Review Article

Management of no-reflow: Still an unsolved problem?

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No-reflow represents an important limitation of percutaneous coronary intervention in patients with ST-elevation myocardial infarction. Importantly, no-reflow is associated with an increased risk of major adverse cardiac events. In this review, we discuss the pharmacological and non-pharmacological interventions proposed for the prevention and treatment of no-reflow, highlighting the new updates and evidences on efficacy of these approaches.

Key Words: *No-reflow; ST-segment myocardial infarction; Percutaneous coronary intervention*

INTRODUCTION

Percutaneous coronary intervention (PCI) is the best available reperfusion strategy in patients with acute ST-segment elevation myocardial infarction (STEMI). Its goal is to restore coronary blood flow and provide tissue reperfusion, thus reducing myocardial infarct size. One of the most important limitation of PCI is no-reflow (NR), a phenomenon consisting in a not optimal myocardial reperfusion despite an effective epicardial recanalization of the infarct-related artery. During the "primary PCI age" NR has been shown to have an incidence of up to 30% according to several reports [1].

In humans, pathophysiology of NR consists of the variable combination of four components: 1) distal atherothrombotic embolization; 2) ischemic injury; 3) ischemia/reperfusion injury; and 4) susceptibility of coronary microcirculation to injury [2].

Diagnosis of NR can be made invasively or non-invasively. This phenomenon can be diagnosed with angiography, using Thrombolysis in myocardial infarction (TIMI) flow grade [3] and myocardial blush grade (MBG) [4], or using a Doppler wire. After PCI, NR can be investigated by electrocardiography, myocardial contrast echocardiography (MCE) or cardiac magnetic resonance imaging (CMR), which is the diagnostic gold standard, being able to quantify the phenomenon [1].

Coronary NR has been shown to increase the risk of cardiovascular events and it has been associated with worse short- and long-term outcomes. This prompted interventionalists to try to overcome this phenomenon using various strategies. However, clear guidelines on the management of NR are still not available.

In this review, we discuss the pharmacological and non-pharmacological interventions proposed for the prevention and treatment of NR, highlighting the new updates and evidences on efficacy of these approaches.

RISK FACTORS AND OUTCOMES OF NO-REFLOW

Detection of patients at higher risk for NR before PCI may be beneficial from the perspective of prevention and treatment of this phenomenon. However, most of the conditions that have been associated with NR overlap with well-known cardiovascular risk factors, such as older age, male gender, arterial hypertension, smoking, diabetes mellitus and dyslipidemia [5]. Unsuccessful myocardial reperfusion after primary PCI has also been linked with Killip class ≥ 2, hypotension at admission, high coronary thrombus burden, low TIMI flow grade before PCI and, importantly, with delayed reperfusion [6,7], recalling the rule "time is muscle, time is outcomes".

Indeed, NR has been linked with severe clinical outcomes [8,9]. A study analysing 4329 patients with STEMI treated with PCI from a Korean multicentre registry has shown that NR was associated with poor in-hospital outcome and increased long-term mortality, mainly driven by increased cardiac mortality [8]. Interestingly, a multicentre study comparing 17547 patients with good final coronary flow with 590 patients with transient and 144 patients with persistent NR confirmed these results showing that in-hospital, 30-day all-cause and one-year all-cause mortalities were higher in patients with persistent NR and with transient no-reflow compared with patients with a normal flow, with the highest mortality occurring early (<30 days) in the persistent NR group ($p<0.0001$) [10].

PREVENTION AND TREATMENT

Considering the well-established association between NR and severe adverse outcomes, many efforts have been made by clinicians and researchers in order to prevent and treat this unsolved PCI complication.

Nevertheless, little progresses have been made in the management of NR, with no treatment having been proved to be decisive for the prevention or treatment of NR in clinical randomized controlled trials or observational studies [7, 10,11].

In the context of management of NR different approaches can be identified, pharmacological and non-pharmacological, that can be performed before, during or after catheterization (Figure 1).

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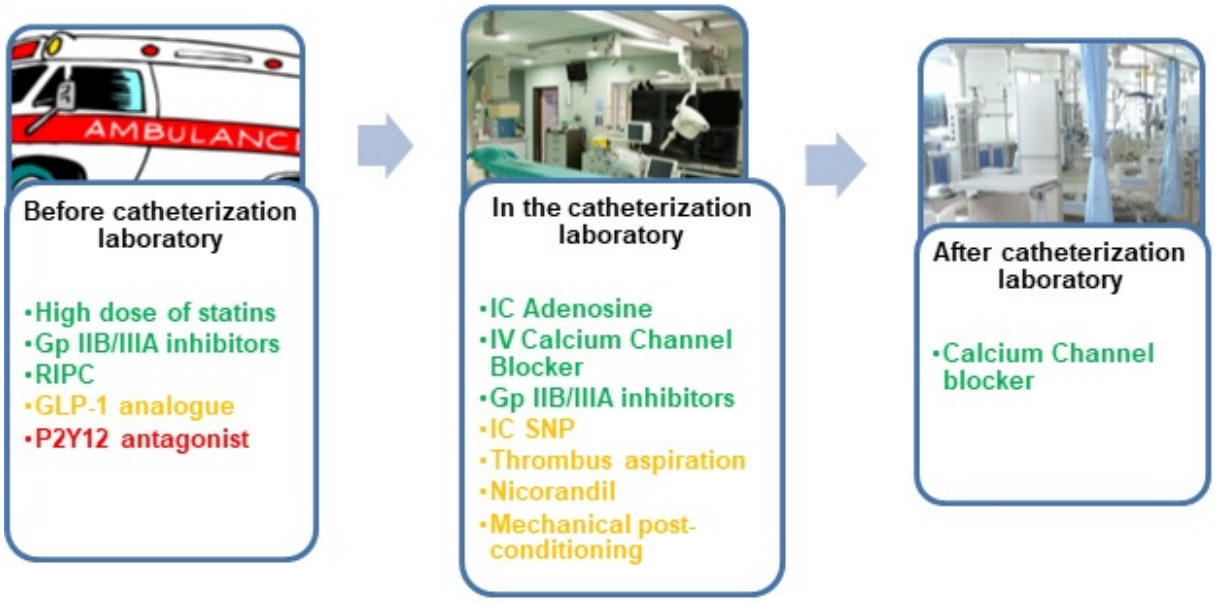

Figure 1) current treatments to prevent or treat no reflow phenomenon in different time windows. RIPC: Remote Ischemic Pre-Conditioning; IC: Intracoronary; IV: Intravenous; SNP: Sodium Nitroprussiate.

PHARMACOLOGICAL TREATMENT

Adenosine

Adenosine, an endogen purine nucleoside with vasodilating and antiplatelet properties, can has been shown to reduce intracellular calcium overload and oxygen free radicals production [12,13]. Moreover, adenosine has well-known negative chronotropic and dromotropic effects. The AMISTAD [14] and AMISTAD-II trials [15], specifically designed to investigate the role of adenosine in STEMI, showed a significant improvement in ST-segment resolution (STR) with high-dose adenosine (70 mg/kg/min intravenously infused for 3 hours started before reperfusion) when compared to placebo. However, there were no significant differences in the primary endpoint of new congestive heart failure, re-hospitalization for congestive heart failure or death from any cause at 6 months among the two groups [14,15]. Nevertheless, in a post-hoc analysis of the AMISTAD II study [16], adenosine was associated with better short- and long-term mortality rates.

Interestingly, other studies were performed in order to investigate differences in administration routes, timing and dosages. The REOPEN-AMI trial [17] showed that high dose intracoronary (IC) adenosine improved STR and enzymatic infarct size compared to placebo or sodium nitroprusside in patients with STEMI [17]. On the opposite, the REFLO-STEMI trial, comparing IC administration of adenosine with IC nitroprussiate or placebo, did not find a significant reduction in infarct size or microvascular obstruction (MVO) measured by CMR between the experimental groups compared to placebo [18]. Moreover, there was a significant increase in adverse cardiac events (HR 6.53, p value 0.01) in the adenosine group compared with control, mainly driven by heart failure at 30 days (HR 5.39, p=0.04) and 6 months (HR 6.53, p=0.01). Also Garcia-Dorado et al. failed in demonstrating that IC administration of adenosine prior to PCI can limit infarct size by CMR when compared to placebo in patients with STEMI (20.8% vs. 22.5%, p=0.40) [19].

Several meta-analyses have been published on this regard in the last years, confirming these conflicting results [20-24]. Polimeni et al. found that adenosine was associated with a reduction in the incidence of heart failure (RR=0.50; p=0.02) and both short- and long-term major adverse cardiac events (MACE) (respectively, RR=0.62; p=0.04; RR=0.61; p=0.03) [23]. Other meta-analyses showed some benefits with adenosine in terms of post-procedural coronary flow but did not show any benefits related to cardiac function and clinical outcomes [20-22]. Interestingly, Bulluck et al. published a meta-analysis of 13 RCTs (4273 patients) dividing them into 2 subgroups according to adenosine administration route: IC (8 RCTs) or intravenous (5 RCTs). IC adenosine was associated with lower incidence of heart failure (RR 0.44; p=0.005) and coronary NR (RR 0.68; p=0.04) whereas, interestingly, there was no significant difference in heart failure and NR between intravenously administered adenosine and placebo [24].

Despite controversial data, IC adenosine may have a role in the treatment of NR, especially when administered IC, early and at high dosages.

Calcium channel blockers

Some different calcium channel blockers, such as verapamil, diltiazem, and nicardipine have been investigated to limit NR phenomenon. These molecules are supposed to improve microvascular function and to prevent arterial microvascular spasm. Small studies investigated their effects on myocardial reperfusion after primary PCI, mostly studying final TIMI flow grade; however, clinical implications of using calcium channel blocker during primary PCI are still controversial or not investigated [25-27]. Rezkalla et al. retrospectively explored the effect of nicardipine, verapamil and nitroprusside on coronary blood flow after primary PCI, finding that pharmacologic therapy was equally effective in improving coronary flow in terms of TIMI flow and MBG (both p value<0.0001) [11]. Furthermore,

patients who received pharmacologic therapy were less prone to develop clinical composite of congestive heart failure, cardiogenic shock or death as compared with patients who did not receive calcium channel blocker (9% vs. 23%) [11]. In RECOVER AMI trial, 102 STEMI patients with NR were randomly treated with verapamil, diltiazem or nitroglycerine. This study showed a significant improvement in final coronary flow with diltiazem or verapamil compared to nitroglycerine [26]. Interestingly, an observational study showed that IC injection of 100-200 γ g verapamil immediately after NR diagnosis improved final coronary flow reaching TIMI 3 in 21 of 25 patients (84%); adverse effects such as bradycardia and transient grade-II sinoatrial block were registered, but all adverse effects were solved with intravenous injection of atropine (Figure 2) [27].

A recent meta-analysis analyzing 8 RCTs including 494 patients showed that IC verapamil and diltiazem injection is safe and significantly decreased NR compared to control group (RR 0.3; p=0.0002) [28]. Also, an improvement in wall motion abnormality and a reduction in 6-months MACEs were found with verapamil and diltiazem. In 2017 a study investigating the effects of verapamil or sodium nitroprusside (SNP) on MVO in 60 patients with STEMI found that verapamil was associated with lower incidence of angiographic MVO compared with SNP (13.3 vs. 40%; p=0.02), as well as higher rate of STR ≥70% (33.3 vs. 6.7%; p=0.01). There was a trend towards improved left ventricular ejection fraction with verapamil compared to SNP (42.6 ± 4.9 vs. 40.4 ± 4.7%, p=0.09), but with similar wall motion score index (1.43 ± 0.1 vs. 1.45 ± 0.2, p=0.14). Both groups had similar 30-day MACEs (3.3 vs. 6.7%, respectively; P=0.55). Verapamil was associated with lower incidence of hypotension compared with SNP (3.3 vs. 20%, p=0.04) [29].

Huang et al. studied the efficacy of nicardipine administered by IC route at the dose of 360–460 mg in 72 patients with NR, finding that 71 patients improved TIMI flow grade with nicardipine from a mean of 1.65 to 2.97 (p<0.001)[30]. Furthermore more recently IC nicardipine has been evaluated in 30 patients with chest pain and a coronary slow-flow phenomenon, characterized by delayed coronary opacification during diagnostic angiography in the absence of epicardial coronary artery disease. IC nicardipine improved coronary flow with a significant reduction in corrected TIMI frame count (CTFC) (47 ± 17 vs. 15 ± 5, p<0.001) [31]. Even if data available in literature are still insufficient for definitive conclusions, angiographical effects of calcium channel blockers in patients with NR are very promising. Large randomized trials, including CMR and clinical endpoints, are needed to confirm these positive observational results.

Nicorandil

Nicorandil is a dual-action potassium channel opener as well as nitric oxide donor; it relaxes vascular smooth muscle through membrane hyperpolarization, increasing transmembrane potassium conductance and intracellular concentration of cyclic GMP; moreover it could regulate plasma NO and endothelin-1 [32]. A recent meta-analysis of 14 RCTs found that nicorandil administered prior to reperfusion in patients with STEMI treated with primary PCI was associated with a significant reduction in the rate of final TIMI flow grade ≤2 (p=0.0006), an increased left ventricular ejection fraction (p=0.008) and a reduction in ventricular arrhythmia (p=0.001) when compared with PCI alone[33]. Furthermore a randomized study assessed the effect of nicorandil and anisodamine on the prevention of NR after primary PCI. In total of 104 consecutive STEMI patients the proportion of patients achieving TIMI flow grade 3 was significantly higher in patients treated with anisodamine plus nicorandil than in the other groups (p=0.014) [34]. An interesting recently published study randomized 120 STEMI patients to IC nicorandil (2 mg, IC at 2 mm beyond the occlusion) or nitroprusside (200 μg, IC) or PCI alone [35]. As compared with PCI, sodium nitroprusside and nicorandil significantly improved TIMI flow grade (p<0.05), STR (p<0.05) and reduced the incidence of angiographical NR (p=0.013) [35].

The effect of nicorandil administration distally to the thrombus during primary PCI was also investigated in a recent randomized controlled trial [36]. 170 STEMI patients underwent thrombectomy and tirofiban (10 μg/kg) injection distal to the culprit lesion and were randomized to nicorandil or saline injection at the same site. The numbers of patients achieving TIMI flow 3 was greater in the nicorandil group compared to control group (95.24% vs. 86.05%; p=0.040). Freedom from MACEs was 92.9% in the nicorandil group and 81.4% in the placebo (p=0.026). Ventricular arrhythmias occurred in 5.95% and 16.28% patients in the nicorandil and control groups, respectively (p=0.032) [36].

These recent data support nicorandil as a possible pharmacological agent in preventing and limiting NR phenomenon after primary PCI in patients with STEMI. Early administration of nicorandil distal to the culprit lesion during PCI in STEMI patients may reduce the incidence of reperfusion injury and may improve short-term clinical outcomes.

Nitroprusside

Nitroprussiate is an iron and cyanide salt and direct donor of nitric oxide (NO); it activates guanylate cyclase in the vascular smooth muscles cells leading to intense vasodilation. In NR setting vasodilators are supposed to improve microvascular function by preventing microvessel spasm and regulating endothelial function. However, the already mentioned REFLO-STEMI trial failed to demonstrate a reduction in infarct size or MVO with 250 γ g IC SNP [18]. Another interesting study comparing IC SNP with nicorandil in 49 patients with STEMI with NR showed that SNP was more effective in reducing CTFC (SNP vs. NC: 0.88 ± 0.79, 0.37 ± 0.37, p=0.008; 0.59 ± 0.23, 0.36 ± 0.27, p=0.003, respectively) [37]. Furthermore, a study investigating the effects of tirofiban plus SNP versus tirofiban alone in 162 consecutive patients with STEMI, found better angiographical and electrocardiographical parameters of myocardial reperfusion in patients treated with IC SNP compared to control group (CTFC 23 ± 7 vs. 29 ± 11, p<0.001; STR 72.5% versus 55.9%, p=0.040) [38].

A recent meta-analysis highlighting the effect of IC SNP on myocardial reperfusion and clinical outcomes in STEMI patients undergoing PCI showed that IC SNP was associated with a significant reduction in the incidence of TIMI flow grade ≤ 2 (RR 0.47; p=0.001) and MACEs (RR 0.43; p=0.001); no significant difference in STR was noted [39]. However, a recent, single-center retrospective study found that thrombus aspiration was associated with a better final TIMI flow compared with early administration of IC SNP, without any difference in short- and long-term MACEs between groups [40]. A recent trial randomized patients with STEMI by administering no SNP (n=40), SNP before balloon dilatation (n=40) or SNP after each balloon dilatation and before contrast agent refilling (n=40) during primary PCI [41]. Angiographical final result was better in patients receiving SNP compared to control group (TIMI grade 3: p=0.025); in particular, the incidence of TIMI grade 3 was higher in patients treated with repeated administration of SNP compared to early SNP administration (p=0.045).

Results from studies investigating the effects of SNP on myocardial reperfusion during primary PCI are conflicting and non-conclusive. In particular, small RCTs reported some promising results (especially with IC administration) that request confirmations from larger randomized studies.

Other pharmacological interventions

Efficacy of several others drugs have been investigated to prevent or treat NR.

Antiplatelet drugs were suggested to be potentially effective in preventing NR, eventually by reducing distal thrombus embolization. Interestingly, a recent study conducted in 140 STEMI patients highlighted that platelet reactivity level, estimated with VerifyNow® assay measured during PCI, is independently associated with NR: mean platelet reactivity was higher in patients with NR compared with patients with effective myocardial reperfusion (268.3 ± 53 vs. 223.8 ± 50.1 reaction units, p=0.002) [42].

A meta-analysis including 14 RCTs and 1 observational study investigated the effect of preoperative loading dose ticagrelor and clopidogrel in patients with STEMI undergoing PCI and showed that the incidence of NR (*I2*=0%, 95% CI: 0.15, 0.39, p<0.05), in CTFC (*I2*=0%, 95% CI: -8.89,-6.91, p<0.05) and the incidence of MACE (*I2*=19%, 95% CI: 0.41, 0.82, p<0.05) were reduced with ticagrelor as compared to clopidogrel, without an increase in bleeding events [43].

Among antiplatelet agents, also glycoprotein IIb/IIIa inhibitors were investigated for the treatment of NR. IC administration of tirofiban in 162 STEMI patients undergoing PCI was associated with higher TIMI flow grade ($p<0.001$) and lower in-hospital MACEs incidence ($p<0.013$) compared to placebo [44].

A study from McCartney et al. published in 2019 showed that low-dose IC alteplase (both 10 mg and 20 mg) did not reduce MVO compared to placebo in 440 patients with STEMI treated with primary PCI [45].

Even if only retrospective data are available, IC epinephrine demonstrated to be effective in restoring TIMI flow 3 in 75% of patients with NR [46]. In that very small study (12 patients with NR) epinephrine was well tolerated, but larger studies are needed to confirm those results.

Liraglutide, a glucagon-like peptide-1 (GLP-1), seems to exert a cardioprotective effect during ischemia/reperfusion injury. In a recent randomized controlled study liraglutide reduced the prevalence of NR (5% vs. 15%, $p=0.01$) compared to placebo in a total of 284 patients with STEMI undergoing PCI [47]. Interestingly, it was associated with a significant reduction in serum high-sensitivity C-reactive protein levels 6 hour after reperfusion; however, no differences were observed in short-term MACEs. The intriguing cardioprotective effect of liraglutide was also suggested by another study showing the association between liraglutide and a significant improvement in left ventricular ejection fraction 3 months after reperfusion [48]. However, despite these enthusiastic initial studies, larger studies are required to confirm this potential treatment area for this hypoglycemic drug.

THROMBUS ASPIRATION

Manipulating plaque area with balloons and stents during primary PCI often results in thrombus distal embolization, which may contribute to the development of NR. Thrombus aspiration (TA) devices have been developed to remove thrombi from coronary arteries, thus reducing thrombus load and distal embolization. However, some recent studies showed no benefit on clinical outcomes of routine thrombus aspiration during primary PCI with some safety concern regarding an increased risk of stroke [49-52]. For this reason ESC and ACC/AHA guidelines relegate to class III indication routine aspiration strategy, which could be considered in the presence of large thrombus burden [53,54].

Data on efficacy of manual thrombectomy in preventing NR are conflicting. In the TOTAL trial that randomized patients to manual thrombectomy versus PCI alone, the rate of STR was lower in the thrombectomy group (28% vs. 30.2%, $p<0.001$); however, the two groups showed the same rate of final TIMI flow 3 ($p=0.12$) [55]. Interestingly, a recent study including 295 patients undergoing TA during primary PCI showed that the effective retrieval of visible aspiration material was associated with a reduction of NR ($p<0.001$) as compared with TA without visible thrombus material [56], thus suggesting a possible role of TA in the management of NR in the presence of large thrombus burden.

Furthermore, the JETSTENT study, including STEMI patients with angiographic evidence of large thrombus burden, demonstrated an improvement in STR with Angiojet mechanical thrombectomy device compared to PCI alone [57]. Of note, the use of Angiojet was associated with a reduction in 1-year MACEs (14.9% vs. 22.7%).

Aspiration strategies are not attractive for routine use during primary PCI due to the lack of clinical benefit and the controversial effects on myocardial reperfusion. However, the abovementioned recent data suggest a possible role of TA in the prevention and treatment of NR in patients with STEMI in the presence of high thrombus burden.

MECHANICAL POSTCONDITIONING

In addition to pharmacological treatment and thrombus aspiration, conditioning strategies have been proposed to optimize myocardial reperfusion and reduce myocardial infarct size. Bøtker et al. investigated the effects of remote ischaemic conditioning before hospital admission in patients with suspected STEMI [58]. Their protocol consisted in applying three 5-min cycles of brief ischaemia and reperfusion of the upper arm and resulted in an increased in myocardial salvage in the conditioning group compared to control group ($p=0.033$). Moreover, remote ischaemic pre-conditioning (RIPC) showed to improve STR when added to morphine before primary PCI [59]. Crimi et al. investigated the effect of RIPC in patients with STEMI after the demonstration of left anterior descending artery in patients with anterior STEMI [60]. Remote conditioning, consisting of 3 cycles of 5-min ischemia/reperfusion of the lower limb by cuff inflation/deflation at the time of primary PCI, was effective in reducing enzymatic infarct size, improving T2-weighted edema volume by CMR and STR as compared with PCI alone [60].

Despite RIPC gave these promising results, post-conditioning, consisting in a series of brief coronary re-occlusion/reperfusion before the final arterial re-opening, showed conflicting results. A recent randomized controlled trial including patients with STEMI and basal TIMI flow 0 or 1, failed to demonstrate an improvement in clinical outcome in the experimental arm compared to conventional PCI [61]. In particular, post-conditioning did not reduce infarct size, myocardial salvage index and the extent of MVO; the rates of final TIMI flow 3 and STR were similar in both groups [61]. However, a study by Traverse et al. showed an association between post-conditioning and an improvement in left ventricular remodeling and MVO by CMR 1 year after primary PCI in patients with STEMI [62].

Conditioning strategies aim at reducing ischemic and ischemia/reperfusion injury and several mechanisms, including both humoral and neural factors, may be involved in cardioprotective effect of conditioning [63]. The currently available conflicting results and the absence of a standardized conditioning protocol should prompt investigators to perform larger, powered studies to define the cardioprotective effect of conditioning in patients with STEMI.

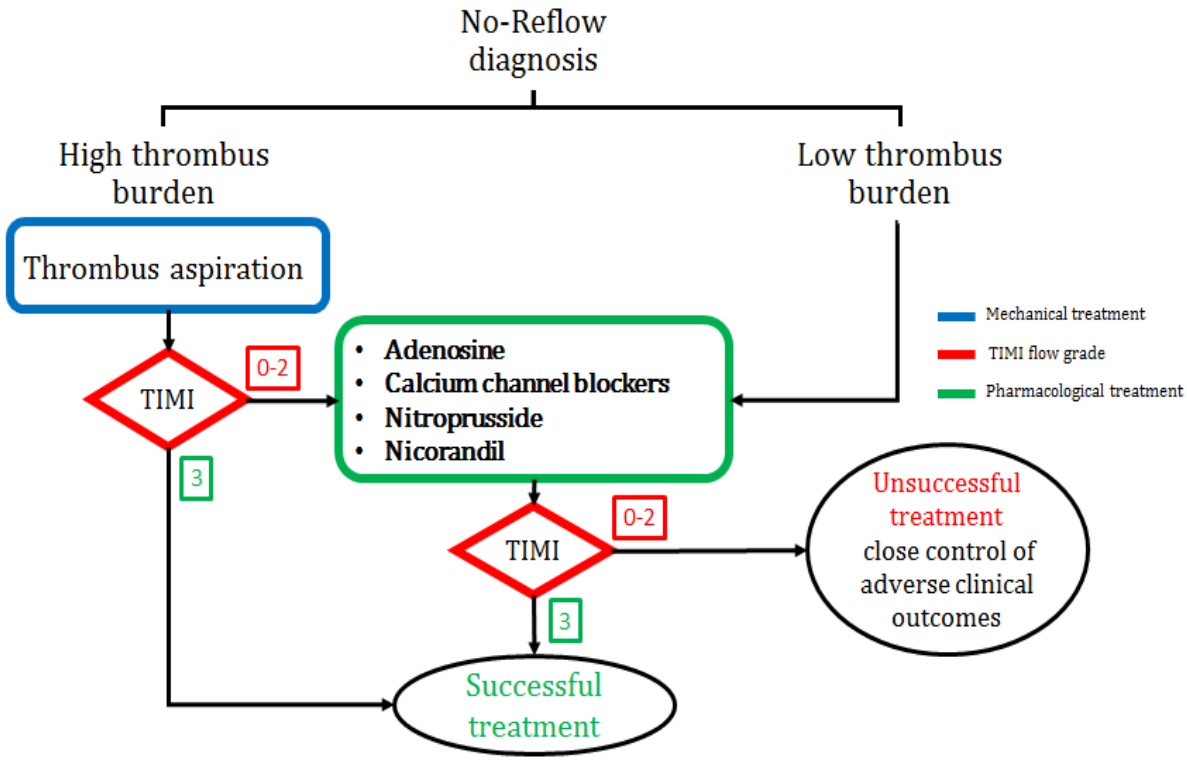

Figure 2) Thrombus aspiration may be a reasonable therapeutic option when high thrombus burden is present. In case of failure of the mechanical procedures, or with a low thrombus burden, pharmacological strategy should be considered according to TIMI flow. TIMI: Thrombolysis in Myocardial Infarction flow grade.

CONCLUSIONS

The NR phenomenon represents an unsolved problem that reduces the benefits of primary PCI in patients with STEMI. Of importance, NR increases the risk of future cardiovascular events and it has been associated with worse clinical outcomes. NR pathophysiology comprises several mechanisms and different preventive and therapeutic strategies, both pharmacological and mechanical, have been tested in the past. Nevertheless, still no standard protocol have been widely validated and no therapy aimed at reducing the rate of NR is clearly linked with improved clinical outcomes. For these reasons, clear recommendations for the treatment of NR are lacking. Reducing myocardial ischemic time represents the best way to prevent the occurrence of NR. However, when this phenomenon has already occurred, taking into account the promising results of some abovementioned studies, it could be suggested that thrombus aspiration may be a reasonable therapeutic option when high thrombus burden is present, whereas thereafter the choice of a pharmacologic strategy, such as IC adenosine, should be personalized according to coronary TIMI flow. Nevertheless, the reduction of ischemic and ischemia/reperfusion injuries with NR remains an unsolved problem and further studies are warranted to better understand the effectiveness of the different therapeutic approaches in terms of net clinical benefit.

REFERENCES

1. Gupta S, Gupta MM. No reflow phenomenon in percutaneous coronary interventions in ST-segment elevation myocardial infarction. Indian Heart J. 2016; 68(4):539-51.
2. Schwartz BG, Kloner RA. Coronary no reflow. J Mol Cell Cardiol. 2012; 52(4):873-82.
3. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002; Apr 23; 105(16):1909-13.
4. Hoffmann R, Haager P, Lepper W, et al. Relation of coronary flow pattern to myocardial blush grade in patients with first acute myocardial infarction. Heart. 2003; 89(10):1147-51.
5. Gupta S, Gupta MM. No reflow phenomenon in percutaneous coronary interventions in st-segment elevation myocardial infarction. Indian Heart Journal. 2016; 68(4):539-51.
6. Fajara JK, Heriansyah T, Rohmand MS. The predictors of no reflow phenomenon after percutaneous coronary intervention in patients with ST elevation myocardial infarction: A meta-analysis. Indian Heart J. 2018; 70: Suppl 3:S406-S418.
7. Tasar O, Karabay AK, Oduncu V, et al. Predictors and outcomes of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron Artery Dis. 2019 30(4):270-76
8. Bouleti C, Mewton N, Germain S. The no-reflow phenomenon: State of the art. Arch Cardiovasc Dis. 2015; 108(12):661-74
9. Kim MC, Cho JY, Jeong HC, et al. Long-Term Clinical Outcomes of Transient and Persistent No Reflow Phenomena following Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction. Korean Circ J. 2016; 46(4):490-98.
10. Papapostolou S, Andrianopoulos N, Duffy SJ, et al. Long-term clinical outcomes of transient and persistent no-reflow following percutaneous coronary intervention (PCI): a multicentre Australian registry. EuroIntervention. 2018; 14(2):185-93.
11. Rezkalla SH, Dharmashankar KC, Abdalrahman IB, et al. No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: incidence, outcome, and effect of pharmacologic therapy. J Interv Cardiol. 2010; 23(5):429–36.
12. Rezkalla SH, Stankowski RV, Hanna J, et al. Management of No-Reflow Phenomenon in the Catheterization Laboratory. JACC Cardiovasc Interv. 2017; 10(3):215-23.

13. Johnson-Cox HA, Yang D, Ravid K. Physiological implications of adenosine receptor mediated platelet aggregation. J Cell Physiol. 2011; 226(1):46–51.
14. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of Adenosine (AMISTAD) trial. J Am Coll Cardiol. 1999; 34(6):1711–20.
15. Ross AM, Gibbons RJ, Stone GW, et al. A randomized, double-blinded, placebo controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol. 2005; 45(11):1775–80.
16. Kloner RA, Forman MB, Gibbons RJ, et al. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J. 2006; 27(20):2400–5.
17. Niccoli G, Rigattieri S, De Vita MR, et al. Open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction: the REOPEN-AMI study (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction). JACC Cardiovasc Interv. 2013; 6(6):580-9.
18. Nazir SA, Khan JN, Mahmoud IZ, et al. The REFLO-STEMI trial comparing intracoronary adenosine, sodium nitroprusside and standard therapy for the attenuation of infarct size and microvascular obstruction during primary percutaneous coronary intervention: study protocol for a randomised controlled trial. Trials. 2014; 15:371.
19. Garcia-Dorado D, Garcia-del-Blanco B, Otaegui I, et al. Intracoronary injection of adenosine before reperfusion in patients with ST-segment elevation myocardial infarction_ a randomized controlled clinical trial. Int J Cardiol. 2014; 177(3):935.41.
20. Gao Q, Yang B, Guo Y, et al. Efficacy of adenosine in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a PRISMA-compliant meta-analysis. Medicine (Baltimore). 2015; 94(32):e1279.
21. Su Q, Nyi TS, Li L. Adenosine and verapamil for no-reflow during primary percutaneous coronary intervention in people with acute myocardial infarction. Cochrane Database Syst Rev. 2015; (5):CD009503.
22. Niu X, Zhang J, Bai M, et al. Effect of intracoronary agents on the no-reflow phenomenon during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction: a network meta-analysis. BMC Cardiovasc Disord. 2018; 18(1):3.
23. Polimeni A, De Rosa S, Sabatino J, et al. Impact of intracoronary adenosine administration during primary PCI: a meta-analysis. Int J Cardiol. 2016; 203:1032–41.
24. Bulluck, H, Sirker, A, Loke, YK, et al. Clinical Benefit of Adenosine as an Adjunct to Reperfusion in ST-Elevation Myocardial Infarction Patients: An Updated Meta-Analysis of Randomized Controlled Trials. Int J Cardiol. 2016; 202: 228–237.
25. Werner GS, Lang K, Kuehnert H, et al. Intracoronary verapamil for reversal of no-reflow during coronary angioplasty for acute myocardial infarction. Catheter Cardiovasc Interv. 2002; 57(4):444–451.
26. Huang D, Qian J, Ge L, et al. REstoration of COronary flow in patients with no-reflow after primary coronary interVEntion of acute myocaRdial infarction (RECOVER). Am Heart J. 2012; 164(3):394–401.
27. Fu Q, Lu W, Huang YJ, et al. Verapamil reverses myocardial no-reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. Cell Biochem Biophys. 2013; 67(3):911–4.
28. Wang L, Cheng Z, Gu Y, et al. Short-term effects of verapamil and diltiazem in the treatment of no reflow phenomenon: a meta-analysis of randomized controlled trials. Biomed Res Int. 2015; 2015:382086.
29. Abdelaziz HK1, Elkilany W, Khalid S, et al. Efficacy and safety of intracoronary verapamil versus sodium nitroprusside for the prevention of microvascular obstruction during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Coron Artery Dis. 2017; 28(1):11-16.
30. Huang RI, Patel P, Walinsky P, et al. Efficacy of intracoronary nicardipine in the treatment of no-reflow during percutaneous coronary intervention. Catheter Cardiovasc Interv. 2006; 68(5):671–6.
31. Mehta HH, Morris M, Fischman DL, et al. The Spontaneous Coronary Slow-Flow Phenomenon: Reversal by Intracoronary Nicardipine. J Invasive Cardiol. 2019; 31(3):42-5.
32. Chen Z, Chen X, Li S, et al. Nicorandil improves myocardial function by regulating plasma nitric oxide and enothelin-1 in coronary slow flow. Coron Artery Dis. 2015; 26(2):114–120.
33. Wu M, Huang Z, Xie H, et al. Nicorandil in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. PLoS One. 2013; 8(10):e78231.
34. Chen C, Fu X, Li W, et al. Intracoronary administration of anisodamine and nicorandil in individuals undergoing primary percutaneous coronary intervention for acute inferior myocardial infarction: A randomized factorial trial. Exp Ther Med. 2015;10(3): 1059-65.
35. Qi Q, Niu J, Chen T, et al. Intracoronary Nicorandil and the Prevention of the No-Reflow Phenomenon During Primary Percutaneous Coronary Intervention in Patients with Acute ST-Segment Elevation Myocardial Infarction. Med Sci Monit. 2018; 24:2767-776.
36. Feng C, Liu Y, Wang L, et al. Effects of Early Intracoronary Administration of Nicorandil During Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction. Heart Lung Circ. 2019; 28(6):858-65.
37. Kobatake R, Sato T, Fujiwara Y, et al. Comparison of the effects of nitroprusside versus nicorandil on the slow/no-reflow phenomenon during coronary interventions for acute myocardial infarction. Heart Vessels. 2011; 26(4):379-84.
38. Zhao YJ, Fu XH, Ma XX, et al. Intracoronary fixed dose of nitroprusside via thrombus aspiration catheter for the prevention of the no-reflow phenomenon following primary percutaneous coronary intervention in acute myocardial infarction. Exp Ther Med. 2013; 6(2):479-84.
39. Zhao S, Qi G, Tian W, et al. Effect of intracoronary nitroprusside in preventing no reflow phenomenon during primary percutaneous coronary intervention: A meta-analysis. J Interv Cardiol. 2014; 27(4): 356-64.
40. Lee WC, Chen SM, Liu CF, et al. Early Administration of Intracoronary Nitroprusside Compared with Thrombus Aspiration in Myocardial Perfusion for Acute Myocardial Infarction: A 3-Year Clinical Follow-Up Study. Acta Cardiol Sin. 2015; 31(5):373-80.
41. Yang L, Mu L, Sun L, et al. Effect of intracoronary nitroprusside injection on flow recovery during primary PCI in acute STEMI patients. Minerva Cardioangiol. 2017; 65(2):111-18.
42. Aitmokhtar O, Paganelli F, Benamara S, et al. Impact of platelet inhibition level on subsequent no-reflow in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Arch Cardiovasc Dis. 2017; 110(11):626-33.
43. Dai W, Ye Z, Li L, et al. Effect of preoperative loading dose ticagrelor and clopidogrel on no-reflow phenomenon during intervention in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. Drug Des Devel Ther. 2018; 12:2039-049.
44. Akpek M, Sahin O, Sarli B, et al. Acute Effects of Intracoronary Tirofiban on No-Reflow Phenomena in Patients With ST-Segment Elevated Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Angiology. 2015; 66(6):560-7.
45. McCartney PJ, Eteiba H, Maznyczka AM, et al. Effect of Low-Dose Intracoronary Alteplase During Primary Percutaneous Coronary Intervention on Microvascular Obstruction in Patients With Acute Myocardial Infarction: A Randomized Clinical Trial JAMA. 2019; 321(1):56-68.

46. Aksu T, Guler TE, Colak A, et al. Intracoronary epinephrine in the treatment of refractory no-reflow after primary percutaneous coronary intervention: a retrospective study. BMC Cardiovasc Disord. 2015; 15:10.
47. Chen WR, Tian F, Chen YD, et al. Effects of liraglutide on no-reflow in patients with acute ST-segment elevation myocardial infarction. Int J Cardiol. 2016; 208:109-14.
48. Chen WR, Hu SY, Chen YD, et al. Effects of liraglutide on left ventricular function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am Heart J. 2015; 170(5):845-54.
49. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during STsegment elevation myocardial infarction. N Engl J Med. 2013;369(17):1587–97.
50. Lagerqvist B, Frobert O, Olivecrona GK, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. N Engl J Med. 2014;371(12):1111–20.
51. Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med. 2015;372(15):1389–98.
52. Jolly SS, Cairns JA, Yusuf S, et al. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. Lancet. 2016;387(10014):127–35.
53. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2):119-77.
54. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation. 2013; 127(4):e362-e425.
55. Jolly SS, Cairns JA, Yusuf S, et al. Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy. N Engl J Med. 2015; 372:1389.
56. Şeker T, Türkoğlu C, Akkuş O, et al. The relationship between visible thrombus aspiration material with no-reflow and in-hospital mortality ratio in patients with anterior ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Turk Kardiyol Dern Ars. 2019; 47(2):95-102.
57. Migliorini A, Stabile A, Rodriguez AE, et al. Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction. The JETSTENT trial. J Am Coll Cardiol. 2010; 56(16):1298-306.
58. Bøtker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet. 2010; 375(9716): 727-34.
59. Rentoukas I, Giannopoulos G, Kaoukis A. Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. JACC Cardiovasc Interv. 2010; 3(1):49-55.
60. Crimi G, Pica S, Raineri C, Bramucci E, et al. Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. JACC Cardiovasc Interv. 2013; 6(10):1055-63.
61. Engstrøm T, Kelbæk H, Helqvist S, et al. Effect of Ischemic Postconditioning During Primary Percutaneous Coronary Intervention for Patients With ST-Segment Elevation Myocardial Infarction: A Randomized Clinical Trial. JAMA Cardiol. 2017; 2(5): 490-97.
62. Traverse JH, Swingen CM, Henry TD, et al. NHLBI-Sponsored Randomized Trial of Postconditioning During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction. Circ Res. 2019; 124(5):769-78.
63. Maslov LN, Tsibulnikov SY, Prokudina ES, et al. Trigger, Signaling Mechanism and End Effector of Cardioprotective Effect of Remote Postconditioning of Heart. Curr Cardiol Rev. 2019; 15(3):177-87.