A acute myocardial infarction (MI) is caused by obstruction of a coronary artery by a thrombus on a ruptured plaque. Salvaging threatened myocardium after acute coronary occlusion has been a key therapeutic objective. Percutaneous coronary intervention (PCI) with coronary stenting is widely performed for this purpose. PCI, however, does not necessarily guarantee the recovery of blood flow at the microvascular level, because myocardial ischemia often injures the coronary microvasculature structurally.1-3 This is called the no-reflow phenomenon.4 If this phenomenon occurs, it significantly attenuates the beneficial impacts of reperfusion therapy, resulting in poor clinical and functional outcomes.1,3,5 The PCI procedure itself may worsen the microvascular function. Balloon inflation and stenting may introduce embolization of plaque and thrombus debris, resulting in obstruction in distal coronary small arteries and arterioles. Atheroembolism and/or thromboembolism could limit the efficacy of PCI.6

Attention is currently shifting from "no-flow" to "no-reflow." We should ascertain the patency to determine the status of the coronary microvasculature in each patient with acute MI in order perform risk stratification. With the advancement of imaging modalities, which include myocardial contrast echocardiography, Doppler guidewire, and cardiac magnetic resonance imaging, the number of patients with the no-reflow phenomenon has increased compared to the rates that we deemed. Our ultimate therapeutic goal is to achieve successful microvascular reperfusion. In this review, I attempt to provide an in-depth understanding of the no-reflow phenomenon from the bench to the bedside.

Two mechanisms of the no-reflow phenomenon: capillary injury and microvascular emboli

The no-reflow phenomenon in the myocardium was originally described in 1974 by Kloner, et al.4 After prolonged coronary occlusion, the no-reflow phenomenon appears in the center of the MI zone, where the capillary structure is completely destroyed. This capillary damage is caused by endothelial swelling, compression by tissue, myocyte edema, and neutrophil infiltration. Coronary reperfusion accelerates myocardial swelling, tissue edema, endothelial disruption, plugging of capillaries by neutrophils and microthrombi, inflammation due to generation of oxygen-free radicals and activation of complements, and contracture of neighboring myocytes.7 Therefore, the no-reflow phenomenon has aspects of reperfusion injury. In clinical settings, PCI potentially accelerates the microvascular damage by another mechanism. Mechanical stress to the vulnerable coronary arterial plaque may accelerate the liberation of micro-thromboemboli and particles of plaque gruels. They are thought to be showered downstream to obstruct small arteries and arterioles, thus increasing coronary arterial resistance and causing small MI.8,9 Therefore, there are at least two mechanisms of the no-reflow phenomenon in patients with ACS, capillary obstruction and microemboli to small arteries and arterioles.10

Key words: Echocardiography, Myocardial perfusion, Reperfusion, Myocardial ischemia, Microcirculation, Myocardial viability, Prognosis, Ventricular function
How to diagnose the no-reflow phenomenon

The importance of the no-reflow phenomenon is not solely because it correlates with infarct size; it also has additional prognostic information. A large no-reflow zone size is associated with reduced left ventricular contractile function. Patients with the no-reflow phenomenon are in the highest-risk subgroup among those undergoing reperfusion, with raised associated risks of congestive heart failure and death. The no-reflow phenomenon is likely to be associated with left ventricular remodelling in the remote stage of MI. The no-reflow phenomenon is also linked to ventricular arrhythmias and even cardiac rupture.

**Myocardial contrast echocardiography:** Until now, myocardial contrast echocardiography (MCE) has been the gold standard examination for diagnosing the no-reflow phenomenon. MCE uses intravascular contrast agents that contain microbubbles as blood tracers, and it enables us to assess the assessment of microvascular integrity and blood flow dynamics in myocardial capillaries. The no-reflow zone is documented as the region of contrast perfusion defect (Figure 2). Substantial sizes of contrast perfusion defects are observed in about 30% of patients with anterior wall acute MI, despite open coronary arteries. The contrast perfusion defects, where the capillaries are completely damaged, appear in the center of the infarct zone. Therefore, the contrast perfusion defects may underestimate the ultimate infarct size.

We can estimate the severity of microvascular damage by analysing MCE images quantitatively. There is a linear correlation between background-subtracted acoustic intensity and concentration of microbubbles. When the myocardial contrast intensity is normalized to the contrast intensity of the adjacent left ventricular cavity, myocardial blood volume fraction can be measured. Since 90% of myocardial blood volume exists in capillaries, myocardial blood volume fraction reflects the density of capillaries, that in turn reflect myocardial viability. About 4 mL of blood exists in 100 g of normal myocardium. In infarcted myocardium, the myocardial blood fraction is reduced to less than 1 mL/100g myocardium. Quantitative analysis of one MCE image provides a map of capillary integrity, reflecting myocardial viability, of the left ventricle (Figure 2).

**Assessment of coronary flow dynamics by coronary angiography and Doppler examination:** Coronary slow flow, which is called Thrombolysis In Myocardial Infarction (TIMI)-2 flow, is sometimes observed after successful PCI. This is caused by the substantial size of the no-reflow phenomenon and is associated with the worse clinical outcomes compared to TIMI-3 flow. However, among the patients with TIMI-3 flow after PCI, MCE study documented the no-reflow phenomenon in 16% of the patients. TIMI perfusion grade has been proposed...
as a measure of the filling and clearance of radiocontrast in the myocardium. The following grades are used: grade 0, no apparent tissue-level perfusion; grade 1, myocardial blush is present but with no clearance from the microvasculature; grade 2, myocardial blush clears slowly; and grade 3, myocardial blush clears within three cardiac cycles of washout. For patients with TIMI-3 flow, the assessment of TIMI perfusion grade allows further risk stratification; only patients with TIMI-3 and normal tissue-level perfusion (TIMI perfusion grade 3) have an extremely low risk of death and cardiac complications.

To determine the mechanisms of coronary slow flow, we assessed the coronary flow velocity pattern in patients with acute MI. During the PCI procedure, we used Doppler guidewire as the guidewire and continuously monitored the coronary blood flow velocity pattern. In patients with the no-reflow phenomenon, the characteristic to-and-fro blood flow pattern is recorded. This pattern had three components: systolic flow reversal, reduced antegrade systolic flow, and forward diastolic flow with a rapid deceleration slope. Increased capillary resistance and a reduced myocardial blood pool by capillary damage are the cause of this flow pattern. This coronary blood flow velocity pattern is different from that in patients with microemboli to resistant vessels. That is characterized with slow forward flow during cardiac cycle and an increase in diastolic-to-systolic flow ratio, implicating increased coronary arterial resistance. We can now assess coronary blood flow velocity at bedside with transthoracic Doppler examination.

The index of microvascular resistance (IMR) is a simple coronary guidewire–based method for assessing coronary microvascular function in patients with acute MI. An increased IMR measured at the end of primary PCI is an independent predictor of the reduced left ventricular ejection fraction in the remote stage of MI. These observations suggest that IMR can be used to study the pathophysiology of microvascular function in ST-elevation MI and that IMR may be clinically useful for very early prognostication.

Electrocardiography: In patients with acute MI, rapid reduction in ST-segment elevation after reperfusion therapy indicates early, full, and prompt restoration of myocardial tissue perfusion. Early T-wave inversion is also a sign of successful tissue perfusion. Sustained elevation of the ST segment after coronary reperfusion therapy is associated with poor functional and clinical outcomes and is thus a crude means of assessing the no-reflow phenomenon.

Cardiac magnetic resonance (CMR): Contrast-enhanced CMR enables evaluation of myocardial perfusion during the first pass of the contrast agent. Alternatively, delayed contrast-enhanced CMR 20 minutes after contrast injection can be used to detect necrosis. The hypo- or no-enhancement zones on first-pass perfusion CMR represent the no-reflow phenomenon. A benefit of contrast-enhanced CMR is high spatial resolution, which allows assessment of the transmural extent of the no-reflow phenomenon as well as necrosis in the infarct region. CMR, however, is not normally performed because of issues around feasibility and cost early after MI. When CMR is available, it is usually performed up to 7 days after hospital admission in medically stabilized patients.

Treatment of the no-reflow phenomenon

It remains controversial as to whether the no-reflow phenomenon can be a therapeutic target. If the tissue perfusion was improved, we could speculate that functional recovery of viable muscle could be promoted. Improved tissue perfusion would enhance the delivery of blood-borne components to the MI zone and this would attenuate the left ventricular remodeling. Among blood components, delivery of endothelial precursors with phenotypic and functional characteristics of embryonic hemangioblasts to the infarct zone is important. These cells can directly induce new blood vessel formation in the infarct bed (vasculogenesis) and proliferation of pre-existing vasculature (angiogenesis) after experimental myocardial infarction. Neovascularization of ischemic myocardium by human bone marrow–derived angioblasts can prevent cardiomyocyte apoptosis and may improve cardiac function. In clinical settings, however, the size of the no-reflow phenomenon is often too large to deliver blood flow to its central zone. Therefore, our interest has shifted to how to improve the patency of the coronary microvasculature in the MI zone.

Catheter-based treatment: Several catheter-based devices have been developed to reduce embolic burden to the coronary microcirculation. Thrombus aspiration devices reduce thrombi at the occlusion site as much as possible before the PCI procedure. Distal protection devices, that are designed to trap embolic materials, are used during PCI to reduce embolic debris. Although several studies demonstrated that thrombus aspiration before PCI is associated with an improvement in clinical outcomes in patients with ACS, a recent multicenter randomized trial demonstrated that routine thrombus aspiration before PCI as compared with PCI alone did not reduce 30-day mortality among patients with STEMI. Distal embolic protection also failed to improve microvascular flow and reperfusion success or to reduce infarct size, or enhanced event-free survival. These results indicate that embolization to microcirculation is not a major cause of the no-reflow phenomenon in clinical settings. Ito, et al, however, reported distal protection during primary PCI procedure is associated with a decrease in IMR, implying an improvement in microvascular function. We need to select patients in whom these devices are to be used. Identification of ruptured plaque by intravascular angioscopy might be useful for identifying patients who could respond to distal protection.

Medical treatment:

Antiplatelet therapy Aggressive antiplatelet therapy with aspirin, clopidogrel, and/or platelet glycoprotein IIb/IIIa receptor inhibitors is a promising adjunctive therapy for improving tissue perfusion. The abciximab before direct Angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADIMRAL) trial provided preliminary evidence that intravenous abciximab is associated with a high incidence of TIMI-3 flow and with an 80% reduction in adverse cardiac events compared with control among acute MI patients undergoing primary PCI. It remains unknown, however, whether the improvement in coronary flow is mediated by inhibition of platelet aggregation or by faster establishment of epicardial artery recanalization.

Pharmacological cardioprotection Clinical trials have found that adenosine and nicorandil have the potential to protect myocardium and the coronary microvasculature against ischemic and reperfusion injury. Adenosine yields benefits beyond simple vasodilation. Adenosine lowers neutrophil counts in the infarct zone, maintains endothelial integrity, and may exert a cardio-
protective effect that is related to ischemic preconditioning. In patients with acute MI, intracoronary administration of 24–48 µg adenosine is well tolerated and improves microvascular and ventricular function in the infarct zone, leading to an improved clinical course after PCI. Intravenous administration of adenosine, however, cannot reduce infarct size. In the AMISTAD II trial, infarct size was reduced with a high-dose infusion (70 µg kg⁻¹ min⁻¹), but clinical outcomes were not improved in 21,118 patients with ST-segment elevation MI.

Nicorandil is a hybrid of a mitochondrial ATP-dependent potassium channel (mKATP) opener and nitric oxide. Nicorandil can augment ischemic tolerance of myocytes and coronary microvasculature because it can mimic and/or augment ischemic preconditioning (IPC). This is because the mKATP is an end-effector of the IPC pathway. Nicorandil also reduces preload and afterload, dilates coronary resistance vessels, reduces Ca²⁺ overload of myocytes, and attenuates neutrophil activation. Studies have demonstrated that among reperfused patients who received intravenously administered nicorandil, infarct size was reduced and clinical outcome improved in patients with acute anterior MI.

Our MCE study showed an associated improvement in microvascular perfusion with intravenous nicorandil treatment. To protect against reperfusion injury, nicorandil should be administered before reperfusion to deliver nicorandil to the postischemic myocardium effectively.

The use of vasodilators including nitrates, verapamil, papaverine, nicardipine, and sodium nitroprusside may also have a role in improving postischemic microvascular function. Intracoronary nitroprusside or verapamil was associated with a significant improvement in coronary flow, with an increase in TIMI flow grade. Intracoronary verapamil was associated with better functional recovery in wall motion abnormalities. The use of these vasodilators is not formally approved for treating the no-reflow phenomenon. However, the use of these vasodilators is a choice to increase coronary blood flow, which is essential for improved left ventricular function, in patients of TIMI-2 flow after PCI.

**Non-pharmacological cardioprotection:**

**Remote ischemic preconditioning** Repeating brief ischemia in a distant organ provides cardioprotection similar to that of regional ischemic preconditioning (IPC). Reducing ischemia-reperfusion injury may improve the outcome of reperfusion therapy for these conditions. The precise mechanisms of remote IPC remain unknown. Mitochondrial permeability transition pore and/or mitochondrial KATP channels play a pivotal role in remote IPC. In patients with ST-elevated MI, remote IPC was performed with intermittent arm ischemia through 4 cycles of 5-minute inflation and 5-minute deflation of a blood-pressure cuff during transport to the hospital. Median salvage index, which was measured by myocardial perfusion imaging at 30 days after the onset, was 0.75 (IQR 0.50-0.93, n = 73) in the remote conditioning group versus 0.55 (0.35-0.88, n = 69) in the control group. Thus, remote IPC before hospital admission is a simple procedure and can increase myocardial salvage. In a substudy of the same patients, remote ischemic conditioning delivered before hospitalization seemed to result in modest improvement in LV function in high-risk patients prone to develop large myocardial infarcts.

**Postconditioning** Experimental studies have demonstrated that multiple, short induced coronary occlusions immediately after sustained myocardial ischemia are associated with reduced MI size compared with sudden reperfusion. This cardioprotective intervention is called postconditioning. The mechanism of protection involves activation of extracellular-signal-regulated kinase, production of nitric oxide, opening of mitochondrial potassium channels, and inhibition of opening of the mitochondrial permeability transition pore. A similar approach could be applied in the cardiac catheterization laboratorv to protect reperfused myocardium after primary angioplasty in patients with acute MI. Staat, et al performed postconditioning during PCI for acute MI in humans, starting within 1 minute of reflow and achieved by injection of an angioplasty balloon for 1 minute followed by deflation for 1 minute 4 times. Improvements were seen in myocardial perfusion and functional outcomes compared with those in patients who did not undergo postconditioning. Thuny, et al randomly assigned 50 patients with STEMI to either a control group or postconditioned group. Postconditioning was associated with smaller infarct size (13 ± 7 g/m² versus 21 ± 14 g/m²; P < 0.01) and creatine kinase peak serum level (median [interquartile range]: 1,695 [1,118 to 3,692] IU/l versus 3,505 [2,307 to 4,929] IU/l; P < 0.003). Cardiac magnetic resonance imaging performed within 48 to 72 hours after admission showed that the extent of myocardial edema was significantly reduced in the postconditioned group as compared with the control group (23 ± 16 g/m² versus 34 ± 18 g/m²; P < 0.03). This catheter-based technique may be clinically applicable in PCI, CAGB, organ transplantation, and peripheral revascularization where reperfusion injury is expressed.

**Conclusions:** After aggressive reperfusion therapy, the no-reflow phenomenon occurs in a notable proportion of patients with ACS, and is associated with a poor prognosis. Assessing microvascular perfusion is useful for risk stratification of patients with ACS, and precise observation of coronary angiography or additional examination of coronary flow dynamics can provide information on microvascular function. Elucidation of the mechanism of microvascular dysfunction in each patient is key for establishing specific therapeutic strategies for the patient. To accelerate development of new reperfusion regimens, an integrated approach that incorporates multiple efficacy variables to assess the success or failure of tissue perfusion might be required.

**References**

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