during examination for conditions other than suspected coronary artery disease (52).

  *Triple-vessel or double-vessel coronary artery disease (including the left anterior descending coronary artery).* There is still a lingering controversy concerning treatment of these patients. Predicted mortality among patients in this group, even if symptoms are minor or are easily controlled medically, is 9–10 percent per year for the first 5 years after clinical manifestation of the disease (30–32). Several studies have demonstrated no improvement in survival, whether therapy is medical or surgical (53–55), whereas others have shown a reduced mortality with surgery (52, 56). Many cardiologists would recommend surgery for a patient

under 70 years of age if good distal runoff, a very proximal left anterior descending lesion, and good ventricular function are part of the angiographic pattern of the double-vessel or triple-vessel coronary disease. This approach would be challenged by others and would certainly not be indicated if distal runoff and ventricular function were poor. However, if symptoms should accelerate and medical therapy prove ineffective in this group of patients, surgery would be indicated.

*A significant isolated lesion of the left anterior descending coronary artery.* Much controversy exists concerning the management of this group of patients. If the patient is symptomatic, even with adequate medical therapy, surgery is appropriate and can be performed with low risk (1–2 percent). Problems arise in those patients whose symptoms are not incapacitating and/or in whom medical therapy produces adequate relief of symptoms, since the mortality rate is higher among patients with an isolated lesion of the left anterior descending coronary artery than in patients with other single-vessel disease (35). Although several studies have reported that the mortality rate remains the same whether medical or surgical therapy is used (1), others maintain that there is improved survival with surgery (56, 57). Of course, much depends on the location of the lesion, state of distal runoff, and ventricular function. An isolated, tight lesion proximal to the first septal perforator, and associated with a good distal vessel and good ventricular function, is ideal for bypass surgery. Coronary occlusion found in this type of patient, especially if onset is sudden, may result in a massive infarction with high mortality and a high incidence of symptomatic ventricular aneurysm in the survivors. Within this group, a surgical approach can be expected to yield better results than a medical one. On the other hand, little can be expected with surgery in those with a more distal lesion, impaired distal runoff, and poor ventricular function, and, unless symptoms cannot be controlled, medical therapy should be used.

- *Isolated lesions in the right coronary artery or the circumflex branch of the left coronary system.* Prognosis is good among these patients (29, 32, 34, 35). Medical management is the preferred approach and usually results in good control of symptoms. Surgery is rarely indicated, but is appropriate in a few instances. When incapacitating pain persists despite maximum medical therapy, surgery may yield excellent results, provided that graft patency is maintained. In patients with a dominant right coronary artery and a congenitally small circumflex system, or with a dominant circumflex system and a small right coronary artery, a critical lesion may seriously jeopardize the inferoposterior wall of the left ventricle. These patients are subject to massive, life-threatening myocardial infarction, possibly associated with acute mitral insufficiency (posterior papillary muscle infarction), right ventricular infarction, or a ventricular septal defect (infarction of the posterior septum). These patients should be considered for surgery, especially if they are

symptomatic. Other prime candidates for bypass surgery are patients with intermittent posterior papillary muscle insufficiency, associated with signs of intermittent, acute, and hemodynamically significant mitral regurgitation. In this instance, surgery may prevent disabling or life-threatening mitral regurgitation, pulmonary edema, and death.

*No response to adequate medical therapy.* It is widely accepted that this group of patients is the most suitable for surgery, provided that medical therapy is determined to be adequate (i.e., the proper drugs and drug dosages are used, and the patient adheres to the therapeutic regimen), distal runoff beyond the obstruction(s) is satisfactory, and ventricular function is adequate (ejection fraction is greater than 0.35–0.40). Mortality from surgery should be extremely low (perhaps 1–2 percent) (3, 50, 56, 58). Both subjective and objective relief of symptoms and improved exercise tolerance have been found in 65–90 percent of these patients (50, 56, 59). Some investigators have claimed that relief of symptoms results from a myocardial infarction of the ischemic segment of the myocardium, which occurs either during or immediately following surgery (60); other studies have shown that improvement is associated with graft patency (3, 50). It was once predicted that early graft-closure rates as high as 25 percent could be expected in the first postoperative year (61, 62). However, as experience and surgical precision have improved, and with the advent of cold potassium cardioplegia (infusion with cold, hypertonic potassium solutions), much lower (about 10 percent) graft-closure rates have been observed (3, 50), and the incidence of perioperative infarction has fallen significantly.

*Evidence of severe left ventricular dysfunction.* Prognosis is poor in these patients regardless of the type of therapy used. Even if the patient survives, surgery is less likely to provide an improvement in symptom relief than treatment with drugs (32, 58, 63, 64). Therefore, surgery should be avoided unless the symptoms of congestive heart failure can be shown to be the result of ventricular aneurysm, mitral regurgitation caused by papillary muscle dysfunction or infarction, ventricular septal defect, or myocardial ischemia. Even under these conditions, surgical mortality is exceedingly high, and it must be recognized that surgery is offered as a last resort to terminally ill patients. It has recently been shown that radioisotope angiography can be used to diagnose the presence of diffuse ventricular dysfunction with a fairly high degree of accuracy, thus obviating, in some instances, the need for cardiac catheterization (43, 44, 65).

Thus far, discussion has centered on patients with stable angina. Although fewer in number, patients with unstable angina (see footnote on page 3) exhibit a variety of different clinical pictures with a poorer prognosis than patients with stable angina. Although a small percentage of these patients have normal coronary arteries, the majority have either

triple-vessel coronary artery disease, left main coronary artery disease, or a very proximal, isolated, left anterior descending lesion.

Immediate hospitalization is indicated for all of these patients and many will respond to bed rest, sedation, long-acting nitrates, and propranolol. When it has been ascertained (by serial blood enzyme studies, electrocardiograms, and radioisotope scans) that no acute infarction has occurred, cardiac catheterization and coronary angiography should be performed to determine the proper approach to therapy. Surgery should be considered for those patients with triple-vessel coronary artery disease, left main coronary artery disease, or isolated, very proximal, left anterior descending stenosis, provided that good distal runoff and good ventricular function are present. If these are not present, continued medical therapy is indicated, unless symptoms begin to appear while the patient is at rest or just beginning mild-to-moderate activity. It must be pointed out that symptomatic, long-term improvement with medical therapy has been reported in only 20 percent of patients in this group, whereas more than 80 percent have remained asymptomatic after surgery was performed (36, 66). Unfortunately, for some of these patients, there appears to be no difference in either short-term mortality or the myocardial infarction rate regardless of the therapy chosen (66, 67), although patients with stenosis of the left main coronary artery clearly have a better prognosis with surgical than with medical therapy. If the patient does not respond to medical therapy and bed rest in 24–48 hours, and if no infarction can be demonstrated, a cardiac catheterization should be done immediately because, in this subgroup of patients, acute infarction and death has been reported to be as high as 50 percent within the first 3 months after onset of symptoms (68–70). If no contraindication exists, surgery should be performed. Long-term postoperative results for this group of patients is still unknown. The insertion of an intra-aortic balloon pump for stabilization before angiography probably results in a much lower incidence of intraoperative infarction and a much improved surgical survival, which may even approach the surgical statistics found in bypass surgery for stable angina.

## The Basis for Medical Therapy

If medical therapy is to be effective, it must be able to bring the myocardial demand for oxygen into balance with its supply. This is accomplished, primarily, by reducing oxygen demand and, secondarily, by attempting to increase the capacity of the coronary arteries to deliver blood. The major factors influencing supply and demand have been carefully delineated (71–76). Oxygen demand is influenced by (*1*) myocardial contractility, (*2*) myocardial wall tension during systole, and (*3*) the duration of systolic tension. Angina is likely to arise in a patient with coronary artery

disease when oxygen demand is increased by such events as (*1*) the release of catecholamines, which increases myocardial contractility, (*2*) an increase in heart rate or systolic ejection time, which increases the duration of systolic tension, or (*3*) an increase in intraventricular volume, intraventricular pressure, or both, which increases intramyocardial wall tension. Oxygen supply to the myocardium is dependent upon the volume of flow through the coronary vascular bed, the oxygen concentration, and the ability of the myocardium to extract oxygen. Only the first of these is theoretically amenable to a significant alteration by medical means.

Blood flow within the coronary vascular bed is dependent on heart rate (diastolic filling time), blood pressure, and sites of resistance within the vascular bed. Usually, pressure-induced changes in coronary flow are due to changes in aortic diastolic pressure. Although coronary flow, in fact, is the difference between aortic diastolic pressure and left ventricular diastolic pressure. Left ventricular diastolic pressure is normally less than 12 mm Hg and, therefore, is generally inconsequential as a determinant of coronary flow. However, during episodes of angina or frank left ventricular failure, compliance is abnormal and often associated with very high ventricular diastolic pressures. This creates a markedly diminished pressure gradient between the aorta and the coronary sinus across the coronary bed, which results in decreased coronary blood flow (77). Sudden elevation of right heart pressure causes acute pulmonary hypertension, and also reduces the pressure differential and coronary flow by elevation of coronary sinus pressure (78). A vicious cycle is thereby established in patients with both coronary artery disease and right and/or left ventricular failure. A reduced coronary flow results in myocardial ischemia, followed by a decreased compliance and a rise in ventricular diastolic pressure. This leads to a further reduction in coronary flow and a worsening of angina. Rapid intervention, to reduce left ventricular diastolic pressure or acute pulmonary hypertension, is essential to break this cycle.

Systolic hypertension may also decrease coronary flow. Normally only 7–45 percent of coronary filling occurs during systole (79) because the marked rise in intramyocardial pressure, caused by ventricular contraction, compresses the coronary arteries. This small, but potentially important, fraction can be further reduced in the presence of systolic hypertension. The reduction in coronary flow is magnified if the patient has the additional complication of obstructive lesions in the coronary arteries.

Normally, coronary resistance is regulated within the coronary arterioles, which can dilate as much as five times their normal size to increase coronary flow (77). Control of this dilatation exists within the myocardium itself, although there is a minor degree of control through beta-adrenergic stimulation (73). In patients with coronary artery disease, the collateral circulation is a primary site of resistance (80), and dilatation occurs primarily through the mechanism of local hypoxia and ischemia (81).

At present, only nitrates, beta-adrenergic blocking agents, and calcium antagonists (slow channel blockers) can provide specific treatment for