Microvascular Obstruction and the No-Reflow Phenomenon After Percutaneous Coronary Intervention
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Case presentation A: A 50-year-old diabetic man presented to the hospital after 8 hours of continuous chest pain. Because of acute myocardial infarction of the anterior wall, he underwent direct stenting to an occlusion in the left anterior descending coronary artery. Despite revascularization, suboptimal coronary flow was achieved, and he subsequently developed heart failure.

Case presentation B: A 77-year-old man underwent elective stenting of a significant stenosis in a degenerated saphenous vein coronary bypass graft. After the procedure, coronary flow in the graft was severely reduced, and he sustained a myocardial infarction in the subtended myocardial territory.

Introduction and Definition
The concept of “no reflow” refers to a state of myocardial tissue hypoperfusion in the presence of a patent epicardial coronary artery. The underlying cause of no reflow is microvascular obstruction, which may be produced by various mechanisms.

No reflow can be classified according to the duration of the preceding myocardial ischemia (Figure 1). “Reperfusion no reflow” occurs after primary percutaneous coronary intervention (PCI) for reperfusion of an infarct artery in the setting of acute myocardial infarction (AMI) and may be asymptomatic or may present clinically with continued chest pain and ST-segment elevation. Reperfusion no reflow is preceded by ischemic cell injury, is confined to the irreversibly damaged necrotic zone, and may be exacerbated at the time of reperfusion. Reperfusion no reflow is an independent predictor of adverse clinical outcome after AMI regardless of infarct size and is associated with heart failure and increased mortality.1

“Interventional no reflow” follows noninfarct PCI and affects myocardium that was not subjected to prolonged ischemia before the procedure. Clinically recognized interventional no reflow that complicates PCI is typically sudden in onset, presenting as acute ischemia with chest pain and ECG changes, and may resolve over the course of several minutes. Patients sustaining interventional no reflow have higher rates of myocardial infarction and mortality.2 Because interventional no reflow is unpredictable and uncommonly recognized in clinical practice, much of the current understanding of this phenomenon originates from studies of reperfusion no reflow in animal models and AMI patients.

Diagnosis of No Reflow
Although ECG ST-segment resolution is a readily available marker of tissue-level reperfusion, persistence of ST-segment elevation in an AMI patient may reflect either epicardial artery occlusion or microvascular obstruction. Coronary angiography allows a semiquantitative grading of epicardial coronary flow according to the Thrombolysis In Myocardial Infarction (TIMI) flow grades. The no-reflow phenomenon is recognized angiographically in >20% of patients undergoing primary angioplasty for AMI and in <2% of elective PCI cases. Reduced coronary flow after primary angioplasty (TIMI flow 0 to 2) is associated with worse outcome than normal (TIMI 3) flow, even when no significant epicardial obstruction remains.1 More sensitive markers of tissue perfusion have now been identified and provide prognostic information beyond that of TIMI flow grade. The TIMI frame count assesses...
the number of angiographic frames required for the contrast medium to reach standardized distal landmarks of the coronary tree, and the myocardial blush grade is a quantitative assessment of myocardial contrast density. Angiographic epicardial flow is a poor surrogate for tissue perfusion, which is the clinically important end point of coronary interventions, and microvascular no reflow occurs much more commonly than is recognized. Myocardial contrast echocardiography has greatly advanced the noninvasive assessment of myocardial perfusion and may demonstrate microvascular no reflow even among patients with angiographic TIMI 3 flow after primary PCI, which predicts worse outcome. Tissue hypoenhancement on contrast-enhanced MRI and CT reflects impaired myocardial perfusion and correlates with histological evidence of microvascular obstruction. A rise in serum cardiac biomarkers after PCI reflects myocardial necrosis secondary to tissue hypoperfusion and ischemia. More than 70% of patients may exhibit elevated troponin values after an otherwise successful elective PCI.

Pathophysiology of No Reflow

No reflow results from obstruction of the myocardial microcirculation, defined as vessels <200 μm in diameter. The pathophysiology and treatment of microvascular obstruction in the setting of reperfusion and interventional no reflow likely differ (Figure 2). Pre-existing microvascular dysfunction may exacerbate the degree of microvascular obstruction that develops after both elective and infarct-related PCI, which may explain the association of diabetes mellitus and hyperlipidemia with no reflow.

Myocardial Infarction Reperfusion No Reflow

Myocardial ischemia-reperfusion injury and endothelial damage underlie the development of reperfusion no reflow. Infarct size and microvascular hypoperfusion may increase at the time of coronary reperfusion beyond that observed during the ischemic period. Endothelial injury is induced by an acute inflammatory response, generation of reactive oxygen species, intracellular calcium overload, and opening of the mitochondrial permeability transition pore. Ultrastructural changes are confined to the necrotic zone, appear first in the subendocardium, and subsequently progress toward the subepicardium after longer periods of occlusion. Endothelial cellular swelling and protrusions, as well as myocyte swelling and tissue edema, may occlude the microvasculature. Vasospasm and downstream embolization of thrombus compound the microvascular obstruction.

Interventional No Reflow

Distal embolization of thrombus and atherosclerotic gruel are the most likely culprits in no reflow complicating non-infarct angioplasty. Microembolization leads to platelet and inflammatory cell activation and to vasospasm, which reduce coronary flow in combination with mechanical plugging of the microcirculation.

Predictors of No Reflow

The degree of reperfusion no reflow that develops after infarct angioplasty is associated with the duration of the preceding myocardial ischemia, infarct size, procedural variables, and patient characteristics. Coronary stenting may lead to reduced tissue perfusion compared with balloon angioplasty. Larger plaque area and eccentric or fissured plaque predict no reflow. These findings reflect the importance of distal embolization in this setting. Diabetes mellitus, absence of preinfarction angina, and advanced age predict no reflow, which reflects the impact of preexisting microvascular damage and dysfunction, as well as ischemic preconditioning, on the subsequent development of no reflow. Interventional no reflow occurs more commonly after angioplasty in degenerated saphenous vein grafts and thrombus-containing lesions and after coronary atherectomy.

Prevention and Treatment of No Reflow

Multiple therapies for no reflow have been tested in animals and to a lesser degree in humans. Interventions for no
Reflow that were efficacious in preclinical research often have failed to translate into effective human therapies owing to limitations of the available animal models. Most research has focused on the setting of AMI, and randomized clinical trials have been confined to preventative therapy. Consequently, data relating to reversal of established no reflow are limited. Because no reflow is dynamic by nature and may spontaneously resolve over time, the contribution of nonrandomized studies to the current understanding of treatment options is limited.

Several pharmacological agents have been studied. Adenosine is an endogenous purine nucleoside that decreases arteriolar resistance and activates intracellular cardioprotective signaling pathways. Its mechanism of action may involve opening ATP-sensitive potassium channels (K\(_{\text{ATP}}\)), inhibition of neutrophil migration, prevention of superoxide generation, or blockade of coronary endothelin release. Nitroprusside and nitroglycerin are nitric oxide donors that vasodilate conductance vessels; however, microvessels are unable to metabolize nitroglycerin to nitric oxide, whereas nitroprusside does not require metabolism. Nicorandil is a hybrid of a K\(_{\text{ATP}}\) opener and nitrate and may prevent reperfusion injury by blocking the mitochondrial permeability transition pore. Calcium channel blockade has several potentially beneficial effects in the setting of no reflow in addition to attenuation of microvascular spasm. Reduction of heart rate and blood pressure may reduce myocardial ischemia and infarct size. Verapamil may inhibit platelet aggregation and thrombus formation in the microvasculature and may have a direct effect on calcium flux across the sarcolemmal membrane or within intracellular compartments that could protect reversibly injured myocytes. Platelet inhibition with glycoprotein IIb/IIIa inhibitors could reduce downstream embolization and in situ microvascular generation of thrombus and reduce the release of vasoactive and chemotactic mediators from platelets.

**Myocardial Infarction**

**Reperfusion No Reflow**

Randomized trials have suggested that the vasodilators verapamil and adenosine may reduce the no-reflow phenomenon after primary PCI. Prevention of upstream and in situ microvascular thrombosis with intravenous abciximab and intracoronary thrombolysis has been shown to improve...
microvascular perfusion. Mechanical devices for prevention of embolization and removal of plaque and thrombus may have a role in the setting of primary PCI. Although thrombus aspiration improves tissue perfusion, deployment of a distal arterial protection device does not.

The concept of ischemic preconditioning and postconditioning refers to a variety of pharmacological and nonpharmacological cardioprotective interventions implemented before the onset of ischemia or at the time of reperfusion. Intracellular signaling is complex and incompletely defined and appears to involve the activation of various survival protein kinase cascades (eg, ERK1/2 and PI3K-Akt), antiapoptotic pathways (eg, Bcl-2 and BAX), protein kinases C and G, intracellular generation of nitric oxide, mitochondrial generation of reactive oxygen species, opening of mitochondrial (and possibly sarcolemmal) KATP, and blockade of the mitochondrial permeability transition pore. These various events culminate in reduction of both necrotic and apoptotic cell death (Figure 3), reduce the degree of no reflow and infarct size, and are suppressed in the presence of diabetes and hyperlipidemia. Intravenous nicorandil, started before PCI, and myocardial postconditioning after direct coronary stenting by intermittent low-pressure balloon inflations in the infarct-related artery have been shown to improve tissue perfusion, reduce infarct size, and improve patient outcome. Papaverine, nitroprusside, and abciximab have been reported to be effective for reversal of existing no reflow after primary PCI; however, no randomized trials have been performed in this setting.

Interventional No Reflow
Prophylactic measures that protect against no reflow after noninfarct PCI include deployment of an embolic protection device for coronary bypass angioplasty and administration of glycoprotein IIb/IIIa inhibitors to patients undergoing PCI to native coronary arteries but not to bypass grafts. Among patients undergoing rotational coronary atherectomy, intracoronary nicorandil reduced no reflow compared with verapamil. As in the case of reperfusion no reflow, treatment of existing interventional no reflow is confined to retrospective reports and case series. Beneficial effects of intracoronary diltiazem, verapamil, epinephrine, nitroprusside, and adenosine have been reported.

How Could No Reflow Have Been Prevented in Our Patients?
In patient A, upstream administration of a glycoprotein IIb/IIIa inhibitor, use of a thrombus aspiration device, and possibly administration of nicorandil or ischemic postconditioning after coronary stenting may have prevented the development of microvascular no reflow in the setting of infarct angioplasty. In patient B, deployment of an embolic protection device may have prevented microvascular obstruction after stenting of the bypass graft.

Conclusions
Myocardial hypoperfusion is common after both elective and infarct-related PCI, is underdiagnosed, and is associated with adverse outcome. Recent advances in noninvasive imaging of microvascular perfusion have enhanced the diagnosis of no reflow. Several prophylactic measures have been identified; however, no treatment has demonstrated proven efficacy for the treatment of existing no reflow. Future directions in no-reflow research include elucidation and targeted activation of intracellular cardioprotective signaling pathways.

Disclosures
None.

References


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