Microvasculature in Acute Myocardial Ischemia: Part II
Evolving Concepts in Pathophysiology, Diagnosis, and Treatment
Sanjiv Kaul, MD; Hiroshi Ito, MD

In the setting of suspected acute myocardial infarction (AMI), a cardiologist needs to know three things: (1) whether there is actually an ongoing infarction, (2) whether reperfusion therapy has succeeded, and (3) how much myocardium was salvaged by reperfusion. Myocardial contrast echocardiography (MCE) can answer the first question by demonstrating the presence of a perfusion defect resulting from reduced microvascular flow because of the presence of a thrombus in an epicardial coronary artery. In a recent multicenter study of 203 patients without ST-segment elevation who presented to the emergency department with chest pain, 21 had AMI, and MCE only missed 1 such patient (sensitivity of 95%).

The success of attempted reperfusion can also be accurately assessed with MCE. Most currently used clinical and electrocardiographic parameters are accurate in ~75% of the cases, whereas MCE has an almost 100% accuracy. Panel B in Figure 1 demonstrates a MCE perfusion defect in a patient presenting to the emergency department with chest pain who was subsequently ruled in for an AMI. The success of reperfusion and degree of myocardial salvage are equally important to know in patients even with ST-elevation AMI. Coronary angiography is not reliable in this regard.

The No-Reflow Phenomenon
Although MCE immediately after reperfusion can provide an accurate assessment of the success of reperfusion, it might underestimate the degree of no reflow because of reactive hyperemia. The degree of reactive hyperemia is influenced by the amount of capillary damage and the degree of residual stenosis in the infarct-related artery. The no-reflow zone also changes dynamically in the first several hours after reperfusion because of vasospasm, myocardial edema, etc. Therefore, the ideal time to measure no reflow to determine the extent of myocardial necrosis is after 48 hours following reperfusion. At that time, dynamic changes in resting tissue perfusion have subsided, and the extent of no reflow correlates well with infarct size and denotes a region of irreversible tissue damage.

The “no-reflow” phenomenon in the heart was originally described in a canine model of coronary artery ligation followed by reperfusion. Despite an open infarct-related artery, regions within the myocardium showed low flow, which were located exclusively within irreversibly injured myocardium. Consequently, the size of the no-reflow zone approximated infarct size. Electron microscopy revealed microvascular obstruction due to endothelial cell blebbing, white cell infiltration, red blood cell stagnation, and extravascular edema. This process can be accelerated after reperfusion due to injury from oxygen free radicals. Unlike the experimental setting, however, AMI in the clinical setting is usually caused by an occlusive coronary thrombus that can embolize distally into the myocardium spontaneously, during thrombolytic therapy, or during percutaneous coronary interventions (PCI). Necropsy studies have demonstrated the presence of thrombi in the coronary microvasculature from patients who have died of AMI. Thus, early after attempted reperfusion, the no-reflow zone can include regions of the myocardium with microthromboemboli. Vasoactive amines from activated platelets cause microvascular spasm that may further impair regional flow and contribute to the no-reflow phenomenon. Furthermore, inflammation itself can limit flow as a result of migration of leukocytes into the injured microvasculature.

In patients with acute coronary syndromes undergoing PCI, aspiration of the coronary artery has revealed thrombus with or without plaque components in half the patients. The other half have only plaque consisting of cholesterol crystals. Thus, a part of the no-reflow phenomenon in these patients may be related to atheroma embolization, and in this study there was concordance between the occurrence of no reflow and finding...
increase in intramural pressure. Consequently, the slope of diastolic coronary flow velocity. In normal subjects, the myocardial blood capacitance (which involves both capillaries and venules) is filled during diastole without an impediment to inflow in diastole resulting in a rapid decrease in coronary flow velocity. This is associated with a shorter diastolic deceleration time, poorer tissue perfusion, worse functional outcomes, LV remodeling, higher early cardiac events, and poorer long-term prognosis.

Systolic flow reversal is another accurate marker of the no-reflow phenomenon and is also due to capillary obstruction. In normal subjects, myocardial impedance increases during systole, and blood is milked from the intramyocardial venules into the coronary sinus, which is the reason why coronary sinus antegrade flow is maximal in systole rather than diastole. In patients with capillary obstruction, the myocardial blood volume is pushed back into the coronary artery because it cannot pass the capillary bed to reach the venules, resulting in systolic flow reversal. This finding is also associated with a high coronary wedge pressure indicating microvascular obstruction as well as low systolic flow in the coronary sinus.

Total coronary arterial resistance is also increased in patients with no reflow leading to a decrease in antegrade mean coronary blood flow (CBF) velocity. In a study of 105 patients with AMI, TIMI grade 2 flow after PCI was associated with 2 distinct Doppler flow patterns; all patients with no reflow had systolic flow reversal, but only 1 in 10 with a sole decrease in antegrade flow exhibited no reflow. Intracoronary thrombus was more frequently found in the latter. The former pattern may indicate the presence of a flow-limiting coronary artery stenosis, and additional stent placement may be effective in improving CBF. Instead, a to-and-fro pattern implies capillary damage, and additional stent placement is not beneficial.

Capillary obstruction often progresses for several minutes to hours after coronary recanalization, possibly as a result of reperfusion injury, and thus, the size and clinical presentation of the no-reflow phenomenon vary greatly with time. Continuous monitoring of CBF velocity with Doppler flow wire shows that the systolic flow reversal is seen in only half the patients with no reflow immediately after reperfusion; the other half develop this abnormality later. Great cardiac vein flow often decreases gradually until the day after reperfusion, and functional recovery in those with this finding is worse than in those without it. Patients who develop no reflow late after reperfusion can have intracardiac hemorrhage.

Microthrombi associated with PCI can also lead to no reflow, which is usually transient. PCI might even invoke neurohormonal reflexes and vasoconstriction that results in hypoperfusion. Elevated coronary resistance from amines released from activated platelets might decrease over time and therefore possibly manifest as a transient phenomenon. Atheroma containing emboli, however, are unlikely to dissolve and may result in necrosis in addition to that caused by prolonged ischemia itself. Thus, TIMI grade 2 flow is likely to occur during mechanical intervention of lipid-rich plaques compared with collagen-rich lesions. It is particularly frequent (10% to 15%) in the setting of unstable angina or PCI of old saphenous vein grafts, and is even observed in 2% to 3% of elective PCIs performed in patients without a prior AMI.

As would be expected, factors associated with the development of no reflow are the size of the risk area, severity of myocardial damage within that area, and the occlusion status of infarct-related artery. Preinfarction angina ameliorates no reflow through collateral flow, ischemic preconditioning, or reduced thrombus. Hyperglycemia in the acute stage of AMI is also associated with an increased risk of in-hospital mortality independent of the presence or absence of diabetes. Whether hyperglycemia occurs secondary to a larger infarction and therefore a larger area of no reflow, or whether it contributes to the no-reflow phenomenon, is not known. Hyperglycemia by itself impairs endothelium-dependent vasodilatation, enhances leukocyte adhesion to endothelial cells by increasing circulating adhesion mole-

cules, and attenuates the beneficial impact of ischemic preconditioning.

Importance of Collateral Blood Flow

Collateral blood flow is very important in the setting of acute ischemia. Necrosis does not occur unless myocardial blood flow is below 25% of normal.\textsuperscript{34,35} In many instances, this amount of flow is available to the myocardium through collateral channels, which are in size and, therefore, not visualized on angiography. The larger epicardial and interventricular septal collateral vessels seen on angiography usually are not the ones that actually connect to the capillaries within the myocardium. The ones that usually feed capillary beds are present below the endocardium and are formed from connections between perforating arteries. These vessels are also too small to be seen on coronary angiography. Therefore, angiographic assessment of collateral channels is highly misleading and has led to an underestimation of collateral flow in humans.

Because collateral flow is generally less than normal flow, regions with adequate collateral flow fill later than the normal myocardium after microbubble destruction. Normal regions fill within 5 seconds during high mechanical index intermittent imaging (B-mode or Power Doppler). Regions with collateral flow fill later depending on the magnitude of flow. If they do not fill by 15 to 20 seconds, then flow to the region is markedly reduced, and it is unlikely to be spared necrosis during coronary occlusion. Infarcts ranging in size from negligible to nearly transmural from 2 dogs are depicted in panel D of Figures 2 and 3. Whereas the perfusion defect size a few seconds after microbubble destruction is very similar for the dogs (panel A), the defect size at longer intervals after microbubble destruction is very different and denotes areas receiving no collateral flow (panel C). These regions without opacification closely resemble the topography of necrosis (panel D). In this study, the MCE measurements were made 20 minutes after coronary occlusion, and infarct size was measured 6 hours later in a model of persistent coronary occlusion.\textsuperscript{36}

Regions supplied by collateral flow (seen on MCE) improve function after revascularization even in patients with recent AMI and totally occluded infarct-related arteries.\textsuperscript{37–39} The degree of improvement in function is related to the magnitude and spatial extent of collateral flow. The majority of patients in these studies had collateral flow on MCE, and only a few exhibited angiographic collaterals. It is possible that if the infarct-related arteries were left occluded, these viable collateral-dependent regions would be subjected to exercise-induced ischemia and its consequences, such as arrhythmias, as well as increased regional dysfunction and wall stress. Revascularization of collateral-dependent viable myocardium is the likely explanation of the benefits of an open artery after AMI.

Similar to collateral flow, low flow through an open infarct-related artery can also be assessed using the microbubble destruction technique. The myocardium supplied with lower levels of anterograde flow will fill slower than normal myocardium. If the capillary blood volume is mostly intact (that is, no reflow is limited to a small zone), and the myocardium fills in <15 to 20 seconds during intermittent high mechanical index imaging, then the myocardium is viable and revascularization will result in improvement in function. This has been confirmed in a study of 96 AMI patients imaged on a mean of 5 days after AMI. If the myocardium did not fill by 10 seconds, it did not recover resting function 84% of the time.\textsuperscript{40}
Imaging Microvascular Inflammation

More recently, it has been possible to quantify the degree of microvascular inflammation after reperfusion using microbubbles that are specially designed for site-specific imaging. Either the microbubble shell surface is modified (to make them more “sticky” to leukocytes) or ligands are incorporated on the shell surface that adhere to specific adhesion molecules expressed either on the leukocytes or the endothelial surface. There, bubbles are injected as a bolus after reperfusion and time is allowed for them to clear from the systemic circulation before imaging is initiated. At that time, microbubbles are seen to be retained at activated sites within the myocardium.

Figure 4 shows examples of the myocardium after 90 minutes of left anterior descending (left top panel) and left circumflex artery (left bottom panel) occlusion followed by 60 minutes of reperfusion. The microbubbles administered in this study had phosphatidyl serine incorporated on their surface, which increases their retention in inflamed tissue via binding to activated leukocytes. MCE shows that the entire reperfused myocardium is inflamed and that the endocardium (where there is necrosis, right panels) has more leukocyte trafficking than the rest of the myocardium. This is also confirmed by technetium labeling of leukocytes in vivo (middle panels). The myocardial signal intensity correlated well with the number of leukocytes in the myocardium as well as myeloperoxidase activity. Interventions aimed at reducing reperfusion injury have demonstrated less microbubble retention within inflamed tissue. Thus, MCE can be used to monitor the degree of inflammation noninvasively. This important technical advance also has obvious implications beyond the myocardium although at present it is limited to research applications.

Treatment of Microvascular Dysfunction After Reperfusion

Evolving treatments of the no-reflow phenomenon are directed toward reversal of microvascular flow abnormalities because these either directly or indirectly contribute to cell death. Promising adjunctive therapies that may reduce microemboli include intensive antiplatelet therapy with aspirin and ticlopidine, platelet glycoprotein IIb/IIIa inhibitors, coronary vasodilators, and embolization protection devices.

Treating platelet microthromboembolism with aggressive antiplatelet therapy has yielded encouraging results. The ADMIRAL trial (Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up) provides preliminary evidence that abciximab improves TIMI flow rates in AMI patients undergoing primary PCI. Abciximab is associated with better TIMI grade flow 2 weeks later with an 80% reduction in adverse cardiac events at 30 days compared with control. Whether the improvement in coronary flow is mediated by inhibition of platelet aggregation or by faster establishment of epicardial artery recanalization, or both, is not known. A more direct method to reduce thrombus or plaque burden is to retrieve embolic material with catheter-based devices.

Therapy targeting microvascular vasospasm also appears promising. Improved TIMI flow has been reported with intracoronary papaverine administered directly into the infarct-related artery. Direct administration of verapamil, but not nitroglycerin, into a degenerated venous bypass graft has been reported to be effective in improving coronary flow after PCI. In patients with TIMI 2 flow immediately after PCI, coronary flow has also been reported to improve with intracoronary verapamil. A modest improvement in both angiographic flow and MCE perfusion, better functional recovery, and less LV remodeling was reported with intracoronary verapamil compared with placebo in AMI patients undergoing PCI.

Intracoronary adenosine after reperfusion attenuates progression of microvascular dysfunction and augments recovery of myocardial contractile function independent of its vasodilator effects. It likely occurs through inhibition of neutrophil migration, maintenance of endothelial integrity, and mimicking and/or potentiation of ischemic preconditioning. The AMISTAD I trial (Acute Myocardial Infarction STudy of Adenosine) reported that adenosine reduces infarct size in patients with anterior AMI.

Recent interest has focused on nicorandil, a hybrid of mitochondrial \(K_{ATP}\) channel opener and a nitrate. It reduces preload and afterload, dilates coronary resistance vessels, reduces myocyte Ca\(^{2+}\) overload, and attenuates neutrophil activation. Because the mitochondrial \(K_{ATP}\) channel is also an end-effector in the ischemic preconditioning pathway, nicorandil may also provide the cardioprotective effect of ischemic preconditioning. Nicorandil has been shown to reduce infarct size and improve microvascular perfusion.

Myocardial microthrombi occur not only from embolization from a proximal site but also from in situ formation due to IIb/IIIa activation. Activated platelets can also release substances causing microvascular spasm and no reflow prior to irreversible myocyte injury. Intravital microscopy studies reveal that a low-flow state (ischemia) can itself lead to platelet aggregation and leukocyte adhesion as well as red blood cell stagnation. If the low-flow state is prolonged, necrosis could result because of low flow rather than vice
versa. Therefore, interventions aimed at reversing tissue hypoperfusion even during coronary occlusion may reduce the extent of no reflow. It is in this regard that intra-aortic balloon pumping could be useful, because it will increase collateral blood flow and ameliorate ischemia.53

Summary

MCE has provided valuable information regarding the microcirculation in animal models as well as in humans. In this brief update, we have tried to summarize the state of the microcirculation during stress-induced ischemia, AMI, and inflammation caused by reperfusion. We have also highlighted the importance of capillary resistance and blood viscosity, as well as collateral blood flow, in maintaining myocardial viability. We have discussed treatment options aimed at increasing flow to regions with microvascular obstruction to improve outcome. Future progress in AMI therapy will be geared toward protecting the myocardium during ischemic and reperfusion injury through improvement in microvascular flow and function. In order to achieve this goal, a comprehensive understanding of the normal and abnormal workings of the coronary microcirculation is essential. We hope this Clinical Update contributes to small measure toward that understanding.

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References


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