Catheterization and Cardiovascular Interventions 60:194–201 (2003)

Society of Cardiac Angiography and Interventions: Suggested Management of the No-Reflow Phenomenon in the Cardiac Catheterization Laboratory

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INTRODUCTION

The interventional cardiologist makes a provisional diagnosis of the no-reflow phenomenon in the presence of an acute reduction in coronary flow despite a widely patent epicardial vessel during percutaneous coronary intervention (PCI). Its occurrence is recognized as a column of contrast arising distal to the original target stenosis that does not rapidly clear [1–3]. The precise pathophysiologic mechanisms are uncertain, although flow-limiting spasm of the distal microvasculature, distal thromboembolism, and microembolization of atherosclerotic debris are believed to be operative, in some combination, in most cases [4,5]. No-reflow as a cardiac phenomenon was originally identified in experimental models of acute myocardial infarction and described as the failure to restore normal myocardial blood flow despite subsequent removal of the coronary arterial obstruction, attributable to microvascular damage related to irreversible ischemic changes and local edema. It has been recognized for over a decade clinically [6,7] as an uncommon (0.6–2.0%) complication of PCI [1,2,6]. It occurs frequently following thrombolytic or mechanical reperfusion for acute myocardial infarction and in the setting of unstable angina [3,7,8]. It is most common during use of rotational atherectomy [9,10] and during PCI in saphenous vein grafts [2]. The purpose of this review is to define the angiographic appearance and clinical outcomes of no-reflow and to summarize the various treatment and prevention options currently available to the interventional cardiologist.

DEFINITION OF NO-REFLOW

There is no universally applicable definition of the no-reflow phenomenon [11]. It is suspected during PCI when an acute ischemic episode accompanies the angiographic appearance of reduced antegrade epicardial flow in the absence of an epicardial lesion of sufficient severity to be flow-limiting [12]. In acute myocardial infarction treated with thrombolytic therapy, a patent vessel subtending nonviable myocardium may suggest that no-reflow occurred, preventing myocardial reperfusion [13]. In the experimental laboratory, after myocardial infarction, no-reflow is believed to be related to reperfusion injury at the tissue level [14]. A completed transmural infarction with disrupted microvasculature may also lead to no-reflow [5].

The common denominator of no-reflow in all of these settings is inadequately perfused myocardium without evidence of persistent mechanical epicardial obstruction, usually with concomitant myocardial ischemia [4]. Subcategorization into three types—experimental no-reflow, myocardial infarction reperfusion-related no-reflow, and angiographic no-reflow depending on the clinical circumstances—has been proposed [11]. No-reflow occurring during primary PCI for myocardial infarction or in the setting of acute coronary syndromes combines the interventional cardiology definition (angiographic no-reflow) with lack of reperfusion after acute myocardial infarction and therefore may be best classified as a com-

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Received 11 April 2003; Revision accepted 25 May 2003

DOI 10.1002/ccd.10620
Published online in Wiley InterScience (www.interscience.wiley.com).

TABLE I. Potential Mechanisms of No-Reflow

Severe microvascular dysfunction due to alpha-adrenergic macro- and microvascular constriction and vasospasm
Distal embolization of thrombus
Distal embolization of atherosclerotic debris
Oxygen free radical-mediated endothelial injury
Capillary plugging by red blood cells and activated neutrophils
Endothelial cell dysfunction/vasoconstriction due to enhanced interaction between neutrophils and damaged endothelium promoted by p-selectin and other mediators
Intracellular and interstitial edema and intramural hematoma
Increased angiotensin II receptor density after myocardial infarction
Loss of capillary integrity due to completed myocardial infarction

bination of angiographic and myocardial infarction no-reflow.

MECHANISMS OF NO-REFLOW

The mechanism of no-reflow (Table I) differs from case to case depending on the clinical setting. In elective PCI of native coronary vessels, no-reflow may be due to microvascular spasm and/or platelet microemboli. Following PCI in thrombotic lesions, such as in acute coronary syndromes or acute myocardial infarction, no-reflow may be due to distal embolization of thrombus. With saphenous vein graft PCI and PCI with rotational atherectomy, it is most often related to embolization of degenerated plaque elements, including thrombotic and atherosclerotic debris. In many instances, a combination of these mechanisms may be present.

Embolization protection devices have demonstrated that distal embolization of particulate debris is at least partially responsible [15] despite early evidence in animal models that embolization during PCI is infrequent [16]. The nature of the particle size found in these cases is instructive. Release of small numbers of 15 micron emboli particles have been shown to cause patchy ischemia and a paradoxical increase in regional blood flow due to local adenosine release in adjacent normal zones. Increasing numbers of emboli cause impaired flow reserve and ultimately a decrease in resting flow. When the particles are larger, in the 100–300 micron range, dramatically fewer emboli are required to produce these physiologic consequences [17].

No-reflow during primary PCI for acute myocardial infarction and following PCI of bulky saphenous vein graft lesions may be explained by embolization of pieces of atherosclerotic and thrombotic material. Often this condition is resistant to therapy; most cases do not respond to thrombolytic agents or glycoprotein receptor inhibitors.

In the animal laboratory, experimental no-reflow has been shown by electron microscopy to be due to increased microvascular impedance to arteriolar flow. The findings are those of erythrocyte and neutrophil plugging of capillaries (p-selectin and other adhesion molecules may promote the interaction between neutrophil and damaged endothelium resulting in constriction), myocyte contracture, local intracellular and interstitial edema, intramural hemorrhage, and endothelial blistering. Unfortunately, it is not certain whether experimental no-reflow is representative of any of the clinical scenarios [4,5] and therefore has not been utilized as a model to assess potential therapies.

A loss of capillary autoregulation and severe microvascular dysfunction are the consequences of these microscopic anatomic alterations. Profound microvascular vasospasm caused by release of serotonin [18] and other potent vasoconstrictors by activated platelets within fibrin clots likely contributes in many cases. Experimental studies have implicated thromboxane-induced capillary vasospasm and oxygen free radical-mediated injury [14]. When the principal mechanism is vasoconstriction, a favorable response with intracoronary administration of vasodilators is anticipated, but how often this succeeds in practice is unknown. Vasoconstriction may also be superimposed on embolic obstruction, explaining why intracoronary vasodilators may be effective even in cases when distal embolization is evident.

Coronary artery occlusion may trigger a sympathetic reflex inducing alpha-adrenergic macro- and microvascular constriction [19,20] and changes in angiotensin II receptor density [21,22]. An increase in the density of angiotensin II receptors in myocardial scar tissue after myocardial infarction may indirectly modulate vasoconstriction by this mechanism.

ANGIOGRAPHIC RECOGNITION

The no-reflow phenomenon produces inadequate myocardial perfusion without angiographic evidence of mechanical vessel occlusion [11]. The observation of reduced TIMI flow with a column of contrast in the vessel distal to the target lesion that does not rapidly clear is sufficient to make this diagnosis [1,2,6]. The original target lesion appears patent without evidence of dissection, thrombus, spasm, or high-grade residual stenosis.

Angiographic no-reflow must be differentiated from other causes of diminished antegrade flow due to epicardial obstruction caused by dissection, thrombus, prolonged focal epicardial spasm, distal macroembolism, air embolism, and competitive flow from persistent collaterals obscuring satisfactory antegrade opacification. Deep seating of a guide catheter may also cause flow diminution that mimics no-reflow. Although no-reflow is a diagnosis of exclusion, from a practical standpoint eliminating all of the possible etiologies may be difficult.

An organized and systematic method is therefore the best approach to diagnosis. Multiple angiographic views to exclude an occult coronary dissection are necessary. Intravascular ultrasound can be helpful in excluding epicardial causes of delayed filling or emptying of the vessel. Some operators find measurement of the translesional pressure gradient useful to exclude significant epicardial obstruction. Others suggest the use of contrast injection into the distal vessel through a subselective catheter to delineate the angiographic status. In some cases, the diagnosis is made only after serial treatment of all of the possibilities, including additional stenting and balloon inflation, fails to resolve the impaired distal perfusion.

The term "no-reflow" should be reserved for a completely static contrast column (TIMI grade 0 or 1 antegrade flow) in the absence of other etiologies. Depending on the degree of flow compromise, "slow flow" or "low flow" have been described when there is sluggish clearing of content, that is, when the vessel fills completely but either fills or empties more slowly than uninvolved vessels, but antegrade flow is not completely absent (TIMI grade 2 flow). These conditions are also indicative of myocardial ischemia with diminished oxygenation at the tissue level [1,2].

CLINICAL MANIFESTATIONS OF NO-REFLOW

In acute myocardial infarction treated with thrombolysis, persistence of contractile dysfunction despite epicardial vessel patency and TIMI 3 flow is due to a combination of myocardial necrosis, edema, and stunning. Irreversible necrosis results from the injury sustained during acute occlusion [23], reperfusion injury [24], and no-reflow [14]. Reperfusion in acute myocardial infarction will be markedly diminished when no-reflow occurs [13]. Compared to similar patients with adequate reflow, those with no-reflow would be expected to have larger infarctions, more congestive heart failure early after myocardial infarction, and demonstrate progressive left ventricular cavity dilation in the convalescent stage of the infarction [19,25–29].

During PCI procedures, clinically recognized no-reflow usually manifests as acute ischemia, including ECG changes and chest pain. Transient or permanent conduction disturbances, including atrioventricular block and bundle branch blocks, may occur if blood flow decreases to specialized conduction tissue. There is a 32% incidence of myocardial infarction when no-reflow is observed after PCI and a 5–15% incidence of death [1,2]. In one series [1], 9 of 28 patients with no-reflow sustained either a Q-wave (3.6%) or a non-Q-wave (28.6%) myocardial infarction, and there was a 7.7% associated mortality. Additionally, hypotension and cardiogenic shock may develop, especially when baseline left ventricular function is diminished. Conversely, many cases of no-reflow are silent without any clinical sequelae.

During elective PCI, no-reflow is uncommon and has been reported to occur in 0.6% to 2.0% of cases [1,4]. No-reflow occurs more frequently in PCI of saphenous vein grafts (5–15%), especially in older grafts (> 7 years old) and those with diffuse or multiple bulky lesion morphologies. It is also more common with rotational atherectomy and PCI and stenting of thrombus-containing lesions. Silva et al. [30] recently reported five cases of transient no-reflow in patients with coronary stent thrombosis treated with rheolytic thrombectomy.

No-reflow associated with rotational atherectomy was found in one series [2] to be reversible in 63%, and this unusually high response to vasodilators suggests that vasospasm is an important component. In contradistinction, no-reflow after extraction atherectomy (TEC) is usually irreversible, suggesting that embolization of bulky plaque and other debris from vein grafts, which does not respond readily to vasodilators, is the cause [31]. Failure to reestablish flow rapidly has been associated with increased morbidity and mortality and a high incidence of myocardial infarction [1,2,32].

The predictors of death with no-reflow include cardiogenic shock, large amount of jeopardized myocardium, history of congestive heart failure or LVEF $< 30\%$, age ≥ 65–70 years, multivessel disease (especially with collaterals from the index vessel to another location), female gender, and prolonged time needed to restore flow [1,2].

PREVENTION OF NO-REFLOW

Unfortunately, there are no effective methods that reliably prevent no-reflow (Table II). In patients undergoing PCI in saphenous vein grafts, the microvascular protection provided by glycoprotein IIb/IIIa antagonists is overestimated by many interventionists. Roffi et al. [33] recently performed a meta-analysis of data from EPIC, EPILOGUE, EPISTENT, IMPACT II, and PURSUIT showing no discernable effect of prophylactic administration of these agents. Ellis et al. [34] analyzed 102 vein graft stenoses from the EPIC and EPILOG trials and failed to demonstrate any clinical benefit. They observed a rate of 18.6% incidence of death, myocardial infarction, and urgent revascularization at 30 days in the abciximab group compared to 16.3% for placebo. They hypothesized that distal embolization of athermomatous plaque from the vein graft is insensitive to the antiplatelet effect of abciximab.

Pretreatment with intracoronary verapamil, adenosine, or nitroprusside is a common strategy prior to PCI of saphenous vein grafts, but there is little evidence to

TABLE II. Prevention of No-Reflow

Distal protection devices when treating diffuse disease or bulky Saphenous vein graft lesions, especially in older grafts
When using rotational atherectomy, use of nitroglycerin, verapamil, and heparin combination in the flush solution
Consider pretreatment with IIb/IIIa inhibitors during PCI in patients with unstable coronary syndromes
Minimize balloon inflations, consider stent deployment without predilation and self-expanding stent designs that do not require high-pressure inflation in vessels with bulky atheroma or in saphenous vein grafts
Pretreatment with verapamil or adenosine

TABLE III. Initial Evaluation and Treatment of No-Reflow

Exclude dissection, thrombus, spasm at lesion site (IVUS, distal contrast injections, and/or translesion pressure gradient may be useful)
Achieve adequate ACT (250–300 sec with unfractionated heparin if a IIb/IIIa inhibitor has been given, $>$ 300 sec if one has not been given, and 325–375 sec with direct thrombin inhibitors)
Ensure sufficient oxygenation and airway management
Treat vagal reactions (intravenous atropine and fluids)
Maintain adequate perfusion pressure with intravenous fluids, vasopressors, inotropes, and IABP if necessary
Administer intracoronary nitroglycerin (100–200 μg up to four doses) to exclude epicardial spasm
Consider administering a glycoprotein IIb/IIIa receptor inhibitor
Administer pharmacologic agents through an infusion catheter or the central lumen of the balloon catheter to ensure drug delivery to the distal bed

support this practice. Sdringola et al. [35,36] reported that prophylaxis with multiple doses of adenosine was ineffective in preventing no-reflow in this setting in a group of 143 patients.

Distal protection devices are effective in decreasing macroembolization in saphenous vein graft PCI and likely diminish the incidence of no-reflow [37]. However, a significant incidence of distal embolization causing no-reflow still occurs. No-reflow complicated 9% of procedures (2/23) in the study by Shaknovich et al. [38] and in 11% (3/27 patients) in the series of Webb et al. [15] using the PercuSurge system. In this latter report, the retrieval of particulate material was documented in 21 out of 23 procedures. Primary stenting without predilation was associated with less collected material than with predilation and subsequent stenting, suggesting that primary stenting may reduce the risk for no-reflow in saphenous vein grafts. Carlino et al. [39] reported a 100% clinical and procedural success rates with the PercuSurge device in 15 degenerated saphenous vein graft lesions. Embolization protection devices are currently being evaluated during interventions for thrombus-containing lesions in native vessels. Further advances to decrease the crossing profile, ischemic time, and improve debris retrieval will probably enhance the utility of this approach.

Older devices that suction or aspirate intragraft material are now generally considered ineffective for this indication. The initial experience with the Angiojet and TEC devices was promising [40–42]. However, widespread anecdotal experience has been quite unimpressive, and the TEC device is no longer available. A recently developed thrombectomy/atherectomy device, the Xciser, and a variety of other new devices are currently being evaluated.

Pharmacological and technical measures to prevent angiographic no-reflow during rotational atherectomy deserve special attention because of the relatively high risk for no-reflow. Suggested preventive technical measures include a burr-to-artery ratio of 0.6–0.8 followed by conventional balloon dilation (conservative rotational atherectomy) and a low rotational speed ($\sim$ 140,000 rpm) [43]. The randomized STRATAS trial comparing conservative with aggressive or standalone rotational atherectomy (burr-to-artery ratios of 0.7–0.9 and low-pressure balloon angioplasty) failed, however, to demonstrate differences in clinical outcomes between these two strategies. Pharmacologic preventive measures in rotational atherectomy cases routinely include abciximab [44], intracoronary adenosine [45], and a drug cocktail in the flush solution including nitrates, verapamil, and heparin [46].

CLINICAL MANAGEMENT

The clinical effects of no-reflow are initially managed by stabilization of the hemodynamic and electrophysiologic sequelae (Tables III and IV). Managing airway and maintaining oxygenation, if they are compromised, are important components. If hypotension results, blood pressure maintenance with pressors and/or inotropes is essential. Fluid resuscitation and atropine when vagal reactions ensue are appropriate, especially when accompanying inferior ischemia (Bezold-Jarisch reflex). Chest pain relief with i.v. nitroglycerin and morphine, treatment of dysrhythmias, and intra-aortic balloon pump placement for low-cardiac-output states [47,48] are mainstays of therapy.

The principal therapy of no-reflow is intracoronary drug administration rapidly to restore antegrade flow and reestablish myocardial blood flow. Although a variety of pharmacologic agents have been advocated for this purpose, none are of proven therapeutic value.

Ascertaining (based on clinical setting and scenario) whether microvascular spasm or particulate embolization is the primary mechanism in a given case might theoretically provide a rational approach to management. However, there is no evidence in the literature that any single approach is effective. Since no-reflow is likely to be multifactorial in nearly all of the usual clinical settings,

TABLE IV. SCAI Suggested Management of No-Reflow*

I, First-Line Management
Adenosine (10–20 μg bolus)
Verapamil (100–200 μg boluses or 100 μg/min up to 1,000 μg total dose with temporary pacer on standby)
Nitroprusside (50–200 μg bolus, up to 1,000 μg total dose)
II, Evidence Less Strong
Rapid, moderately forceful injection of saline or blood (to unplug microvasculature)
Diltiazem (0.5–2.5 mg over 1 min up to 5 mg)
Papavarine (10–20 μg)
Nicardipine (200 μg)
Nicorandil (2 μg)
Epinephrine (50–200 μg)
III, Never Shown to be Effective
Intracoronary nitroglycerin (for microvascular causes)
CABG (contraindicated)
Stent placement (if site of original stenosis is widely patent)
Thrombolytics (e.g., urokinase, t-PA)

*All agents and dosages are for intracoronary use. Careful administration of smaller doses of these agents if hypotension is present may be appropriate.

and there is no definitive method to make these distinctions, multiple agents that target a variety of pathophysiologic substrates are given in sequence.

The operator should be aware that agents administered through the guiding catheter may preferentially distribute to areas with retained flow rather than at the site of activity. Therefore, when practical, drugs should be administered either through an infusion catheter placed distally or through the central lumen of an over-the-wire balloon catheter.

Intracoronary nitroglycerin is usually suggested as the first-line agent, mainly to reverse epicardial vessel spasm, even if the blood pressure is reduced. Theoretically, nitroglycerin should have little impact on arteriolar tone and hence on no-reflow since physiologically it produces little effect in the microvasculature. Piana et al. [1] showed that no-reflow during PCI generally responds poorly to i.c. nitroglycerin.

Based on the limited knowledge at present, the suggested management of no-reflow is to administer several intracoronary boluses of one or two of the agents listed in section II of Table IV (adenosine, verapamil, or nitroprusside). Although the evidence demonstrating clinical utility for each of these agents is surprisingly weak, they are the most appealing, given their known impact on distal arteriolar function.

The best clinical evidence exists for the use of intracoronary verapamil. Piana et al. [1] showed that i.c. verapamil (50–900 μg total dose) improved TIMI flow grade in 89% of cases. Abbo et al. [2] had a success rate of 67%, but the highest resolution was in Rotablator cases. In a small nonrandomized prospective trial in 36 degenerated vein graft lesions in 32 patients, Kaplan et al. [32] compared intragraft verapamil (100–550 μg) with nitroglycerin (100–300 μg). TIMI flow improved in all patients who received verapamil, while those who received nitroglycerin had no change in flow. Pomerantz et al. [49] and Taniyama et al. [50] had similar results. Nevertheless, the total number of cases reported in the literature is well under 100.

Adenosine is frequently utilized in this setting and would seem to be an ideal distal arteriolar vasodilator for this purpose. In one series of 11 events related to vein graft PCI [51], adenosine was effective in improving flow in many cases. In another experience of 20 cases of saphenous vein graft PCI [52], multiple boluses and higher doses of adenosine were found to be more effective than low doses.

Only a single series of 19 cases demonstrating efficacy of i.c. nitroprusside exists [53], despite the favorable anecdotal experiences of numerous interventionists. Physiologically, nitroprusside is a nitric oxide donor, which may have beneficial effects on arterioles in this setting.

Reports of improvement with multiple, forcefully injected boluses of normal saline or blood have been anecdotally successful in unplugging the arteriolar bed [31]. Multiple high-velocity boluses of adenosine may also be effective [51,52]. Intravenous platelet glycoprotein IIb/IIIa inhibitors are usually administered in these circumstances to resolve any platelet-rich thrombi that may have occurred and prevent platelet plugs from developing. However, only a single case report suggests utility in this setting [54].

If these treatments fail, the next step might be to consider one of the agents listed in section III of Table IV. The evidence for efficacy with these agents is even weaker than those listed above. Of these, the most clinical experience exists with diltiazem [55–57]. Papaverine has been reported to be beneficial, as assessed by improved TIMI flow grade in nine cases [58]. Intracoronary epinephrine has recently been reported to be effective in this setting [59]. Nicardipine has only been formally studied in animal models [60] but some of its pharmacologic properties are attractive. Nicorandil may also have a role in treating no-reflow when given intravenously [61].

A number of therapies are not considered effective in no-reflow, either based on clinical reports or on persuasive theoretical grounds. While intra-aortic balloon pump is effective in raising perfusion pressure in hemodynamically unstable patients, it has not been shown to increase myocardial flow in this setting [62,63]. Both theoretically and practically, neither stenting nor bypass surgery should have any benefit, since the level of obstruction is in the arteriolar bed. Additional heparin beyond achieving a therapeutic level will not resolve thrombotic mi-

croembolism and may cause hemorrhage. Intracoronary heparin and thrombolytics (e.g., urokinase, t-PA) have been advocated in the past, but have no demonstrated efficacy, even when thrombotic macroembolization is evident angiographically [64,65]. Repeat balloon inflations is a more efficacious therapy for embolization of thrombus to the distal epicardial vessel.

FUTURE INVESTIGATIONS

In developing this suggested management scheme, it should be made clear that none of these agents have been prospectively tested for efficacy in clinical trials for no-reflow against a control. In part, this lack of objective evidence exists because no-reflow occurs infrequently, and it is unlikely that any operator or institution can plan to have enough of these cases to design a prospective evaluation of any particular regimen. Given its unpredictable occurrence, 100 elective PCI patients would have to consent to enroll just 2 or 3 cases in such a study. Further, assessing its presence and severity initially, and quantifying the impact of any agent on reestablishing flow, is daunting. For these reasons, such a trial has never been attempted on a multicenter scale, and all available studies are observational in nature. While changes in TIMI flow are sometimes quantitated, even this parameter depends on a subjective unblinded interpretation of flow pre- and posttherapy. No existing analysis includes an assessment of myocardial viability or function at follow-up to demonstrate salvage after flow is restored. For these reasons, any rigid approach to the problem at this stage cannot be supported by published reports.

Clearly, clinical trials in this area are necessary. The optimal study design would ideally include clear objective criteria for the diagnosis of no-reflow and exclusion of unrelated problems that can masquerade as no-reflow, a defined experimental protocol evaluating an agent or sequence of therapies versus a specific comparator or control group, an objective measure of flow pre- and posttherapy such as TIMI frame count or an assessment by a core laboratory, and a method of evaluating regional viability and/or function at a distant time period.

In conclusion, current pathophysiologic concepts and the pharmacologic background with which the interventional cardiologist should be familiar have been reviewed. The suggested practical management strategies are those that have the highest likelihood of improving patient outcomes but have not been definitively evaluated. Consequently, guidelines developed from an evidence-based approach cannot be conveyed at this time.

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