# Prevention and Treatment of No-Reflow Phenomenon by Targeting the Coronary Microcirculation

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The coronary no-reflow phenomenon refers to the post–percutaneous coronary intervention (PCI) state in which, despite successful revascularization of the epicardial conduit coronary arteries, substantial regions of the myocardium do not receive adequate perfusion. In most cases, the underlying mechanism can be attributed to alterations in the microvascular circulation caused by factors intrinsic or extrinsic to the coronary microcirculation. Because the no-reflow phenomenon is associated with poor clinical outcomes, it is of great importantance to identify and apply effective strategies for reducing post-PCI morbidity and mortality. Successful prevention strategies aim to address increased vasoreactivity, intravascular platelet aggregation, microvascular inflammation, and down-stream plaque particle embolization. This review provides an updated overview on the pathomechanism of no-reflow and the current available prevention strategies from the perspective of coronary microcirculation. Although large randomized clinical trials have not yet identified any effective treatment, studying the coronary microcirculation may reveal new therapeutic targets for successful amelioration of the adverse clinical consequences from no-reflow phenomenon.

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**KEY WORDS**

No-reflow • Coronary microcirculation • Microvascular obstruction

In patients with acute myocardial infarction (MI) undergoing primary percutaneous coronary intervention (PCI), restoration of blood flow in the culprit epicardial coronary artery leads to normalization of, or increased blood flow to, the affected coronary microcirculation. Coronary arterioles have an intrinsic capability to respond to sudden increases in flow with vasodilation. When this response fails, or the microvasculature becomes obstructed by debris, despite successful reperfusion of the obstructed epicardial artery, the affected myocardium does not receive adequate perfusion for the maintenance of its function and cellular integrity. Coronary *no-reflow phenomenon*

**TABLE 1**

**Comparison of the Most Routinely Used Modalities for Diagnosing No-Reflow**

| Diagnostic Approach | Assessment | Sensitivity/ Specificity | Advantage | Disadvantage |
|---|---|---|---|---|
| Electrocardiography | ST-segment resolution | Moderate/moderate | Rapid, simple, readily available, inexpensive | Crude estimation, less accurate in anterior MI |
| TIMI flow | Epicardial blood flow | Moderate/good | Rapid, simple, readily available, inexpensive | Interobserver variability, no assessment of tissue perfusion |
| Corrected TIMI frame count | Number of cine frames to reach distal landmark | Moderate/good | Simple, readily available, inexpensive | Interobserver variability, no assessment of tissue perfusion |
| Myocardial blush grade | Opacification of myocardial tissue | Good/good | Simple, readily available, inexpensive | Interobserver variability |
| Myocardial contrast echocardiography | Amount of visualized contrast in ventricular segments | Excellent/good | High spatial and temporal resolution, good reproducibility, low cost, imaging of all cardiac segments | Requires contrast administration, potential underestimation of infarct size |
| Contrast-enhanced cardiac MRI | Hypoenhancement on first-pass perfusion or delayed enhancement images | Good/excellent | High spatial resolution, good reproducibility, detects myocardial wall motion abnormalities | Requires contrast administration, expensive, limited availability, difficult to perform in acutely ill patient |

TIMI, Thrombolysis In Myocardial Infarction; MRI, magnetic resonance imaging; MI, myocardial infarction.

refers to this post-PCI state, in which, despite the effective dilation of an occluded vessel in the absence of vascular dissection, delayed or absent distal flow is detected on angiography. Patients undergoing no-reflow usually experience chest pain and develop electrocardiographic ST-segment elevation. The presence of no-reflow is associated with worse clinical outcomes, higher incidence of left ventricular remodeling, reinfarction, congestive heart failure (CHF), and death.[1] In patients with ST-elevation MI (STEMI) treated by primary PCI, Ndrepepa and colleagues[1] identified angiographically detected no-reflow as a strong predictor of 5-year mortality associated with a hazard ratio of 1.66 (95% confidence interval [CI], 1.17-2.36; $P = .004$). Selecting proper diagnostic tools can aid in clenching the correct diagnosis of no-reflow and moving to apply microvascular therapeutic strategies. The recent breakthrough in the field of cardiac imaging provides us highly detailed information about the perfusion of a given myocardial segment at a given time point. Myocardial contrast echocardiography and contrast-enhanced cardiac magnetic resonance imaging (MRI) are excellent modalities for making a sensitive and specific diagnosis of no-reflow. Table 1 briefly summarizes the most routinely used modalities aiming to diagnose no-reflow; more detailed and comprehensive reviews about the diagnostic approaches can be found elsewhere.[2,3] Recently, a large multicenter study aiming to characterize the predictors of no-reflow identified age, prolonged symptom onset to admission time, acute STEMI, and cardiogenic shock as clinical variables to be independently associated with the development of no-reflow.[4] Application of early interventions aiming to ameliorate the degree of coronary no-reflow can significantly impact short- and long-term outcomes. Recently, it has become more widely accepted that abnormal coronary microvascular reactions can contribute significantly to common cardiac pathologies such as coronary artery disease. Both experimental models and in vivo measurements suggest that alterations in the coronary microcirculation can reproduce angina-like features without the involvement of large epicardial arteries. Extensive research in the field revealed

**TABLE 2**

**Pathophysiology of No-Reflow**

| Mechanisms Intrinsic to the Microcirculation | Mechanisms Extrinsic to the Microcirculation |
|---|---|
| Endothelial dysfunction | Microvascular embolization |
| Intravascular inflammation | Leukocyte plugging |
| Endothelial swelling and disruption of the endothelial glycocalyx | Myocardial edema and hemorrhage |

invaluable information about the regulation of the coronary microcirculation in health and disease. This review provides detailed information about the role of the coronary microcirculation in the development of no-reflow, and reviews the available therapeutic modalities to improve microvascular function.

## Pathophysiology of No-Reflow

The inadequate perfusion of the myocardium in the absence of significant stenosis of large epicardial arteries is universally assumed to be the consequence of impairment in the functionality of the coronary microcirculation. Evidence obtained with coronary blood flow studies and ultrastructural changes observed in microvascular endothelial cells in the area of no-reflow support this notion.[5,6] Successful application of vasodilators in distinct cases of no-reflow provided further evidence to localize the disease etiology in the microcirculation.[7,8]

Anatomically, the coronary microcirculation refers to a well-characterized part of the coronary vasculature that represents blood vessels with diameter $< 500$ µm.[9] From a functional point of view, the microcirculation can be segregated into different areas. For example, nutrients, oxygen, and waste products are exchanged primarily in capillaries and postcapillary venules, whereas coronary vascular resistance resides predominantly in arterioles. Because the abrupt increase in coronary microvascular resistance is the hallmark feature of no-reflow,[10] arterioles are assumed to play a key role in the disease pathogenesis. The primary function of the arterioles is to adjust blood supply to oxygen demand. Because the oxygen extraction is approximately 70% to 80% under resting conditions,[11] increases in myocardial oxygen consumption can only be met with subsequent proportionate increases in arteriolar blood flow. In the coronary microcirculation arterioles have particularly high basal tone, which gives them sufficient dilation reserve when increased myocardial demand arises.[11] Additionally, increased cardiac work results in accumulation of cardiac metabolites that promote prominent vasodilation of the arterioles.[11] The dilation of coronary resistance vessels leads to increases in shear stress, which dilates the arterioles further via flow-dependent dilation.[12] When coronary arterioles are not able to secure the adequate blood flow to the myocardium, the supplied cardiac tissue becomes ischemic despite patent epicardial arteries and no-reflow develops.

## Intrinsic Mechanisms of No-Reflow

In view of the coronary microcirculation, the distinguished pathophysiologic processes leading to no-reflow can be categorized by their origin as being intrinsic or extrinsic to the coronary microcirculation (Table 2). Intrinsic mechanisms represent etiologies that are primarily localized in microvascular structures. Abnormality of both endothelium-dependent and -independent vasodilation has been reported in no-reflow; the most frequent finding is endothelial dysfunction.[13] Endothelial dysfunction develops when arterioles lose their responsiveness to vasodilator stimuli or demonstrate enhanced vasoconstriction. As an index of the impaired vasodilator function of microvessels after revascularization, Montisci and colleagues[14] found an inverse correlation of the 2-day post-MI coronary flow reserve (as assessed by intravenous [IV] adenosine infusion) and the extent of initial no-reflow as detected by myocardial contrast echocardiography. Additionally, when endothelium loses its integrity, it can further propagate the disease by releasing vasoconstrictors such as constrictor prostanoids or endothelin-1.[15] Patients with angiographically

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(Thrombolysis In Myocardial Infarction [TIMI] flow ≤ 2 or TIMI flow 3 with final myocardial bush grade ≤ 2 after PCI), electrocardiographically (ST-resolution < 30%), and MRI-detected no-reflow were reported to have significantly higher endothelin-1 levels on admission.[16] Moreover, two distinct multivariable logistic regression analyses identified admission endothelin-1 level as a significant predictor of angiographic and MRI-detected no-reflow.[16,17] In a study of 47 consecutive patients, plasma levels of thromboxane A2 on admission have also been associated with no-reflow after PCI.[18] In this study, thromboxane A2 was found to be an independent predictor of both angiographic no-reflow and lack of ST-segment resolution (odds ratio [OR] 3.5; 95% CI, 1.1-11 and OR 3; 95% CI, 1.3-7). These findings indicate enhanced vasoconstrictor production to be a crucial determinant of no-reflow.

It is widely recognized that normal endothelial functions are disrupted by ischemia and ischemia/reperfusion injury, initiating inflammation in the reperfused tissue.[19] The failure to detect significant association between admission serum C-reactive protein levels and the incidence of coronary no-reflow[20] suggests that localized, not systemic, inflammation is more likely to be responsible for the impairment of microvascular perfusion. In microvessels, the localized inflammatory response is primarily mediated by the generation of reactive oxygen species (ROS). Under normal conditions superoxide radicals are produced in low levels by the mitochondrial electron transport system. Contrary to normal circumstances with the restoration of oxygen tension in the previously hypoxic tissues, profuse generation of ROS is initiated.[21] Several enzymes have been identified as potential sources of superoxide during reperfusion injury; among others, xanthine oxidase, uncoupled endothelial nitric oxide synthase (eNOS), nicotinamide adenine dinucleotide phosphate-oxidase, cytochrome P450, and the uncoupled mitochondrial electron transport system have been proposed to participate in ischemia/reperfusion associated superoxide production.[21] Nitric oxide (NO) generated by eNOS plays a particularly important role in ischemia-reperfusion injury. At the time of reintroducing blood flow to the coronary microcirculation, abrupt increases in shear stress cause increased NO release from endothelial cells through elevated eNOS activity.[22] In the previously ischemic tissue, in spite of promoting vasodilation, NO is consumed by reacting with superoxide to produce peroxynitrite. In addition to the loss of NO, peroxynitrite can cause further damage by irreversibly destroying the heme component of eNOS and by oxidizing its cofactor, tetrahydrobiopterin.[23] Once generated, ROS exert their harmful effects via lipid peroxidation, protein oxidation and nitration, ROS-mediated DNA damage, and activation of calpains and extracellular matrix metalloproteinases.[21]

Aside from the observed alterations in vasomotor control in experimental models of no-reflow, endothelial cells show prominent ultrastructural changes on electron microscopy images.[5,6] Swollen intraluminal protrusions, large intraluminal membrane-bound bodies (membrane blebs), and the absence of pinocytotic vesicles have been described in endothelial cells in the area of no-reflow.[5] Nuclear chromatin clumping and margination were also noted.[6] The disruption in the microvascular endothelial glycocalyx, the 0.2- to 0.8-μm large inner polysaccharide coating of the endothelial wall, has also been demonstrated in a canine model of no-reflow by myocardial contrast echocardiography.[24] Because the glycocalyx serves as the site for multiple physiologic processes, its disruption can affect endothelial flow sensation and the binding of several vasoactive hormones (eg, endothelin and members of the renin-angiotensin-aldosterone and kallikrein-kinin system). Ultrastructural changes, ROS generation, and impaired vasomotor responses lead to the deterioration of endothelial function and integrity to a degree that the injured endothelium is not able to maintain its proper physiologic function; thus, myocardial perfusion suffers, and no-reflow readily develops.

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## Extrinsic Mechanisms of No-Reflow

Extrinsic mechanisms of no-reflow facilitate the development of mechanical obstructions in the microcirculation, therefore preventing blood flow to critical areas of the heart. During PCI, the release of plaque materials can result in microembolization, which leads to occlusion of microvessels.[25] Aspiration devices used during PCI capture debris containing typical cholesterol crystals, foam

cells, hyaline material, calcium deposits, platelets, and coagulation material.[26,27] Fokkema and colleagues[28] demonstrated that, in the absence of angiographically visible distal embolization (no abrupt cutoff distal from the culprit lesion, 94% of cases), the majority of thrombus aspirates (56%) were smaller than 0.5 mm, which strongly suggested that a substantial percentage of the emboli might reach the coronary microcirculation. Minute thrombi during angiography can often remain unrecognized, especially with thrombi in the very distal portion of coronary beds because of the quality of angiography and visual limitations.

no-reflow.[31] Recently, an increase in the neutrophil: lymphocyte ratio has been independently associated with the development of TIMI flow grade detected no-reflow in patients undergoing primary PCI for the treatment of STEMI.[32]

The increased rate of no-reflow has also been demonstrated in patients presenting with myocardial hemorrhage.[33,34] Intramyocardial hemorrhage can contribute to the development of no-reflow by creating microvascular obstruction, and can be detected by MRI in approximately 50% of patients with no-reflow after undergoing successful PCI.[33] The presence of hemorrhage correlates well with markers of infarct size and myocardial function.[35] It has also been reported that the angiographic outcome is worse in patients with MRI-detected hemorrhagic MI.[33] In contrast to hemorrhage, myocardial edema potentially resolves with time and myocardial reperfusion, and may account for the fact that no-reflow may spontaneously improve or resolve in 50% of cases after PCI.[36]

***Recent studies suggest that leukocyte entrapment in capillaries can also contribute to the obstruction of the microcirculation.***

Recent studies suggest that leukocyte entrapment in capillaries can also contribute to the obstruction of the microcirculation.[29] Physiologically, when leukocytes undergo deformation in order to go through intact capillaries, their membranes are in close proximity to the surface of endothelial cells.[30] When the microcirculation is undisturbed, leukocytes can travel along capillaries; however, when the capillary endothelium is damaged or the capillary lumen is narrowed by edema or hemorrhage, leukocytes are likely to to be trapped inside the microcirculation where they can develop stronger adhesion with the endothelium. When this happens, reintroducing normal perfusion pressure might not be able to dislodge the leukocytes and restore blood flow. As an indication of advanced leukocyte activation, higher plasma myeloperoxidase levels (an enzyme secreted by activated neutrophils) were observed in patients with

Although mechanisms leading to no-reflow can be divided into separate intrinsic and extrinsic factors, each component augments the other. For example, thrombus aspirates gained during PCI procedures also contain soluble substances including vasoconstrictors, such as serotonin and thromboxane, as well as inflammatory mediators, such as tumor necrosis factor α.[26, 27] Using a rodent microvessel bioassay system, Kleinbongard and associates[27] demonstrated profound vasoconstriction in response to human plasma aspirated by coronary protection devices. Of note, the inflamed, dysfunctional endothelium is more prone to leukocyte adhesion. On the other hand, upon plug formation, leukocytes become activated and release numerous inflammatory mediators and ROS that deteriorate endothelial function.[29] Although intramyocardial hemorrhage can contribute to the development of no-reflow, it is also a sign of severe microvascular injury, resulting in extravasation of erythrocytes into reperfused myocardium.[5] In conclusion, despite some major advancement in our understanding about the key contributors to the no-reflow phenomenon in the past decade, its pathophysiology remains incompletely understood. The fact that no-reflow is a major determinant of post-PCI mortality urges the scientific community to continue its efforts in studying the coronary microcirculation in order to identify the potential underlying mechanisms. As of now, extrinsic mechanisms seem to provide excellent targets for prevention strategies, whereas most of the limited therapeutic approaches rely on vasodilator agents aiming to overcome intrinsic causes.

## Prevention Strategies for Intrinsic Causes of No-Reflow

### *Vasodilators for Prevention*

The vasospasm of the coronary arterioles is a commonly observed phenomenon in primary coronary microvascular dysfunction[9]; it is usually associated with prompt relief of symptoms when intracoronary vasodilators are given. Decreased vasodilator capacity of the coronary arteriole has also been observed in settings of no-reflow.[37] Among all vasodilators with innate biologic mechanisms, adenosine was studied most extensively (Table 3). Adenosine readily

**TABLE 3**

**Vasodilators for the Prevention and Treatment of No-Reflow**

| Study | | N | Dose | Administration Time in Relation to PCI | Incidence of Angiographic No-Reflow | Mortality | Infarct Size | Incidence of Complete ST-Segment Resolution |
|---|---|---|---|---|---|---|---|---|
| Mahaffey KW et al[44] | IV adenosine vs placebo | 236 | 70 μg/kg/min 3 h | Before + under + after | | – | ↓ | |
| Marzilli M et al[40] | IC adenosine vs placebo | 54 | 4-mg bolus | Before | ↓ | ↓ | | ↑ |
| Micari A et al[45] | IV adenosine vs placebo | 30 | 50-70 μg/kg/min 3 h | Before + under + after | | | ↓ | |
| Ross AM et al[46] | IV adenosine vs placebo | 2118 | 50-70 μg/kg/min 30 min | Before + under + after | | – | ↓ | |
| Vijayalakshmi K et al[41] | IC adenosine vs placebo | 150 | 30-μg bolus | After | ↓ | – | | |
| Stoel MG et al[42] | IC adenosine vs placebo | 49 | 60-mg bolus | After | ↓ | | | ↑ |
| Grygier M et al[43] | IC adenosine vs placebo | 70 | 2 × 1- to 2-mg bolus | Before + after | ↓ | | | ↑ |
| De Luca G et al[87] | IC adenosine vs placebo | 260 | 120- to 180-μg bolus | Before | – | – | | – |

IC, intracoronary administration; IV, intravenous administration; PCI, percutaneous coronary intervention.

dilates the coronary arterioles by binding to $A_{2A}$ receptors expressed on the surface of arteriolar smooth muscle cells and subsequently activates calcium-activated potassium channels.[38] Adenosine also exerts an inhibitory effect on platelet activation and aggregation.[39] Although a large number of randomized clinical trials had investigated the effect of adenosine on no-reflow, their results remained controversial (Table 3). Almost all of the small clinical trials identified some beneficial effect of adenosine administration when compared with the placebo group such as lower incidence of angiographically assessed no-reflow,[40-43] decreased mortality,[40] decreased infarct size,[44,45] or higher incidence of complete ST-segment resolution.[40,42,43] However, trials evaluating long-term mortality, including the largest trial—the Acute Myocardial Infarction Study of Adenosine (AMISTAD) II trial—of 2118 patients with anterior STEMI who were followed for 6 months, failed to demonstrate a reduction in the composite primary endpoint of death, new CHF, or the first rehospitalization for CHF.[46] Nonetheless, a subsequent post hoc analysis of the results of AMISTAD II did reveal that the subset of patients that received adenosine and reperfusion within 3.17 hours from the onset of symptoms demonstrated significant improvement in mortality and event-free survival.[47] Recently, a meta-analysis including 3821 patients from 10 randomized clinical trials revealed that adenosine compared with placebo was associated with a significant reduction in postprocedural no-reflow (OR 0.25; 95% CI, 0.08-0.73); however, at a median follow-up of 6 months, prior treatment with adenosine did not confer significant benefits in terms of reduction of mortality, as well as reoccurrence of MI, heart failure symptoms, and ST-segment resolution.[48] In the studies investigating the role of adenosine used for the prevention of coronary no-reflow, the route of administration and the dosing varied widely. The trials using adenosine at a higher dose range via the intracoronary route seemed to have better outcome profiles compared with the trials using smaller doses of adenosine or IV administration (Table 3).

*Recently, a meta-analysis including 3821 patients from 10 randomized clinical trials revealed that adenosine compared with placebo was associated with a significant reduction in postprocedural no-reflow.*

Numerous other vasodilators have also been studied for prevention of no-reflow (Table 4). Calcium channel blockers are very potent vasodilators in the coronary microcirculation, acting via opening L-type calcium channels on vascular smooth muscle cells. In small randomized clinical trials, intracoronary verapamil improved myocardial perfusion and left ventricular function as assessed by myocardial contrast echocardiography[49] and myocardial blush grade (MBG),[41] yet no large randomized clinical trial has validated their clinical benefit. Intracoronary verapamil was also frequently associated with transient heart block and hypotension that can limit its use in no-reflow setting.[41]

NO-releasing substances are endothelium-independent pathways aiming for the prevention of no-reflow. NO is one of the key regulators of coronary blood flow through the coronary microcirculation.[50] Although the NO donor glyceryl trinitrate only exerts its vasodilator effect on large epicardial vessels, other agents such as nitroprusside have more pronounced vasodilator potential in the coronary arterioles.[51] Few nonrandomized studies reported prevention of no-reflow after pretreatment with intracoronary-administered nitroprusside.[7,52] The largest randomized clinical trial with 98 patients investigating the prevention potential of nitroprusside had found no change in complete ST-segment resolution or in myocardial blush grade (MBG), but surprisingly showed decreases in rate of recurrent acute MI, need for target vessel revascularization, and increased 6-month survival rate in the nitroprusside-treated group when compared with the placebo group.[53] The authors implied that the lower rates of adverse events in the nitroprusside group were due to more optimal stent deployment resulting from better visualization achieved by nitroprusside-mediated dilation of the target vessel. Another vasodilator, nicorandil, promotes vasodilation by releasing NO and by opening adenosine triphosphate-sensitive potassium channels on smooth muscle cells of coronary arterioles. Although IV administered nicorandil failed to improve left ventricle ejection fraction compared with placebo in the largest clinical trial of 545 patients,[54] in a pooled analysis of 10 studies including 1337 patients, nicorandil treatment before PCI was shown to associate with significant improvement in the TIMI flow grade detected after the intervention.[55]

*Few nonrandomized studies reported prevention of no-reflow after pretreatment with intracoronary-administered nitroprusside.*

**TABLE 4**

**Vasodilators for the Prevention and Treatment of No-Reflow**

| Study | | N | Dose | Administration Time in Relation to PCI | Incidence of Angiographic No-Reflow | Mortality | Incidence of Complete ST-Segment Resolution/ Cardiac Biomarkers |
|---|---|---|---|---|---|---|---|
| Vijayalakshmi K et al[41] | IC verapamil vs placebo | 150 | 30-μg bolus | After | ↓ | — | |
| Hang CL et al[88] | IC verapamil vs retrospective lone PCI | 50 | 50- to 100-μg boluses | Before + under | ↓ | — | |
| Michaels AD et al[89] | Intragraft verapamil vs placebo | 22 | 50-70 μg/kg/min 30 min | Before | ↓ | | — |
| Amit G et al[53] | IC nitroprusside vs placebo | 98 | 60-μg bolus | Before | — | ↓ | — |
| Shinozaki N et al[52] | IC nitroprusside vs retrospective lone PCI | 120 | 120-μg bolus | Before | ↓ | | |
| Kobatake R et al[7] | IC nitroprusside vs nicorandil | 49 | 50 μg nitroprusside vs 2-mg nicorandil bolus | After | ↓/↓ vs pretreatment | | — |
| Ito H et al[90] | IV nicorandil vs placebo | 81 | 4-mg bolus, then 6 mg/h for 24 h, then po nicorandil till discharge | Before | ↓ | ↓ | |

IC, intracoronary administration; IV, intravenous administration; PCI, percutaneous coronary intervention.

## Prevention by Targeting Intravascular Inflammation

In patients with STEMI, myocardial ischemia and the ongoing atherothrombotic process generate prolonged and pronounced endothelial injury.[56] Endothelial dysfunction occurs well before the development of myocardial cell necrosis and the duration of the ischemic event is critical regarding endothelial function.[57] In a randomized clinical trial, De Luca and colleagues[58] assessed the correlation of symptom onset to balloon time and the occurrence of no-reflow in 1791 STEMI patients. Symptom onset to balloon time was found to be significantly associated with the rate of postprocedural TIMI 3 flow ($P = .012$), MBG ($P = .033$), and 1-year mortality ($P = .02$). A multivariate analysis performed within this study identified symptom onset to balloon time $> 4$ hours as an independent predictor of 1-year mortality. Interestingly, no relationship was detected between door-to-balloon time and mortality or the occurrence of no-reflow. The authors implicate that their results can be explained by the fact that door-to-balloon time represents only a part of the total ischemia time; therefore, it might not reflect the overall endothelial and myocardial injury.

During reperfusion the augmented release of ROS causes inflammation in the microvascular endothelium. In animal models of ischemia-reperfusion injury, inhibition of ROS production by targeting xanthine oxidase,[59] eNOS,[60] and mitochondrial enzyme complex[61] has been shown to protect ROS-associated tissue damage. A small clinical trial also demonstrated that intracoronary administration of the N-acetylcysteine, a reduced thiol that modulates redox state, improved human coronary endothelium-dependent vasodilation as determined by enhanced increase in coronary blood flow and more prominent decrease in coronary vascular resistance in response to intracoronary infusion of acetylcholine.[62] In patients with CHF, 3-month treatment with the xanthine oxidase inhibitor allopurinol resulted in significant improvement in echocardiography-assessed coronary flow reserve.[63] Interestingly, to date, no clinical trial has investigated the incidence of coronary no-reflow after the application of ROS-producing enzyme inhibitors.

Hyperglycemia is well known for its association with intravascular inflammation.[64] High blood glucose level was found to be an independent risk factor of no-reflow, as higher short-term mortality rate and higher incidence of no-reflow were observed in both diabetic and nondiabetic patients with acute hyperglycemia who were undergoing PCI.[65] Even in nondiabetic patients without coronary artery disease, elevated fasting plasma glucose levels were found to be associated with increased coronary vascular resistance as calculated from coronary Doppler measurements.[66] In long-term hyperglycemia (eg, type 2 diabetes), alterations in the vasodilator pathways can put the coronary arteriole at high risk for vasoconstriction, which predisposes patients to no-reflow.[67] Henriques and associates[68] assessed the degree of myocardial reperfusion using MBG prospectively in 924 acute MI patients with successful angioplasty and restoration of TIMI 3 flow. Lower MBG (0 and 1) was associated with a statistically significant higher rate of mortality and total major adverse cardiac events with 6-month follow-up. The group with lower MBG profiles included a statistically significantly higher proportion of patients with type 2 diabetes than the group with an MBG of ≥ 2. These findings suggest that better glucose control in the PCI setting might be beneficial to preventing no-reflow.

Statins aim to lower cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which plays a key role in cholesterol generation by the liver. It is widely accepted that statins have pleotropic properties beyond their lipid-lowering therapeutic effects, as they may facilitate the synthesis of endothelial NO and also can reduce ROS production.[50] A retrospective analysis by Oduncu and colleagues[69] highlighted that long-term statin treatment prior to PCI was associated with a higher rate of complete ST-segment resolution, better MBG profile, and preserved ejection fraction. Recently, it has been reported that pretreatment with high-dose atorvastatin before PCI resulted in improved myocardial perfusion.[70]

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Intrinsic mechanisms are excellent targets for preventing no-reflow. Ischemic time reduction has to be the cornerstone of the treatment of every patient diagnosed with STEMI as substantial evidence supports its association with lower incidence of the no-reflow phenomenon and lower 1-year mortality. The evidence supporting the association between vascular inflammation and the incidence of no-reflow continues to grow. Targeting ROS-producing enzymes, achieving better glycemic control, and the use of statins might be able to reduce the absolute risk of no-reflow. Unfortunately,

in spite of their potential to prevent no-reflow, there are no large clinical trials comparing the effects of different vasodilators or anti-inflammatory agents on coronary no-reflow by their route of administration, nor have there been any trials to investigate whether routine pre-PCI use of vasodilators can affect the occurrence of no-reflow. Until investigations furnish direct evidence regarding the effectiveness of vasodilators, their routine pre-PCI use remains debated.

## Prevention Strategies for Extrinsic Mechanisms of No-Reflow

### *Preventing Distal Coronary Embolization*

Distal coronary embolization in the coronary microcirculation is a well-recognized pathologic contributor to no-reflow. Several devices have been designed to reduce thrombus burden in an elegant way, either by aspiration or by preventing distal embolization with filterwire technology. The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS ) enrolled 1071 STEMI patients and provided strong evidence that manual aspiration of thrombi resulted in better MBG, higher rate of ST-segment resolution, and significant decrease in 1-year all-cause mortality.[71] The results of this trial highlight the fact that the no-reflow phenomenon is not only an indicator of disease severity, but is closely associated with increases in mortality; it serves as a real target for prevention strategies. A recent meta-analysis also revealed that, although manual thrombus aspiration was associated with decrease in long-term mortality, using mechanical thrombectomy devices for removing thrombi did not show significant survival benefit.[72] Distal embolic protection devices using either balloon occlusion or filterwires were developed to aspirate or capture debris resulting from coronary intervention. Although distal embolic protection demonstrated significant benefits in percutaneous intervention of saphenous vein graft lesions,[73] in PCI of native coronary arteries, it failed to sustain similar benefits in ST-segment resolution, reduce infarct size, and reduce major adverse cardiac events.[74] Moreover, recently the Drug Elution and Distal Protection in Acute Myocardial Infarction (DEDICATION) trial reported that use of distal embolic protection devices in patients with STEMI from native coronary arteries can also be harmful because of the increased occurrence of definite stent thrombosis.[75] A meta-analysis looking at the effectiveness of different modalities of embolic protection showed that catheter-based thrombus aspiration is beneficial, mechanical thrombectomy could be maleficent, and distal embolic protection appeared to be neutral regarding the incidence of mortality when compared with PCI alone.[76]

### *Antiplatelet Therapy In Prevention of No-Reflow*

In randomized clinical trials of patients undergoing PCI, administration of glycoprotein IIb/IIIa inhibitors was associated with better microvascular perfusion when compared with placebo.[77,78] The use of intracoronary abciximab was superior to IV abciximab in mortality, which was further validated by a meta-analysis of four trials of 1148 subjects.[79] However, the recently published Abciximab Intracoronary versus intravenously Drug Application in STEMI (AIDA STEMI) trial, with 2065 STEMI patients randomized to intracoronary versus IV abciximab, did not result in a difference in combined endpoint of death, reinfarction, and CHF.[80] The intracoronary-administered abciximab arm showed a significant decrease in the rate of CHF when compared with the IV arm.[80] The Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI) study randomized 452 patients with proximal or mid left anterior descending artery STEMI to intracoronary abciximab using a balloon catheter versus a manual aspiration catheter. The intracoronary administration of abciximab delivered to the infarct lesion site resulted in a significant, albeit modest reduction in infarct size in patients presenting with a large anterior STEMI, whereas the use of aspiration thrombectomy failed to have any demonstrable effect on myocardial infarct size. At 30 days, neither intracoronary abciximab nor thrombectomy improved myocardial reperfusion, ST-segment resolution, or 30-day clinical event rates.

Thienopyridines provide another effective means for the prevention of platelet activation via adenosine diphosphate receptor/$P2Y_{12}$ inhibition. In two separate studies investigating the effects of clopidogrel, patients receiving a 600-mg loading dose of clopidogrel developed significantly less no-reflow phenomenon compared with those receiving a 300-mg loading dose.[81,82] This observed decrease in no-reflow is a potential contributor to the clinical benefit of the higher clopidogrel loading dose in patients undergoing PCI.

In summary, catheter-based thrombus aspiration is a very efficient tool to reduce clot burden, which may in turn reduce the likelihood of no-reflow. The use of other distal embolic protection devices to

reduce coronary no-reflow remains inconclusive and necessitates further study. Although the results of the AIDA STEMI trial eliminated intracoronary abciximab from the list of major potential therapeutic tools for the prevention of no-reflow, the effect of high-dose thienopyridine administration still needs further investigation.

## When Prevention Fails: Treatment Options

When no preventive measures are undertaken or when prevention strategies fail, no-reflow may develop and lead to unfavorable outcomes. Currently, there are no proven therapies backed by large-scale randomized studies to treat coronary no-reflow. Current therapeutic options aim to improve myocardial perfusion by promoting vasodilation in the coronary microcirculation. When treating no-reflow, the most difficult problem can be failure to deliver therapeutic agents to the sites of microvascular dysfunction. In the AMISTAD[44] and AMISTAD-II[46] trials, IV administration of adenosine was started 30 minutes before thrombolysis or primary angioplasty and the infusion was continued for 3 hours. In these trials, the IV administered adenosine failed to produce the desired reduction in composite endpoints. Of note, IV administered adenosine is rapidly cleared from the circulation by cellular uptake; therefore, adenosine might not reach the coronary microcirculation with enough concentration to exert its biologic effect. Although IV administered adenosine in the AMISTAD II trial did show reduction in infarct size in the adenosine group, the available data do not provide direct evidence that adequate amount of adenosine actually reached the coronary microcirculation. A recently identified method using two boluses of high-dose adenosine separately before and after successful balloon inflation for the reduction of incidence of no-reflow resulted in a favorable clinical outcome.[43] Large randomized clinical trials are needed to investigate the therapeutic potential of high-dose intracoronary adenosine in the setting of no-reflow following PCI.

Small studies have provided clinical evidence that intracoronary nitroprusside, verapamil, and nicorandil are potential options to treat coronary no-reflow.[7,41] Recently, Rezkalla and associates[8] reported a retrospective study comparing different therapeutic modalities for the treatment of no-reflow. In this analysis, intracoronary verapamil, nicardipine, nitroprusside, and adenosine therapies were equally effective in restoring normal flow and increasing TIMI and MBG scores. In addition to the improvement in the angiographic parameters, clinical composite of CHF, cardiogenic shock, and/or death was observed in 23% of the patients who were not treated for no-reflow and in only 9% of those who received pharmacologic therapy. This report provides a good example that treating no-reflow is an achievable goal, and urges the clinical investigator to initiate randomized controlled trials for identification of the best treatment protocols.

Careful investigation of the coronary microcirculation may reveal new therapeutic tools for the amelioration of no-reflow. Unlike NO-mediated dilation, endothelium-derived hyperpolarizing factor (EDHF)-mediated responses seem to be protected against ROS-mediated injuries.[83] Therefore, therapeutic strategies aiming to improve EDHF vasodilation might provide alternative means when NO-releasing agents fail to improve microvascular perfusion. Angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors are both effective ways of improving EDHF-mediated vasodilator function.[84] ACE inhibitors also readily block the degradation of the potent coronary vasodilator bradykinin, therefore promoting excessive vasodilation.[85] To date, no clinical studies have assessed whether acute intracoronary administration of ACE inhibitors can reverse the no-reflow phenomenon. Activating endothelial small and intermediate conductance calcium-activated potassium channels and improving intravascular gap-junction communication are other potential ways of improving EDHF-dependent vasodilator function; however, no drugs are currently available that target these microvascular structures. Overcoming the augmented microvascular vasoconstriction might be another therapeutic strategy to improve coronary microvascular flow. It is known that the level of the potent endothelium-independent vasoconstrictor endothelin-1 highly correlates with the angiographically assessed presence of no-reflow and acts as a significant predictor of long-term mortality.[16] There is emerging evidence that long-term administration of endothelin receptor antagonists can improve coronary endothelial function[86]; however, no study has investigated the use of endothelin antagonists in the setting of PCI-related no-reflow.

***Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are both effective ways of improving EDHF-mediated vasodilator function.***

Coronary vasodilators or blocking agents targeting vasoconstrictor mechanisms can aid in reverting the diminished microvascular perfusion. Intracoronary administration of adenosine, verapamil, nicardipine, and nitroprusside are currently available therapies, although large randomized clinical trials are awaited to evaluate their effectiveness in the no-reflow setting. The need for other potential coronary vasodilator agents warrants further careful investigation of the coronary microcirculation to identify new therapeutic strategies for the treatment of no-reflow.

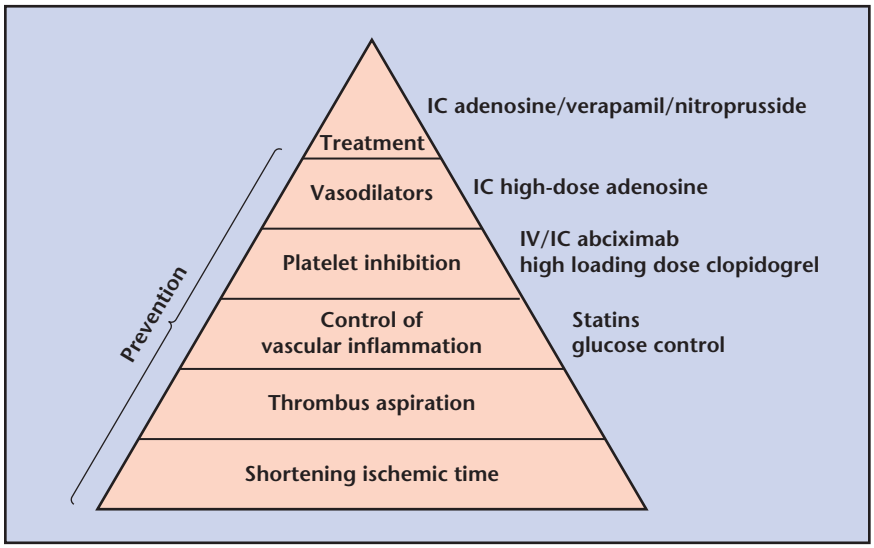


**Figure 1.** Clinical approach to no-reflow. The base of the pyramid represents highly supported strategies, and the top of the pyramid represents the ones supported by less evidence. IC, intracoronary; IV, intravenous.

## Conclusions

The ultimate goal for coronary intervention is to restore adequate perfusion to the injured myocardium, which is highly dependent on the patency and functionality of the microcirculation. Management of no-reflow should be started ahead of coronary intervention using evidence-based prevention strategies (Figure 1). Substantial evidence has proven that the reduction of ischemic time and the application of thrombus aspiration devices are able to reduce the incidence of no-reflow in the coronary microcirculation. A low threshold should be applied to detect the occurrence of no-reflow, because the diagnosis carries prognostic relevance. Once the diagnosis is made, arteriolar vasodilators can provide salvage, although their proof of effectiveness still needs to be validated. Studying the coronary microcirculation might reveal new therapeutic targets for the successful amelioration of the adverse clinical consequences of no-reflow. ■

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## MAIN POINTS

- In patients with acute myocardial infarction undergoing primary percutaneous coronary intervention (PCI), restoration of blood flow in the culprit epicardial coronary artery leads to normalization of or increased blood flow to the affected coronary microcirculation. The coronary no-reflow phenomenon refers to the post-PCI state in which, despite successful revascularization of the epicardial conduit coronary arteries, substantial regions of the myocardium do not receive adequate perfusion.
- Normal endothelial functions are disrupted by ischemia and ischemia/reperfusion injury, initiating inflammation in the reperfused tissue. The failure to detect significant association between admission serum C-reactive protein levels and the incidence of coronary no-reflow suggests that localized, not systemic, inflammation is more likely to be responsible for the impairment of microvascular perfusion.
- Targeting reactive oxygen species-producing enzymes, achieving better glycemic control, and the use of statins might be able to reduce the absolute risk of no-reflow.
- Reduction of ischemic time and the application of thrombus aspiration devices are able to reduce the incidence of no-reflow in the coronary microcirculation.

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