No-Reflow Phenomenon
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Because total coronary artery occlusion was found in the early hours of transmural myocardial infarction, most of our research interest and treatment strategies focus on epicardial coronary arteries. Little attention, however, is paid to the coronary microvasculature. When a coronary artery is occluded, detrimental changes occur in the cardiac capillaries and arterioles. After relief of the occlusion, blood flow to the ischemic tissue may still be impeded, a phenomenon known as no reflow. This article attempts to provide an in-depth understanding of this phenomenon from the laboratory bench to the clinical arena.

Historical Perspective
The no-reflow concept was first suggested in brain ischemia. Brains of rabbits that suffered a brief 2 1/2 minutes of ischemia had normal blood flow when the ischemia was relieved. When the rabbits were exposed to longer ischemic periods, normal flow to brain tissues was not restored, even after relief of the vessel obstruction. Prolonged ischemia resulted in significant changes in the microvasculature that interfered with normal flow to the brain cells. The existence of this phenomenon was confirmed in a variety of animal models of brain ischemia. It was also shown in a variety of other organs, including skin, skeletal muscle, and the kidney. Kloner et al sought to find out whether the no-reflow phenomenon would be observed in ischemic canine hearts and whether it was related to microvascular damage. Dogs were subjected to 40 or 90 minutes of proximal coronary artery occlusion. When the coronary occlusion was relieved after 40 minutes of occlusion, the blood flow was restored to the damaged myocardium as assessed by markers of perfusion such as thioflavin S and carbon black. However, after 90 minutes of coronary occlusion, there was only partial restoration of blood flow to the myocardial tissue, despite virtual elimination of the coronary occlusion. Anatomical perfusion defects were prominent in the subendocardial myocardium when thioflavin S or carbon black was injected into the vasculature after restoration of epicardial coronary flow. Electron microscopic examination of the cardiac microvasculature within the anatomic no-reflow zones revealed significant capillary damage in the form of swollen endothelium and intraluminal endothelial protrusions and, less commonly, intraluminal platelets and fibrin thrombi. These changes, coupled with interstitial and myocardial edema, could compress the capillaries and be responsible for the no-reflow phenomenon. The longer ischemia lasts, the more likely the no-reflow phenomenon is to occur. Microvascular damage did not appear to be the primary cause of myocardial cell damage because the no-reflow area appeared to be confined to areas of tissue that were already necrotic. In a similar model, Willerson et al documented reduced myocardial blood flow in no-reflow zones and an increase in the coronary vascular resistance, specifically in the subendocardium. As suggested in 1974, “recent advances, such as coronary bypass surgery and the development of fibrinolytic agents, eventually may make it possible to release coronary occlusions.” Twenty-six years later, these techniques and transluminal coronary interventions became the standard therapy of acute myocardial infarction. It was percutaneous coronary interventions in particular that brought the no-reflow phenomenon to light because it could be seen with the naked eye in human hearts in the setting of acute myocardial infarction.

Pathophysiology
Understanding the pathophysiology of the no-reflow phenomenon is the key for managing this condition. After prolonged cessation of coronary occlusion and restoration of blood flow to the epicardial coronary arteries, there is sufficient structural damage to the microvasculature to prevent restoration of normal blood flow to the cardiac myocytes. This may lead to inadequate healing of the cardiac scar. In addition, it may prevent the development of future collateral flow. This phenomenon appears to be more pronounced in the subendocardium in a manner similar to the wavefront phenomenon of the ischemic cardiac death. It is more pronounced with longer periods of coronary occlusions. No reflow appears to be a process rather than an immediate event that occurs at the moment of reperfusion. Experimental studies showed that the no-reflow area increases with time after reperfusion. Although it is clear that abnormalities at the level of the microvasculature caused the no-reflow phenomenon, the exact mechanism is uncertain; a variety of factors probably contribute to it (the Figure).

Microscopic examination showed that the cardiac cells within the no-reflow area were swollen. The capillary endothelium was damaged and exhibited areas of regional swelling with large intraluminal protrusions that in some cases
A. No reflow is a process that starts during the ischemic period and then increases during reperfusion. Atheroembolism adds to the extent of it, particularly during short-term intervention. B. Various mechanisms are implicated in the genesis of the no-reflow phenomenon.

appear to plug the capillary lumen.13 Cellular edema compressing the capillaries was confirmed in more than one experiment.10,21,22 This may explain the occasional benefit noted with dexamethasone23 or mannitol.16,24 Cell contracture in the ischemic zone also may contribute to the microvascular compression.25,26

Intravascular plugging by fibrin or platelets may also contribute to the no-reflow phenomenon.27–30 Beneficial effects of ibuprofen,31 prostaglandin E1,32 and vascular washout with heparinized saline33 support the concept that these blood elements may be important. In a no-reflow model of a New Zealand white rabbit study by Golino et al,34 platelet depletion markedly reduced the extent of no-reflow zones.

Leukocyte intravascular plugging appears to play an important role in the pathophysiology of no reflow. Engler et al35 showed that the no-reflow areas had evidence of capillary leukocyte plugging. Although there was no difference in no-reflow zones between the neutropenic animals and the control group in a gerbil cerebral ischemia model,36,37 other studies showed that reperfusion leads to rapid accumulation of leukocytes in the microvasculature of the dog heart.38 This may be mediated by CD18-dependent leukocyte adhesion39 and may play some role in the genesis of the no-reflow phenomenon. Byrne et al40 found that reperfusion with leukocyte-depleted blood may reduce cardiac no reflow. Furthermore, in a rat model of irreversible hemorrhagic shock, the no-reflow phenomenon was prevented by rendering the animals neutropenic.41 Leukocytes may interfere with blood flow by mechanical plugging and perhaps by their release of oxygen free radicals that will add further injury to the capillary endothelium.42–46 Thus, the no-reflow phenomenon is likely multifactorial. During the ischemic phase, endothelial damage, including endothelial swelling and myocyte edema, led to initial no-reflow zones. With reperfusion, additional edema, myocyte contraction, platelets, fibrin, and leukocyte plugging resulted in expansion of the no-reflow zones over the early hours of reperfusion. Platelet and leukocyte depletion and vasodilators appeared to lessen no reflow.47–49

Diminished flow through the microvasculature compared with normal zones is usually referred to as “low reflow.”50 An additional mechanism plays a very important role during short-term intervention in acute myocardial infarction. Microemboli of atheroembolic debris, blood clots, and platelet plugs are released into the microcirculation, particularly with restoration of normal blood flow by thrombolysis, angioplasty, stenting, or other percutaneous intervention. Although this is more common in vein graft intervention, it is to be expected in native coronary arteries. A variety of new, innovative devices are now in clinical practice and in the research phase to filter these microemboli during the interventional procedure.

Diagnosis

The model that provides a definite diagnosis for no reflow in humans is coronary intervention in acute myocardial infarction. A patient may present to the catheterization laboratory with total coronary occlusion. After elimination of the epicardial coronary occlusion, the blood flow may slow down or cease in some patients. To define various coronary blood flow patterns, Thrombolysis in Myocardial Infarction (TIMI) blood flow grades were established in the early 1980s.51 Grade 0 refers to no flow at all after the obstruction point. In grade 1, the contrast material flows beyond the area of obstruction but fails to opacify the entire artery. Grade 2 refers to opacification of the entire artery distal to the occlusion site but at a slower rate than normal, and grade 3 refers to normal coronary flow. A coronary Doppler flow wire may show the characteristic rapid deceleration of diastolic flow velocity in patients with no reflow.52 This technique also confirmed that the no-reflow phenomenon in humans may occur immediately after reperfusion or shortly thereafter.53 Digital coronary angiography54 and various algorithms55 were described to aid in the diagnosis of no reflow. The diagnosis can be suspected with serial 12-lead ECGs obtained after treatment of acute myocardial infarction. With successful thrombolysis or coronary intervention, the ST-segment elevation returns gradually to baseline. If there is impaired microvascular perfusion despite successful thrombolysis or coronary intervention, the ST-segment elevation persists.56–58 Nuclear imaging,59–62 contrast-enhanced magnetic resonance,63–66 and PET67 also may aid in the diagnosis.

Myocardial contrast echocardiography, however, is particularly helpful in identifying no-reflow zones. In this technique, a high-energy sonicated microbubble is injected either intravenously or via an intracoronary route, and an echocar-
diagram is obtained. No flow to the area at “risk following opening of the epicardial coronary artery”768 or a paradoxical persistence of the bubbles in the myocardium89 usually signifies the no-reflow phenomenon. With this technique, the no-reflow phenomenon was noted in 29% of patients with acute myocardial infarction.70 The test also provided prognostic value.71 In a study of 45 consecutive patients of acute myocardial infarction, a persistent contrast defect in the infarct zone identified patients likely to have systolic dysfunction. That finding was somewhat comparable to the dobutamine echocardiography test.72 It correlated reasonably well with TIMI flow grade during coronary angiography73 and measurement of coronary flow reserve.74 Once this technique is improved both qualitatively and quantitatively, it may become an invaluable asset in the management of acute ischemic syndromes.

A more accurate technique to identify no reflow on coronary angiograms was developed by the TIMI group. The number of angiographic frames required for the dye to reach a specified distal segment in the coronary artery was referred to as the corrected TIMI frame count. Gibson et al75 studied 1248 patients with myocardial infarction who were enrolled in the TIMI studies. The corrected TIMI frame count was an independent predictor of in-hospital mortality. A less recognized form of the no-reflow phenomenon occurs during coronary artery bypass surgery. Not surprisingly, the occasional patient will suffer a decrease in ejection fraction despite completely successful revascularization.76–78 Various cardioplegic protocols, less bypass time, and more recently off-pump bypass will help to decrease the incidence and the magnitude of this problem.

**Clinical Presentation**

Clinical presentation of the no-reflow phenomenon varies greatly, depending on the clinical setting, despite often being related to the moment of reperfusion.79 In the catheterization laboratory, the clinical presentation of no reflow during short-term intervention in myocardial infarction patients is often sudden and dramatic. The dye will stagnate in the coronary artery, the patient will complain of chest pain, and hemodynamic compromise soon follows. The sudden hemodynamic deterioration may also be related to atheroembolism80 and slowing of blood flow in the nonculprit arteries.81 In the coronary care unit, the presentation is usually less dramatic. After thrombolytic therapy, the patient will experience chest pain and ST-segment elevation and may have hemodynamic deterioration.82 New Q waves may appear,83 and some of those patients may be diagnosed as having infarct extensions. In a study by Komamura et al,84 9 patients with acute anterior myocardial infarction, early reperfusion, and probable no reflow were studied. The patients had continuous monitoring of the great cardiac vein blood flow. The flow appeared to decrease gradually with time, suggesting that the no-reflow phenomenon is a process that advances with time, a pattern similar to experimental studies.85 In another clinical study, patients with no reflow were older and had a lower incidence of preinfarction angina.86 The absence of preinfarction angina was also noted in the series of Komamura et al.84 This may be related to the concept that the presence of preinfarct angina is associated with smaller infarcts and a possible preconditioning-like effect and may correlate with collateral formation.87 The no-reflow phenomenon was also linked to ventricular arrhythmias,88 early congestive heart failure,89 and even cardiac rupture.90 There is also evidence that it may have an adverse effect on left ventricular remodeling after myocardial infarction.91 To determine the prognosis of no-reflow phenomenon, Morishima et al92 followed up 30 patients who demonstrated no reflow for a mean period of 1.2 years. They compared this group to a control group of 90 patients. No reflow was associated with malignant arrhythmias, lower ejection fraction, or more cardiac death.

**Management**

Despite emerging efforts in the management of this phenomenon during thrombolytic therapy, most of the existing experience focuses on its management in the setting of percutaneous coronary intervention. Here, we explore the potential advantages of treating no reflow and its focus on preventive measures and then discuss the various treatment modalities.

Treating no reflow may not necessarily reduce the size of myocardial infarction because the microvascular damage is usually confined well within the zone of myocardial necrosis. However, treating no reflow may enhance the delivery of blood and blood-borne elements to the necrotic area, thus speeding healing. This could reduce the presence of infarct expansion and left ventricular remodeling.93 Salvage of the small vessels may help promote collateral circulation and perhaps serve as a site for neovascularization. Salvage of flow will ensure drug delivery to the necrotic zone. In a clinical situation in which no reflow is caused mainly by distal emboli, treating this condition may prevent infarct extension.

To decrease the incidence of this phenomenon during short-term intervention for myocardial infarction, patients need to undergo the intervention as soon as possible. The no-reflow phenomenon tends to occur more often with prolonged coronary occlusion. Retrieval devices need to be used in treating degenerated vein grafts to avoid the microembolic phenomenon in humans.94 General measures, including the use of intra-aortic balloon pumps, may be used as needed.95,96 Because platelet and fibrin plugging is an important contributor to the pathogenesis of the no-reflow phenomenon,27–30 glycoprotein IIb/IIIa platelet receptor inhibitor may be beneficial in the prevention of the no-reflow phenomenon during percutaneous coronary intervention. Studies have shown that this group of drugs is beneficial in reducing rates of death, reinfarction, and urgent revascularization when used in conjunction with percutaneous coronary intervention.97–99 They are particularly beneficial as a rescue strategy.100 in certain settings such as vein graft intervention,101 and in conjunction with the extraction atherectomy catheter.102 Few controlled studies have confirmed their beneficial effect on the microcirculation. Williams et al103 placed a rotablation burr in platelet-rich plasma from 28 healthy human volunteers. The samples were randomized to preincubation with glycoprotein IIb/IIIa receptor blocker or control. High-speed rotablation induced platelet activation. Glycoprotein IIb/IIIa
blocker (abciximab) decreased platelet activation and aggregation during rotational atherectomy. Further controlled clinical trials confirmed that glycoprotein IIb/IIIa receptor blockers result in less angiographic no-reflow phenomenon\textsuperscript{105} and improved coronary flow velocity as measured by Doppler wire.\textsuperscript{105} They were more likely to have complete ST-segment resolution.\textsuperscript{106} In a recent study of 300 patients with acute myocardial infarction,\textsuperscript{107} patients were randomized to abciximab or placebo. Patients who received abciximab (a glycoprotein IIb/IIIa receptor inhibitor) before coronary intervention had significantly more TIMI grade 3 flow compared with patients who received placebo. Thus, these groups of platelet aggregation inhibitor drugs not only result in better epicardial blood flow but also lead to less no-reflow phenomenon and better flow at the level of the microcirculation.

Another strategy for the prevention of no reflow is focused on the polymorphonuclear leukocytes. At the onset of coronary occlusion, leukocytes are trapped in the capillaries and adhere to the endothelium, resulting in leukocyte capillary plugging,\textsuperscript{46,108} and release various injurious oxygen free radicals.\textsuperscript{109} Monoclonal anti-leukocyte antibodies and complement receptor inhibitors\textsuperscript{110} may have a potential therapeutic role. Animal studies suggested that endothelin A–selective antagonists\textsuperscript{111} and blockers of factor VIIa\textsuperscript{112} decrease the size of the no-reflow zone. However, preliminary data from clinical trials on the effect of leukocyte antibodies that prevent neutrophil adhesion to the endothelium have in general been negative.

Once the no-reflow phenomenon is established, other treatment options are available. The 2 most studied agents are verapamil and adenosine. Calcium channel blockers have shown a benefit in the management of no reflow in laboratory animals.\textsuperscript{113,114} Intracoronary verapamil is quite useful in treating low reflow in patients after short-term intervention. Taniyama et al\textsuperscript{115} administered 500 μg intracoronary verapamil or placebo to patients with acute myocardial infarction. The patients’ coronary flow was measured by myocardial contrast echocardiography before and after verapamil injection. Wall motion abnormalities were scored at baseline and 1 month after the infarction. The verapamil group had improved flow after verapamil injection, and the same group of patients had better functional recovery in wall motion abnormalities. Despite improvement in flow with verapamil, flow did not completely normalize. It appeared that some structural changes were either irreversible and/or unaffected by verapamil. Other calcium channel blockers, particularly nicardipine, will enhance coronary blood flow. In a small, double-blinded, randomized study, Fugit et al\textsuperscript{116} found that nicardipine in a dose of 200 μg given via an intracoronary route was more potent and more prolonged in action than either verapamil or diltiazem.

Another widely used medication in the management of no reflow in the catheterization laboratory is adenosine. Engler\textsuperscript{117} first suggested a role for adenosine in treating the no-reflow phenomenon. Olafsson et al\textsuperscript{118} randomized 20 dogs with 90 minutes of coronary occlusion to adenosine or placebo. The adenosine dose was 3.75 mg/min for 60 minutes starting at reperfusion. Regional myocardial blood flow was significantly better in the adenosine-treated animals. The beneficial effect was associated with a decrease in neutrophil count in the ischemic zone and relative preservation of endothelial integrity in the same areas. Thus, the adenosine benefit was beyond simple vasodilatation and extended to maintain normal endothelial structure in the previously ischemic areas. Similar findings were reported by Kaminski and Proctor.\textsuperscript{119} Marzilli et al\textsuperscript{20} randomized 54 patients undergoing short-term intervention for myocardial infarction to intracoronary adenosine or placebo. The adenosine group had better coronary flow and less adverse cardiac events. Further studies confirmed the benefit of adenosine. A retrospective study\textsuperscript{121} showed that adenosine in a dose of 24 to 48 μg before intervention was well tolerated and decreased the incidence of no reflow compared with patients who did not receive it. A second retrospective study confirmed these benefits in patients undergoing rotational atherectomy.\textsuperscript{122}

Because opening ATP-sensitive potassium channels may be involved in the vasodilatory effect of adenosine, a direct ATP potassium channel opener, nicorandil, was attempted in treating the no-reflow phenomenon. Sakata et al\textsuperscript{123} reported a 54-year-old patient with anterior myocardial infarction who, despite responding to thrombolytic therapy, had a large no-reflow zone. Nicorandil was injected via an intracoronary route in a dose of 2 mg with total elimination of no reflow. In addition, in a randomized study in patients with acute myocardial infarction,\textsuperscript{124} intravenous nicorandil was associated with better functional recovery and improved microvascular flow. This is particularly important because such treatment may be applied to patients presenting to the emergency room with myocardial infarction who do not necessarily require cardiac catheterization.

Other medications were tried with variable success. Intracoronary papaverine was beneficial\textsuperscript{125} but is rarely used in the catheterization laboratory. Intracoronary urokinase is ineffective.\textsuperscript{126} Although various intravenous thrombolytic agents are beneficial in lysing thrombi, they do not appear to have a direct effect on the no-reflow phenomenon.\textsuperscript{43,127}

The no-reflow phenomenon is becoming increasingly recognized because of the spread of primary intervention for acute myocardial infarction and the emergence of contrast myocardial echocardiography. With the clinician focusing on both epicardial coronary arteries and the microvasculature, there is a need for a safe and effective treatment for no reflow. The treatment will have a bigger impact if it can be applied to acute myocardial infarction patients in the emergency department. Although the previous 2 decades were the decades of reperfusion of large epicardial arteries, we predict that the first decade of the new millennium will be the decade of microvasculature perfusion.

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