Editorial Comment

New Mechanisms of Action for Tissue-Type Plasminogen Activator?*

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In the 2 years since the first description of the effects of tissue plasminogen activator (t-PA) in patients (1), it has emerged as the drug of choice for the treatment of patients with acute myocardial infarction who require fibrinolysis. In this issue of the Journal, Darius et al. (2) present data that suggest that t-PA may influence the development of myocardial necrosis by mechanisms other than its well-documented ability to lyse coronary thrombi. They report a 38% reduction (47 ± 4 to 23.9 ± 4%) in the percent of the risk area that develops necrosis in a cat model in which occlusion is induced by tightening a ligature and reperfusion by loosening it (2). These results potentially have important implications for the long-term use of t-PA.

Possible limitations of the study. Certain experimental caveats need to be appreciated. It is possible that the effects observed are unique to the melanoma-derived activator, unique to cats, unique to low doses of activator because the amounts used in this investigation are lower than those usually used to achieve fibrinolysis or that the benefit observed occurs only during a very narrow time window after ischemia. A more important experimental question concerns the use of tetrazolium stains for the assessment of infarct size. Many questions remain concerning the mechanism by which these agents delineate myocardial injury (3) and there are few data validating this approach in models of occlusion followed by very early reperfusion. The loss of reduced coenzymes (for example, NADH), which are critical for the identification of infarction with tetrazolium stains (3), could occur after occlusion and reperfusion because of the prolonged metabolic derangements in high energy phosphate stores known as "metabolic stunning" that occur after occlusion and early reperfusion (4). Thus, t-PA, either directly or by improving the time course or extent of reperfusion, may have reduced stunning rather than actual infarction. Alternatively, the osmotic effects of a t-PA infusion may inhibit the swelling associated with cellular injury and thus delay the loss of coenzymes. This possibility could be excluded by the evaluation of the effects of an inactivated solution of t-PA in this experimental model. In each case, measurements after more prolonged reperfusion (24 to 48 hours) may have revealed the lack of a difference between treated and control animals. Thus, these findings need to be confirmed after more prolonged intervals of reperfusion and with additional methods (for example, creatine kinase depletion) to quantify the extent of necrosis.

Mechanisms for myocardial salvage. The enhanced myocardial salvage observed by Bergmann et al. (5) with positron tomography with t-PA compared with streptokinase and cited by Darius was probably due, in large part, to more rapid fibrinolysis with t-PA. The potential mechanisms responsible for the extensive myocardial salvage induced by t-PA in this study are unclear. Although minor changes in the rate-pressure product, which could be cumulative over time were observed, these changes are unlikely to explain the marked changes observed. The creatine kinase data and experiments on isolated normal coronary arteries add little to explain the possible beneficial effects of t-PA. A large number of possible explanations exist: 1) t-PA may affect the adequacy of reperfusion by influencing vasomotion or thrombus formation in large epicardial coronary arteries that may be damaged during occlusion by the ligature; 2) t-PA may have influenced smaller collateral vessels or inhibited circulating products such as platelets, red cells or white cells that may be responsible for reducing the adequacy of reperfusion in small vessels (the no reflow phenomenon); 3) t-PA could have effects on the release of intramyocardial catecholamines, which may be important, because both alpha- and beta-blockade have been shown to reduce the extent of necrosis after reperfusion; and 4) these beneficial effects of t-PA could be due to a direct protective effect on ischemic tissue during reperfusion. At present, inhibition of calcium influx and inhibition of the production of oxygen free radicals or a combination of both, are the most attractive mechanisms being evaluated.

Clinical implications. It is difficult to anticipate the clinical impact of these experimental findings, particularly when the mechanisms are unknown. If t-PA reduces the ultimate extent of necrosis after more prolonged intervals of reperfusion by mechanisms other than lysis of coronary thrombi in epicardial or intramural coronary arteries, the implications are profound. Substantial efforts are now being focused on the use of pharmacologic agents that may protect ischemic myocardium before or during fibrinolysis, in an attempt to enhance myocardial salvage. Most of these experimental studies have evaluated the effects of beta-adrenergic blocking agents, calcium channel blockers (6) and alpha-adrenergic blocking agents with reperfusion (7). As pointed out by Darius et al., streptokinase may also have additional effects because it reduces nucleoside and lactic

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dehydrogenase depletion and improves ventricular function in isolated perfused heart preparations (8,9). It is unclear whether these protective effects are mediated by the same mechanisms as those reported for t-PA. Can we be confident that the pharmacologic agents being investigated to improve salvage during thrombolysis will be synergistic with the potential protective effects of t-PA, or will the effects be antagonistic?

The issue poses a major dilemma for modern day cardiology. In an atmosphere where the rapid translation of a laboratory finding into the clinical arena is the rule, statements urging caution or further investigation before implementation are rarely viewed favorably, even when they are prudent. Right or wrong, these findings should remind us of how little we know about the pharmacology of fibrinolysis and myocardial salvage and reinforce the need for solid experimental confirmation before embarking on clinical investigation.

References


