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Clinical Perspective

The coronary no-reflow phenomenon: a review of mechanisms and therapies

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Introduction

The phenomenon of no-reflow is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction[1]. Temporary occlusion of the artery, a prerequisite condition for no-reflow, may be produced in the experimental setting or occur during reperfusion of an infarct-related artery or following percutaneous coronary intervention[1–2]. No re-flow implies abnormal tissue perfusion and persistent no-reflow is associated with higher clinical complication rates[2–4]. The concept of coronary no-reflow was first described in experimental models in 1966[5] and then in the clinical setting of reperfusion after myocardial infarction in 1985[6]. Although often debated by fundamentalists, the term no-reflow was used to describe the same phenomenon in the field of interventional cardiology in 1989[7].

No-reflow has been documented in $\geq$30% of patients after thrombolysis or mechanical intervention for acute myocardial infarction[2,4,8]. Compared to similar patients with adequate reflow, those with no-reflow have more congestive heart failure early after myocardial infarction and demonstrate progressive left ventricular cavity dilatation in the convalescent stage of the infarction[2,4].

During coronary intervention, no-reflow has been reported in 0·6% to 2% of cases and has been identified with treatment of saphenous vein grafts, atherectomy, and PTCA and stenting of thrombus containing lesions[3,9]. Persistent no-reflow has been associated with increased mortality and a high incidence of myocardial infarction[3,9].

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The article will review no-reflow from a historical perspective, discuss the postulated mechanisms, examine the techniques for correct diagnosis, and address the treatment options. A clear distinction has to be made between the two clinical conditions in which the no-reflow phenomenon is observed; following reperfusion of acute myocardial infarction and during percutaneous coronary intervention. Throughout the paper, both conditions will be discussed separately, taking into account certain similarities which have led previous authors to extrapolate the same definition from the experimental set-up to the various clinical situations. The authors propose a new classification of no-reflow with respect to the different settings.

Historical overview

The term no-reflow was first used by Majno and colleagues[10] in the setting of cerebral ischaemia in 1967. This phenomenon was initially described by Krug *et al.*[5] during induced myocardial infarction in the canine model in 1966 and again by Kloner *et al.*[1] in 1974 in which it occurred for 90 min after temporary epicardial coronary artery occlusion. Myocardial tracers, such as carbon black or thioflavin S (a fluorescent stain for endothelium) were injected to document uniform flow distribution across the myocardial tissue after 40 min of occlusion. After 90 min, persistent subendocardial perfusion defects were seen with no-reflow. Electron microscopic examination showed severe myocardial capillary damage with loss of pinocytotic vesicles in the endothelial cells, endothelial blisters or blebs and endothelial gaps with neutrophil infiltration. Intraluminal capillary plugging by neutrophils and/or microthrombi with myocardial cell swelling was also noted. Kloner *et al.*[1] thus added the concept of 'coronary' no-reflow, in accordance with previous descriptions of this phenomenon in brain, kidney and skin tissues, as the absent or greatly impeded arterial flow into previously ischaemic tissue[10–12].

The first clinical observation of coronary no-reflow was reported by Schofer *et al.*[6] in 1985 in 16 patients

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Table 1 Classification, definitions and mechanisms of no-reflow

Experimental no-reflow	
Definition	no-reflow induced under experimental conditions.
Mechanisms	myocardial necrosis — stunning[22,23] reperfusion injury — oxygen free radical production[22–26] α-adrenergic macro- and microvascular constriction[28,31] local increase in angiotension II receptor density[29,32] neutrophil activation — interaction with endothelium[30,33,34]
Myocardial infarction reperfusion no-reflow	
Definition	no-reflow in the setting of pharmacological and/or mechanical revascularization for acute myocardial infarction
Mechanisms	as for experimental no-reflow
Angiographic no-reflow	
Definition	no-reflow during percutaneous coronary interventions
Mechanisms	distal embolization of plaque and/or thrombus[3,9] local release of vasoconstrictor substances[35]

with a first anterior myocardial infarction. Patients were studied with dual scintigraphic studies using thallium-201 (myocardial uptake) and technecium-99m micro-albumin aggregates (myocardial perfusion). Amongst 11 patients studied prior to and immediately after thrombolysis, one patient who had identical defects by both techniques prior to thrombolysis developed a further extension of the perfusion defect after thrombolysis with technecium-99m without changing the thallium-201 uptake defect. Therefore, Schofer *et al.*[6] concluded that no-reflow also occurred in humans during reperfusion of acute myocardial infarction. One year later, Bates *et al.*[13] reported the angiographic correlation of no-reflow as abnormally slow antegrade contrast filling in the infarct-related artery.

In 1989, Wilson *et al.*[7] observed persistent angina with ST elevation in association with a slow angiographic antegrade flow despite a widely patent angioplasty site in five patients immediately after PTCA of a thrombus containing lesion. Coronary dissection was excluded by an absence of a pressure gradient across the treated lesion. Wilson *et al.*[7] concluded that intense microconstriction was a possible mechanism for the no-reflow induced ischaemia. It was notable that there was a lack of response to nitroglycerin and thrombolytic drugs but a favourable reaction to papaverine in one patient. Consequently, the concept of no-reflow entered the field of interventional cardiology with the emphasis on the angiographic aspect of the definition. In 1991, Pomerantz *et al.*[14] reported five more cases of no-reflow successfully treated by intracoronary verapamil. The first clinical case of no-reflow during PTCA for acute myocardial infarction was reported by Feld *et al.* in 1992[15]. Thereafter, Piana *et al.*[3] and Abbo *et al.*[9] presented the results of two large clinical series, where no-reflow was reported between 0·6% and 2% of all patients[3,9]. The highest incidence occurred in patients undergoing primary and/or rescue PTCA for acute myocardial infarction, use of an atherectomy device and intervention on saphenous vein grafts. The overall incidence of in-hospital death and myocardial infarction was 15% and 31%, respectively, for patients with no-reflow in the series of Abbo and co-workers[9]. Although rotational atherectomy had the highest incidence of no-reflow (7·7%), it also had the most favourable reaction to pharmacological therapy with restoration of normal TIMI flow in 63% of cases[9].

Defining no-reflow: a proposal for a new classification

No-reflow has been variously referred to as slow flow, slow re-flow, no-flow and/or low-flow. As these terms all describe, essentially, the same phenomenon and are all equally indicative of myocardial ischaemia, we recommend the term no-reflow to simplify terminology. Similarly, a concise review of the literature reveals that there is no uniform definition for the no-reflow phenomenon. The interventional cardiologist focuses on the angiographic appearance, quantifying the importance of the reduced antegrade epicardial flow, while the research cardiologist identifies no-reflow at the tissue level, as demonstrated by myocardial imaging techniques and/or post-mortem studies. A common definition that suits well may be adapted from the work of Kloner *et al.*[1], who described the condition as the inability to adequately perfuse myocardium after temporary occlusion of an epicardial coronary artery without evidence of persistent mechanical obstruction, thus implying ongoing myocardial ischaemia. One may then distinguish between experimental no-reflow, myocardial infarction reperfusion no-reflow and angiographic no-reflow depending on circumstances. No-reflow occurring during primary PTCA or stenting for myocardial infarction encompasses the field of interventional cardiology (angiographic no-reflow) but also reperfusion after acute myocardial infarction and may therefore be better classified as myocardial infarction reperfusion no-reflow (whether it is documented by angiography or by the more sensitive myocardial imaging techniques).

Table 1 summarizes this classification including postulated mechanisms that will be discussed hereafter.

Postulated mechanisms of no-reflow

Myocardial infarction reperfusion no-reflow

The widespread introduction of thrombolysis has dramatically changed the prognosis of patients with acute myocardial infarction[16]. Nevertheless, in the early days of thrombolysis, it was observed that some patients demonstrated little or no improvement in ventricular function despite apparent reopening of the infarct-related artery[17]. This paradox led the TIMI study group in 1985[18] to propose a score (the TIMI score) which subjectively evaluates the speed of progression of contrast medium in the coronary epicardial circulation. More recently, a TIMI frame count (correlating contrast progression and the cineangiographic run count) has been proposed as a quantitative estimate of vessel patency[19]. Why was there a need for this TIMI frame count? Obviously, this may be explained by the need for a more objective measure of vessel patency. However, it may also be that vessel patency and myocardial perfusion have been confused and that in order to explain persistent contractile dysfunction, despite a TIMI 3 flow, a more objective measure of myocardial perfusion was needed. As no-reflow zones and/or left ventricular dysfunction have been demonstrated despite a TIMI 3 flow, one can only conclude that TIMI flow measures greatly over-estimate the success of thrombolysis and that these measures are only valid as an estimation of vessel patency and not for myocardial perfusion[2,20,21].

The persistence of contractile dysfunction despite vessel patency and TIMI 3 flow after pharmacological and/or mechanical intervention for acute myocardial infarction may be explained by irreversible injury (myocardial necrosis) or by reversible injury (myocardial stunning) or a combination of both[22,23]. These areas of injury can easily be demonstrated by different cardiac imaging techniques and both are found in no-reflow zones. However, whether this is the cause or the effect of no-reflow is still not clearly understood.

Dr Kloner considers experimental and myocardial infarction reperfusion no-reflow as indirect proof of vascular reperfusion injury, one form of reperfusion injury[22]. There are four basic forms of reperfusion injury: lethal reperfusion injury (a controversial subject), vascular reperfusion injury, myocardial stunning and reperfusion arrhythmias[22,23]. The mechanism of vascular reperfusion injury and myocardial stunning (which is common) is multifactorial, extremely complex and has not been completely elucidated. Most attention has been directed to the role of oxygen free radicals as oxygen radical scavengers (despite the absence of direct proof in humans) have been shown to limit infarct size and to attenuate the stunning phenomenon under experimental conditions[22–26]. In 1995, Grech *et al.*[27] provided the first direct evidence of oxygen free radical production in humans by coronary sinus sampling during primary PTCA for myocardial infarction. Free radicals have the capacity to modify membrane permeability and function, calcium homeostasis and the integrity of the microcirculation[22].

More recent data have indicated that other mechanisms may play a role in the myocardial infarction reperfusion no-reflow phenomenon: cardiocardiac sympathetic reflexes with resulting α-adrenergic macrovascular and microvascular constriction[28], regional changes in angiotension II receptor density[29] and interactions through selectins between activated polymorphonuclear leukocytes and the endothelium[30].

It has been known since 1969 that a sympathetic reflex may be triggered by coronary artery occlusion, inducing α-adrenergic macrovascular and microvascular constriction[31]. Gregorini *et al.*[28] monitored left ventricular function and proximal left anterior descending coronary artery blood flow velocity by transoesophagal echocardiography in a series of patients treated by stent placement of the culprit artery 72 h after successful thrombolysis. They demonstrated that α-adrenergic blockade by urapidil attenuated epicardial vasoconstriction, improved coronary blood flow at the microvascular level as well as left ventricular function. This was not the case for patients not pre-treated by urapidil, indicating that this neural trigger may play some role in the myocardial infarction reperfusion no-reflow phenomenon.

Lefroy and colleagues[29] demonstrated an increase over time of the density of angiotension II receptors in the scar tissue after experimental myocardial infarction. Angtension II has been shown to facilitate the sympathetic modulation of coronary vasomotor tone and may therefore indirectly be implemented in coronary vasoconstriction[32].

Experimental studies have demonstrated neutrophil activation and accumulation in the myocardial segment affected by acute ischaemia and coronary occlusion[33]. This accumulation is increased further after reperfusion and is another potential source of free radical production[33]. Selectin adhesion molecules promote interaction between activated neutrophils and damaged endothelium, which may induce endothelial dysfunction and/or vasoconstriction[30]. Inhibition of these selectin adhesion molecules has been shown to limit infarct size in the canine and feline models but not in the rabbit model[34].

Thus the mechanism of myocardial infarction reperfusion no-reflow seems to imply many pathways, of which probably only a part has been clarified. Further basic research (we may assume that the mechanism of experimental and myocardial infarction reperfusion no-reflow are essentially the same) is needed to gain a better understanding of the specific mechanism of no-reflow.

Angiographic no-reflow

The mechanism of angiographic no-reflow can be more easily conceptualized as there is a direct relationship between the application of a percutaneous device and the subsequent reduced flow. Distal embolization of

plaque and/or thrombus from the lesion site are likely mechanisms[3,9]. A loss of capillary autoregulation with the local release of vasoconstrictor substances has also been postulated as an additional mechanism[35]. If the principal mechanism is vasoconstriction, this would explain the favourable response seen with intracoronary administration of calcium antagonists.

Myocardial infarction reperfusion no-reflow during primary PTCA and/or stenting may be explained by the mechanisms discussed in the previous chapter. Often this condition is extremely therapy resistant and most likely if following percutaneous intervention of acute total occlusion, flow is totally absent or greatly reduced. If flow deteriorates again after initial successful percutaneous reperfusion, embolization of the thrombus from the lesion site should be suspected.

Techniques for the demonstration of no-reflow

Whether it be experimental no-reflow, myocardial infarction reperfusion no-reflow or angiographic no-reflow, several techniques may be used alone or in combination to make the diagnosis.

The following methods will briefly be described: myocardial scintigraphy, myocardial contrast echocardiography, magnetic resonance imaging, positive emission tomography, coronary angiography (selective or subselective), intracoronary Doppler and pressure measurements, intravascular ultrasound and the conventional 12 lead ECG.

Myocardial scintigraphy

Myocardial infarction reperfusion no-reflow was first documented by Schofer *et al.* by using dual myocardial scintigraphy in a patient before and after thrombolysis for acute myocardial infarction[6]. The work is still considered as the first evidence for the no-reflow phenomenon in humans. As the technique is quite cumbersome, we do not recommend it in the emergency clinical setting.

Myocardial contrast echocardiography, nuclear magnetic resonance and positron emission tomography

Myocardial contrast echocardiography, nuclear magnetic resonance and positron emission tomography studies in the experimental and clinical setting have been used to document myocardial infarction reperfusion no-reflow and its negative clinical implications[4,21,36–43]. Ito and colleagues studied 126 patients with a first anterior myocardial infarction treated by thrombolysis[4]. Patients with no-reflow on myocardial contrast echocardiography presented significantly more frequently with congestive heart failure and pericardial effusion. At 1 month there was a progressive increase in their end-diastolic volumes, whereas in those patients with reflow on myocardial contrast echocardiography the end-diastolic volumes decreased. Asunuma *et al.*[39], combining myocardial contrast echocardiography and magnetic resonance, found that patients without intramyocardial haemorrhage had a significantly improved left ventricular wall motion score at 1 month follow-up compared to patients with such a reperfusion injury.

Myocardial contrast echocardiography has led to tremendous progress in the understanding of the functional significance of the myocardial infarction reperfusion no-reflow phenomenon, indicating clearly the weakness of any angiographic measure of epicardial coronary flow[4,21,39–43]. Several reports have demonstrated that despite a TIMI 3 flow (vessel patency, 'normal' epicardial flow), a tissue no-reflow phenomenon could be documented by contrast echocardiography[21,40]. Myocardial contrast echocardiography should therefore be considered as the gold standard for the assessment of adequate myocardial perfusion in this setting, i.e. the negative predictive value of functional recovery at 10 days (or in other words to exclude acute no-reflow) is higher than 90%[21]. Experimental studies have shown that vasoactive drugs such as adenosine delineate the no-reflow zone more accurately as flow reserve abnormalities may underestimate this zone[43]. This has not been investigated in humans to date, but seems more than worthwhile to further increase the diagnostic accuracy of the technique.

Other myocardial imaging techniques such as nuclear magnetic imaging and positron emission tomography have also been shown to be useful diagnostic tools for no-reflow[36–38]. The major disadvantages of these investigations are their costs, technical difficulty and invasive character (myocardial contrast echocardiography). Their application remains limited to highly specialized and research centres.

Coronary angiography

Angiographic no-reflow should be suspected when there is reduced TIMI flow, as first described by Wilson *et al.*[7]. It needs to be differentiated from other causes of slow flow due to epicardial obstruction caused by dissection, thrombus, prolonged spasm, distal macroembolization or competitive flow obscuring satisfactory antegrade opacification. Is TIMI grading completely worthless for assessing myocardial infarction reperfusion no-reflow, as alluded to in the previous paragraph? Whilst we have seen that it is not reliable, the large thrombolysis trials have demonstrated an equally poor prognosis for patients with TIMI ≤ 1 and 2 flow compared to those with TIMI 3 flow[44] and therefore, the diagnosis of myocardial infarction reperfusion no-reflow would be consistent with a TIMI <3 flow. If interpreted with caution, coronary angiography is still

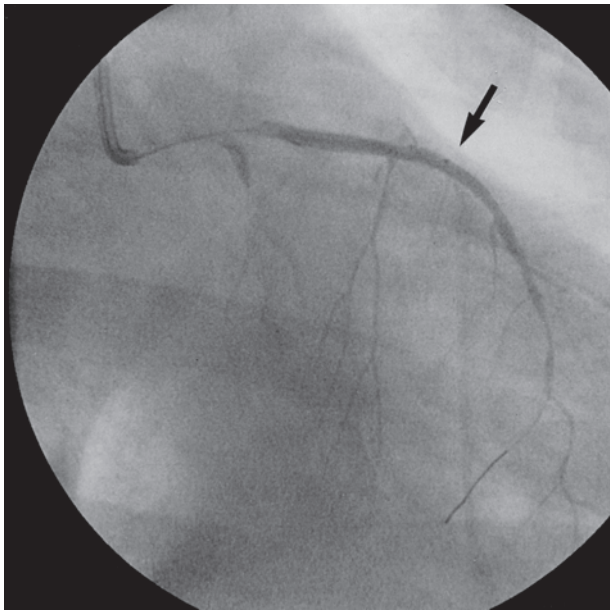

Figure 1 **Subselective coronary angiography through a double-lumen, side-hole catheter during primary angioplasty in a patient with acute anterior myocardial infarction. Angiography demonstrates integrity without major obstruction of the left anterior descending artery, mild distal vessel spasm and antegrade flow through the proximal circumflex branch. The black dot indicates the distal part of this catheter located in the mid left anterior descending artery.**

an essential and simple way to diagnose any clinical form of no-reflow. In addition, subselective contrast injection through a double-lumen catheter, as another technique to document angiographic no-reflow (Fig. 1), permits a more detailed, visual analysis of the integrity of the artery to identify thrombus or distal vasospasm.

Intracoronary pressure measurements

An adjunctive method which confirms the angiographic no-reflow phenomenon, described by Sherman *et al.*[45], uses a double-lumen, side-hole catheter to measure any pressure gradient across the target artery. The absence of a significant pressure gradient indicates the absence of mechanical obstruction, thus establishing a key element of angiographic no-reflow. Although elegant and attractive, pressure measurements through a non-dilatation catheter creates an artificial stenosis and may thus overestimate the real gradient. High-fidelity, low profile (0·014 inch) pressure guide wires may truly quantify pressure gradients. At present, no clinical data on the use of these pressure guide wires during angiographic no-reflow is available.

Intracoronary Doppler

Intracoronary Doppler measurements may be extremely helpful to diagnose angiographic no-reflow. Iwakura and colleagues[46] described a typical Doppler pattern of angiographic no-reflow: a reduced or even absent antegrade systolic flow followed by a retrograde systolic flow and rapid deceleration of diastolic flow. These authors postulated that the intramyocardial blood pool in patients with no-reflow is markedly reduced because of severe microvascular obstruction. Such a condition would explain the rapid diastolic flow deceleration as the myocardial blood pool is rapidly filled during diastole. This pooled blood is then partially expelled back into the epicardial coronary artery capacitor during systole, producing retrograde systolic flow. Figure 2 illustrates coronary Doppler flow in the first septal branch of the left anterior descending coronary artery of a patient with no-reflow during alcohol-induced septal occlusion for therapy-resistant hypertrophic obstructive cardiomyopathy. Conventional angiography had demonstrated abnormally slow progression of contrast in this septal branch.

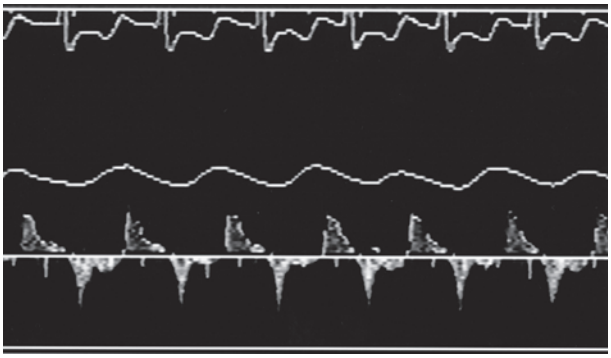

Figure 2 **Intracoronary Doppler flow pattern in the distal first septal branch following alcohol-induced septal ablation for therapy-resistant hypertrophic obstructive cardiomyopathy. Angiography demonstrated a typical no-reflow pattern while intracoronary Doppler shows systolic retrograde flow followed by an early deceleration of diastolic flow.**

Intravascular ultrasound

There are no data on the use of intravascular ultrasound for the diagnosis of angiographic no-reflow. Progress in imaging resolution is ongoing and for the completeness of this paper, this technique is mentioned as a possible aid in the differential diagnosis of angiographic no-reflow, as it permits accurate analysis of the epicardial vessel integrity.

Conventional 12-lead ECG

Recent investigation has demonstrated the usefulness of a simple standard ECG in the diagnosis of myocardial infarction reperfusion no-reflow. Santoro *et al.*[21] studied the relationship between ST-segment changes and myocardial perfusion evaluated by myocardial

Table 2 Techniques for demonstration of no-reflow

Myocardial infarction reperfusion no-reflow	
Conventional 12-lead ECG[21]	Persistent ST-segment elevation
Coronary angiography[13]	Suspected if TIMI <3 flow
Dual myocardial scintigraphy[6]	Uptake/perfusion mismatch
Myocardial Tc-99m sestamibi scintigraphy[57]	No-reflow zone
Myocardial contrast echocardiography[4,21,39–43]	No-reflow zone
Nuclear magnetic resonance studies[36,37]	No-reflow zone
Positron emission tomography[38]	No-reflow zone
Intracoronary Doppler registration[46]	Typical Doppler pattern
Angiographic no-reflow	
Conventional coronary angiography[7,3,9]	TIMI <3 flow
Subselective coronary angiography[45]	Examines distal vessel integrity
Distal coronary pressure measurements[7,45]	No significant pressure gradient.
Intracoronary Doppler registration[46]	Typical Doppler pattern

contrast echocardiography in patients with acute myocardial infarction treated with primary PTCA. All patients had restoration of TIMI 3 flow after intervention. A rapid ST-segment decrease was highly specific (91%) for myocardial reperfusion (or the absence of no-reflow on myocardial contrast echocardiography) although less sensitive (77%). Taking in account these limitations, ST-segment monitoring is a helpful, inexpensive method to evaluate myocardial reperfusion.

The different techniques which may be of help to assess no-reflow are summarized in Table 2.

Therapies of no-reflow

Treatment options for angiographic no-reflow constitute a large majority of current literature. However, with increasing use of primary PTCA for acute myocardial infarction, clinicians have come to realize that the problem of myocardial infarction reperfusion no-reflow is often underestimated and may be more 'therapy' resistant.

Pharmacological approaches for angiographic no-reflow

A variety of pharmacological agents, including heparin, intracoronary nitrates and/or thrombolytics, have been advocated but generally are of little proven therapeutic value[3,9]. Anecdotal reports have shown normalization of coronary flow with intracoronary administration of papaverine, adenosine, nicorandil, nitroprusside and systemic abciximab[47–51]. The calcium antagonist, verapamil, has been shown to be effective for the treatment of no-reflow[3,9,52]. Data from retrospective studies[3,9] as well as a small comparative trial[52] consistently demonstrated improvement of TIMI flow following intracoronary administration of verapamil. Kaplan *et al.*[52] compared intracoronary verapamil (100–500 μg) with nitroglycerin for the treatment of no-reflow in degenerated vein grafts. This non-randomized study demonstrated improved TIMI flow in all patients treated by verapamil (from $1{\cdot}4 \pm 0{\cdot}8$ at baseline to $2{\cdot}8 \pm 0{\cdot}5$ after treatment), while the flow pattern did not change with nitrates (from $1{\cdot}2 \pm 0{\cdot}6$ at baseline to $1{\cdot}4 \pm 0{\cdot}8$ after treatment). For patients with saphenous vein graft disease, microvascular protection with glycoprotein IIb/IIIa antagonists may not occur. Ellis and colleagues[53] analysed 102 vein graft stenoses from the EPIC and EPILOG trials and failed to demonstrate any clinical benefit with the active drug treatment with an 18·6% incidence of death, myocardial infarction and urgent revascularization at 30 days compared to 16·3% for placebo. They hypothesized that distal embolization of athermomatous plaque from the vein graft wall is less sensitive to the antiplatelet effect of abciximab.

Pharmacological and technical measures to prevent angiographic no-reflow during rotational atherectomy deserve special attention because of the high risk for angiographic no-reflow. The following preventive technical measures[54–56] have been suggested: a low burr to artery ratio (0·6–9·8) followed by conventional PTCA (conservative rotational atherectomy) and/or a low rotational speed ($\pm$ 140 000 rounds per minute). The randomized STRATAS trial[54] comparing conservative with aggressive or stand-alone rotational atherectomy (burr to arterio ratios of 0·7–0·9 and low pressure PTCA) failed to demonstrate differences in clinical outcomes between the techniques. In the porcine model, Reisman *et al.*[55] demonstrated fewer and smaller sized platelet aggregates at the minimum approved speed of 140 000 rounds per minute. Plasma-free haemoglobin, a measure of cell damage, also decreased with decreasing rotational speed. Low speed rotational atherectomy would therefore appear to be a useful technical measure to prevent angiographic no-reflow. The following pharmacological preventive measures have been proposed: abciximab[56,57], intracoronary adenosine[58], drug cocktails including nitrates, verapamil and heparin[59]. Koch and co-workers[57] compared myocardial perfusion by

scintigraphy in patients treated by rotational atherectomy with and without abciximab treatment and demonstrated a reduction in the incidence, extent and severity of myocardial hypoperfusion in the treated group. An in-vitro study by Williams *et al.*[56] demonstrated substantial reduction of platelet aggregation with abdciximab which was rotational speed dependent, reconfirming high rotational speed as a risk for rotablator induced angiographic no-reflow and the role of platelet aggregation in this phenomenon. In a non-randomized study, Hanna *et al.*[58] demonstrated a lower incidence of angiographic no-reflow (1 4%) in patients treated by slow intracoronary boluses of 24 to 48 μg of adenosine compared to those (11·6%) receiving usual care. Cohen *et al.*[59] proposed a cocktail of verapamil ($10\ \mu g\ .\ ml^{-1}$), nitroglycerin ($4\ \mu g\ .\ ml^{-1}$) and heparin ($20\ IU\ .\ ml^{-1}$) to be infused through the sheath of the Rotablator system as an effective and safe regimen to prevent angiographic no-reflow. Thus, a single technical preventive measure (low rotational speed) and any of the above drug regimes may be considered to prevent angiographic no-reflow during rotational atherectomy.

Mechanical approaches for angiographic no-reflow

Fischell *et al.*[48] demonstrated improved TIMI flow after rapid, high velocity intracoronary delivery of adenosine boluses (3 ml of adenosine in saline, concentration unstated, using small syringes to increase velocity) for no-reflow in 10 out of 11 stented sephenous vein grafts. In the absence of a control group treated by saline, the authors concluded that any forceful fluid injection using small syringes might stimulate reflow through mechanical means. This observation has not been confirmed by other investigators, but rapid, high-velocity delivery of saline and/or adenosine boluses might be considered for drug resistant no-reflow. Adenosine has the advantage of producing vasodilation of the microcirculation.

The use of intra-aortic balloon counterpulsation has been suggested by some authors for drug resistant no-reflow with ongoing ischaemia[60,61]. Controversy exists regarding the ability of intra-aortic balloon pumping to increase blood flow in patients with coronary artery disease. Port and co-workers[62] failed to demonstrate improvement in distal blood flow in patients with severe obstructive coronary artery disease. Kern *et al.*[63] confirmed this observation but showed that, once coronary angioplasty was successfully accomplished, the coronary blood flow beyond the treated lesion significantly increased. Given this, one may consider this technique for drug resistant no-reflow and haemodynamic instability.

Very recently, two measures for the prevention of no-reflow during saphenous vein graft intervention have been proposed[64–66]. Both are based on distal balloon occlusion of the graft at the site of the anastomosis with the native artery prior to intervention at the lesion site. Once this distal protection device is in place, PTCA or primary stenting can be performed and the effluent aspirated through the guiding catheter[64] or a specially designed aspiration catheter (PercuSurge device, Sunnyvale, CA, U.S.A.[65,66]). Although not clearly stated, no-reflow probably still occurred in 2 out of 23 patients (9%) in the study by Shaknovich and co-workers[65] and in 11% of cases (3/27 patients) in the series of Webb *et al.*[64]. Webb *et al.*[64] reported the presence of particulate material in 21 out of 23 procedures. Pathological examination revealed the presence of particles with a necrotic core of cholesterol clefts, lipid-rich macrophages and fibrin. Semiquantitive analysis showed that primary stenting without pre-dilation was associated with less material than with pre-dilation and subsequent stenting, indicating that primary stenting may reduce the risk for no-reflow in saphenous vein grafts. Carlino *et al.*[66] reported a 100% clinical and procedural success rates with the PercuSurge device in 15 degenerated saphenous vein graft lesions. These devices are currently being evaluated during interventions for thrombus-containing lesions.

A variety of other new technologies have been proposed to the interventional cardiologist to prevent the angiographic no-reflow phenomenon in high-risk subsets such as thrombus-containing lesions. The AngioJet™ coronary thrombectomy device (Possis Medical, Minneapolis, MN, U.S.A.) has been evaluated in a randomized trial (VEGAS II) where it was compared to prolonged intracoronary urokinase infusion for the treatment of thrombotic vein graft disease[67]. The authors report a higher procedural success and lower 30 day complications rate with the thrombectomy device. Nevertheless the control arm (urokinase infusion) of this trial can hardly be considered as standard clinical practice. The TEC (transluminal extraction atherectomy) device (InterVentional Technologies Inc, San Diego, CA, U.S.A.) is another aspiration device that has the potential to remove thrombus and/or plaque material at risk for embolization[68]. Braden *et al.*[68] reported their experience in 49 patients with degenerated saphenous vein grafts where the TEC device was combined with stent implantation. Procedural success (98%) and acute outcomes (90% event-free) were good but the 1 year cumulative event rate was high at 28%. Rosenschein *et al.*[69] recently published their initial clinical experience in 20 patients with the ultrasound thrombolysis device (Acolysis, Angiosonics, Morrisville, NC, U.S.A.), which, in contrast to TEC and AngioJet™ devices, may lyse clot in-vivo. They concluded that the procedural success rate was 65% in a study population where the graft was occluded in 75% of cases. At present, the role of high level medical technology for the treatment and prevention of angiographic (and maybe of myocardial infarction reperfusion) no-reflow has not been established. Clinical experience with these devices remains limited, peer-reviewed literature data scarce and financial interests may obscure their true scientific value.

Table 3 Strategic approaches for no-reflow

Angiographic no-reflow
1. Check ACT levels (250–300 s)
2. Intracoronary nitrates (ISDN 1 mg) to exclude epicardial coronary artery spasm.
3. Consider using a double-lumen, side-hole catheter for pressure measurements, subselective angiography and drug delivery[45]
4. Consider pharmacological treatment:
   - Abciximab: 0·25 mg . kg^{-1} bolus, followed by 10 μg . min^{-1} infusion for 12 h[5] (questionable for saphenous vein graft disease)[53]
   - Subselective, intracoronary verapamil (0·25 mg to 2·5 mg)[3,9,52]
   - Intracoronary papaverine (10–20 mg), nicorandil (2 mg), nitroprusside (50–200 μg), high-velocity bolusses of adenosine (up to 50 μg)[25–27]
5. Consider intraaortic balloon counterpulsation for haemodynamic instability[60–63]
6. Consider preventive measures:
   - Thrombus-containing lesions — saphenous vein graft disease
     - Distal protection devices[64–66] — new technology[67–69]
     - Prior to intended rotational atherectomy
       - Consider abciximab: see point 4[56,57]
       - Consider additional drugs: verapamil, adenosine, nitroprusside, see also point 4 [50,58,59]
       - Consider rotational speed of 140 000 rounds per minute[55,56]

Myocardial infarction reperfusion no-reflow during primary PTCA/stenting:
1. Consider previous steps 1–3
2. Consider pharmacological treatment:
   - Temporary flow improvement: Abciximab[72]
   - True no-reflow: intracoronary verapamil, intravenous nicorandil[70,71]

ACT = activated clotting time; ISDN = isosorbidedinitrate.

A strategic and therapeutic approach for angiographic no-reflow is proposed in Table 3.

Treatment of myocardial infarction reperfusion no-reflow

Taniyama *et al.*[70] randomized 40 patients with a first acute myocardial infarction treated by primary PTCA to intracoronary verapamil vs control and performed myocardial contrast echocardiography prior and immediately after successful PTCA. Echocardiography was repeated at a mean of 24 days after intervention with analysis of left ventricular wall motion score. Catheterization was performed on average 25 days after intervention. Myocardial contrast echocardiography in the verapamil group showed improved microvascular function with a significant reduction of the area of no-reflow (by 45 ± 32% on average) while coronary angiography demonstrated an improvement in TIMI flow. At follow-up, the functional outcome was significantly better in the verapamil group with greater reduction in the wall motion score index on echocardiography, improved left ventricular ejection fraction and end systolic/diastolic volume indexes compared with controls.

Ito *et al.*[71], from the same group of investigators, repeated the concept of the previous experiment but with intravenous nicorandil in 81 patients. Again, the active treatment group had a smaller no-reflow zone on contrast echocardiography and improved regional left ventricular function and wall motion score. Postulated mechanisms were a positive influence on the calcium homeostasis during reperfusion and attenuation of neutrophyl activity.

Neumann and co-workers[72] demonstrated that abciximab improved the microvascular integrity during stent placement for acute myocardial infarction[29]. Patients (n = 200) were randomized to stent placement with abciximab or usual care with heparin. Although no-reflow was not reported, patients treated with abciximab showed improved wall motion scores coupled to higher intracoronary Doppler hyperemic peak flow velocity at 2 weeks follow-up. Again, the weakness of the TIMI score as a marker for myocardial perfusion emerges from this study.

Most frequently, myocardial infarction reperfusion no-reflow will be encountered in the catheterization laboratory. Percutaneous interventions are increasingly performed for acute coronary syndromes while myocardial imaging techniques are not readily accessible. As mentioned previously, 'true' myocardial infarction reperfusion no-reflow implies the inability to restore any flow or a greatly impeded flow. In contrast, if flow decreases again after initial successful reperfusion, embolization of thrombus is a suspected mechanism. In the first case, intracoronary verapamil or intravenous nicorandil would appear to be useful therapeutic measures. Is there a role for antioxidants, α-lytic agents, selectin adhesion molecules antagonists, adenosine and other molecules postulated to be involved in myocardial infarction reperfusion no-reflow? The question remains to be answered but trials are currently underway with a variety of drugs to evaluate their role for this particularly therapy resistant

phenomenon. In the second case, abciximab should be given in addition to verpamil or nicorandil.

Conclusions

Coronary no-reflow results in prolonged myocardial ischaemia after temporary occlusion and reperfusion of an epicardial artery during percutaneous coronary intervention or after acute myocardial infarction. This complication requires prompt diagnosis and treatment due to the negative prognostic relationship. Patients undergoing primary PTCA and stenting for acute myocardial infarction, atherectomy and intervention on saphenous vein grafts are high-risk subsets.

In the setting of angiographic no-reflow, assessment of coronary pressure and subselective angiography have been used as diagnostic tools to differentiate correctable causes. Subselective delivery of therapeutic agents, in particular verapamil, seems to be the most appropriate pharmacological treatment. The role of distal protection devices, thrombectomy and thrombolytic technologies in the prevention of angiographic no-reflow requires further investigation.

Myocardial infarction reperfusion no-reflow is an under-estimated problem as accurate diagnosis can often only be made by relatively sophisticated myocardial imaging techniques. The mechanisms are complex, multifactorial and incompletely elucidated. Relatively small but well conducted randomized trials have shown the efficacy of systemic abciximab, intracoronary verapamil and intravenous nicorandil in reducing areas of no-reflow.

Further investigation into the mechanisms and therapy of no-reflow will benefit patients having this complication in the short and long-term.

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