Reperfusion Revisited: Beyond TIMI 3 Flow

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Summary: Therapy for acute myocardial infarction has advanced dramatically since the early 1980s with the use of early intravenous fibrinolytic therapy. Combining low-dose fibrinolysis and platelet lysis appears to provide an additional increase in infarct-related artery (IRA) patency, but the large-scale mortality reduction trials evaluating this strategy are just getting under way. Recently, considerable attention has shifted away from the epicardial arteries to the microvasculature. Contemporary evidence suggests that epicardial patency does not necessarily translate to actual perfusion at the myocardial level. Techniques to evaluate beyond thrombolysis in myocardial infarction (TIMI) epicardial flow are now available and validated. In addition, there are promising treatments for the prevention or alleviation of certain forms of microvascular obstruction. This review attempts to clarify the confusion surrounding epicardial flow and “myocardial malperfusion” and to provide some insight into the next direction in acute myocardial infarction therapeutics.

Key words: TIMI flow, perfusion, echocardiography, infarct-related artery

Introduction

Therapy for acute myocardial infarction (MI) has advanced dramatically since the early 1980s with the use of early intravenous fibrinolytic therapy. Current therapy provides an almost 30% mortality decrease in randomized, controlled trials,^{1–4} with infarct-related artery (IRA) patency rates of approximately 50% at 90 min.^{5,6} Mechanical recanalization provides IRA patency rates of 75% [Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade], with a modest benefit in death and reinfarction rates compared with optimal fibrinolytic therapy.⁷

Combining low-dose fibrinolysis and platelet lysis appears to provide an additional increase in IRA patency,^{8–11} but the large-scale mortality reduction trials evaluating this strategy are just getting under way.

Recently, considerable attention has shifted away from the epicardial arteries to the microvasculature. Contemporary evidence suggests that epicardial patency does not necessarily translate to actual perfusion at the myocardial level. Techniques to evaluate beyond TIMI epicardial flow are now available and validated. In addition, we have promising treatments for prevention or alleviation of certain forms of microvascular obstruction. In this review, we will attempt to clarify the confusion surrounding epicardial flow and “myocardial malperfusion,” and provide some insight into the next direction in acute MI therapeutics.

Beyond Epicardial Patency

Coronary atherosclerotic plaque rupture and thrombosis of a major epicardial vessel are the underlying cause of acute ST-segment elevation MI. The ability to remove the occluding thrombus, by utilizing either fibrinolytic agents or mechanical techniques, and thus open the IRA, is referred to as “recanalization” or establishing IRA “patency.” “Reflow” is the visualization of contrast dye flowing beyond the site of the previous obstruction to the distal vessel. The quality of flow has been quantified by TIMI flow grade since the early days of intravenous fibrinolytic reperfusion therapy. “Myocardial perfusion” is the ultimate goal and reflects the distribution of blood to the capillary and tissue level. Despite the important differences in their meanings, these terms have unfortunately often been used interchangeably to characterize the outcomes of MI therapy.

The TIMI flow grades (Table I)¹² were established to provide a semiquantitative categorization of *epicardial* blood flow, with the implicit assumption that this would reflect *myocardial* reflow. TIMI 0/1 flow was deemed to be failure of “reperfusion,” while TIMI 2 and 3 flow grades were considered to be similar and denote successful reperfusion. Subsequently, numerous trials have proven this categorization as faulty. Clinical outcomes, such as ejection fraction, regional wall motion, risk of congestive heart failure, and mortality, are all inferior with TIMI 2 flow compared with TIMI 3 flow.^{13–19} In fact, the clinical outcomes with TIMI 2 flow are much closer to TIMI 0/1 than to TIMI 3 flow outcomes.

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TABLE 1 Thrombolysis in Myocardial Infarction (TIMI) flow grade

Grade 0	No penetration of contrast past the clot in the infarct-related artery
Grade 1	Contrast flows past vessel occlusion but does not fill to terminal portion of vessel
Grade 2	Infarct-related vessel fills to full length, but slower than adjacent normal vessels
Grade 3	Normal filling of infarct-related artery in comparison with adjacent vessels

Table adapted from data published in the TIMI Study Group: The Thrombolysis in Myocardial Infarction (TIMI) trial: Phase I findings. *N Engl J Med* 1985;312:932-936.

As defined, TIMI 2 flow indicates a patent epicardial vessel with contrast reaching the distal segments but at a slower filling rate or slower efflux when compared with flow in a normal vessel. There are two potential reasons for this delay in blood flow. Complex plaque fracture, dissection, or residual thrombus in the epicardial vessel can give the appearance of a widely patent vessel and yet inhibit blood flow to the distal segments. Angiographic signs are usually suggestive, and further evaluation with intravascular ultrasound can be definitive. In addition, stenting of the IRA reduces the likelihood of dissection as the principal etiology of slow flow. The second reason involves the distal microcirculation. Obstruction to flow at this level prevents brisk, complete emptying of the epicardial vessel due to a decrease in the total cross-sectional area of the aggregate vessels. Overall, with current fibrinolytic therapy, optimal myocardial perfusion is established in only approximately 25% of patients (Fig. 1).²⁰

Microcirculatory Malperfusion

There are two broad categories related to abnormal microcirculation in the setting of myocardial reperfusion. The early phase, referred to as microvascular obstruction, is due to platelet microembolism and de novo thrombosis. The later phase represents reperfusion injury and involves tissue edema, neutrophil aggregation, and free-radical release.

Microvascular obstruction: The initial event, acute microvascular obstruction due to platelet microemboli/thrombi, begins concurrently with fibrinolytic therapy. A combination of red (fibrin- and red blood cell-rich) and white (platelet-rich) clots is responsible for coronary obstruction after plaque rupture. Current MI therapy does not affect the platelet component, such that as fibrinolysis occurs (and fibrin is lysed), and fragments consisting of platelet aggregates may be dislodged and become microemboli, which can wedge in the microcirculation and cause obstruction to flow at that level. Furthermore, fibrinolysis generates elevated levels of free thrombin, which is one of the most potent platelet agonists known. In the setting of microcirculatory spasm, due to the release of platelet products (adenosine diphosphate, serotonin, thromboxane A₂), and sluggish flow after an ischemic insult, these activated platelets are prone to aggregate, thus causing further microvascular obstruction.

FIG. 1 Anticipated diminishing proportion of patients successively meeting each of the criteria for optimal reperfusion after treatment for acute myocardial infarction with an accelerated regimen of tissue-type plasminogen activator. Although individual outcomes are treated as independent in this schematic, there probably is some degree of interaction between outcomes, such as TIMI grade 2 flow and reocclusion, although the magnitude of such interactions has not yet been defined. To the extent that this figure fails to account for these interactions between outcomes, the attrition in optimal reperfusion is exaggerated. The adverse effects of critical residual stenosis, relatively late administration of thrombolytic therapy, and reperfusion injury are not included in this diagram; to the extent that these factors limit effective reperfusion, this figure underestimates the attenuation of thrombolytic benefit. Reproduced with permission from Lincoff AM, Topol EJ: Illusion of reperfusion: Does anyone achieve optimal reperfusion during acute myocardial infarction? *Circulation* 1993;88:1361-1374.

Pathologic studies have found coronary microcirculatory thrombi in the hearts of patients who died of ischemic heart disease.^{21, 22} Animal studies provide further evidence of microcirculatory thrombosis and embolization.²³ Our neurology colleagues have provided the most convincing evidence for postischemic microvascular thrombosis in animal stroke models. Indium-111 (In)-labeled platelets have been shown to accumulate in the ipsilateral cerebral cortex in cat,²⁴ rat,²⁵ and dog^{26, 27} models of stroke and reperfusion.

Reperfusion injury: The second cause of myocardial malperfusion is a manifestation of reperfusion injury. Beginning in the first few hours after recanalization of the IRA, and probably continuing for a few days, is the process of reperfusion injury "no reflow." Described originally by Kloner *et al.*²⁸ in 1974, this process involves the evolution of tissue level pathologic changes that hinder microvascular flow. On histologic examination, myocyte necrosis alone, or in combination with microvascular damage, is observed.²⁹ However, microvascular damage in isolation is not found. This suggests that microvascular obstruction can be the result, not the cause, of tissue damage. Contraction band necrosis³⁰ and tissue level edema are also characteristic features. In light of our recent understanding of the process of microvascular platelet embolism/thrombosis, the reason for the lack of isolated microvascular involvement is unclear. A possible explanation for the lack of microvascular thrombosis in the original work of Kloner *et al.* relates to the

mechanism of obstruction. Coronary obstruction was produced by an external snare; therefore, there would have been no fragmentation of thrombus or increased platelet activation.

Neutrophil accumulation appears to occur over the first 24 h after recanalization.³¹ Neutrophils and the inflammatory response play a role in normal healing after MI. In excess, neutrophils may accumulate in the microvasculature, further obstructing flow in the later hours after recanalization. Furthermore, with the release of inflammatory enzymes by the excess neutrophils, additional tissue damage and necrosis may occur. Neutrophil depletion has been shown to decrease reperfusion injury in animal models.³²⁻³⁵ Oxygen free radicals are generated soon after the release of the epicardial obstruction. Free-radical scavengers have proven to be effective in reducing reperfusion injury in animal models.³⁶⁻³⁸ Unfortunately, this success has not been replicated in clinical trials.³⁹⁻⁴¹ Microvascular spasm, dysfunction, and hyperpermeability⁴² have been implicated in this process as well.

From this discussion it is clear that the term "no reflow" is being applied much too broadly and imprecisely. It was initially meant to refer to the pathologic changes associated with late reperfusion injury. Clinical trials of potential treatments for this process have thus far been consistently negative. Microvascular obstruction, which may occur well before there is an inflammatory reaction, is a separate entity entirely. Reversal of this microvascular obstruction would improve flow in the distal vascular bed and maximize myocardial salvage. This improved flow could translate into improved clinical outcomes. Figure 2 demonstrates the time course of events.

Clinical Diagnostic Evaluation

While TIMI flow grade is easily ascertained, it does not provide determination of actual myocardial perfusion status. Techniques that are more sensitive to microcirculatory flow have been developed and validated over the last decade. Four techniques are well studied and available in the clinical setting: myocardial contrast echocardiography (MCE), Doppler flow

wire studies, magnetic resonance imaging (MRI), and nuclear scintigraphy. These techniques can not only define the presence or absence of myocardial perfusion, but also grade the degree of perfusion. An important clue to the mechanism of malperfusion (microembolism/de novo thrombosis versus reperfusion injury/necrosis) is the length of time between epicardial patency and microvascular imaging. Evaluation performed in the early hours would be indicative of microvascular obstruction by platelet emboli/thrombi. Evaluations after the first 2 to 3 h would reflect progressively more reperfusion injury.

MCE is a technique that provides significant amounts of information in patients with acute MI. Echo contrast injections prior to establishing patency of the infarct-related vessel can define the area of myocardium at risk and in doing so establish a baseline for determining the adequacy of myocardial reperfusion. MCE perfusion patterns have been correlated with TIMI flow grades. In a study by Ito *et al.*,⁴³ 18 of 18 patients with TIMI 2 flow after IRA recanalization displayed reduced myocardial perfusion on MCE, as defined by a ratio of contrast defect area (postrecanalization to prerecanalization) >25%. However, of greater significance is the fact that 11 of 68 patients (16%) with TIMI 3 flow also showed reduced myocardial perfusion. Patients with TIMI 3 epicardial flow, but reduced myocardial perfusion on MCE, had reduced wall-motion scores and ejection fraction at 28 days (Table II), similar to patients with TIMI 2 flow. Other studies have corroborated these findings.^{44, 45} These studies verify that not only is there dissociation between epicardial flow and myocardial perfusion but there is significant correlation with myocardial performance parameters.

Ultimately, the goal of reperfusion therapy is to salvage the maximal amount of myocardium in an area of infarction. Several studies have evaluated the comparison of myocardial con-

FIG. 2 Schematic demonstrating potential outcomes at the microvascular and myocardial level after fibrinolysis. * = The potential target for therapeutic intervention to increase myocardial salvage. PMN = polymorphonuclear monocytes.

TABLE II Functional outcomes

	Day	TIMI 2	TIMI 3	
			No reflow	Reflow
WMS	1	19 ± 3 ^a	20 ± 4 ^b	15 ± 5
	28	18 ± 3 ^b	17 ± 4 ^b	9 ± 6 ^c
LVEF, %	1	38 ± 8 ^a	35 ± 11 ^a	46 ± 13
	28	40 ± 8 ^b	44 ± 12 ^b	57 ± 12 ^c
RWM, SD/chord	1	-3.35 ± 0.40	-3.62 ± 0.40 ^a	-3.01 ± 0.61
	28	-3.20 ± 0.39 ^b	-3.00 ± 0.53 ^b	-2.09 ± 0.93 ^c

^a P < 0.05 versus TIMI 3/reflow.

^b P < 0.001 versus TIMI 3/reflow.

^c P < 0.001 versus Day 1.

Values are mean ± SD (standard deviation).

Abbreviations: TIMI = Thrombolysis in Myocardial Infarction, WMS = wall motion score, LVEF = left ventricular ejection fraction, RWM = regional wall motion. Reproduced with permission from Ito H, *et al.*: Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. *Circulation* 1996;93: 1993-1999.

trast echo to dobutamine stress echo (DSE) in determining myocardial viability.^{46, 47} The absence of MCE evidence of perfusion demonstrates a strong correlation with nonviable myocardium on DSE. Presence of contrast perfusion at the myocardial level shortly after recanalization indicates probable viability but does not predict it absolutely. Overall, the sensitivity and specificity for defining myocardial viability for MCE are 100 and 46%, and for DSE are 71 and 88%, respectively. This correlates with data from Bolognese *et al.*⁴⁸ in a study using primary angioplasty for recanalization. The sensitivity and specificity for predicting viability with MCE were 96 and 18%, while for DSE they were 89 and 91%, respectively. This gives MCE a positive predictive value of 41% while DSE is 86%, along with a negative predictive value of 89% (MCE) and 93% (DSE). The reason for this discrepancy of nonviable tissue demonstrating perfusion is unclear. However, it probably represents areas of myocardium that will undergo further evolution from ischemic injury to reperfusion injury to necrosis. Further evidence for this phenomenon comes from Ito *et al.*, who found that a moderate correlation between MCE and late functional improvement increased when the MCE was performed late (i.e., Day 28) (Fig. 3).⁴⁹

The largest drawback to the routine use of MCE is that intracoronary injection of echo contrast is needed. This would typically necessitate echocardiography personnel to be available around the clock or for the invasive catheterization to be performed during the usual hours of echo support availability. Porter *et al.*⁵⁰ have recently demonstrated adequate coronary imaging with a new generation echo contrast agent, perfluorocarbon-exposed sonicated dextrose albumin (PESDA), during intravenous injection. Along with harmonic imaging, the use of this contrast agent would allow studies to be performed at a time separate from any angiography.

The second technique to evaluate microvascular flow is Doppler flow wire studies. In animal studies, basal flow in viable tissue is unimpaired but coronary flow reserve (CFR) decreases initially and then returns to normal within the first week. Intracoronary adenosine improves this flow reduction in viable tissue. Irreversibly damaged tissue shows a decrease in both basal flow and CFR, which does not improve with pharmacologic treatment.⁵¹

Correlation between Doppler flow wire studies and MCE was demonstrated in a study by Iwakura *et al.*⁵² Patients with MCE perfusion defect and TIMI 2 or 3 epicardial flow exhibited three Doppler findings: (1) a reduction in systolic antegrade flow, (2) an abnormal early systolic retrograde flow, and (3) a rapid deceleration of the diastolic flow velocity. Other studies have found a decreased diastolic-to-systolic flow ratio⁵³ or decreased CFR^{54, 55} in coronary arteries even after successful recanalization for acute MI.

To understand these findings, we need to look closely at the pathophysiology involved in either microvascular obstruction from platelet emboli/thrombi or reperfusion injury. Coronary flow patterns consist of predominant antegrade flow during diastole with lesser flow during systole. This is due to the increase in tissue pressure with each cardiac systole, which in turn increases the downstream pressure against which blood must flow. In the absence of a flow-limiting lesion in the epicardial vessel, the microcirculation defines the flow rate of blood in the coronary circulation by autoregulation. In the presence of microvascular obstruction due to either platelet emboli/thrombi, vascular spasm, or injury, there will be a decrease in the aggregate cross-sectional area of the vessels. This decreased area will in turn increase the downstream pressure and decrease the velocity of blood flow. Upon evaluation of epicardial flow, the coronary reserve, diastolic-to-systolic

Fig. 3 Comparisons of the late-stage regional wall motion (RWM) with (A) perfusion index (PI) ratio at Day 1 and (B) PI ratio at day 28. ● = Patients with no reflow; ○ = patients with coronary reflow. (A) There is only a rough correlation between the two variables. (B) A correlation between two variables is improved. SD = standard deviation. Reproduced with permission from Ito H, *et al.*: Temporal changes in myocardial perfusion patterns in patients with reperfused anterior wall myocardial infarction: Their relation to myocardial variability. *Circulation* 1995;91: 656-662.

flow ratio, and individual flow patterns will be affected. To distinguish between necrotic tissue and potentially reversible changes, the degree of abnormality, effects of pharmacologic treatments, and time course need to be evaluated.

The third diagnostic tool available is MRI. Most of the data on the use of MRI for evaluating myocardial perfusion/microvascular integrity after coronary occlusion and reperfusion come from animal studies. Rat and canine studies using various contrast agents and techniques (first-pass signal, microvascular leak/tissue accumulation) have shown promise for application in clinical settings. MRI has been able to distinguish reversibly reperfused myocardium from irreversibly damaged myocardium,^{56,57} to evaluate the microvascular integrity,^{42,58} and to correlate defect size with infarct size.^{59,60} In a study by Wu *et al.*,⁶¹ MRI-defined perfusion defects have been correlated with clinical outcomes.

The benefit of MRI is its ability to provide a measure of infarcted territory as well as to evaluate microvascular obstruction and reperfusion. Unfortunately, this means that the patient must be stable enough for transport and a prolonged study in a relatively insecure location. This limitation mandates that the study be performed days after the initial event. The obligatory time delay confounds the ability to distinguish between microvascular perfusion defects due to microvascular obstruction versus evolving reperfusion injury. As discussed earlier, we have been unsuccessful at reversing or altering the process of reperfusion injury. For a diagnostic tool to be clinically useful in tailoring therapy, it must provide the necessary information within the window of time when an intervention can affect the outcome. That window is the first 1 to 2 h of reperfusion, when a significant amount of microvascular obstruction can be expected to be attributable to platelet microemboli/thrombi.

Nuclear imaging with thallium/technetium or positron emission tomography (PET) is the fourth diagnostic modality available. This modality is also the least well investigated in terms of post-MI evaluation. Animal studies have shown that PET can demonstrate the presence or absence of microvascular flow.^{62,63} Schofer *et al.*⁶⁴ were the first group to demonstrate abnormal microvascular perfusion in the setting of acute MI. Kondo *et al.*⁶⁵ demonstrated that patients with normal reperfusion on technetium-99m scintigraphy immediately after recanalization had improved wall motion in the at-risk area on follow-up.

Nuclear evaluation of myocardial perfusion in the setting of acute MI has many of the same disadvantages as MRI. It requires that the patient be transported to a less medically secure environment. Furthermore, imaging must occur within 4 to 6 h of injection, which influences which form of microvascular obstruction (platelet-mediated or reperfusion injury) is being evaluated. Overall, each of these diagnostic tools has advantages and disadvantages, which are summarized in Table III.

Clinical Relevance

Among patients with "successful" infarct vessel recanalization (TIMI 3 flow), the reported incidence of myocardial

malperfusion ranges from 22 to 50%, with the majority of studies reporting approximately 30%. Alterations in myocardial blood flow and microvascular function over time have been evaluated in both animals and humans. Coronary blood flow was originally measured with radiolabeled microspheres in animal models. Cobb *et al.*⁶⁶ demonstrated that after 2 h of coronary occlusion in a dog model, vasodilation and hyperemia were seen at 15 min of reperfusion. However, by 4 h and again at 3 days, flow was significantly decreased in the previously ischemic region. Later animal studies corroborated these findings and provided comparisons utilizing PET imaging and MCE^{62,63,67,68} techniques.

The duration of follow-up has been extended to 2 weeks in patient trials. Neumann *et al.*⁵⁴ demonstrated improvement in basal flow and coronary flow reserve between Doppler flow studies immediately after percutaneous transluminal coronary angioplasty (PTCA)/stent placement for acute MI at Day 14 follow-up. Studies utilizing MCE provide further evidence of improved myocardial perfusion over several weeks.⁴⁹ Brochet *et al.*⁶⁹ evaluated patients at Days 1 and 9 after recanalization for acute MI. They found three distinct patterns: sustained myocardial perfusion, sustained nonperfusion, and improved perfusion. The groups with sustained or improved perfusion exhibited the most improvement in wall-motion scores in the risk areas compared with areas of sustained perfusion defects (Fig. 4).

The available data suggest a rapid fall-off in myocardial perfusion after a brief period of hyperemia and vasodilation. This result is consistent with the development of microvascular thrombosis and microvascular spasm in the first several hours after recanalization of the IRA. This is followed by a period of evolution in the tissue and microvasculature. Some patients progress and maintain a level of microvascular obstruction. These are the patients with the most significant ischemic injury, either from the epicardial occlusion or microvascular obstruction in the first few hours, and have the least salvageable tissue and most necrosis. A second group of patients demonstrate a significant decrease in flow initially, with

TABLE III Quantitative comparison of the diagnostic techniques for evaluating myocardial malperfusion

	Early evaluation after MI	Strength of supporting data	Amount of data collected by study	Accessibility
Myocardial contrast echo	+++	+++	++	++
Doppler flow wire studies	+++	++	++	+++
MRI	+	+	+++	+
Nuclear imaging	+	+	+	+

+++ = Highest rating; + = lowest rating.

Abbreviations: MI = myocardial infarction, MRI = magnetic resonance imaging.

FIG. 4 Bar graph showing serial changes in mean segmental wall motion score between Day 0 (solid bars), Day 9 (hatched bars), and follow-up (open bars) in the three groups of segments defined on the basis of changes in myocardial contrast echo pattern between Day 0 and Day 9. NS = not significant. Reprinted with permission from the American College of Cardiology (*J Am Coll Cardiol*, 1998;32:2011–2017).

subsequent improvement. These patients have resolution of the microvascular obstruction and salvage of a larger proportion of tissue. The last group of patients has evidence of myocardial perfusion that is stable throughout their follow-up. These patients have the most effective recanalization and myocardial salvage. If we can alleviate the initial microvascular obstruction, we can most likely increase the percentage of patients in the latter two groups and provide a better outcome in acute MI care.

The lack of myocardial perfusion after IRA recanalization affects functional improvement and myocardial viability. How does this translate into clinical outcomes? Three small patient series have evaluated the correlation between myocardial per-

fusion defects and clinical outcomes. Those results are summarized in Table IV^{61, 70, 71} and Figure 5.⁶¹ All reported comparisons attain statistical significance.

Treatment Options

Treatment of myocardial malperfusion has to be directed at the potential mechanisms involved. Treatment of the newly recognized entity of platelet microembolism-induced microvascular obstruction demonstrates encouraging results. In contrast, therapeutic interventions for delayed reperfusion injury have provided limited, if any, benefit to date.

The most promising advance in the treatment of myocardial malperfusion is directed against the platelet microemboli/thrombi formation causing early microvascular obstruction. A murine model of ischemic stroke/reperfusion⁷² demonstrates a decrease in platelet accumulation in the ipsilateral hemisphere in mice treated with a novel IIb/IIIa receptor antagonist (SDZ GPI 562) (Fig. 6). Clinical anecdotal evidence⁷³ also exists of the benefit of IIb/IIIa antagonists in reversing early malperfusion after coronary interventions. Neumann *et al.*⁵⁵ reported the most convincing clinical evidence. Two hundred patients with acute MI undergoing primary PTCA/stent placement were randomized to receive abciximab or conventional therapy. The groups exhibited similar basal and peak flows immediately after recanalization; however, the abciximab group demonstrated a significantly greater increase in both basal and peak flows at the Day 14 evaluation (Fig. 7). Furthermore, the groups demonstrated significant improvement in wall motion scores in the treated group compared with controls (Fig. 8). A comparison of 30-day clinical outcome (death, nonlethal reinfarction, target lesion reintervention) demonstrated an 80% reduction with abciximab [odds ratio of 0.20 (confidence interval: 0.04–0.94); $p = 0.031$].

The utilization of IIb/IIIa antagonists as a treatment modality for early myocardial malperfusion has far-reaching implications. In addition to the benefits in maintaining epicardial vessel patency, IIb/IIIa antagonists can decrease or eliminate

TABLE IV Summary of clinical outcomes on the basis of myocardial malperfusion

Study	Patients (n)	Diagnostic modality	Follow-up	Results
Sakuma <i>et al.</i> ⁷⁰	50	MCE	22 Months (median)	<ul style="list-style-type: none"> • Compared with patients with <45% risk area and minimal defect • Major cardiac events of death, MI, CHF, admission with relative risk of 10.7 • Major cardiac events and target lesion revascularization with relative risk of 3.69
Ito <i>et al.</i> ⁷¹	126	MCE	Hospital stay	<ul style="list-style-type: none"> • Comparison with patients with MCE-defined reflow • Reperfusion arrhythmia 19 vs. 14% • Any arrhythmia except reperfusion 10 vs. 6% • Early CHF 21 vs. 12% • Late CHF (after 3 days) 6 vs. 1%
Wu <i>et al.</i> ⁶¹	44	MRI	16 Months (median)	<ul style="list-style-type: none"> • Cardiac death, reinfarction, CHF, stroke • Comparison of patients with vs. without MRI defect (45 vs. 9%)

Abbreviations: MCE = myocardial contrast echocardiography, MI = myocardial infarction, CHF = congestive heart failure, MRI = magnetic resonance imaging.

FIG. 5 Event-free survival (clinical course without cardiovascular death, reinfarction, congestive heart failure, or stroke) for patients with and without magnetic resonance imaging microvascular obstruction. Reproduced with permission from Wu K, *et al.*: Prognostic significance of microvascular destruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998;97:765-772.

the downstream microembolization and thrombosis that cause early microvascular obstruction. In doing so, these agents should alleviate ongoing ischemia, reduce the evolution of reperfusion injury, and maximize myocardial salvage.

The treatment of the multiple mechanisms involved in reperfusion injury has been less successful than that for platelet microcirculatory obstruction. Vasodilators have been used in an attempt to target vasospasm as a potential contributor to early abnormal tissue perfusion. Nicorandil⁷⁴ and papaverine⁷⁵

FIG. 7 Plot of the differences between 14-day follow-up and initial postinterventional study in basal flow velocity and in papaverine-induced peak flow velocity at treated lesion. Columns represent mean difference. Error bars indicate 95% confidence interval. Error bars not including zero indicate that change between initial study and follow-up is statistically significant at 0.05 level. P values above columns refer to differences between two treatment groups. ■ = abciximab, □ = heparin. Reproduced with permission from Neumann FJ, *et al.*: Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695-2701.

FIG. 6 Indium-111-labeled platelet accumulation expressed as a ratio of ipsilateral/contralateral cpm in control (No stroke, n = 11) and experimental animals. Stroke + vehicle = saline (n = 10), Stroke + GPI = glycoprotein IIb/IIIa inhibitor (n = 10). Data are shown as mean $\pm$ SEM. *P < 0.005 versus No stroke and Stroke + GPI; p = not significant between No stroke and Stroke + GPI. Reproduced with permission from Choudhri TF, *et al.*: *J Clin Invest* 102:1301-1310 (1998).

have been utilized in small series, with improvement noted in perfusion grades. Verapamil administered via intracoronary injection has been reported to improve angiographic^{76,77} and MCE⁷⁸ defined abnormal perfusion.

Adenosine has been successful in animal models in reducing infarct size and improving regional myocardial blood flow.⁷⁹ This benefit was initially considered a function of its vasodilatory effects. However, recent evidence from Mina-

FIG. 8 Plot of differences between 14-day follow-up and initial postinterventional study in wall-motion index (A) and in chords with hypokinesis (B). Columns represent mean difference. Error bars indicate 95% confidence interval. Error bars not including zero indicate that change between initial study and follow-up is statistically significant at 0.05 level. P values above columns refer to differences between the two treatment groups. ■ = abciximab, □ = heparin. Reproduced with permission from Neumann FJ, *et al.*: Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695-2701.

mino *et al.*²³ supports an additional effect of adenosine on decreasing P-selectin-dependent platelet thromboembolism. Among patients with anterior wall MI, the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial⁸⁰ demonstrated a decrease in infarct size in patients administered adenosine compared with placebo, when administered in conjunction with fibrinolytics.

Conclusion

The realization has been reached that the static appearance of the epicardial artery is often dissociated from the underlying myocardial perfusion. Tissue level perfusion is an evolving process and early microvascular embolization or de novo thrombus formation can be resolved, providing increased myocardial salvage. Both ongoing ischemia and the progression of reperfusion injury can lead to further myocardial necrosis, despite the angiographic appearance of a patent IRA.

In 1999, we have the ability to look beyond the epicardial vessel and evaluate the true tissue perfusion status. The understanding of the various tissue and microvascular level processes allows therapy to be tailored appropriately. Currently available IIb/IIIa receptor antagonists have been demonstrated to alleviate the early platelet-mediated microvascular obstruction, with subsequent increase in myocardial salvage. This has already proven to improve myocardial functional status and is associated with improved clinical outcomes as well.

The future of true myocardial reperfusion hinges on our ability to achieve a further decrease in microvascular obstruction in the early and delayed phases. Currently, the combination of low-dose fibrinolytics and platelet-lysis therapy is being evaluated for clinical outcomes. Further study of the impact of IIb/IIIa receptor antagonists on early microvascular obstruction should be evaluated to corroborate the initial trials. Direct thrombin antagonists or low-molecular-weight heparin could potentially have an additive benefit due to their ability to block the effects of thrombin on the coagulation cascade and platelet activation. Finally, work still needs to be done to decrease the delayed microvascular obstruction and tissue damage from reperfusion injury. It appears that the confusion surrounding myocardial reperfusion is gradually lifting and potential avenues of therapeutic intervention are being pursued.

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