

STATE-OF-THE-ART PAPER

Myocardial No-Reflow in Humans

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In a variable proportion of patients presenting with ST-segment elevation myocardial infarction, ranging from 5% to 50%, primary percutaneous coronary intervention achieves epicardial coronary artery reperfusion but not myocardial reperfusion, a condition known as no-reflow. Of note, no-reflow is associated with a worse prognosis at follow-up. The phenomenon has a multifactorial pathogenesis including: distal embolization, ischemia-reperfusion injury, and individual predisposition of coronary microcirculation to injury. Moreover, it is spontaneously reversible in some patients, thus suggesting that it might be amenable to treatment also when we fail to prevent it. Several recent studies have shown that biomarkers and other easily available clinical parameters can predict the risk of no-reflow and can help in the assessment of the multiple mechanisms of the phenomenon. Several therapeutic strategies have been tested for the prevention and treatment of no-reflow. In particular, thrombus aspiration before stent implantation prevents distal embolization and has been recently shown to improve myocardial perfusion and clinical outcome as compared with the standard procedure. However, it is conceivable that the relevance of each pathogenetic component of no-reflow is different in different patients, thus explaining the occurrence of no-reflow despite the use of mechanical thrombus aspiration. Thus, in this review article, for the first time, we propose a personalized management of no-reflow on the basis of the assessment of the prevailing mechanisms of no-reflow operating in each patient. (J Am Coll Cardiol 2009;54:281-92) © 2009 by the American College of Cardiology Foundation

Definition and Clinical Relevance of No-Reflow

Prompt referral for mechanical reperfusion by urgent primary percutaneous coronary intervention (PPCI) represents the pivotal step in the current management of ST-segment elevation myocardial infarction (STEMI) (1). Yet, in a sizable proportion of patients PPCI achieves epicardial coronary artery reperfusion but not myocardial reperfusion, a condition known as no-reflow (2). In particular, the term “no-reflow” has been increasingly used in published medical reports to describe microvascular obstruction and reduced myocardial flow after opening an occluded artery.

The existence of no-reflow phenomenon was initially debated; however, a large amount of experimental and clinical data have clearly shown that it occurs after reperfusion with a variable prevalence, ranging from 5% up to 50%, according to the methods used to assess the phenomenon and to the population under study (2,3).

In 1993, at the climax of the thrombolytic era, Lincoff and Topol (4) wrote a provocative editorial wondering whether reperfusion was just an illusion. At that time, they estimated that only “25% or less” of patients treated by thrombolysis had an optimal reperfusion, defined as a rapid,

complete, and sustained coronary recanalization with adequate myocardial tissue perfusion. What is this figure after 15 years at the climax of the PPCI era? As shown in Figure 1, a reasonable estimate of the proportion of patients who get optimal myocardial reperfusion, among those without cardiogenic shock undergoing PPCI, is approximately 35%.

A series of consistent data has clearly shown that no-reflow has a strong negative impact on outcome, negating the potential benefit of PPCI (5-11). Indeed, patients with no-reflow exhibit a higher prevalence of: 1) early post-infarction complications (arrhythmias, pericardial effusion, cardiac tamponade, early congestive heart failure); 2) left adverse ventricular remodeling; 3) late repeat hospital stays for heart failure; and 4) mortality (Fig. 2).

Therefore, detection, prevention, and treatment of no-reflow are likely to have an important impact on the outcome of PPCI. Here we propose possible personalized forms of prevention and treatment, on the basis of the notion that no-reflow is a dynamic process characterized by multiple pathogenetic components.

Time-Course and Pathogenetic Components of No-Reflow

Kloner et al. (12) described no-reflow for the first time in a canine model, demonstrating that it occurs after prolonged (90 min) coronary occlusion followed by reperfusion. The

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**Abbreviations
and Acronyms**

- ATP** = adenosine triphosphate
- CMR** = cardiac magnetic resonance
- ECG** = electrocardiogram/electrocardiographic
- ET** = endothelin
- IR** = ischemia-reperfusion
- IRA** = infarct-related artery
- LV** = left ventricle
- MBG** = myocardial blush grade
- MCE** = myocardial contrast echocardiography
- m-PTP** = mitochondrial permeability transition pore
- PPCI** = primary percutaneous coronary intervention
- STEMI** = ST-segment elevation myocardial infarction
- STR** = ST-segment elevation resolution
- TIMI** = Thrombolysis In Myocardial Infarction
- TxA2** = thromboxane-A2

consequences of coronary ligation of a nonatherosclerotic coronary artery, however, cannot be directly extrapolated to the human situation where myocardial infarction is caused by occlusive coronary thrombosis superimposed onto an atherosclerotic unstable plaque (13).

Galiuto et al. (14), with sequential measurements of myocardial perfusion by myocardial contrast echocardiography (MCE), have recently shown that in humans no-reflow detected 24 h after successful PCI spontaneously improves over time in approximately 50% of patients. Thus, no-reflow can be categorized as sustained and reversible. Sustained no-reflow is probably the result of anatomical irreversible changes of coronary microcirculation, whereas reversible no-reflow is the result of functional and, thus reversible, changes of microcirculation. Interestingly, whereas patients with sustained no-reflow undergo unfavorable left ventricle (LV) remodeling, patients with reversible

no-reflow maintain their LV volumes unchanged over time (14). Similar findings were shown by Hoffman et al. (15) by analyzing changes of myocardial blush grade (MBG) over time. In this study also the evolution of MBG was a potent predictor of LV remodeling.

Taken together these studies demonstrate that no-reflow, at least in some patients, is reversible, thus opening a new scenario on the search for no-reflow reversal.

In humans, no-reflow is caused by the variable combination of 4 pathogenetic components: 1) distal atherothrombotic embolization; 2) ischemic injury; 3) reperfusion injury; and 4) susceptibility of coronary microcirculation to injury (Fig. 3). As a consequence, appropriate strategies to prevent or treat each of these components are expected to reduce the prevalence of sustained no-reflow.

Distal embolization. Emboli of different sizes can originate from epicardial coronary thrombus and from fissured atherosclerotic plaques, in particular during PPCI (16). Experimental observations have shown that myocardial blood flow decreases irreversibly when microspheres obstruct more than 50% of coronary capillaries (17). Okamura et al. (18) used a Doppler guidewire in humans to detect high-intensity transient signals, which allowed the counting of the number of embolic particles. The average number of emboli throughout PPCI was 25. Thus, this small number of emboli is unlikely to affect coronary blood flow. Yet, large

emboli (>200- μ m diameter) can obstruct pre-arterioles, causing infarctlets.

Ischemia-related injury. Changes in endothelial cells, visible after prolonged ischemia, are represented by endothelial protrusions and membrane-bound bodies, which often fill the capillaries up to luminal obliteration. Furthermore, large endothelial gaps with extra vascular erythrocytes are common (19). Morphological findings are accompanied by a reduction of regional myocardial blood flow within the previously ischemic region (20). Moreover, myocardial cell swelling associated with interstitial edema might cause microvascular compression (21).

Reperfusion-related injury. A massive infiltration of coronary microcirculation by neutrophils and platelets occurs at the time of reperfusion (19,22). Indeed, reintroduction of neutrophils in post-ischemic myocardium results in their activation, with subsequent adhesion to the endothelial surface and migration in the surrounding tissue. Activated neutrophils, in turn, release oxygen free radicals, proteolytic enzymes, and pro-inflammatory mediators that can directly cause tissue and endothelial damage. Neutrophils also form aggregates with platelets that plug capillaries, thus mechanically blocking flow (23,24). Finally, vasoconstrictors released by damaged endothelial cells, neutrophils, and platelets contribute to sustained vasoconstriction of coronary microcirculation (25).

From a molecular point of view inflammatory mediators are involved in a complex interaction between platelets, neutrophils, and endothelium. In particular, tumor necrosis factor- α expression is induced by reperfusion, and it can impair endothelium-dependent coronary flow reserve (26). Furthermore, interleukin-1 β has recently been associated with ischemia-reperfusion (IR) injury, because interleukin-1 β knockout animals exhibit marked reduction of ischemic induced inflammation (27). Selectin expression on cell surfaces is also important for mechanical plugging of the microcirculation (28). Finally, the balance between nitric oxide and superoxide is tipped in favor of superoxide within minutes of reperfusion of ischemic tissues, due to increased production of xantine oxidase by neutrophils, endothelial cells, and cardiac myocytes, which leads to an exacerbation of the inflammatory state (29).

Reperfusion might also cause irreversible injury to myocytes (30). During ischemia there is an increase of intracellular content of sodium (Na⁺) due to accumulation of hydrogen (H⁺) that are exchanged by the Na⁺/H⁺ exchanger. The subsequent exchange of doubly charged positive calcium ion (Ca⁺⁺) with Na⁺ by sarcolemmal Na⁺/Ca⁺⁺ exchanger produces a calcium overload that triggers uncontrolled hypercontraction and stimulates opening of the mitochondrial permeability transition pore (m-PTP), which further enhances calcium overload. Furthermore, Na⁺ extrusion through Na⁺/potassium (K⁺) adenosine triphosphate (ATP)-ase is impaired and together with Ca⁺⁺ accumulation leads to myocyte cell swelling, which contributes to subsequent

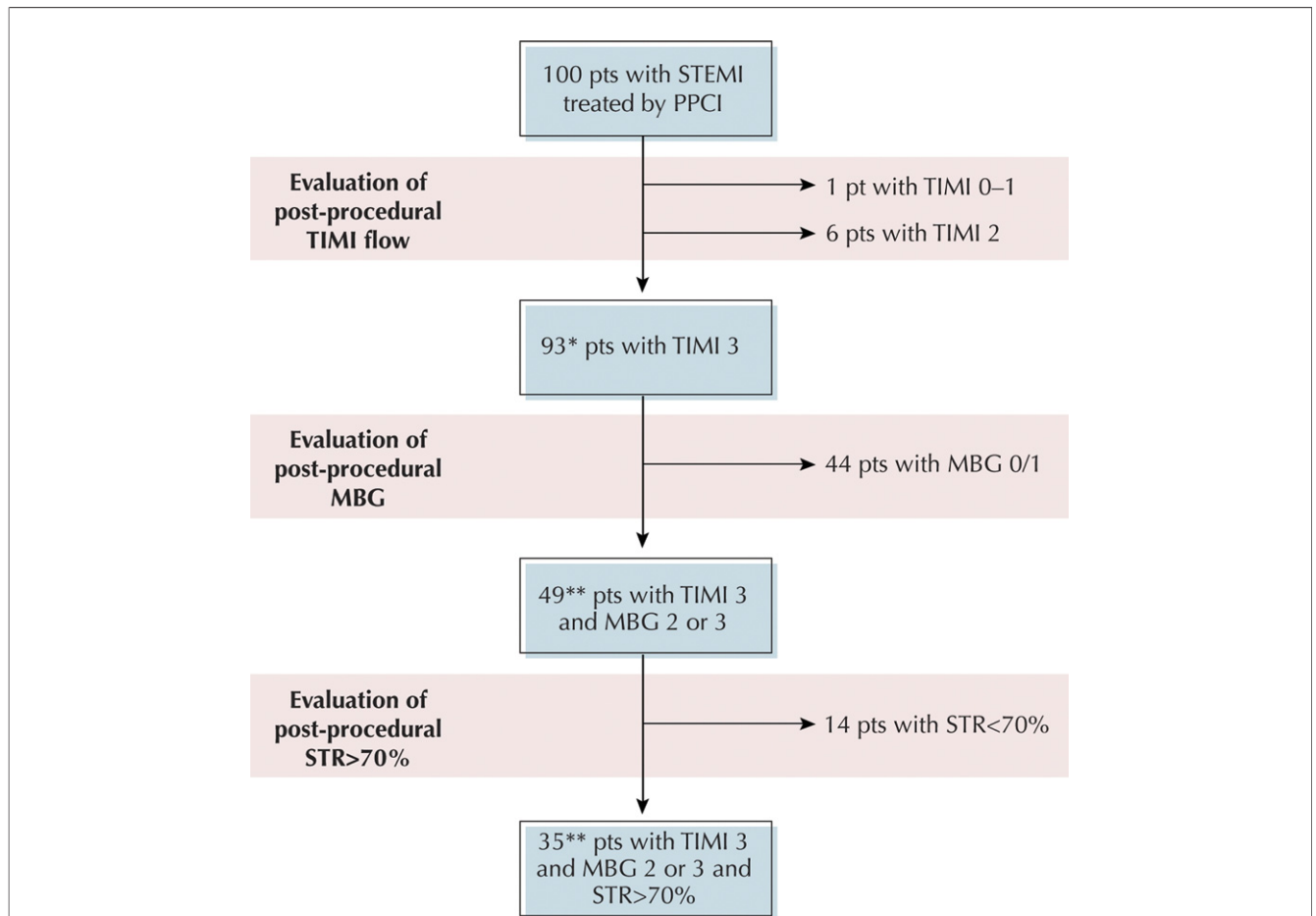


Figure 1 Prevalence of Myocardial No-Reflow

Estimate of the number of patients (pts) receiving optimal reperfusion according to Thrombolysis In Myocardial Infarction (TIMI) flow grade, myocardial blush grade (MBG), and ST-segment resolution (STR) of 100 patients without cardiogenic shock treated by primary percutaneous coronary intervention (PPCI). *Estimation derived from 20 randomized trials comparing standard percutaneous coronary intervention with thrombectomy or distal protection (75). **Estimation derived from core laboratory analysis of the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial (8). STEMI = ST-segment elevation myocardial infarction.

rupture of the cell membrane when the extracellular osmolality is rapidly normalized by reperfusion. Of note, cyclosporine, which blocks the m-PTP, has been recently shown to reduce infarct size by 20% when administered intravenously in patients undergoing PPCI (31). Finally, ischemic pre-conditioning might also reduce infarct size by blockade of m-PTP (32).

Natriuretic peptides might modulate IR injury. Atrial natriuretic peptide might suppress the renin-angiotensin-aldosterone system and endothelin (ET)-1 that increase infarct size, microvascular obstruction, and cardiac remodeling (33). Accordingly, Hayashi *et al.* (34) showed that infusion of atrial natriuretic peptide in patients with their first anterior myocardial infarction is associated with lower concentration of ET-1, angiotensin-II, and aldosterone. Of note, B-type natriuretic peptide limits infarct size when administered before and during coronary occlusion through a KATP channel-dependent mechanism, which requires nitric oxide synthase activity (35).

Individual predisposition of coronary microcirculation to injury. In humans, no-reflow associated with ST-segment elevation is occasionally observed during elective procedures (36), whereas it can be absent after PPCI carried out several hours after coronary occlusion. Predisposition might be genetic and/or acquired. In particular, diabetes has been associated with impaired microvascular reperfusion after PPCI, and hypercholesterolemia in the animal model aggravates reperfusion injury by enhancing endothelial oxidative stress (37,38). Finally, pre-conditioning seems to have a beneficial effect on microvascular function (39).

Predictors of the Pathogenetic Components of No-Reflow

Predictors of distal embolization. Some angiographic findings predict the risk of distal embolization possibly favoring no-reflow (Table 1). Yip *et al.* (40) proposed a score to assess thrombus burden on the basis of the

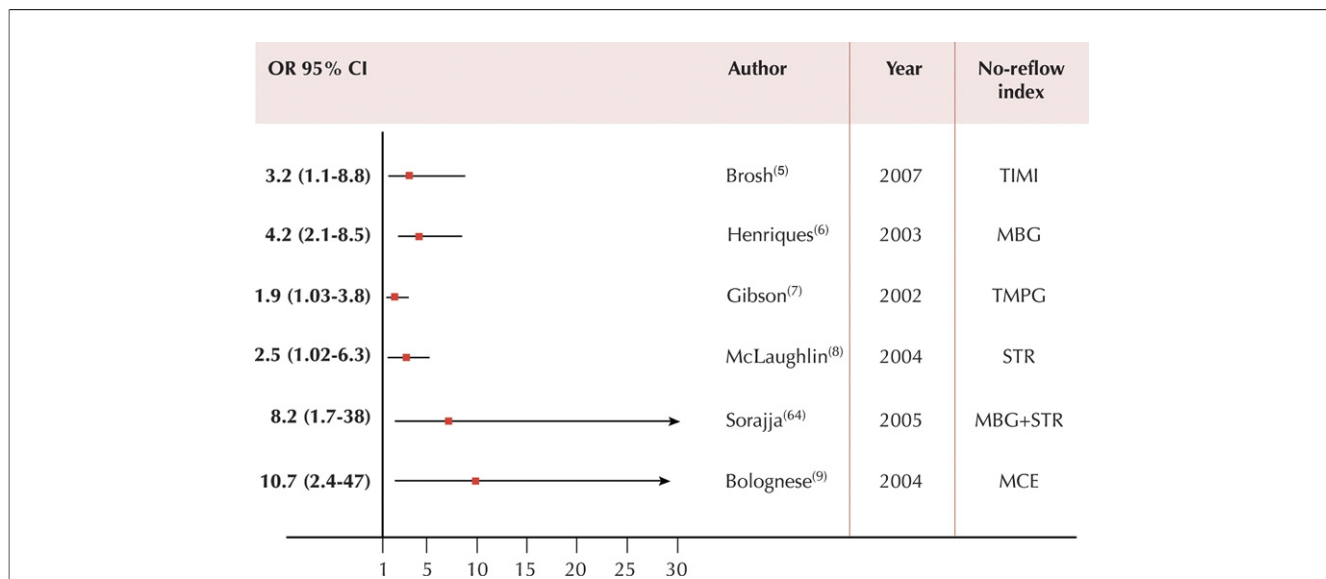


Figure 2 Prognostic Value of No-Reflow According to Angiographic, Electrocardiographic, and Echocontrastographic Indexes

The end point was cardiac death (9) or total mortality (4,6-8,64). Data are presented as odds ratio (OR) and 95% confidence interval (CI). MCE = myocardial contrast echocardiography; TMPG = TIMI myocardial perfusion grade; other abbreviations as in Figure 1.

following features: 1) an angiographic thrombus with the greatest linear dimension more than 3 times the reference lumen diameter; 2) cutoff pattern (lesion morphology with an abrupt cutoff without taper before the occlusion); 3) presence of accumulated thrombus (>5 mm of linear dimension) proximal to the occlusion; 4) presence of float-

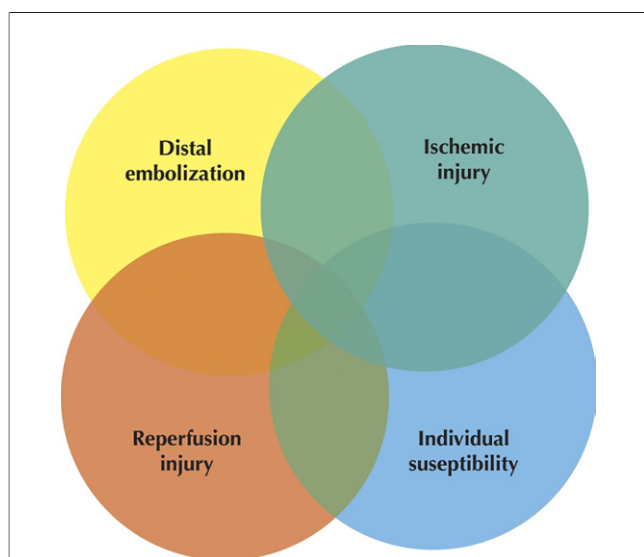


Figure 3 Mechanisms Responsible for No-Reflow

Four interacting mechanisms (distal embolization, ischemia-related injury, reperfusion related injury, and individual susceptibility to microvascular injury) are responsible for no-reflow phenomenon. The individual contribution of these mechanisms to the pathogenesis of no-reflow is likely to vary in different patients.

ing thrombus proximal to the occlusion; 5) persistent contrast medium distal to the obstruction; and 6) reference lumen diameter of the infarct-related artery (IRA) >4.0 mm. All of these features were independent predictors of no-reflow in 800 patients undergoing PPCI. The relevance of high thrombus burden at the site of the culprit artery in predicting distal embolization has also been shown by Limbruno et al. (41). Indeed, in a series of patients with STEMI undergoing PPCI with distal filter protection, they found that Yip's score was an independent predictor of total debris volume captured in the filter's basket. Of note, distal embolization of thrombotic debris typically occurs after stent placement in large coronary vessels, whereas in small vessels it is possible that the stent itself might fix the thrombus to the vessel wall, especially if the thrombus is not fresh anymore, as also suggested by the analysis of Yip et al. (40).

Predictors of ischemia-related injury. A longer time to reperfusion is associated with a higher prevalence of no-reflow and with a larger no-reflow region (42) (Table 2). Interestingly, Turschner et al. (43) showed that prolonged ischemia followed by reperfusion is associated with increased thickness of the myocardium due to tissue edema, which eventually leads to no-reflow for mechanical reasons.

The extent of the ischemic region is another important determinant of no-reflow, as demonstrated in animal models (Table 2). This is confirmed in man by the association of electrocardiographic (ECG) and echocardiographic indexes of the extent of ischemic region, such as QRS score and wall motion score index, respectively, and prevalence of no-reflow (44,45). The higher prevalence of no-reflow when the left anterior descending is the IRA artery as compared

Table 1 Predictors of Pathogenetic Components of No-Reflow and Therapeutic Implications

Pathogenetic Mechanism of No-Reflow	Predictor	Therapeutic Implications
Distal embolization	Thrombus burden (40)	Thrombus aspiration
Ischemia	Ischemia duration (42,43)	Reduction of coronary time
	Ischemia extent (44,45)	Reduction of oxygen consumption
Reperfusion	Neutrophil count (46)	Specific antineutrophil drugs
	ET-1 levels (51)	ET-1r antagonists
	TXA2 levels (49)	TXA2r antagonists
	Mean platelet volume or reactivity (47,48)	Antiplatelet drugs
Individual susceptibility	Diabetes (37)	Correction of hyperglycemia
	Acute hyperglycemia (57)	Correction of hyperglycemia
	Hypercholesterolemia (38)	Statin therapy
	Lack of pre-conditioning (58)	Nicorandil

ET = endothelin; TXA2 = thromboxane A2.

with other epicardial coronary arteries confirms that a larger extent of the ischemic area is an important predictor of no-reflow (45).

Predictors of reperfusion-related injury. An easily available clinical predictor of no-reflow is neutrophil count, which has been recently associated with microvascular injury after PPCI (46) (Table 2). Platelets also play an important role in no-reflow. Accordingly, platelet reactivity on admission, as assessed by the Platelet Function Analyzer-100 (Dade Behring, Milan, Italy), is associated with the prevalence of no-reflow and adverse remodeling (47). Furthermore, Huczek et al. (48) demonstrated that mean platelet volume on admission is an important predictor of impaired reperfusion. Interestingly, early data from our group indicate that plasma levels of thromboxane-A2 (TxA2) predict no-reflow (49) (Table 2).

Natural antioxidant levels might protect from no-reflow as suggested by Matsumoto et al. (50), who demonstrated that levels of vitamin C, vitamin E, and glutathione peroxidase obtained from coronary sinus before PPCI were significantly lower in patients exhibiting no-reflow than in patients exhibiting myocardial reperfusion.

ET-1 plays a key role in no-reflow, depending on its strong vasoconstrictive effect exerted on small-resistance

coronary arteries, on the enhancement of neutrophil adhesion to the endothelium, and on the induction of elastase release, which might also mediate tissue injury and edema (51). Of note, we recently demonstrated that ET-1 levels on admission are an independent predictor of no-reflow (51) (Table 2). ET-1 is a possible therapeutic target, and this notion is supported by the beneficial effect of selective ET-1 antagonist in animal models of IR (52).

Thus, the severity of reperfusion injury might be assessed with clinical predictors such as neutrophil count, mean platelet volume, platelet reactivity, TxA2, and ET-1 levels. **Predictors of individual susceptibility to microvascular injury.** Genetic and acquired susceptibility to microvascular injury might play an important role in the modulation of no-reflow (Table 2).

Interestingly, a recent study suggested that the 1976T>C polymorphism of the adenosine 2A receptors gene is associated with a higher prevalence of no-reflow (53). Furthermore, patients with no-reflow show a more compact fibrin network, possibly suggesting a genetic mediated resistance to lysis (54).

Baseline reactivity of inflammatory cells also might modulate the severity of no-reflow. Yet, we failed to find a

Table 2 Main Randomized Trials for the Management of No-Reflow

Treatment (Ref. #)	No. of Patients	Dose	Administration Timing	Primary End Point	Event Rate		
					Treatment	Control	NNT
Thrombectomy (77)	1,071	—	During PCI	MBG 0-1	17.1	26.3	10.7
Adenosine IV (89)	2,118	50 or 70 µg/kg/min	Pre-post PCI	Clinical*	16.3	17.9	59.0
Adenosine IC (86)	54	4 mg	Pre-PCI	TIMI flow grade <3	0.0	30.0	3.4
Adenosine IC (87)	51	60 mg	Post-PCI	STR	67.0	91.0	4.1
Nitroprusside IC (90)	98	60 µg	During PCI	STR	48.3	48.8	1,200
Nicorandil IV (94)	81	4 mg bolus + 6 mg/infusion + oral nicorandil	Pre-post PCI	MCE	15.0	33.0	5.2
Nicorandil IC + IV (95)	92	0.5 mg IC + 4 mg IV bolus and continuous infusion of 6 mg/h	Pre-post PCI	Clinical†	9.6	33.3	4.2
Abciximab IV (84)	2,082	0.25 mg/kg + 12 h infusion	Pre-during-post PCI	Clinical‡	10.2	20.0	10.0
Abciximab IV (83)	90	0.25 mg/kg + 12 h infusion	Pre-during-post PCI	LV remodeling	7.0	30.0	4.3

*Occurrence of in-hospital heart failure, repeat hospital stay for heart failure, or 6-month death. †Composite incidence of reperfusion arrhythmias, chest pain, no-reflow/slow flow. ‡Death, recurrent acute myocardial infarction, target vessel revascularization, major stroke.

IC = intracoronary; IV = intravenous; LV = left ventricular; MBG = myocardial blush grade; MCE = myocardial contrast echocardiography; NNT = number needed to treat; PCI = percutaneous coronary intervention; STR = ST-segment elevation resolution; TIMI = Thrombolysis In Myocardial Infarction.

correlation between C-reactive protein serum levels measured within 6 h of chest pain onset and the prevalence of no-reflow (55). In contrast, peak C-reactive protein reflecting necrosis extent has been associated with no-reflow (56).

Acquired risk factors such as diabetes and hypercholesterolemia might predispose to no-reflow, as suggested by observation carried out in humans and in animal models (37,38).

Recent studies have demonstrated an association between acute hyperglycemia and no-reflow, which was independent of previous glycemic control evaluated by glycosylated hemoglobin A1c levels and might suggest a direct detrimental effect of acute hyperglycemia on reperfusion injury (57). Finally, pre-infarction angina might have a protective effect, because it induces ischemic pre-conditioning (58), which, in contrast, is abolished by binge drinking (59).

Diagnosis

Coronary angiography. No-reflow can be assessed during PPCI with Thrombolysis In Myocardial Infarction (TIMI) flow grade and MBG in the coronary care unit by assessing the ST-segment elevation resolution (STR) after PPCI and can be better quantified by noninvasive imaging techniques, such as MCE and contrast-enhanced cardiac magnetic resonance (CMR) (Fig. 4).

No-reflow can initially be demonstrated by analysis of TIMI flow grade (60). Indeed, TIMI flow grade 0 to 2, observed in 5% to 10% of patients, is predictably associated with no-reflow. The latter, however, also occurs in a sizeable proportion of patients with apparent successful large epicardial vessel reopening resulting in TIMI flow grade 3. Thus, the sensitivity of TIMI flow assessment in the detection of no-reflow is rather low. At the time of PPCI, no-reflow can be inferred more efficiently by assessing MBG, which describes the relative “blush” or intensity of the radiopacity of myocardial tissue achieved with an epicardial coronary injection of contrast medium and the rapidity that this enhancement clears with. The more intense the myocardial blush and the faster its clearance, the better the microvascular perfusion. The MBG is scored on a scale of 0 to 3, with higher scores indicating better perfusion. An MBG 0 to 1, suggestive of no-reflow, is observed in as high as 50% of patients with TIMI flow grade 3 (61). Taken together, angiographic no-reflow can be defined as a TIMI flow grade <3 or 3 with an MBG 0 to 1.

ECG. Largely used in the clinical arena and in trials is the measurement of STR 1 h after PPCI. Different methods have been proposed to measure STR. Lack of STR <50% or 70% is considered as an established marker of no-reflow, because its predictive value was demonstrated at the start of the pharmacological reperfusion era and has been confirmed in the contemporary mechanical reperfusion era (62). Notably, approximately one-third of patients with TIMI flow grade 3 and MBG 2 to 3 do not exhibit STR (63).

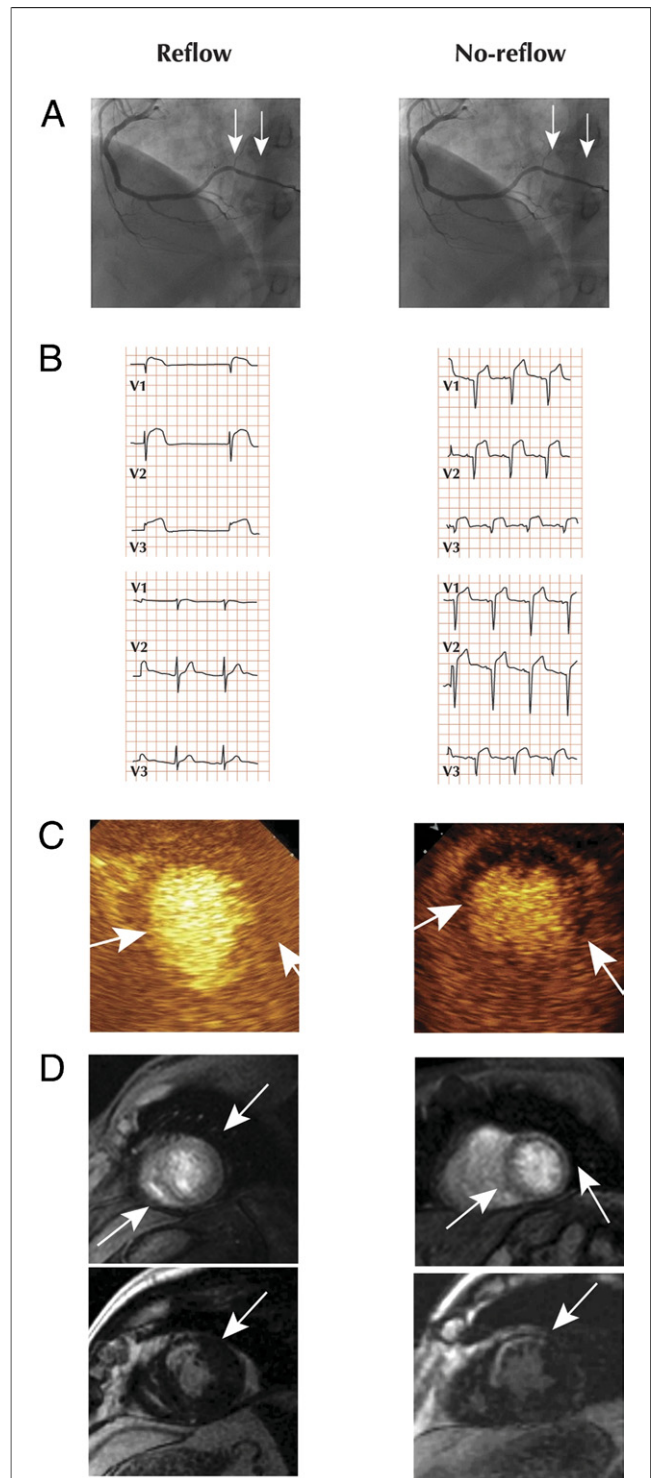


Figure 4 No-Reflow as Assessed by Angiography (MBG), ECG, and Imaging Techniques

(A) Right: MBG 0 (white arrows); left: MBG 3 (white arrows). (B) Right: lack of STR; left: complete STR. (C) Right: no-reflow assessed by MCE (white arrows); left: reflow assessed by MCE (white arrows). (D) Right: no-reflow assessed by magnetic resonance imaging with first-pass of gadolinium (top) or the delayed enhancement (bottom) (white arrows); left: reflow assessed by magnetic resonance imaging with first-pass of gadolinium (top) or the delayed enhancement (bottom) (white arrows). Abbreviations as in Figures 1 and 2.

Because TIMI flow grade, MBG, and STR might be obtained from the routine management of STEMI patients, are inexpensive, and provide additional prognostic information, their assessment should become current clinical practice. Notably, the integration of MBG and STR has been shown to improve patient risk stratification. Indeed, 2 independent studies, in patients treated by either PPCI (64) or pharmacological reperfusion (63), have reported very good outcomes in patients with an MBG 2 to 3 and STR >70%, very poor outcomes in patients with MBG 0 to 1 and STR <70%, and an intermediate prognosis in patients with discordant results of angiographic and ECG indexes of no-reflow.

Noninvasive imaging techniques. Although easily available in the clinical arena, neither blush grade nor ECG resolution provide a direct assessment of myocardial perfusion. In contrast, noninvasive imaging techniques such as MCE and CMR provide a more direct assessment of myocardial perfusion.

Myocardial contrast echocardiography uses ultrasound to visualize contrast microbubbles that freely flow within patent microcirculation. Such microbubbles are injected in the peripheral circulation, safely pass the pulmonary circulation, and reach intact coronary bed. They have a rheology similar to that of red blood cells and thus freely flow within coronary microvessels, as the only 1 pure intravascular tracer. Lack of intramyocardial contrast opacification is due to microvascular obstruction; thus, it represents the extent of no-reflow (65,66). In the AMICI study, the extent of no-reflow at MCE was demonstrated to be the best predictor of adverse LV remodeling after acute myocardial infarction, being superior to STR and to MBG among patients exhibiting TIMI flow grade 3 (10).

Cardiac magnetic resonance imaging uses gadolinium to assess regional cardiac perfusion. No-reflow can be diagnosed as: 1) lack of gadolinium enhancement during first pass; and 2) lack of gadolinium enhancement within a necrotic region, identified by late gadolinium hyper-enhancement (67). In particular, very good correlation has been found between gadolinium enhancement during first pass and MBG, thus suggesting that these 2 parameters might reflect the microvascular integrity within the infarct zone (68). Studies performed by CMR have confirmed that no-reflow is a powerful predictor of LV remodeling and of patient survival (11).

Prevention and Treatment of No-Reflow According to Timing and Pathogenetic Components

Several therapeutic strategies have been tested for the prevention and treatment of no-reflow with inconsistent results, possibly because they have been applied indiscriminantly to all patients. It is conceivable that the relevance of each pathogenetic component of no-reflow is different in different patients. Therefore, the assessment of the multiple mechanisms of no-reflow might guide the development of personalized forms of treatment (Table 2). Thus, it is

possible to envision a personalized treatment of no-reflow that stems from the assessment of the predictors of the 4 pathogenetic components of the phenomenon. The treatment should then aim at counteracting the prevailing mechanism(s) of no-reflow (Fig. 5).

Management of distal embolization. Although the detrimental effects of distal embolization during PCI are well-recognized, thus prompting its prevention during reperfusion, no specific technique is currently recommended in guidelines to prevent distal embolization during PPCI. Direct stent implantation, by avoiding balloon-induced thrombus fragmentation and by entrapping the atherothrombus under the stent struts, has been suggested as a possible technique to reduce distal embolization. One trial (69) showed improved reperfusion in selected patients randomized to direct stenting as compared with standard PPCI. However, only a specific subset of patients (those with good distal visualization of the IRA after guidewire passage through the culprit lesion) is suitable for direct stenting.

A more promising technical approach to prevent no-reflow during mechanical reperfusion is the use of thrombectomy devices and of distal filters. Yet, skepticism arose after publication of 2 large trials showing that rheolytic thrombectomy (70) and distal occlusive protection (71) do not improve reperfusion, as compared with standard PPCI. The negative results of these trials, however, should be interpreted within the limitations of their design, which was characterized by the enrollment of patients at low risk of no-reflow and by the use of first-generation, complex devices. Another study conducted by skilled operators with another complex thrombectomy device (the X-sizer) in high-risk patients did show improvement of myocardial reperfusion (72). These inconsistencies prompted us to design the REMEDIA (Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus-Aspiration in Primary and Rescue Angioplasty) trial, which was the first randomized trial to assess the role of thrombectomy performed with a simple manual aspiration catheter, as compared with conventional PPCI (73). The results of the REMEDIA trial were promising, because manual thrombectomy was safe and resulted in better myocardial perfusion indexes as compared with standard PPCI. The benefit was particularly evident in the subset of patients with higher thrombus burden and with total IRA occlusion, thus suggesting that the efficacy of thrombectomy might be dependent on individual patient characteristics (73). In the MCE substudy of the same trial thrombus-aspiration significantly reduced no-reflow (74). A recent meta-analysis showed that thrombectomy was associated with a significant improvement of reperfusion as assessed by STR and MBG, whereas distal protection was not (75). Finally, a very recent, large trial by Svilaas *et al.* (76) confirmed the improvement of reperfusion associated with manual thrombus-aspiration as compared with standard PPCI. This landmark study has been the first to show that

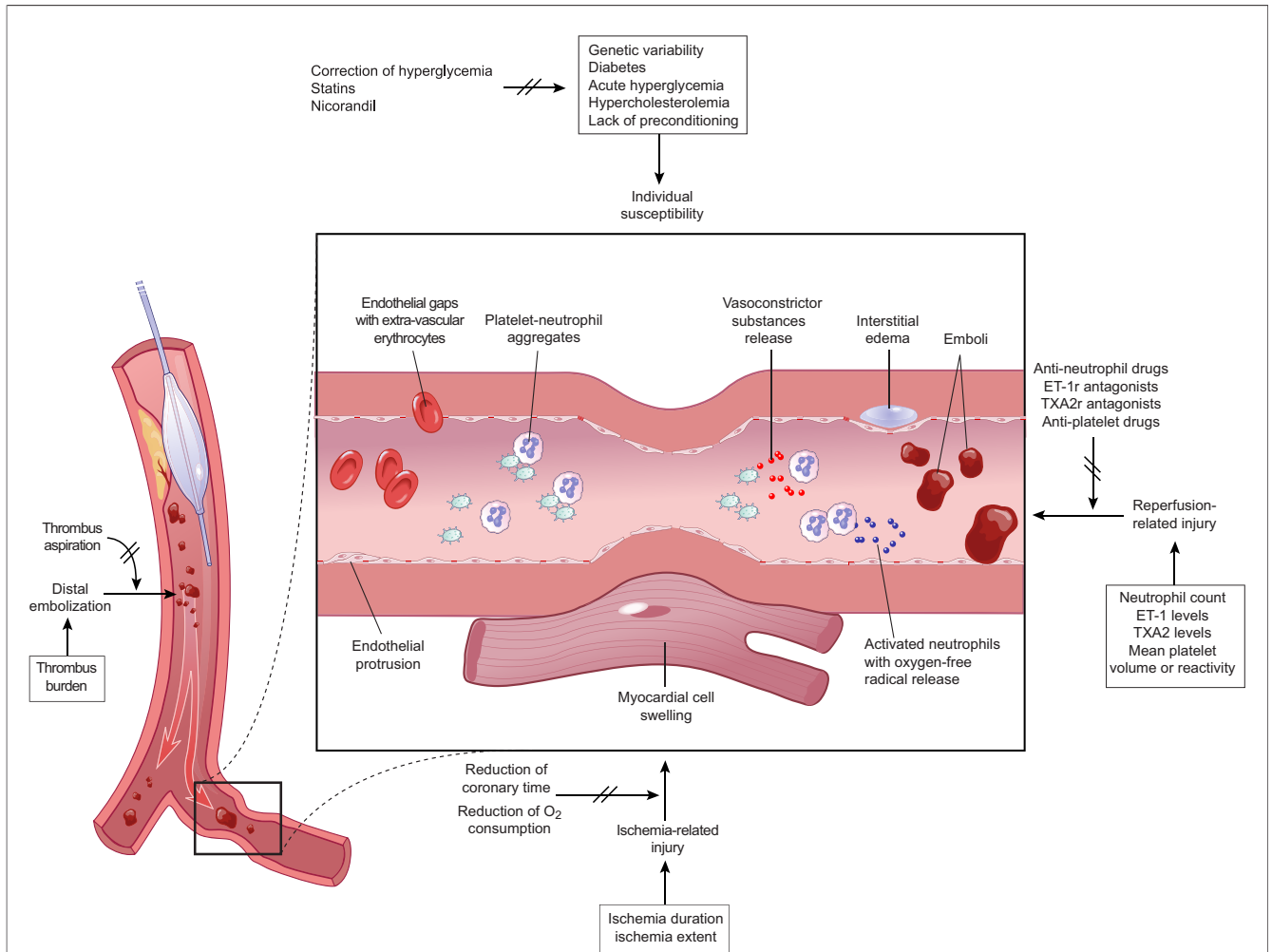


Figure 5 Therapies of No-Reflow Targeted to Main Pathogenetic Mechanisms

A comprehensive figure showing multiple mechanisms involved in the pathogenesis of no-reflow that might be targeted by appropriate therapy. Figure illustration by Rob Flewell. ET = endothelin; TxA2 = thromboxane-A2.

improvement of myocardial perfusion by manual thrombus aspiration translated in a strikingly lower mortality at 12-month follow-up (77). Taken together, these studies suggest that manual thrombus aspiration should be used in the setting of PPCI, particularly in patients with a high thrombus burden (78).

Management of ischemia-related injury. Strategies aimed at reducing pain-onset-to-balloon time are currently widely investigated and might reduce the prevalence of no-reflow by reducing total ischemic time. Similarly, drugs known to reduce myocardial oxygen consumption and consequently the severity of ischemia might improve the outcome, at least partially, through an improvement of myocardial perfusion (79). The beneficial effects of carvedilol, fasinopril, and valsartan on coronary no-reflow have indeed been recently demonstrated (80,81).

Management of reperfusion-related injury. Patients at high risk of no-reflow on the basis of the presence of

predictors of reperfusion-related injury can be treated with drugs like glycoprotein IIb/IIIa antagonists, adenosine, nicorandil, and nitroprusside aimed at counteracting endothelial, platelet, and neutrophil activation. Selective ET-1 or TxA2 antagonism might represent novel therapeutic approaches.

Among glycoprotein IIb/IIIa antagonists, abciximab has been found to improve myocardial perfusion when started during PPCI and infused for 12 h thereafter, as assessed by a higher rate of STR >50% at 60 min after PCI (73% vs. 57%, $p < 0.05$) (82). The beneficial effects of abciximab on microvascular reperfusion in the setting of PPCI parallel and might at least partially account for those on clinical endpoints (83). Conversely, the effects of peptidic glycoprotein IIb/IIIa antagonists on no-reflow and long-term mortality still need to be tested in randomized trials. Interestingly, in a small randomized study of abciximab versus tirofiban for patients undergoing PPCI, Danzi et al. (84) demonstrated

similar rates of final TIMI flow grade 3 (86% vs. 88%), of adverse cardiac remodeling, and of clinical events at 1 month in the 2 arms. Taken together, these findings suggest that glycoprotein IIb/IIIa antagonists prevent no-reflow. Interestingly, intracoronary abciximab has been proven to be superior to intravenous abciximab in patients treated by primary PPCI (85). The evidence that this beneficial effect on myocardial perfusion translates into an improvement of the outcome, however, has convincingly been obtained for abciximab only.

Adenosine is an endogenous nucleoside mainly produced by the degradation of adenosine triphosphate, which antagonizes platelets and neutrophils, reduces calcium overload and oxygen free radicals, and induces vasodilation (86). In a randomized trial, intracoronary administration of 4 mg of adenosine before complete vessel reopening resulted in a lower rate of no-reflow as compared with the control arm (86). More recently, intracoronary administration of a very high dose of adenosine (60 mg) was found to reduce the rate of incomplete STR after PPCI. In this study, patients were randomized to intracoronary adenosine or placebo if STR after PPCI was <70%. The authors found that more patients showed STR after adenosine as compared with placebo (33% vs. 9%) (87). Intravenous adenosine has been tested in 2 large randomized trials (AMISTAD [Acute Myocardial Infarction Study of Adenosine] I and II) (88,89). Both studies showed a reduction of incomplete STR with a 3-h infusion of adenosine, but in-hospital and 6-month clinical outcome were similar to those observed in the placebo group.

Nitroprusside is a nitric oxide donor that does not depend on intracellular metabolism to derive nitric oxide, with potent vasodilator properties. Intracoronary administration of nitroprusside, compared with control, failed to improve corrected TIMI frame count and rate of complete STR (90). Conversely, 2 small registries showed an improvement of final TIMI flow grade after administration of intracoronary nitroprusside given in the attempt to reverse no-reflow (91,92).

Nicorandil is a hybrid drug of ATP-sensitive K⁺ channel opener and nicotinamide nitrate and has been shown to decrease infarct size and incidence of arrhythmias after coronary ligation and reperfusion in experimental animals, probably by suppressing free radical generation and by modulating neutrophil activation (93). Intravenous infusion of nicorandil for 24 h after PPCI resulted in better angiographic, functional, and clinical outcome as compared with placebo in 2 randomized studies (94,95).

Among potential new therapeutic approaches against IR injury, the use of atrial natriuretic peptide has been tested recently in a large-scale randomized trial. Indeed, Kitakaze et al. (96) in the J-WIND (Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage) trial, which randomized 227 patients to receive intravenous atrial natriuretic peptide and 292 patients to placebo, demonstrated that atrial natriuretic peptide treat-

ment was associated with a reduction of 14.7% in infarct size, an increase in the 6 to 12 months of LV ejection fraction by 5%, and an improved myocardial perfusion. In the same trial the authors randomized 276 patients to intravenous nicorandil or placebo but failed to show any reduction in the infarct size or improvement in LV ejection fraction in the nicorandil group. However, oral nicorandil prescribed during the follow-up improved LV ejection fraction.

Verapamil is a calcium-channel blocker that has been used for the prevention and therapy of no-reflow. In a small randomized study by Taniyama et al. (97) in 40 patients with first STEMI, intracoronary verapamil as compared with placebo was associated with better microvascular function as assessed by MCE. Accordingly, intracoronary verapamil has been successfully used to reverse no-reflow after PPCI (98).

Management of individual susceptibility to microcirculatory injury. Although genetically determined susceptibility to microcirculatory injury is difficult to modulate, acquired susceptibility might be treated. Indeed, optimal and prompt treatment of hyperglycemia is likely to be an important target in the prevention of no-reflow. Accordingly, the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) study demonstrated that periprocedural reduction of blood glucose was associated with a reduction of infarct size (99). Furthermore, statins are emerging as drugs potentially able to reduce reperfusion injury (99). Iwakura et al. (100) have demonstrated that chronic statin therapy in patients with or without hypercholesterolemia is associated with lower prevalence of no-reflow and better functional recovery.

Finally, induction of ischemic pre-conditioning by drugs or nonpharmacologic stimuli such as remote ischemia of the arms (101) and avoidance of substances potentially blocking pre-conditioning like sulfonylureas and high doses of alcohol might be other measures able to prevent no-reflow (102).

Future Perspectives

The understanding of the prevailing pathogenic mechanism(s) of no-reflow in the individual patient is probably important in the selection of the most appropriate therapeutic approach. Indeed, patients with a high thrombus score are more likely to benefit from thrombus aspiration, whereas those at high risk of reperfusion injury are more likely to benefit from pharmacotherapy. New drugs such as ET-1 or TxA₂ antagonists and the combination of old drugs such as adenosine, nitroprusside, and nicorandil should be tested in large controlled randomized trials in patients at high risk of reperfusion injury. Finally, optimal and prompt risk factor control and induction of pre-conditioning represent additional therapeutic options that, again, should be tested in large controlled randomized trials.

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Key Words: microcirculation ■ myocardial no-reflow ■ primary percutaneous coronary intervention ■ ST-segment elevation myocardial infarction.