Treatment of Intractable Angina Pectoris

By BRUCE LOGUE, M.D.

ANGINA PECTORIS responds within a few minutes of the administration of sublingual nitroglycerin in the overwhelming majority of instances. Many attacks are prevented by its prophylactic use prior to effort, emotional stress, meals, intercourse, and re-cumbency. One should be certain that the preparation is effective and has not lost its potency. This can readily be ascertained by the occurrence of the nitrite effect of fullness or throbbing sensation in the head. If this does not occur, a new supply should be obtained. Often after prolonged use of nitroglycerin, effectiveness may be enhanced by increasing the size of the dose from 1/200 gr. to 1/150 or 1/100 gr. At times it may be helpful to use nitroglycerin prophylactically every hour or 2 throughout the day. Nitroglycerin ointment, 1/8 to 1 inch spread on the skin without massage, may give a sustained nitrite effect for several hours. It is particularly helpful when applied at bedtime to reduce nocturnal attacks. It may be repeated at intervals of 4 hours.

Long-acting vasodilators have limited value. We prefer erythrol tetranitrate (Cardilate), 7.5 to 15 mg. buccally every 2 to 4 hours. Pentaerythritol tetranitrate (Peritrate) 10 to 20 mg. is widely used and is occasionally helpful. The dosage must be individually adjusted to secure full pharmacologic effect with minimum side effects such as headaches.

Weight reduction should be undertaken for the overweight patient. It is a common clinical observation that angina may improve after weight reduction but little may be expected from such a program for frequently recurring pain. A diet low in saturated fats is widely used for weight reduction with the hope that over a long term atherosclerosis may be lessened. There is as yet no evidence that diet or agents to lower the levels of serum cholesterol alter the natural history of atherosclerosis in man.

For those patients who develop angina during or after meals, prophylactic nitroglycerin and frequent small feedings with 5 to 6 meals daily may be indicated. Food should be easily digestible and foods that induce gaseous distention such as cabbage, onions, garlic, dried beans, should be eliminated. Constipation should be avoided by the use of appropriate laxatives. The close relation between distention of the stomach or intestines and development of angina is well known.

Tobacco should be avoided in patients having frequent angina. Occasionally there is a striking decrease in frequency of attacks when smoking is omitted; most individuals, however, notice no change in the pain pattern.

The initial onset of angina pectoris may be related to myocardial infarction. When there is an abrupt change in the pattern of angina pectoris, one should suspect myocardial infarction. This may be the result of further occlusion of a coronary artery or of an increase in the metabolic demands of the myocardium. The latter might be due to prolonged emotional tension, acute infection, blood loss, the onset of cardiac arrhythmia, pulmonary embolism, hypoglycemia, etc. Sharp curtailment of physical activity by a period of several weeks of modified bed rest may be followed, after the development of collateral circulation, by gradual improvement of angina. Since angina, when severe, is commonly

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experienced in the recumbent position, attacks may be lessened by sitting in a chair for most of the day and by having the head of the bed elevated at night.

The classic association between emotional tension and angina demands recognition. The use of sedatives may lessen the frequency of attacks. Heavy sedation over a period of days when emotional factors are dominant may bring improvement. The long-term administration of phenobarbital in the usual doses should be tried. There is rarely any superiority in the host of more expensive tranquilizing agents available on the market. It is probable that the beneficial effect of alcohol is through its effect on the central nervous system rather than any local effect on the heart. Whiskey may relieve mild distress or perhaps lessen attacks but is of little help with frequently recurring and prolonged attacks. The patient-physician relation is important, and strong reassurance and expert handling by the knowledgeable physician may produce benefit. Some patients with severe angina pectoris improve spontaneously, and every patient should be informed of this fact. False optimism may back-fire but the knowledge that his condition is not necessarily static and irrevocable may help sustain the weary patient. Reactive depression should be sought for and treated. In our opinion, the early successes with the amine oxidase inhibitor drugs were probably due to their effect on the mental depression that so often darkens the picture in severe angina pectoris. These drugs do not alter the electrocardiogram or the underlying coronary disease, and their use is associated with side effects that include postural hypotension. They should not be used routinely in the treatment of angina but reserved for trial in selected patients with refractory angina.2

Arrhythmias including frequent premature beats may aggravate angina. Control of arrhythmias occasionally is beneficial. Frequent premature beats may at times be associated with myocardial insufficiency otherwise unrecognized, and digitalization may dissipate the arrhythmia and lessen the attacks. In the digitalized patient, the occurrence of coupling, paroxysmal atrial tachycardia with atrioventricular block, interference dissociation, ventricular tachycardia, atrial flutter or fibrillation, demands temporary omission of the drug and determination of the need for potassium replacement. Cellular depletion may occur despite normal serum values for potassium. Persistent arrhythmias in the euthyroid patient may respond to the induction of hypothyroidism by I131. Kurland et al.3 have reported instances of recurrent arrhythmias in euthyroid patients associated with rapid turnover of thyroxine in the red cells that respond to large doses of inorganic iodine. Quinidine on occasion may lessen angina through prevention of arrhythmia.

Where nocturnal angina occurs, a trial period of digitalization is advisable even though usual symptoms and signs of left ventricular failure may be lacking. Elevation of the pulmonary artery and pulmonary capillary pressures may occur during angina in patients with hearts of normal size.4 Often times digitalization is followed by lessening of the attacks. Chlorothiazide, 500 mg, daily, combined with accessory potassium salts may bring benefit through lessening interstitial pulmonary congestion and perhaps its effect in lowering the blood volume. It is not widely appreciated that mild left ventricular failure may occur without diastolic gallop rhythm, rales, or paroxysmal nocturnal dyspnea and in the presence of a heart of clinically normal size.

Rauwolfia derivatives are generally ineffective but in the occasional patient with anxiety and sinus tachycardia may be beneficial. The frequency of side effects, particularly the development of mental depression (up to 20 per cent of cases), limits their use. Benefit may result from a combination of their psychic effect combined with slowing of the pulse rate. Their use should be undertaken only on a trial basis, with their common side effects well in mind and with the caution that mental depression may appear only after many months of therapy.

When significant hypertension is present,
anginal attacks may lessen with lowering of the blood pressure. Caution should be exercised, since bouts of prolonged pain may be induced if the blood pressure drops too low. In general, one depends on chlorothiazide derivatives with or without a Rauwolfia preparation and reluctantly adds one of the ganglion-blocking agents, since they are dangerous. Apresoline should be used cautiously, and only in doses of less than 100 mg. per day because of the frequency of tachycardia and pain with larger doses. The benefits from lowered blood pressure are more marked in the management of congestive heart failure than in the treatment of angina pectoris. The place of monamine oxidase inhibitors and the newer sympatholytic drugs in the management of hypertension is still to be determined.

Anginal attacks of 5 to 15 minutes in duration may be managed with some degree of success; however, the common occurrence of prolonged bouts of pain requiring opiates is the greatest problem in the field of coronary disease. Such attacks occur independently of usual precipitating causes and may not be accompanied by evidence of muscle necrosis such as electrocardiographic changes, fever, elevated sedimentation rate, and elevations of serum enzymes. Subendocardial infarction of a patchy nature may occur in electrically silent areas. Such attacks may be repeated over a period of many months and may eventuate in drug addiction. The precipitating factor remains unknown at this time, but the possible effects of release of increased amounts of catechol amines are under study. Only rarely does collateral circulation develop sufficiently to bring spontaneous improvement. One often wishes for transmural infarction, with the hope that alleviation will follow destruction of the pain-producing focus. Prinzmetal et al. have reported that Arlidin is of value, presumably by reducing spasm of the coronary arteries; but we have been unable to confirm its value.

When angina is frequent and disabling, and when repeated bouts of prolonged pain have occurred and the condition has not improved over a period of 3 months, the production of hypothyroidism by the use of radioactive iodine offers the best hope of benefit. It requires 2 to 3 months before an optimal effect is obtained and occasionally even longer. I$^{131}$ may be given in a single dose or in repeated doses. Thyroiditis may at times be produced, but responds to a brief period of steroid therapy. The side effects of myxedema may be troublesome. Paresthesias and pains in the extremities, abdominal swelling, puffiness of the face, drowsiness, anemia, and weight gain are the most distressing symptoms. At the onset of symptoms a small dose of thyroid such as 1/10 to 1/4 gr. is instituted. Increments are made at intervals of 7 to 10 days, depending upon tolerance until a level is reached at which pain and side effects are minimal. About two-thirds of patients receive benefit of varying degree, and one-third are unaffected. Blumgart and associates reported that 43 per cent of 84 patients obtained excellent results, 24 per cent had worthwhile results, and 33 per cent had no benefit. In a previous combined study from a number of clinics about 75 per cent of 1,070 patients with angina showed improvement.

Patients with thyrotoxicosis may have dramatic improvement of angina when normal metabolism is restored. Study of serum protein-bound iodine and I$^{131}$ uptake is valuable in the detection of masked thyrotoxicosis. Furthermore, the use of scanning technics in the presence of an adenoma may at the times reveal toxicity even when other studies are normal. The administration of I$^{131}$ in appropriate doses or thionauracil derivatives may bring lasting benefit.

Angina pectoris secondary to congenital or acquired aortic stenosis may be alleviated following aortic commissurotomy; the trend at this time is surgical correction using open-heart technics with or without coronary artery perfusion. The surgery of aortic stenosis when it has become symptomatic still leaves much to be desired. When angina is secondary to aortic insufficiency, the patient is under 50 years of age, and congestive heart failure can be controlled, surgery with the insertion of a Hufnagel valve may be bene-
ficial. In Hufnagel's hands the risk approaches 15 per cent. 8

Syphilitic aortitis may produce angina pectoris either by swelling and narrowing of the coronary ostia or by development of free aortic insufficiency. Antisyphilitic therapy with penicillin does not alter the disease at this stage but should be given in the customary schedule of 600,000 units of procaine penicillin daily for 10 days.

Anticoagulants are widely employed in the long-term treatment of coronary disease, but they do not alter the course of angina pectoris. Many times they are used in the hope that infarction might be prevented or forestalled in the face of increasing frequency of angina. In one series 6 per cent of 96 treated patients died, whereas 19 per cent of 32 who stopped anticoagulants died, and another 4 of 10 controls with impending infarction died. 9 The data are still inconclusive. Anticoagulants should be used in any instance in which there is suspicion of pulmonary embolism. Refractory angina often improves when thromboembolism is controlled. Some have recommended intermittent heparin in the management of angina but a beneficial effect has not been corroborated by other studies.

As with all therapy, medical or surgical, placebo effects make evaluation of any drug or surgical procedure difficult. Ligation of the internal mammary artery is an example with claims of benefit in about 60 per cent of patients; but double-blind studies did not bear out the previous uncontrolled experience. 10 The revascularization procedure of Beck and Leichninger, 11 consisting of abrasion of the epicardium by a burr, instillation of powdered silicate, and subtotal ligation of the coronary sinus, has few adherents. The Vineberg procedure 12 of implantation of the internal mammary artery in the myocardium is of debatable value.

Harken et al. 13 claimed that improvement of pain follows the application of phenol on the epicardium, presumably through destruction of pain fibers, but we have observed no substantial benefit in a small group of cases. Thromboendarterectomy of the coronary arteries is still in the experimental phase; 6 of 11 severely ill patients died of the procedure. 14 Grafting of segments of a vessel has been impractical because of invariable thrombosis, and the problems of direct relief of coronary occlusion are numerous. 15 Sympathectomy and rhizotomy for relief of pain may require bilateral operations, and rhizotomy entails laminectomy. The risk of anesthesia in patients with refractory angina is great. Painful causalgia is common following sympathetic nerve surgery and may be more distressing than pain of coronary disease over the period of months of its duration.

Diabetes is a common accompaniment of coronary disease. When mild it may be well controlled by diet or oral or hypoglycemic agents such as Orinase, 0.5 to 1.0 Gm. 3 to 4 times daily. There is no evidence that rigid control of diabetes alters the course of coronary disease. Attempts to control glycosuria and hyperglycemia strictly with medication are fraught with dangers of hypoglycemia. Such attacks may induce angina or myocardial infarction. The use of NPH or globin insulin in appropriate amounts for more severe diabetes is indicated. When diabetic acidosis occurs, epigastric pain simulating coronary pain may occur and the problem of differentiation are made more difficult by the changes in the ST-T interval due to potassium shifts. These include prolongation of Q-U interval, S-T depression, and T-wave inversion. Since myocardial infarction may occur without the complaint of pain in the stuporous patient and since infarction may induce diabetic acidosis, it is well routinely to check the electrocardiogram when there has been an otherwise unexplained abrupt change in the diabetic state. For the patient who has been receiving protamine zinc insulin and develops refractory angina pectoris or myocardial infarction, it is desirable to change to regular or Lente insulin until the condition is stabilized.

Treatment of anemia may change refractory angina to one that is readily amenable. The increase in oxygen-carrying capacity of hemoglobin may be obtained by appropriate
therapy such as iron or vitamin B₁₂. Occasionally, when blood loss has occurred, rapid replacement may be needed with transfusion of red cells to avoid pulmonary edema.

Angina of brief duration related to usual precipitating causes may become refractory with the onset of infection and the consequent increase in metabolic demands. Prompt recognition and appropriate treatment of pulmonary infection, urinary tract infection, and gallbladder disease may be beneficial. The relief of overlooked urinary tract obstruction such as that due to prostatic disease may lessen anginal attacks. The common occurrence of associated gallbladder disease poses a problem. Cholecystectomy with prevention of recurrent infections may lessen bouts of pain; it is to be emphasized, however, that such surgery has no direct effect on the coronary circulation. Furthermore, in the presence of angina decubitus the risk of general anesthesia and any type of major surgery approaches 50 per cent. Elective surgery in the patient with a history of angina pectoris on effort, on the other hand, carries a risk on the order of 5 per cent.

**Summario in Interlingua**

Es revistate le currentemente disponibile medios in le trattamento de angina de pector. Le revista include le medios medical e etiam chirurgie.

**References**

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