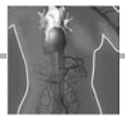
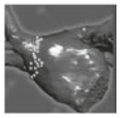


Managing no-reflow during percutaneous coronary intervention

Visible impairment of epicardial coronary flow associated with ischemia may occur during percutaneous coronary intervention (PCI). This so called no-reflow phenomenon is found despite any evidence for distal embolic cutoff, obstruction or vessel dissection. It occurs in patients who undergo PCI, typically of a lesion responsible for recent myocardial infarction, or treatment of a saphenous vein graft. Various mechanisms leading to microvascular obstruction induce no-reflow. No-reflow has a strong negative impact on clinical outcome. Administration of adenosine, a calcium-channel blocker, or nitroprusside is appropriate to treat PCI-related no-reflow that occurs during primary or elective PCI. In the setting of acute myocardial infarction, evidence for a beneficial effect on no-reflow also exists for abciximab and nicorandil. Thrombectomy and/or embolic protection devices should be used for the prevention of no-reflow in the setting of high thrombus burden and during saphenous vein graft intervention.

KEYWORDS: acute myocardial infarction ■ embolization ■ microcirculation ■ percutaneous coronary intervention ■ thrombectomy ■ vasoconstriction

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The term 'no-reflow' describes a condition of myocardial tissue hypoperfusion despite patent epicardial coronary arteries. Initially, it was used to describe the inability to reperfuse a previously ischemic region [1]. Microvascular obstruction is considered to be the underlying cause of no-reflow and may be provoked by various mechanisms. For diagnosis of no-reflow, other possibilities such as dissection, local thrombus formation, stenosis or epicardial spasm have to be excluded. In ≥30% of patients, after thrombolysis or mechanical intervention for acute myocardial infarction (AMI), no-reflow has been reported [2–5]. No-reflow has been observed in 0.6–2% of cases during percutaneous coronary intervention (PCI) and has been identified especially during PCI of thrombus-containing lesions, saphenous vein grafts (SVG) or when performing atherectomy, despite optimal anticoagulation with heparin [6–10]. There is evidence that no-reflow has a strong negative impact on clinical outcome after PCI [3,11–16]. Patients with no-reflow during PCI have a higher incidence of early postinfarction complications, adverse left ventricular remodeling, repeat hospitalizations for heart failure and higher mortality [2,3]. Despite continuous improvements of PCI procedures, no-reflow remains a constant threat. Prevention, diagnosis and treatment of no-reflow are essential to improve outcome after PCI. The purpose of this review is to give an overview about pathophysiology, predictors and management options for no-reflow.

Classification

According to the duration of the preceding myocardial ischemia, no-reflow may be classified as interventional or reperfusion no-reflow.

■ Interventional no-reflow

Interventional no-reflow occurs following non-infarct PCI and involves heart muscle that was not exposed to prolonged ischemia prior to the procedure. It is unpredictable, sudden in onset and presents clinically as acute ischemia with chest pain and electrocardiography changes. It is known that patients with interventional no-reflow that complicates PCI have higher rates of myocardial infarction and mortality [17].

■ Reperfusion no-reflow

Reperfusion no-reflow follows PCI for reperfusion of an infarct-related coronary artery in the setting of AMI. Reperfusion no-reflow is preceded by ischemic cell injury. It is limited to the irreversibly damaged necrotic zone and may be exacerbated during reperfusion. Clinically, it may present with continued chest pain and failure of ST-resolution. Reperfusion no-reflow is an independent predictor of adverse clinical outcome after AMI and is associated with increased mortality [18].

Diagnosis of no-reflow

This is a brief overview of various modalities for the diagnosis of no-reflow. Different sensitivities of diagnostic tests explain the wide variety of

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reported incidence of the no-reflow phenomenon. Routine and nonroutine diagnostic options for no-reflow are listed in Box 1.

■ Electrocardiography

Due to the fact that electrocardiography ST-segment resolution is a marker of myocardial tissue reperfusion, persistence of ST-segment elevation in AMI may be an indicator of microvascular obstruction and no-reflow.

■ Angiographic assessment

According to the Thrombolysis In Myocardial Infarction (TIMI) flow grades, coronary angiography allows a semiquantitative grading of epicardial coronary flow [19]. It is known that reduced coronary flow after primary angioplasty (TIMI flow grade: 0–2) is associated with worse outcome, even when no significant epicardial obstruction remains [18]. However, angiographic epicardial flow is a poor substitute for tissue perfusion and microvascular obstruction often occurs unrecognized. More sensitive markers of tissue perfusion have been identified and provide prognostic information beyond that of TIMI flow grade. With the use of computerized myocardial blush grade analysis a qualitative assessment of myocardial contrast density exists. Catheter-based methods, such as with a Doppler guidewire or pressure/temperature guidewire for the assessment of the index of microcirculatory resistance, may also be used [20].

■ Echocardiography

Noninvasive assessment of myocardial perfusion with myocardial contrast echocardiography may demonstrate microvascular no-reflow even in patients with angiographic TIMI flow grade 3 after PCI [21].

■ MRI/computed tomography

Tissue hypoenhancement in contrast-enhanced MRI or multidetector computed tomography indicates impaired myocardial perfusion and correlates with evidence of microvascular obstruction [22,23].

■ Biomarkers

A rise in serum cardiac biomarkers after PCI reflects myocardial necrosis secondary to tissue hypoperfusion and ischemia. More than 70% of patients may exhibit elevated troponin values after an otherwise successful elective PCI [24].

Box 1. Diagnosis of no-reflow.

Routine
- ST-segment resolution
- Angiographic thrombolysis in myocardial infarction flow grade

Nonroutine
- Myocardial blush grade
- Contrast echocardiography
- MRI
- Computed tomography

Pathophysiology of no-reflow

No-reflow was described for the first time by Kloner *et al.* [25]. In a canine model, no-reflow occurred after prolonged coronary occlusion followed by reperfusion. Contrary to epicardial spasm, no-reflow during coronary intervention generally responds poorly to intracoronary-administered nitroglycerin. This phenomenon corresponds with the observation that the microcirculation responds poorly to nitroglycerin [26–29]. During ischemia, small vessel vasoconstriction may occur due to impaired local synthesis of endothelium-derived relaxing factor. Calcium antagonists act directly on the vascular smooth muscle rather than endothelium-derived relaxing factor, and constitute a more effective treatment for no-reflow during coronary intervention. Taken together, this observation suggests that no-reflow may be due to distal microvascular spasm caused by the release of potent vasoconstrictors. The severity of microvascular obstruction that develops after both elective and infarct-related PCI may be influenced by pre-existing microvascular obstruction and/or endothelial dysfunction. This may explain the association of diabetes mellitus and hyperlipidemia with the no-reflow phenomenon.

Four pathogenetic mechanisms may contribute to the development of no-reflow.

■ Distal embolization

Previous experimental studies have shown that myocardial blood flow decreases irreversibly when more than 50% of coronary capillaries are obstructed [30]. During PCI, emboli of different sizes can originate from atherosclerotic plaques or coronary thrombus [31]. Okamura *et al.* used a Doppler guidewire during coronary intervention in patients with AMI, to count the number of embolic particles [32]. The average number of emboli during primary PCI was 25. Emboli can obstruct prearterioles and may induce no-reflow. Distal embolization plays an important role in situations in which the amount of debris is largest, particularly during SVG PCI [33].

■ Ischemia-related injury

Endothelial dysfunction may occur after prolonged ischemia. Morphological changes include endothelial protrusions and membrane-bound bodies, which may fill the capillaries up to luminal obliteration. Moreover, endothelial gaps with extravascular erythrocytes are common after ischemia [34]. These morphological findings are accompanied by a reduction of regional myocardial blood flow within the previously ischemic region and may result in no-reflow [35]. Furthermore, interstitial edema due to myocardial cell swelling might cause microvascular compression [36].

■ Reperfusion-related injury

Reperfusion of ischemic tissues is often associated with microvascular dysfunction, which is characterized as impaired endothelium-dependent dilation in arterioles and the trafficking of leukocytes and plasma protein extravasation in postcapillary venules. Activated endothelial cells in all segments of the microcirculation produce more oxygen radicals but less nitric oxide in the initial period following reperfusion [37]. The resulting imbalance leads to the production and release of inflammatory mediators and enhances the biosynthesis of adhesion molecules that mediate leukocyte endothelial cell adhesion [37]. Activated platelets and neutrophils can aggregate and obstruct capillaries [38,39]. Vasoconstrictive mediators released by activated neutrophils, platelets and damaged endothelium contribute to sustained vasoconstriction of the coronary microcirculation [40]. Several inflammatory mediators are involved in a complex interaction between platelets, neutrophils and endothelial cells. TNF-α, IL-1β, selectin and endothelin-1 (ET-1) seem to play an important role in reperfusion-related injury and consecutive no-reflow [41–43]. Natriuretic peptides might suppress ET-1 expression, limiting infarct size when administered before and during coronary occlusion [44]. Reperfusion might also cause irreversible injury to myocytes [45]. Ischemia may result in a cellular calcium overload that triggers uncontrolled hypercontraction and stimulates opening of the mitochondrial permeability transition pore (m-PTP), which further enhances calcium overload. Cyclosporine, which blocks the m-PTP, has been shown to reduce infarct size by 20% when administered intravenously in patients undergoing primary PCI [46]. Furthermore, ischemic preconditioning might also reduce infarct size by blockade of m-PTP [45,47].

■ Individual susceptibility

Predisposition to no-reflow can be genetic and/or acquired. Conditions such as diabetes or hypercholesterolemia have been associated with impaired microvascular reperfusion after primary PCI and enlarged reperfusion injury [48,49].

Predictors of no-reflow

■ Predictors of distal embolization

Thrombus burden at a lesion site in the coronary artery is a major risk factor for distal embolization. Angiographic morphologic features of infarct-related arteries as a predictor for no-reflow have been proposed by Yip *et al.* [50]. The score to assess thrombus burden included the following characteristics: 1: an angiographic thrombus with the greatest linear dimension being more than three 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 floating thrombus proximal to the occlusion; 5: persistent contrast medium distal to the obstruction; and 6: reference lumen diameter of the infarct-related artery being >4 mm. Yip *et al.* reported that all of these characteristics were independent predictors of no-reflow in 800 patients undergoing primary PCI. Distal embolization of thrombotic debris typically occurs after stent placement in large coronary vessels. In small vessels, the stent might fix the thrombus to the vessel wall, especially if the thrombus is not fresh anymore. Similar findings have been described by Limbruno *et al.* [51]. In a series of patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI with distal filter protection, they found that Yip's score was an independent predictor of total debris volume captured in the filter's basket. Another risk factor for no-reflow is SVG PCI. The incidence of major adverse cardiac events doubles with SVG PCI compared with native-artery PCI [52].

■ Predictors of ischemia-related injury

Time to treatment in PCI plays an important role for the occurrence of the no-reflow phenomenon. The longer the time to reperfusion, the higher is the prevalence of no-reflow [53]. A relationship between myocardial thickness and occurrence of no-reflow was proposed by Turschner *et al.* [54]. They 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 determinant of no-reflow, as demonstrated by Iwakura *et al.* A higher prevalence of no-reflow when the left anterior descending is the infarct-related artery as compared with other epicardial coronary arteries proposes that a larger extent of the ischemic area is a predictor of no-reflow [55].

■ Predictors of reperfusion-related injury

Several studies have demonstrated that platelets may play a role in no-reflow. Campo *et al.* demonstrated a relationship between platelet reactivity on admission and prevalence of no-reflow [56]. Huczek *et al.* showed that mean platelet volume on admission predicts impaired reperfusion and long-term mortality in AMI treated with primary percutaneous coronary intervention [57]. Niccoli *et al.* suggested that plasma levels of thromboxane-A2 (TxA2) predict no-reflow [58]. Other data indicate that depletion of antioxidants might be associated with the no-reflow phenomenon in AMI [59]. The strong vasoconstrictor ET-1 seems to play a key role in no-reflow. ET-1 levels on admission are an independent predictor of no-reflow [60]. Another easily available predictor is the neutrophil count, which has been related to microvascular injury after primary PCI [61].

■ Predictors of individual susceptibility

Acquired and genetic factors might play a role in the development of the no-reflow phenomenon. Studies have suggested that conditions such as diabetes and hypercholesterolemia might predispose to no-reflow [48,49]. Iwakura *et al.* revealed a relationship between hyperglycemia and the no-reflow phenomenon in patients with AMI [62]. Furthermore, data revealed an association between C-reactive protein and myocardial perfusion in patients with ST-elevation AMI [63]. Preinfarction angina, another aquired factor, might have a protective effect due to induction of ischemic preconditioning [64]. Vignali *et al.* suggested that the 1976T>C polymorphism of the adenosine 2A receptor gene is associated with a higher prevalence of no-reflow [65]. Other data revealed that patients with no-reflow show a more compact fibrin network [66]. This might be a genetically mediated resistance to lysis. Among the individual predictors of no-reflow, coronary anatomy, as quantified by the SYNTAX score, has also recently been demonstrated to be a reliable predictor [67].

Prevention & treatment of no-reflow

Prevention and treatment options of no-reflow can be divided in pharmacological and mechanical approaches. A number of therapeutic strategies have been tested for prevention and treatment of no-reflow with inconsistent results, but the reason may be a random use for all patients without considering the underlying pathogenetic components. Furthermore, often experimental data cannot be translated into clinical practice [68]. As a function of the pathophysiology of no-reflow, management options should be used individually (Figure 1). Table 1 lists selected positive randomized trials for the management of no-reflow.

■ Prevention of distal embolization

PCI in thrombus-containing lesions carries a high risk of no-reflow. With the technique of direct stent implantation, balloon-induced thrombus fragmentation is avoided and the atherothrombus is fixed under the stent struts. Loubeyre *et al.* demonstrated improved reperfusion in patients randomized to direct stenting as compared with standard primary PCI [69]. However, only patients with good distal visualization of the infarct-related artery after guidewire passage are suitable for direct stenting. The use of thrombectomy and distal protection devices is a more sophisticated technical approach for the prevention of distal embolization, although early studies using this technique showed no significant benefit compared with standard primary PCI [70,71]. However, the negative results of these trials should be interpreted within the limitations of their design, which was characterized by the enrollment of patients at low risk for no-reflow and by the use of first-generation, complex devices. A further study that used another still complex thrombectomy device in high-risk patients did show improvement of myocardial reperfusion [72]. The first randomized trial assessing the role of thrombectomy, performed with a simple manual aspiration catheter, was the REMEDIA trial [73]. This study proved that manual thrombectomy was safe and resulted in better myocardial perfusion as compared with standard primary PCI. Especially in the subset of patients with a high thrombus burden, a benefit was evident. A further substudy of the REMEDIA trial showed that thrombus aspiration significantly reduced no-reflow [74]. Svilaas *et al.* confirmed the improvement in reperfusion associated with manual thrombus aspiration as compared with standard primary

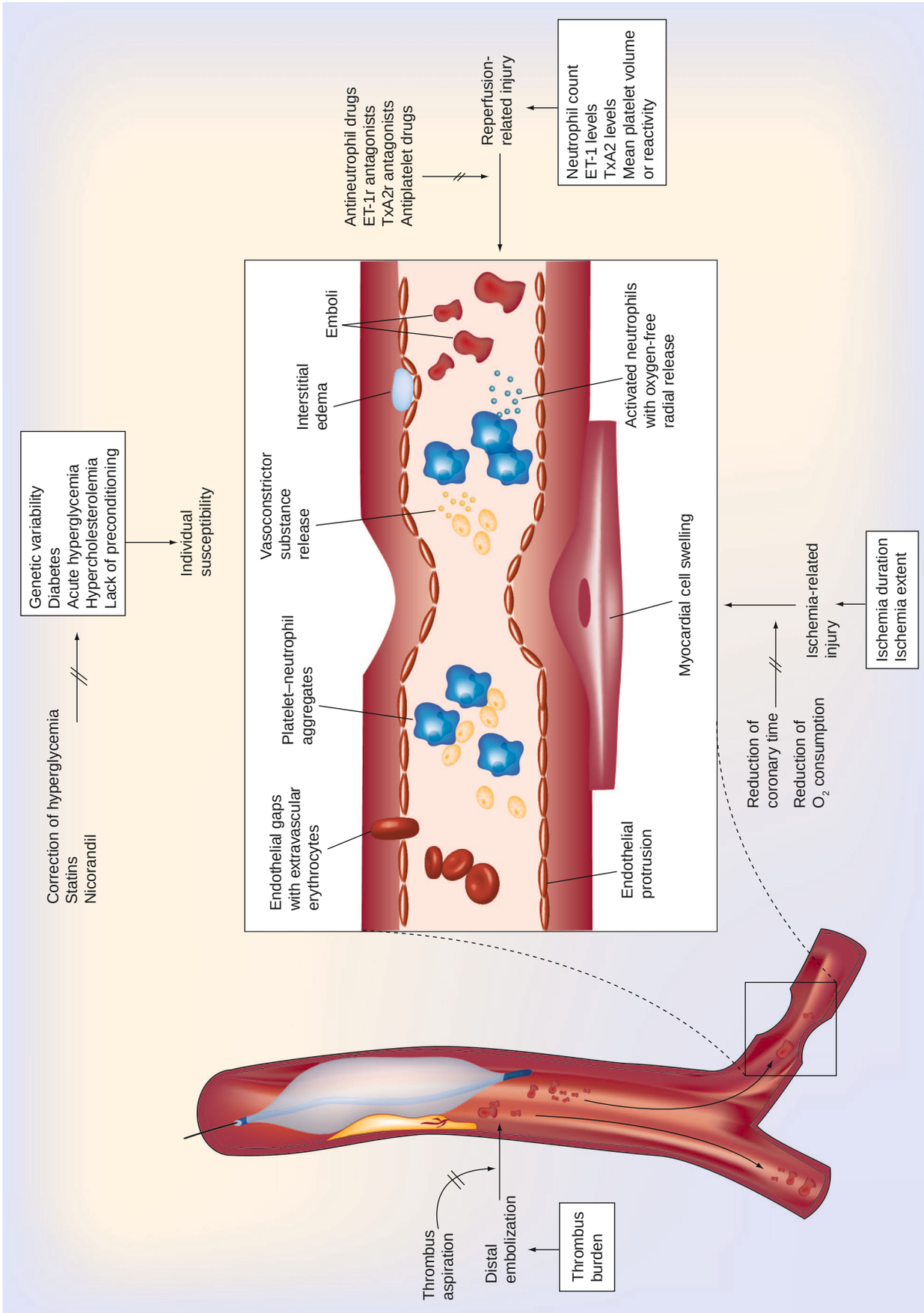

Figure 1. Therapies of no-reflow targeted to main pathogenetic mechanisms.
ET-1: Endothelin-1; ET-1r: Endothelin-1 receptor; TxA2: Thromboxane-A2; TxA2r: Thromboxane-A2 receptor.
Reproduced with permission from [4].

PCI [75]. The TAPAS study was the first to show that improvement of myocardial perfusion by manual thrombus aspiration results in a lower mortality at 12-month follow-up [76]. In a recent study, in patients with large anterior STEMI undergoing primary PCI, infarct size at 30 days was not significantly reduced by manual aspiration thrombectomy [77]. However, in this study, thrombus mass after wire passage was not taken into account. Taken together, manual thrombus aspiration should be used in the setting of primary PCI in patients with a high thrombus burden [78,79]. Figure 2 shows an aspirated thrombus mass in AMI. Furthermore, embolic protection devices should be used during SVG PCI when technically feasible [80,81]. However, distal embolic protection devices do not improve survival or re-infarction rates in patients undergoing native-artery PCI [82,83]. The reason for this might be that distal protection devices must cross the thrombotic lesion and so the risk of releasing thrombi during this passage is much higher in native vessels compared with the bigger SVG. In a recent retrospective study, the infusion of intracoronary drugs using a novel perfusion catheter seemed to be safe and could help to improve myocardial perfusion in a selected group of patients presenting with ACS who developed no-reflow during PCI [84]. Another issue is the role of antiplatelet therapy pretreatment in AMI. Mangiacapra *et al.* compared clopidogrel 600 and 300 mg loading doses in patients with ST-segment elevation myocardial infarction. Patients receiving the 600-mg loading dose of clopidogrel showed a significantly lower incidence of post-PCI myocardial blush grade 0 or 1 and the no-reflow phenomenon was significantly less common [85].

■ Prevention of ischemia-related injury

Strategies of reducing total ischemic time might reduce the prevalence of the no-reflow phenomenon. Pharmacologic drugs reducing myocardial oxygen consumption and, consequently, the severity of ischemia might improve outcome [86]. Beneficial effects of carvedilol, fosinopril and valsartan on coronary no-reflow have been demonstrated [87,88].

■ Prevention & treatment of reperfusion-related injury

Several studies have demonstrated that, in particular, drugs with the effect of counteracting endothelial dysfunction or platelet and neutrophil activation may be a prevention and/or treatment option for reperfusion no-reflow.

Antiplatelets

■ Glycoprotein IIb/IIIa antagonists

Petronio *et al.* demonstrated that abciximab improves myocardial perfusion when started during primary PCI and infused for 12 h thereafter [89]. In a small randomized study of abciximab versus tirofiban in patients undergoing primary PCI, Danzi *et al.* demonstrated similar rates of final TIMI flow grade 3 (86 vs 88%), adverse cardiac remodeling and clinical events at 1 month in both arms [90]. Stone *et al.* showed recently that in patients with large anterior STEMI presenting early after symptom onset and undergoing primary PCI with bivalirudin anticoagulation, infarct size at 30 days was significantly reduced by

Table 1. Positive randomized trials for the management of no-reflow.

Treatment	Patients (n)	Dose	Administration	Primary end points	Ref.
Thrombectomy	1071	–	During PCI	MBG 0–1	[76]
Abciximab iv.	100	0.25 mg/kg + 12-h infusion	Pre-, during and post-PCI	Clinical	[90]
Adenosine ic.	54	4-mg bolus	Pre-PCI	TIMI flow grade <3	[92]
Adenosine iv.	2118	50 or 70 µg/kg/min	Pre- and post-PCI	Clinical	[94]
Verapimil ic.	40	0.5 mg ic. + oral verapimil	Post-PCI	MCE	[95]
Nicorandil iv.	81	4-mg bolus + 6-mg/h infusion + oral nicorandil	Pre- and post-PCI	MCE	[100]
Nicorandil ic. + iv.	92	0.5 mg ic. + 4 mg iv. bolus and infusion of 6 mg/h	Pre- and post-PCI	Clinical	[101]
Atrial natriuretic peptide iv.	569	0.025 µg/kg per min for 3 days	Pre-, during and post-PCI	Infarct size and LVEF	[104]
Cyclosporine iv.	58	2.5 mg/kg bolus	Pre-PCI	Infarct size	[46]
Dipyridamole ic.	46	0.56 mg/kg bolus	During PCI	TIMI flow grade <3	[102]

ic.: Intracoronary; iv.: Intravenous; LVEF: Left ventricular ejection fraction; MBG: Myocardial blush grade; MCE: Myocardial contrast echocardiography; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction.

bolus intracoronary abciximab delivered to the infarct lesion site [77].

By contrast, glycoprotein IIb/IIIa receptor antagonists have failed to mitigate the impact of distal embolization in SVG intervention [91].

Vasodilators

■ Adenosine

Adenosine is mainly produced by the degradation of adenosine triphosphate, which antagonizes platelets and neutrophils, reduces calcium overload and oxygen free radicals, and induces vasodilation. Marzilli *et al.* showed that intracoronary administration of 4 mg of adenosine as an adjunct to primary PCI in AMI resulted in a lower rate of no-reflow as compared with the control arm [92]. Intravenous adenosine has been tested in two large randomized trials [93,94]. Both studies showed a significant reduction of infarct size, but in-hospital and 6-month clinical outcomes were similar to those observed in the placebo group.

■ Calcium-channel blocker

Taniyama *et al.* conducted a small randomized study and showed in patients with first STEMI that intracoronary verapamil compared with placebo was associated with better microvascular function [95]. Accordingly, intracoronary verapamil has been successfully used to reverse no-reflow after primary PCI [96]. For the prevention of no-reflow in vein grafts, nicardipin may be used [97].

■ Nitroprusside

Nitroprusside is a nitric oxide donor that does not depend on intracellular metabolism to derive nitric oxide. Two small registries showed an improvement in final TIMI flow grade after administration of intracoronary nitroprusside, given in an attempt to reverse no-reflow [98,99].

■ Nicorandil

Nicorandil is a hybrid drug consisting of an ATP-sensitive potassium ion channel opener and nicotinamide nitrate. Intravenous infusion of nicorandil for 24 h after primary PCI resulted in better angiographic, functional and clinical outcomes compared with placebo in two randomized studies [100,101].

■ Dipyridamole

Dipyridamole is a thromboxane synthase inhibitor and stops the effects of TxA2 (platelet aggregation and vasoconstriction). In a small randomized trial it was superior to verapimil for the treatment of no-reflow during primary angioplasty [102].

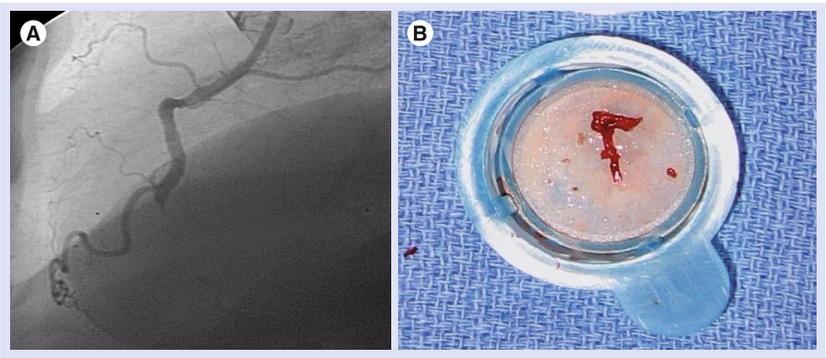

Figure 2. Aspirated thrombus in acute myocardial infarction. (A) Occluded right coronary artery. **(B)** Aspirated thrombus mass.

Hormones

■ Epinephrine

Skelding *et al.* analyzed 29 consecutive patients in whom intracoronary epinephrine was administered for refractory no-reflow [103]. Intracoronary epinephrine resulted in a significant improvement in coronary flow. These findings indicate that intracoronary epinephrine may exert salutary effects in patients suffering refractory no-reflow following elective or acute coronary interventions.

■ Atrial natriuretic peptide

Kitakaze *et al.* randomized 277 patients to receive intravenous atrial natriuretic peptide and 292 patients to receive placebo [104]. They showed that atrial natriuretic peptide treatment was associated with a significant reduction in infarct size, an increase in left ventricular ejection fraction and an improved myocardial perfusion.

Mitochondrial permeability transition pore inhibitors

■ Cyclosporine

Cyclosporine inhibits the opening of mitochondrial permeability transition pores and attenuates myocardial injury that occurs at the time of reperfusion. In a small randomized trial, administration of cyclosporine at the time of reperfusion was associated with a smaller infarct size than that seen with placebo [46].

Novel therapies

■ Exenatide

Exenatide is a glucagon-like peptide-1 analog. In patients with STEMI who are undergoing primary PCI, intravenous administration of exenatide at the time of reperfusion increased myocardial salvage [105].

■ Ischemic pre- & post-conditioning

One or several short cycles of ischemia before (preconditioning) or after (post-conditioning) a sustained coronary occlusion with subsequent reperfusion reduces the ultimate infarct size [45]. Ischemic post-conditioning, a mechanical maneuver at the onset of reperfusion, reduces infarct size after ischemia and was first described in 2003 by Zhao *et al.* [106]. Staat *et al.* showed that post-conditioning by coronary angioplasty protects the human heart during AMI [107]. Similar results were achieved by remote ischemic conditioning prior to PCI [108]. Current research is being addressed to understand the molecular mechanism of this protection.

■ Prevention of individual susceptibility

Unfortunately, genetically determined susceptibility to microcirculatory injury cannot be influenced yet. However, predisposition, as with diabetes and hypercholesterolemia, can be treated. Treatment of hyperglycemia might be an important target in the prevention of no-reflow. The DIGAMI study demonstrated a reduction of infarct size following a periprocedural reduction of blood glucose [109]. However, the DIGAMI 2 follow-up study demonstrated no effect on mortality [110]. In addition, the treatment of hypercholesterolemia by the use of statins might reduce reperfusion injury. Iwakura *et al.* demonstrated that chronic statin therapy in patients with or without hypercholesterolemia is associated with a lower prevalence of no-reflow [111].

Conclusion

The no-reflow phenomenon occurs both in elective and primary PCI and is associated with adverse outcomes. Microvascular obstruction is believed to be the underlying cause of no-reflow, which is induced by various pathophysiologic mechanisms. Coronary no-reflow results in prolonged myocardial ischemia. Owing to its negative prognostic relationship, this complication requires prompt diagnosis and treatment. Patients undergoing PCI for AMI and intervention of SVG are high-risk subsets. Several trials have demonstrated some benefit of intracoronary calcium-channel blockers, adenosine, nitroprusside, nicorandil and systemic abciximab in the treatment of no-reflow. Fewer data support the use of epinephrine, atrial natriuretic peptide, cyclosporine and dipyridamole. In the setting of high thrombus burden, thrombectomy and/or distal protection devices should be used for the prevention of no-reflow.

Future perspective

Future directions in no-reflow research include elucidation and targeted activation of intracellular cardioprotective signaling pathways. For example, ET-1 antagonists have shown beneficial effects in animal models [112]. M-PTP blockers or selective TxA2 antagonists might be other promising approaches for the treatment of no-reflow [46,58].

Executive summary

Myocardial tissue hypoperfusion despite patent epicardial coronary arteries

- No-reflow can be caused by microvascular obstruction.
- There are four pathogenetic mechanisms: distal embolization, ischemia-related injury, reperfusion-related injury and individual susceptibility.
- No-reflow has a negative impact on clinical outcome due to myonecrosis of the heart muscle.

Classification according to the duration of the preceding myocardial ischemia

- Interventional no-reflow: occurs following noninfarct percutaneous coronary intervention (PCI).
- Reperfusion no-reflow: follows PCI for reperfusion of an infarct-related coronary artery in the setting of acute myocardial infarction.

Different sensitivity of diagnostic tests explains the wide variety of reported incidence

- Routine diagnostic tests: angiographic thrombolysis in myocardial infarction flow grade; electrocardiography ST-segment resolution (in ST elevation myocardial infarction).
- Nonroutine diagnostic tests: myocardial blush grade; contrast echocardiography; computed tomography; MRI.

Prevention & treatment of no-reflow can be divided into pharmacological and mechanical approaches

- Administration of an intracoronary vasodilator (adenosine, calcium-channel blocker or nitroprusside) is reasonable to treat PCI-related no-reflow that occurs during primary or elective PCI.
- In the setting of acute myocardial infarction, evidence for a beneficial effect on no-reflow exists for abciximab, adenosine, nicorandil and nitroprusside.
- Epinephrine, atrial natriuretic peptide, cyclosporine and dipyridamole might have beneficial effects.
- Thrombectomy and/or embolic protection devices should be used for the prevention of no-reflow in the setting of high thrombus burden and during saphenous vein graft intervention.

Future perspective

- The elucidation and targeted activation of intracellular cardioprotective signaling pathways is a possible research direction.
- Development of more sophisticated mechanical devices will be seen in the future.

The development of better mechanical devices to prevent or reduce distal embolization is another area of potential advance in this field.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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