A Handbook of Primary PCI: No-Reflow Management

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17.1 Introduction

Although substantial progress has been made in recent decades in reducing mortality and performing optimal revascularization in patients with acute coronary syndrome (ACS) and stable coronary artery disease (CAD), one of the remaining challenges is to better prevent and treat extended myocardial damage despite "apparent" angiographic optimal percutaneous coronary intervention (PCI). The presence of no-reflow is related to higher risk of major adverse cardiac events (MACE) due to the poor healing of the infarct, adverse left ventricular remodelling, congestive heart failure occurrence and death. Despite optimal epicardial coronary artery reperfusion performed by PCI, distal microembolization into the coronary microcirculation limits myocardial salvage especially during ACS. No-reflow represents the ultimate stage of extended myocardial damage after PCI with absence of contrast medium progression in the coronary artery. This complication occurs mainly during ACS or during PCI of rotational atherectomy and venous graft in stable patients. The objective of this chapter is to describe how to manage a no-reflow phenomenon from the pathophysiology to the management in order to help physician to prevent this complication and if no-reflow occurs adapt therapeutics to limit myocardial damage and reduce poor outcomes.

17.2 Definition

The no-reflow phenomenon is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical obstruction [1].

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17.3 Pathophysiology

Understanding the pathophysiology of the no-reflow phenomenon is the key to manage this phenomenon and prevent poor outcome. After prolonged coronary occlusion and restoration of coronary blood flow, structural damage to the micro-vasculature reduces the amount of blood flow to the cardiac myocytes. This may lead to inadequate healing of the cardiac scar.

17.4 Aetiology

No-reflow phenomenon is commonly the consequence of distal embolization and reperfusion injury such as:

- Thrombus containing lesions (ACS)
- Oxygen free radical or cellular-mediated endothelial injury (ACS)
- Loss of microvascular compartment due to completed myocardial infarction
- Cellular and interstitial oedema
- Atherosclerotic debris (venous bypass graft or rotational atherectomy)
- Microvascular constriction of vasospasm (drugs, choc)

No-reflow generally occurs immediately after PCI between 1 and 3% of PCI and can arise in different clinical settings [2–8]:

- Late presentation ACS
- Large thrombus burden
- Venous bypass graft PCI
- Rotational atherectomy
- Cardiogenic shock

17.5 Diagnosis

17.5.1 Clinical Presentation

Generally during ACS, revascularization is associated with relief of symptoms such as chest pain and regression of the ST-segment elevation in the electrocardiogram (ECG) in absence of no-reflow. In the presence of no-reflow, in the catheterization laboratory, the clinical presentation of no-reflow is often sudden and tragic. Control of coronary angiography confirms contrast medium staining in the coronary artery; the patient might complain of chest pain and symptoms persistence with a residual or increase elevation of the ST segment generally followed by haemodynamic instability.

17.5.2 Coronary Angiography

Contrast medium progression speed into the coronary artery is preserved in the absence of sub occlusive coronary stenosis (<90%) and in the absence of microcirculation damage. Therefore, after successful revascularization of an epicardial coronary stenosis, contrast medium progression impairment could reflect microcirculation damage. From the Thrombolysis in Myocardial Infarction (TIMI) study group, two indices were described: TIMI flow grade 0–3 is a semi-quantitative variable that ranges from no contrast medium progression (0) to normal progression (3); TIMI frame count is a quantitative index calculating the number of frames between two landmarks proximal and distal to the interrogated coronary artery [9]. In patients with ACS and preserved TIMI grade flow after revascularization, microcirculation can also be evaluated with myocardial blush, which corresponds to a densitometric method, assessing maximum intensity of contrast medium in the microcirculation. In practice, coronary microvascular obstruction is defined as TIMI grade flow ≤3 with myocardial blush stagnation (grade 0 or 1) [10] and no-reflow as the absence of contrast progression in the coronary vessel of interest in his most evident form. However, this may be subtle with preserved TIMI flow and absence of myocardial blush.

17.6   Management of No-Reflow

17.6.1 No-Reflow Prevention: Before the Procedure

No-reflow phenomenon is rare among overall PCI (1–3%) although some situations are associated with higher rate of no-reflow; therefore, management of some factors could help to prevent its occurrence according to the aetiology. Traditional cardiovascular risk factors are associated with poor outcome and no-reflow increase rate. In patients with diabetes, optimal blood sugar control before the procedure could reduce the occurrence of no-reflow [11, 12]. An animal study suggests that hypertension might be associated with increased risk of no-reflow [13]. Meta-analysis showed that pre-procedural use of statins was associated with significant reduction rate of no-reflow by 4.2% in all PCI patients (risk ratio (RR) 0.56, 95% confidence interval (CI) 0.35–0.90, $P = 0.016$) and attenuated by 5.0% in non-STEMI patients (RR 0.41, 95% CI 0.18–0.94, $P = 0.035$). This benefit was mainly observed in the early or acute intensive statin therapy populations (RR 0.43, 95% CI 0.26–0.71, $P = 0.001$) [14]. Active double antiplatelet therapy will prevent PCI complications such as acute stent thrombosis, periprocedural myocardial infarction (MI) and no-reflow (Fig. 17.1).

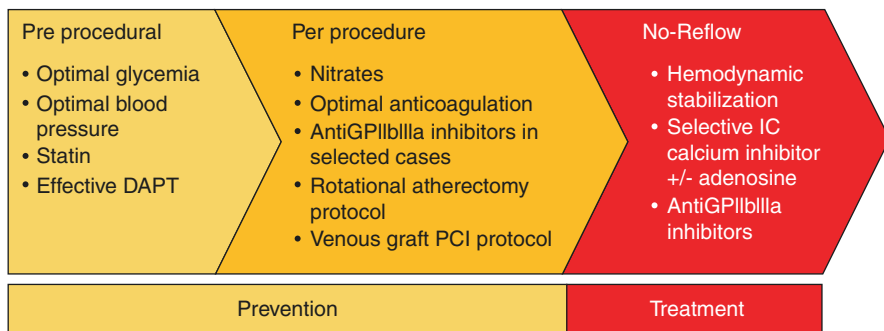### 17.6.2 No-Reflow Prevention: During the Procedure

General good practice of PCI could limit the no-reflow occurrence. Anticoagulation should be performed at the early phase of the procedure with unfractionated heparin

(70–100 UI/Kg) and monitored with the activated clotting time (ACT) (200–250). Intracoronary nitrates should be administered (100–200 mcg) as well at the early phase, i.e. second angiographic view of diagnostic procedure. Optimal catheter selection is key to avoid damping intracoronary pressures, which can reduce coronary flow due to catheter induced obstruction and thereby lead to thrombus formation. Regular and systematic flushing of catheters can avoid thrombus and air emboli. Because new microthrombus composed of platelet and fibrin is an important contributor to the pathogenesis of the no-reflow phenomenon, glycoprotein IIb/IIIa platelet receptor inhibitor (anti-GPIIb/IIIa) may be beneficial in prevention during PCI. Studies suggest that anti-GPIIb/IIIa is beneficial in reducing rates of death, reinfarction and urgent revascularization when used in conjunction with PCI particularly as a rescue strategy [15] (Fig. 17.1).

17.6.2.1 Rotational Atherectomy

Balloon angioplasty exerts beneficial effects by enlarging the weakest part of coronary artery wall thereby producing intimal splits and medial dissections in calcified lesions. In contrast, rotational atherectomy aims to weaken calcified lesions, erode calcium spicule protrusion and thereby obtains a relatively smooth luminal surface. Rotational atherectomy use a burr rotation with high speed which generate friction (microembolization) and heat (platelet activation) between the burr and calcify plaque.

In experimental modelling, heat varies with technique from 2.6 °C using intermittent ablation and permitting minimal decelerations (5000 rpm) to 13.9 °C using continuous ablation allowing excessive decelerations (16,000 rpm) [16]. Along with microembolization of debris associated with thrombi, thermal injury may contribute to microvascular obstruction and no-reflow. To prevent these phenomena, medical therapy includes effective dual antiplatelet therapy, vasodilators and proper use of rotablational atherectomy. The benefit of antiplatelet therapy was established with the use of anti-GPIIb/IIIa reducing procedural morbidity and CK-MB elevation [17]. Preventive vasodilators are used for the purpose of reducing slow-flow and no-reflow, combining nitrates with calcium inhibitors and sometimes adenosine in the flush solution associated with heparin. Nicardipine may be effective when administered in a flush solution with other drugs during rotational atherectomy [18]. Recommended manipulation of the rotational atherectomy to reduce the risk of

Pre procedural	Per procedure	No-Reflow
• Optimal glycemia • Optimal blood pressure • Statin • Effective DAPT	• Nitrates • Optimal anticoagulation • AntiGPIIbIIIa inhibitors in selected cases • Rotational atherectomy protocol • Venous graft PCI protocol	• Hemodynamic stabilization • Selective IC calcium inhibitor +/- adenosine • AntiGPIIbIIIa inhibitors
Prevention		Treatment

**Fig. 17.1** No-reflow prevention and treatment

complications is to perform short runs (15 s) with a pecking motion to preserve flow at a speed rate of 140,000 rpm and avoid deceleration >5000 rpm with maintained patient haemodynamics [19].

### 17.6.2.2   Venous Graft PCI

Venous graft intervention is associated with higher rates of periprocedural MI and in-hospital mortality compared with PCI of native coronary arteries due to highly friable atherothrombotic debris of venous graft lesion. Therefore, distal embolization may result in slow or no-reflow phenomenon in more than 10% of cases. To prevent this distal embolization, it is recommended (IA) [20] to use distal protection device during stent implantation. In practice an American national registry showed that this protection device was used only in less than 25% of venous graft PCI, but still, the use of protection device was independently associated with a lower incidence of no-reflow but not in-hospital mortality [21]. It is interesting to notice this study evaluated the use of intragraft infusion of adenosine during peri procedure venous graft PCI. The study showed a significant reduction of no-reflow rate and increase average peak velocity compared to control group [22]. Nicardipine may be effective when administered before PCI in vein grafts to prevent no-reflow with minimal systemic depressant effect [18].

17.6.3   No-Reflow Confirmation

Priority is to exclude other mechanical aetiology which could occur after PCI and limit the contrast progression (Fig. 17.2). After PCI other causes such as coronary spasm, diffusion of coronary haematoma, coronary dissection, intracoronary occlusive thrombus or distal coronary stenosis could have similar angiographic and clinical presentation. Therefore, the easiest way to confirm this diagnosis is to perform,
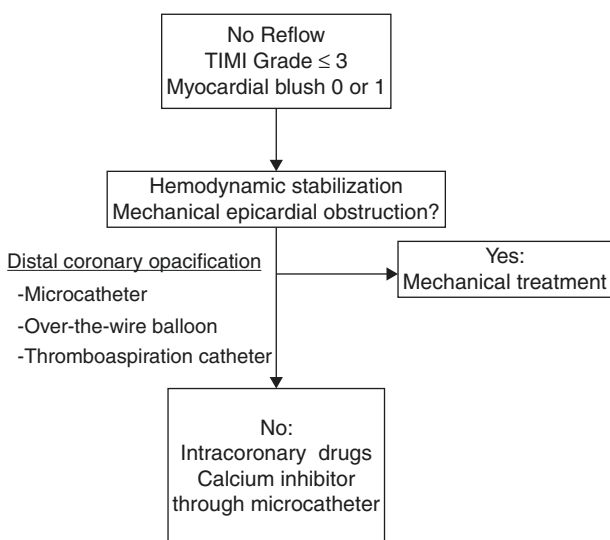
Fig. 17.2   No-reflow diagnosis and management
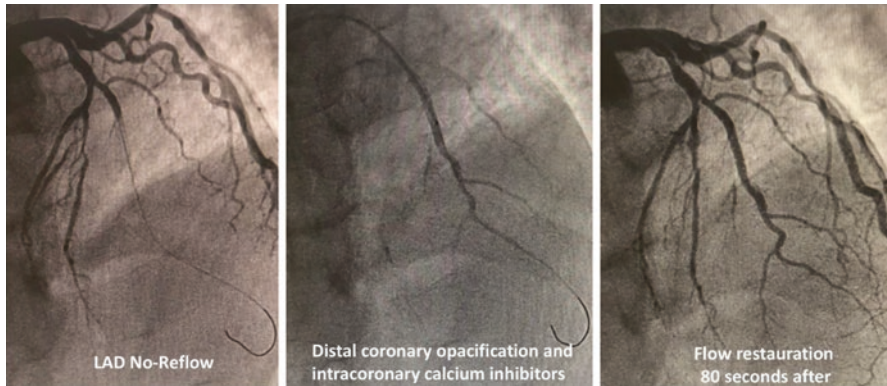
Fig. 17.3 Example of no-reflow management in a 72-year-old patient with anterior MI and no-reflow after DES implantation in the mid-left anterior descending artery

after nitrates administration, distal coronary opacification using extension of guiding catheter, intracoronary microcatheter, thromboaspiration catheter or over-the-wire angioplasty balloon. Careful and gentle distal contrast injection should be performed after aspirating some blood to confirm the true lumen position and the absence of obstruction due to thrombus or coronary wall at the exit of the catheter. Visualization of the distal part of the coronary artery is precious to exclude other causes of epicardial obstruction and confirm the no-reflow. Furthermore, microcatheters allow distal administration of drugs such as calcium inhibitors or adenosine which, by definition, could not reach the microvasculature in the no-reflow area from a guiding administration. An example is provided in Fig. 17.3.

17.6.4 No-Reflow Treatment

In no-reflow, microvascular damage is usually confined in the related coronary artery territory which constitutes a myocardial necrosis area. Therefore, treating no-reflow may not necessarily reduce the infarcted size but might improve blood flow to the necrotic area to improve area healing, infarction expansion and prevent left ventricular remodelling. Furthermore, restauration of flow will salvage the small vessels which may help promote collateral circulation and ensure drug delivery to the necrotic zone. To decrease the incidence of this phenomenon, short-term intracoronary and systemic drugs were studied to restore coronary flow within the no-reflow area (Table 17.1).

17.6.5 Haemodynamic Stabilization

Before starting dedicated therapeutics to treat no-reflow, it is essential to evaluate the patient haemodynamic to maintain optimal aortic blood pressure. Of note, no-reflow of the right coronary artery is prone to reflex hypotension or bradycardia which needs atropine administration. General supportive measures are usually used to maintain stable haemodynamic such as fluid administration and if necessary

Table 17.1 No-reflow aetiology, prevention and treatment

	Aetiology	Prevention	Treatment
Myocardial infarction	Thrombotic	Optimal anticoagulation Consider thrombectomy or balloon inflation to restore TIMI III flow with minimal invasive strategy	Anti-GPIIb/IIIa Intracoronary calcium inhibitors Adenosine
	Microvascular vasospasm	Nitrates	
Rotablator	Atherothrombotic embolization Platelet activation Vasospasm	Optimal anticoagulation Nitrates Maintained stable haemodynamic (temporary pacemaker/atropine in case of severe bradycardia) Flush infusion with nitrates and or calcium inhibitors	Intracoronary calcium inhibitors Adenosine
Venous graft	Atherothrombotic	Distal protection Adenosine intra graft Nicardipine	Intragraft calcium inhibitors Adenosine
Iatrogenic	Thrombotic	Optimal anticoagulation with ACT monitoring	Heparin anti-GPIIb/IIIa Consider balloon inflation or thrombectomy

inotrope support such as epinephrine. In rare refractory cases intra-aortic balloon pump might be an option to maintain overall coronary perfusion.

17.6.6 Thromboaspiration

One must realize that manipulating the occluded thrombotic vessel with balloons and stents often results in distal embolization of the thrombus, which might contribute to no-reflow occurrence. To prevent distal embolization, thromboaspiration might help to reduce the thrombus burden and therefore the degree of no-reflow. Thromboaspiration was widely used in the past years in STEMI patients, but recent study results and meta-analyses failed to show benefit with an increased risk of stroke. Therefore, actual guidelines do not recommend to perform systematic thromboaspiration [23].

17.6.7 Pharmacological Therapeutics

17.6.7.1 Adenosine

Adenosine used in myocardial infarction might have some benefit in terms of pre-venting extensive microcirculation injury. Intravenous adenosine, given before reperfusion therapy, was suggested to reduce infarct size compared with placebo in the AMISTAD randomized clinical trial [24]. Similarly, the larger AMISTAD II trial demonstrated infarct size reduction in the adenosine group compared with the placebo group, but without significant benefit in terms of clinical outcome [25].

When looking at the post hoc analysis of the AMISTAD II trial, in the subgroup with successful reperfusion within 3 h, the adjunct of adenosine infusion enhanced early and late survival and reduced the composite clinical endpoint of death or congestive heart failure at 6 months [26]. In addition, during reperfusion, the addition of intracoronary adenosine after thromboaspiration, through the thrombectomy catheter, showed a significant improvement in STR, with better 1-year left ventricular remodelling and reduction in clinical events compared with saline and nitroprusside [27, 28].

17.6.7.2 Statins
Based on STR, TIMI frame count and myocardial blush, Kim et al. showed that a high dose of atorvastatin may produce an optimal result in patients with STEMI undergoing PCI by improving microvascular myocardial perfusion, without significant clinical improvement [29].

17.6.7.3 Calcium Inhibitors and Other Drugs
Finally, intracoronary calcium inhibitors (verapamil, diltiazem and nicardipine) are probably the most evaluated and effective drugs available for the prevention and treatment of no-reflow phenomenon. In a meta-analysis by Su et al., including 7 trials involving 539 patients with intracoronary verapamil administration at a dosage of 200 µg to 2 mg, the authors showed a significant decrease in no-reflow incidence, a better TIMI grade and frame count and a reduction in major adverse cardiac events (MACE), 2 months after PCI (relative risk 0.56, 95% confidence interval 0.33–0.95) [30]. Another Meta-analysis of 8 randomized controlled trials involving 494 patients evaluated the efficacy of the combination of verapamil and diltiazem or verapamil alone to treat no-reflow which suggested significant clinical benefit over standard of care with respect to no-reflow [31].

Nitroprusside is an effective intracoronary drug in the treatment of no-reflow. Two meta-analyses showed that intracoronary nitroprusside is beneficial in preventing no-reflow in reducing TIMI frame count and in improving left ventricular ejection fraction. It is also likely to reduce MACE [32, 33].

17.7 Outcome

After the procedure, non-invasive indexes are of importance to evaluate the myocardial damage and assess potential poor outcome.

17.7.1 ECG

Among several indices to assess microvascular obstruction with ECG, only the residual ST-segment elevation was an independent predictor of microvascular injury (odds ratio 19.1, 95% confidence interval 2.4–154; $P = 0.005$) in multivariable analysis in a study evaluating ECG in 180 patients with STEMI. Interestingly,

ST-segment resolution was not associated with LV function, infarct size, transmurality indexes or microvascular injury in multivariable analysis [34] (Fig. 17.4a). A distortion of the terminal portion of the QRS complex was significantly associated with infarct size, impaired myocardial salvage and reperfusion injury in 572 patients with reperfused STEMI as assessed by cardiac magnetic resonance imaging (CMR). Moreover, this QRS modification was independently associated with MACE [35].

17.7.2 Echocardiography

Myocardial contrast echocardiography (MCE) is a bedside technique that can be used to assess microvascular perfusion (Fig. 17.4c). Echo contrast agents are microbubbles of inert gases of sizes and rheology similar to that of red blood cells and can be administered intravenously. Myocardial uptake of microbubbles is delayed in areas of "no-reflow" and MVO. MCE is able to detect only 1/3 of patients with a no-reflow phenomenon after ACS [36, 37]. However, widespread use of MCE has been hampered by a long learning curve for image acquisition and reporting,
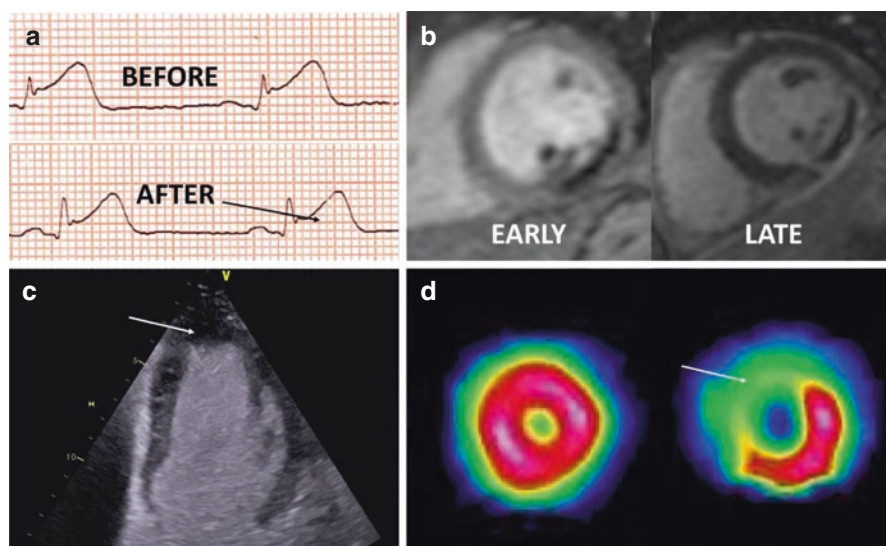
Fig. 17.4 Non-invasive tools to assess microvascular obstruction. (**a**) ST-segment resolution represents a useful tool of coronary microvascular obstruction after myocardial infarction. Black arrows showing absence of ST-segment resolution after artery recanalization. (**b**) Cardiac magnetic resonance. On late gadolinium enhancement, areas of microvascular obstruction are seen, hypoenhancement (so-called "dark zones") within an avidly enhancing site of myocardial infarction. (**c**) Myocardial contrast echocardiography showing lack of intra-myocardial contrast opacification (indicated by white arrow). (**d**) Single-photon emission computed tomography showing absent tracer uptake (white arrow, scintigraphic no-reflow phenomenon), as compared to normal uptake (left position). Adapted from Adjedj, J., et al. (2018). "Coronary microcirculation in acute myocardial ischaemia: From non-invasive to invasive absolute flow assessment." *Arch Cardiovasc Dis*

uncertain reproducibility, concerns over microbubble contrast safety. Moreover, MCE has some limitations such as operator skills, moderate spatial resolution, incomplete left ventricular coverage and semi-quantitative assessment of MVO.

17.7.3 Cardiac Magnetic Resonance

CMR is the non-invasive gold standard to assess MVO. It allows multislice imaging with high tissue contrast and high spatial resolution, enabling accurate quantification and localization of MVO and the infarct size relative to the entire left ventricle (Fig. 17.4b). CMR-defined MVO has been well correlated with MCE, angiographic and invasive indices used for the assessment of MVO [38]. Symons et al. demonstrated that early post-infarction CMR-based MVO was a strong independent predictor of MACE in reperfused STEMI patients at long-term follow-up. Remarkably, MVO extent ≥2.6% of LV was the strongest independent predictor of death and heart failure hospitalization, overriding the prognostic performance of traditional outcome predictors and leading to better long-term risk stratification [39].

17.7.4 Nuclear Imaging

Both single-photon emission computed tomography [40] and positron emission tomography (PET) [41] demonstrated the "no-reflow" phenomenon in humans could be detected by nuclear imaging. Nuclear imaging no-reflow phenomenon can occur in a subgroup of patients without angiographic no-reflow phenomenon, that the myocardial damage depends on the severity of microvascular damage and that prolonged ischemia time may increase the likelihood of "microvascular no-reflow phenomenon" (Fig. 17.4d) [42]. However, PET scanning is still underutilized in clinical practice, and its clinical use is limited to sites with PET scans and cyclotrons or generators.

Conclusion

Currently, there is still a lack of an optimal treatment for no-reflow phenomenon. Prevention is effective to reduce no-reflow occurrence with medical therapy and proper use of dedicated techniques such as rotational atherectomy and venous graft PCI. The diagnosis of no-reflow remains a challenge and, if not recognized, may be treated inadvertently by additional PCI which will only harm the situation. When no-reflow occurs, the main objective is to diagnose properly, stabilize the patient and treat this condition by sub selective administration of vasodilator drugs to "open" the microcirculation, avoiding a systemic effect on the blood pressure. No-reflow management aims to improve coronary blood flow at the level of microcirculation to reduce myocardial damage and improve clinical outcome.

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