Editorial:
Thrombolysis in Acute Myocardial Infarction: Treatment of the Underlying Coronary Artery Disease

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While our understanding of the pathophysiologic processes that underlie acute evolving myocardial infarction has exploded over the last decade, true progress in the effective treatment of evolving infarction has been disappointing. Although early interventions in animal models have decreased myocardial ischemic injury and, at times, limited infarct size, no intervention has proved sufficiently effective to warrant routine clinical use. Necrosis of normothermic myocardium is inversely time-dependent according to blood flow below a level critical to myocardial cellular survival — the wave of necrosis passing outward from the subendocardial to the subepicardial myocardium. The majority of interventions have sought to decrease factors directly related to myocardial oxygen consumption; current interventions, including direct surgical myocardial revascularization and nonsurgical revascularization, are directed at the more fundamental issue of restoration of the profound decrease of coronary blood flow to the region at risk that precipitated acute symptoms.

Thrombosis in Acute Evolving Myocardial Infarction

It is now generally accepted that an acute soft thrombus on preexisting atherosclerotic coronary artery disease is present in a high proportion of patients with evolving transmural myocardial infarction. The initiating causes and exact sequence of events are not germane to the present editorial. DeWood and colleagues demonstrated that 87% of patients studied by angiography within 4 hours after the onset of symptoms had a completely occluding thrombus; the proportion fell to 65% in patients studied 12–24 hours after the onset of symptoms. Subsequently, several groups in West Germany and in the United States have confirmed that such thrombi are present in most patients studied within the first few hours after the onset of symptoms of evolving myocardial infarction. Mechanical interventions or intracoronary infusions of streptokinase or thrombolysin result in dissolution of such thrombi and reestablishment of blood flow with few immediate serious complications. However, in almost all patients, myocardial necrosis of differing magnitudes has been demonstrated. Other aspects of thrombolysis have generated considerable controversy.

Streptokinase dose and its optimal administration have yet to be defined, and the extent of restoration of ventricular function is uncertain, although there is evidence of preservation of at-risk myocardium in many patients. Likewise, further studies are needed on the relationship of the extent of necrosis to the interval from the initiation of symptoms to effective thrombolysis and on factors or interventions that may modify this interval. Spontaneous or mechanically induced clot dissolution in acute ischemic syndromes, the role of collateral coronary circulation and the potential adjunctive or alternative effects of i.v. streptokinase, with or without nifedipine and nitroglycerin, are incompletely understood, as are the late complications.

Residual Coronary Artery Disease

The study of Meyer and colleagues addresses another relevant issue: the management of residual coronary disease in the patient who has undergone successful thrombolysis. While this study presents data from relatively few patients, it provides direction for future evaluation of the efficacy of thrombolysis in the management of one of the important clinical syndromes of ischemic heart disease: acute myocardial infarction and its sequelae. A 60–95% occlusive lesion of the vessels subserving the territory at risk is present at the point of thrombus in virtually all patients. Management of the patient after thrombolysis to date has included no definitive treatment directed to the vascular disease per se, i.e., surgical myocardial revascularization or percutaneous transluminal coronary angioplasty (PTCA). Anticoagulant agents and vasodilators may be important, but their role has not been systematically studied.

Meyer et al. report a retrospective review and short-term follow-up in which the results of PTCA in 21 patients who had been treated successfully with intracoronary streptokinase were compared with a second group of 18 patients who were angiographic "candidates" for PTCA but had been treated by thrombolysis alone before the time at which suitable patients were considered for PTCA. Of the candidates, four suffered from a reinfarction during the hospital course. Three of 18 patients died within 2–8 months and four underwent bypass surgery or PTCA. No patient was in functional class I. Eight of these patients (44%) were in class II on the basis of thrombolysis alone. While this experience may appear unfavorable, it is similar to that of patients surviving a relatively severe myocardial infarct.

In contrast, of the 21 patients in whom PTCA was attempted and who were followed for 4–6 months, one died because of diffuse epicardial bleeding. Four patients in whom angioplasty was unsuccessful underwent coronary artery bypass surgery, with two reinfarctions with one reocclusion in the follow-up period. Seventeen patients (80%) were in functional class I or

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II. Advancement of the balloon dilatation catheter to the stenotic area was "much easier" than in patients with stable or unstable angina. This may be related to the highly variable degrees of stenosis associated with thrombotic myocardial occlusion in contrast to the severe (> 90%) stenosis characteristic of the recurrent anginal syndromes. Combination of the PTCA patients and of the candidates indicates that 40% of the patients in the study of Meyer et al. were considered objectively to be suitable for PTCA. Rutsch et al. reported subtotal stenosis (> 90%) in only 27% of 204 patients, suggesting that the majority of patients who have undergone thrombolyis might be appropriate candidates for PTCA as well.

Mathey et al. reported 48 patients subjected to surgical revascularization after successful thrombolysis in evolving myocardial infarction and followed 3-9 months. Thirty-four of these patients were operated on within 10 days of thrombolyis therapy; the remaining 14 were operated after 10 days. There were two late deaths, two nonfatal infarcts, two patients with mild angina pectoris and one patient with heart failure as late complications. Forty-one patients (85%) were asymptomatic. The indications for myocardial revascularization were recurrent angina pectoris in 13 cases, severe stenosis in the "infarct vessel" in 19, severe multivessel coronary disease in 14 and spasm in two.

Implications for Optimal Therapy

The early application of thrombolytic therapy in evolving myocardial infarction frequently results in a benign hospital course. However, one cannot conclude that this intervention alone results in a satisfactory outcome. Inferior myocardial infarction, particularly when due to isolated disease of the right coronary artery, is not accompanied by serious depression of ventricular function and has a favorable prognosis. Yet, more than half of the thrombolyis cases reported to date relate to the "successful" management of this relatively benign manifestation of ischemic heart disease. Thus, although this intervention must be regarded as one of the most exciting recent developments in the management of coronary heart disease, the role of thrombolysis in clinical practice itself has been incompletely assessed. Successful thrombolysis, even with satisfactory myocardial salvage, does not modify the underlying coronary artery disease and the long-term outlook in such patients may be expected to relate closely to the location, severity and extent of residual disease. Certain patients may be at greater risk after thrombolysis alone than after an uncomplicated completed infarction.

Specific indications for thrombolysis according to subsets remain to be established; the "all comers" philosophy is illogical and unacceptable. Only a brief report of favorable results with i.v. streptokinase alone has been published. Rational treatment requires clear demonstration of favorable alteration of both short- and long-term outcome in the known high-risk groups. Ongoing randomized trials on thrombolysis should recognize the different outlooks according to anatomic and functional subsets. They should not be restricted to short-term outcomes alone but address also the long-term results with or without interventions directed toward the management of residual coronary disease, which remains a primary factor in prognosis.

The short- and long-term outcomes of treatment of chronic coronary artery disease by coronary artery bypass surgery are well documented. Also, there is substantive information on the efficacy of PTCA, and recent reports indicate that this technique may be usefully applied in patients with multivessel disease. However, an intermediate (6 months) and longer term (1-2 years) follow-up on patients subjected to thrombolysis alone is not available, even on perusal of the most recent abstracts of the American Heart Association (1981) and the American College of Cardiology (1982). The current report from Meyer et al. suggests that a more aggressive approach to the longer-term management of residual coronary artery disease after successful early thrombolysis may be warranted.

In conclusion, in skilled and experienced hands, PTCA should be considered, when possible, in non-critical occlusions (± 75% cross-sectional narrowing) and coronary artery bypass surgery considered in high-grade (> 90%) or multivessel disease. Our own experience remains consistent with our published results: that approximately one-third of our patients undergoing thrombolyses continue to be referred promptly for surgical intervention. With this policy from the initiation of our program, the late complication rate in the remaining patients has been extremely low. Both problems — the acute thrombus and the underlying vascular disease — must be effectively evaluated and treated.

Thrombolysis remains an investigative, if highly promising, procedure. Widespread application in the routine care of many cases of evolving acute myocardial infarction at the community level is not yet justified.

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