Improved Early Infarct-Related Vessel Patency After Thrombolytic Therapy*

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The major goal of reperfusion strategies in patients with acute myocardial infarction is to achieve patency of the infarct-related artery. Improvement in ventricular function and survival are related to initial and continued patency of this artery. The greater initial patency of the infarct-related artery after intravenous recombinant tissue-type plasminogen activator (rt-PA) compared with that achieved with intravenous streptokinase in the Thrombolysis in Myocardial Infarction (TIMI) trial (1) led to the selection of rt-PA as the thrombolytic agent of choice in the United States.

With current intravenous thrombolytic strategies, the highest patency rate achieved is 75%. Early use of intravenous heparin and the use of combined thrombolytic regimens have failed to break through this ceiling (2-4), which may be a result of several factors. These include complexity of the atherosclerotic plaque with intramural plaque hemorrhage (5), ongoing platelet deposition into the thrombus with resistance to thrombolysis (6), as well as inadequate thrombolytic effectiveness or dose of the chosen thrombolytic agent.

The failure of current intravenous thrombolytic strategies to achieve a higher patency rate of the infarct-related artery has led to several adjunctive and alternative strategies for reperfusion. Rescue angioplasty for patients with failed intravenous thrombolysis has been evaluated in several trials (7). However, initial results have been disappointing because of a relatively high rate of complications including death. The failure of rescue angioplasty may be related to platelet activation, particularly after rt-PA and mechanical trauma to the residual thrombus, resulting in reocclusion. Several investigators (8) have achieved a high patency rate by using direct coronary angioplasty without intravenous thrombolytic therapy ("direct" angioplasty). A patency rate of >90% has been achieved with a relatively low complication rate with this strategy. Although feasible, this strategy has only limited applicability because of the limited availability of angioplasty facilities and laboratories willing to operate on a 24-h basis with immediate access for the patient with acute infarction. Even if further randomized trials show an advantage for this strategy, it is unlikely that, given the logistic difficulties associated with its use, we will achieve a major improvement in ventricular function and survival in large numbers of patients with acute myocardial infarction.

The present study. The recent study by Neuhaus et al. (9) demonstrating an improved early patency rate of >90% with front-loaded rt-PA, infusing 100 mg of rt-PA over 90 min without an apparent increase in bleeding risk, is therefore of great interest and has important therapeutic potential. Should this strategy result in an improved early and sustained patency rate there would be a lesser impetus to pursue the strategy of rescue angioplasty and a lesser justification for early coronary arteriography. The strategy of direct coronary angioplasty without thrombolytic therapy might also lose some of its appeal if early administration of front-loaded rt-PA achieves a high rate of initial and sustained patency of the infarct-related artery. The study by Neuhaus et al. (10) in this issue of the Journal is therefore of importance in giving us some initial perspective on the potential of the front-loaded rt-PA regimen to achieve and maintain patency of the infarct-related artery in comparison with intravenous APSAC. Neuhaus et al. (10) show that front-loaded rt-PA achieved a 90-min patency rate of 64.4% versus 70.3% for intravenous APSAC. However, because of a higher reocclusion rate with front-loaded rt-PA, at 14 to 21 days the two regimens had a similar patency rate. The greater initial patency rate with the front-loaded rt-PA regimen was associated with a significantly lower in-hospital mortality rate. The finding in this study that initial infarct-related vessel patency is associated with improved survival lends encouragement to the development of combined thrombolytic strategies (11) and further use of adjunctive strategies with antithrombin or antihirin platelet agents such as hirudin or antagonists to the glycoprotein IIb/IIIa platelet receptor (12-14). These agents have the potential to achieve even greater initial patency as suggested by initial animal studies (13). If the high rate of reocclusion associated with rt-PA, as documented in this study (10), could be reduced by adjunctive antiplatelet therapy, one might expect even greater benefit for survival since reocclusion is associated with a loss of functional recovery and an increase in mortality (15).

Implications. One should, however, be cautious in adopting the strategy of front-loaded rt-PA before seeing the results of far larger prospective randomized trials demonstrating its safety and efficacy over a longer period of time. The greater early patency of the infarct-related vessel with standard rt-PA dosing regimens than with intravenous streptokinase (1) did not result in improved survival when these agents were compared in the GISSI-2 (16) and ISIS-3 (17) trials. Although there has been criticism of both of these trials relating to their delayed subcutaneous heparin regimens, one would have expected that intravenous rt-PA in these trials should have achieved greater initial patency of

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the infarct-related artery, at least in comparison with intravenous streptokinase. The lack of early intravenous heparin in these trials would be expected to have a greater influence on reocclusion than on initial patency. Because Neuhas et al. (10) suggest that early rather than late patency is of importance in improving survival, one would have expected improved survival in the r-PA arm of the GISSI-2 (16) and ISIS-3 trials (17), at least in comparison with intravenous streptokinase. Whether trial design or factors other than infarct-vessel patency account for the failure of r-PA to demonstrate improved survival despite its early patency advantage remains to be determined. A far larger number of patients, in the range of 10,000 per treatment arm, will also be needed to be studied before we can assess the effect of front-loaded r-t-PA or any other regimen on the incidence of major bleeding, which is approximately 1% with standard thrombolytic regimens (17). Although there was a lower incidence of bleeding reported in the trial by Neuhas et al. (10), with front-loaded r-t-PA than with APSAC, as the authors point out, this difference may be due to the use of early intravenous heparin, which may not be necessary with intravenous APSAC given the lower incidence of reocclusion associated with its use.

Conclusions. Thus, while it appears that we can achieve improved early patency by front-loaded r-t-PA and could likely achieve even better initial and sustained patency by the addition of adjunctive antiplatelet therapy, we still have much to learn concerning the dose of thrombolytic therapy as well as the addition and timing of heparin and other adjunctive therapies. Neuhas et al. (10) have given us hope for improved survival by improved early infarct vessel patency. To achieve the full potential of the thrombolytic era we will need to further explore this and other dosing regimens of thrombolytic agents with new adjunctive therapies. Clearly we have much to learn. The GISSI 2 (16) and ISIS-3 (17) trials mark the end of one phase of our exploration for the optimal reperfusion strategy. The next phase is just beginning. Although it is premature to predict which thrombolytic agent will be the agent of choice, it is not too early to predict that we will achieve greater early and sustained patency with improved functional recovery and survival by further careful study of strategies now under development and in or soon to be in clinical trial.

References


