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STATE-OF-THE-ART REVIEW

Management of No-Reflow Phenomenon in the Catheterization Laboratory

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ABSTRACT

At the conclusion of a primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, and after the cardiologist makes certain that there is no residual stenosis following stenting, assessment of coronary flow becomes the top priority. The presence of no-reflow is a serious prognostic sign. No-reflow can result in poor healing of the infarct and adverse left ventricular remodeling, increasing the risk for major adverse cardiac events, including congestive heart failure and death. To achieve normal flow, features associated with a high incidence of no-reflow must be anticipated, and measures must be undertaken to prevent its occurrence. In this review, the authors discuss various preventive strategies for no-reflow as well as pharmacological and nonpharmacological interventions that improve coronary blood flow, such as intracoronary adenosine and nitroprusside. Nonpharmacological therapies, such as induced hypothermia, were successful in animal studies, but their effectiveness in reducing no-reflow in humans remains to be determined. (J Am Coll Cardiol Intv 2017;10:215–23) © 2017 by the American College of Cardiology Foundation.

Coronary no-reflow phenomenon occurs when cardiac tissue fails to perfuse normally despite opening of the occluded vessel (1). When a short (40-min) proximal coronary artery occlusion was applied and then released in an experimental canine model of myocardial infarction, blood flow was distributed normally to the perfused myocardial segment. By contrast, after prolonged occlusion (90 min), a portion of the cardiac tissue did not regain normal perfusion despite opening of the large epicardial coronary artery, demonstrating that prolonged ischemia leads to damage of the microvasculature and precludes normal perfusion (1). Electron microscopy studies of the damaged tissue demonstrated the presence of membrane-bound blebs protruding from the endothelial lining and swelling of the endothelial cells of the small blood vessels causing luminal obstruction. These changes are thought to be at least partially responsible for slow blood flow in the microcirculation (1).

This no-reflow phenomenon was later shown to occur in humans as well (2), where no-reflow during ST-segment elevation myocardial infarction (STEMI) has an additional pathological variable not present in animal models. The thrombus and atherosclerotic materials invariably present in the human coronary artery may produce small distal emboli, causing further reduction in the coronary flow during percutaneous intervention, particularly in the short-term setting. In the era of reperfusion in the 1980s, the pathophysiological phenomenon of no-reflow became increasingly recognized, and its significance understood (3,4). The underlying pathological mechanisms are now known to include injury related to ischemia, reperfusion, endothelial dysfunction, and distal thromboembolism (5). Microvascular arteriolar spasm

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ABBREVIATIONS AND ACRONYMS

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction risk score

is another contributing factor in the pathogenesis of this phenomenon in humans (6). Of great importance to the clinician are the long-term consequences of no-reflow. If blood flow cannot enter or leave an area of necrotic myocardium, the cells, such as macrophages (7), necessary for the removal of debris, cannot function, and humoral factors necessary for proper healing cannot access the tissue. Therefore, no-reflow results in poor healing of the infarct, adverse remodeling with an increase in left ventricular failure, and higher mortality (8–10).

The goal of reperfusion is to resume normal blood flow to the cardiac tissues, and not just to achieve an open epicardial artery. Although no-reflow may occur regardless of the method of revascularization, it is easily diagnosed with certainty during acute percutaneous coronary intervention (PCI) in STEMI. After opening the occluded artery, the blood should flow normally, achieving Thrombolysis In Myocardial Infarction risk score (TIMI) III coronary flow, low TIMI frame count and normal myocardial blush grade (11,12). If there is damage to the microcirculation, no-reflow will be evident by slowing of the coronary flow, higher TIMI frame count, and abnormal or absent myocardial blush.

Estimates regarding the frequency of no-reflow vary with the method of assessment, ranging from 5% to 60% in the published data (5,13). It is particularly more common in degenerated vein grafts and following rotational atherectomy. In a 2010 review of 347 patients with STEMI treated with percutaneous coronary stenting, Rezkalla et al. (14) found no-reflow to be common and observed the phenomenon in 32% of patients. No-reflow was defined as TIMI < III and as myocardial blushing grade < III. Consistent with the published data, patients with no-reflow had worse outcomes, characterized by a significant increase in the incidence of congestive heart failure, cardiogenic shock, and death. Patients with no-reflow who received pharmacological therapy in the form of intracoronary nitroprusside, nicardipine, or verapamil had an improvement in coronary flow and better prognosis, demonstrating the importance of recognition and appropriate management of this condition (14). Despite considerable insight in recent years regarding who is at risk for no-reflow and how management strategies work, no specific therapies have been devised, and the evidence in support of their use remains contentious in many cases. Here, we will review available strategies for the prevention and management of no-reflow phenomenon during revascularization, particularly during percutaneous intervention.

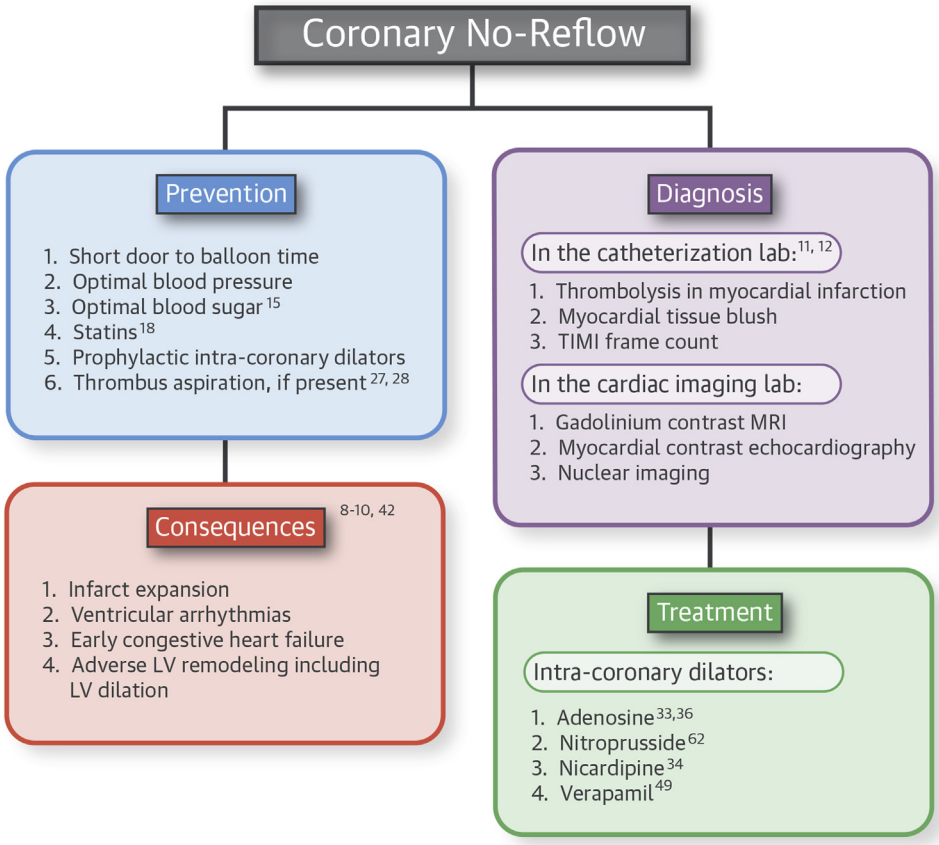
PREDICTION OF NO-REFLOW AND STRATEGIES FOR PREVENTION

Many of the well-accepted risk factors for no-reflow are similar to other well-accepted cardiovascular risk factors, such as hypertension, smoking, dyslipidemia, diabetes, and other inflammatory processes. As such, there are some generally accepted measures associated with a lower incidence of no-reflow following PCI for STEMI. For example, in patients with diabetes, optimal blood sugar control before the procedure can reduce the occurrence of no-reflow (15). This effect is both indirect via improvement of coronary microvascular circulation (16) as well as direct via the effects of acute hyperglycemia on reperfusion injury (17). Similarly, in individuals with hyperlipidemia, intensive statin therapy before PCI is beneficial in reducing no-reflow. In a meta-analysis of 7 studies that examined 3,086 patients treated with statins before PCI, there was a complete prevention of no-reflow in 4.2% and attenuation of no-reflow in an additional 5% of patients treated with statins, compared with control patients receiving placebo, usual care, or lower dose statin therapy (18). Effects were seen when statins were started anywhere from 2 h to 30 days before PCI. Although these general measures are simple and part of established guidelines in patients with coronary artery disease, their benefits are limited in those with acute presentation of STEMI.

Prediction of patients at risk for no-reflow before PCI may be beneficial from the perspective of prevention. Risk awareness will lead to the use of certain techniques that may ameliorate the degree of no-reflow. Such prevention strategies include primary stenting, avoidance of high pressure stent deployment, and thrombectomy before the intervention. Patient-specific features known to be related to high risk of no-reflow in patients with STEMI include delayed presentation to the catheterization laboratory (14), hyperglycemia, and hypercholesterolemia. More recent evidence suggests that no-reflow is more frequently encountered in association with female sex, hypertension, mild-to-moderate renal insufficiency, and elevated inflammatory markers (19–22). There are also lesion-specific features that may influence the risk of no-reflow, such as plaque composition and thrombus burden as detected by intravascular ultrasound (23,24). However, the time consumed by performing the ultrasound may delay door-to-balloon time and should be discouraged in patients with STEMI.

In the original canine study performed by Kloner et al. (1), more prolonged ischemia was associated

CENTRAL ILLUSTRATION **PCI Flowchart for Coronary No-Reflow**



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Flowchart demonstrating prevention, diagnosis, treatment, and complications of coronary no-reflow during coronary percutaneous intervention (PCI). LV = left ventricular.

with microcirculatory damage and the development of no-reflow phenomenon. Consistent with this finding, in humans a shortened door-to-balloon time is associated with less myocardial damage, a lower incidence of no-reflow (25), and better clinical outcomes. Every effort should be made to have clear processes in place involving the community, emergency medical system, and interventional cardiology team in various hospitals with the goals of shortening door-to-balloon time to reduce the occurrence of no-reflow following revascularization.

THROMBUS ASPIRATION

In the initial animal studies that served to describe the no-reflow phenomenon, coronary occlusion was achieved via mechanical means. A seminal difference between such models and clinical STEMI in humans is that there is often a thrombus at the site of the occlusion. Manipulating the occluded area with balloons and stents often results in distal embolization of the thrombus, which may contribute to the development of no-reflow. Attempts to prevent distal embolization may help lessen the degree of no-reflow.

Use of coronary Doppler studies allows for the monitoring of no-reflow during the course of the intervention (26), including thrombus aspiration. This strategy allowed Svilaas et al. (27) to demonstrate that thrombus aspiration before PCI results in better clinical outcomes. This finding was later confirmed in the ATTEMPT (Analysis of Trials on Thrombectomy in Acute Myocardial Infarction Based on Individual Patient Data) study (28), and thrombus aspiration has since become an integral part of the intervention

procedure for STEMI. Thrombus aspiration must begin with forward aspiration starting proximal to the occlusion, making multiple passes, until canalization of the vessel with improved antegrade flow is demonstrated. Although a meta-analysis published by Mongeon et al. (29) failed to show long-term benefit, thrombus aspiration is still performed by many cardiologists during intervention for STEMI, particularly when a visible thrombus is present. Of note, the aforementioned meta-analysis included many different studies using various techniques, including rheolytic thrombectomy, which may increase no-reflow in some patients (30). In a more recent meta-analysis (31), aspiration was associated with a lower incidence of no-reflow, yet there was no evidence of long-term clinical benefit. Routine aspiration should be avoided and should probably be limited to the presence of angiographically visible thrombus (32). Other complementary techniques that may help prevent distal embolization include avoidance of high-pressure stent deployment and full coverage of the disease segment in the coronary artery.

PHARMACOLOGICAL THERAPY

When confronted with no-reflow during PCI, the first priority is to ensure that the epicardial arteries are optimally treated. At that time, coronary injection with various vasodilator drugs should be initiated. Adenosine at a dose of 100 to 200 μg (33), nicardipine at a median dose of 400 μg (34), or nitroprusside at doses ranging from 50 to 300 μg (35) are the current standard of care. In a retrospective study, there was no significant difference between various pharmacological intervention strategies, but significant clinical benefit was observed when no-reflow was resolved (14). To achieve successful intervention, the authors prefer distal coronary administration of pharmacological agents using a microinfusion catheter. Injection through the guiding catheter may have significant systemic effects and is considered less effective, because only a small amount of the agent is likely to actually reach the distal coronary bed. Frequent consecutive doses may be administered as long as they are tolerated as shown by the blood pressure. Common vasodilators used in catheterization laboratories include adenosine, nicardipine, and calcium channel blocking agents as well as nicorandil, which is used in some laboratories.

ADENOSINE. Adenosine is a purine nucleoside that binds to adenosine receptors and exerts its effects on cardiac myocytes and blood vessels. Its main effect is in smooth muscle relaxation in the coronary circulation, although evidence also suggests that adenosine has antiplatelet properties (36). Adenosine also has negative chronotropic and dromotropic effects. On the basis of the potential benefits of adenosine on the microcirculation of the heart, it was investigated in acute myocardial infarction. PCI and thrombolytic therapy result in opening of the occluded epicardial coronary artery, but are not expected to always benefit the coronary microcirculation; adenosine may do that. The exact mechanism by which adenosine exerts its effects is not well identified.

In initial investigations of the use of adenosine to improve outcomes following intervention for STEMI, the AMISTAD (Acute Myocardial Infarction Study of Adenosine) and AMISTAD-II trials (37,38) demonstrated a significant reduction in infarct size with high-dose adenosine (70 μg/kg/min infused for 3 h). However, there was no benefit in the adenosine group with respect to clinical outcomes, including congestive heart failure, re-hospitalization for congestive heart failure, or death. In a separate analysis of the AMISTAD II study by Kloner et al. (39), adenosine administration was associated with better clinical outcomes in patients who achieved early reperfusion. These findings paved the way for further investigation regarding the use of adenosine for the treatment of no-reflow (40).

Currently, adenosine is not used routinely during PCI, but may be used to treat no-reflow. The REOPEN-AMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial published by Niccoli et al. (41) in 2013 investigated the effect of adenosine or nitroprusside in 240 patients with STEMI. Following intracoronary thrombus aspiration, patients were randomized to receive adenosine as a 120-μg bolus followed by slow infusion of 2 mg in 33 ml of saline over 2 min, nitroprusside as a 60-μg bolus followed by 100 μg in 33 ml of 5% glucose administered over 2 min, or placebo. ST-segment resolution at 90 min was markedly better in the adenosine group, but not with intracoronary nitroprusside. There was no statistically significance clinical benefit observable at 30 days in the adenosine group, but at 1 year of follow-up, only the adenosine group, not the nitroprusside group, had more favorable remodeling of the left ventricle. This favorable effect was associated with a lower incidence of composite events of myocardial infarction, heart failure, and death (42). Smaller studies were done using prolonged 3-h intravenous infusion of adenosine (43). The intravenous adenosine improved no-reflow compared with the control group and was associated with improved left ventricular function. However, patients also received intracoronary nitroprusside or

verapamil, casting some doubt on the conclusion regarding the effect of adenosine specifically. To increase the number of patients analyzed regarding the efficacy of adenosine, multiple meta-analyses were performed (44–46). Although there was some overlap, studies included in each meta-analysis varied, and their ultimate conclusions differed. Although there is a potential benefit from intracoronary or intravenous adenosine administration, there is a need to conduct large controlled trials to have a definitive answer. The protocol for such a trial examining treatment with adenosine, nitroprusside, or standard therapy was published in 2014, and results should be forthcoming (47).

A limitation of adenosine is that it has a very short half-life. Recent data from animal models showed that a 2-h intracoronary adenosine infusion is superior to an adenosine bolus in ameliorating no-reflow (48). The primary concern surrounding use of adenosine is that infusion into the arterial bed supplying conduction system may result in atrioventricular block.

CALCIUM CHANNEL BLOCKERS. Several calcium channel blockers have been investigated for use in the context of no-reflow, including verapamil, diltiazem, and nicardipine. As early as 1982, Kloner et al. (49) showed that verapamil therapy is beneficial in animal models of coronary ischemia in conjunction with coronary reperfusion. In the early days of coronary angioplasty, it was thought that prolonged balloon inflations might deliver better results. Devices such as autoperfusion balloons were used for that purpose, but it was later found that use of intracoronary diltiazem allows for longer balloon inflations with less coronary ischemia as measured by a 12-lead electrocardiogram. Unfortunately, no-reflow was not assessed at that time, and the number of patients was small. At present, some interventionalists use intracoronary verapamil, nicardipine, or diltiazem with variable success for the treatment of no-reflow, and there are several small studies investigating the efficacy for the prevention or treatment of no-reflow (50–56). Recently, meta-analyses assessing the efficacy of verapamil and diltiazem or verapamil alone for the treatment of no-reflow have demonstrated significant benefit over standard of care with respect to no-reflow (57,58). In particular, nicardipine was beneficial when administered to prevent no-reflow during rotational atherectomy (59) and percutaneous interventions in vein grafts (60) with minimal myocardial depressant effect (61). However, the data in the published reports are currently insufficient to allow for definitive conclusions regarding efficacy, but rather suggest the need for the conduct of a large, randomized, controlled trial.

NITROPRUSSIDE. Nitroprusside activates guanylate cyclase in the vascular smooth muscles leading to intense vasodilation. Intracoronary nitroprusside at doses of 50 to 300 μg is quite effective in the treatment of no-reflow. When injected distally in the coronary artery, it will have negligible systemic effect on the blood pressure but will induce marked improvement in coronary flow and myocardial tissue blush. Zhao et al. (62) investigated the effects of nitroprusside in 162 consecutive patients with STEMI. Patients were randomized to the use of tirofiban plus nitroprusside versus tirofiban alone. The nitroprusside group fared better, including more rapid ST-segment elevation resolution, fewer major adverse cardiac events, and higher left ventricular ejection fraction (62). However, TIMI flow grade was not different between groups, suggesting that it is not the most sensitive method of defining coronary blood flow, and myocardial blush grade may be more sensitive.

Another study assessing the use of nitroprusside for the treatment of no-reflow in patients with acute myocardial infarction compared nitroprusside to nicorandil (63). Although both medications improved coronary blood flow, nitroprusside was more effective when TIMI frame count was measured. Although the number of patients was relatively limited ($n = 49$), the difference was statistically significant (63).

Among the various medications used in the management of no-reflow, nitroprusside appears to have a more sustained effect. Parham et al. (64) administered intracoronary adenosine or nitroprusside to normal coronary arteries. Coronary hyperemia was measured using coronary Doppler. Nitroprusside and adenosine had equivalent effects, yet the nitroprusside effect was more sustained (64). Moreover, intracoronary nitroprusside administered following adenosine injection results in significantly better coronary flow in most patients (65).

Because most studies reporting the effect of nitroprusside are small, 2 meta-analyses have been conducted. Both confirmed a clear benefit of nitroprusside in the management of no-reflow during PCI (66,67). As described in the preceding text, a large randomized, controlled trial was reported in 2014 and will likely serve to further highlight the role of nitroprusside in the treatment of no-reflow following STEMI (47).

OTHER PHARMACOLOGICAL INTERVENTIONS. Although no single pharmacological agent targeted for the prevention or treatment of no-reflow after STEMI has been described, numerous possibilities have been

and are currently being pursued. A single small retrospective study investigated intracoronary epinephrine in 12 patients with refractory no-reflow. Administration of 100 to 400 μg of epinephrine to 12 patients in the distal coronary bed resulted in improvement in 9 of 12 patients (68). The study is small, retrospective, and uncontrolled, and needs confirmation before routine clinical use can be recommended.

Nicorandil, a hybrid of K_{ATP} channel opener and nitrate, is a drug used in the management of acute coronary syndromes. It is available in Japan and some other Asian and European countries. It is not available in the United States. In a meta-analysis of patients with myocardial infarction, those treated with intravenous nicorandil showed better coronary perfusion and less no-reflow than control subjects (69). Cyclosporine-A has also been shown to have a beneficial effect in preventing no-reflow during experimental and clinical skin grafting (70); however, in a recently published clinical trial of cyclosporine-A treatment before PCI in patients with acute myocardial infarction, no effect of cyclosporine-A treatment was observed between groups with no-reflow occurring in 5.7% of patients regardless of treatment (71). Similarly, IIb/IIIa platelet receptor antagonists have some promise but are not currently routinely used in clinical practice for the treatment of no-reflow (72–74). More recently, a targeted strategy combining adjunctive IIb/IIIa platelet receptor antagonist administration with aspiration and prolonged balloon inflation was described in a series of 71 patients undergoing PCI for ST-segment elevation, and this combination of therapies appeared to prevent no-reflow (75). Although the study lacks a control group, this promising prevention strategy warrants further investigation. The anticoagulant dabigatran has also been considered, but a recent animal study failed to show a benefit of intravenous dabigatran treatment for no-reflow in a rabbit model of coronary occlusion/reperfusion (76).

More recently, Chen et al. (77) reported the results of a small, randomized, controlled trial conducted in 210 subjects demonstrating a potential for the glucagon-like peptide (GLP)-1 analog liraglutide to reduce no reflow. Proposed mechanisms include modulation of glucose levels, reduced inflammation, and improved endothelial function (77), and further study has been proposed.

NONPHARMACOLOGICAL INTERVENTIONS. In addition to the prevention strategies and thrombus aspiration procedures described in the preceding text, other, less well-supported, nonpharmacological treatment strategies for no-reflow have been described. Induced hypothermia is known to reduce myocardial infarct size. Herring et al. (78) investigated the cooling effect on 2 animal models of myocardial infarction and found a marked reduction in no-reflow in animals that were hypothermic. No human data on no-reflow are available using the technique that Herring et al. used (ThermoSuit System, Life Recovery Systems, Kinnelon, New Jersey) to induce hypothermia, and the expected benefit needs to be weighed against prolonging door-to-balloon time and the logistics of using this technique in the catheterization laboratory. Similarly, ischemic post-conditioning has been shown to reduce no-reflow in small trials (79,80). However, similar studies have failed to find such an effect, and long-term clinical follow-up and conduct of phase III trials are currently lacking (5,81,82).

CONCLUSIONS

Coronary no-reflow is a frequent occurrence during PCI in the setting of STEMI. Prevention and treatment are of paramount importance because the full benefit of reperfusion is recognized only when coronary flow is normal (**Central Illustration**). No-reflow is associated with larger infarct size, reduced ejection fraction, and higher mortality. To prevent no-reflow, long door-to-balloon times, long stents, and high-pressure stent development should be avoided. When there is angiographic evidence of a thrombus burden, intracoronary thrombectomy may be used. Distal protection devices have less proven long-term benefits. When no-reflow is recognized, pharmacological intervention proves beneficial. The authors prefer intracoronary adenosine or nitroprusside to be repeated as needed. Distal intracoronary infusion via infusion catheter is preferred over guiding catheter injection to avoid systemic hemodynamic effects. We believe a consensus statement about no-reflow phenomenon by the American College of Cardiology/American Heart Association will go a long way toward increasing awareness of this complication and its management. This will result in improved outcome of percutaneous coronary intervention.

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