AIMS Medical Science, Volume 2 (4): 374–395.
DOI: 10.3934/medsci.2015.4.374
Received date 29 June 2015,
Accepted date 24 November 2015，
Published date 30 November 2015

http://www.aimspress.com/

Review article

No Reflow-phenomenon: from Current State of the Art to Future Perspectives

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Abstract: Early and successful myocardial reperfusion with primary percutaneous coronary intervention (pPCI) is the optimal therapy for patients presenting with ST segment elevation myocardial infarction (STEMI). Despite successful epicardial reopening of the infarct related artery, myocardial perfusion may not be restored in up to 40–50% of patients. This phenomenon, referred to as no-reflow (NR), recognizes several pathogenetic components including distal atherothrombotic embolization, ischaemic injury, reperfusion damage, intramyocardial hemorrhage and individual susceptibility of coronary microcirculation. However the complexity of pathogenesis remains still unclear. Moreover, cause NR plays a crucial role in patients prognosis, accurate detection is critical and multiple novel diagnostic modalities has been recently assessed.The NR phenomenon represents a challenge in the management of STEMI patients and has recently captured a growing interest of both basic scientists and interventional cardiologists. Although relevant efforts to transfer into real world practice new therapeutic strategies, to date there is still weak evidence of clinical improvement in this setting. Several strategies of prevention and treatment of NR have been proposed in the clinical arena including pharmacological and mechanical interventions. Nevertheless, the complexity

of the phenomenon makes extremely unlikely for a single therapy to be effective. Understanding the interaction between the components of this pathway, along with exploring newer and more effective agents may enable patients to be treated with the most appropriate therapy.

Keywords: No reflow; primary percutaneous coronary intervention; STEMI; pharmacological therapies; ischemia-reperfusion injury

1. Introduction

The major goal in the treatment of ST-segment elevation myocardial infarction (STEMI) is early reperfusion. Despite improvement of emergency medical system and percutaneous coronary intervention (PCI) techniques, the mortality associated with STEMI remains not negligible: about 7% at 1 month [1].

The no-reflow (NR) phenomenon can be defined as an inadequate myocardial reperfusion, despite adequate culprit epicardial coronary artery treatment with no angiographic evidence of epicardial obstruction, flow-limiting dissection or vasospasm. In the setting of STEMI, NR has a prevalence ranging from 5% up to 50%, depending on the method of assessment, and impacts remarkably on patients prognosis [2,3]. Nevertheless, NR could also occur in the setting of non ST-elevation myocardial infarction (NSTEMI) or during elective PCI, though with lower frequency.

The “ancient” idea that "no reflow" was a synonym of distal embolization has been largely overcome. NR is now considered a composite and dynamic process; growing interest in other pathophysiological mechanisms and new pharmacological therapies has been raised. In particular, new insights of ischemia-reperfusion related injury provides a pathological background for emerging cardioprotective agents.

NR occurrence during pPCI worsens patient prognosis resulting in adverse left ventricle (LV) remodeling, higher rates of mortality, early post-infarction complications, and late re-hospitalization for congestive heart failure (CHF) [4–6]. In a prospective observational study on 1406 patients with STEMI undergoing pPCI, NR was diagnosed in 410 patients (29%). The NR group, as compared to control group, showed not only larger infarct size (15% VS 8%) but also higher mortality at 5 years follow up (18.2% VS 9.5%) [7].

Therefore it becomes crucial to define and detect the multiple pathological pathways involved in this phenomenon in order to actuate the most effective counteracting strategies.

2. Time Course and Pathophysiology

NR is a dynamic process: within the ischemic area, in the time course between 2 minutes and 8 hours after reperfusion, the no-reflow area can increase by 3-fold [8]. The phenomenon typically involves first the subendocardium and then spreads to the subepicardium. Surrounding the no-reflow

zone there is a low-reflow zone, which can either reverse to normality or be involved in the no-reflow area; the presence of collateral blood plays a key role in this dynamic evolution.

NR remains an evolving phenomenon also at mid-term: it has been demonstrated that NR can spontaneously recover in approximately 50% of patients at one month. On this basis NR is currently categorized as reversible or sustained; while the former is more frequently the result of functional and reversible changes of microcirculation, the latter is associated with irreversible damage and results in worse outcome [9].

NR recognizes a combination of several pathogenetic components which can have a different weight in each single patient. To date, the complexity of pathogenesis remains still unclear, but microembolization, ischemia/reperfusion damage, intramyocardial hemorrhage and susceptibility of coronary microcirculation to injury are world-wide accepted as the most relevant.

2.1. Distal embolization

Microembolization referred to cholesterol crystals, hyaline and platelets aggregates which embolize downstream from an epicardial coronary artery plaque. During pPCI the use of embolic filters demonstrated distal emboli capture in 89% of patients [10]. Despite more frequent during pPCI, microembolization also occurs during elective PCI, particularly in vein grafts angioplasties. By the use of intracoronary Doppler guidewires, microemboli have indeed been detected during each phase of PCI and a strict correlation between number of microemboli and periprocedural troponin I elevation has been found [11]. Distal embolization results in mechanical microvasculature occlusion but also contributes to inflammatory reaction and contractile dysfunction. Moreover, the plaque debris embolization induces vasoconstriction as confirmed by the high levels of serotonin in aspirated samples before and after stenting [12].

2.2 Ischemia related injury

A prolonged ischemia causes endothelial and myocardial degenerative changes. Endothelial protrusions and membrane-bound bodies contribute to capillaries luminal obliteration: the endothelial gaps allow extravascular erythrocytes migration and, as a consequence, extravascular compression [13]. In addition, endothelial activation promotes expression of new adhesion molecules which contributes to leucocytes accumulation.

On the other hand, cardiac myocytes are the final target of prolonged ischemia: the decreased production of adenosine triphosphate, caused by the lack of oxygen, impairs the sodium-potassium pump (Na^+/K^+-ATPase) and results in cardiac myocytes swelling. This irreversible damage leads to edema and contributes to extravascular compression.

2.3. Ischemia/reperfusion damage

Despite strictly linked, ischemia and reperfusion injuries recognize distinguishable pathophysiological mechanisms. The reperfusion injury carries a paradoxical additional irreversible myocardial damage which may account for as much as 50% of the infarct size [14]. During reperfusion, neutrophils and platelets massively infiltrate coronary microcirculation with a consequent burst of reactive oxygen species (ROS) generation [15].

ROS are generated by several mechanisms, including the xanthine/xanthine oxidase reaction, NADPH oxidase and cytochrome P450 activity; the mitochondrial respiratory chain represents moreover a subcellular site of ROS production, particularly relevant in cardiac myocytes rich in mitochondria. ROS production and respiratory chain impairment are linked by a cause-effect correlation and create a vicious cycle that leads to the decline in mitochondrial bioenergetics and subsequent mitochondrial dysfunction. Considering that ROS are high-reactive and short-lived species, mitochondria are at the same time one of the major sources and the targets of ROS attack. By dissipating the mitocondrial membrane potential and opening the mitochondrial permeability transition pore (MPTP), ROS production leads to swelling of mitochondrial matrix and release of cytochrome c to the cytoplasm which initiates pro-apoptotic signals. Mitochondria dysfunction is known to be intimately involved in both necrotic and apoptotic processes that lead to cell death following reperfusion and therefore are potential target for protective intervention [16].

Moreover, the accumulation of neutrophils and platelets in the reperfused area, beside causing mechanical plugging of the coronary microcirculation, can also directly damage endothelial cells by releasing inflammatory mediators. In particular, tumor necrosis factor-alpha and interleukin-1β have been proved to be associated with reperfusion-injury by increasing the inflammatory reaction [17,18].

All these metabolic alterations may ultimately cause cardiac myocytes deaths and myocardium architecture disarray. This phenomenon, combined with vascular cell damage, leads to leakage of blood out of the injured vessels and contributes to external compression.

2.4. Intramyocardial hemorrhage

Intramyocardial hemorrhage is considered a severe form of MVO caused by vascular endothelial damage and accumulation of red blood cells in the myocardial extracellular space. Histologic assessment of the microvasculature within the zones of no-reflow shows endothelial membrane-bound blebs which plug the lumen. Endothelial gaps are occasionally found adjacent to platelets plugs and are supposed to allow extravascular erythrocyte migration and loss of fluid from the vessels. Swollen cardiac myocytes appear to compress capillaries, contributing to microvascular obstruction. Multiple factors are involved in the severity of this phenomenon, including the extent of collateral flow and ischemic preconditioning. It is supposed to expand for several hours after percutaneous coronary intervention and has been found to be significantly related to the infarct size

and to the coronary occlusion time [19].

2.5. Individual susceptibility of coronary microcirculation

The combination of all the above described mechanisms contributes to the NR phenomenon but damage severity is modulated by individual predisposition of coronary microcirculation to injury. This vulnerability recognizes genetic but also acquired and adjustable causes. In animal studies hypercholesterolemia has been demonstrated to exacerbate reperfusion injury by enhancing endothelial oxidative stress [20,21]. Similarly, diabetes has been associated to impaired microvascular reperfusion after pPCI; moreover multiple studies have found that hyperglycemia, regardless of the diabetic status, might exacerbate myocardial ischemic and reperfusion related damage by increasing oxidative stress, apoptosis and platelets activation [22].

3 Assessment of No-reflow

The extent of no-reflow can be measured using multiple modalities, including new emerging techniques.

3.1. Angiography

For the last two decades angiography has played the major role in NR assessment. TIMI flow grade (TFG) measures epicardial blood flow by using a scale from 0 to 3 and its association to clinical outcomes has been largely demonstrated: NR occurrence can be assessed by a TFG < 3. However the qualitative and categorical nature of this method limits its sensitivity. Myocardial tissue perfusion may indeed remain impaired even after angiographic successful reperfusion and final TFG 3.

Corrected TIMI frame count (cTFC) is a quantitative parameter used to assess myocardial perfusion in the setting of myocardial infarction (MI) able to reflect both epicardial coronary flow and microvascular circulation. cTFC is defined as the number of cineframes required for dye to reach standardized distal markers of the coronary tree. Lower cTFCs after pPCI have been associated with more favorable prognosis [23].

Myocardial Blush Grade (MBG) technique assesses the intensity of myocardial staining; MBG is scored on a scale of 0 to 3, with score 3 indicating normal perfusion. Previous studies have shown that MBG was the best predictor of impaired perfusion and of one-month major adverse cardiac events (MACE) [24,25]. Nevertheless, MBG sensitivity in quantifying microvascular obstruction (MVO) has been recently questioned by the comparison with emerging techniques such as cardiac magnetic resonance imaging (CMRI) [26].

3.2. Electrocardiography

Serial electrocardiograms, aimed to monitor ST-resolution (STR), are the simplest way to determine myocardial reperfusion in STEMI patients. STR, measured 60 minutes after pPCI, is defined as incomplete if less than 30%, partial if ranges from 30 to 70% and complete if above 70% [4–6]. In the fibrinolysis era STR has provided a simple, but delayed, evaluation of reperfusion success; its usefulness has been largely overcome in pPCI era because coronary angiography allows an immediate assessment of coronary flow restoration.

An innovative method able to provide the interventional cardiologist with a "real-time" information on STR is the Intracoronary Electrocardiogram: performed by advancing an unipolar electrode equipped guidewire distally to the lesion of the culprit artery, this simple and inexpensive method has shown a 91% sensitivity and a 97% specificity in predicting NR. Despite a world-wide accepted cut-off for STR, measured by this emerging technique, needs to be validated by further studies, this method might aid the diagnostic and decision making process within the cath-lab [27].

3.3. Cardiac magnetic resonance imaging

Nowadays, CMRI represents the most sensitive and specific method of NR assessment. The optimal timing to get the higher predictive value for infarct size is one week after MI [28]. MVO can be detected by the injection of gadolinium, an extracellular agent. Necrotic or fibrotic myocardium enhances gadolinium distribution into the interstitium, which appears as a bright signal: hyperenhancement. The severe microvascular damage in the context of MVO prevents gadolinium from entering the injured myocardium which appears dark and hypoenhanced, surrounded by the hyperenahnced infarcted myocardium (Figure 1).

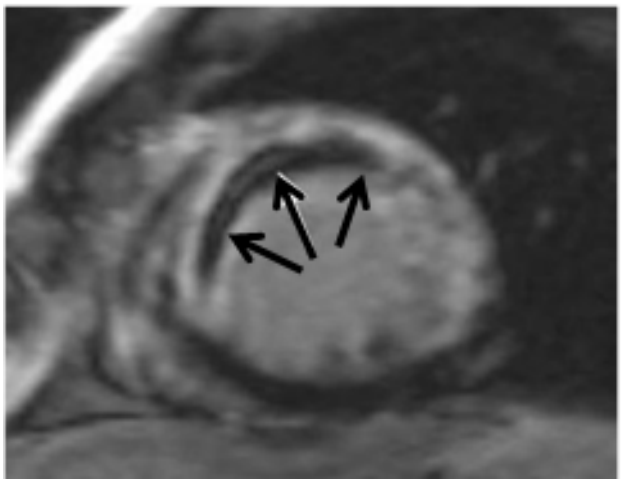

Figure 1. CMR showed an area of MVO (dark and hypoenhance), surrounded by the hyperenahnced transmural infarcted myocardium.

NR phenomenon can be assessed by two gadolinium-based techniques: “late MVO” is performed 10–15 minutes after the injection of the extracellular agent, while "early MVO” is simultaneous. Even though “early MVO” is generally considered more sensitive [29] both tecniques can accurately define the presence and the spatial extent of MVO which has been validated not only as predictor of LV remodeling but also of long-term prognosis [30].

3.4. Myocardial contrast echocardiography (MCE)

MCE has recently been suggested as a diagnostic and accurate method to assess NR phenomenon. MCE is performed by intravenous injection of ultrasound contrast agents containing small microbubbles. These agents have rheology features similar to red cells and freely flow within the uninjured microvasculature achieving a steady state in few minutes. The absence of intramyocardial contrast opacification detects NR areas (Figure 2).

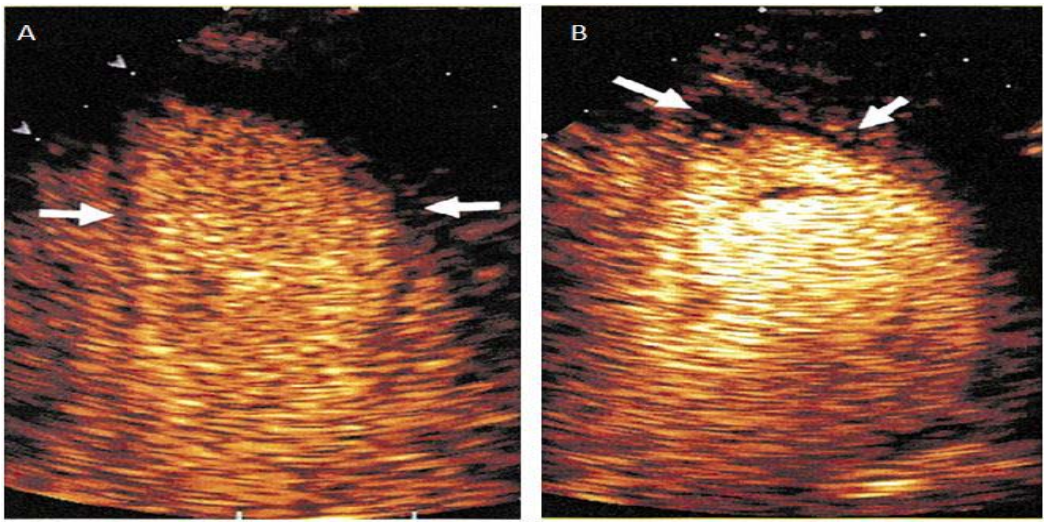

Figure 2. NR assessment in 2-chamber views by MCE at (A) 24 hours and (B) 1 week after pPCI in a STEMI patient.

Being non invasive, economic and easy to perform, this imaging technique allows frequent and repeated re-assessment in the early post-intervention period. Moreover, overcoming claustrophobia-related issues, MCE represents a valid alternative method to CMRI in detecting microvascular injury. Despite the mentioned encouraging characteristics, this novel technique presents anyway some limitations such as moderate spatial resolution, operator dependency and incomplete LV coverage [31].

3.5. The role of intravascular imaging

Recently, intravascular imaging has been utilized to investigate potential predictors of NR phenomenon.

To date intravascular ultrasound (IVUS) has played the major role. Small studies have shown that lipid pool-like image and positive remodeled vessels are able to predict the occurrence of angiographic NR in the setting of acute myocardial infarction [32,33]. A sub-analysis of 364 patients enrolled in the randomized HORIZONS-AMI trial has demonstrated that the amount of echo-attenuated plaque, containing more fibrofatty tissue and necrotic core as compared to non-attenuated, strongly correlated with NR [34].

Optical Coherence Tomography (OCT) is a promising light-based intravascular imaging modality, with higher resolution than IVUS, able to provide accurate morphologic characteristics of the plaque contents. Due to the limited penetration depth, the plaque burden and arterial remodeling cannot be detected by OCT. Nevertheless, thin-cap fibroatheroma (TCFA), identified by OCT, have been more frequently observed in the NR group among a cohort of NSTEMI patients (Figure 3) [35].

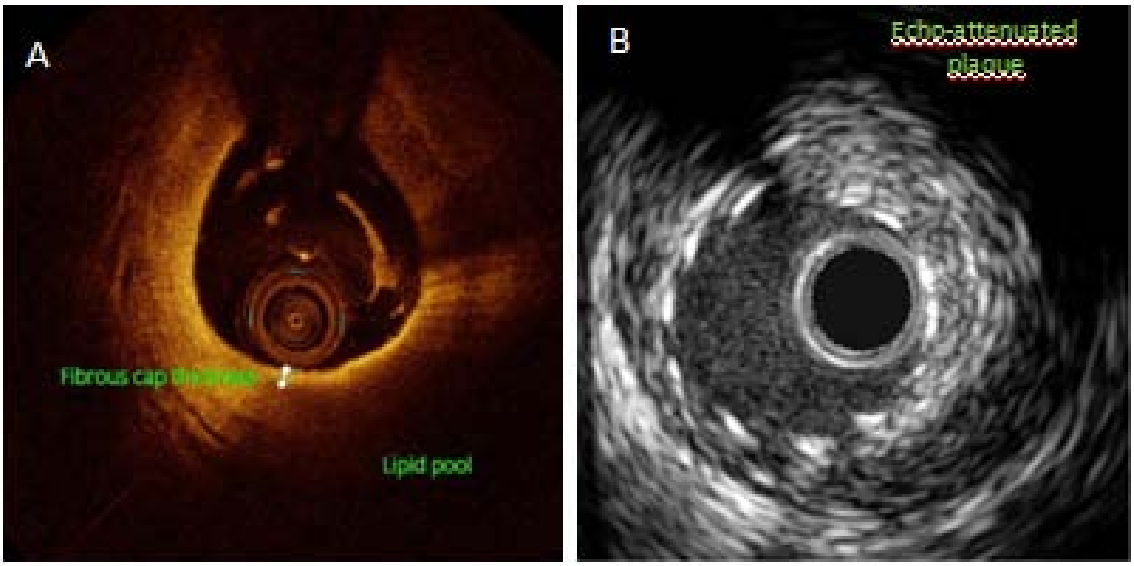

Figure 3. Predictors of NR phenomenon with intravascular imaging. (A) OCT evaluation of TFCA and lipid pool. (B) IVUS detection of echo-attenuated plaque.

4. Therapies

NR phenomenon is an independent predictor of adverse LV remodeling, adverse clinical events and death. Therefore, NR has become an area of great interest for both basic scientists and clinical cardiologists. Despite improvement of interventional cardiology techniques and pharmacology, an effective and definite treatment has not been clearly defined yet. Several strategies for prevention and treatment of NR have been proposed in the clinical arena. Promising results from pre-clinical

researches have often failed when translated into human therapies. Most of current animal models lack some of the pathophysiological mechanisms responsible for NR phenomenon, including atherosclerosis or pre-existing microvascular damage. The multifactorial nature of NR makes extremely unlikely for a single therapy to be effective (Figure 4).

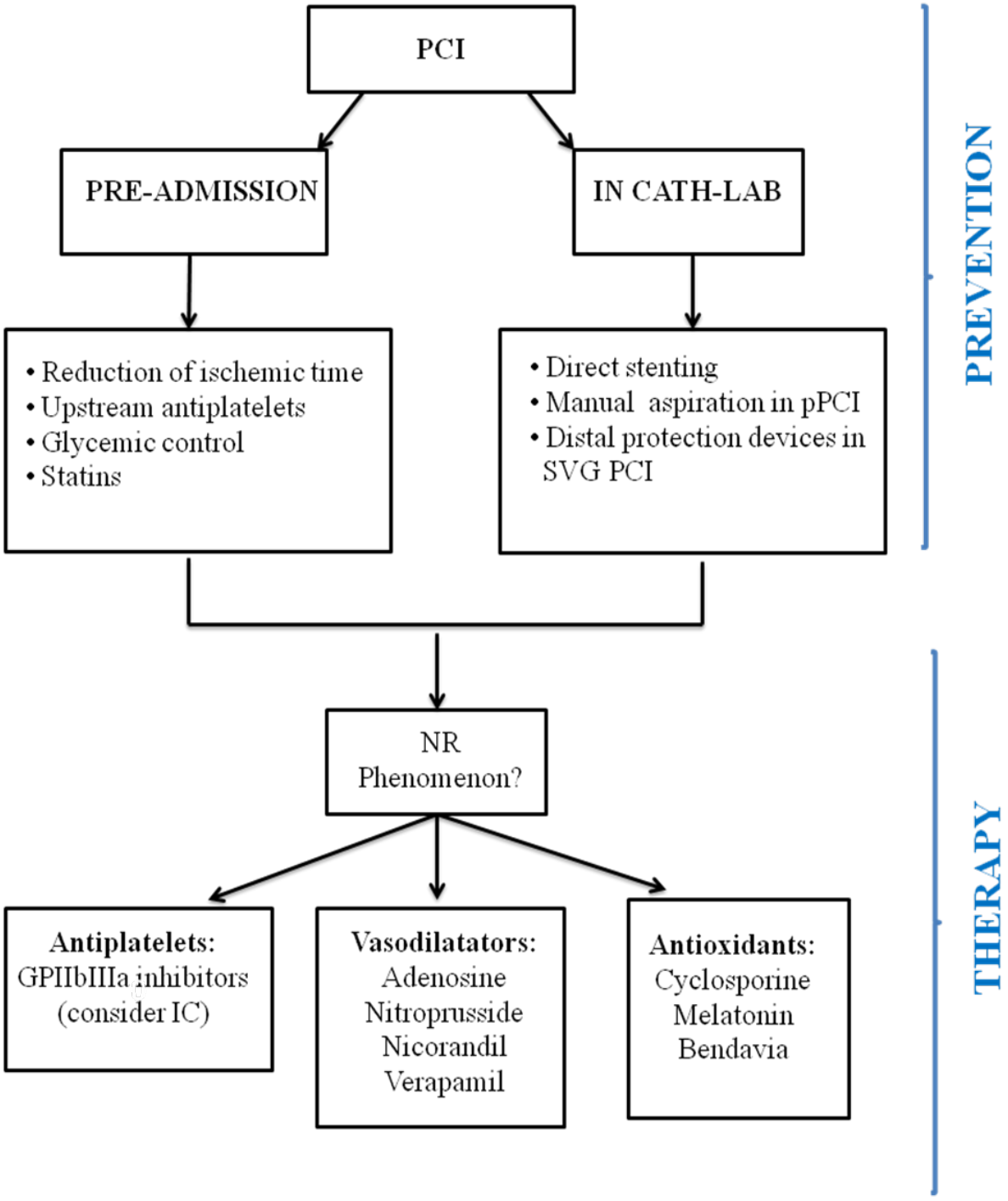

Figure 4. NR phenomenon treatment flow chart.

4.1. Mechanical interventions

Distal embolization during pPCI is one of the most relevant pathophysiological mechanisms responsible for NR and several strategies has been thus developed to counteract this phenomenon. Direct stent implantation, by entrapping atherotrombotic debris, reduces the risk of distal embolization; however this technique is only feasible in patients with a good visualization of the infarct related artery after the wire passage.

By facilitating, even partially, the infarct related artery recanalization, increasing direct stent deployment and reducing post-dilatations need, thrombectomy devices have initially shown promising results, particularly evident within the subset of patients with large thrombus burden. More than 20 randomized trials have investigated the beneficial effect of manual thrombectomy over conventional PCI. Three landmarks have influenced the central role of this adjunctive strategy in the setting of STEMI. The large randomized trial TAPAS has shown in the manual thrombus aspiration group better angiographic outcomes and reduction in cardiac death [36]. Both the TASTE and the more recent TOTAL trials have failed in corroborating these initial encouraging results [37,38]. Nevertheless a meta-analysis of the available randomized trials has shown an overall reduction of all-cause mortality, MACE and stent thrombosis with the use of this adjunctive approach. The reasons for such non-univocal results can be sought in the heterogeneity of PCI tecniques, the relatively short follow-ups and the exclusion from the abovementioned trials of higher risk subgroups of patients who might have benefited more from thrombus aspiration. Taken together, these results suggest manual thrombectomy in selected STEMI patients with high thrombus burden; nevertheless the widespread uptake of this device in US has reached a peak of 60% of pPCI cases [39–42].

Rheolytic thrombectomy system is an alternative to manual aspiration and is designed to remove thrombus by delivering high-pressure heparined saline solution from the cathether, thus creating Venturi-Bernoulli effect. This device has been tested in several trials, whit conflicting results. When compared to conventional PCI, it improved both myocardial reperfusion and clinical outcome [43]. Nevertheless, manual thrombectomy is a simpler technique and more recent trials have shown no clinical benefit of routine rheolytic thrombectomy during pPCI [44–47].

Another mechanical approach to prevent embolization is the deployment of distal protection devices. Both filters and balloon devices have shown no benefit in the setting of STEMI but have demonstrated, only in saphenous vein graft PCI, to reduce the incidence of NR and of 30-days composite of death/MI/target lesion revascularization (TLR) [44,45]. Moreover proximal protection devices, rather than distal ones, have proved to prevent microemboli embolization in large side branches during complex PCI procedures [46]. Therefore this technique deserves a pivotal role in particular subsets of patients.

Future weapons in the war to distal embolization will probably include devices like the MGuard stent, a bare-metal stent covered by a polyethylene theraphthalate mesh designed to entrap debris during PCI. The first randomized trial investigating MGuard implantation in STEMI, has shown

higher rate of complete STR and TFG3 when compared to conventional stenting [48]. More recently, in the MASTER trial a lower 1 year mortality rate has been found in STEMI patients treated with Mguard stent [49]. These findings should be interpreted with caution: the device use has been associated to higher rates of ischemic TLR and MACE (cardiac mortality, re-MI and ischemia driven TLR); thus the restenosis issue should be carefully evaluated and weighted. Randomized clinical trials powered for hard clinical end points are needed to balance the competing risks and benefits of the MGuard stent.

4.2. Pharmacological therapies

There is a growing enthusiasm in the ischemia-reperfusion related injury prevention strategies. As stated before reperfusion injury begins with infiltration of neutrophils and platelets in the microvasculature and the subsequent release of ROS; this process is exacerbated by concomitant sustained vasoconstriction (Table 1).

4.2.1. Antiplatelet drugs

The pivotal role of platelets in the activated clotting cascade is well established; strong platelets inhibition with GPIIb/IIIa inhibitors decreases thrombus formation and improves myocardial reperfusion after pPCI [50–52]. Direct intracoronary GPIIb/IIIa inhibitors injection has proved to be more effective than intravenous administration in reducing infarct size and MVO extent, probably by driving greater local concentration of the drug [50,53,54]

In STEMI patients undergoing pPCI, an intracoronary bolus of Abciximab has been found to decrease both infarct size and MVO by MRI measurement [50]. Conversely, the large randomized trial AIDA-STEMI has failed to demonstrate significant differences in the primary composite outcome of all-cause mortality, recurrent infarction or new congestive heart failure between intracoronary and intravenous administration. However, the low event rate in the trial suggests a low-risk population without sufficient thrombus burden to truly test the hypothesis [54]. Moreover, a recent meta-analysis, including the same AIDA-STEMI, has found a significant lower incidence of MACE at the short-term follow-up [55].

Despite also other GPIIb/IIIa inhibitors, such as tirofiban, given in upstream administration to STEMI patients, have shown to reduce STR [56], current guidelines recommend GPIIb/IIIa inhibitors administration only for bail-out, evidence of NR or thrombotic complications [57].

4.2.2. Statins

Previous evidences have suggested the protective pleiotropic effect of statins on the preservation of microvasculature during the ischemia/reperfusion phenomenon; it is known that

some statins beneficial effects, such as atherosclerotic plaque stabilization and trombogenic and inflammation response inhibition, go beyond the simple lipid-lowering achievement [9].

Two retrospective analyses on STEMI patients have demonstrated that long-term statin pretreatment is associated with better myocardial perfusion after pPCI, regardless of the blood lipid level [48,53]. A meta-analysis including twelve trials on statin pretreatment effect on myocardial perfusion in STEMI patients, has shown a significant lower cTFC and a trend toward lower MBG in the statin arm. However, if the chronic use of statins showed a favorable effect on myocardial perfusion, the effectiveness of acute preprocedural statin administration to achieve additional benefit remains unclear.

4.2.3. Vasodilators

The role of vasodilators to counteract NR has been studied in several randomized clinical trials. Adenosine is an endogenous nucleoside, proved to inhibit neutrophil adhesion and migration, and to reduce calcium overload and ROS formation. AMISTAD II trial was aimed to assess the benefit of adenosine routine use in 2118 patients presenting with STEMI: authors found no significant difference in clinical outcome but a significant reduction in infarct size [63].

Nitroprusside is a nitric oxide donor with vasodilatators, antiplatelet, and anti-inflammatory properties; the potential benefits of this agent should be weighted against the possible harm of systemic hypotension (Figure 5).

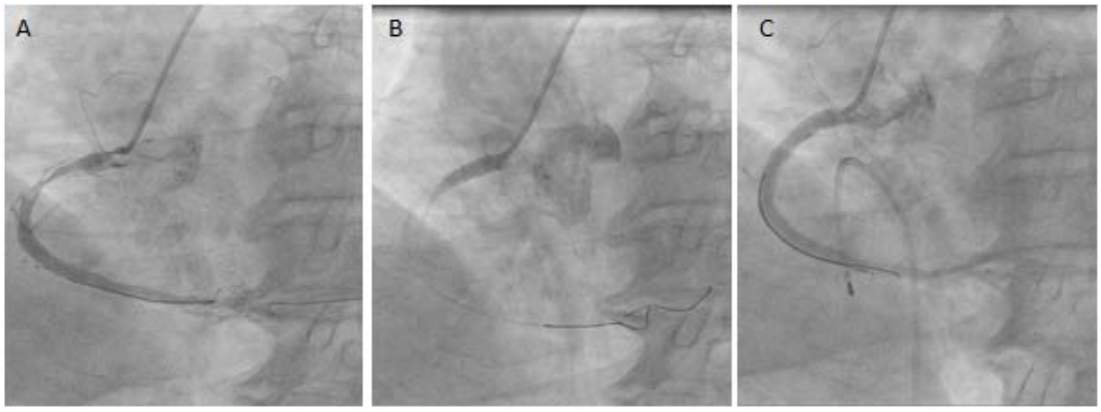

Figure 5. (A) Right coronary artey stenosis. (B) Angiographic image of NR phenomenon after stent deployment. (C) Angiographic result after i.c. GP IIb/IIIa inhibitors and nitroprusside administration.

The recent randomized REOPEN-AMI trial has found a significant improvement in MVO, assessed by STR, with additional administration of adenosine, but not with nitroprusside [64]. The beneficial effects of both adenosine and nitroprusside have been demonstrated in several other small

trials, despite with inconclusive results. As a consequence there is currently no definite consensus on the routine administration of these adjunctive pharmaco-therapeutic agents to prevent or reduce MVO. The ongoing multicentre, prospective, randomized REFLO-STEMI study will address this issue by comparing the benefits in terms of MVO and infarct size of intracoronary adenosine, sodium nitroprusside and standard therapy; primary endpoint of the trial is CMRI measured infarct size at 48 and 72 h after pPCI [65].

Nicorandil is an adenosine triphosphate-sensitive K^+ channel opener; this further vasodilator agent has proved in experimental models to reduce both infarct size and arrhythmias, but these results have not been reproduced in human trials [66].

Also calcium channels blockers have been shown to improve microvascular dysfunction by regulating endothelial function and preventing microvessel spasm. Intracoronary verapamil demonstrated in STEMI patients a significant improvement in coronary artery flow measured by cTFC [67]. In the VAPOR trial intragraft verapamil administration has showed beneficial effect in patients undergoing vein grafts PCI [68]. A recent meta-analysis has confirmed that intracoronary verapamil injection, is able to prevent NR and reduce major adverse events in patients with acute coronary syndromes undergoing PCI [69].

4.2.4. Antioxidants: novel perspectives in therapy

As mentioned before, ROS are centrally involved in NR phenomenon. They cause peroxidation of membrane lipids, denaturation of proteins, and DNA damages, ultimately leading to cardiac myocytes death. Based on this strong evidence, a growing interest for antioxidants agents is spreading. Nevertheless, the effectiveness of this therapy is limited by the low capability of antioxidants to cross the mitochondrial cell membrane. As mitochondria are known to be intimately involved in ROS production, these sub-cellular organelles have been targeted by novel protective interventions. Growing evidence supporting the crucial role of MPTP in ischemia-reperfusion related injury are now available: massive MPTP opening during reperfusion causes efflux of cytochrome c and activation of other proapoptotic signals. As a consequence, identification of agents able to protect the heart from MPTP related damage are of considerable relevance.

In addition to its well-known immunosuppressive properties, cyclosporine was found to be a potent MPTP inhibitor. In a small pilot trial on 58 patients, the administration of this agent was associated with a smaller infarct size [70]. However, the lack of large trials and the potential adverse effects of cyclosporine has limited the interest for this drug.

Several recent publications demonstrated that melatonin has significant protecting actions against ischemia-reperfusion cardiac damage. Melatonin is an endogenous antioxidant scavenger, able to cross all the physiological barriers. In experimental models melatonin has shown to inhibit MPTP opening, probably via prevention of cardiolipin peroxidation, and to reduce the infract size when administered in isolated reperfused rat heart. On the basis of this finding an ongoing

prospective trial is evaluating the possible cardioprotective effect of exogenous melatonin when administered in STEMI patients [71].

A novel class of cell-permeable peptides has been recently developed to prevent ischemia-reperfusion injury. By targeting mitochondria this new agent, called Bendavia, has demonstrated cardioprotective effects both in vitro and in vivo experimental models [72]. Although these findings are extremely promising, nanoparticles studies are still at the starting blocks and their efficacy in humans needs to be validated.

5. Conclusions

Beyond the growing enthusiasm around the variety of these novel pharmacological therapies, scientists have often to face the failure of these agents when translated to human studies. To date the weapons in the hands of the interventional cardiologists are limited to mechanical therapies and a small pool of well studied drugs. The prevalence and the prognostic impact of the NR phenomenon deserve great attention by the biomedical community aimed to find more effective therapeutic devices, either pharmacological or mechanical.

Conflict of Interest

The authors have no conflict of interest to declare.

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Table 1: Pharmacological therapies to counteract NR phenomenon.

Drug	Study	Patients (n)	End-points	Results
Abciximab IV vs IC	Kakkar et al. (52)	173	Composite of death or MI at 6 months	Worse clinical outcome in IV group
Abciximab IV vs IC	Thiele et al. (50)	154	Infarct size and MVO	Significantly decreased in IC group
Abciximab IV vs IC	Thiele et al. (54)	2065	Composite of all-cause mortality, recurrent MI, or new congestive heart failure (CHF)	No difference in clinical endpoint
Abciximab IV vs placebo (metanalysis)	Kandzari et al. (73)	3266	Composite of death, reinfarction, or ischemic or urgent TVR at 6 months	Better clinical outcome in abciximab group Increase of bleeding
Tirofiban upstream vs placebo	Van't Hof et al.(56)	984	Extent of residual ST-segment deviation 1 h after PCI	Significantly lower in pre-treated patients
Statins vs placebo (metanalysis)	Lyu et al.(61)	1058	cTFC and MBG	Significantly lower cTFC and trend toward lower MBG in statin arm
Adenosine vs placebo	Ross et al. (63)	2118	Infarct size Composite of CHF, re-hospitalization for CHF and death at 6 months	Infarct size reduction in adenosine group No difference in clinical endpoint
Nitroprusside vs placebo	Amit et al. (74)	98	cTFC and STR; composite of TLR, MI and death at 6 months	No difference in cTFC and STR. Better clinical outcome in nitroprusside group

Table 1: Pharmacological therapies to counteract NR phenomenon (cont).

Drug	Study	Patients (n)	End-points	Results
Adenosine vs nitroprusside vs placebo	Niccoli et al.(64)	240	STR, TFG and MBG Composite of death, MI, TLR and re-hospitalization for CHF at 30 days	STR reduction in adenosine but not nitroprusside group. No significant difference for TFG, MBG and clinical outcome
Adenosine vs nitroprusside vs placebo	Nazir et al. (65)	240	Infarct size and MVO at cardiac MRI Angiographic measures Composite of death, TLR, recurrent MI, severe CHF and cerebrovascular events at 1 month	On going
Nicorandil vs placebo	Ishii et al. (66)	368	cTFC and STR. Composite of death and CHF	Reduction of cTFC and STR and better clinical outcome in nicorandil group
Verapamil vs placebo	Su et al.(69)	539	MACE all-cause death, TVR, recurrent angina or MI, and severe CHF	Reduction of MACE in Verapamil group
Cyclosporine vs placebo	Piot et al. (70)	58	Infarct size at cardiac MRI	Reduction of infarct size in cyclosporine group
Melatonin vs placebo	Dominguez-Rodriguez et al. (71)	272 (estimated)	Infarct size. Death, sustained ventricular arrhythmias, cardiac arrest, cardiogenic shock, CHF, major bleedings, stroke, TVR, recurrent ischemia, re-IM and re-hospitalization	On going