Medical Management of Angina Pectoris

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SUMMARY
The successful medical management of a patient with angina pectoris requires careful attention to many factors including omission of smoking, control of hypertension, and weight reduction for the obese person. Newer knowledge of the importance of the product of the systolic blood pressure and the pulse rate in determining the threshold of angina affords a more meaningful approach to therapy. Each individual must be educated regarding the factors that aggravate and precipitate his distress so that these can be minimized, or prophylactic nitrite therapy can be appropriately applied. Emotional stress is of equal importance to effort in the production of angina. The maintenance of treatment is nitroglycerin and sublingual nitrates combined with beta-blocking drugs. Each drug or combination must be properly readjusted for the individual to assure optimum benefit. Digitalis, diuretics, antiarrhythmic drugs, antihypertensive agents, and radioiodine may be useful in selected cases.

In the medical management of angina pectoris due to coronary atherosclerosis, proper identification of the type of ischemic discomfort is often helpful. Several types can be categorized: (1) initial, (2) stable, (3) progressive, and (4) preinfarction. The initial onset of angina suggests an acute dynamic change in the coronary arterial circulation. Rarely in such instances one may be surprised to find electrocardiographic evidence of myocardial infarction, even though the duration of distress may have been only 5-10 min. When infarction is not suspected, reduction of the myocardial work load and oxygen consumption by a judicious short period of modified rest may be helpful. On the other hand, a recent progression of previously stable angina so that it occurs at rest, nocturnally, or with slight exertion may indicate impending infarction. In such instances, the drug therapy, period of rest, and prognostic implications may be quite different from those of initial or stable angina. A history of this progressive pattern of distress over a period of days or weeks can be elicited from one half to two thirds of patients hospitalized with acute myocardial infarction.

Although no statistical data are available, it is the authors’ experience that many patients traversing a period of progressive or “preinfarction” angina may revert to their previous stable pattern after an appropriate interlude of rest and tailored modification of their therapeutic regimen. During these crescendo periods, the risk of death from ventricular fibrillation or standstill is increased.

Risk Factors
Risk factors are not only of epidemiologic importance but also play a limited role in the management of the individual patient. The influence of smoking is paramount. Nicotine mobilizes catecholamines and increases myocardial oxygen consumption. It also acts on the carotid and aortic bodies, causing increased heart rate and blood pressure. The pressure-rate product, an important determinant of oxygen consumption, may reach a level sufficient to produce angina. Improvement may ensue after smoking is stopped.

The control of hypertension by lowering peripheral resistance and external cardiac work may produce amelioration of angina. In practice, the beneficial effect may not be dramatic. In the authors’ experience the omission of smoking is more often accompanied by improvement of angina than the control of hypertension.

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Weight reduction may reduce the frequency of angina in some patients, but increased physical fitness and a heightened sense of well-being seem to be more significant by-products.

Lowering the levels of cholesterol and triglycerides are laudable long-term goals, but little influence on angina has been demonstrated. Leren has claimed reduction of the incidence of fatal and nonfatal myocardial infarction in patients on diets low in saturated fats and cholesterol. The study of the British Medical Research Council known to occur proved physical fitness can be done without angina. Such improvement may result from the reduction of heart rate and/or blood pressure during exercise, known to occur with training. There is no factual data that the natural history of coronary disease is altered, or that the collateral circulation is enhanced.

Difficulties of Assessment of Drug Therapy

Angina is a subjective complaint recognized by history. Response to treatment is likewise subjective so that evaluation of any therapy is notoriously difficult. The many variables and subtle factors that influence angina often prevent accurate assessment of ongoing studies of response to treatment. The placebo effect of any therapy for coronary disease must always be taken into consideration. The approach, interest, and technics of the physician influence the response to any given therapy.

To assess the effectiveness of drugs, they should be administered so that their maximal effect is timed to occur when an individual’s angina develops. Thus the patient who develops angina on first awakening or on assuming the recumbent position or postprandially may not be protected by medication given on an arbitrary schedule such as four times daily. Such routine dosage has led to criticism of double-blind studies of one or another drug. One might conclude that a drug is ineffective because the design of the study was improper or conversely that an inert drug was effective. A single drug studied may seem to be ineffective and yet when combined with another drug significant improvement may be noted. Negative results may be obtained with a given dose of a drug, yet benefit may be obtained with a larger dose. For example, the response to administration of beta-blockers is dose related. To quote Russek “it can be seen, therefore, that while uncontrolled clinical observation has often falsely endowed inert agents with powers which they do not possess, improperly designed double blind studies have frequently divested potent agents of action clearly and consistently evident to patient and physician alike.”

Objective data such as the electrocardiographic response to treadmill exercise and to atrial pacing provide some help in weighing the effects of short-term drug administration. One should be mindful that pain may occur without changes in the electrocardiogram, and the threshold for pain in a given patient may be altered by a variety of factors including emotional state and amount of rest. Long-term studies professing beneficial therapeutic effects are suspect because of the great variability in the natural history of coronary disease. Improvements in any parameter may be independent of treatment.

Redwood et al. emphasized the pitfalls if only one level of exercise is used in the evaluation of efficacy of a drug. For example, when the work load is intense and excessive, angina may occur before a drug could be evaluated and, conversely, when the work load is gradually increased resulting in a pressure-rate product less than that needed to produce angina, one might erroneously infer that a given drug was effective. Loss of an ischemic area by infarction may be followed by improvement of angina. At times this may be the reason for the disappearance of
ischemic distress in patients following coronary artery surgery. It is not always easy for the clinician to be certain that infarction has occurred, since electrocardiographic evidence may be lacking or there may be T-wave alterations compatible with the inevitable pericarditis incident to incision of the pericardium. Electrically silent areas may be present in the septal, apical, subendocardial, high posterior, or intramural regions. The acquisition of extracardiac causes such as the chest-wall syndrome, hyperventilation syndrome, reflux esophagitis, and postinfarction pericarditis may complicate evaluation.

Management of Aggravating and Precipitating Factors

The education of the patient by the physician is the most important facet of management. Time spent in understanding a patient's emotional undergirding, psychophysologic responses, behavioral idiosyncracies, motivations, and life style is often more valuable than that expended in exercise testing, diet instruction, drug juggling, and stereotyped instruction. Without accurate assessment of the nature of the patient's ischemic distress no determination of the efficacy of therapy can be accomplished. Clarification of patterns in some patients may require exercise testing until angina ensues.

The dominant influence on the frequency and severity of angina is emotional stress. It is far more important than exercise in producing angina in many patients. A rise in pulse and blood pressure is probably responsible. Examples of sources of tension are: driving in heavy traffic, business reversals, family conflict, hurrying to make a deadline, job insecurity, a lawyer addressing a jury, the surgeon during an operation, or worry regarding well-being of loved ones. The natural history of angina is characterized by episodic variation in frequency and intensity of symptoms coincident with periods of increased emotional stress. Anniversary reactions to some emotionally charged event such as loss of a loved one or prior heart attack are not uncommon. Stress incident to holidays or preparations for graduation or weddings may induce ischemic symptoms.

Pain in other organ systems may influence myocardial oxygen consumption and cause angina. Examples may be cited such as gallbladder distress, abscessed tooth, arthritis of spine, peptic ulcer, pancreatitis, diverticulitis, renal colic or infection, ischemic peripheral vascular disease, and diabetic neuropathy. There is not agreement among all observers that these factors are of importance, but long clinical experience attests to their significance. Many patients develop symptoms after voiding and returning to bed. This is probably related to blood volume shift from the peripheral vascular bed to the heart on assuming the recumbent position. The increase in ventricular volume and wall tension may offer an explanation for recumbent angina. Parker and associates demonstrated the subsidence of angina produced by atrial pacing when 300 cc of blood were removed. Pain returned when blood was reinfused with a constant heart rate. Relief of angina may occur with peripheral pooling incident to rising to a sitting or standing position. Likewise, it is theoretically possible that the contraction of blood volume due to chronic diuretic therapy may explain occasional improvement of angina in the normotensive patient. This reduced volume may also limit the abrupt rise in blood pressure that precipitates or results from angina. The product of the systolic pressure and pulse rate is one determinant of increased oxygen consumption. Prostatic obstruction with straining can aggravate symptoms. Pulmonary infection and embolism may precipitate or aggravate angina. Occult arrhythmia not appreciated by the patient is probably not an uncommon cause of pain. While we emphasize the influence of chilling and cold on the production of pain we should not overlook the effects of heat and humidity. Sudden changes in blood volume such as excessive administration
of fluid or contraction of intravascular space due to blood loss may increase angina. Correction or control of linked disorders may bring overall improvement. The patient with stable angina may develop a preinfarction pattern in the presence of significant anemia and revert to a stable condition when red blood cell volume is restored to normal. Angina due to coronary atherosclerosis may improve dramatically when significant associated valve disease such as aortic stenosis or insufficiency is corrected surgically.

The patient should be taught to identify and avoid precipitating factors as far as possible. A list of common factors follows:

1. Emotional tension (anger, excitement).
2. Walking up an incline.
3. Sudden effort.
4. Heavy lifting.
5. Hurrying (planes, trains, busses, etc).
7. Intercourse.
8. High altitude.
9. Hypoglycemia.
10. Isometric exercise such as lifting, raising a window, sweeping, work involving use of hands overhead.
11. Epinephrine or other sympathomimetic amines.
12. Dental work.
13. Chilling by cold wind.
14. Iced drinks or ice cream.
15. Hot weather and high humidity.
16. Excitement incident to television or sports.
17. Funerals, reunions.
18. Foreign travel.
19. Mowing a lawn.
20. Shovelling snow.

Precipitating or aggravating factors may cause catastrophic change in the natural history of coronary disease by inducing preinfarction angina or acute myocardial infarction. Patients should be instructed to notify their physician when there is an abrupt change in the character and duration of pain. For example, when stable angina of 5-min duration is replaced by distress lasting $\frac{1}{2}-1$ hour, prompt hospitalization and surveillance in a coronary care unit may be indicated. Unless this advice is followed, it may turn out that the physician is the greatest barrier to solving the problem of sudden death due to coronary disease.

**Nitroglycerin**

Nitroglycerin is the mainstay in the treatment of angina, yet it is shocking to find worthless long-acting preparations prescribed when the patient has never received nitroglycerin. Nitroglycerin acts to reduce myocardial ischemia in a local area of the myocardium, even though the total coronary blood flow may remain unaltered. This improved distribution of blood flow and oxygenation may be due to an effect on collateral channels. It is well accepted that nitroglycerin dilates major coronary arteries but it is probable that dilatation of small collaterals in a local area is of greater importance in producing relief. This can be demonstrated by recording oxygen potentials using platinum electrodes placed in both the endocardium and epicardium. The administration of nitroglycerin improves the ratio of endocardial to epicardial flow suggesting improved blood flow to the endocardium.

By contrast, dipyridamole increases total coronary blood flow which is confined largely to the epicardium. It is ineffective in the treatment of angina. Many studies indicate that benefit accrues from the other effects of nitroglycerin that reduce oxygen consumption: (1) reduction in arterial blood pressure with decrease in the afterload of the heart, (2) reduction in venous tone with reduced preload, (3) reduction in ventricular volume, (4) reduction in left ventricular end-diastolic pressure, (5) reduction in wall tension, (6) decrease in the rate of rise of left ventricular pressure, (7) decrease in ejection time, and (8) reversal of ischemic bulges. Detry and Bruce have demonstrated that maximal total-body oxygen consumption could be reached without angina...
in some patients pretreated with nitroglycerin. Nitroglycerin may delay and reduce the degree of ischemic S-T depression produced by exercise.

Nitroglycerin should be used initially in small dose such as 0.15 mg to avoid headache. The “nitrite effect” must be explained to the patient so that he may better accept the drug. The dose is adjusted to avoid headache but, if headache accompanies full therapeutic effect, analgesics may be added. Unfortunately, headache from an excessive dose may prevent a patient from taking nitroglycerin subsequently. The supply of nitroglycerin should be replenished periodically to assure potency. If the tablets do not produce burning of the tongue or the characteristic sensation of fullness in the head they must be replaced. As with the chronic use of many drugs, tachyphylaxis may occur, and the dosage may need to be increased. An effective dose must be determined individually and reevaluated after prolonged use. Care should be taken to avoid significant postural hypotension, particularly in the elderly where this is more common. The blood pressure should be taken in the recumbent and upright position after initial use of the drug. Nitrite syncope may occur after multiple doses taken at short intervals, particularly if the patient is standing. This phenomenon may be confused with acute myocardial infarction. Nitroglycerin should be used prophylactically before known precipitating events. It should be taken promptly when discomfort occurs and repeated twice at 5-min intervals if there is no relief. Nitroglycerin is taken not for pain alone, but for whatever symptoms characterize the patient’s myocardial ischemia. Thus, it may be administered for heaviness, pressure, burning, indigestion, tightness, constriction, breathlessness, aching, or expanding sensation, whether it be in the epigastrum, chest, jaw, throat, shoulder, back, or arms. Paradoxic worsening of angina due to an inordinate drop in mean aortic pressure and coronary filling may rarely occur. Exceptionally, this phenomenon may be observed in patients with severe aortic stenosis or hypertrophic subaortic stenosis.

Long-Acting Nitrites

Long-acting nitrites remain controversial, and studies of their benefits give conflicting results. The duration of action claimed by pharmaceutical houses has been disputed. Many of the timed-release preparation appear to act selectively on the cerebral rather than the coronary circulation, producing headache without significant improvement of angina. Countless patients are taking expensive and ineffective drugs. It may be trying for the physician to decide when therapy is indicated, what dosage is required, and which drug is effective. Should drugs be prescribed for the patient with only occasional angina? Does such therapy offer any beneficial effect where recurrent arrhythmia or myocardial failure is present? Is it possible to forestall prolonged pain and thereby reduce the probability of finite muscle necrosis? The answers are not available.

On one hand, the clinician may satisfy himself that a drug is effective, yet its action in terms of reduction of the triple product of pulse rate, systolic blood pressure, and ejection time may be negligible. Thus Goldstein et al. claimed that isosorbide sublingually may be shown to be no more effective than nitroglycerin. They found that 21 of 24 patients exercised longer without developing angina 10 min after receiving 5 mg isosorbide dinitrate sublingually. Benefit was present at 1 hour in the minority, and no persistent effect was apparent at 2 hours. Aronow and Chesluk claimed isosorbide was no more effective than placebo but Bunn and Cheremos concluded that its action was more prolonged than that of nitroglycerin and there was less S-T depression with exercise at the end of ½ and 1 hour. Russek noted that 5 mg sublingual isosorbide was effective up to 2 hours. Oral preparations of isosorbide in a dose of 10 mg four times daily have not produced worthwhile benefits, but studies
using larger doses more frequently have not been reported. Despite this evidence, isosorbide 10-20 mg four times daily, is widely used. Russek reported that pentaerythritol tetranitrate, 20-40 mg, produced less benefit with delayed onset of 1-1½ hours, but some effect was present up to 4 hours. The sustained-action preparations were ineffective. Erythrityl tetranitrate in a 10-mg chewable form may produce an effect within 5 min that is claimed to last several hours. There are no precise studies of the effect of this drug.

Sublingual isosorbide, 2.5-5.0 mg, is useful prior to meals or intercourse or anesthesia, and an effect may be obtained for 1 hour. The dosage must be carefully titrated and gradually increased to avoid headache and to ensure optimum effect. In selected patients, it may be helpful when given orally as often as every 1-2 hours. The major side effects of nitrates are headache and symptoms due to postural hypotension. The use of long-acting nitrates does not impair the tolerance or effectiveness of nitroglycerin. Synergistic effect has been noted when isosorbide dinitrite has been used in conjunction with beta-blocking agents. The decrease in pulse rate, prolongation of systole, and increase in ventricular volume are counteracted partially by nitrite effects of increase in pulse rate, decrease in systolic time intervals, and decrease in ventricular volume and end-diastolic pressure.

Nitroglycerin ointment is helpful, especially in preventing nocturnal angina. The 2% ointment is applied over an area 2-5 cm in diameter on the forearm at bedtime. Occasionally, reapplication may be needed after 4-6 hours.

**Beta-Blockers**

Beta-blockers exemplified by propranolol act to decrease myocardial oxygen consumption. At the same time there is a negative inotropic effect with decrease in the force of myocardial contraction. The effects of propranolol may be summarized as follows: (1) decrease in myocardial contractility; (2) decrease in pulse rate; (3) mild decrease in blood pressure; (4) decrease in rate of rise of pressure in the left ventricle; (5) increase in left ventricular volume; (6) increase in left ventricular end-diastolic pressure; (7) reduction in stroke output; (8) shortening of systolic ejection; and (9) quinidinelike effect.

The preponderant effect of propranolol is the reduction of oxygen consumption through hemodynamic changes. An additional factor may be an effect on oxygen delivery to the myocardium. Propranolol may increase coronary vascular resistance, largely through decreased myocardial oxygen demand, but also by vasoconstriction of coronary resistance vessels. In some instances the A-V oxygen difference is increased. Studies in dogs indicate that, while coronary blood flow to normal myocardium is reduced, blood flow to regional areas of ischemia may remain unchanged. There are divergent effects on determinants of myocardial oxygen consumption. Rarely, propranolol decreases exercise capacity and increases oxygen consumption via a disproportionate increase in left ventricular volume and ejection time. Thus, the drug is contraindicated in the patient with congestive heart failure and should be used with great caution in the presence of ventricular dysfunction. Rarely, left ventricular failure may be precipitated in the absence of clinical evidence of dysfunction (fig. 1). In the majority of patients, however, there is evidence of improved exercise tolerance and reduction of electrocardiographic changes of ischemia. Not all studies have reported beneficial effects in angina. This may be due to difference in patient selection, dosage, protocol, and associated medication. Scriverstava et al. could show no statistical evidence of benefit in a double-blind study using 30-60 mg propranolol daily. Using a larger dosage of 30 mg three times daily Kellan found 13 of 19 patients had fewer attacks and 14 required less nitroglycerin as compared to placebo. Long-term studies of 65 patients on 160-400 mg propranolol daily resulted in 37-50% reduction of anginal attacks and nitroglycerin
Figure 1

(Left) C. H., age 51 years. Interstitial pulmonary edema in patient with preinfarction angina that developed while receiving digitalis and 120 mg propranolol daily over a period of 1 week. (Right) Clearing 4 days later after omission of propranolol and administration of diuretics.

requirements. Eight of 65 patients died suddenly, 9% developed left ventricular failure, and two developed asthma. There was an average decrease of 18% in the resting pulse rate.40

The dose required to produce an effect has varied widely, but evidence suggests there is a dose relation. Prichard and Gillam in a double-blind study of 16 patients noted maximum benefit with an average dose of 417 mg (range 80–1280).41 Progressive decrease in benefit was noted as the dose was reduced to one half, one fourth, and one eighth. The one-eighth dose was still superior to placebo. Some studies indicate no improvement with less than 160 mg daily,40 whereas 40 mg daily may be beneficial when combined with nitrites such as isosorbide dinitrate. Mizagala et al. reported that propranolol produced sustained improvement in 13 of 15 patients with acute coronary insufficiency refractory to all medical treatment.42 Papazoglou noted benefit in six of seven cases of preinfarction angina that were refractory after 2 weeks' treatment with drugs.43 The dose ranged from 80 to 160 mg. Our experience with preinfarction angina has been less impressive, however.

When instituting propranolol therapy, one should begin with small amounts of the drug such as 10 mg three to four times daily and gradually increase the dose to tolerance or until clinical benefit ensues. The side effects that may be encountered are: (1) feeling of fatigue; (2) headache; (3) diarrhea; (4) nausea; (5) bradycardia; (6) postural hypotension; and (7) bronchospasm.

Many prefer to digitalize patients on propranolol to counteract the decrease in force of myocardial contraction. The combination of digitalis and propranolol may limit the dose because of bradycardia. A rule of thumb is to choose the dose that will decrease the resting pulse rate 20 beats or to a rate no less than 55 beats/min. Ordinarily, there is only a slight decrease in blood pressure but postural hypotension is not uncommon, particularly when propranolol is administered in conjunction with other drugs such as nitrites, diuretics, Rauwolfia derivatives, or tranquilizers. Extra care is needed in the elderly patient.
with basilar-vertebral arteriosclerosis in whom postural hypotension may occur in the absence of drug therapy. Propranolol should be omitted 96 hours prior to anesthesia and surgery, in order to lessen the possibility of refractory cardiac arrest.

Newer beta-blocking agents that lack myocardial depressant effects are being studied. These agents slow the pulse rate and decrease the blood pressure but lack the anesthetic properties of propranolol. Practolol, sotalol, and oxyprenolol have been reported to give comparable beneficial effects in the treatment of angina.46-48 Sowton et al. reported that the total work performance before the development of angina increased 40% on a daily dose of 400 mg practolol.49 The heart rate at which angina occurred was approximately 15% lower. These drugs, unlike propranolol, do not increase airway resistance or produce bronchospasm.

Alprenolol produces a dose-dependent decrease in pulse rate and systolic blood pressure when patients with angina are exercised. Sealey et al. noted a 24–31% delay in onset of angina and a 25% increase of total work with decrease in degree of S-T depression after alprenolol.47

Perhexiline maleate is a new antianginal drug that in animal experiments produces coronary, systemic, and pulmonary vasodilation. It reduces left ventricular work and decreases myocardial oxygen consumption. Slowing of the cardiac rate and reduction of the pressure-rate index occurs.50 It has a quinidinelike action and prolongs depolarization and repolarization. Its effect is not altered by vagotomy, atropine, or sotalol.51 Limited human experience has given favorable response.52

**Diuretics**

Diuretic therapy is theoretically beneficial in: (1) ventricular dysfunction or failure, (2) hypertension, (3) limiting peak rise of systolic pressure in the normotensive, and (4) producing mild contraction of blood volume. Diuretic therapy may be used in conjunction with digitalis when borderline or overt congestive heart failure is suspected of initiating or exacerbating angina pectoris. Maintenance therapy must be tailored to each patient. Potassium chloride supplementation is usually necessary but serum levels should be checked and special care taken with patients who have renal insufficiency. The addition of spironolactone or triamterene to reduce potassium loss may be helpful. Potassium chloride and spironolactone should not be administered in conjunction since severe, perhaps lethal, hyperkalemia could result.

**Digitalis**

Ventricular dysfunction is common during angina, and the pulmonary wedge pressure may or may not be elevated during an attack.53 Digitalis has been used with conflicting results. The majority of studies indicate no benefit in angina, even though there may be improvement of the ventricular performance. Most of the studies have been carried out over a period of 1–2 hours, using limited amounts of glycosides intravenously. There are no data on the effects on angina by optimal digitalization over weeks or months. Clinical impressions of benefit cannot be substantiated, particularly since nitrates and beta-blockers may be used in conjunction with digitalis. Some authors have expressed the fear that digitalis would aggravate angina,54 but in practice this must be a rare occurrence.

Digitalis increases the force of myocardial contractions with subsequent rise in oxygen consumption. In many patients with angina, the left ventricular volume and end-diastolic pressure may be reduced along with a decrease in the rate of rise of left ventricular pressure. The net effects of this improved myocardial performance may be reduction of oxygen consumption and lessening of angina. On the other hand, there may be an increased rate of rise of left ventricular pressure that offsets the decreased left ventricular volume and end-diastolic pressure causing angina at a lower level of exercise. We have observed improvement in occasional patients with complaint of easy fatigability in the absence of clinical evidence of ventricular dysfunction.
following digitalization. It would seem reasonable to try digitalis when there is evidence of ventricular dysfunction manifested by the following: (1) S3; (2) S3 gallop; (3) pulsus alternans; (4) reverse split of second sound not due to complete left bundle-branch block; (5) ischemic bulge; (6) well-marked mitral regurgitation due to papillary muscle dysfunction; and (7) venous hypertension or interstitial edema in the chest X-ray.

Nocturnal angina has been a conventional indication for digitalization. A trial of the drug is warranted for angina decubitus or progressive angina. Frequently ventricular premature beats may impair coronary perfusion. These may subside following digitalis administration, even in the absence of clinical evidence of ventricular dysfunction or failure. Digitalization may be helpful when there is a history of paroxysmal atrial tachycardia, atrial fibrillation, or atrial flutter.

**Antiarrhythmic Drugs**

Uncommonly there are patients whose angina results from one or more of a variety of arrhythmias. Most such patients are unaware of their cardiac irregularity, regardless of its origin. Documentation of this cause-and-effect relationship is difficult. Therapy is usually dictated by clinical inference and/or by electrocardiographic clues. All types of arrhythmias are more common in the setting of: (1) acute injury of myocardial cells, which may be occult without change in the electrocardiogram or enzymes; (2) severe ventricular dysfunction from prior infarction; (3) significant mitral regurgitation due to papillary muscle dysfunction; (4) ventricular aneurysm; (5) sinus bradycardia or second- and third-degree A-V block due to disease of the sinus and A-V nodes or to drugs such as digitalis and propranolol; and (6) potassium depletion due to diuretic drugs such as those used in the treatment of hypertension.

In some instances, angina probably results from inadequate coronary perfusion secondary to reduced stroke volume coincident with frequent premature beats or tachyarrhythmia. In others, bradyarrhythmias are responsible. Resting and exercise electrocardiograms or monitoring over a period of hours with a portable monitor recorder may help in identifying the rhythm disturbance.

When angina is associated with frequent ventricular premature beats or ventricular tachycardia, propranolol, quinidine, procainamide, or rarely diphenylhydantoin, individually or in combination, may be successful in reducing or eliminating the episodes of rhythm-induced angina.

Where paroxysmal atrial tachycardia has been documented or is strongly suspected clinically by the patient’s evaluation of the rhythm’s classically abrupt inception and cessation, quinidine, digoxin, or propranolol alone or in combination is usually adequate. These drugs are equally useful in paroxysmal nodal tachycardia or paroxysmal atrial fibrillation. When paroxysmal supraventricular arrhythmia and angina are associated with the Wolff-Parkinson-White syndrome, propranolol has been found to be effective. When bradyarrhythmias are responsible for angina, propranolol and digitalis are contraindicated because of their bradycardic effects. Parenteral atropine or methylscopolamine bromide may be helpful in the short-term management of bradyarrhythmia but temporary or permanent pacing may be required.

**Sedatives, Tranquilizers, and Antidepressants**

In those patients whose angina is adversely affected by emotional stress, tension, depression, worry, hyperreactivity, and agitation, the judicial use of sedatives, tranquilizers, or antidepressants may be indicated. However, close patient-physician relationship with properly tailored education of the patient regarding the nature of his disease cannot be replaced by hastily written prescriptions for medications that temporarily alleviate concern, allay anxiety, or lift his mood. Concerted effort must be made by the physician to identify the role of emotional factors in the patient’s anginal pattern. Eliciting a history of precipitating events and contributory mental stresses can be obtained from the patient but
MEDICAL MANAGEMENT OF AP

quite often are more accurately assessed by consulting the spouse or reliable family members and friends.

It is not unusual to find an individual who can mow his lawn, trim hedges, or hoe his garden without angina, yet develops classical pain when talking about business problems, his adolescent's hostility, or while watching wrestling on television. Some will develop symptoms when they merely think about sexual intercourse. In such individuals catechol release results in an increased blood pressure and pulse sufficient to exceed the anginal threshold. In 23 healthy medical students studied by Hickam et al.57 the anxiety before an examination produced epinephrine-like increased oxygen consumption.

In those individuals whose emotional responses must be curbed to control their angina, mild tranquilizers such as diazepam, 2 or 5 mg three or four times a day, or phenobarbital, 15-30 mg three or four times a day, may suffice. Often a short-acting barbiturate such as sodium amytal, 30-60 mg every 4 hours, is adequate.

Nocturnal angina may not be the early manifestation of congestive heart failure but the product of an exciting or disturbing dream. Not infrequently patients relate dream content that has produced angina. Studies of these individuals during sleep have shown that rapid eye movements occur first followed by some elevation in the blood pressure and increase in the pulse rate with subsequent S-T depression in the ECG, as the patients awaken with angina. Barbiturates in this setting, especially in older individuals, have not been found to reduce significantly the incidence of dreaming. Diazepam, 5 or 10 mg, may be better tolerated by the older individual and may be tried in this situation.

Depression with or without agitation may produce angina. A trial of antidepressant drugs is warranted. Due caution should be taken when nortriptiline hydrochloride (Aventyl), thioridazine (Mellaril), and amitriptyline hydrochloride (Elavil) are used since they raise the heart rate and blood pressure with worsening of angina. In addition, thioridazine has been known to produce a variety of arrhythmias.

Exercise

In patients with angina a properly designed exercise program not only reduces the frequency and severity of attacks of ischemic discomfort,58-61 but also increases their work capacity and sense of well-being. Redwood6 has demonstrated that the exercise protocol for evaluation of any particular program of training must be carefully controlled. The training carried out in a properly equipped laboratory has been shown to be of significant benefit. Such exercise is usually accomplished on a bicycle ergometer with graded increase in work loads. A characteristic protocol involves two training periods a day for 5 days a week. If the bicycle ergometer is used, the work load is begun at 20 w and increased by 20 w every 3 min until angina occurs.58 Obviously this type of program is not practical for the mass of patients encountered daily in the physician's office, but often a satisfactory substitute can be found in a graduated walking program. The usual patient submitted to such an exercise schedule has mild-to-moderate stable angina. He may be receiving both propranolol and isosorbide dinitrate, as well as nitroglycerin, but ordinarily is not digitalized. Although some authors advise prophylactic isosorbide dinitrate or nitroglycerin, these are not usually necessary. If possible, walking should be done on level ground when the temperature is between 55 and 75°F.Extremes of temperature will often precipitate angina,6 thwarting the walker and occasionally permanently discouraging him. Beginning at a slow pace for 3-5 min during each exercise period, the patient should be instructed to increase both his speed and distance until he can walk a mile in 15-20 min after 4-6 weeks of training. There may be complaints that: (1) there are no sidewalks; (2) the ground is too uneven; or (3) it's too hilly. However, there are few who can't drive to a nearby shopping center, many of which have large air-conditioned malls permitting daily strolls under all weather conditions. If
the patient finds walking inconvenient, an exercycle or treadmill may be purchased or rented for home use. It is foolhardy to prescribe an exercise program for the patient who develops angina with slight exertion. Many patients are made miserable by such unwarranted and misdirected advice. Furthermore, it is probably unwise to recommend that the patient "walk through" angina since the risk of ventricular fibrillation is surely enhanced. The presence of ventricular premature beats following exercise is not uncommon in normal people as well as those with coronary heart disease. On the other hand, when they occur close to the T wave or in salvos and when short runs of ventricular tachycardia occur exercise should be prohibited.

The mechanism by which exercise improves angina is unknown. Studies have demonstrated that benefit is not correlated with increased coronary collaterals nor with significant change in cholesterol or blood pressure or cardiac output. However, physical working capacity is improved and seems to be related to increased stroke volume and decreased tension-time index for a given load. Training apparently enhances circulatory efficiency. For a given work load, total-body oxygen consumption has been shown to be reduced by 57%. There is a decrease in the product of the blood pressure and pulse rate. In some patients, there may be, in addition, an increase in oxygen delivery.

Because of the significant role of the emotional and psychological state of the patient with angina, his reassurance in realizing that he not only can exercise but also is able to reduce the frequency and severity of his ischemic episodes is of immeasurable benefit.

Anticoagulants

Anticoagulation offers no benefit in the management of stable angina. Some feel that it may be useful in the treatment of preinfarction angina, with the hope of forestalling infarction. It should be recalled that only approximately 50% of patients dying with transmural infarction have demonstrable thrombi in the coronary arteries and these may develop subsequent to onset of infarction. A trial of anticoagulant therapy is warranted when there is clinical suspicion of pulmonary embolism with or without documentation.

Radioactive Iodine

Myxedema induced by radioactive iodine decreases oxygen consumption and may sharply reduce the frequency of angina. This therapy is applicable to those with disabling angina not controlled by medical measures and who are not suitable candidates for saphenous vein bypass grafts. It should be confined to those willing to accept the side effects of hypothyroidism. These include weight gain, puffiness of face and abdomen, dry skin, sensitivity to cold, constipation, muscle aching, and some slowing of the physical and mental processes. The latter symptoms need not be marked if thyroid replacement therapy is titrated carefully. Unfortunately, the low level of metabolism required for benefit often limits replacement therapy. An increase of as little as ½ gr of thyroid extract or 5-10 μg of L-triiodothyronine may bring a return of angina to its previous frequency and severity. Many patients are able to carry on satisfactorily in their occupation after thyroid ablation. However, hypothyroidism is more acceptable to the older, retired person. It generally requires 2-3 months before benefit is obtained. One cannot use conventional studies such as 131I uptake to determine dosage since there is a lag between the development of symptoms and depression of function tests. Skill and judgment are required to find the optimal level of control of angina without side effects. Thyroiditis may develop within several weeks of 131I administration. At this time the release of increased amounts of thyroxin may aggravate angina. Prompt recognition of the syndrome with the institution of prednisone, 40-60 mg daily, and propranolol, 10-20 mg four times a day, for 1-2 weeks will minimize symptoms. Thyroiditis is more common when large doses are required.
because of low 131I uptake. The uptake by the gland can be increased by administration of 40–60 mg methimazole (Tapazole) daily for 1 week before uptake studies are repeated and the therapeutic dose calculated. An average dose of 7 mCi delivered to the gland will generally produce a satisfactory degree of hypothyroidism. Supplemental dosage after 3–4 months may be required on rare occasions.

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