Successful reperfusion after acute myocardial infarction (MI) has traditionally been considered to be restoration of epicardial patency, but increasing evidence suggests that disordered microvascular function and inadequate myocardial tissue perfusion are often present despite infarct vessel patency. Thus, optimal reperfusion is being redefined to include intact microvascular flow and restored myocardial perfusion, as well as sustained epicardial patency. Coronary angiography has been used as the gold standard to define failed reperfusion, according to the Thrombolysis In Myocardial Infarction (TIMI) flow grades. However, new angiographic techniques, including the corrected TIMI frame count and myocardial blush grade, have been used to show that epicardial TIMI flow grade 3 may be an incomplete measure of reperfusion success. Furthermore, evolving noninvasive diagnostic techniques, including measurement of infarct size with cardiac marker release patterns or technetium-99m–sestamibi single-photon emission computed tomographic imaging and analysis of ST segment resolution appear to be useful complements to angiography for the assessment of myocardial tissue reperfusion. Promising adjunctive therapies that target microvascular dysfunction, including platelet glycoprotein IIb/IIIa inhibitors, and agents designed to improve tissue perfusion and attenuate reperfusion injury are being evaluated to further improve clinical outcomes after acute MI. To accelerate development of these new reperfusion regimens, an integrated approach to phase II clinical trials that incorporates multiple efficacy variables, including angiography and noninvasive biomarkers of microvascular dysfunction, should be considered. Thus, as the reperfusion era moves into the next millennium, the open-artery hypothesis is expected to shift downstream and guide efforts to further improve myocardial salvage and clinical outcomes after acute MI. (J Am Coll Cardiol 2001;37:9–18) © 2001 by the American College of Cardiology

The goal of reperfusion therapy for acute myocardial infarction (MI) is to quickly re-establish the flow of nutritive, oxygenated blood to myocytes, whose function and survival are threatened by thrombotic occlusion of the infarct-related artery (IRA) (1,2). Correlations between sustained patency of the IRA and improved clinical outcomes culminated in the “open-artery hypothesis,” which has been the cornerstone of therapeutic strategies for acute MI for over a decade. The open-artery hypothesis suggests that re-establishing a patent IRA with normal anterograde flow salvages stunned myocardial tissue, preserves left ventricular mechanical function and positively influences clinical outcomes (3). The benefits of IRA patency also may extend beyond myocardial salvage, because late restoration of IRA patency does not improve global left ventricular function, but appears to improve long-term survival (4). Approximately 25% of patients with restoration of normal anterograde flow in the epicardial IRA, however, do not have reperfusion of the myocardium at the tissue level (5). Thus, the open-artery hypothesis may be an oversimplification, because the goal of reperfusion therapy should be to restore not only upstream epicardial patency and flow, but also downstream myocardial tissue perfusion.

Despite significant advances in the treatment of acute MI over the last decade, new therapies continue to emerge in an effort to further improve clinical outcomes. With numerous potential combinations of primary and adjunctive therapies for acute MI, however, a more precise and comprehensive definition of “optimal reperfusion” is needed so that a clear target for new therapies can be established (6). The purposes of this review are to explore advances that point us downstream from the open-artery hypothesis to the characterization of myocardial tissue perfusion and to determine the ideal approach for the evaluation of new reperfusion strategies.

HISTORIC PERSPECTIVE

The therapeutic approach to acute MI was pioneered by Braunwald and Maroko (7), who focused on treatments designed to limit infarct size by improving myocardial oxygen supply and limiting autolytic damage to myocytes. Techniques used to determine infarct size included mapping of precordial ST segment elevation and disappearance curves of serum cardiac markers (8,9). By showing that quantification of infarct size was critical to the assessment of new therapies for acute MI, these early studies emphasized...
After plaque rupture and intracoronary pathophysiology.

MICROVASCULAR DYSFUNCTION

The importance of restoring global myocardial perfusion to the recovery of left ventricular function.

Despite the initial focus on myocardial tissue perfusion, attention soon shifted to the epicardial vessel. Using canine models of coronary occlusion in the late 1970s, Reimer et al. (1) showed that infarct size was directly related to the duration of epicardial occlusion—a finding later termed the “wave front phenomenon” of myocyte death. Although prompt relief of epicardial occlusion was clearly shown to halt the wave front of ischemic myocyte death, microvascular dysfunction in the infarct zone was identified as the limiting factor for the restoration of myocardial tissue perfusion (this phenomenon was called “no-reflow”) (1,10). Paradoxically, epicardial reperfusion also was shown to exacerbate microvascular dysfunction when blood flow was restored to the infarct region (11,12). Therefore, historic observations defined the continuum of reperfusion from upstream epicardial patency to downstream tissue perfusion and emphasized that the ultimate goal of treatment strategies for acute MI should be the prompt restoration of normal epicardial and myocardial perfusion.

MICROVASCULAR DYSFUNCTION

Pathophysiology. After plaque rupture and intracoronary thrombus formation, ischemia causes ultrastructural damage to myocytes and the coronary microcirculation soon after coronary occlusion (13). Once epicardial reperfusion occurs and blood flow to the infarct zone is restored, reperfusion injury caused by neutrophil infiltration, generation of oxygen free radicals and activation of the complement system and adhesion molecules may further damage the microcirculation (11,14,15). Damaged myocytes and arterioles are thought to hinder microvascular flow by increasing distal vascular resistance, stimulating arteriolar spasm and causing endothelial dysfunction. In addition, platelet microemboli are thought to be “showered” downstream of the microcirculation after plaque rupture, causing microvascular obstruction that further limits tissue perfusion once the epicardial infarct vessel is recanalized (16). Microvascular dysfunction also appears to occur in non–infarct-related vessels, suggesting that myocardial ischemia may stimulate a global inflammatory response through the release of cytokines (17). Thus, microvascular dysfunction after epicardial reperfusion is a complex process with several probable interrelating stimuli and factors (Fig. 1).

Clinical significance. Microvascular perfusion is disrupted in a significant proportion of patients with patent epicardial infarct-related vessels after fibrinolysis or primary angioplasty (5,18). The clinical significance of microvascular dysfunction after epicardial reperfusion has been evaluated in multiple studies that used surrogate markers, such as myocardial contrast echocardiography (MCE) and ST segment resolution, to evaluate tissue-level reperfusion (19–24) (Table 1). These studies collectively showed less recovery of left ventricular ejection fraction, progressive left ventricular dilation and increased mortality and congestive heart failure in patients who had microvascular dysfunction after epicardial reperfusion. However, the extent of myocardial damage that occurs before reperfusion may limit further myocardial salvage, even if normal tissue perfusion is restored.

INSIGHTS FROM ANGIOGRAPHY

Since DeWood et al. (2) first used coronary angiography to show that thrombotic occlusion of the epicardial coronary artery caused acute MI, angiography has been a valuable tool for the evaluation of patients treated with reperfusion therapies. The Thrombolysis In Myocardial Infarction (TIMI) investigators categorized epicardial coronary flow into grades to standardize the angiographic characterization of reperfusion (25). Flow grade 0 or 1 represented failed reperfusion, whereas flow grade 2 or 3 represented epicardial patency and successful reperfusion. However, the angiographic substudy of the Global Utilization of Streptokinase and TPA (alteplase) for Occluded coronary arteries (GUSTO-I) showed that restoration of TIMI flow grade 3 (normal epicardial flow) alone is associated with improved survival and enhanced recovery of left ventricular function (26,27). The survival advantage shown with TIMI flow
grade 3 in the GUSTO-I angiographic substudy closely matched the mortality rates observed with the different fibrinolytic regimens tested in the overall trial (28). These findings, which linked therapeutic efficacy of treatments for acute MI to the early, complete restoration of anterograde flow in the epicardial IRA, validated angiography as a surrogate end point for mortality in trials of acute MI. Although restoration of TIMI flow grade 3 has been used as the gold standard for reperfusion success, distal coronary flow can vary considerably despite flow grade 3 in the epicardial vessel (29). The corrected TIMI frame count (cTFC) was developed to quantify distal coronary flow and can further risk-stratify patients with TIMI flow grade 3 after fibrinolysis into lower-and higher risk subgroups (21,29). Furthermore, the angiographic “blush” score appears to assess myocardial tissue perfusion more accurately than does cTFC and may be an even better method of risk stratification (22,30). Therefore, refinement of the angiographic characterization of reperfusion has emphasized the importance of restored myocardial tissue perfusion in determining the ultimate success of reperfusion strategies (6) (Fig. 2). However, angiography is a “snapshot” technique that may not adequately assess the continuum of reperfusion; it is also expensive and cannot be performed early at most hospitals (31).

**DIAGNOSIS OF REPERFUSION SUCCESS AT THE CELLULAR LEVEL**

Promising diagnostic tests that focus on the identification of patients with microvascular dysfunction after epicardial reperfusion may complement the angiographic characterization of reperfusion.
Coronary Doppler flow wires. Coronary Doppler flow wires can be used to measure coronary flow velocity and coronary flow reserve after epicardial reperfusion in order to estimate the degree of microvascular dysfunction in the infarct zone. Disruption of coronary flow velocity and reserve after successful epicardial reperfusion appears to predict recovery of regional left ventricular function and contractile reserve (32,33). Myocardial tissue perfusion cannot be assessed directly with coronary Doppler flow wires, however, coronary angiography is required, and the reproducibility of this technique has not been studied.

Myocardial contrast echocardiography. Myocardial contrast echocardiography was first performed during angiography by injecting a sonicated contrast solution into the recanalized IRA to evaluate myocardial contrast enhancement in infarct-zone tissue (5). It has shown that up to 25% of patients with acute MI do not have adequate restoration of myocardial tissue perfusion in the infarct region, despite TIMI flow grade 3 in the epicardial IRA (5,18). New contrast agents that can be injected intravenously are being developed, but have not been adequately tested in a large cohort of patients with acute MI (34).

Magnetic resonance imaging. Cardiac magnetic resonance imaging (MRI) appears to be one of the most comprehensive imaging techniques used to evaluate microvascular dysfunction, because it can be used to assess coronary flow, myocardial tissue perfusion, left ventricular volumes and regional and global left ventricular function (24,35). However, high costs, long procedure times and the inability to accommodate unstable patients are significant limitations of cardiac MRI.

Technetium-99m-sestamibi single-photon emission computed tomography. Cumulative infarct size measurement with technetium-99m (99mTc)-sestamibi single-photon emission computed tomography (SPECT) appears to be a promising technique to determine left ventricular damage and the amount of myocardial salvage after reperfusion therapy (36,37). Initial 99mTc-sestamibi SPECT imaging is often difficult to perform while treating acute MI, however. The ideal time to perform follow-up imaging after administration of reperfusion therapy is unclear.

Cardiac markers. After coronary occlusion, myocyte necrosis leads to the release of cardiac markers into the serum, including creatine kinase (CK), CK-MB fraction, myoglobin, alpha-hydroxybutyrate dehydrogenase and troponins I and T. Initial studies by Witteveen et al. (9) and Sobel et al. (38) showed that the cumulative release of cardiac markers after acute MI could be used to estimate infarct size, predict recovery of left ventricular function and predict survival. In the modern reperfusion era, release patterns of cardiac markers have been used to compare primary angioplasty with fibrinolytic agents and to compare different fibrinolytic regimens (39–41). Furthermore, we have shown that the peak serum CK-MB concentration and the cumulative area under the CK-MB release curve after fibrinolysis independently predict in-hospital mortality and congestive heart failure, but do not relate to TIMI flow grades (42). The area under the curve is a technique that accounts for the cumulative marker release, regardless of the peak and width of the curve. The curve of cardiac marker release can therefore be used to represent an overall measure of myocardial cellular injury. However, the optimal number of samples needed to assess infarct size accurately, the best marker to use for infarct size measurement and how curves of marker release correlate with myocardial salvage and other markers of reperfusion success remain unclear.

Successful reperfusion is associated with a rapid, early increase in serum cardiac marker concentrations, which is thought to represent the “washout” of tissue cardiac markers after restoration of epicardial coronary blood flow (43) (Fig. 3). Thus, isolated ratios of early cardiac marker levels have been used to predict successful reperfusion after fibrinolysis in studies that confirmed epicardial patency angiographically (44–47). Myoglobin appears to be the most useful marker to evaluate early reperfusion success, because it has a rapid peak and early decay after successful reperfusion (47). Because isolated cardiac marker levels may represent only a “snapshot” time point in the process of reperfusion, however, cumulative marker release curves may better reflect overall reperfusion success. Further study is needed to determine how to use cardiac markers as surrogate markers of reperfusion.

ST segment resolution. Evaluating ST segment resolution with serial electrocardiograms was first recommended as a useful bedside marker of reperfusion success by Braunwald and Maroko 25 years ago (48). The clinical impact of the degree of ST segment resolution was defined by Schroder et al. (49), who showed a stepwise increase in mortality with complete (≥70%), partial (31% to 69%) or no (<30%) resolution of ST segment elevation after fibrinolytic administration. The prognostic significance of Schroder’s criteria for ST segment resolution after fibrinolysis has been validated in multiple studies (50–52) (Table 2). Thus, the degree of ST segment resolution after reperfusion therapy is a reliable, noninvasive predictor of mortality.

ST segment resolution appears to reflect restoration of myocardial tissue perfusion, not just epicardial flow. Rapid ST segment resolution within 30 to 60 min of successful primary angioplasty (patent IRA with TIMI flow grade 3) predicts greater improvement in ejection fraction, reduced infarct size and improved survival as compared with delayed ST segment resolution (23,53–55). Microvascular dysfunction may explain these findings because rapid ST segment resolution after successful primary angioplasty correlates with microvascular reflow into the infarct region as measured by MCE (56). Therefore, ST segment resolution at serial, static time points appears to represent a “snapshot” of global tissue reperfusion. Because reperfusion is a dynamic and often cyclic process, however, the ideal time to measure ST segment resolution after fibrinolysis is unclear.
Continuous monitoring of ST segment resolution is advantageous because it can be used to determine the exact time of reperfusion, to detect intermittent reocclusion that often occurs after fibrinolysis and to assess ST segment resolution at multiple time points (57) (Fig. 4). Multiple studies have shown the potential of continuous ST segment monitoring for detection of failed reperfusion and early risk stratification of patients with acute MI (58–60). The temporal pattern of ST segment resolution appears to estimate infarct size and left ventricular contractile recovery and can be used to identify ST segment re-elevation, which signifies infarct vessel reocclusion and is associated with higher mortality (59,61–63). Furthermore, compared with the angiographic assessment of reperfusion, the continuous ST segment resolution pattern was found to be the only independent predictor of mortality or congestive heart failure in patients treated with fibrinolytic agents (64). Therefore, continuous ST segment monitoring measures not only the degree of ST segment resolution, but also the speed and stability of reperfusion, and thus may be more useful than evaluating ST segment resolution at isolated, static time points.

**IMPROVING REPERFUSION THERAPY**

Fibrinolytic therapy is limited by inadequate epicardial patency and intermittent vessel reocclusion, whereas primary angioplasty is limited by treatment delays and lack of widespread access to catheterization facilities (31,65). New fibrinolytic agents that accelerate and enhance clot lysis have been developed, and coronary stenting produces higher initial rates of TIMI flow grade 3, as compared with primary angioplasty, but survival rates have not improved with these advances (65,66). Targeting the microcirculation with new adjunctive therapies, however, may help to breach the therapeutic "plateau" that exists with current reperfusion strategies.

**Antiplatelet therapy.** Platelet glycoprotein IIb/IIIa inhibitors are a promising adjunctive therapy for both fibrinolysis and primary angioplasty (67). In phase II, dose-ranging trials, the combination of partial-dose fibrinolytic agents and glycoprotein IIb/IIIa inhibitors accelerated and improved epicardial reperfusion, as compared with fibrinolytic therapy alone (68,69). The glycoprotein IIb/IIIa inhibitors also have been shown to improve outcomes in small studies.

**Table 2. Mortality by Degree of ST Segment Resolution After Fibrinolysis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time of ST Segment Analysis (min)</th>
<th>Follow-Up (days)</th>
<th>n</th>
<th>Complete</th>
<th>Partial</th>
<th>None</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAM (49)</td>
<td>180</td>
<td>35</td>
<td>1,516</td>
<td>2.8%</td>
<td>4.3%</td>
<td>9.2%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>INJECT (50)</td>
<td>180</td>
<td>35</td>
<td>1,398</td>
<td>2.5%</td>
<td>4.3%</td>
<td>17.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HIT-4 (51)</td>
<td>180</td>
<td>35</td>
<td>998</td>
<td>2.8%</td>
<td>6.0%</td>
<td>14.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI-14 (52)</td>
<td>90</td>
<td>30</td>
<td>444</td>
<td>1.0%</td>
<td>4.2%</td>
<td>5.9%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Complete ST segment resolution was ≥70% from baseline; partial resolution was 31% to 69% from baseline; no resolution was <30% from baseline.

HIT = Hirudin for Improvement in Thrombolysis; INJECT = International Joint Efficacy Comparison of Thrombolytics; ISAM = Intravenous Streptokinase in Acute Myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.
of patients undergoing primary angioplasty (70–72). Preliminary evidence suggests that reperfusion is enhanced with adjunctive glycoprotein IIb/IIIa blockade, but large mortality trials are needed to verify that such a strategy would reduce mortality when used with fibrinolytic agents or primary angioplasty.

The mechanism of benefit of glycoprotein IIb/IIIa blockade for both pharmacologic and mechanical reperfusion strategies may be related, in part, to enhanced myocardial tissue reperfusion. In patients with TIMI flow grade 3 in the IRA after primary stenting for acute MI, treatment with abciximab appeared to improve tissue reperfusion by improving peak flow velocity in the recanalized IRA, wall motion index values and global left ventricular function (73). Similarly, among patients with TIMI flow grade 3 in the IRA, the combination of abciximab and partial-dose alteplase improved distal coronary flow and the degree of ST segment resolution, as compared with alteplase alone (52,74). Continuous ST segment monitoring has also shown that combination therapy with fibrinolytic agents and glycoprotein IIb/IIIa inhibitors improves the speed and stability of myocardial tissue reperfusion, as compared with fibrinolytic monotherapy (75). Adjunctive glycoprotein IIb/IIIa blockade may improve endothelial function after epicardial reperfusion and may relieve microvascular obstruction caused by platelet-thrombin microemboli, but the mechanisms by which augmented antiplatelet therapy improves microvascular flow remain unclear.

Agents designed to improve tissue perfusion. Other adjunctive therapies that target microvascular dysfunction are thought to improve endothelial function of distal arterioles, restore myocardial metabolic homeostasis and ameliorate the inflammatory response initiated by myocyte necrosis and reperfusion injury. When used during a primary percutaneous coronary intervention, the intravenous vasodilators verapamil and nicorandil have been shown to enhance tissue perfusion in the infarct region, as measured by MCE (76,77). Glucose/insulin/potassium therapy appears to improve cellular metabolism in the infarct region after acute MI (78), but this therapy has not been tested in a large mortality trial (79). Despite promising studies of anti-inflammatory therapies in animal models of reperfusion injury, human clinical trials of agents designed to limit infarct size have been disappointing (79–87) (Table 3). The recent Acute Myocardial Infarction Study of ADenosine (AMISTAD) trial showed a reduction in infarct size when
Table 3. Randomized Trials of Agents Designed to Improve Myocardial Tissue Reperfusion

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>n</th>
<th>Primary End Point(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-2 (80)</td>
<td>IV metoprol</td>
<td>Lowers oxygen demand</td>
<td>1,390</td>
<td>EF at discharge</td>
<td>Negative (50.5% vs. 50.0%)</td>
</tr>
<tr>
<td>TAMI-4 (81)</td>
<td>Prostacyclin</td>
<td>Inhibits neutrophils; scavenges free radicals</td>
<td>50</td>
<td>IRA patency, EF</td>
<td>Negative (both lower)</td>
</tr>
<tr>
<td>TAMI-9 (82)</td>
<td>Fhosol</td>
<td>Inhibits neutrophils; improves oxygen delivery</td>
<td>430</td>
<td>Infarct size</td>
<td>Negative (22% vs. 17%)</td>
</tr>
<tr>
<td>ISIS-4 (83)</td>
<td>Magnesium</td>
<td>Stabilizes myocardial membranes</td>
<td>58,050</td>
<td>Death at 35 days</td>
<td>Negative (7.6% vs. 7.2%)</td>
</tr>
<tr>
<td>CORE (84)</td>
<td>RheothRx</td>
<td>Oxygen delivery</td>
<td>2,780</td>
<td>Death/shock/repeat MI</td>
<td>Neutral (13.6% vs. 12.7%)</td>
</tr>
<tr>
<td>AMISTAD (85)</td>
<td>Adenosine</td>
<td>Inhibits neutrophils; scavenges free radicals</td>
<td>236</td>
<td>Infarct size</td>
<td>Positive (13% vs. 19.5%)</td>
</tr>
<tr>
<td>HALT-MI (86)</td>
<td>Hu23F2G</td>
<td>Inhibits neutrophil adhesion to endothelial cells</td>
<td>420</td>
<td>Infarct size</td>
<td>Neutral (17.1% vs. 19.3%)</td>
</tr>
<tr>
<td>ADMIRE (87)</td>
<td>AMP579</td>
<td>Inhibits neutrophils; scavenges free radicals</td>
<td>311</td>
<td>Infarct size</td>
<td>Negative (11.8% vs. 9.9%)</td>
</tr>
</tbody>
</table>

*TThe primary end point included a multivariable regression analysis, which revealed a 33% relative reduction in infarct size with adenosine treatment (p = 0.03). ‡High dose Hu23F2G versus placebo. ¶High dose AMP579 versus placebo.

Adapted from Granger (79), with permission.

IMPLICATIONS FOR CLINICAL TRIALS

Because TIMI flow grades have been shown to correlate directly with mortality (28), the evaluation of new reperfusion therapies usually involves angiographic verification of patency in phase II, dose-ranging trials, followed by large, phase III mortality trials. With an expanded definition of reperfusion success that includes restoration of microvascular flow and myocardial tissue perfusion, however, other surrogate end points also appear promising. The amount of myocardial salvage in fibrinolytic and primary angioplasty trials, for example, has been determined by measurement of infarct size with cardiac markers and 99mTc-sestamibi SPECT (37,39,40,86,87). The relative efficacy of different fibrinolytic agents with regard to myocardial tissue reperfusion has also been evaluated with ST segment resolution at serial, static time points and with continuous ST segment monitoring (52,88–91). Other techniques to evaluate myocardial tissue perfusion, including coronary Doppler flow wires, MCE and cardiac MRI, have not been widely tested.

Despite the enthusiasm for these new surrogate end points (biomarkers) for acute MI trials, they should be carefully evaluated before they are routinely incorporated into clinical trials. Such biomarkers should correlate closely with mortality (the gold standard clinical end point), should be easily measured in most patients and should statistically explain the magnitude of the observed treatment effect with more than one therapy (92). Left ventricular ejection fraction was widely used as a surrogate end point for acute MI trials early in the development of fibrinolytic agents, but it later proved to be an unreliable measure of therapeutic efficacy (93). Despite the potential of infarct size measurement with cardiac markers or 99mTc-sestamibi SPECT and ST segment resolution as biomarkers of reperfusion success, therapies associated with reduced infarct size or improved ST segment resolution have not been proven to reduce mortality in large, phase III trials (52,85,88).

Given the changing definition of optimal reperfusion, phase II trials for acute MI should be reconfigured to include parallel efficacy arms that evaluate both epicardial and myocardial perfusion with invasive and noninvasive techniques (Table 4). Because early angiography after fibrinolysis can be performed only at a limited number of sites, the use of noninvasive techniques may allow more sites to participate in such trials and may accelerate their completion. Furthermore, the optimal integration of data collected for disparate biomarkers has not been determined. The use of parallel efficacy arms in phase II trials may help determine how to combine data to evaluate the overall therapeutic efficacy of a new reperfusion regimen and to validate noninvasive biomarkers as reliable surrogate end points. However, strategies will need to be developed to account for missing or uninterpretable data before biomarkers other than angiography can be routinely incorporated into phase II clinical trials in acute MI.

Conclusions. As the reperfusion era moves into the new millennium, the downstream shift of the open-artery hypothesis is expected to redefine the goals of reperfusion therapies to include not only rapid and sustained epicardial patency, but also restored microvascular flow and myocardial tissue perfusion. Given the rapid evolution of pharma-

Table 4. Redesigning Phase II Acute MI Trials

<table>
<thead>
<tr>
<th>Invasive End Points</th>
<th>Non-Invasive End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>Myocardial Reperfusion</td>
</tr>
<tr>
<td>TIMI flow grades</td>
<td>ST-segment resolution</td>
</tr>
<tr>
<td>cTFC</td>
<td>Serial static ECGs</td>
</tr>
<tr>
<td>MPG</td>
<td>Continuous ST monitoring</td>
</tr>
<tr>
<td></td>
<td>Myocardial Salvage/Infarct Size</td>
</tr>
<tr>
<td></td>
<td>Cardiac markers</td>
</tr>
<tr>
<td></td>
<td>99mTc-sestamibi SPECT imaging</td>
</tr>
</tbody>
</table>

cTFC = corrected TIMI frame count; ECGs = electrocardiograms; MPG = myocardial perfusion grade; SPECT = single-photon emission computed tomography; TIMI = Thrombolysis In Myocardial Infarction.
cologic and mechanical reperfusion strategies, phase II clinical trials for acute MI will need to be streamlined to accelerate the development of the most promising therapies and reperfusion strategies. Noninvasive biomarkers that assess myocardial tissue perfusion may therefore prove to be useful complements to angiography for evaluation of new reperfusion regimens. However, therapies that improve microvascular flow and myocardial perfusion must be proven to reduce mortality before the open-artery hypothesis can be shifted downstream.

Reprint requests and correspondence: Dr. Matthew T. Roe, Duke Clinical Research Institute, P.O. Box 17969, Durham, North Carolina 27715. E-mail: roe0001@mc.duke.edu.

REFERENCES