Medical Management of Angina

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Evaluation of medical therapy of angina pectoris can be approached in many ways, but the objectives remain the same: (1) to relieve the acute attack of angina pectoris, (2) to prevent its recurrence, (3) to allow the patient to lead a normal lifestyle or, at least, one that is acceptable to him or her, and (4) to prevent myocardial infarction.

Major problems are incurred when one attempts to evaluate the natural history of angina pectoris with the effects of various treatments. Angina pectoris is a subjective complaint and therefore the response to therapy is also subjective. As angina frequently waxes and wanes, improvement of the patient's condition does not necessarily indicate a direct correlation with treatment, nor does the fact that a patient has angiographically proven coronary artery disease and chest pain mean that the coronary lesion is causing the patient's complaint. Furthermore, many patients treated for angina pectoris who were later catheterized demonstrated that, despite the fact that they had classical angina, upwards of 10% to 20% of them had insignificant coronary artery disease.[1]

Thus there are problems in defining the criteria by which to judge the patient's response to medical therapy. Electrocardiograms as well as exercise stress testing may show false-positive as well as false-negative patterns. Despite the fact that not all angiographically demonstrated lesions cause symptoms, coronary angiography remains the best method by which to judge the etiology of the patient's complaint. In serving as the standard by which to define the presence of coronary artery disease it also provides a basis for the determination of the effectiveness of both medical and surgical interventions.

When correlating the natural history of angina pectoris and its treatment to this standard, one should remember that there are different types of angina. Basically, patients demonstrate either simple stable angina or unstable angina—the latter often being termed "preinfarction angina" or intermediate syndrome. After reviewing a number of clinical studies, it becomes apparent that different investigators have different definitions of the forms of the angina they describe and hence these studies are not always comparable. The prognosis of angina varies with the form of angina being considered. In addition, when the true natural history of angina pectoris could have been studied—that is, before medical or surgical intervention was possible—arteriography was not available. All of these factors have precluded the exact determination of the effectiveness of medical therapy based on the true natural history of angina pectoris. At the present time, there is no means by which such a study could be done. Despite all the problems and lack of exactitude, one can evaluate, to some extent, how modern medical therapy may or may not help the patient reach the therapeutic goals outlined above.

In approaching the medical management of angina, one must be aware that not all angina is the result primarily of coronary artery disease. As mentioned earlier, there are other causes of angina such as arrhythmias, severe anemias, aortic valve disease, hypertensive cardiovascular disease, and idiopathic hypertrophic subvalvular aortic stenosis which need to be ex-

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cluded or, if included, to be treated. In many instances therapy (which may include surgery) aimed at these particular abnormalities may alleviate the patient's angina and make the use of specific antianginal drugs unnecessary.

The physician should first try to remove any recognized cause of the angina. The next step should be an attempt to change the patient's lifestyle without turning the individual into a cardiac cripple. The physician should advise the patient to stop smoking, avoid situations which might precipitate angina, avoid extreme environmental hazards, lose weight if necessary, and switch to an appropriate diet to decrease, or possibly reverse the progression of the atherosclerotic process. Participation in physician-approved exercise programs may allow the patient to maintain an acceptable lifestyle with a minimum of pain. If the patient is unhappy with the changes in lifestyle or if the angina persists, the physician must employ additional medical (nitroglycerin may have already been prescribed) or surgical therapy.

To understand why certain drugs are used for the relief of angina, one needs to understand the pathophysiology of ischemia (Fig 1). An individual develops angina or ischemic pain (which may be manifested by sudden death, angina pectoris, myocardial infarction, or the intermediate syndrome) when the myocardial oxygen demand exceeds the myocardial oxygen supply. Basically, medical therapy attempts to decrease oxygen demand whereas surgical therapy attempts to improve oxygen supply.

Medical therapy for noncoronary-artery-disease-induced angina pectoris may also involve changes in the myocardial oxygen-demand. For instance, treatment of hypertension reduces intramyocardial tension and thus decreases oxygen demand. Treatment with digitalis of heart failure associated with angina may decrease angina by lowering both the ventricular volume and the heart rate, and this, too, reduces oxygen demand; also, by lowering the left ventricular end-diastolic pressure, coronary vascular resistance is theoretically decreased and the subendocardial oxygen supply improved. Although digitalis increases the contractile state, thus increasing oxygen demand, it is hoped that the abatement in heart rate and ventricular volume will produce a greater decrease in oxygen demand, thereby relieving the angina.

Cigarette smoking causes undesirable effects on both oxygen supply and oxygen demand; it increases the heart rate and causes vasoconstriction, both of which increase oxygen demand, and it also decreases the oxygen supply by shifting the oxygen hemoglobin dissociation curve so that hemoglobin releases oxygen less readily to the tissues. In addition, smoking increases the carbon monoxide content of the blood, which is bound by hemoglobin in preference to oxygen; this, too, decreases the oxygen supply.

Treatment with certain drugs which can reduce or alleviate the angina may be indicated. Specific antianginal drugs include nitroglycerin, isosorbide dinitrate, topical nitroglycerin, propranolol and metoprolol.

The various nitrates decrease angina by causing peripheral venous pooling, thus lowering the intraventricular volume which lessens oxygen requirements. Intraventricular pressure may also abate, thereby decreasing coronary vascular resistance and theoretically improving subendocardial blood flow. Nitrates may also lower arterial blood pressure and, as a result, effect a decrease in impedance to blood flow; hence, less intraventricular tension will be necessary for blood to be ejected. Problems occasionally arise if a decrease in blood pressure caused by nitrates produces reflex tachycardia which in turn causes an increase in the contractile state of the myocardium. Both the increased heart rate and the increased contractility will increase oxygen demand and may cause angina. Furthermore, marked hypotension may develop with the administration of sublingual nitroglycerin which may decrease oxygen supply. However, these problems are infrequent.

The broad beta-blocker, propranolol, and the more specific beta-one-blocker, metoprolol, both decrease oxygen demand[2] by decreasing the heart rate, the force of myocardial contractility, and the systolic blood pressure. The theoretical problems of beta-blockers causing increased ventricular volume which in turn increases oxygen demand and left ventricular end-diastolic pressure, thus producing increasing coronary resistance and decreasing oxygen supply, is usually not of clinical significance. Contraindications for the use of these drugs, however, are very important. If the patient's heart rate prior to institution of therapy is 45 or

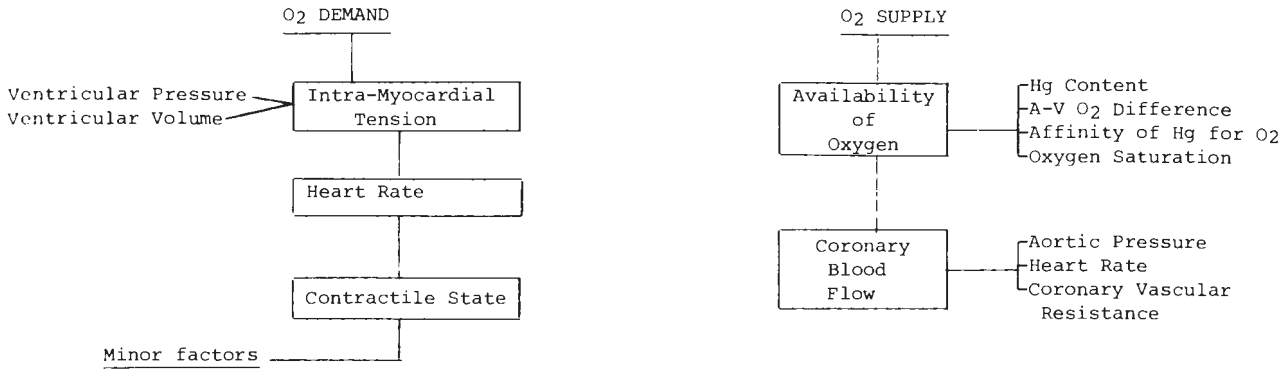

Fig 1—Schematic representation of determinants of myocardial oxygen demand and myocardial oxygen supply. When the demand is greater than the supply, angina may develop.

50, beta-blockers should not be used or else used with extreme caution. Insulin-dependent diabetics who are poorly controlled or who are unreliable, in general, are not candidates for beta-blocking drugs. Propranolol should not be used on patients with severe bronchospastic disease. Metoprolol, being a more specific beta-one-blocker, theoretically should not cause as many problems as propranolol, especially with brochospastic disease; however, it may be desirable to have these patients on a beta-one agonist prior to the institution of metoprolol.

Though the dose of these various anti-anginal drugs will vary from individual to individual, a few broad guidelines can be set (Fig 2). Nitroglycerin is usually the first anti-anginal drug utilized. Sublingual nitroglycerin should be begun in the lowest dose possible and the first dose should be given in the physician's office while the patient is seated to observe any untoward reactions. Some patients complain of severe headaches and a few may be intolerant of the drug for this reason. The dose of nitroglycerin should be increased as necessary to achieve control of the patient's angina. Sublingual nitroglycerin is not solely used for acute anginal attacks but may also be given prophylactically to patients who routinely develop angina with certain situations such as climbing or engaging in anxiety-producing confrontations.

If angina is frequent, if the patient cannot tolerate the nitroglycerin or if it is advisable to avoid using prophylactic nitroglycerin, then either the long-acting nitrates or propranolol should be used. Neither the long-acting nitrates nor propranolol are effective in terminating the acute anginal attack; Isordil®'s effect lasts longer than the 15-minute changes induced by nitroglycerin and is often better tolerated by the patient. However, the duration of Isordil®'s action is variable, and is partially determined by the route of administration. Sublingual Isordil® has a shorter onset of action than the oral form, but its effect lasts only 3 to 4 hours whereas oral Isordil® may be given at 4- to 6-hour intervals. Topical nitroglycerin action lasts for from 4 to 6 hours.

The dose of sublingual Isordil® may vary from 2.5 mg up to 20 mg every 3 to 4 hours, depending on the patient's response. If one uses oral Isordil®, it is important to realize that higher dosages must be used compared to sublingual Isordil® to produce the same hemodynamic effects; however, the use of oral Isordil® may be preferred, as it is often better tolerated by the patient. Though one often starts with at least 10 mg of oral Isordil® every 6 hours, usually at least 20 mg every 6 hours is necessary to achieve improvement. The dosage of topical nitroglycerin, like Isordil®, must be titrated by the patient's response. Its advantage is that a single evening application may prevent nocturnal angina and permit the patient to sleep through the night; a major disadvantage is that, as a paste, it may be aesthetically unpleasing. Topical nitroglycerin is usually applied in terms of inches or fractions of an inch and its efficacy is partially dependent upon the site of application—better absorption obtained when it is applied above the waist—and the area over which the paste is applied—the greater the area, the better the absorption.

All nitrates have the potential problem of decreasing blood pressure and causing reflex tachycardia. Patients can usually tolerate headache, although aspirin or acetominophen may have to be added to the regimen.

Propranolol is an effective drug for treat-

		UNDESIRABLE EFFECTS
Nitroglycerin	SL, PRN	
Isordil, SL	2.5 - 10 mg. q4h	
Isordil, PO	20 - 40 mg. q4-6h	Tachycardia Hypotension Headache
Topical Nitroglycerin	1/2 - 2" q4-6h	
Propranolol	40 - 80 mg. q6h	Bradycardia Bronchoconstriction Congestive Heart Failure Rebound Angina Block Hypoglycemic Symptoms

Fig 2—Commonly used anti-anginal drugs.

ing angina and the best results appear to occur in patients who have either an elevated blood pressure or an increased heart rate prior to institution of the drug. In treating angina, one usually prescribes propranolol every 6 hours and the total daily dose is at least 160 mg. The drug is begun at a lower dose of 10 to 20 mg every 6 hours and increased every 2 to 3 days, depending on the patient's response in terms of blood pressure, heart rate and symptoms. One should carefully evaluate the patient for the appearance of peripheral edema, rales, weight gain or other evidence of heart failure. The end point for increasing the propranolol varies: precipitation of congestive heart failure, alleviation of symptoms, or a decrease in heart rate to less than 50 beats per minute. In some patients, one may have to stop the drug because of bronchospasm.

Metoprolol was recently introduced in the United States but has been used in Europe for a long time. It is quite similar to propranolol but has less effect on beta-two receptors. It is therefore preferable for patients with lung disease. Otherwise, the many side effects are similar to those of propranolol. One must remember that both propranolol and metoprolol are associated with rebound angina if the drug is rapidly withdrawn from patients who have responded. Equipotent dosages of propranolol and metoprolol are about 40 mg of propranolol and 50 mg metoprolol and appear to produce the same decrease in heart rate, reduction of angina pectoris, reduction of nitroglycerin consumption and improvement in exercise tolerance testing. In European studies, propranolol and metoprolol were given every eight hours, but in the United States, administration of propranolol every six hours is more common.

Specific studies with Isordil®, in which the drug was continued for up to 5 to 6 months, have shown sustained symptomatic relief in terms of the decreased frequency of anginal attacks, the number of nitroglycerin tablets used by the patient, and improved exercise tolerance. Other studies have shown that continued administration of Isordil® does not interfere with the patient's usual response to sublingual nitroglycerin: it does not blunt hemodynamic effects induced by nitroglycerin or the relief of angina. Similar results have been obtained with long-term studies of nitroglycerin ointment. One can therefore conclude that there is good evidence that Isordil® and topical nitroglycerin do cause improvement in the patient's symptoms and functional status both subjectively and objectively, possibly for several months. However, none of these studies answer the question "will they prevent myocardial infarction and sudden death?"

Propranolol and metoprolol have been studied in a similar manner. In 1969,[3] patients clinically defined as having angina pectoris were further subdivided into those having coro-

nary artery disease as judged by coronary arteriography (50% occlusion of at least one coronary artery) or a demonstrated transmural infarction, and a second group of patients with clinical angina but negative coronary arteriograms. Successful response to propranolol was defined by at least a 50% decrease in incidence of angina, a 50% decrease in the number of nitroglycerin tablets used, or loss of one or more provoking factors of angina. Only 23% of patients with clinical angina but without proven coronary artery disease responded to the drug; the patients with proven coronary artery disease responded 86% of the time. Thus, without employing coronary arteriography one could have concluded that propranolol was less successful in the treatment of angina pectoris than it really is. This study showed that the dose of propranolol required for a favorable response was 160 to 240 mg a day and that the response to the drug did not correlate with the number of vessels involved or the severity of the patient's pretreatment angina.

In 1976 another study[4] attempted to show that the patient's response to propranolol appeared to affect mortality. Despite some loopholes the study did clearly indicate that patients who failed to respond to medical management appeared to have a worse prognosis than the responders; these nonresponders are therefore the patients who are usually referred for surgery.

Most studies conclude that high doses of propranolol clearly decrease the incidence of angina and allow the patients to lead more normal lives. Other evidence has shown that exercise tolerance also improves, although if metoprolol and propranolol are used, it is often not angina that curtails the patient's activity but frequently a fatigue-like syndrome; some studies have shown that if the patient is maintained on a combination of propranolol and isosorbide dinitrate, exercise tolerance improves even more. It would seem logical that as these two drugs affect different determinants of oxygen demand, a combination of the two might be more effective than either one used singly.

In summary, one can clearly state that the medical therapy of angina pectoris is better than no therapy at all and that some patients clearly do obtain subjective as well as objective improvement. However, one still cannot determine whether or not there is clear improvement utilizing medical therapy in terms of mortality relative to the natural history of the disease. There are also limitations to the use of the drugs and there are clearly failures; these drugs do not halt progression of the underlying atherosclerotic process and therefore do not cure. The choice between medical or surgical therapy depends on many factors which are often defined by angiography, determined by the failure of whatever the physician believes to be maximum medical therapy, and commonly influenced by the local surgeon's skills. The patient as well as the physician has a profound influence on whether medical or surgical therapy is ultimately used.

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