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NO-REFLOW

Robert D. Safian, M.D.

- A. DEFINITION.** The no-reflow phenomenon was originally observed in experimental models of acute myocardial infarction (MI) and was described as a failure to restore normal myocardial blood flow despite removal of the coronary obstruction.^{1,2} Since that time, no-reflow has been shown to complicate thrombolytic therapy and percutaneous revascularization with PTCA and other devices.³⁻⁹ Defined angiographically, no-reflow manifests as an acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion. Lesser degrees of flow impairment (TIMI grade 2) are generally referred to as “slow-flow.” However, studies of acute MI patients have reported that scintigraphic evidence for no-reflow may occur in the *absence* of angiographic slow-flow, suggesting that microvascular injury may be angiographically inapparent in some patients.²³ Using the Doppler Flowwire, flow velocity patterns of no-reflow in patients with acute MI include systolic retrograde flow, diminished systolic antegrade flow, and rapid deceleration of diastolic flow.²⁴
- B. ETIOLOGY.** The mechanisms and mediators responsible for no-reflow remain speculative, but the end result appears to be severe microvascular dysfunction. Potential mechanisms of microvascular dysfunction include vasospasm, distal embolization of thrombus or other debris, oxygen free radical-mediated endothelial injury, capillary plugging by erythrocytes and neutrophils, and intracellular/interstitial edema with intramural hemorrhage.^{1,2,33}
- C. INCIDENCE.** The reported incidence of no-reflow or slow-flow after percutaneous intervention ranges from 0.6-42%, depending on the definition used and the clinical setting (Table 21.1).^{4,5,7,11,12,19,21,25,26,40} Among 2318 patients undergoing contemporary percutaneous intervention, TIMI-flow ≤ 2 was present in 5.8%.⁴⁰ No-reflow is more common after mechanical revascularization of thrombus-containing lesions (i.e., acute MI) and degenerated vein grafts containing friable debris. Among mechanical devices, no-reflow is highest after Rotablator atherectomy (1.2-9.0%) (Table 21.2), correlates with total burr activation time,¹³⁻¹⁵ and is reversible in $> 60\%$ of episodes; the frequent response to intracoronary calcium antagonists is strongly suggestive of microvascular spasm.⁷ Other risk factors for slow-flow after Rotablator include lesion length (odds ratio 33.3), recent unstable angina (odds ratio 15.8), and use of β -blockers within 24 hours (odds ratio 3.3).¹⁹ In contrast, no-reflow after TEC atherectomy is frequently irreversible,⁷ suggesting microembolization with vessel debris and capillary plugging. While the use of TEC correlated with persistent flow impairment,⁷ these results may have been biased by its use in situations known to be associated with no-reflow (degenerated vein grafts, salvage revascularization after failed thrombolytic therapy for acute MI).
- D. CLINICAL MANIFESTATIONS AND PROGNOSIS.** In the catheterization laboratory, no-reflow usually manifests as ECG changes and chest pain.⁷ However, depending on the myocardial territory,

Table 21.1. No-Reflow After Percutaneous Intervention: Incidence and Outcome

Series	Incidence	Definition	Clinical Setting	Comments
Wainstein ⁴¹ (2001)	135/4264 (3.1%)	-	All devices	No-reflow was associated with a 4-fold increase in MACE (18.1% vs. 4.6%, $p < 0.001$). Neither intracoronary sodium nitroprusside (SNP) nor verapamil improved outcome, despite angiographic improvement in blood flow with SNP
Leopold ⁴⁰ (2000)	134/2318 (5.8%)	TIMI ≤ 2	All devices	No-reflow was associated with more in-hospital death (1.5% vs. 0.14%), CK elevation (14.9% vs. 5.9%), and MACE (15.7% vs. 7.0%). Predictors of no-reflow included thrombus, emergency procedure, prior MI, and prior CABG
Diez ²⁵ (1998)	12/140 (8.6%)	TIMI ≤ 2	Rotablator	Nearly 4-fold reduction in the incidence of slow-flow after pretreatment with abciximab
Tsubokawa ²⁶ (1998)	13/99 (13%)	TIMI ≤ 2	Rotablator	Less slow-flow with IC infusion of nicorandil (2.7%) than verapamil (16.1%)
TOPIT ⁴² (1997)	11/134 (8.2%)	No-reflow	TEC for thrombus	Randomized trial. Incidence of no-reflow after PTCA (5%)
Sharma ¹⁹ (1997)	22/225 (10%)	TIMI ≤ 2	Rotablator	Predictors of slow-flow were lesion length, recent unstable angina, and use of β -blockers
Kaplan ²¹ (1996)	15/36 (42%)	TIMI ≤ 2	Vein grafts	No response to NTG; all responded to verapamil
Abbo ⁷ (1995)	66/10,767 (0.6%)	TIMI ≤ 1	All devices; patients with and without acute MI	Best response to verapamil (67%); worst response to urokinase (10%); high rate of adverse outcome (death 15%, MI 31%)
Wyrens ¹¹ (1995)	24/614 (4%)	TIMI ≤ 1	All devices	Excellent response to diltiazem (96%)
Safian ⁴³ (1994)	14/158 (8.8%)	No-reflow	TEC for SVG	
Piana ⁵ (1994)	39/1919 (2%)	TIMI ≤ 2	PTCA, DCA	Excellent response to verapamil (95%)
Shani ¹² (1992)	11/90 (12.2%)	"slow-flow"	PTCA for acute MI	All 6 patients treated with verapamil had improvement in flow
Wilson ⁴ (1989)	5/370 (1.3%)	"slow-flow"	PTCA; patients with and without acute MI	No response to NTG, papaverine, or lytics

Abbreviations: DCA = directional coronary atherectomy; MI = myocardial infarction; MACE = death, MI, stroke, or repeat revascularization; NTG = nitroglycerin; PTCA = percutaneous transluminal coronary angioplasty; SVG = saphenous vein graft; TEC = transluminal extraction catheter

baseline ventricular function, and the presence of other coronary artery disease, no-reflow may be clinically silent, or induce a spectrum of ischemic manifestations including conduction disturbances, hypotension, myocardial infarction, cardiogenic shock, and death.^{3,5,7} No-reflow was associated with a 10-fold higher incidence of death and myocardial infarction compared to patients without no-reflow (even after excluding patients with acute MI).^{7,40}

- E. PROPHYLAXIS.** Prophylaxis against no-reflow has not been systematically studied. Some Rotablator operators add a cocktail of nitroglycerin (4 mcg/ml) and either verapamil (10 mcg/ml), diltiazem, or adenosine to the heparinized (20 units/ml) Rotablator flush solution^{20,34} (Chapter 27). Pretreatment with calcium antagonists for high-risk lesions is currently under evaluation. Distal protection devices are currently under evaluation for preventing distal embolization and no-reflow, especially in vein grafts.^{27,35-37} In the recent multicenter randomized SAFER trial, distal protection with the GuardWire (PercuSurge) resulted in 50-60% reduction in in-hospital death and major ischemic events (Chapter 17).³⁹

Table 21.2. No-Reflow or Slow-Flow After Rotablator Atherectomy

Series	Type*	Incidence
Kini ⁴⁴ (1999)	Slow-flow	90/1000 (9%)
STRATAS ⁴⁵ (1998)	Slow-flow	12/104 (11.3%)
DART ⁴⁶ (1997)	Slow-flow	35/442 (8.0%)
Sharma ¹⁹ (1997)	Slow-flow	22/225 (10%)
Ellis ¹⁴ (1994)	Slow-flow	28/308 (9.1%)
Warth ¹⁵ (1994)	No-reflow	9/743 (1.2%)
Safian ¹³ (1993)	No-reflow	7/116 (6.1%)

DART = Dilatation vs. Ablation Revascularization Trial; STRATAS = Study To Determine Rotablator and Transluminal Angioplasty Strategy

* Slow-flow = TIMI-2 flow; no-reflow = TIMI flow \leq 1

F. MANAGEMENT (Figures 21.1, 21.2). The optimal treatment of no-reflow is unknown. Since it occurs in a variety of clinical settings and is likely to have more than one mechanism, it is unlikely that a single definitive treatment will be appropriate for all cases. It is important to remember that no-reflow is a diagnosis of exclusion: High-grade residual stenosis due to flow-limiting dissection, thrombus, and spasm should be systematically excluded since their treatment and outcome are generally more favorable than those of no-reflow. Pullback angiography and distal pressure gradient measurement may be useful to distinguish no-reflow (no angiographic lesion, no pressure gradient) from distal dissection or stenosis (distal lesion by angiography with pressure gradient).³¹ Although mild degrees of flow impairment may improve spontaneously, active therapy is always recommended for no-reflow, as summarized in Figure 21.1 and detailed here:

- 1. Reverse Superimposed Spasm.** Intracoronary nitroglycerin (200-800 mcg) rarely has any effect on no-reflow but may reverse superimposed spasm.^{4,7} Since its use is not associated with unnecessary delay or enhanced risk, it should be used in all cases.
- 2. Exclude Coronary Dissection.** Multiple angiographic views should be obtained to exclude a flow-limiting dissection. Even following “successful” PTCA, angiography often demonstrates intimal disruptions or frank dissections that are underestimated by angiography.^{10,16} Pullback angiography with or without pressure gradient measurements may also be useful.³¹ If contrast stains at the PTCA site, a flow-limiting dissection and/or thrombus is likely, and further treatment (PTCA or stent for dissection, thrombectomy for thrombus) should be performed. Caution should be used in stenting lesions with no-reflow since poor distal runoff may increase the likelihood of stent thrombosis.
- 3. Administer Intracoronary Calcium Antagonists.** The most important strategy in the treatment of no-reflow is the use of intracoronary calcium antagonists. Intracoronary administration of verapamil (100-200 mcg, total dose up to 1.0-1.5 mg) or diltiazem (0.5-2.5 mg bolus, total dose up to 5-10 mg) has been shown to reverse no-reflow in 65-95% of cases.^{5,7} In one report, resolution of no-reflow was 3-4 times more likely if verapamil was administered.⁷ These agents should be administered through the central lumen of the balloon or transfer catheter to facilitate drug delivery to the distal vascular bed;^{3,4,11} drug administered through the guiding catheter may not reach the distal vessel. Although high-degree AV block is unusual following intracoronary calcium antagonists, a temporary pacemaker should be readily available. Hypotension caused by no-reflow is not a contraindication to intracoronary calcium blockers—adjunctive therapy with pressors, inotropes, and IABP should be used as needed to support the systemic circulation while the calcium antagonist is administered. Despite the use of intracoronary calcium antagonists, ischemic complications remain higher than normal.⁴¹
- 4. Consider Platelet Glycoprotein IIb/IIIa Inhibitors (Chapter 34).** The use of potent platelet receptor antagonists for preventing or reversing no-reflow is controversial. While some studies suggest benefit, other studies in vein grafts do not.²⁹ In EPIC, abciximab was associated with less distal embolization in vein grafts, but no difference in final TIMI flow.³⁰

5. **Treat Distal Embolization.** If no-reflow persists despite these measures, especially following intervention on a thrombus-containing lesion, an intracoronary thrombolytic agent may be considered for presumed distal embolization (e.g., urokinase 100,000-500,000 units over 5-30 minutes or tPA 5-20 mg). However, in several clinical and experimental studies, urokinase alone was ineffective in reversing no-reflow, so its risks should be carefully weighed against its benefits.^{4,7,17,18}
6. **Clear Microvascular Plugging.** A rapid and moderately forceful injection of intracoronary saline or contrast may help clear microvascular plugging due to damaged endothelial cells, erythrocytes, neutrophils or thrombus.
7. **Increase Coronary Perfusion Pressure.** Although intra-aortic balloon counter pulsation (IABP) may augment coronary perfusion pressure, promote clearance of vasoactive substances, and limit infarct size, it has not been shown to reverse no-reflow. We recommend an IABP for patients with ongoing ischemia, hemodynamic compromise, or final TIMI flow < 3. For patients with hemodynamic collapse, percutaneous cardiopulmonary bypass may provide circulatory support during sustained periods of no-reflow.
8. **Coronary Artery Bypass Surgery.** Unfortunately, CABG is not beneficial for no-reflow, since the epicardial coronary artery is widely patent and the obstruction to coronary flow is at the capillary level.
9. **Triage to ICU.** Because of the adverse outcome associated with no-reflow, patients who do not respond immediately to treatment should be monitored in an intensive care unit. Serial cardiac enzymes should be measured and a noninvasive assessment of LV function should be obtained. If myocardial infarction ensues, routine post-MI care should be administered.
10. **Other Approaches.** Potent coronary vasodilators such as papaverine, sodium nitroprusside,⁴¹ and adenosine^{22,28,38} have been used in some cases of refractory no-reflow. Intracoronary adenosine (10-20 mcg) is theoretically attractive because it inhibits neutrophil function and decreases neutrophil-mediated free-radical formation and endothelial injury. We have had favorable experience with intracoronary sodium nitroprusside (10-50 mcg), particularly when no-reflow occurs in the setting of acute MI or vein graft intervention. Antioxidants such as superoxide dismutase and allopurinol (to decrease reperfusion injury) and mannitol (to reduce myocardial edema) have been studied in experimental MI, but their value for no-reflow is unknown.

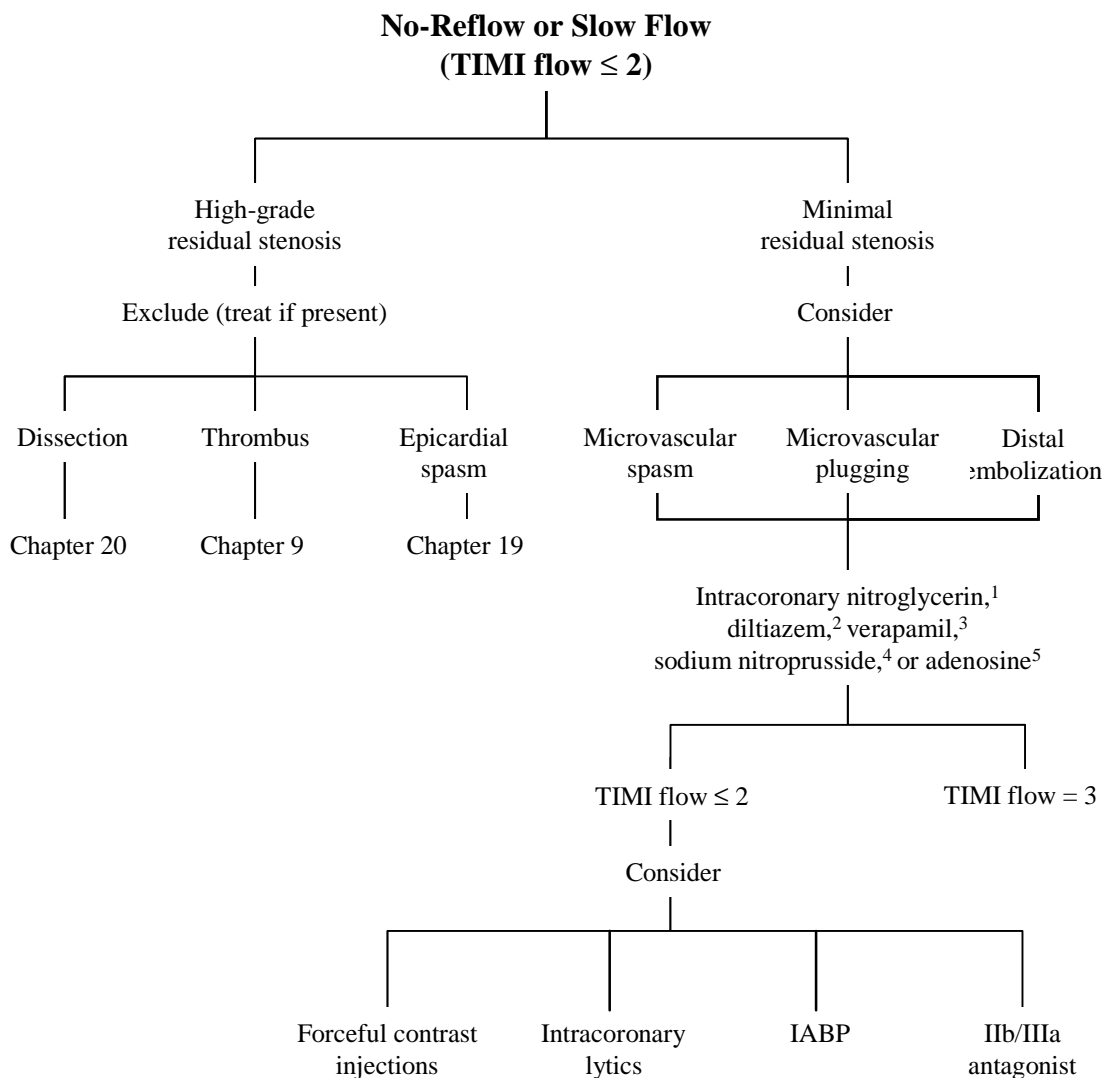


Figure 21.1. Management of Impaired Flow After Intervention

1. Nitroglycerin 200-800 mcg IC to reverse superimposed spasm; little effect on no-reflow
2. Diltiazem 0.5-2.5 mg IC over 1 min up to 5-10 mg as needed; temporary pacemaker on standby; limited clinical experience
3. Verapamil 100 mcg/min IC up to 1-1.5 mg; temporary pacemaker on standby
4. Sodium nitroprusside 10-50 mcg IC as needed
5. Adenosine 10-20 mcg IC as needed

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