The No-Reflow Phenomenon: Epidemiology, Pathophysiology, and Therapeutic Approach

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Over the past 20 years, advances in the management of ST segment elevation myocardial infarction have focused on the rapid achievement of patency in the infarct-related artery. The limitation of this therapeutic strategy has been exposed with the development of diagnostic techniques to assess coronary microcirculation, including myocardial contrast echo, magnetic resonance imaging, myocardial perfusion grading, and the coronary flow wire. These methods have expanded our ability to understand and recognize the no-reflow phenomenon, which describes the absence of tissue perfusion despite epicardial coronary artery patency and flow. Although the mechanisms responsible for the development of no reflow are not fully understood, the end result is microvascular damage produced by microvascular obstruction or reperfusion injury. Ideally, early recognition of the no-reflow phenomenon should provide an opportunity for therapeutic intervention designed to augment tissue perfusion and maintain the viability of myocardium at risk. A number of pharmacologic agents are being used in conjunction with percutaneous transluminal coronary angioplasty in an attempt to improve microvascular perfusion. These include IIb/IIIa receptor antagonists, adenosine, verapamil, and the experimental agent nicorandil. In the new millennium, the emphasis of reperfusion therapy is being shifted downstream from its exclusive focus on the epicardial artery to assuring normal blood flow at the tissue level. This article will review the epidemiology, pathophysiology, and therapeutic approach to this vexing clinical problem. [Rev Cardiovasc Med. *2005;6(2):72-83*]

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It is well established that myocardial necrosis is progressive after acute coronary occlusion. Restoration of blood flow within approximately 6 hours can interrupt this process and reduce the ultimate extent of infarction. For this reason, the immediate goal of therapy in patients with acute ST elevation myocardial infarction (STEMI) is to establish patency of the infarct related artery (IRA) as quickly as possible through either pharmacologic or mechanical means. A large

body of clinical data indicates that establishment of normal (TIMI-3) blood flow limits infarct size, improves systolic function, and reduces short- and long-term morbidity and mortality.

In some patients, however, achievement of epicardial artery patency does not produce clinical benefit. In fully 25% of patients in whom arterial obstruction is successfully relieved, little or no additional myocardial perfusion results. These patients demonstrate the phenomenon termed "no reflow" and exhibit a substantial increase in overall morbidity and mortality.[1] This article will review the epidemiology, pathophysiology, and therapeutic approach to this vexing clinical problem.

Historic Perspective
Animal Models
The term "no reflow" was initially described by Ames and colleagues based on experimental studies of cerebral ischemia in rabbits.[2] When the brains of these animals were subjected to interruption of cerebral blood flow for less than 2 minutes, normal cerebral perfusion was observed as soon as blood flow was restored. Longer periods of ischemia, however, resulted in the absence of reperfusion despite relief of vessel obstruction. Kloner and colleagues documented a similar phenomenon during studies of experimental myocardial infarction in dogs.[3] Animals subjected to transient occlusion of the proximal coronary artery for 40 minutes showed normal myocardial reflow. However, transient coronary occlusion for more than 90 minutes resulted in only partial restoration of myocardial blood flow following relief of obstruction. Pathological examination of the no-reflow zones showed significant microvascular damage in the form of swollen endothelium, endothelial

protrusions, and interstitial and myocardial edema. This microvascular damage was confined to infarcted areas and was thought an unlikely cause of myocyte necrosis.

These initial studies provided the basis for conventional wisdom regarding the phenomenon of no reflow (ie, it is mainly a result and not a cause of myocyte necrosis).

However, this infarction model, directly occluding an artery followed by reperfusion, does not simulate the pathophysiology of acute myocardial infarction in man. In the latter circumstance, coronary occlusion results from thrombus formation at the site of a disturbed plaque and reperfusion is achieved by chemical thrombolysis or direct mechanical percutaneous transluminal coronary angioplasty (PTCA).

Sakuma and associates[4] provided further insight into this phenomenon in a study in which a thrombus was created in the left anterior descending artery (LAD) of 6 dogs and angioplasty was performed, achieving TIMI 3 flow. Myocardial contrast echo (MCE) studies showed that the no-reflow zone immediately after reperfusion overestimated the infarct size compared to postmortem pathological examination. This larger no-reflow zone decreased with time and more closely approximated the infarct size at 60 minutes post-reperfusion. The study thus demonstrated that the extent of the no-reflow zone

immediately after reperfusion is not the result of myocardial necrosis and is potentially reversible.

Clinical Observations
In man, the no-reflow phenomenon was first recognized in the cardiac catheterization laboratory following percutaneous coronary intervention (PCI) and thrombolytic therapy. In this setting, angiographic no reflow is defined as any TIMI flow of less than 3, despite restored target vessel patency, in the absence of dissection, thrombus, spasm, or high-grade, residual stenosis. No reflow is conceptually distinct from the phenomenon of reperfusion injury, which refers to myocyte damage resulting from the complex interaction between leukocytes, platelets, and endothelial cells following reperfusion.

The classification of angiographic coronary blood flow introduced by the TIMI investigators[5] (Table 1) has gained widespread acceptance. Historically, TIMI 0-1 was considered failed reperfusion therapy, where achievement of TIMI 2 or TIMI 3 was considered successful. Subsequently, meta-analysis of 5 thrombolytic trials[6] showed that similar morbidity and mortality were observed for patients with TIMI grade 2 flow as was seen in the 0-1 range and that only the achievement of TIMI 3 flow resulted in significant improvement in clinical outcome. Similar findings were replicated in angioplasty trials in

Table 1
Thrombolysis in Myocardial Infarction (TIMI) Flow Grade
Grade 0 — No penetration of contrast past the thrombus in the infarct related artery (IRA)
Grade 1 — Contrast flows past the thrombus but does not fill the terminal portion of the vessel
Grade 2 — IRA fills to full length but slower than adjacent vessels
Grade 3 — Normal filling of IRA in comparison with adjacent vessels

acute MI.[7] Therefore, TIMI 2 flow is no longer considered successful reperfusion. However, it was presumed that the achievement of TIMI 3 flow indicated complete blood flow restoration.

Concomitant evaluation of tissue blood flow using MCE has added an additional dimension to our understanding. In a study by Ito and coworkers,[8] intracoronary injection of sonicated microbubbles was used to evaluate microvascular perfusion in 86 patients who received immediate reperfusion therapy for acute anterior wall MI. Twenty-one percent had TIMI 2 and 79% had TIMI 3 flow. The study validated the lack of tissue perfusion in patients with TIMI 0-2 flow. Interestingly, the study also demonstrated that 16% to 25% of patients with TIMI 3 flow had areas with absent tissue perfusion.

The prognostic importance of myocardial perfusion has been demonstrated in multiple clinical trials. Data from Ito's study suggest that patients with normal epicardial flow and absent myocardial perfusion have similar outcomes compared to patients with angiographic no reflow in terms of residual left ventricular systolic function. In those patients with TIMI 3 flow, greater improvement in left ventricular ejection fraction (LVEF) was observed in patients with normal perfusion documented by contrast echo, whereas those with TIMI 3 flow and evidence of no reflow at the tissue level had a relative lack of functional recovery similar to that observed in patients with TIMI 2 flow.

Recently, Constantini and colleagues[9] evaluated the impact of myocardial blush grades on mortality in 1301 patients enrolled in the CADILLAC trial, which randomized patients with acute MI into angioplasty versus stenting arms, with or without abciximab therapy. Despite TIMI 3 flow in 96.1% of patients,
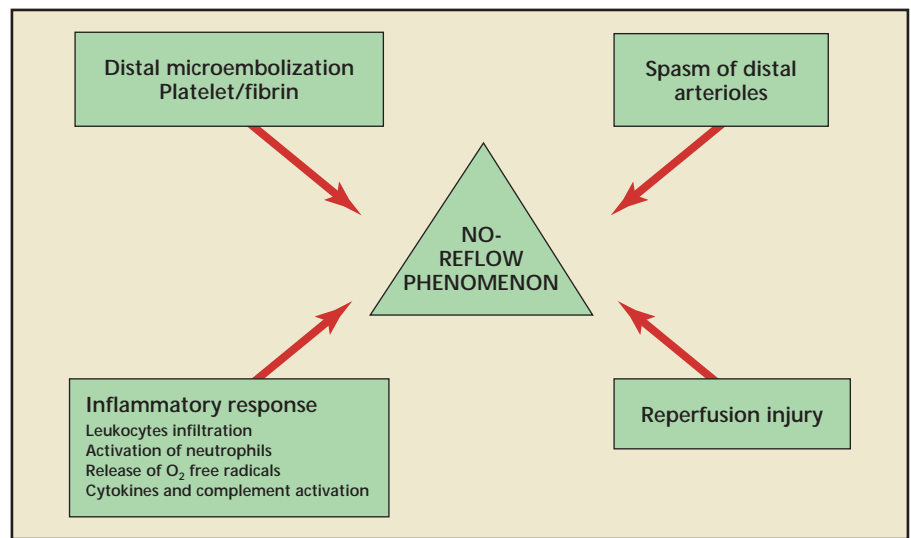

Figure 1. *Pathophysiology of microvascular dysfunction after epicardial perfusion in patients with acute myocardial infarction.*

myocardial perfusion was normal in only 17.4% of patients, reduced in 33.9%, and absent in 48.7%. Myocardial perfusion grades subclassified patients into 3 distinct groups: those with normal blush (1-year mortality of 1.4%), reduced blush (1-year mortality of 4.1%), and absent blush (1-year mortality of 6.2%) (P = .01). These important prognostic values of myocardial perfusion have been replicated in other smaller trials evaluating myocardial perfusion by different modalities including MCE using intravenous contrast agents, contrast enhanced MRI, and the Doppler flow wire.

That the phenomenon is potentially reversible in man is evident in reports that perfusion defect size (PDS) on MCE immediately after PTCA may be larger than that seen a few days later.[10] In addition, medical interventions during or immediately after PTCA for patients with acute MI have also shown reduction in PDS as measured by MCE.

Pathophysiology

The mechanisms responsible for the development of the no-reflow phenomenon are not fully understood, but the end result appears to be microvascular damage produced by one of two mechanisms: microvascular obstruction or reperfusion injury (Figure 1).

Microvascular Obstruction

A large body of evidence suggests that distal microembolization of platelet aggregates to capillaries following plaque rupture, thrombolytic therapy, or PTCA causes microvascular obstruction, limiting tissue perfusion.[11] Autopsy studies in patients with acute MI fatality demonstrate the presence of microthromboemboli within the capillaries of the injured myocardium. In an experimental model in dogs,[4] a thrombus was created in the LAD and labeled in vivo by 99mTc-DMP-444 that binds the glycoprotein IIb/IIIa receptor on the platelet surface. Angioplasty was performed to obtain TIMI 3 flow.

MCE with and without the administration of intravenous adenosine was performed at 15 minutes and 60 minutes after recanalization to evaluate perfusion defect size. Infarct size was determined post-

mortem. Dogs subjected to temporary coronary artery ligation followed by reperfusion served as a control group. The duration of occlusion was the same in both groups.

Uptake of the radioisotope was significantly higher in the reperfused bed in dogs with thrombus compared with the control dogs, indicating the presence of microthromboemboli. Perfusion defect size immediately after reperfusion overestimated infarct size. However, in the presence of adenosine, infarct size was not overestimated in dogs undergoing coronary ligation followed by reperfusion.

The size of the perfusion defect decreased with time and more closely approximated infarct size 60 minutes after reperfusion. The dogs with thrombi demonstrated larger infarct size/risk area compared with the control group. This study suggests that part of the no-reflow zone created after PTCA for acute coronary thrombosis is due to microthromboemboli obstructing the microvasculature and is mostly reversible, whereas no reflow seen later reflects tissue necrosis. The effects of adenosine suggest that spasm within the coronary circulation also contributes to the no-reflow phenomenon.

Microvascular obstruction may also result from leukocyte entrapment in capillaries. Leukocytes are large, stiff cells, which are capable of adherence to the vascular endothelium. Engler and coworkers[12] studied dogs subjected to coronary occlusion followed by reperfusion with Ringer's lactate containing a carbon suspension. In nonischemic tissue, 98% of the capillaries contained carbon, indicating reperfusion, and leukocytes were rarely seen. Tissue from the distribution of the occluded artery was heterogeneous. However, 60% of the capillaries showed no reflow and the presence of approximately one leukocyte per capillary; 40% demonstrated normal tissue perfusion and no leukocytes. A significant correlation between capillaries with no reflow and the presence of leukocytes was found, indicating that progressive leukocyte capillary plugging during myocardial ischemia may prevent full restoration of flow.

Reperfusion Injury

The effect of leukocytes on the no-reflow phenomenon may not be confined to microvascular obstruction. Experimental evidence suggests that it may also involve a complex interaction of leukocytes with platelets, endothelial cells, and myocytes leading to a type of cellular damage commonly referred to as reperfusion injury.

Production of platelet activation factor by endothelial cells induces platelet activation and enhances neutrophil integrin expression and the release of oxygen free radicals.[13] Attachment of activated neutrophils to the ischemic reperfused endothelium is mediated by adhesion molecules expressed on their surface, including integrins, selectins, and CD11b and CD18.[14] Following adhesion, transendothelial migration leads to infiltration of the myocytes by activated neutrophils, which release oxygen free radicals such as hydrogen peroxide, leading to tissue injury. In certain animal models, the use of the free radical scavenger superoxide dismutase[15] and monoclonal antibodies directed against various adhesion molecules including P-selectin,[16,17] ICAM-1,[18,19] and CD 18[20,21] significantly reduced the degree of myocyte injury resulting from coronary occlusion and reperfusion. However, these observations have not been replicated in other animal studies.[22,23] Moreover clinical trials of antineutrophil intervention in acute MI have been consistently unrewarding. The effect of recombinant, humanized, monoclonal CD 18 antibody (rhuMAB CD18) in reducing infarct size in patients with MI was evaluated in the LIMIT AMI trial, a double-blinded, placebo-controlled trial, which randomized 394 patients with acute STEMI, treated with t-PA, to receive 0.5 or 2.0 mg/kg of IV rhuMAB CD 18 or placebo.[24] Despite the expected induction of peripheral leukocytosis with rhuMAB CD18, infarct size measured by sestamibi scan more than 120 hours after treatment, rate of resolution of ST segment elevation, and coronary flow evaluated by angiogram 90 minutes after therapy were the same in both groups. These findings were replicated in the HALT MI trial, which randomized 420 patients with acute STEMI undergoing primary PTCA into placebo versus anti-CD 11/18 (Hu23F2G).[25] The primary endpoint of infarct size, measured by sestamibi scan 5 to 9 days after the intervention, was the same in both arms.

At present, the weight of evidence is against a pivotal role for neutrophils as a causal factor in most forms of ischemia/reperfusion injury, with the possible exception of microvascular obstruction produced by activated neutrophils.[26]

Microvascular Flow in Reperfused Acute Myocardial Infarction

Animal studies demonstrate that microvascular flow to the reperfused myocardium is heterogeneous and complex, following the establishment of infarct-related artery patency. Areas of no reflow, low reflow, impaired flow reserve, normal flow, and hyperemia may coexist within the region of myocardium directly perfused by the infarct-related artery. As illustrated in Figure 2, the reperfused segment will have both necrotic and viable but postischemic (stunned) myocardium.[27] The region of myocar-
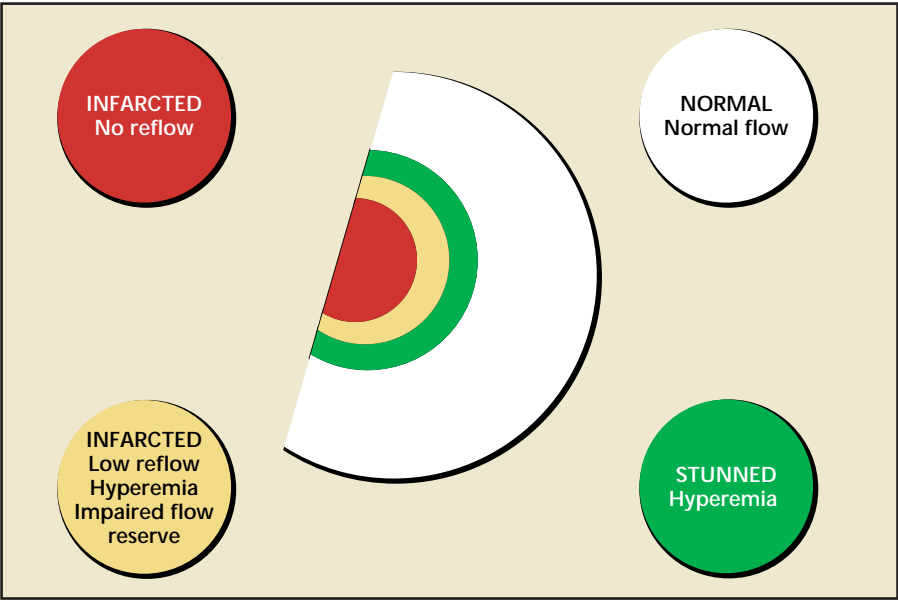
Figure 2. *Heterogeneity of flow to the area at risk after reperfusion (post-myocardial infarction).*

dial stunning will have normal or hyperemic flow, whereas the necrotic region will have segments exhibiting varying degrees of absent, reduced, or normal perfusion. This heterogeneous perfusion pattern in the immediate period after reperfusion is dynamic and may change or fluctuate.

Clinical Recognition of No Reflow

TIMI Frame Count and Myocardial Blush Grade
Because 25% of patients with TIMI 3 flow exhibit the no-reflow phenomenon, 2 other angiographic techniques have been introduced to provide a semi-quantitative assessment of microvascular integrity and perfusion: the TIMI frame count and myocardial blush grade (MBG).

TIMI frame count is defined as the number of angiographic frames required for the contrast medium to reach standardized distal landmarks of the coronary tree.

MBG is a promising technique introduced initially by van't Hof and colleagues.[28] It describes myocardial contrast density on the final

angiogram obtained after reperfusion, which presumably reflects tissue flow (Table 2). In the TIMI-10B trial, which randomized patients with acute MI to receive either t-PA or tenecteplase, MBG provided further risk stratification for total

mortality in patients with TIMI 3 flow.[29] In patients with TIMI 3 flow following primary angioplasty for acute MI, MBG was found to be an

independent predictor of total mortality,[9] correlated well with ST segment resolution and coronary flow velocities,[30] and predicted recovery of left ventricular function immediately and late after the coronary intervention.[31]

Resolution of ST Segments
Incomplete resolution of ST segments after catheter-based reperfusion for acute MI is a marker for microcirculatory dysfunction and the presence of no reflow.[32] ST segment resolution requires restoration of both epicardial and myocardial perfusion. Resolution of ST elevation within 1 hour of successful angioplasty correlates well with myocardial perfusion as assessed by myocardial contrast echo studies.[33] Recently, incomplete (defined as < 50%) resolution of ST segment elevation following successful angioplasty was shown to correlate closely with coronary flow velocity features suggestive of microvascular dysfunction, including early systolic retrograde flow, shorter

systolic and diastolic duration times, lower maximum and mean systolic peak velocities, and reduced coronary vascular reserve.[34]

TIMI frame count is defined as the number of angiographic frames required for the contrast medium to reach standardized distal landmarks of the coronary tree.

Table 2 Myocardial Perfusion Blush Grade (MBG)	
MBG 0	No apparent tissue level perfusion
MBG 1	Presence of myocardial blush but no clearance from the microvasculature
MBG 2	Blush clears slowly
MBG 3	Blush clears within 3 cardiac cycles of washout
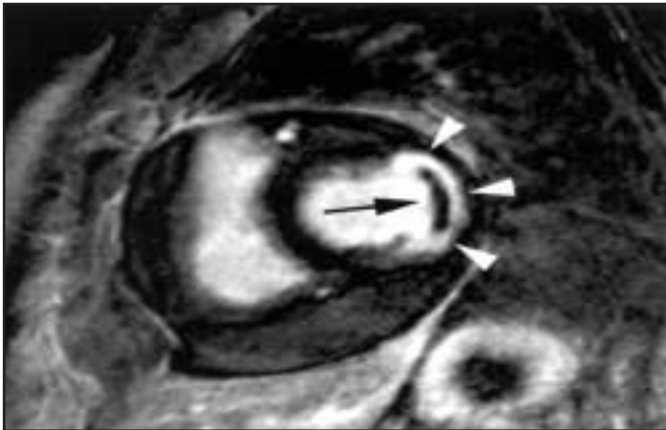
Figure 3. *Midventricular short-axis magnetic resonance image demonstrating acute transmural infarction of the lateral wall (arrowheads). A dense rim of subendocardial signal void (black arrow) corresponds to the region of no reflow or microvascular obstruction. Because gadolinium does not reach this portion of the myocardium, there is no T1 shortening. Therefore, no hyperenhancement can be visualized.*

Magnetic Resonance Imaging

Contrast enhanced magnetic resonance imaging (MRI) is one of the most accurate methods presently used to evaluate the extent of reperfusion.[35] Areas with high signal intensity following contrast administration represent damaged or infarcted myocardium whereas those with hypo-enhancement signal represent microvascular obstruction and zones of no reflow (Figure 3). Wu and associates[36] first reported that lack of reperfusion as assessed by contrast-enhanced MRI was due to microvascular obstruction and constitutes a poor prognosis. In one study, 69 patients with TIMI 3 flow following angioplasty for acute MI underwent MRI after gadolinium injection to evaluate both myocardial perfusion and function.[37] Segmental thickening was statistically correlated to hypo-perfusion. Perfusion scores obtained after gadolinium injection were also well correlated with global left ventricular function. MRI may become a primary method for evaluating treatments directed at improving myocardial perfusion.

Coronary Flow Velocity

Following PCI, the Doppler flow wire can be used to provide insight into the status of the microvasculature. Clinical studies have shown that the appearance of early systolic reversal of flow,[38] decrease in systolic forward flow, and a steep deceleration of diastolic flow velocity (see Figure 4) are predictors of no reflow at the level of microvasculature.[39,40] It was recently reported that coronary flow patterns both immediately following and 24 hours after a PCI procedure correlate with measures of myocardial perfusion determined by MCE echo and with left ventricular systolic function at 4 weeks.[41]

## Myocardial Contrast Echocardiography

MCE provides excellent physiological and clinically relevant information regarding the state of the coronary microcirculation in patients with acute MI. Initial studies with MCE used intracoronary injection of microbubbles to achieve myocardial contrast enhancement.[7] Because microbubbles will not enter a region in which the microvasculature is destroyed or dysfunctional, a persistent defect after recanalization of the infarct-related artery indicates no reflow and is a marker of myocardium at risk for eventual infarction. These studies showed that patients with persistent early defects detected by MCE had an adverse outcome in terms of regional and global LV function.[42-44]

Recent advances in echo technology and the development of new contrast agents allow MCE to be performed using intravenous, rather than intracoronary, injection.[45,46] This greatly enhances the practicality of the technique by allowing routine, bedside studies, even in clinically unstable patients.

Because of reactive hyperemia immediately after reperfusion, infarct size can be underestimated on MCE unless a coronary vasodilator is given. Administration of a coronary vasodilator will unmask the abnormal microvascular reserve and thus allow an accurate estimation of areas of absent blood flow immediately after attempted reperfusion, a fact that has been shown in animal studies[9,40] but not clinically as of yet. In addition, it has been shown that the presence of normal perfusion prior to PTCA predicts maintenance of

Figure 4. *Coronary flow velocity spectrum in a patient exhibiting no reflow on myocardial contrast echo. In this case, retrograde flow was observed throughout the systolic phase and no antegrade systolic flow was observed during systole.*
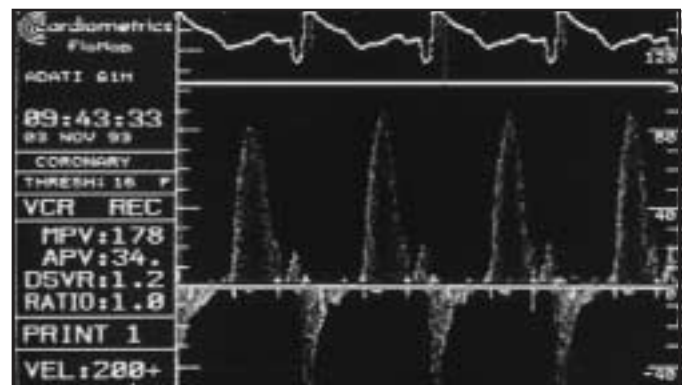
perfusion and recovery of systolic function following restoration of infarct-related artery patency.[47,48]

Because initial studies[10] suggested that perfusion defect size measured immediately after reperfusion underestimated ultimate infarct size, it has been recommended that MCE be delayed until 3 to 5 days after reperfusion. However, recent animal stud-

Ideally, early recognition of the no-reflow phenomenon should provide an opportunity for therapeutic intervention designed to augment tissue perfusion and maintain the viability of myocardium at risk.

ies[4,27] demonstrate that perfusion defect size determined immediately following reperfusion does accurately predict the size of the ultimate infarct if the study is done with concurrent adenosine infusion. If this finding is confirmed in man, MCE may become the gold standard for recognition of poor distal perfusion and the need for further treatment to reduce the ultimate extent of myocardial necrosis.

Management

Ideally, early recognition of the no-reflow phenomenon should provide an opportunity for therapeutic intervention designed to augment tissue perfusion and maintain the viability of myocardium at risk. A number of pharmacologic agents are being used in conjunction with PTCA in an attempt to improve microvascular perfusion. The platelet IIb/IIIa receptor antagonists target distal microembolization and platelet activation. Adenosine, nicorandil, and verapamil have been used to reduce vascular spasm and modulate the inflammatory response that accompanies acute MI. Other experimental agents that have been used to reduce reperfusion injury and enhance survival of the ischemic

myocardium include sodium hydrogen exchange inhibitors, the anticomplement agent pexelizumab, and the combination of glucose, insulin, and potassium.

Platelet IIb/IIIa Receptor Antagonists

Few clinical trials have specifically evaluated the direct effect of IIb/IIIa antagonists on the no-reflow phenomenon. However, there is indirect evidence of a beneficial effect on microcirculatory flow. Patients given these drugs at the time of PTCA demonstrate a higher incidence of TIMI 3 flow,[49-51] more complete ST-segment resolution,[52] and improved coronary flow velocity[53] compared to those who do not receive them. Abciximab has been the most commonly utilized agent in major clinical trials evaluating IIb/IIIa inhibitors in the setting of acute STEMI and the only one showing consistent benefit.

Adenosine

Adenosine is an endothelium-independent vasodilator, which also inhibits neutrophil-mediated endothelial damage in vitro[54] and decreases the generation of oxygen free radicals. In pilot studies conducted in the setting of acute MI, administration of adenosine before and after PCI appeared to prevent and reverse angiographic no reflow.[55] In one small study, 54 patients with

acute MI undergoing PTCA were randomized to intracoronary adenosine versus saline. Nine patients in the saline group had angiographic no reflow compared to only 1 patient in the adenosine group ($P = .02$). This beneficial effect was also reflected in improved LV function and reduced incidence of adverse cardiac events.[56]

However, larger randomized trials have not supported the concept that adenosine infusion improves microvascular flow in the setting of acute MI. In the AmP579 Delivery for Myocardial Infarction Reduction (ADMIRE) trial, 311 patients undergoing primary PTCA for acute STEMI were randomized to receive the adenosine agonist (AmP579), or a saline infusion, for 6 hours. Infarct size was evaluated by c-99m sestamibi scan. LV function and incidence of heart failure at 4 to 6 weeks did not differ between the two groups.[57] In the Attenuation by Adenosine of Cardiac Complication (ATTACC) trial, 680 patients were given a 6 hour infusion of adenosine or saline beginning at the time of thrombolytic therapy. At 1 year, the adenosine infusion group showed no advantage in terms of left ventricular function evaluated by 2D echo or in terms of total mortality.[58]

The Acute Myocardial Infarction Study of Adenosine (AMISTAD) I

Larger randomized trials have not supported the concept that adenosine infusion improves microvascular flow in the setting of acute MI.

trial was an open label pilot study, which examined the effect of adenosine administered as a 70 μg/kg/min infusion for 3 hours in 236 patients with acute MI, randomized to adenosine or placebo.[59] Although patients randomized to adenosine had smaller infarction size measured by sestamibi scan, there was no dif-

ference in the clinical event rate between the 2 groups. AMISTAD II was a large, double-blinded, placebo-controlled trial that randomized 2084 patients with acute MI into 3 hours of 50 or 70 μg/kg/min of adenosine infusion versus placebo, beginning 15 min after reperfusion.[60] Adenosine therapy was significantly associated with smaller infarction size measured by sestamibi scan 120 to 216 hours after therapy, with a median infarction size of 27% in the placebo group, 23% in the 50 μg/kg/min adenosine group, and 11% in the 70 μg/kg/min group ($P < .05$ vs placebo). The trend toward less congestive heart failure (CHF) or death in the adenosine group was statistically not significant.

No trials directly evaluating the effect of adenosine on microvascular perfusion in the setting of primary angioplasty have been performed. At present, however, there is little evidence to justify the routine use of adenosine in the setting of acute MI.

Verapamil
Verapamil is a promising agent for reversal of angiographic no reflow during PCI for acute MI.[61] This cardioprotective effect is ascribed to verapamil's reduction of calcium influx into the ischemic myocardial cells and improvement of myocardial blood flow by relief of microvascular spasm.[62,63] Verapamil may also affect platelet aggregation by reducing the effect of catecholamines.[64] In one study,[65] 40 patients with acute STEMI undergoing PTCA were randomly assigned to intracoronary verapamil versus placebo. Verapamil-augmented myocardial blood flow was evaluated by MCE and improved LV function. Larger randomized trials to confirm this finding are lacking.

Nicorandil
Nicorandil is a hybrid nitrate and a K+ ATP channel opener used in Japan and Europe but not available in the United States. It appears to have a cardioprotective effect, the exact mechanism of which is unknown. One possible mechanism involves reduction of neutrophil infiltration into ischemic myocardium,[66] an effect that may attenuate microvascular injury. Moreover, nicorandil has a vasodilatory effect, which is greater than that of nitroglycerin, particularly in vessels larger than 100 micrometers in diameter.[67] Several studies in the setting of PTCA for acute MI have shown that intracoronary nicorandil[68] is associated with improved TIMI flow and that use of intravenous nicorandil[69] is associated with better tissue perfusion as measured by MCE.

Ito and coworkers[69] randomized 81 patients undergoing PTCA as treatment for an acute anterior MI to receive intravenous nicorandil (n = 40), 6 mg/hr for 24 hours, followed by oral nicorandil, for 28 days after infarction. The frequency of no reflow as measured by MCE was significantly lower in the nicorandil group compared to placebo (n = 41) ($P < .05$). The degree of improvement in LV function was also better in the nicorandil group ($P < .05$).

In a retrospective study of 272 patients with acute MI, 158 patients received nicorandil in a 4 mg intravenous bolus dose, followed by 6 mg/hr infusion for 24 hours and 15 mg/day for 1 month. The other 114 patients received placebo. Nicorandil treatment was associated with better tissue perfusion measured by MCE, better LV function, and a higher likelihood of freedom from adverse cardiac events ($P < .01$), a difference that was maintained for 4 years.[70]

Recently, in a double blinded trial, Ikeda and colleagues[71] randomized 60 patients with acute MI into 2 treatment groups, a nicorandil group (n = 30) and an isosorbid dinitrate (ISDN) group (n = 30). Each drug was infused at 6 mg/hr for 72 hours, starting at admission, and was administered directly to the target coronary artery immediately after angioplasty. Nicorandil use was associated with improved recovery of ST-segment elevation when compared to the ISDN (55% vs 19%, $P < .006$), higher value of peak velocity after reperfusion (24.8 cm/s vs 16 cm/s, $P = .045$), and higher values of regional wall motion of the infarcted area 3 weeks after MI (-1.78 [1.11] vs -2.5 [1.04] SD/Chord, $P = .046$).

The J WIND-KATP trial[72] is a currently ongoing, double-blinded, placebo-controlled trial in 26 hospitals in Japan. Patients undergoing PCI for acute MI are randomized to nicorandil versus placebo. Primary endpoints are estimated infarct size and LV function. It is expected that J WIND-KATP will provide important data on the effect of nicorandil as an adjunct therapy to PCI for acute MI.

Sodium-Hydrogen Exchange (NHE) Inhibitors
The use of sodium-hydrogen exchange (NHE) inhibitors, predominantly cariporide, in the setting of acute MI, has been evaluated in both animal models[73] and clinical settings. Reduction of sodium influx into the myocyte and inhibition of sodium/calcium exchange, leading to reduction of myocyte Ca overload following reperfusion, is believed to be the mechanism of action for this agent. In a multicenter, randomized, placebo-controlled trial, Rupprecht and associates[74] randomized 100 patients with acute anterior wall MI to receive placebo (n = 51) versus 40 mg intravenous bolus dose of cariporide (n = 49) before reperfu-

sion. Ejection fraction before PTCA and 21 days later was unchanged in the placebo group (40% vs 40%) but increased in the cariporide group (from 44% to 50%, $P < .05$). Also, cariporide was associated with smaller infarct size, as the area under the CK-MB curve was smaller in this group when compared to placebo.

The GUARDIAN trial was not a Q wave MI trial; however, it randomized 11,590 patients with non-STEMI, unstable angina, or who were undergoing high-risk percutaneous or surgical revascularization to receive 1 of 3 doses of cariporide versus placebo. The primary endpoint of all-cause mortality or MI was the same in all groups.[75] Additional studies evaluating the role and beneficial effect of NHE in the setting of acute STEMI are required.

Pexelizumab

Because complement activation might mediate myocardial damage that occurs during ischemia and reperfusion through multiple pathways, the use of a complement blockade system has been suggested to reduce ultimate infarct size. Pexelizumab is a novel C5-complement, monoclonal antibody fragment that has been used in 2 large, double-blinded, placebo-controlled trials of patients with acute MI, receiving either thrombolytic therapy in the Complement Inhibition in MI Treated with Thrombolytics (COMPLY) trial,[76] or in patients with MI undergoing PTCA in the Complement Inhibition in Myocardial Infarction Treated With Angioplasty (COMMA) trial.[77]

In COMPLY, 943 patients with acute STEMI receiving fibrinolysis within 6 hours of symptom onset were randomized to a 2.0 mg/kg bolus dose of pexelizumab with or without 0.05 mg/kg/min infusion for 20 hours, or placebo. The infarct size as measured by the area under

CK-MB curve did not differ among the 3 groups nor did the 90-day combined clinical endpoint of death, stroke, shock, or new CHF.

In COMMA, 960 patients with acute MI undergoing PTCA were randomized to placebo or pexelizumab using the same dose protocol as that of COMPLY. Although the primary outcome of infarction size measured by area under CK-MB curve and the combined clinical endpoint of all-cause mortality, stroke, shock, or new CHF at 90 days was the same in all groups, 90-day mortality was significantly lower with pexelizumab bolus plus infusion compared to that seen with placebo (1.8% vs 5.9%, $P < .014$).

The Terminal Complement Blockade with Pexelizumab During Coronary Artery Bypass Graft Surgery Requiring Cardiopulmonary Bypass (PRIMO-CABG) trial evaluated the effect of pexelizumab on MI and total mortality in patients undergoing CABG with or without valve surgery.[78] Out of the 3099 patients enrolled in this double-blind, placebo-controlled trial, 1553 were assigned to receive intravenous pexelizumab (2.0 mg/kg bolus + 0.05 mg/kg/hr for 24 hrs) whereas 1546 received placebo. Compared with placebo, pexelizumab was not associated with a significant reduction in the risk of the composite endpoint of death or MI in the 2746 patients who had undergone CABG surgery only (9.8% vs 11.5%, $P = .07$) but was associated with a statistically significant risk reduction 30 days after the procedure among all 3099 patients undergoing CABG with or without valve surgery (11.5% vs 14.0 %, $P = .03$). The role of pexelizumab in the management of patients with acute MI is still to be determined.

Glucose-Insulin-Potassium

Most studies that have investigated

the role of combination glucose, insulin, and potassium (GIK) in the setting of acute MI are from the prethrombolytic era. Although some of these trials showed trends toward improved morbidity and mortality rates, this result could not be consistently replicated. In fact, a Polish GIK trial, which randomized 954 patients with acute MI to GIK (n = 494) versus placebo (n = 460) was terminated prematurely because of increased mortality in the GIK arm.[79] In a recent open label study, GIK was compared to placebo in 940 patients with acute MI undergoing PCI. The 30-day mortality rate was 4.8% in the GIK group versus 5.8% in the placebo group (P = ns).[80]

The REVIVAL trial was also an open label study that randomized 312 patients with acute MI undergoing PCI to GIK (n = 155) versus placebo (n = 157). The primary endpoint was the salvage index, measured as the proportion of initial perfusion defect (acute technetium-99m sestamibi scan) salvaged by therapy (follow-up scan performed at 7 to 14 days). The use of GIK was not associated with significant improvement in salvage index or mortality.[81] The current body of evidence does not justify routine use of GIK in patients with acute MI as an adjunct therapy to PCI.

Distal Protection Devices

Mechanical distal protection devices have emerged recently as an attractive tool to prevent both microvascular embolization and no reflow. However, data on their beneficial effect in reducing the risk or consequences of distal embolization in the setting of acute MI are limited. The Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial[82] was an open-label, multicenter study that randomized 505 patients with acute STEMI, undergo-

ing PCI within 6 hours of symptom onset, to either the GuardWire® (Medtronic, Inc, Minneapolis, MN) distal protection device or a control arm. The majority of patients in both arms received IIb/IIIA inhibitors. Despite the capture of visible debris in 73% of patients in the GuardWire arm, there was no significant difference in the primary endpoints of resolution of ST segment elevation within 30 minutes or infarct size measured by sestamibi scan 5-14 days after the intervention. Also, the rate of MACE, TIMI flow, and myocardial blush was the same in both groups.

Recently, the PercuSurge (Medtronic) distal balloon protection device was compared to tirofiban as an adjuvant therapy to PCI in 199 patients with acute MI and large infarct-related artery with high thrombus burden. Final epicardial flow and myocardial blush grades were significantly higher in the PercuSurge arm and the major adverse cardiac events were lower in the same arm.[83] Further trials are needed to evaluate the role of distal protection devices in the setting of acute MI.

Conclusion

Over the past 20 years, advances in the management of STEMI have focused on rapid achievement of patency in the infarct-related artery. Recognition of the no-reflow phenomenon has exposed an important limitation of this therapeutic strategy. In the new millennium, the focus of reperfusion therapy is being shifted downstream from its exclusive focus on the epicardial artery to assuring normal blood flow at the tissue level. ■

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Main Points

- In 25% of patients undergoing percutaneous coronary transluminal angiography (PTCA), in whom arterial obstruction is successfully relieved, little or no additional myocardial perfusion results. These patients demonstrate the phenomenon termed "no reflow" and exhibit a substantial increase in overall morbidity and mortality.

- The mechanisms responsible for the development of the no-reflow phenomenon are not fully understood, but the end result appears to be microvascular damage produced by one of two mechanisms: microvascular obstruction or reperfusion injury.

- Patients with TIMI 3 flow can still exhibit the no-reflow phenomenon. Two other angiographic techniques have been introduced to provide a semi-quantitative assessment of microvascular integrity and perfusion: the TIMI frame count and myocardial blush grade.

- Pharmacologic agents currently used in conjunction with PTCA, in an attempt to improve microvascular perfusion, include platelet IIb/IIIa receptor antagonists; adenosine, nicorandil, and verapamil; and experimental agents such as sodium hydrogen exchange inhibitors, the anticomplement agent pexelizumab, and the combination of glucose, insulin, and potassium.

- Mechanical distal protection devices have emerged recently as an attractive tool to prevent both microvascular embolization and no reflow. However, data on their beneficial effect in reducing the risk or consequences of distal embolization in the setting of acute MI are limited and further studies are required.

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