The Modern Treatment of Coronary Thrombosis with Myocardial Infarction

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Coronary thrombosis with myocardial infarction is an extremely serious disease to the individual and to the nation. It kills at least 200,000 persons a year and cripples unknown numbers. The modern treatment is herein outlined. Established therapy is reviewed and evaluated. The use and technics for the control of anticoagulant therapy are discussed.

CORONARY thrombosis kills at least 200,000 people a year in the United States, and this figure will increase inexorably as the average age of our population continues to increase. It occurs in all ages but is predominantly encountered in persons over the age of 40. In general, it may be said that coronary thrombosis occurs at an average age which is approximately 6 years younger in men than in women. More men than women suffer and die from it in every age group under the age of 80. It has been encountered in infants as young as 3 months. One of the most unfortunate characteristics of this disease is that it strikes down many persons at the height of their productive years and activity, at times when they have the greatest responsibilities toward their communities and their families. It is a problem of increasing importance in national and community life.

The underlying process responsible for this condition is almost invariably arteriosclerosis, frequently a special type of intimal atherosclerosis. There are rare instances in which narrowing of a coronary artery has occurred either as a result of some other disease process or as a congenital anomaly, or in which myocardial infarction has occurred as a result of overstrain without adequate blood supply to an area of the myocardium. But such situations are so infrequent that for purposes of this discussion they may be ignored. The usual sequence is that arteriosclerotic plaques narrow the lumen of the coronary artery to such a degree that a thrombosis eventually occurs. This in turn produces the sudden occlusion which results in marked ischemia of the muscle, with subsequent necrosis and a profound effect on the efficiency of the heart muscle. This may occur as a result of occlusion of a small branch of the coronary tree, in which case recovery is very likely to occur. On the other hand, it may be a very extensive process involving a large area of the myocardium (or a key area of the myocardium); in which case a very serious illness and even death may ensue. Death, however, may not be the result of the myocardial infarction per se. Complications and death are frequently the result of secondary thromboembolic phenomena rather than of the
original insult. These phenomena may include:
(1) Subsequent extension of the original thrombus to block off additional arteries or branches of the artery which was primarily involved.
(2) Involvement of some other branch of the coronary tree which further embarrasses the heart action.
(3) The development of mural thrombi, attached to the endocardium at the location of the original infarction, which are capable of releasing emboli to various parts of the body, either from the right side or the left side of the heart depending upon the location of the mural thrombus.
(4) The development of thromboses elsewhere in the body, particularly in the veins of the legs, which are in turn capable of producing fatal and nonfatal emboli.

Treatment, Other Than with Anticoagulants
Curiously enough, until very recently, therapy has been directed for the most part in such a manner as to encourage the tendency to clot formation. Rest has been emphasized and has usually been accompanied by heavy sedation, in itself conducive to slowing of the blood flow and the development of thrombosis. While many forms of therapy have been recommended in the past, those which have stood the test of time and are still considered to be of value are as follows:

1. Rest. There is no question but that rest is essential in the treatment of this condition. A myocardial infarction goes through stages during which the initial anoxemia results in the development of necrosis. Thereafter it takes a considerable period of time for fibrosis and scarrring, accompanied by development of a collateral circulation, to restore the muscle to anything like its former strength. In most instances it appears that necrosis is at its maximum about 10 days after the original infarction, and thereafter recovery takes place very slowly and depends to a considerable degree on the size and location of the infarction. It seems quite illogical therefore to place any strain on the heart muscle above minimal activity during the first three or, better, four weeks. If the infarction is large, or if there is evidence of cardiac embarrassment, this period may well be extended to from six to eight weeks. During this time the patient should be at bed rest. There is one exception to this ruling. There are many patients who have great difficulty in using the bed pan. It is the author's belief, and that of many others, that the use of a commode by the bedside, with the assistance of nurses and orderlies, may require much less effort on the part of the patient than the use of a bed pan. A commode is therefore recommended as soon as the patient appears to be able to make the short move from the bed which is required. Most patients are extremely grateful for this accommodation. After a period from three to eight weeks, depending on the condition of the patient and the reaction of his pulse to the initiation of activity, he should begin to sit up in bed and exercise, using the arms and legs quietly at first. Finally, he is moved from the bed to a chair and gradually begins to assume increasing activity. The pulse is watched very carefully during this period. A pulse rate exceeding 100 means that exercise should be discontinued for the time being, to be started again after a period of rest. Dyspnea is also evidence that the patient should not force activity without further rest.

2. Sedation. Patients with coronary thrombosis usually suffer from marked apprehension and extreme nervousness, both at the time of their attack and subsequent to it. This cannot but aggravate the situation since the release of adrenaline and nervous stimuli tend to increase vasoconstriction. The sedatives of choice still remain morphine sulfate given in doses of 0.015 grams, the precise amount depending on the degree of pain suffered by the patient; Panto-pon, 0.02 gram, appears to produce less nausea than does morphine in many people. These drugs are preferably given by hypodermic, because nausea is frequently present and an oral narcotic may not be adequately absorbed. Papaverine, 0.1 grams given intravenously, may also be administered for severe pain but sometimes produce disagreeable side reactions. As the pain decreases, other forms of sedation, such as Demerol or the barbiturate compounds, may be used as indicated. It is customary to use sedation and narcosis freely
during the first several days if the pain warrants it and thereafter to give only sufficient so that the patient is prevented from becoming apprehensive as a result of sensations of compression or pain.

3. Alcohol. Whiskey, or alcohol in other forms, may be used freely. Its benefits may be due to its vasodilating effects or to its sedative and relaxing action, but it frequently proves as effective as the opiates. A few patients become excited rather than relaxed by alcohol, and under such circumstances it is of course contraindicated. Alcohol so used should be regarded as a medication and the patient’s tolerance, and the possible development of addiction to it, must be considered.

4. Oxygen. Oxygen is being used with increasing frequency in the treatment of myocardial infarction. It is especially indicated if there is evidence of appreciable pain, dyspnea, or cyanosis. It is important to watch the nail beds of a patient as well as his lips and face for evidence of cyanosis. One should not reserve oxygen for an emergency, or as a lifesaving procedure, but should give it freely so that the myocardium can be saved any unnecessary labor during the time when it is being repaired. When it is to be administered, the patient may be kept in an oxygen tent, or a mask may be used. If the dyspnea or cyanosis are extreme, concentrations up to 100 per cent should be used without hesitation. In very mild cases, its use may never be necessary.

5. Infusion and Transfusions. It is not uncommon for patients with coronary thrombosis and myocardial infarction to become dehydrated, either because they are not given sufficient fluids by mouth or because they are nauseated at the time of their admission. Furthermore, prolonged sedation and narcosis decrease the natural intake of fluid. If dehydration or shock are pronounced, 0.1 N saline infusions with 5 to 10 per cent glucose are indicated in quantities of 500 cc. Infusions of this nature however should be given very slowly in order to avoid imposing an additional strain upon the heart.

Gold, Prinzmetal, and others have shown that transfusions of plasma or whole blood are useful to combat shock in the care of these patients. Prinzmetal demonstrated in animals that, if the heart muscle is weak and herniating as a result of insufficient blood, the addition of fresh blood or plasma may reduce the tendency towards herniation within a very short time. The restoration of blood pressure and general tone which is observed in patients suggests that a not dissimilar procedure may take place in human beings, although this cannot be regarded as definitely established at present. When transfusions are given the amount should probably be not more than 250 to 300 cc. This procedure may be repeated in four hours. Whenever patients are receiving fluids intravenously they must be under continuous observation.

6. Other Drugs. In general, it is no longer considered good practice to give digitalis in the treatment of coronary thrombosis with myocardial infarction unless there is pronounced evidence of cardiac failure and the status appears to be deteriorating. The question has been debated widely but at present this position is regarded as justified. If digitalis is to be administered, it may be given in the form of extract of digitalis, powdered digitalis, digi-toxin, or other glucosides having a similar action. The dosage should be sufficient to produce satisfactory digitalization but it is our impression that it is less hazardous to digitalize with moderate rapidity than by using a single massive dose.

Quinidine should be used in case of paroxysmal ventricular tachycardia. Some cardiologists also use it in the presence of evidence of cardiac irritability such as numerous premature beats. Under these circumstances, the dosage is 0.3 gram three to five times a day. In extreme conditions, this dosage may be doubled.

While aminophylline has been used the evidence that it has altered the mortality in any significant fashion is, in our opinion, inconclusive. If it is desired to administer it, with the hope that it will serve as a coronary vasodilator or for any other reason, it should be given in dosages of 0.25 gram intravenously every four to six hours. It should be administered slowly, preferably as a drip infusion in
100 cc. of a solution of sodium chloride or glucose in distilled water. There have been some fatalities resulting from the rapid injection of aminophylline in patients who were doubtless sensitive to the drug.

There have also been advocates of the use of atropine, 1 mg. every four hours, in the treatment of coronary thrombosis. Here, also, there is inconclusive evidence of a demonstrable beneficial effect. A definite indication for its use exists, however, when carotid sinus hypersensitivity is present.

The Use of Anticoagulants

1. Experimental and Clinical Results. As early as 1938, Solandt and Best reported animal experiments in which coronary thrombosis was produced by isolating the coronary artery and injecting sodium ricinoleate into its lumen. The injected material was kept in contact with the intima for 5 minutes and the clamps on the vessel were then released. Thrombosis developed in almost every case in which heparin was not used whereas, in a corresponding study in which heparin was used, it was almost never observed. Solandt, Nassim, and Best continued their studies by producing intracardiac mural thrombi and, in turn, preventing their formation by the administration of heparin. In these latter experiments, a technic was evolved by which large mural thrombi could be regularly reproduced in the lumen of the left ventricle: its endocardium was injured by injecting sodium ricinoleate, and the myocardium was damaged by ligating the anterior descending branch of the left coronary artery. When heparin was not used, there was rapid formation of a thrombus, but none was seen in those experiments in which heparin was given before the injury was produced. The results of these studies left no doubt that under certain experimental conditions the effect of heparin in preventing thrombosis could be readily demonstrated.

Following these studies, sporadic efforts were made to use heparin in the treatment of clinical coronary thrombosis but as far as is known no large, well-controlled series were conducted because of the difficulties of continued heparinization. The question of increasing hemorrhage in the intima was also raised, although more as a theoretic than a proved risk. Following the early clinical use of dicumarol, it was used in a few patients with coronary thrombosis and myocardial infarction. The author began the study of dicumarol in the treatment of coronary thrombosis during May, 1942. After three and one-half years of experience involving 80 patients, the following conclusions seemed warranted. The use of dicumarol had not aggravated the condition in any patient. It appeared physiologically sound to give anticoagulant therapy when (1) there was a tendency for propagation of the original thrombus, (2) multiple thrombi tended to form in the coronary arteries or elsewhere, and (3) one or more emboli had occurred. The thromboembolic processes appeared to have been interrupted. There was no evidence that thrombi, once formed, had been dissolved. The progression of established infarctions did not appear to be interrupted. The rate and rhythm of the heart was not directly affected. These results were reported in December, 1945. In January, 1946, Nichol and Page, who had been studying this problem during the same period as the author, published their experience with dicumarol in the treatment of acute coronary thrombosis. They reported results in 50 attacks occurring in 44 unselected patients observed between June, 1943 and October, 1945. Their results appeared to be favorable. In February of 1946, Peters, Guyther, and Brambel reported their experience with acute coronary thrombosis, and they also believed their results to be favorable. Following these early papers a series of other papers have appeared confirming these observations.

These series, however, were not sufficiently large or well-controlled to warrant detailed and final conclusions. The Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction was therefore established by the American Heart Association. This committee, on which the author served as chairman, was composed of teams in 16 leading hospitals in the United States; each team was headed by an outstanding cardiologist and included statisticians, chemists, and various consultants. A
total of 1,031 cases have been studied in detail and submitted to careful statistical analysis. Of these, 442 cases received excellent conventional treatment for coronary thrombosis with myocardial infarction, while 589 received the same treatment plus the addition of the anticoagulants heparin or dicumarol, or both. The majority of this latter group received dicumarol alone. The composition of the sample as to age, sex, and previous history was remarkably similar in the two groups.

Of those patients not receiving anticoagulant therapy, referred to hereafter as the control group, 23.4 per cent died. Of those who received anticoagulant therapy, referred to hereafter as the treated group, 16.0 per cent died. There was therefore a saving of life of approximately one-third in the group receiving anticoagulant therapy. This does not represent the full potential benefits of treatment, since careful analysis has shown that many of the patients who received anticoagulants did not receive what is now regarded as ideal anticoagulant therapy. When the cases were analyzed on the basis of deaths per week, it became clear that the control group showed a greater incidence of death each week up to and including the fourth. Thereafter, the deaths were so few that differences between the two were not statistically significant. Analyzed according to age, the control group showed a higher death rate than did the treated group in each series from those under 50 to those 70 or over. The difference was more pronounced in the older age groups and in those with one or more thromboembolic complications.

When the percentage of cases developing thromboembolic complications was examined, the following findings were noted. In the control group, 26.0 per cent developed one or more thromboembolic complications as compared with 10.9 per cent in the treated group. When the series was evaluated from the viewpoint of the average number of thromboembolic complications per hundred cases, it was found that there were 41.8 thromboembolic complications per hundred cases in the control group as against only 13.1 per hundred cases in the treated group. The number of thromboembolic complications of various types and locations per hundred cases in the control and treated groups showed a highly significant difference. Secondary myocardial extensions occurred in 9.7 per cent of the control group but only in 3.2 per cent of the treated group. New infarcts occurred in 6.1 per cent in the control as contrasted with 1.9 per cent in the treated group. Pulmonary emboli were encountered in 11.6 per cent in the controls against 4.8 per cent in the treated group. Cerebral emboli were diagnosed in 4.9 per cent of the controls but only in 0.7 per cent of the treated group. Peripheral emboli occurred in 2.7 per cent of the controls as compared with 0.5 per cent of the treated group. Venous thrombosis developed in 6.8 per cent of the control group and in 2.0 per cent of the treated group. The review of these figures, which will appear in the final report of the Committee on Anticoagulants, demonstrates conclusively that the administration of anticoagulants produces a marked reduction in death rate from coronary thrombosis and has an even greater effect in preventing thromboembolic complications. These complications cannot be regarded lightly since they leave some patients hopeless hemiplegics, others with the loss of one or more limbs by amputation, or with similarly serious disabilities.

In the light of these figures and of an extensive experience with the use of anticoagulants, it is difficult to avoid the conclusion that anticoagulants should be administered to every patient suffering from an acute coronary thrombosis unless the definite contraindications which will be subsequently mentioned are present. On the other hand, as is widely recognized, anticoagulant drugs are not without their hazards. They, like most other forms of medical treatment, require skill and knowledge of the technic for their use. The incidence of bleeding which occurred per hundred cases in the series under discussion should be considered. In the control group, episodes of bleeding occurred 5.9 times in each hundred cases. This incidence was a surprise to some physicians who had assumed that bleeding was an uncommon occurrence in coronary thrombosis. The episodes included hematuria, epistaxis, and numerous other minor evidences of bleeding. In the treated group, there were a total of 15.3 episodes per hundred
cases. Of these 15.3, 2.7 occurred before the anticoagulants had been administered, and 3.4 were believed to be due to causes other than anticoagulant administration; 9.2 were believed to be due to or aggravated by anticoagulant therapy. Hematuria was the most common example and should be watched for carefully in all cases receiving anticoagulant therapy. It occurred in 7 episodes per hundred cases of which 5.3 were microscopic and 1.7 gross. Hemoptysis occurred in 1.8 episodes per hundred cases in the control group and 3.2 in the treated group. Epistaxis occurred less than 0.2 times per hundred cases in the controls but 1.5 times per hundred cases in the treated group; other bleeding occurred 0.2 times per hundred in the control group and 1.0 in the treated group. There is, then, no question but that the incidence of bleeding is higher in the cases receiving anticoagulant therapy.

In the entire series, there were only 3 or possibly 4 patients who might be considered to have died as a result of bleeding associated with the use of anticoagulants. On the other hand, it would appear that 46 lives were saved. There is, therefore, a calculated risk in return for which the dividends, in terms of lifesaving and reduced disability, are high.

2. Technic of Administration. The following technic of administration is recommended in the case of heparin: it should be injected intravenously in doses of 50 to 75 mg. every four hours until the action of dicumarol is evident in terms of an effect upon prothrombin time. Administration should be controlled by use of the Lee-White test tube method for the determination of clotting time. No additional heparin should be given if the clotting time exceeds 20 minutes when measured prior to the next injection; it may be measured again in four to eight hours to determine if it has decreased to less than 20 minutes. Recently a heparin preparation in a retarding menstruum (Depo-Heparin) has been made available for intramuscular use. The author gives 300 mg. in the first dose and 200 mg. every 12 hours thereafter, always providing that the clotting time is less than 20 minutes before the next dose is administered.

Dicumarol should be administered as follows: Following a prothrombin determination which is within normal limits (12-18 seconds depending on the exact technic used; Quick, or Link-Shapiro modification of the Quick technic), an initial dose of 300 mg. of dicumarol should be given. Each morning thereafter a prothrombin test should be performed. If the control time is 15 seconds, as it is in the author's laboratory, the following schedule can be used. Until the prothrombin time reaches 30 seconds, from 100 mg. to 200 mg. of dicumarol should be given after the prothrombin time for that day is known. When the level of 30 seconds is reached, the dosage should be reduced to 100 or 50 mg. daily until a level of 35 seconds is obtained. After this level is reached, no further dicumarol should be given until the level descends to approximately 30 seconds or lower. The purpose of this procedure is to keep the prothrombin time between 25 and 40 seconds if possible, on the basis of a control prothrombin time of approximately 15 seconds. The ideal prothrombin time during adequate therapy is between two and two and one-half times the control if this be below 20 seconds. If the prothrombin time reaches 50 seconds, the patient should be observed carefully for evidence of bleeding. If this occurs, or if the prothrombin time reaches 60 seconds, a dose of vitamin K (Hykinone, Synkovite, or menadione bisulfite) of 64 to 72 mg. should be given intravenously, and this should be followed by a similar dose in another four hours. On the following day, the prothrombin time should again be determined. It will usually be lower. If this is not the case, further dosages of vitamin K may be given. In the event of bleeding of any marked degree, or if the prothrombin time reaches 100 seconds or more, this treatment should be supplemented by transfusions of fresh whole blood. Banked blood of more than 1 or 2 day's age is definitely less satisfactory. Using the technic outlined above, we have very rarely had need for transfusions during the last several years nor, since 1941 when the author began the use of anticoagulants (and this experience has involved their use in several thou-

* This formula was first suggested by E. Sterling Nichol.
sand cases), has death from their use occurred on his service.

This experience is cited to indicate that if anticoagulant therapy is employed with proper care the risks are not excessive. They have been grossly exaggerated as a result of poorly controlled therapy, or by the use of these drugs in the face of definite contraindications which may or may not have been recognized.

3. Contraindications. Under the following circumstances, anticoagulants must be used cautiously or not at all:

a. Prothrombin deficiency (hypoprothrombinemia or potential prothrombin deficiency).
(1) Vitamin K deficiency.
(2) Severe hepatic disease.
b. Vitamin C deficiency.
c. Renal insufficiency.
d. Blood dyscrasias with impairment of the mechanism of hemostasis.
e. Interruptions of the continuity of the vascular system; for example, by surgical operation:
(1) Recent operations on the brain or spinal cord.
(2) Recent surgical operations leaving raw surfaces.
(3) Postoperative tube drainage of wounds of viscera.
(4) Operations performed in the presence of obstructive jaundice, external biliary fistula, or severe liver damage.
f. Late pregnancy.
g. Subacute bacterial endocarditis.

Summary

Coronary thrombosis with myocardial infarction is one of the most serious diseases which is frequent in the population over the age of 40. Until recently, treatment consisted of measures including rest and sedation which have the unfortunate effect of encouraging thrombosis. While these and other measures outlined in this paper have aided in the comfort of the patients and are believed to have influenced the course of the disease favorably, their usefulness has never been conclusively established. Clinical experience has nevertheless led to their acceptance, and they are recommended in the light of our present knowledge.

The anticoagulants, dicumarol and heparin, were first used experimentally and, thereafter, clinical experience seemed to justify their more general acceptance in practice. In the case of these drugs, however, another step of importance was taken. The Committee on the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction studied 1,031 cases under a statistically valid program. Approximately one-half of these received the best available type of treatment used prior to anticoagulant therapy; the other half received anticoagulant therapy in addition. The results were strongly in favor of the use of anticoagulants in the sense that both the death rate and the incidence of complications were decreased. A brief summary of these findings has been presented above. On the basis of this study the more general use of anticoagulants in the treatment of this serious disease is recommended. It is also suggested that other drugs be subjected to similarly controlled studies before they are accepted by the medical profession as being of established value.

Addendum

Since this paper was prepared, Tromexan, another coumarin, has become available. It acts more quickly than dicumarol (18 to 24 hours) and does not have so lasting an effect. The dosage is five or six times that required for dicumarol, and administration of the drug must be controlled by the prothrombin time determination. Further reports evaluating Tromexan will appear within the next few months.

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