Incidence and Treatment of ‘No-Reflow’ After Percutaneous Coronary Intervention

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Background Profound reduction in antegrade epicardial coronary flow with concomitant ischemia is seen occasionally during percutaneous coronary intervention despite the absence of evident vessel dissection, obstruction, or distal vessel embolic cutoff. In a prior small series of cases, this “no-reflow” phenomenon appeared to be promptly reversed by the intracoronary administration of verapamil.

Methods and Results To further understand the prevalence of this syndrome and its responsiveness to the proposed therapy, we reviewed 1919 percutaneous interventions performed between January 1991 and April 1993. During the study period, 39 patients (2.0%) met our criteria for no reflow, 37 of whom were treated with intracoronary nitroglycerin followed by intracoronary verapamil and 2 of whom received intracoronary nitroglycerin alone. An additional 16 patients (0.8%) were given verapamil as part of the management of a flow-limiting dissection or distal embolus (mechanical obstruction). Intracoronary verapamil (50 to 900 μg, total dose) improved TIMI flow grade in 89% of no-reflow patients and markedly reduced the number of cineframes between contrast injection and opacification of a selected distal landmark (from 91±56 to 38±21 frames, P<.001). By contrast, only 19% of patients with epicardial mechanical obstruction showed improvement in TIMI flow grade after verapamil, with minimal reduction in frames to opacification (from 107±42 to 101±69, P=.73).

Conclusions The no-reflow phenomenon—reduction in distal flow without apparent dissection or distal embolization—occurs in 2% of coronary interventions. It generally responds promptly to intracoronary verapamil administration, suggesting that distal microvascular spasm may be its etiology. (Circulation. 1994;89:2514-2518.)

Key Words • no-reflow phenomenon • verapamil • percutaneous transluminal coronary angioplasty

Reduction in coronary flow with associated myocardial ischemia during percutaneous coronary intervention is generally caused by damage of the large epicardial vessels (dissection) and is typically treated by additional balloon inflation, stent placement, or bypass surgery. Ischemia also may result from either focal epicardial spasm (which responds promptly to intracoronary nitroglycerin) or from distal embolization of plaque or thrombus (marked by a characteristic angiographic cutoff of the distal vessel). We recently reported five patients in whom epicardial flow reduction occurred without any of these findings and was refractory to nitroglycerin, although it responded promptly to the administration of low doses (100 μg) of intracoronary verapamil. This suggested that flow-restricting spasm of the distal microvasculature might be responsible.1 No systematic study of the incidence of this “no-reflow” phenomenon and no quantitation of the effectiveness of the proposed therapy have yet been reported.

Methods

Study Patients

A computerized database of 1919 coronary procedures (balloon angioplasty [n=1448], directional atherectomy [n=228], or stent placement [n=243]) performed between January 1991 and April 1993 was screened for the occurrence of no-reflow or the use of intracoronary verapamil during these interventions. This review identified 55 (2.9%) potential no-reflow patients. Detailed review of the cineangiograms and clinical records revealed that 39 (2.0%) actually met the criteria for no-reflow in that they developed substantial flow reduction (less than TIMI 3 flow) in the absence of apparent dissection, thrombosis, or distal vessel cutoff suggestive of macroembolization. All of these patients had been treated with intracoronary verapamil except for two patients who received intracoronary nitroglycerin alone. In 16 (0.8%) additional patients who did not meet criteria for no-reflow, verapamil was given as part of the pharmacological management of overt epicardial mechanical obstruction by dissection or thrombus (mechanical obstruction group).

Background Drug Therapy

All patients undergoing coronary intervention were pretreated with aspirin (325 mg/d), dipiridamole (200 mg/d), and an oral calcium channel blocker. Intravenous heparin was titrated to prolong the activated clotting time (ACT) to >300 seconds. In addition, stent patients received a loading dose (300 mL) of dextran-40 before stent placement. Intracoronary nitroglycerin (200 μg) was given immediately before intervention.

Management of No Reflow

When reduction in flow was detected, initial therapy consisted of a repeat intracoronary dose (200 to 400 μg) of nitroglycerin. If flow reduction persisted and there was no angiographic evidence of proximal dissection, thrombus, spasm, or a discrete distal vessel cutoff, intracoronary verapamil was prepared as previously described. Briefly, a single vial of verapamil (5 mg) was diluted with saline to a total volume of 5 mL (1 mg/mL). One milliliter of this solution was further...
diluted to a total volume of 10 mL (100 μg/mL) and was administered in 100-μg doses through the guiding catheter or the central lumen of the dilating balloon after removal of the guide wire. A temporary pacing catheter was immediately available but was not introduced unless significant bradycardia developed.

**Angiographic Assessment**

Cineangiographic runs (all performed at 30 frames per second) were matched to detailed technical logs of each case, showing their timing relative to balloon inflations, drug administration, and other interventions. These cineangiograms then were evaluated by two angiographers to exclude other mechanical causes of flow reduction, as described above. The TIMI flow grade was determined for each treated vessel, using a modified scheme in which TIMI 2 flow was further resolved into TIMI 2 slow flow and TIMI 2 fast flow. Using a cine-projection equipped with a frame counter, the number of cineframes required from initiation of contrast injection to the opacification of a specified distal landmark (frames to opacification) was recorded. These measurements were performed at baseline, at the onset of flow reduction, and after the administration of intracoronary verapamil at all times when TIMI grade flow was above grade 1 and the distal landmarks could be reliably assessed.

**Statistical Analysis**

All data are expressed as mean±SD. Differences in TIMI flow grades before and after treatment or among groups were compared using the Wilcoxon signed ranks test and rank sum test, respectively. Differences in frames to opacification were assessed using unpaired and paired Student’s *t* tests. Comparisons between categorical variables were made using the χ² test.

**Results**

**Patient Characteristics**

The 39 of 1919 patients (2.0%) who exhibited no reflow after coronary intervention in general had similar clinical characteristics to the 16 patients who had reduced flow due to mechanical obstruction as well as to the remaining 1864 patients without flow reduction. Two groups of patients, however, appeared to be particularly susceptible to no reflow. Patients directly revascularized for acute myocardial infarction had a sevenfold higher incidence of no-reflow (11 of 95, 11.5%) compared with noninfarct patients (28 of 1824, 1.5%; *P*<.001). Similarly, patients undergoing treatment of saphenous vein grafts developed no reflow (10 of 249, 4.0%) at twice the rate seen for patients being treated for native vessel disease (29 of 1670, 1.7%; *P*=.03). There was also a trend for no reflow to be more common with stenting or directional atherectomy (14 of 471, 3.0%) compared with conventional balloon angioplasty (25 of 1448, 1.7%; *P*=.14).

In the no-reflow group, 11 of 39 (28.2%) were undergoing recanalization of an occluded vessel and 18 of 39 (46.1%) had angiographic evidence suggestive of intracoronary thrombus (haziness or a filling defect) at the start of the procedure. After intervention, all of these patients had good epicardial vessel results, with 90% showing a large and smooth lumen at the treatment site and 10% (four patients) showing only mild (nonobstructive) dissection. Despite these widely patent epicardial lumens, no reflow was associated with angina and ischemic ST-segment shifts in 78% of patients.

**Response to Pharmacological Treatment**

Of the 37 no-reflow patients treated with intracoronary verapamil, 68% had first received one or more doses of intracoronary nitroglycerin without apparent benefit. Intracoronary verapamil (234±142 μg; maximum, 600 μg) then increased TIMI flow grade in 33 of 37 no-reflow patients (89.2%) (Fig 1). Of 29 no-reflow patients with at least TIMI grade 2 slow flow both at the time of impaired flow and after verapamil (and thus suitable for measurement of frames to opacification), 24 had angiograms adequate for measurement of frames to opacification both before and after verapamil administration. In these 24 patients, verapamil therapy was associated with marked reduction in frames to opacification (from 91±56 to 38±21, *P*<.001; Fig 2). Reversal of no reflow was generally accompanied by resolution of angina and ischemic ST-segment changes. No patient developed systemic hypotension, and only one patient (2.7%) developed bradycardia requiring temporary pacing. The two no-reflow patients treated with nitroglycerin and additional balloon inflations (but not verap-
amil) also demonstrated partial improvement in TIMI flow grade and frames to opacification.

In contrast, among the 16 patients who received intracoronary verapamil as part of treatment for evident ongoing mechanical obstruction, a mean cumulative dose of 279±239 µg (maximum, 900 µg) caused an increase in TIMI flow grade in only 3 (18.8%) and reduced frames to opacification only modestly (from 107±42 to 101±69, \( P = .73 \)). Their response to verapamil thus differed from the group with no reflow both in terms of TIMI flow grade (\( P < .001 \)) and frames to opacification (\( P < .06 \)).

**Clinical Consequences**

Of the 28 no-reflow patients treated with verapamil in a setting other than direct intervention for acute myocardial infarction, 1 (3.6%) patient sustained a Q-wave myocardial infarction, whereas 8 (28.6%) sustained a larger non–Q-wave myocardial infarction with a CK-MB >50 IU/L (mean peak CK, 935±1014 IU/L). These incidences of Q-wave and larger non–Q-wave myocardial infarctions are thus nearly eightfold higher than the 4% incidence of such events seen in our broader stent and atherectomy population. Three patients (7.7%) with no reflow died in the hospital: two had developed large myocardial infarctions after treatment of diffusely diseased saphenous vein grafts and exhibited sustained no reflow despite verapamil therapy. The third was undergoing treatment for an acute myocardial infarction and succumbed to intracranial hemorrhage.

Patients who died had a poorer flow response to intracoronary verapamil, as reflected by more frames to opacification after treatment than patients who survived no reflow (91±30 versus 35±14, \( P < .001 \)).

**Discussion**

The term no reflow was coined to describe the persistence of reduced flow and regional myocardial dysfunction after the removal of an experimental epicardial coronary occlusion. This finding implicated ongoing structural or functional problems in the distal microcirculation. This phenomenon was subsequently observed clinically after recanalization of an infarct-related artery by either thrombolytic or balloon angioplasty. More recently, a similar situation has been described in yet another setting—catheter intervention of older saphenous vein grafts or native arteries in patients with unstable angina. Like patients with the classic no-reflow phenomenon, this newest class of patients exhibits substantial reduction in postprocedure coronary flow despite the absence of proximal epicardial obstruction (by clot, dissection, or spasm) or distal vessel cutoff suggestive of macroembolization.

Unlike epicardial spasm, no reflow during coronary intervention generally responds poorly to intracoronary nitroglycerin. This is consistent with the observations that the distal microcirculation responds poorly to nitroglycerin and that further small vessel vasoconstriction may occur in the setting of ischemia due to impaired local synthesis of endothelium-derived relaxing factor (EDRF). We thus wondered whether calcium antagonists, which act directly on the vascular smooth muscle rather than EDRF, might constitute a more effective treatment for no reflow during coronary intervention.

We have previously described the success of verapamil treatment of the no-reflow phenomenon in an initial series of five patients. Similar results have now been observed at other centers. As yet, however, there has been no comprehensive assessment of either the frequency of this phenomenon during coronary intervention or of its responsiveness to verapamil therapy.

**Incidence**

The current study shows that the no-reflow phenomenon is uncommon after catheter intervention, occurring in only 2.0% of nearly 2000 consecutive interventions. The incidence is much higher, however, in patients undergoing intervention for acute myocardial infarction (11.5%) or treatment of a saphenous vein graft (4.0%). The fact that both of these lesion types tend to contain platelet fibrin thrombus suggests that vasoconstrictive substances may be released when such lesions are disturbed, which could trigger distal microvascular spasm sufficiently intense to overcome local autoregulatory control.

**Outcome**

Although most patients with no reflow failed to respond to intracoronary nitroglycerin, 89.2% responded promptly to intracoronary verapamil at a mean dose of 243 µg. This response was reflected by an improvement in TIMI flow grade and by an improvement in the frames to opacification of a specified distal vascular landmark. Angina and ST-segment elevation present in 78% of the noninfarct patients with no reflow resolved promptly as normal flow returned. To the extent that these improvements were not seen in a small cohort of patients who received intracoronary verapamil as part of a pharmacological effort to manage evident epicardial obstruction, the beneficial response in patients with no reflow appears to be specific for that condition. Moreover, this beneficial response was achieved without producing systemic hypotension and minimal bradycardia requiring temporary pacing (2.7% of patients treated).

Even with verapamil therapy, the occurrence of no reflow during coronary intervention carried significant consequences. Nine (32.1%) of the 28 patients with no reflow who were not undergoing intervention as primary treatment for acute myocardial infarction sustained either Q-wave (3.6%) or non–Q-wave (28.6%) myocardial infarction after the procedure. Three of the four patients who showed a poor flow response to intracoronary verapamil went on to die in-hospital from extensive evolving myocardial infarction, contributing to the 7.7% overall mortality in patients with no reflow. Survival correlated with a more complete response to verapamil therapy, but it is not clear whether this reflects the putative mechanism (relief of ischemia as a result of microvascular spasm and avoiding consequent myocardial necrosis) or other associated factors.

**Proposed Pathophysiology**

The mechanism of classic no reflow in the animal laboratory has been derived from electron microscopic findings suggesting increased microvascular impedance to flow (neutrophil plugging of capillaries, myocyte contracture and edema, and endothelial blistering). It is not clear whether these same findings are associated with the no-reflow phenomenon observed in humans after thrombolytic or mechanical restoration of epicardial patency in the context of acute myocardial infarc-
tion or whether the no reflow that we have now observed in the setting of mechanical disturbance of plaques that tend to contain platelet fibrin thrombi (lesions in acute myocardial infarction, unstable angina, and diseased saphenous vein bypass grafts). It seems most plausible, however, that profound spasm of the distal microvasculature caused by the release of potent vasoconstrictors (eg, serotonin) from cellular elements (platelets) contained within the thrombus16-18 contributes to the development of no reflow in these settings. The observation that neither thrombolytic agents nor salicylates19,20 fully prevent no reflow in humans and in animal models would suggest that other triggers such as neutrophil infiltration may be operative or that microscopic platelet fibrin clots may persist despite such therapies.

The hypothesis of distal microvascular spasm as an underlying etiology is supported by the poor responsiveness of no reflow to nitroglycerin. In experimental studies, the microvasculature dilates minimally to nitrates.11-14 Distal vasodilation can be enhanced by administration of L-cysteine, suggesting that the distal vessels may lack a sufficient local sulfhydryl pool to convert nitroglycerin to its active nitrosothiol form. In contrast, calcium channel antagonists may avoid this problem by acting directly on vascular smooth muscle, and these agents have been found to limit infarct size, abort myocardial stunning, and alleviate the impairment of endothelium-dependent vasorelaxation caused by transient ischemia in the canine model.21-23 Their potent vasodilation of the microcirculation may contribute to these benefits and may explain the favorable response of no reflow to intracoronary verapamil seen in our study. Anecdotally, other calcium channel blockers (such as diltiazem) appear to be equally effective in reversing no reflow, although we have no direct experience with these agents at our center.

Study Limitations

There are several limitations to this retrospective study. While cases were assigned to the no-reflow or the mechanical obstruction groups based on the existing catheterization reports and confirmed by review of the catheterization films, the potential for bias in group assignment exists. Quantification of TIMI flow grades and frames to opacification was performed retrospectively, although two cardiologists reviewed the films to reduce potential bias in these measurements. TIMI flow grade is only a surrogate for direct measurement of coronary blood flow, and without such measurements and quantification of oxygen consumption, the influence of local autoregulation cannot be excluded. The fact that heart rate and blood pressure remained stable after verapamil, however, suggests that there were not major changes in oxygen consumption. Importantly, there was no randomization of treatment in this study between therapy with verapamil versus nitroglycerin. While the catheterization reports documented poor response to intracoronary nitroglycerin, cineangiography was not routinely performed after nitroglycerin and before verapamil, as would have been required for quantification of the change in flows with each treatment. The possibility that the effects of intracoronary nitroglycerin were delayed and thereby potentiated or simulated a response to verapamil administration cannot be excluded.

Even patients treated primarily with verapamil (without prior nitroglycerin), however, showed brisk response.

Conclusions

Marked impairment of coronary flow without evident epicardial obstruction or distal embolization—the no-reflow phenomenon—occurs in roughly 2% of coronary interventions, particularly those performed for acute myocardial infarction or in a saphenous vein bypass graft. Even after unsuccessful therapy with intracoronary nitroglycerin, nearly 90% of such patients respond promptly to intracoronary verapamil therapy with improvement in TIMI flow grade, reduction in cineframes to opacification of a distal vascular landmark, and relief of chest pain and ischemic ST-segment shifts. This suggests that the observed phenomenon may be due to distal microvascular spasm caused by the release of potent vasoconstrictors from lesion-associated thrombus. The no-reflow phenomenon and its presumptive treatment (intracoronary verapamil) should therefore be included in the differential diagnosis of impaired flow after coronary intervention, along with classic epicardial (dissection, thrombus, spasm) and macroembolic etiologies.

References


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Circulation. 1994;89:2514-2518
doi: 10.1161/01.CIR.89.6.2514

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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