Chapter 15
Management of No-Reflow

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The goal of myocardial reperfusion is not just to achieve an open epicardial artery, but to restore the normal blood flow to cardiac tissues. Classically, the"no-reflow phenomenon" (NR) is defined as a lack of myocardial perfusion despite thesuccessful opening of the occluded epicardialartery [1]. It most frequently happens in the setting of primary percutaneous coronary intervention (pPCI), but it can also be seen during elective PCI. No-reflow is evident by the slowing of the coronary flow, a higher TIMI frame count, and an abnormal or absent myocardial blush. The frequency of NR varies with the methodology used to assess it, ranging from 5% to 60% in the published data [2].

The pathophysiology of NR is still not fully elucidated, and several mechanisms are proposed. The main mechanism is the microvascular injury that can be caused both by *intrinsic* and by*extrinsic* vascular processes [3]. The intrinsic phenomena leading to microvascular obstruction (MVO) include microvascular thrombosis, the distal embolization of a thrombus/atheroma, vasospasm and endothelial damage. The extrinsic problems include microvascular compression due to edema and inflammation. Endothelial damage harms capillary integrity causing edema and the hemorrhagic transformation of the infarct core. Microvascular obstruction precedes myocardial hemorrhage. While MVO can be reversible, myocardial hemorrhage is not because iron deposition within the infarcted myocardium drives inflammation, increasing the likelihood of ventricular arrhythmias, adverse remodeling and

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adverse cardiac events [4]. Management strategies, at least theoretically, should be focused on preventing or modulating those mechanisms in order to avert the consequences of NR.

Sometimes, the term NR is also used to describe a sudden loss of epicardial flow, typically after ballooning a lesion or placing a stent. In this setting, NR might be secondary to incomplete lesion dilation, epicardial spasm, or epicardial dissection with or without *in situ* thrombosis. In these cases, the first step would be to use intravascular ultrasound to distinguish a dissection and a spasm from a microvascular phenomenon [5].

Despite considerable progress in the identification of the risks to NR development and the improvement of the management strategies for NR, no specific therapies have been developed so far. Unquestionably, those patients with NR who have received therapy and who succeed to improve coronary flow have a better prognosis [6]. These observations strongly suggest the importance of the recognition and appropriate management of NR.

Prevention of No-Reflow

Many classical risk factors for cardiovascular diseases are also the well-defined risk factors for NR, including hypertension, smoking, dyslipidemia, diabetes, and other inflammatory processes. The general measures taken in order to control these factors can reduce the occurrence of NR. Optimal blood glucose control before PCI reduce the occurrence of NR [7], both presumably improving the coronary microcirculation and avoiding the poor effects of acute hyperglycemia on reperfusion injury [8]. Similarly, intensive statin therapy before PCI in individuals with hyperlipidemia is advantageous in reducing NR. A meta-analysis of seven studies with pre-procedural statin therapy in 3086 patients has demonstrated the complete prevention of NR in 4.2% and the attenuation of no-reflow in the additional 5% of the patients treated with statins, compared with the control patients receiving a placebo, usual care, or lower-dose statin therapy [9].

Prediction of No-Reflow

The risk awareness of NR development is important. In the case of a patient at risk for NR, certain techniques might have some potential to reduce the degree of NR: primary stenting, the avoidance of high-pressure stent deployment and thrombectomy before the intervention [2].

The *patient-specific* features carrying a high risk for NR in STEMI patients include the following: a delayed presentation to the catheterization laboratory [6], hyperglycemia, and hypercholesterolemia, the female gender, hypertension, mild-to-moderate renal insufficiency, and elevated inflammatory markers [10–13].

The *lesion-specific* features affecting the risk for NR include plaque composition and a thrombus burden detected by intravascular ultrasound [14, 15]. However, any time-consuming procedure that might delay the door-to-balloon time is not recommended in the management of STEMI patients because a prolonged ischemic time is one of the strongest factors leading to a microcirculatory damage and the consequent development of NR [1].

The possible treatment modalities of NR include: (1) pharmacological therapy, (2) interventional treatment, and (3) non-invasive treatments.

Pharmacotherapy

Pharmacotherapy includes vasodilatators, antiplatelet drugs and fibrinolytic drugs. Basically, no significant difference was demonstrated between various pharmacological intervention strategies, but a significant clinical benefit was observed when NR was resolved [6].

Vasodilatators

In the majority of centers, the current standard of care when NR happens during PCI first includes checking whether the epicardial artery is optimally treated, only to be followed by the initiation of the intracoronary injection of a vasodilatator such as *adenosine*, at a dose of 100–200 mcg [16]; *nicardipine*, at a median dose of 400 mcg [17], or *nitroprusside*, at doses ranging from 50 to 300 mcg [18]. Other vasodilators include *nicorandil* (used in some laboratories). Frequent consecutive doses of the previously mentioned vasodilators may be repeated as long as they are well-tolerated by blood pressure. Distal coronary administration using a microinfusion catheter is preferred over injection through the guiding catheter because the latter may have significant systemic effects and because only a small amount of the agent is likely to actually reach the distal coronary bed [2].

Adenosine is a purine nucleoside that binds to adenosine receptors and exerts effects both on cardiac myocytes and on blood vessels. In ischemic cardiomycites within a few seconds of ischemia, the levels of endogen interstitial adenosine increase and cause arteriolar vasodilatation. In addition to vasodilatation, in experimental studies, adenosine had an inhibitory (protective) effect on many other mechanisms involved in myocardial ischemia and infarction, such as platelet aggregation, inflammatory cell activation, the generation of oxygen free radicals, and decreasing the cellular calcium overload [19]. Adenosine also has negative chronotropic and dromotropic effects.

Initial larger clinical trials investigating the use of adenosine to improve outcomes following intervention for STEMI were AMISTAD (Acute Myocardial Infarction Study of Adenosine) [20] and AMISTAD II [21]. In the AMISTAD trial,

the investigators examined if a continuous adenosine infusion [70 mcg/kg/min for 3 h or a placebo given before thrombolytic therapy) would reduce the myocardial infarct size as measured by SPECT imaging. In the AMISTAD II trial, the patients were randomized to a placebo or one of the two doses of intravenous adenosine (50 mcg/kg/min or 70 mcg/kg/min) in adjunction to either thrombolysis or PCI. In both trials, adenosine was shown to reduce the infarct size (if the dose of adenosine was 70 mcg/kg/min), but they failed to show improvements in clinical outcomes unless the patients had achieved early reperfusion with either thrombolysis (60%) or primary PCI (40%).

Vijayalakshmi et al. compared the use of intracoronary adenosine or verapamil in patients with STEMI and NSTEMI, thus showing that the use of either of the two agents was correlated with an improvement in coronary blood flow and, subsequently, in the wall motion index. Although both drugs had similar benefits, verapamil was associated with hypotension and complete heart block lasting up to 3 h in 18% of the cases [22]. The REOPENAMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial published by Niccoli et al. investigated the effect of intracoronary adenosine or nitroprusside in 240 patients with STEMI following intracoronary thrombus aspiration and showed a better ST-segment resolution at 90 min, as well as the more favorable remodeling of the left ventricle in the adenosine groupat 1 year of follow-up [23]. This positive effect was also translated into a lower incidence of the composite events that included myocardial infarction, heart failure, and death. These favorable effects were not seen in the nitroprusside group.

Multiple meta-analyses were performed regarding adenosine efficacy in preventing NR [24–28]. Although there was an overlap, the studies included in each meta-analysis varied, and their ultimate conclusions differed. The first conclusion of the meta-analysis performed by Su et al. [26] published in 2015 that included 11 randomized clinical trials with 1027 patients was that the quality and quantity of available research studies were insufficient and that the overall risk of the bias of the included studies was moderate. Secondly, they concluded that adenosine as a treatment for NR during pPCI could, on the one hand, reduce angiographic no-reflow (TIMI flow grade <3) (a relative risk 0.62, 95% CI 0.42–0.91, p value = 0.01), whereas on the other, it could also increasethe occurrence of adverse events such as: bradycardia (RR 6.32, 95% CI 2.98–13.41, p value <0.00001), hypotension (RR 11.43, 95% CI 2.75–47.57, p value = 0.0008) and atrioventricular (AV) block (RR 6.78, 95% CI 2.15–21.38, p value = 0.001). Indeed, Su et al. were unable to find supportive pieces of evidence suggesting that adenosine reduced all-cause mortality, non-fatal myocardial infarction or the incidence of the myocardial blush grade from 0 to 1. However, an updated meta-analysis performed by Bulluck et al. in 2016 including 13 randomized controlled trials investigating adenosine as an adjunct to reperfusion in 4273 STEMI patients revealed less heart failure (the risk ratio of 0.44 [95% CI 0.25–0.78], p = 0.005) and alower incidence of coronary no-reflow (the risk ratio for TIMI flow <3 post-reperfusion 0.68 [95% CI 0.47–0.99], p = 0.04) in patients given adenosine intracoronary, but not intravenously, compared to the control [28].

The dose of adenosine for NR treatment is obviously important. High-dose intracoronary adenosine (2–3 mg in total) and sodium nitroprusside (500 μg in total) during pPCI in a REFLO-STEMI study did not reduce the infarct size or the MVO measured by cardiac magnetic resonance. Furthermore, in this study, adenosine adversely affected the mid-term clinical outcome [29].

Adenosine has a very short half-life, which is its limitation. Data from animal models showed that a 2-h intracoronary adenosine infusion is superior to an adenosine bolus in ameliorating no-reflow [30]. However, adenosine infusion into the arterial bed may result in atrioventricular block. Summarizing the data, adenosine is not currently routinely used during PCI, but it may be used to treat no-reflow, preferably by intracoronary administration at a dose up to 2 mg.

Several *calcium channel blockers (CCB)* have been investigated for the efficacy in the treatment of NR, these including verapamil, diltiazem, and nicardipine.

Verapamil is an L-type CCB inhibiting the calcium ion influx through *slow channels* into the myocardium and the coronary arteries. Consequently, it relieves coronary vasospasm and improves myocardial perfusion. Indeed, this CCB agent has proven to be very efficient in relieving the anginal symptoms caused by coronary vasospasm. Intracoronary administered verapamil injection was associated with a reduction incoronary NR and short-term MACEs in the patients undergoing pPCI, whereas it had no impact on improving the ejection fraction [31]. Kaplan et al. compared intracoronary verapamil (100–500 g) with nitroglycerin for the treatment of NR in degenerated vein grafts and demonstrated an improved TIMI flow in all the patients treated with verapamil [32]. The meta-analyses assessing the efficacy of verapamil and diltiazem or verapamil alone for the treatment of NR have demonstrated a significant benefit over the standard of care with respect to NR [26, 33]. *Nicardipine* was beneficial in the studies of NR prevention during rotational atherectomy [34] and percutaneous interventions in vein grafts [35] with a minimal myocardial depressant effect [36]. At present, some interventionalists are using intracoronary verapamil, nicardipine, or diltiazem with a variable success for the treatment of NR. However, the present data are not sufficient to allow for definitive conclusions regarding CCB efficacy, but rather suggest the need for a large, randomized, controlled trial.

Nicorandile is a hybrid of the mitochondrial potassium-channel opener and nitrate, with a potential to mitigate NR. When isolated after reperfusion, mitochondria are structurally altered, contain large quantities of Ca2+, and produce an excess of oxygen free radicals. Their membrane pores are stimulated and the capacity for oxidative phosphorylation is irreversibly disrupted [37]. Nicorandil reduces intracellular calcium and leads to a relief from coronary vasospasm. Although therapy with nicorandil prior to reperfusion in the meta-analysis performed by Wu et al. in 2013 [38] was associated with the improvement of coronary reflow, as well as with the suppression of ventricular arrhythmia, and further improved the left ventricular function in the patients who underwent pPCI, the definite clinical benefits of nicorandil were not found due to the small sample size of the selected studies.

Sodium nitroprusside releases the nitric oxide (NO) that activates guanylate cyclase in the vascular smooth muscle. This leads to the increased production of

intracellular cGMP, which stimulates calcium ion movement from the cytoplasm to the endoplasmic reticulum, thus reducing the level of the available calcium ions that can bind to calmodulin. This ultimately results in the vascular smooth muscle relaxation and the vessel dilation. Intracoronary nitroprusside at the doses of 50–300 mcg was demonstrated to be quite effective in the treatment of no-reflow [2], especially so when injected distally in thecoronary artery. In this manner, it has a negligible systemic effect (on blood pressure), but induces a marked improvement of the coronary flow and the myocardial tissue blush. Nitroprusside combined with tirofiban was more effective compared to tirofiban alone in 162 STEMI patients who underwent pPCI with thrombus aspiration, including a more rapid ST-segment elevation resolution, fewer major adverse cardiac events, and a higher left ventricular ejection fraction [39]. However, the TIMI flow grade did not differ between the groups (rather suggesting that the TIMI flow grade is not the most sensitive method for defining coronary blood flow). In a small study assessing NR in STEMI patients, both nitroprusside and nicorandil improved coronary blood flow; however, nitroprusside was more effective when the TIMI frame count was measured [40]. Compared to the other drugs used for NR, nitroprusside appears to have a more sustained effect, especially when compared to adenosine [39], with which it may be combined in order to prolong adenosine effects [41]. There are also negative studies dedicated to the application of nitroprusside in the treatment of NR. In a study concerning the role of nitroprusside in the prevention of NR, nitroprusside failed to improve the coronary flow and myocardial tissue reperfusion, but it did improve the clinical outcomes at 6 months [42]. In order to overcome the limitations of small studies, two meta-analyses have been conducted with nitroprusside, both confirming a clear benefit of nitroprusside in the management of no-reflow during PCI [43, 44]. The total dose of nitroprusside given for NR is important. The high dose of intracoronary delivered nitroprusside (500 mcg total) immediately following thrombectomy and again following the stenting did not reduce the infarct size or the MVO measured by CMR (the REFLO-STEMI study) [29].

Anisodamine, a belladonna alkaloid employed in traditional Chinese medicine, is a non-subtype-selective muscarinic, and a nicotinic cholinoceptor antagonist, which has antioxidant, antithrombotic and antiarrhytmicproperties [45]. Like atropine and scopolamine, anisodamine exhibits the usual spectrum of the pharmacological effects of this drug class, although being less potent and less toxic than atropine. It also has a relatively weak alpha (1) adrenergic antagonistic activity, which may explain its vasodilatation capacity. It also interacts with and disruptsthe liposome structure which may reflect its effects on cellular membranes. The mechanism of the action of anisodamine implies the blockage of the intracelular Ca overload, which is one of the main apoptoic mehanisms due to the membrane protein damage by reactive oxygen species (ROS). Animal and clinical studies have shown that *anisodamine* can increase blood pressure and coronary perfusion pressure, and improve the microcirculation, thus making it a potentially useful drug for preventing NR. Recent meta-analysis comprising 41 RCTs involving 4069 patients showed

that, when compared to the standardly used vasodilatators (verapamil, adenosine, diltiazem and nicorandil), anisodamine is associated with higher LVEF and a lower risk from MACEs [46]. However, the authors of this meta-analysis suggested that, given the limited quality and quantity of the included studies, more rigorous randomized trials are needed to verify the role of this regimen.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa inhibitors) are powerful antiplatelet drugs proven to lower the thrombus burden in patients with myocardial infarction. According to the current ESC guidelines for the management of STEMI and NSTEMI [47, 48] GP IIb/IIIa inhibitors are the only drugs officially recommended as bailout therapy in the case of the angiographic evidence of a slow- or no-reflow, as reasonable (the class of recommendation IIa, the level of recommendation C) although this strategy has not been tested in a randomized trial. The AIDA AMI trial compared intracoronary to intravenous abciximab and found that the intracoronary abciximab bolus administration could possibly be related to the reduced rates of congestive heart failure at 90 days, but there were no differences in the combined endpoint of death, reinfarction, or congestive heart failure [49]. Unfortunately, there are no studies comparing the relative efficacy of a prolonged intravenous infusion compared to a single or multiple intracoronary boluses of abciximab. A small study of 49 patients compared anintracoronary bolus-only with an intravenous bolus plus the infusion of tirofiban, but found no superiority in either of the two [50]. According to a recent meta-analysis, the intralesional administration of IIb/IIIa compared to intracoronary administration yielded favorable outcomes in terms of myocardial tissue reperfusion as evidenced by the improved TIMI flow grade, a complete ST-segment resolution, and decreased MACE without increasing in-hospital major bleeding events [51]. The targeted strategy combining adjunctive IIb/IIIa platelet receptor antagonist administration with aspiration and prolonged balloon inflation was described in a series of 71 patients undergoing PCI for the ST-segment elevation, and this combination of therapies appeared to prevent NR [52].

Glucagon-Like Peptide (GLP)-1 Analog

A potentialof the *glucagon-like peptide (GLP)-1 analog*liraglutide to reduce NR was shown in a small, randomized, controlled trial conducted in 210 subjects [53]. The proposed mechanisms include the modulation of the glucose levels, reduced inflammation and the improved endothelial function, and a further study has been proposed.

Intracoronary Fibrinolytic Therapy

Intracoronary fibrinolytic therapy as an adjunct to pPCI in patients with a large intracoronary thrombus burden was tested only in few RCTs and registry studies [54]. The majority of the data suggested that fibrinolytic therapy as an adjunct to PCI is not useful in everyday clinical practice including the treatment of NR, and that a critical reappraisal of this therapy is needed. The studies of adjunctive fibrinolytic therapy to pPCI have multiple limitations; nevertheless, several of them demonstrate a positive effect on myocardial perfusion [55–57]. It is not known at present how much of this improvement may translate into a prognostic benefit.

Invasive Treatment

Deferred Stenting

The important mechanism behind NR is the embolization of the atherothrombotic debris during the manipulation of the culprit vessel and stent deployment is identified as a step with the highest risk of distal embolization. A deferred or delayed stenting strategy might be a feasible alternative to the conventional approach with immediate stenting in the selected STEMI patients undergoing pPCI. By delaying a stent implantation after mechanical flow restoration, vasodilators, antithrombotic drugs (GP IIb/IIIa inhibitors) and statins might be initiated, which can remove vasospasm, dissolve an intracoronary thrombus and stabilize an atherosclerotic plaque. Also, as the acute phase is resolved, this strategy allows the simultaneous intervention of the IRA and non-IRA vessels in patients with a multivessel disease. In the meta-analysis that included eight studies with 744 patients, deferred stenting satisfactorily improved the TIMI flow grade, TMBG, and a complete ST-segment resolution, and decreased MACEs without increasing the major bleeding events in patients with STEMI and a high thrombus burden [58].

Postconditioning

Postconditioning consists of brief, repeatedly induced coronary occlusions immediately after prolonged myocardial ischemia. Some evidences suggested that it is associated with a reduction in the myocardial infarct size compared with sudden reperfusion. The protection mechanism involves the activation of extracellular signal-regulated kinase, the production of nitric oxide, the opening of the mitochondrial potassium channels and the inhibition of the opening of the mitochondrial permeability transition pore. Staat et al. performed a study of 30 patients, in which the patients in the experimental group were submitted to the repeated inflation and

deflation of the angioplasty balloon (four times) immediately after coronary flow had been obtained. Compared to the control group, in the experimental group there was a significant decrease in the creatine kinase peak, the infarct size (as assessed by the level of creatine kinase) was lower (by 36%), and the blush grade was significantly higher [59].

Distal Embolic Protection Devices

There are two distal protection devices to capture embolic debris during PCI that have proven to be clinically beneficial for the PCI of saphenous vein graft lesions [60, 61]. However, the Protection Devices in PCI-Treatment of Myocardial Infarction for Salvage of Endangered Myocardium (the PROMISE study) by the FilterWire was announced as a negative one [62]. Nevertheless, the second generation of the FilterWire EZ System was further examined in the treatment of an acute myocardial infarction in the FLAME study and compared with aspiration alone by using the Export or Rescue catheter. This study showed that a combination of distal embolic protection with aspiration vs aspiration alone was significantly more efficient regarding the capture of embolic debris. However, despite those encouraging results seen in the combined group, no effect on the infarct size, or a clinical benefit was demonstrable [63]. There are currently no data to support the routine use of distal protection in the routine cases of pPCI.

Thrombus Aspiration

Manipulating the occluded area with balloons and stents might result in the distal embolization of a thrombus, thus contributing to the development of NR. Therefore, the prevention of distal embolization by thrombus aspiration before PCI should lessen the degree of NR and the results in better clinical outcomes. Indeed, this concept was initially confirmed in the ATTEMPT (Analysis of Trials on Thrombectomy in Acute Myocardial Infarction Based on Individual Patient Data) study [64], and thrombus aspiration has since become an integral part of the intervention, particularly when a visible thrombus is present. Thrombus aspiration must begin with forward aspiration starting proximal to the occlusion, making multiple passes, until the canalization of the vessel with an improved anterograde flow is demonstrated. However, a meta-analysis published by Mongeon et al. [65] failed to show a long-term benefit of thrombus aspiration in STEMI patients. Of note, it included many different studies applying various techniques, including rheolyticthrombectomy, which may increase NR in some patients [66].

In a more recent meta-analysis [67], large ($n \geq 1000$), randomized, controlled trials comparing manual thrombectomy and pPCI alone in STEMI patients were included (TAPAS, TASTE and TOTAL). The prespecified primary efficacy outcome

was cardiovascular mortality within 30 days, and the primary safety outcome was a stroke or a transient ischemic attack within 30 days. The authors concluded that routine thrombus aspiration during PCI for STEMI did not improve the clinical outcomes. However, in the high-risk subgroup (i.e. the one with a high thrombus burden), the trends toward reduced cardiovascular death, although coupled with an increased risk for a stroke or a transient ischemic attack, provide a rationale for future trials of improved thrombus aspiration.

The other complementary techniques that may help prevent distal embolization include the avoidance of high-pressure stent deployment and the full coverage of the diseased segment in the coronary artery [2].

Nonpharmacological Interventions

In addition to the procedures described in the preceding text, otherless well-supported, nonpharmacological treatment strategies for no-reflow have been described.

Hypothermia

There is some evidence that therapeutic hypothermia, given after initial reperfusion, can be beneficial in reducing the infarct size and the prevention of NR [68]. By using the rat model, Dai et al. showed that late hypothermia (performed by initiating a room-temperature saline solution 60 min after reperfusion) reduced the extent of the no-reflow size, but had no effect on the infarct size, suggesting that no-reflow is a true form of the reperfusion injury and is likely due to damage done to the microvasculature by reactive oxygen radicals.

The recently published COOL AMI EU pilot trial [69] investigated the rapid induction of therapeutic hypothermia (20 min of endovascular cooling at 33.6 °C) by using the ZOLL Proteus Intravascular Temperature Management System in 50 patients with anterior STEMI without cardiac arrest. Except for self-terminating atrial fibrillation, there was no excess of adverse events and no clinically important cooling-related delay to reperfusion. A statistically non-significant numerical 7.1% absolute and 30% relative reduction in the infarct size (measured by CMR) was reported, warranting a pivotal trial powered for efficacy.

Ischemic Postconditioning

Ischemic postconditioninghas been shown to reduce no-reflow in small trials, but similar larger studies failed to find such an effect [70, 71]. Long-term clinical follow-up and conduct of phase III trials are currently lacking.

Conclusion

No-reflow is a frequent occurrence during PCI in the setting of STEMI. Prevention and treatment are of supreme importance because NR is associated with a larger infarct size, a reduced ejection fraction, and higher mortality. The prevention of NR necessitates shorter door-to-balloon times and the avoidance of long stents and high-pressure stent development. When there is angiographic evidence of a thrombus burden, intracoronary thrombectomy might be used. Distal protection devices have less proven long-term benefits. When NR is recognized, pharmacological intervention proves to be beneficial (according to the current knowledge, preferably the distal intracoronary infusion of adenosine or nitroprusside with a repetition if needed). The problem of NR has not yet been solved and further work in this field is needed.

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