REVIEW

No-Reflow Phenomenon: A Major Issue Concerning Revascularization in Acute Coronary Syndromes

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ABSTRACT

The no-reflow phenomenon (NRp), a dreaded complication of primary and also of any complex percutaneous coronary intervention (PCI), is characterized by insufficient myocardial perfusion in a territory of a coronary artery without evidence of mechanical obstruction. Microvascular injury is the underlying mechanism of NRp and its manifestation is not only impaired TIMI flow (<3), but also impaired TIMI myocardial perfusion grade (TMPG) which should be assessed in case of chest pain, persistent ST segment elevation or hemodynamic compromise despite the presence of TIMI III flow. The NRp mechanism is multifaceted, the evidence base for its treatment is inconsistent and limited, but its predictors are well known. The armamentarium against NRp consists of preventive and therapeutic strategies, both mechanical and pharmacological. A brief overview of all the above issues concerning NRp is attempted herein. ***Rhythmos 2019;14(2):27-30.***

Key words: no-reflow; revascularization; acute coronary syndromes

Abbreviations: LAD: left anterior descending; MI: myocardial infarction; MRI: magnetic resonance imaging; NRp: no-reflow phenomenon; PCI: percutaneous coronary intervention**;** TMPG: TIMI myocardial perfusion grade

Introduction

Myocardial infarction (MI) and acute coronary syndromes in general remain principal causes of mortality despite major treatment advances during the last decades. Coronary artery reperfusion by percutaneous coronary intervention (PCI) represents the cornerstone of the current therapeutic approach since it contributes to decreasing the infarct size and improving prognosis. However, despite the rapid recanalization of epicardial arteries that are responsible for initial ischemia there may still persist perfusion anomalies at the level of microcirculation that are sometimes responsible for the dreaded no-reflow phenomenon (NRp), which is characterised by inadequate myocardial perfusion in a coronary artery territory without angiographic evidence of vessel obstruction.[1]

Pathophysiology of no-reflow phenomenon

The NRp exact pathophysiology has not been yet totally elucidated despite the fact that it had been initially described for the first time in an experimental myocardial infarction model in dogs more than forty years ago.[2] Multiple mechanisms seem to be in action in order to induce a perfusion defect (**Fig**. 1). Ischemia-reperfusion injury lesions related directly to the reopening of the culprit artery are implicated, as well as a systemic inflammatory reaction with neutrophil infiltrates, a tissue edema because of increased vascular permeability that is responsible for extravascular compression and narrowing of the microvessels lumen, a component of coronary spasm, as well as distal intravascular microemboli at the moment of reperfusion.

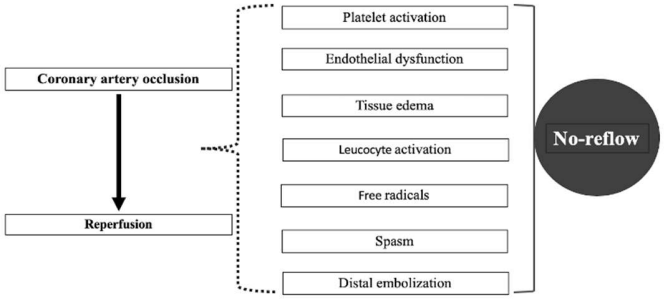

Figure 1. No-reflow phenomenon pathophysiology.

No-Reflow: Clinical Implications

The diagnosis and treatment of NRp are currently a central element of the interventional treatment of acute MI due to its prognostic impact at short and long term. Actually the presence of NRp is directly correlated to a more extensive necrosis area due to the MI, more severe left ventricular dysfunction, increased risk for cardiac rhythm disorders and constitutes an independent prognostic factor for heart failure, rehospitalization, recurrent MI and a cardiovascular mortality risk multiplied by a factor of 5.[3,4] Thus being a major risk factor NRp must be promptly recognized among patients with MI. Multiple predictors for the occurrence of NRp have been identified, such as primary PCI with possible multiple distal emboli, a long ischemic time, an extensive ischemic zone such as in case of proximal left anterior descending (LAD) occlusion, a large thrombus burden, a high neutrophil count, the presence of diabetes, the absence of pre-conditioning, e.tc. .[5]

No-Reflow: Diagnosis

The means to diagnose NRp are relatively limited and well defined. The first among them and mostly used is the

TIMI flow, which permits the assessment of the quality of reperfusion of the culprit artery during primary PCI (Table 1).[6] NRp is defined by a flow <3 at the end of the procedure. The TIMI flow assessment is convenient and straightforward but gives limited information concerning only the epicardial arteries but not the microcirculation. It should be coupled with TIMI myocardial perfusion (blush) grade (TMPG), which more specifically evaluates the clearance of the contrast medium from the myocardium and thus the myocardial perfusion and the microcirculation function. As with TIMI flow it is graded from 0 to 3 (Table 2).[7] The NRp is defined by a MBG <2. Beyond angiographic scores the electrocardiogram holds a central role in MI after revascularization through the assessment of ST segment resolution 90 minutes after reperfusion. In case of an ST segment resolution less than 50-70% an "electric" NRp is diagnosed. A combination of the above criteria allows for a most accurate assessment of the reperfusion quality and the patient prognosis. When only TIMI score is used as a criterion NRp is found in 7% of acute MI patients, while when TBG and the ST segment resolution are used after revascularization NRp is detected in 65% of them.[5]

Table 1. TIMI flow classification.

TIMI flow grade	
0	Total coronary obstruction.
I	Slow flow, not opacifying totally the coronary artery.
II	Slow flow, totally opacifying the coronary artery.
III	Normal flow.

Table 2. TIMI myocardial perfusion grade (TMPG) classification.

TIMI myocardial perfusion (blush) grade (TMPG)	
0	Failure of contrast medium to enter the microcirculation
I	Contrast agent slowly enters but fails to exit from the microcirculation
II	Slow entry and delayed exit of contrast medium from microcirculation
III	Normal entry and exit of contrast medium from microcirculation.

Therefore, it seems that NRp is rather frequent and has major clinical implications, but unfortunately it can be underestimated and undetected due to imperfect diagnostic tools. The advent of magnetic resonance imaging (MRI) for the myocardium has permitted a significant progress in NRp diagnosis, since it offers a direct evaluation of myocardial perfusion and the microcirculation and actually holds the position of a true gold standard. NRp is defined by a delay of myocardial perfusion during the three first minutes after the gadolinium injection and is interpreted by a zone of low signal during the initial acquisition phase. Being a highly sensitive and noninvasive exam MRI carries the advantage of being able to be performed at a distance from the MI event. It has been shown that NRp is a progressive and dynamic phenomenon possibly extending up to 48 hours after the MI.[8] Thus it is recommended to wait for at least 2 days before performing a myocardial MRI after a coronary occlusion in order not to underestimate the extent of NRp.

No-Reflow: Treatment

Due to the multiple mechanisms that are implicated in its pathophysiology NRp treatment has many aspects . (Fig. 2).

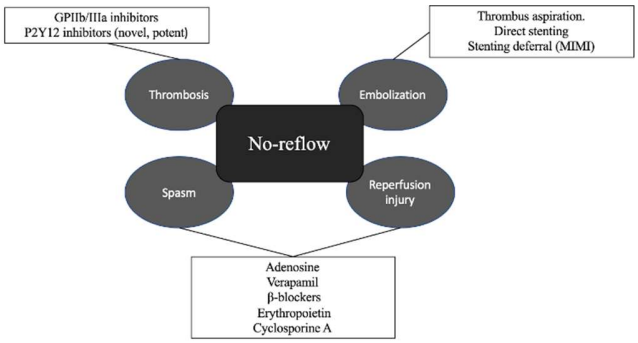

Figure 2. No-reflow phenomenon mechanisms and respective preventive and therapeutic measures.

- Preventive measures: During the acute MI phase thrombus aspiration coupled with intracoronary administration of GPIIb/IIIa antagonists has demonstrated its benefit on blush score in TAPAS study.[9] However, a benefit has not been confirmed concerning hard clinical endpoints in TASTE and TOTAL multicentre studies and routine thrombus aspiration during primary PCI is not supported by current guidelines.[10,11] On the other hand there does not exist to that day a potential effect of the novel potent P_2Y_{12} inhibitors (prasugrel and ticagrelor) on the NRp.

The technique and the delay of the PCI can potentially have a positive effect on NRp. The minimally invasive strategy (MIMI) consists of deferring stenting after reperfusion and performing it following several days of antithrombotic therapy, which could potentially limit the possibility of distal embolization after stent deployment. However such a strategy has not until now been shown to be effective regarding the infarct size or mortality and is not recommended by current guidelines.[12,13] The most widespread technique is direct stenting of a well-defined lesion underlying a thrombotic occlusion in order to entrap potentially embolic material, despite the fact that its evidence base is limited.[13]

Post-conditioning represents a promising new concept with the ambition to decrease reperfusion injury. This refers to the activation of intracellular protective mechanisms by inducing ischemia in a vascular territory in the setting of MI as an additional potential strategy to prevent reperfusion injury associated with no-reflow. Mechanical post-conditioning has been shown to significantly decrease the extent of NRp.[14,15] Ischemic post-conditioning in this context means repeated balloon occlusions of an infarct related artery and evidence in support of this technique is strong in experimental animal models but also in a recent randomized study in selected patients with MI.[16] Remote ischemic conditioning during evolving ST-elevation MI has been shown to increase myocardial salvage. It consists of intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff during transport for the hospital before primary PCI and has as most probable mechanism of action the activation of mitochondrial intracellular pathways that facilitate preconditioning.[17]
The β-blockers use early after MI has been questioned but could regain potential after a recent demonstration of benefit regarding the infarct size of a bolus of metoprolol at the moment of reperfusion.[18,19] Finally after the repetitive failures of erythropoietin still some hope rests upon cyclosporine A which has been shown to be effective in reducing infarct size in a pilot study when administrated immediately before reopening of the culprit artery and is actually the object of further research.[20,21]

- Therapeutic measures: Since the NRp is installed the therapeutic maneuvers are limited. The intracoronary administration of vasodilators (most commonly adenosine and verapamil) to fight against microvascular dysfunction is a widespread practice, but has not been definitely shown to be effective regarding infarct size.[22] Adenosine is considered to be a first line drug due to its ease of application, short half-life and strong vasoactive properties. Also widely used in case of NRp is verapamil (an L-type calcium channel antagonist) that acts on both vascular smooth muscle cells and conductive tissue, thus back-up temporary pacing should be available when it is used for intracoronary administration. Apart from adenosine and verapamil, papaverine, sodium nitroprusside, cyclosporine, streptokinase and epinephrine have all been successfully used after the development of NRp. Especially intracoronary epinephrine has been successfully used and must be considered in patients with refractory no-reflow. Each catheterization laboratory must have a certain protocol to treat NRp and it is important to administer any chosen drug as distally as possible in the coronary bed (through microcatheters) in order to act specifically on the microcirculation and thus achieve the best possible result.

Conclusions

After a myocardial infarction NRp is a strong predictor of mortality and is present in more than 50% of cases despite apparent successful revascularization. A TIMI III flow at the end of the PCI is necessary but not sufficient in order to guarantee a good prognosis. The assessment of the TMPG and the electrocardiographic ST segment resolution are important in order to accurately detect NRp even at the presence of TIMI III flow. After the MI the performance of a cardiac MRI would be beneficial since the presence of no-reflow is even retrospectively detected and accounted for prognosis. The treatment of NRp is not yet well defined in the guidelines and is currently the object of various research efforts.

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