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Review

Novel insights into an "old" phenomenon: the no reflow

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ABSTRACT

Coronary artery diseases and particularly acute myocardial infarction are the leading causes of mortality and morbidity in western countries. Despite the achievements of the last decades with the advent of double antiplatelet therapy, new antithrombotics and reperfusion strategies (either pharmacological or mechanical), many patients still have adverse cardiovascular events after ST-segment elevation acute myocardial infarction; at least some of these adverse events are related to the no reflow phenomenon that occurs after primary percutaneous coronary intervention. In our review we will discuss the various aspects of this phenomenon.

1. The no reflow phenomenon

Coronary artery diseases (CAD), and particularly acute myocardial infarction (AMI), are the leading causes of morbidity and mortality in Western countries. However the prognosis of AMI improved in the last decades due to the introduction of new pharmacological and mechanical reperfusion treatments allowing recanalization of the infarct-related epicardial coronary artery (IRA) [1].

There are three main variables that influence the infarct size after an acute coronary occlusion: the extent of the territory subtended by the coronary lesion (area at risk), the degree of residual flow (total or subtotal occlusion and collaterals) and the duration of ischemia. During the pre-recanalization era there was a higher incidence of transmural AMI with larger infarct areas due to longer ischemic times, thus leading to a higher incidence of post-AMI complications such as ventricular arrhythmias, electromechanical dissociation, cardiogenic shock, cardiac rupture, mitral valve regurgitation, aneurysm (and pseudoaneurysm) formation and mural thrombosis. Also late adverse events were more common, such as maladaptative left ventricular remodeling, chronic heart failure and sudden death. The introduction of pharmacological and mechanical IRA recanalization therapies infarcts size mainly confined to the subendocardial layers. The consequence was a significant reduction of the length of hospital stay and, above all, an improvement of both short- and long-term mortality [2].

The benefits derived from reperfusion depend on total ischemic time and the effectiveness of reperfusion itself. In fact, transmural AMI and its complications could develop also in case of late or ineffective recanalization (the longer the ischemic time, the higher the rate of complication and the larger the infarct size and the transmural extension of the necrosis). In this setting, however, IRA recanalization is not necessarily synonymous of myocardial reperfusion. Despite the new percutaneous coronary intervention (PCI) techniques and development of effective emergency transports resulting in shorter ischemic times, ST-segment elevation acute myocardial infarction (STEMI) mortality remains considerable, with estimates of 7% at 1 month and 15% at 1 year [3]. This significant mortality is, at least in part, related to the development of the so called no reflow phenomenon (NR). NR consists in the inability of a previously ischemic region in the territory of a recanalized IRA to be effectively reperfused. NR has an incidence varying between 5 and 50% after primary PCI for STEMI, depending on the method of assessment [4,5]. NR can deny, at least in part, the benefits of primary PCI, thus contributing to post-AMI complication and, eventually, to a worse outcome [6–12].

The downstream of the open-artery hypothesis has redefined the goals of reperfusion strategies to include not only rapid and sustained epicardial patency, but also restored microvascular flow and myocardial tissue perfusion. This should be the goal also of primary PCI.

Considering that the incidence of NR is not negligible, a better understanding of this phenomenon could lead to advances in its treatment.

Abbreviations: AMI, Acute Myocardial Infarction; CAD, Coronary Artery Diseases; IRA, Infarct Related Artery; PCI, Percutaneous Coronary Interventions; STEMI, ST-segment Elevation Acute Myocardial Infarction; NR, No Reflow; CMR, Cardiac Magnetic Resonance; MBG, Myocardial Blush Grade; CMD, Coronary Microvascular Dysfunction; MVO, Microvascular Obstruction; MCE, Myocardial Contrast Echocardiography; CRP, C-reactive Protein; STR, ST-segment Resolution; SLE, Systemic Lupus Erithematosus.

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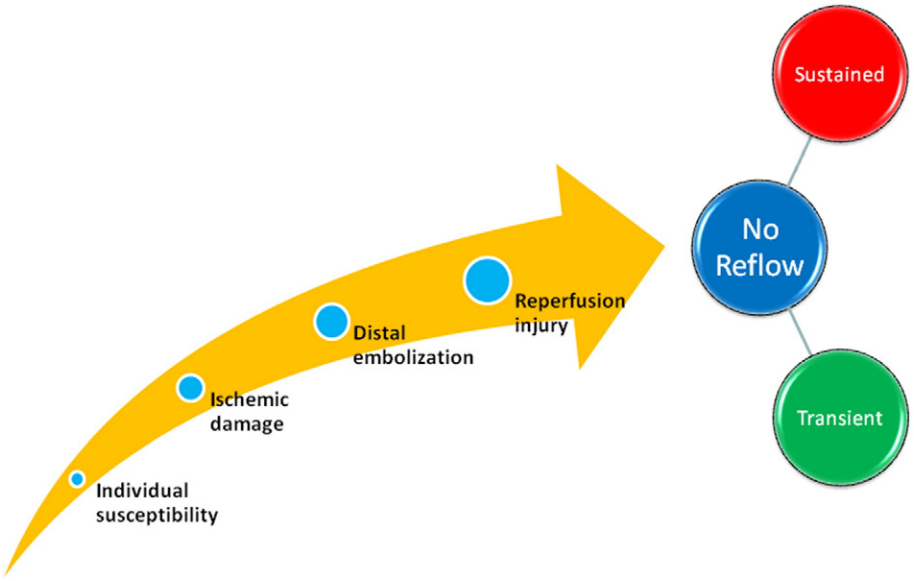

Fig. 1. The pathogenesis of no reflow is multifactorial. Individual susceptibility is influenced by genetic and clinical risk factors. Consecutive injuries (ischemic and reperfusion damages, and distal embolization) act on the substrate of individual susceptibility to cause transient or sustained no reflow.

2. Historical overview

NR was first described in 1966 by Krug et al. and then in 1973 by Kloner et al. in a canine model [13,14]. Despite the initial focus on myocardial tissue perfusion, attention soon shifted to the epicardial vessel patency. Using canine models of coronary occlusion in the late 1970s, Reimer et al. showed that infarct size was directly related to the duration of epicardial occlusion, a finding later termed as the "wave front phenomenon" of myocyte death. Although prompt relief of epicardial occlusion was clearly shown to halt the wave front of ischemic myocyte death, coronary microvascular dysfunction (CMD) in the infarct zone was identified as the limiting factor for the restoration of proper myocardial perfusion (this phenomenon was called NR). Since the early 1980s, the development of pharmacological and mechanical reperfusion therapies helped to reduce mortality in ischemic patients by allowing rapid, complete, and prolonged restoration of coronary blood flow. This is in keeping with the "open-artery" hypothesis first proposed by Braunwald in 1989, when he observed that patients with spontaneous recanalization of an IRA had fewer adverse events during follow-up [15]. Despite these observations, paradoxically, also epicardial vessel reopening was shown to exacerbate microvascular dysfunction when blood flow was restored to the infarct area. Therefore, historic observations defined the continuum of reperfusion from upstream epicardial patency to downstream tissue perfusion and emphasized that the ultimate goal of treatment strategies for acute MI should be the prompt restoration of normal epicardial flow and myocardial perfusion. Although restoration of TIMI flow grade 3 has been for a long time used as the gold standard for reperfusion success, distal tissue perfusion can vary considerably despite TIMI flow grade 3 in the epicardial vessel [16].

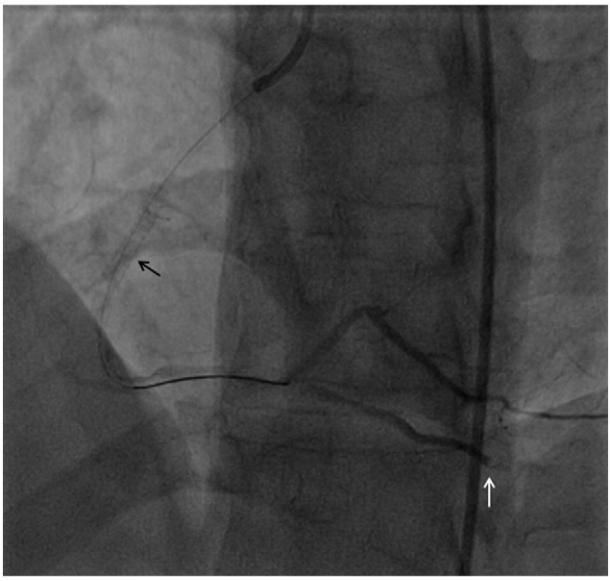

Fig. 2. After primary PCI with stent implantation (black arrow) in right coronary artery, distal embolization with incomplete filling of posterior descending artery is evident (white arrow).

NR could also develop during non ST-elevation myocardial infarction or elective PCI, but its incidence is by far higher in primary PCI for STEMI. It has been noticed that a proportion of patients do not achieve TIMI flow grade 3 after emergency and non-emergency PCI and that successful reopening of an occluded coronary artery does not necessarily lead to recovery of left ventricular function. In 1993 Lincoff and Topol [17] wondered whether reperfusion was just an illusion. At that time, they thought that only "25% or less" of patients treated by thrombolysis had an optimal myocardial reperfusion. Nowadays it is difficult to estimate the real incidence of NR phenomenon since it depends on the method of assessment and the population considered [4,5].

3. Pathogenesis

NR is related to different etiological mechanisms. Each of these mechanisms could play a different role in each single patient. The complexity of the pathogenesis of NR is incompletely understood.

NR can be sustained by three main pathogenic mechanisms, namely structural or functional alterations of the microvasculature and extravascular compression. All these mechanisms can be caused by both ischemia and reperfusion injury. Despite the tight link between ischemia and reperfusion injury and their overlap, it is sometimes possible to distinguish the contribution of each of them in the development of NR (Fig. 1).

CMD plays a key role in the development of NR. CMD refers to the impairment of resting and stimulated blood flow in the presence of patent epicardial arteries. CMD per se is associated to a worse