Refractory No-Reflow Phenomenon: Do We Need a New Player?

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Abstract:

Primary percutaneous coronary intervention is now considered the standard treatment for patients with ST Elevation Myocardial Infarction according to the latest guidelines. No-reflow is defined as the lack of myocardial perfusion despite opening the epicardial coronary vessels in the setting of PCI. It may be observed in up to 0.6 – 5 % of elective cases and up to 50% of primary PCI cases. Pharmacotherapy for the treatment of no-reflow had focused primarily on local vasodilator and antiplatelet therapy. Despite different agents used, no-reflow continues to be refractory in large percentage among primary PCI patients. Accordingly, the need for a new agent to be used in management of refractory no-reflow urged many investigators to study the effect of epinephrine in no-reflow. Although epinephrine has been used clinically to treat cardiopulmonary arrest, there is a paucity of published data regarding its effectiveness in no-reflow.
Keywords: No-reflow; Primary PCI; Acute myocardial infarction; Epinephrine; Adenosine.

Definition & History

In the era of immediate reperfusion for patients presenting with ST elevation myocardial infarction (STEMI), all the efforts are devoted to shorten the duration of culprit vessel occlusion and reverse myocardial ischemia in order to reduce myocardial necrosis. However, despite all these efforts, there is still a residual risk of myocardial ischemia which emerged under the title of no-reflow phenomenon (Menees et al. 2013).

No-reflow phenomenon represents impaired myocardial perfusion which is attributed to microvascular obstruction (MVO) despite opening the occluded epicardial coronary artery (Jaffe et al. 2008).

Classically, no-reflow phenomenon was defined in 2001 by Eeckhout and Kern as incomplete myocardial perfusion in absence of angiographic evidence of mechanical obstruction during primary percutaneous coronary intervention (PCI) (Eeckhout and Kern 2001).

Incidence

No-reflow incidence varies according to the clinical presentation of the patient, being around 2% in elective native coronary percutaneous coronary
interventions (PCI), 20% in saphenous venous graft (SVG) intervention and up to 26% - 50% in primary PCI (PPCI) in acute myocardial infarction (AMI) (Svilaas et al. 2008).

Pathophysiology

Since no-flow has been firstly described in 1974 (Kloner et al. 1974), several mechanisms have been proposed for development of no-reflow phenomenon. The mechanism of no-reflow is complex, multifactorial and it could be explained by the following theories:

A) Ischemia injury

Changes at the endothelial level start to occur with prolonged myocardial ischemia, bleb formation and endothelial protrusion obstructing the microcirculation. On the other hand, endothelial cell necrosis impairs vascular integrity and increase permeability with extravasation of fluid and blood cells which eventually compress coronary microvasculature (Bouleti et al. 2015).

B) Reperfusion injury

Reperfusion injury starts to appear with establishment of myocardial flow which in turn accelerates tissue edema and endothelial disruption. Also, damaged endothelial cells, neutrophils, and platelets share in prolonged vasoconstriction of coronary microcirculation. Autonomic dysfunction as well plays a role in
development of no-reflow through alpha adrenergic receptor mediated vasoconstriction of coronary microcirculation (Hearse and Bolli 1992).

C) Endothelial injury

Myocardial ischemia dissociates the vascular endothelial growth factor receptor 2/ VE-cadherin complex, leading to increased endothelial permeability that share in development of no-reflow (Weis and Cheresh 2005).

D) Distal atherothrombotic embolization

Primary PCI is usually performed in situations with high thrombus burden and manipulations during the procedure leads to distal dislodgment of microthrombi and plaque components (Jaffe et al. 2010).

Therefore, based on these underlying mechanisms, no-reflow can be classified into two main categories, structural (irreversible) and functional (reversible) no reflow (Figure 1: Classification of different types of no-reflow) (Gupta and Gupta 2016).

**Predictors of no-reflow phenomenon**

Several studies have been conducted to identify the risk factors and predictors for development of no-reflow phenomenon. A meta-analysis of 27 studies in
2018 suggested that advanced age, male gender, elevated blood pressure, smoking, elevated blood glucose, family history of coronary artery disease, delayed reperfusion, elevated serum creatinine, Killip class ≥2, tachycardia, impaired left ventricular function, long lesion length, multivessel disease and high thrombus burden were proven to be predictors of no-reflow development (Fajar et al. 2018).

Recently in 2020, a study conducted on 1658 patients proposed a new risk scoring model as a predictor for development of the no-reflow during primary PCI (Table 1) (Yang et al. 2020).

**Clinical Impact of no-reflow phenomenon**

Considerable number of patients undergoing primary PCI has impaired myocardial reperfusion despite opening the culprit vessel, establishment of the myocardial blood flow and absence of thrombosis or spasm (Roe et al. 2001). This may be justified by irreversible myocardial necrosis, reversible myocardial stunning or combination of both (Niccoli et al. 2010).

On short term follow up, no-reflow phenomenon has been associated in different studies with prolonged hospitalization compared with patients without no-reflow (Bouleti et al. 2015). In a study conducted on 1140 patients, development of no-reflow during primary PCI was associated with larger infarct...
size, impaired left ventricular systolic function at six months and increased one year mortality risk (Ndrepepa et al. 2010). On long term follow up, no-reflow was proven to be a strong predictor of five years mortality (Ndrepepa et al. 2010).

**Diagnosis of no-reflow**

Diagnosis of no-reflow starts from the clinical scenario of the patient and pass through various diagnostic modalities. Clinical presentation of no-reflow is almost acute where the patient experiences severe agonizing chest pain together with hemodynamic instability (Rezkalla and Kloner 2002).

1- Coronary Angiography

The no-reflow phenomenon should be suspected in any situation of impaired TIMI flow after rule out of similar situations. Spasm of the epicardial coronary arteries should be excluded by the administration of intracoronary nitroglycerin boluses (Muller et al. 2008).

In fact, the term no-reflow phenomenon emerged after the observation of absence of coronary flow despite stent deployment and opening the occluded coronary vessel. TIMI flow scale has been developed for evaluation of different coronary flow grades during PCI procedures as following:

- Grade 0: No detected flow or penetration
- Grade 1: Minimal penetration and no myocardial perfusion
- Grade 2: Partial myocardial perfusion
- Grade 3: complete myocardial perfusion in which blood flow distally is as rapid as flow proximally (Appleby et al. 2000).

On the other hand, TIMI flow possess low sensitivity and specificity for accurate assessment of capillary blood flow and a significant number of patients who established TIMI III flow has impaired capillary perfusion (Henriques et al. 2003). Accordingly, Myocardial Blush Grade (MBG) is considered a more reliable and accurate measurement of coronary flow depending on contrast opacification as following:

- 0: Absent myocardial opacification
- 1: Mild myocardial opacification
- 2: Moderate myocardial opacification but less than that of normal coronary angiography
- 3: Normal contrast opacification similar to that of normal coronary angiography (Henriques et al. 2003).

Another angiographic method for assessment of no-reflow phenomenon is TIMI frame count (TFC) which is calculated from the first frame in which dye completely appears at infarcted vessel and ending with the frame in which it reaches standardized distal coronary landmarks (Gibson et al. 1996).
Intracoronary pressure measurements are another adjunctive method that could confirm diagnosis no-reflow phenomenon. However, up till now, no enough available clinical data suggests standard use of these pressure wires for evaluation of no-reflow (Eeckhout and Kern 2001). Finally, local contrast injection through a double-lumen catheter or aspiration catheter is another technique through which the operator can confirm angiographic no-reflow (Eeckhout and Kern 2001).

2- Cardiac magnetic resonance imaging (CMR)

Cardiac magnetic resonance imaging with gadolinium enhancement is considered the gold standard non-invasive modality for assessment of microvascular obstruction (MVO) (Pineda et al. 2008). Up till now, no specific guideline recommendations for the best timing or type of sequence to assess MVO by CMR. However, in most of the studies, CMR after STEMI was usually performed between 2 and 9 days post primary PCI, as the extent of both MVO and infarction significantly increases in the first 48 hours post reperfusion. The distribution of extracellular contrast agent (gadolinium chelate) after injection reflects the state of coronary microcirculation. Gadolinium enhancement can identify MVO in two ways:
• First-pass perfusion imaging: it is measured immediately after contrast injection to assess microvascular obstruction (MVO) that is defined as a persistent area of hypoenhancement in the center of the infarcted myocardial territory.

• Late MVO: it is measured within 15 min after contrast injection (Kaur et al. 2021).

In homogenous study among primary PCI patients, it has been found that late MVO is superior to early MVO as a predictor for regional and global left ventricular functional recovery (Nijveldt et al. 2008).

Also, addition of CMR T2 weighted sequences adds important information regarding tissue edema and intramyocardial hemorrhage (Allencherril et al. 2019).

3- Other Techniques

Other diagnostic modalities may be used to confirm presence of no-reflow such as the electrocardiogram (ECG), contrast echocardiography and nuclear imaging studies but because of their low sensitivity, they are rarely used in clinical practice for diagnosis of no-reflow (Table 2) (Galasso et al. 2014).

Management of No-reflow phenomenon
Several studies and meta-analysis have addressed the different therapeutic approaches for management of no-reflow phenomenon. However, up till now there is no universal agreement on a certain approach for management of no-reflow phenomenon. European Association of Percutaneous Cardiovascular Interventions (EAPCI) has proposed a check-list algorithm to deal with no-reflow phenomenon in catheterization lab (Figure 2: Check-list for management of no-reflow phenomenon).

A) Prevention of no-reflow

Management of no-reflow starts by precautions that should be undertaken to prevent rather than treat no-reflow phenomenon. Shorter door to balloon time, optimal blood glucose and optimal blood pressure are the first steps that should be achieved to prevent no-reflow phenomenon (Malmberg et al. 1995; Rezkalla et al. 2017).

B) Treatment of no-reflow

Pharmacotherapy for the management of no-reflow had always been considering two main strategies: local vasodilator and antiplatelet therapy.

1- Thrombus Aspiration

Thrombus aspiration was suggested as potential solution to minimize the risk of distal embolization which shares in no-reflow pathophysiology.
Routine use of thrombus aspiration has been a matter of debate until 2017 ESC guidelines for STEMI that settled this debate and gave class III recommendation to routine use of thrombus aspiration in primary PCI (Class III) (Dizdarevic 2017). However, in cases of large thrombus burden, the operator could consider thrombus aspiration as part of the preliminary steps for prevention and management of no-reflow (Fröbert et al. 2013; Jolly et al. 2015).

2- Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors are antiplatelets that minimize and abort thrombotic events by inhibiting platelet aggregation and vascular clotting. INFUSE-AMI trial which was conducted on acute myocardial infarction patients undergoing primary PCI showed that intracoronary abciximab injection significantly decreased the infarct size at 30 days post myocardial infarction as demonstrated by Cardiac MRI (Stone et al. 2012). On the other hand, due to high bleeding risk, the 2017 ESC guidelines for STEMI stated that glycoprotein IIb/IIIa inhibitors should be considered only for bailout situation in case of no-reflow or impaired TIMI flow ( Class IIa recommendation ) (Dizdarevic 2017).

3-Nitroprusside
The 2011 American colleague of cardiology (ACC) Percutaneous coronary intervention guidelines give a class IIa recommendation for using intracoronary vasodilator namely: adenosine, nitroprusside or calcium channel blocker for management of no-reflow that may occur during primary or elective PCI (Levine et al. 2011).

Nitroprusside is one of the agents that could abort no-reflow by guanylate cyclase activation resulting in smooth muscle relaxation and vasodilation. Local distal administration of nitroprusside usually doesn’t affect systemic blood pressure with a significant improvement in myocardial perfusion. A meta-analysis published in 2014 showed that intracoronary sodium nitroprusside reduces corrected TIMI frame count, improves left ventricular function and reduces occurance of major adverse cardiovascular events (Zhao et al. 2014).

4-Calcium channel blockers

A meta-analysis of seven trials on 539 patients has showed that intracoronary verapamil administration decreases the rate of major adverse cardiovascular events after 2 months in patients who underwent PCI (Su et al. 2013). In particular, nicardipine was shown to be beneficial in prevention of no-reflow in venous grafts intervention and during using rotablator (Fischell et al. 2008). However, up till now, published data are insufficient to validate use of calcium channel blocker as standard
treatment for no-reflow and larger randomized controlled trials are still needed.

5-Adenosine

Adenosine is one of the agents recommended by ACC guidelines for management of no-reflow phenomenon. It exerts its effect through relaxation of coronary microcirculation smooth muscles beside having antiplatelets properties (Rezkalla et al. 2017). The beneficial effect also extended beyond vasodilatation to preservation of vascular endothelium in the ischemic areas (Marzilli et al. 2000).

The evidence behind use of adenosine in management of no-reflow came from AMISTAD-II trials in which high adenosine dose administration (70 mg/kg/min infused for 3 h) resulted in a significant reduction in infarct size (Kloner et al. 2006). Also, the REOPENAMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial showed that ST-segment resolution after 90 min was significantly better in the adenosine arm compared to nitroprusside arm (Niccoli et al. 2013).

Dilemma about need for a new agent

On the other hand, a major limitation of adenosine is having very short half-life. Recent studies revealed that two hours intracoronary adenosine infusion is better than an adenosine bolus in aborting no-reflow. However, the main issue regarding adenosine infusion is that it may result in atrioventricular block.
Accordingly, adenosine can’t be used in the setting of heart block, sinus bradycardia and Juntional rhythm which are not uncommon during STEMI and primary PCI (Rezkalla et al. 2017).

In addition, despite different agents used, refractory no-reflow which is defined as no-reflow that don’t resolve even after using at least two agents of adenosine, verapamil and glycoprotein IIb/ IIIa inhibitors still exists in large percentage among primary PCI patients.

Accordingly, the need for a new agent to be used in management of refractory no-reflow phenomenon and in the situations where adenosine is contraindicated urged many investigators to study the effect of epinephrine in no-reflow. Although epinephrine is one of the main agents in resuscitating arrested patients, only few available published data regarding its effectiveness in coronary no-reflow is available (Aksu et al. 2015).

In 2002, Skelding et al. were the first to study epinephrine effect in no-reflow and showed that intracoronary epinephrine administration resulted in significant improvement of coronary flow and successful resolution of no-reflow phenomenon in 29 patients underwent PCI (Skelding et al. 2002). Later on, Aksu et al. (2015) declared that intracoronary epinephrine was effective in 12 patients suffering refractory no-reflow during primary PCI. They reported that intracoronary epinephrine administration significantly improved TIMI flow, TFC, and TIMI myocardial blush grade in almost all patients (Aksu et al. 2015).
Recently, Navarese et al. (2021) revealed that Intracoronary administration of epinephrine for treatment of no-reflow phenomenon during primary PCI yielded significantly better coronary flow patterns compared to those treated with conventional agents alone including nitrates, adenosine, thrombectomy and glycoprotein IIb/ III a inhibitors (Navarese et al. 2021). This may be explained by the well-known inotropic and chronotropic properties of epinephrine (DiCarlo et al. 1988). Patients who develop no-reflow usually presented with hypotension and intracoronary epinephrine administration may restore normal blood pressure in those patients through alpha vasoconstrictor receptors stimulation. In addition, correction of hypotension improves coronary perfusion which may be another potential mechanism in aborting no-reflow (Aksu et al. 2015).

Another potential explanation for the role of epinephrine in no-reflow is that it has potent beta-2 receptor agonist properties that mediate coronary vasodilatation (Skelding et al. 2002).

**Conclusion**

During Primary PCI, Intracoronary epinephrine may be an effective agent for management of refractory no-reflow phenomenon in cases of contraindication or failure of other conventional agents. Further larger studies are still needed to confirm efficacy and safety of epinephrine as one of the standard treatment of no-reflow phenomenon.
Key Points

- No-reflow phenomenon is not uncommon during Primary percutaneous coronary intervention (PCI) which is the standard guidelines based treatment for patients with ST-segment Elevation Myocardial Infarction (STEMI).

- No-reflow can be either structural (irreversible) due to endothelial and ischemic injury or functional (reversible) due to distal embolization, reperfusion injury and vasospasm.

- No-reflow is diagnosed in catheterization laboratory using TIMI flow, MBG and TIMI frame count. However, cardiac magnetic resonance imaging with gadolinium enhancement is considered the gold standard non-invasive modality for assessment of microvascular obstruction (MVO).

- Pharmacotherapy for the management of no-reflow had always been considering two main strategies: local vasodilator therapy specially adenosine and local antiplatelet therapy.

- According to few recent studies, intracoronary epinephrine has been proven to be an effective agent for management of refractory no-reflow phenomenon specially in cases of contraindication or failure of other conventional agents.
References


percutaneous coronary intervention in patients with acute myocardial infarction.


