Prevention and Treatment of Microvascular Obstruction-Related Myocardial Injury and Coronary No-Reflow Following Percutaneous Coronary Intervention

A Systematic Approach

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Microvascular obstruction (MVO) commonly occurs following percutaneous coronary interventions (PCI), may lead to myocardial injury, and is an independent predictor of adverse outcome. Severe MVO may manifest angiographically as reduced flow in the patent upstream epicardial arteries, a situation that is termed “no-reflow.” Microvascular obstruction can be broadly categorized according to the duration of myocardial ischemia preceding PCI. In “interventional MVO” (e.g., elective PCI), obstruction typically involves myocardium that was not exposed to acute ischemia before PCI. Conversely “reperfusion MVO” (e.g., primary PCI for acute myocardial infarction) occurs within a myocardial territory that was ischemic before the coronary intervention. Interventional and reperfusion MVO have distinct pathophysiological mechanisms and may require individualized therapeutic approaches. Interventional MVO is triggered predominantly by downstream embolization of atherosclerotic material from the epicardial vessel wall into the distal microvasculature. Reperfusion MVO results from both distal embolization and ischemia-reperfusion injury within the subtended ischemic tissue. Management of MVO and no-reflow may be targeted at different levels: the epicardial artery, microvasculature, and tissue. The aim of the present report is to advocate a systematic approach to prevention and treatment of MVO in different clinical settings. Randomized clinical trials have studied strategies for prevention of MVO and no-reflow; however, the efficacy of measures for reversing MVO once no-reflow has been demonstrated angiographically is unclear. New approaches for prevention and treatment of MVO will require a better understanding of intracellular cardioprotective pathways such as the blockade of the mitochondrial permeability transition pore. (J Am Coll Cardiol Intv 2010;3:695–704)

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Mechanisms of MVO include mechanical plugging secondary to distal embolization from the epicardial coronary arteries, external compression by edematous tissue, in situ thrombosis, vasospasm, activation of inflammatory cascades with leukocyte stasis and extravasation, and reperfusion injury (2). Interventions for optimizing tissue perfusion following PCI may be targeted at the epicardial coronary artery, the microvasculature, and the subtended myocardial tissue (Figs. 1 and 2).

Multiple therapies for MVO and no-reflow have been tested in animals and to a lesser degree in humans. Efficacy of therapies may depend on the experimental model and clinical context in which they are studied, as well as the specific dosage, route of administration, and timing of treatment in relation to the PCI. Treatments for MVO that were shown to be effective in pre-clinical research have often failed to translate into effective human therapies, due to limitations of the available animal models (2). Current animal models lack several features, including atherosclerotic vascular substrate and pre-existing microvascular dysfunction. Distal embolization models have rarely used biologically active material. Ischemia-reperfusion models have not included distal embolization. An ideal experimental model should incorporate downstream embolization of plaque constituents or thrombus into a distal coronary bed that has been subjected to ischemia in a hyperlipidemic or hyperglycemic animal.

Because alterations in flow (either no-reflow or slow flow) are dynamic by nature and may spontaneously resolve over time, the contribution of nonrandomized studies to the current understanding of treatment options is limited. Although several randomized trials have studied different preventive strategies, data regarding interventions for reversal of MVO once it exists is confined to retrospective case reports, due to the rarity and unpredictability of this phenomenon. End points for clinical trials have been defined at the level of the microvasculature (tissue perfusion), organ (cardiac function), and clinical outcomes (survival, functional capacity). Whereas reduced tissue perfusion following PCI is associated with adverse outcomes, therapeutic strategies targeted at MVO must be shown to improve clinical end points in order to gain widespread acceptance.

The concept of ischemic pre- and post-conditioning refers to a variety of pharmacological and nonpharmacological cardioprotective interventions implemented before the onset of ischemia or at the time of reperfusion. Short episodes of ischemia before the onset of prolonged ischemia produce “ischemic preconditioning.” Intermittent reperfusion with repetitive episodes of recurrent ischemia is termed “ischemic post-conditioning.” Transient ischemia in remote organs, which prevents ischemia-reperfusion injury at a distance, is termed “remote ischemic conditioning.” These interventions involve a complex and incompletely understood network of molecular triggering and signaling pathways. Agonists that may trigger cardioprotection include adenosine, opioids, nitric oxide, bradykinin, tumor necrosis factor-alpha, brain and atrial natriuretic peptides, and interleukin-6. Putative signaling pathways include opening of sarcolemmal and/or mitochondrial adenosine triphosphate-dependant potassium channels and activation...
of prosurvival kinases (Akt and ERK-1/2), protein kinase C and G, hypoxia-inducible factor-1 and endothelial nitric oxide synthase. Blockade of the mitochondrial permeability transition pore (MPTP) is considered a final common pathway (3–6). “Pharmacological pre- and post-conditioning” may be achieved by administration of agents that activate these cytoprotective pathways. Recently, exenatide, an antiapoptotic glucagon-like peptide-1 analogue, which also activates prosurvival kinases, has been shown to reduce infarct size after experimental ischemia reperfusion (7).

Pharmacological agents may potentially act at more than 1 level to improve tissue perfusion. Platelet inhibition with glycoprotein IIb/IIIa inhibitors may reduce downstream embolization and local generation of thrombus, and reduce release of vasoactive and chemotactic mediators from platelets (8). Nitroprusside and nitroglycerin are nitric oxide donors that vasodilate conductance vessels >200 μm. Microvessels are unable to metabolize nitroglycerin to nitric oxide; in contrast, nitroprusside does not require metabolism. Calcium channel blockers may attenuate microvascular spasm and reduce myocardial ischemia and infarct size by lowering heart rate and blood pressure. Verapamil may inhibit platelet aggregation and thrombus formation in the microvasculature (9) and may have a direct effect on calcium flux across the sarcolemmal membrane or within intracellular compartments that could protect reversibly injured myocytes (10). Nicardipine, a vasoselective dihydropyridine calcium channel blocker, offers more potent and prolonged vasodilation with less risk of serious systemic side effects than verapamil (11). Adenosine is an endogenous purine nucleoside, which decreases arteriolar resistance and activates prosurvival kinases (12). Nicorandil is a hybrid adenine triphosphate-dependant potassium channel opener and nitrate and may prevent reperfusion injury by blocking the MPTP (13). The immunosuppressive agent cyclosporine is also a MPTP blocker with potential cardioprotective properties.

**Myocardial Infarction Reperfusion MVO (Table 1)**

**Vasodilators.** The role of vasodilators in prevention of MVO has been studied in several randomized clinical trials. Intracoronary verapamil administered following primary PCI and followed by oral treatment improved myocardial perfusion and regional left ventricular wall motion in treated patients when compared to a control group (10). Intracoronary adenosine and verapamil administered following primary PCI achieved equivalent improvement of myocardial perfusion, which was superior to placebo (14). Intracoronary administration of nitroprusside to the distal vascular bed via a perfusion catheter before primary PCI failed to improve coronary flow and myocardial tissue reperfusion when compared to placebo, but was associated with a statistically borderline improvement in clinical outcomes at 6 months (p = 0.05) (15). In small randomized studies, intravenous (16) and distal intracoronary adenosine administration (17) during primary PCI achieved superior flow and ventricular function in comparison to a control group. The larger AMISTAD-II (Acute Myocardial Infarction Study of Adenosine-II) trial (18), which compared intravenous adenosine to placebo, did not show a clear clinical benefit in the treatment arm; however, a post hoc analysis suggested a reduction in mortality and heart failure in patients treated within the first 3 h after onset of evolving anterior ST-segment elevation myocardial infarction (19). In summary, vasodilators appear to reduce MVO in the setting of infarct PCI, although the clinical significance of these findings is unclear.

**Antiplatelet therapy and thrombolysis.** Antiplatelet and thrombolytic therapy may prevent MVO. In randomized trials of patients undergoing primary PCI, abciximab improved microvascular perfusion and myocardial contractility when compared to placebo (20,21). In the RELAx-AMI (Randomized Early Versus Late Abciximab in Acute Myocardial Infarction Treated With Primary Coronary Intervention) trial (22), upstream administration of abciximab achieved better tissue perfusion and 1-month left ventricular function than did treatment in the catheterization laboratory. A recent trial (23) showed that intracoronary versus intravenous administration of abciximab during primary angioplasty increased tissue perfusion and reduced infarct size. This was attributed to improved delivery of the drug to the flow-limiting thrombus, resulting in improved dissolution of thrombi and microemboli at the ruptured plaque and further downstream in the microcirculation. In the ON-TIME 2 (Ongoing Tirofiban in Myocardial Infarction
Evaluation Trial), patients with acute myocardial infarction were randomized to receive either pre-hospital tirofiban or placebo before undergoing primary PCI (24). Tirofiban-treated arteries achieved superior tissue perfusion following angioplasty, as evidenced by resolution of the electrocardiographic ST-segment elevation. A meta-analysis (25) of early trials comparing abciximab to placebo as adjunctive therapy in acute infarct PCI showed a significant reduction in early ischemic adverse events with a trend toward reduction in mortality. Conversely, in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) study (26), abciximab did not im-

| Table 1. Randomized Clinical Trials of Interventions for Prevention of MVO-Related Myocardial Injury and Coronary No-Reflow Following Primary Infarct PCI |
|-----------------------------|---------------------|---------------------------------|------------------|
| Interventions               | Patients, n         | End Point Effect                | First Author (Ref. #) |
| Vasodilators                |                     |                                 |                  |
| IC Verapamil vs. placebo    | 40                  | Improved tissue perfusion by myocardial contrast echocardiography and improved left ventricular function | Taniyama et al. (10) |
| IV Adenosine vs. placebo    | 30                  | Improved tissue perfusion by myocardial contrast echocardiography and improved left ventricular function | Micari et al. (16) |
| IC Adenosine vs. placebo    | 54                  | Reduced angiographic no-reflow and infarct size, improved clinical outcome | Marzilli et al. (17) |
| IV Adenosine (low vs. high dose) vs. placebo | 2,118       | High-dose adenosine reduced infarct size | Ross et al. (18) |
| IC Adenosine vs. verapamil vs. placebo | 150       | Reduced angiographic no-reflow and improved left ventricular function when compared to placebo. Increased transient heart block with verapamil | Vijayalakhmi et al. (14) |
| IC Nitroprusside vs. placebo | 98                  | Similar angiographic tissue perfusion and ST-segment resolution, improved clinical outcome | Amin et al. (15) |
| Glycoprotein IIb/IIIa inhibitors, thrombolysis, and blockade of the complement cascade |                     |                                 |                  |
| IV Abciximab vs. placebo    | 2,082               | Similar ST-segment resolution and myocardial blush grade | Stone et al. (26) |
| IV Abciximab vs. placebo: meta-analysis | 3,266       | Increased bleeding, improved overall clinical outcome | Kandzari et al. (25) |
| Early vs. late IV abciximab  | 210                 | Reduced angiographic no-reflow, improved left ventricular function | Maioi et al. (22) |
| IC vs. IV abciximab         | 154                 | IC abciximab reduced infarct size and no-reflow by ST-segment resolution, MRI assessment of tissue perfusion | Thiele et al. (23) |
| IV Tirofiban vs. placebo    | 984                 | Reduced no-reflow by ST-segment resolution | Van’t Hof et al. (24) |
| IC Streptokinase vs. placebo | 41                  | Reduced no-reflow by Doppler wire flow velocity. No difference in left ventricular function | Sezer et al. (27) |
| IV Pexelizumab vs. placebo  | 5,745               | Similar clinical outcomes | Armstrong et al. (76) |
| Cardioprotectants           |                     |                                 |                  |
| IV Nicorandil vs. placebo   | 368                 | Reduced angiographic no-reflow, improved ST-segment resolution and clinical outcomes | Ishii et al. (39) |
| IV Cyclosporine vs. placebo | 1,216               | No reduction in infarct size | Kitakaze et al. (40) |
| IC hyperoxemic reperfusion  | 58                  | Reduced infarct size | Piot et al. (43) |
| Myocardial post-conditioning| 391                 | Reduced infarct size | Stone et al. (37) |
| Myocardial remote conditioning and morphine | 30                  | Reduced angiographic no-reflow and infarct size | Staat et al. (41) |
| Myocardial remote conditioning and morphine | 38                  | Reduced infarct size and improved left ventricular function | Thibault et al. (42) |
| Thrombectomy and distal embolic protection |                     |                                 |                  |
| X-sizer mechanical thrombectomy | 201                | Reduced angiographic no-reflow, improved ST-segment resolution | Lefevre et al. (77) |
| Thrombus aspiration         | 215                 | Increased infarct size | Kaltoft et al. (30) |
| Thrombus aspiration: meta-analysis | 1,071       | Reduced angiographic no-reflow, improved ST-segment resolution and clinical outcomes | Vlaar et al. (32) and Svilaas et al. (78) |
| Thrombectomy: meta-analysis  | 2,417               | Reduced angiographic no-reflow and 30-day mortality | De Luca et al. (79) |
| Distal embolic protection   | 2,686               | Mortality reduction limited to manual thrombectomy devices. Synergistic benefit of thrombectomy and glycoprotein IIb/IIIa inhibitors | Burzotta et al. (33) |
| Proximal embolic protection | 501                 | Similar ST-segment resolution, infarct size, and clinical outcomes | Stone et al. (34) |
| Thrombectomy and distal embolic protection devices: meta-analysis | 284                 | Improved ST-segment resolution | Haeck et al. (35) |
| Thrombectomy and distal embolic protection devices: meta-analysis | 6,415               | Thrombus aspiration reduced mortality, mechanical thrombectomy increased mortality, and distal embolic protection had a neutral effect on mortality | Bavry et al. (80) |

IC = intracoronary; IV = intravenous; MRI = magnetic resonance imaging.
prove microvascular perfusion when compared to placebo. This unexpected result may be due to the relatively low-risk population recruited to the study and a short time interval from initiation of the therapy to the coronary intervention. There is a paucity of trials that have reevaluated the current role of glycoprotein IIb/IIIa inhibitors in patients who receive adequate thienopyridine loading before acute infarct PCI. In summary, current data suggests that glycoprotein IIb/IIIa inhibitors are especially beneficial when given upstream in patients who have not received thienopyridine loading.

In a small randomized trial, intracoronary thrombolysis immediately following primary PCI improved microvascular integrity and tissue perfusion measured 2 days later by coronary flow reserve, microvascular resistance, and TIMI (Thrombolysis In Myocardial Infarction) frame count (27). These findings suggest a role for in situ microvascular thrombosis in the pathogenesis of no-reflow, although the study was underpowered to study the clinical impact of this approach.

Thrombus aspiration and embolic protection devices. Several mechanical approaches for prevention of distal embolization have been studied in the setting of primary PCI. Initial small trials of thrombus aspiration reported conflicting results (28–30). In the study by Kaltoft et al. (30), thrombectomy did not improve ST-segment resolution and was associated with increased infarct size. Conversely, in the REMEDIA (Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus-Aspiration in Primary and Rescue Angioplasty) (28) and DEAR-MI (Dethrombosis to Enhance Acute Thrombectomy and Reperfusion in Myocardial Infarction) (31) studies, thrombectomy improved microvascular perfusion. In the pivotal TAPAS (Thrombosis Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction) trial (32), thrombectomy improved tissue perfusion and reduced cardiac death. In a pooled analysis of 11 randomized trials that examined the role of different thrombectomy devices in primary PCI, thrombectomy improved survival in patients treated with glycoprotein IIb/IIIa inhibitors (p = 0.049) and survival advantage was confined to manual thrombectomy (p = 0.011) (33). Another mechanical approach for prevention of distal embolization consists of deployment of embolic protection devices before stenting. Distal embolic protection has several theoretical disadvantages when compared to proximal protection, including potential trauma to the vessel and induction of embolization as the device is maneuvered across the lesion before deployment, lack of protection to side branches located proximal to the device, and the ability of potent vasoconstrictors to pass through filter micropores and reach the distal microvasculature. Distal protection with a balloon occlusion and aspiration system (GuardWire, Medtronic, Santa Rosa, California) effectively retrieved embolic debris in the EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) study (34), but did not improve microvascular flow, decrease infarct size, or improve clinical outcome. In the PREPARE (Proximal Embolic Protection in Acute MI and Resolution of ST-Elevation) trial (35), proximal embolic protection (Proxis, St. Jude Medical, St. Paul, Minnesota) improved microvascular flow as reflected by improved immediate complete ST-segment resolution; however, the study was underpowered to detect clinical benefit. No trials have directly compared these different strategies for prevention of distal microembolization. In summary, current data supports routine manual thrombectomy during primary PCI. Distal embolic protection is of unproven benefit and the role of proximal embolic protection, though promising, remains to be defined.

Hyperoxemic reperfusion. Intracoronary hyperoxemic reperfusion has been advocated for prevention of reperfusion injury. Hyperoxemic reperfusion improved microvascular blood flow and decreased infarct size in a canine model of ischemia reperfusion (36). In the AMIHOT-II (Acute Myocardial Infarction With Hyperoxemic Therapy II) trial (37), this approach reduced infarct size but was not associated with improved tissue perfusion as assessed by ST-segment resolution. In this trial, only 22% of the patients underwent thrombectomy and 67% received glycoprotein IIb/IIIa inhibitors. Because the clinical benefit of hyperoxemic reperfusion has yet to be shown, the routine use of this invasive strategy in the current era of routine thrombectomy cannot be recommended at present.

Cytoprotection. Activation of intracellular prosurvival pathways has been studied in the setting of primary PCI. In 1 study, intravenous nicorandil started before PCI improved myocardial perfusion and ventricular contraction (38), as well as long-term clinical outcome (39). However, a larger study found no reduction in infarct size with nicorandil versus placebo (40). Myocardial post-conditioning after direct coronary stenting by use of intermittent low-pressure balloon inflations in the infarct-related artery reduced infarct size and improved microvascular perfusion as assessed by myocardial blush (41), and long-term functional recovery (42). Pharmacological post-conditioning by intravenous administration of cyclosporine, a direct MPTP blocker, versus placebo, at the time of primary PCI decreased infarct size (43). Remote post-conditioning by intermittent inflations of a blood pressure cuff on the upper limb before reperfusion improved ST-segment resolution following primary PCI, an effect that was enhanced by administration of morphine (44). These preliminary studies suggest a beneficial role for conditioning strategies in the setting of primary infarct PCI. However, their efficacy in patients undergoing thrombectomy and receiving glycoprotein IIb/IIIa inhibitors remains to be defined.

Reversal of reperfusion no-reflow. Appearance of angiographic no-reflow reflects the presence of severe MVO and
myocardial ischemia and is associated with serious adverse clinical events. Various interventions for reversal of existing angiographic no-reflow following primary PCI have been reported, although no randomized trials have been performed in this setting (45). Nitroglycerin was not found to be effective (46). Other reports suggested efficacy of papaverine (47), nitroprusside (48,49), nicardipine (50), and abciximab (51). At present, there are no data from randomized trials showing the clinical benefit of these therapies.

**Interventional MVO (Table 2)**

**Embolic protection devices.** Several randomized trials have studied the role of embolic protection devices in the treatment of diseased saphenous vein aortocoronary bypass grafts. Occlusive protection devices, either distal (GuardWire, Medtronic) or proximal (Proxis, St. Jude Medical) have a theoretical advantage over distal filter catheters in that they capture vasoactive, proinflammatory and thrombotic factors that might pass through filter pores and induce microvascular obstruction (52). However, clinical studies to date have not demonstrated superiority of a specific protection device. In the SAFER (Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial) (53), distal embolic protection with a balloon occlusion and aspiration system (GuardWire) reduced angiographic no-reflow from 9% to 3% and improved clinical outcome. In the FIRE (FilterWire Ex Randomized Evaluation) trial (54), distal protection with a filter-based catheter (FilterWire EX, Boston Scientific, Natick, Massachusetts) was noninferior to the GuardWire system. In the PROXIMAL (Proximal Protection During Saphenous Vein Graft Intervention) trial (55), the efficacy of proximal embolic protection (Proxis, St. Jude Medical) was noninferior to distal protection. In an analysis of the 19,546 vein graft PCI procedures in the American College of Cardiology–National Cardiovascular Data Registry (56), use of embolic protection devices was independently associated with a lower incidence of no-reflow (odds ratio: 0.68, \(p = 0.032\)), although these devices were only used in 22% of the cases. The underuse of this technology may be due to complexity of use and cost, reflecting the need for more user-friendly and cheaper devices.

**Antipla telet therapy and vasodilators.** Although distal embolization is the predominant mechanism leading to MVO and no-reflow in interventional no-reflow, particularly during vein graft interventions, there still may be a role for vasodilator and antiplatelet therapies to modify the flow abnormalities. In noninfarct interventions, glycoprotein IIb/IIIa inhibitors enhanced microvascular perfusion among patients undergoing PCI to native coronary arteries (57), but did not improve clinical outcomes in patients undergoing PCI to coronary bypass vein grafts (58). In a registry of 83 consecutive degenerative vein grafts undergoing stenting following intragraft administration of nicardipine (59), a significant rise in serum creatine kinase levels was documented in only 4.4% of the cases and no patients sustained a Q-wave myocardial infarction. In the VAPOR (Vasodilator Prevention of No-Reflow) trial (60), pre-intervention intragraft verapamil achieved a significant improvement in coronary flow measured by the TIMI frame count in patients undergoing PCI to vein grafts. Among patients undergoing rotational coronary atherectomy, intracoronary nicorandil reduced no-reflow when compared to verapamil (61,62).

**Cytoprotection.** In patients undergoing elective PCI, remote conditioning by transient upper-limb ischemia reduced myocardial injury following the procedure (63).

**Reversal of interventional no-reflow.** As in the case of reperfusion no-reflow, angiographic evidence of no-reflow in the setting of noninfarct PCI reflects severe MVO and extensive myocardial ischemia. Treatment of existing inter-
Microvascular obstruction following PCI is a multifactorial phenomenon with diverse etiologies in different clinical settings and is associated with adverse outcome. Prevention of MVO following elective coronary intervention is beneficial in reducing cardiac injury and improving clinical outcome. Until recently, it was unclear whether the unfavorable outcome associated with MVO following primary infarct PCI reflected a causal effect or whether the microcirculatory injury was an epiphenomenon mirroring greater myocardial damage. The TAPAS study has proven that prevention of MVO during primary PCI may reduce cardiac injury and improve clinical outcome. Several preventive measures effectively decrease the degree of MVO and improve clinical outcome in the setting of both acute infarct and elective PCI. Unfortunately, there is limited data comparing the efficacy of different strategies. There is no randomized data to guide selection of therapies for reversal of existing no-reflow.

The goal of the various pharmacological and mechanical therapeutic strategies that are targeted at prevention and reversal of MVO and no-reflow is to minimize cardiac injury. Specific interventions targeted at reperfusion injury that activate intracellular cardioprotective signaling pathways have been shown to improve tissue perfusion and decrease myocardial injury following PCI. These approaches hold great promise for achievement of further myocardial preservation. Ultimately, strategies designed to reduce MVO and to activate intracellular cardioprotective mechanisms converge at the tissue level. Reduction of MVO is cardioprotective and cardioprotection is associated with improved tissue perfusion. Future research should be directed at refining these techniques and implementing them for reversal of no-reflow once it has occurred.

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