Systemic thrombolytic therapy of acute myocardial infarction?

D. Collen, M.D., Ph.D., and M. Verstraete, M.D., Ph.D.

Rationale for thrombolytic therapy of myocardial infarction

The rationale for thrombolytic treatment of acute myocardial infarction is based on two established facts and a reasonable assumption. The first fact is that a thrombus obstructing an atherosclerotic coronary artery is the most frequent precipitating cause of acute transmural infarction. The second fact is that intracoronary administration of thrombolytic agents (streptokinase or urokinase) can reopen the occluded coronary artery within 1 hr and that reperfusion of ischemic myocardial tissue is generally well tolerated. The reasonable assumption is that timely reopening of an occluded coronary artery will save myocardial tissue and therefore may improve myocardial function, reduce infarction rate, and possibly decrease early and late mortality.

Thrombosis of an atherosclerotic coronary artery is the most frequent cause precipitating a transmural myocardial infarction.

The long-standing debate among cardiologists and assertive pathologists as to whether coronary thrombosis is the immediate cause rather than a consequence of myocardial infarction has been based mainly on analysis of pathologic findings. Recently, it has been convincingly demonstrated by results of coronary angiography and surgery that in the early stages of transmural myocardial infarction, thrombotic occlusion of a coronary artery is present in well over 80% of patients. Cardiologists were prompted to reexamine their concepts concerning the significance of coronary thrombosis in and optimal treatment of acute myocardial infarction. In particular, the question of recanalization with thrombolytic agents or with angioplasty of an occluded atherosclerotic coronary artery has been reexamined.

Intracoronary infusion of streptokinase can safely reopen a thrombosed coronary artery.

Rentrop et al.1 and other investigators demonstrated that patients with acute myocardial infarction tolerate intracoronary administration of streptokinase and that acute coronary occlusions (occurring less than 4 hr before treatment) can readily be lysed in about 80% of cases, resulting in restoration of coronary flow. Since then, many American and European catheterization laboratories have confirmed and elaborated on these observations. Because of patient selection, however, the frequency of coronary reperfusion in all patients is not exactly known.

Thrombolysis induced within the first 4 to 6 hr after the onset of myocardial infarction in patients is much less frequently associated with uncontrollable reperfusion tachyarrhythmias and hypotension than in experimental animal models. Reperfusion of the right coronary artery apparently carries a substantially higher risk. Because the risk of myocardial hemorrhage and edema due to microvascular damage probably increases with the duration of ischemia, early thrombolysis may be imperative for both efficacy and safety.

The first reports of intracoronary thrombolysis were received with great expectation by the cardiologic community and enjoyed more credit than the earlier controlled clinical trials on systemic administration of streptokinase and urokinase in patients with acute myocardial infarction. The latter trials were conducted between 1959 and 1980, when the causative role of coronary thrombosis in the pathogenesis of myocardial infarction was not fully established and coronary thrombolysis had not been conceived. However, it is possible that coronary thrombolysis accounted for the 50% decrease in mortality observed in the European Cooperative Study.2

Does reopening of a thrombosed coronary artery salvage contractile myocardium, decrease early and late mortality, and improve the quality of life?

Coronary thrombolysis is not a goal in itself but is employed to prevent necrosis and dysfunction of jeop-
ardized myocardial cells. Because severely ischemic cells inevitably progress to necrosis within 20 min, thrombolysis can save only those myocardial cells that are incompletely deprived of blood, a twilight state maintained through collateral channels. Consequently, the interval between the sudden reduction of blood flow and reopening of the supplying coronary vessel is a critical factor.3

There is satisfactory evidence in animals that infarct size is smaller and myocardial function better when an occluded coronary artery is reopened within the first 3 to 4 hr. The evidence that timely reopening of a coronary artery in man also leads to an improved myocardial function is limited and most often indirect. Relief of chest pain is a welcomed but complex and subjective criterion, and even when associated with a reduction in ST segment changes may not correlate with early improvement of the left ventricular ejection fraction. Nevertheless, left ventricular function appears to be improved at the time of discharge from the hospital in patients with reperfusion. Similarly, the immediate and short-term (3 months) uptake of thallium-201 by the human myocardium, which requires an intact membrane Na+, K+- ATPase, is improved after coronary thrombolysis. In addition, metabolic recovery after coronary reperfusion has been demonstrated by increased accumulation of 11C-palmitate, measured by positron emission tomography.

The yardsticks to determine whether coronary reperfusion is of benefit to the patient are long-term contractile recovery and reduced mortality. Proof is not yet available. Although there is limited evidence that inhospital mortality is lower in those patients with re-opened coronary arteries than in those in whom reperfusion could not be obtained, the data demonstrating that infarction rate, angina, heart failure, arrhythmia, and long-term survival substantially improve after flow restoration in the coronary circulation are still lacking. To this end, well-mounted large-scale trials are required.

**Toward simplified therapeutic regimens for thrombolytic therapy of myocardial infarction**

If the assumption that early reperfusion of a thrombosed coronary artery may be of benefit to the patient is correct, practical therapeutic schemes should fulfill or approach the following requirements: (1) coronary catheterization with its unavoidable morbidity, delay, and cost should be circumvented; (2) the thrombolytic agent should be effective and specific and should not produce a generalized breakdown of the hemostatic system; and (3) the agent should be widely applicable and safe, and should not require specific laboratory monitoring.

**Can coronary thrombolysis be achieved by systemic infusion of thrombolytic agents?** Many experienced catheterization laboratories have administered low-dose streptokinase (2000 U/min during 60 to 120 min) through standard or selective coronary catheters with very significant success. However, in less experienced hands, complications such as coronary dissection or perforation will be more frequent. In addition, there is considerable time loss before a catheter can be placed in the coronary artery (minimum 1 hr?). Finally, not all hospitals have a catheterization laboratory and in many of those that do, the technical staff most often is not on permanent stand-by. Furthermore, at times of economic restrictions it is unrealistic to equip, staff, and maintain around-the-clock facilities for intracardiac catheterization. For all these reasons it is obvious that the widespread application of coronary thrombolysis will depend on the development of simple therapeutic regimens that do not require coronary catheterization.

Schröder et al.4 and others have demonstrated by coronary angiography that systemic administration of a high dose (1.5 million units) of streptokinase over 60 min results in a frequency of coronary reperfusion comparable to that obtained with intracoronary streptokinase in patients with acute myocardial infarction (occurring less than 5 hr before treatment). Furthermore, there is some evidence that reocclusion of the coronary artery is less frequent within the first 3 to 4 weeks after intravenous administration of streptokinase than after intracoronary administration.

These results suggest that systemic thrombolytic therapy initiated sooner (compared to intracoronary administration) after the onset of infarct pain may enhance the lysis of the fresher thrombus, maximizing efficacy, safety, and practicability of this procedure.

As will be described in more detail below, intravenous infusion of tissue-type plasminogen activator may constitute an alternative to systemic infusion of streptokinase.

**On the specificity of thrombolytic agents.** Physiologic fibrinolysis appears to be regulated by specific molecular interactions between plasminogen activator (tissue-type plasminogen activator originating from the vessel wall) and fibrin, between plasminogen and fibrin, and between plasmin and α2-antiplasmin. On the basis of these specific interactions, a molecular model for the regulation of fibrinolysis in vivo, characterized by the following main characteristics, was formulated.5 Tissue-type plasminogen activator has a weak affinity for plasminogen in the absence of fibrin (Km =
65 \mu M), but when a thrombus is formed, plasminogen activator binds (relatively weakly) to fibrin (K_D = 0.16 \mu M) and plasminogen binds with high affinity to this binary complex (K_m = 0.14 \mu M). Fibrin essentially increases the local plasminogen concentration by creating an additional interaction between tissue-type plasminogen activator and its substrate plasminogen through a cyclic fibrin bridge ("surface assembly"), which results in efficient plasminogen activation but confined to the fibrin surface. In this reaction, plasminogen binds to fibrin primarily via specific structures called the "lysine-binding sites." Plasmin formed on the fibrin surface has its lysine-binding sites and its active site occupied and is only slowly inactivated by \alpha_2-antiplasmin. However, liberated plasmin is very quickly inactivated by \alpha_2-antiplasmin.

This molecular model for the regulation of fibrinolysis has important consequences for the development of specific thrombolytic agents. Indeed, the presently available thrombolytic agents streptokinase and urokinase have no specific affinity for fibrin and therefore activate circulating and fibrin-bound plasminogen relatively indiscriminately. Consequently, plasmin formed in circulating blood will initially be neutralized very rapidly by \alpha_2-antiplasmin and will be lost for thrombolysis. Once the inhibitor becomes (nearly) exhausted, residual plasmin will degrade several plasma proteins (fibrinogen, Factor V, Factor VIII, etc.), which may cause a serious bleeding tendency. Exhaustion of circulating plasminogen will result in a decrease of fibrin-bound plasminogen and in less effective thrombolysis. This probably explains why treatment with streptokinase or urokinase has only a limited efficacy and may be associated with serious, sometimes life-threatening, side effects.

From this reasoning it appears that specific thrombolysis will be possible only if the activation process of plasminogen can be localized at and confined to the fibrin surface. According to the present knowledge, this can only adequately be achieved with the use of an activator that, like the physiologic activator, adsorbs to the fibrin surface and becomes active in loco.

We have found a stable cell line of human origin that produces a large amount of tissue-type plasminogen activator and have developed a purification procedure to obtain relative large quantities of the purified activator. With use of this material, Bergmann et al. demonstrated that intravenous infusion of tissue-type plasminogen activator in dogs with experimental myocardial infarction resulted in thrombolysis within 10 min, restoration of myocardial perfusion, and reduction of the extent of metabolically compromised myocar-

dium, without inducing a systemic fibrinolytic state.

Potential of tissue-type plasminogen activator, obtained by recombinant DNA technology, for widely applicable coronary thrombolysis. The production of tissue-type plasminogen activator from tissue culture fluids is prohibitively laborious and expensive for large-scale studies and for routine clinical applications. Tissue-type plasminogen activator, produced by recombinant DNA technology, could in principle constitute an alternative and more economical source of purified material for human application. In a further development, Pennica et al. have recently synthesized and cloned the human tissue-type plasminogen activator gene. In a collaborative study with the Cardiovascular Divisions of Washington University, St. Louis, and of the University of Leuven, Belgium, a translation product of this gene was applied to dogs with experimental myocardial infarction and was found to have thrombolytic properties very similar to those of the natural activator produced from cell culture fluids (unpublished results).

Although these results are most encouraging, it is necessary to stress that before recombinant tissue-type plasminogen activator can be used as a thrombolytic agent in man, much additional work is required.

Conclusions

There is increasing evidence that the treatment of acute-phase myocardial infarction will involve thrombolysis to offer patients a greater chance to survive with a better functional myocardium. No doubt, none of the thrombolytic agents, whether applied intravenously or directly in the coronary artery, will influence atherosclerotic lesions or prevent coronary spasm. However, coronary thrombolysis may be useful to help the patient through the acute phase of myocardial infarction until additional secondary measures for prevention can be applied.

To be able to offer the benefit of an effective and safe thrombolytic treatment to a greater number of patients with acute myocardial infarction, short and simple therapeutic schemes must be developed. On the basis of recent animal data, we believe that tissue-type plasminogen activator provides a promising approach.

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