Editorial Comment

Angiographic Monitoring of Reperfusion Therapy for Acute Myocardial Infarction
TIMI Grade 3 Perfusion Is the Goal

Michael L. Stadius, MD

Angiography has been used to monitor the effects of thrombolytic therapy on coronary artery anatomy and flow during the early hours of acute of myocardial infarction since the early 1980s. Several early investigators noted a spectrum of responses of initially occluded coronary arteries to thrombolytic therapy using angiographic assessment. The Thrombolysis in Myocardial Infarction (TIMI) investigators formalized a set of definitions describing the angiographically monitored response of the infarct artery to thrombolytic therapy; these definitions have become known as TIMI perfusion grades, and the grading scheme has achieved widespread acceptance as a useful technique for characterizing coronary artery response to thrombolytic therapy. The TIMI perfusion grades classify the responses of infarct-related arteries to thrombolytic therapy into four categories with grade 0 perfusion indicating occlusion of the infarct artery, grade 3 perfusion indicating normal rates of antegrade contrast flow and clearing in the infarct artery (and therefore presumably normal perfusion of myocardium in the infarct bed), and grades 1 and 2 indicating intermediate levels of flow between grades 0 and 3. In the first description of this perfusion-grading scheme, the investigators grouped grades 0 and 1 perfusion together as indicators of failure of reperfusion therapy and grouped grades 2 and 3 together as markers of successful reperfusion therapy. Since the TIMI perfusion-grading scheme (and its dichotomization into successful and failed reperfusion groups) first appeared in 1985, there has been little study of the clinical outcomes associated with the individual TIMI perfusion grades. The dichotomization of the TIMI grading scheme into successful and failed reperfusion groups also has been widely used to characterize the outcomes of many trials involving thrombolytic therapy; furthermore, this dichotomization of infarct artery response to thrombolytic therapy has been used to stratify patients after thrombolytic therapy for evaluation of subsequent percutaneous transluminal coronary angioplasty (PTCA) in a number of studies evaluating the efficacy of combined thrombolytic and PTCA therapy.

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In this issue of Circulation, Anderson and colleagues present their careful evaluation of the association between clinical markers of infarct severity and TIMI perfusion grades. The authors hypothesized that TIMI grade 3 perfusion would result in more beneficial indexes of infarct severity compared with the indexes that would be associated with TIMI perfusion grades 0, 1, and 2. This study was carried out in the setting of the third Thrombolysis Trial of Anistreplase in Acute Myocardial Infarction (TEAM-3). Because the clinical outcomes after anistreplase and alteplase—the two thrombolytic treatment regimens used in this study—were similar, the authors were able to combine both treatment groups in this evaluation of TIMI perfusion grades. Using entry criteria that are similar to those for most recent studies of thrombolytic therapy in acute myocardial infarction, patients were treated with one of the thrombolytic agents within 4 hours of onset of chest pain. Infarct artery patency was studied approximately 30 hours after entry. Three patency groups were defined for statistical comparisons: grades 0 and 1 were considered perfusion failure, grade 3 was considered complete perfusion, and grade 2 was considered partial perfusion. Radionuclide ventricular angiography was performed at hospital discharge and a mean of 1 month after entry. At both hospital discharge and 1-month evaluations, patients with grade 3 perfusion had significantly better left ventricular ejection fraction (globally and within the infarct region) than did patients with TIMI grade 0 or 1 or TIMI grade 2 perfusion. According to hospital discharge ECG QRS scoring, patients with grade 3 perfusion demonstrated a significantly lower QRS score than those with grades 0 or 1 or grade 2 perfusion. Peak and time-to-peak lactate dehydrogenase (LDH) values were lower in patients with grade 3 perfusion. In a subset of patients, time-release LDH and LDH-1 isoenzyme kinetic curves could be constructed, and lesser amounts of LDH and LDH-1 were released in patients with TIMI grade 3 perfusion. Finally, there was a trend toward lesser morbidity in patients with grade 3 perfusion than in those with grades 0 or 1 or grade 2 perfusion. In this analysis based on TIMI grade perfusion assessed at 30 hours after initiation of thrombolytic treatment, the authors conclude that “patients with grade 3 flow differ significantly from those having grades 0/1 and 2 (flow),
suggesting a significantly smaller infarct occurred in those patients who have achieved ‘complete’ (TIMI grade 3) perfusion.”

In a separate study (the Second Thrombolysis Trial of Anistreplase in Acute Myocardial Infarction [TEAM-2]), these same authors evaluated the same issues using coronary angiographic assessment of infarct artery patency obtained 2 hours after initiation of thrombolytic therapy. With this earlier coronary angiographic assessment of TIMI perfusion grade after thrombolytic therapy, patients with grade 3 perfusion demonstrated smaller indirect measures of infarct size using ECG QRS scoring at hospital discharge and cardiac enzyme peak and time-to-peak activity. The hospital phase outcome observations from the TEAM-2 and TEAM-3 studies are consistent with 1-year mortality findings from the Western Washington Randomized Trial of Intracoronary Streptokinase. Kennedy et al reported a similar 1-year mortality in patients with no reperfusion after streptokinase therapy and in those who had partial reperfusion after streptokinase therapy (similar to TIMI grade 2 perfusion). Patients who had complete reperfusion in this early study (those who now would be classified as having TIMI grade 3 perfusion) experienced a significantly lower 1-year mortality than did those with no reperfusion or partial reperfusion. Finally, Topol et al evaluated the relation between TIMI perfusion grade based on angiograms obtained 90 minutes after initiation of thrombolytic therapy and inhospital mortality in 708 patients evaluated in the Thrombosis and Angioplasty in Myocardial Infarction Trials 1, 2, and 3. TIMI grade 3 perfusion—but not TIMI grade 2 perfusion—was associated with improved probability of hospital survival. The results of these four different observational studies evaluating the relation between TIMI perfusion grades assessed angiographically after initial thrombolytic therapy and clinical measures of infarct severity indicate that complete perfusion (TIMI grade 3 perfusion) is associated with improved clinical outcomes compared with patients who achieve lesser TIMI grades of perfusion after thrombolytic therapy. Based on the findings of these studies, it seems most reasonable to conclude that TIMI grade 3 perfusion should be the treatment goal for reperfusion therapy of acute myocardial infarction.

Identification of TIMI grade 3 perfusion as the goal of reperfusion therapy for acute myocardial infarction has a number of important implications for future investigations in this field. First, this conclusion highlights the relative ineffectiveness of current thrombolytic treatment regimens in achieving optimal rates of successful reperfusion. Even the most optimistic studies reporting patency rates of 84–91% for “front-loaded” dosing of alteplase need to be reevaluated. These high patency rates have included a notable minority of patients who achieved only TIMI grade 2 perfusion. When patients with TIMI grade 2 perfusion are reclassified as having unsuccessful reperfusion, patency rates assessed 90 minutes after initiation of front-loaded alteplase peak at about 75%. Another implication of this new understanding of TIMI perfusion grades concerns the triage of patients for “rescue” angioplasty after initial thrombolytic therapy. In previous studies, patients with TIMI grade 2 perfusion after thrombolytic therapy have been considered to be successfully treated with thrombolytic agents and have been triaged away from consideration of rescue angioplasty treatment. In the future, it would be more appropriate to consider patients with TIMI 2 perfusion as unsuccessfully treated and, therefore, appropriate candidates for evaluation of “rescue” treatments. Third, the importance of achieving TIMI grade 3 perfusion may explain, at least in part, the apparent benefit of direct PTCA as a reperfusion strategy compared with thrombolytic therapy alone, as reported recently by the Primary Angioplasty in Myocardial Infarction (PAMI) investigators. Observational studies of direct angioplasty in acute myocardial infarction report infarct artery patency rates in excess of 90%. In the PAMI trial, successful angioplasty was reported in 97% of patients receiving direct PTCA; clinical end points, including mortality, were more favorable in patients assigned to direct PTCA in this trial. Certainly, patency—the term commonly used to describe successful outcome in the direct PTCA literature—need not correspond in all cases to TIMI grade 3 perfusion, but it appears reasonable to conclude that TIMI grade 2 perfusion is an uncommon correlate of successful direct PTCA. Additional studies will be necessary to further evaluate the relative effectiveness of direct angioplasty compared with other reperfusion strategies for acute myocardial infarction, but the available direct angioplasty experience appears to be consistent with the conclusions being drawn regarding the relative importance of achieving TIMI grade 3 perfusion. Finally, the debate regarding the importance of the “early open infarct artery” in reperfusion therapy may be influenced by the observations discussed here. Some investigators seriously question the importance of achieving early patency of the infarct artery with reperfusion treatment strategies. Other investigators emphasize the consistent relation seen in observational studies between presence of coronary artery patency early in the infarct event and more beneficial clinical and mortality outcomes compared with findings in patients who have failure of coronary artery reperfusion early in the infarct event. Future studies that are designed to address this controversy must consider carefully what constitutes successful reperfusion. Grouping TIMI grades 2 and 3 perfusion results together in this type of study may diminish some of the benefit that appears to be associated with achievement of complete (TIMI grade 3) perfusion.

In summary, TIMI grade 3 perfusion has been associated with better clinical outcomes compared with outcomes associated with TIMI grades 0, 1, and 2 perfusion in at least four studies. TIMI grade 2 perfusion can no longer be accepted as a marker of successful reperfusion therapy in the acute myocardial infarction setting. When angiographic monitoring is available in the early hours after myocardial infarction, the goal of reperfusion therapy is achievement of TIMI grade 3 perfusion.

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Key Words: Editorial Comments • reperfusion • angiography • acute myocardial infarction
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M L Stadius

Circulation. 1993;87:2055-2057
doi: 10.1161/01.CIR.87.6.2055
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/6/2055.citation

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