EDITORIAL

No-reflow phenomenon: Achilles' heel of primary coronary angioplasty in acute myocardial infarction

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Introduction of percutaneous coronary intervention (PCI) as a method of choice for the treatment of patients with ST-segment elevation myocardial infarction has brought a marked improvement in short- and long-term prognosis in this group of patients. Nevertheless, despite restoring complete patency of epicardial coronary vessels, in some patients the blood flow through these vessels remains diminished to a lesser or greater degree. This finding is due to post-reperfusion restriction in the blood flow at the microcirculation level and is known as the no-reflow phenomenon. Originally, the phenomenon was recognized exclusively on the basis of angiographic assessment of epicardial flow, using the TIMI scale (Thrombolysis In Myocardial Infarction). Progressively, angiographic assessment was reinforced with estimation of microcirculation basing on TMPG (Thrombolysis In Myocardial Infarction myocardial perfusion grade) and cTFC (corrected Thrombolysis In Myocardial Infarction frame count) [1].

No-reflow after myocardial infarction, as assessed by angiography, is a strong predictor of major cardiac complications, including heart failure, malignant arrhythmias and cardiac death [2]. Unfavourable clinical consequences and unpredictable occurence of no-reflow are triggers for further research upon its pathomechanism, risk factors, therapeutic options and further improvement of the tissue perfusion assessment techniques [3].

Direct invasive coronary flow velocity measurement, reflecting microvascular injury, may be obtained by Doppler flow wires [4]. However, this method due to its expensiveness and technical limitations is more frequently applied in scientific setting rather than in clinical practice.

An excellent method for microvascular perfusion assessment is myocardial contrast echocardiography (MCE). MCE assessment results are closely related to myocyte viability and LV remodeling occurence at follow-up [5, 6]. The method is widely available, may be performed in the bed-side setting and is patient-friendly. Thus MCE may be currently regarded as the gold standard to investigate the no-reflow phenomenon [1].

The main limitation of other diagnostic methods, including SPECT and MRI, is their unapplicability immediately after recanalization of the infarct related artery in the catheterisation laboratory or in the coronary care unit.

Olszowska et al. [6] looking for predictors of no-reflow phenomenon compared clinical, hemodynamic and electrocardiographic parameters in patients with acute myocardial infarction after PCI characterised by reflow and those featuring no-reflow phenomenon. Post-intervention perfusion was assessed with MCE, providing reliable and thorough tissue perfusion estimation.

Several risk factors for no-reflow phenomenon have been indentified so far, amongst which, the coronary vessel closure time (period of time between the symptom onset and reperfusion) seems to play the dominant role. It has been more than 20 years since Kloner et al. [7] proved on animal models that prolongation of ischemia escalates the damage of microcirculation.

Various mechanisms of such lesions have been postulated. Oxygene-free radicals (OFR), which appear almost immediately following reperfusion, produce lesions of coronary endothelium and thus,

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cause severe deficiency of endothelium derived relaxing factor (ERDF) with all consequences of this fact, such as relaxation of vascular smooth muscle impairment and augmentation of platelet aggregation and neutrophil adherence [1, 8].

Prolonged ischemia compromises active transmembrane transport and leads to a raise in intracellular calcium levels. This phenomenon, additionally amplified by sympathetic activation, produces extensive coronary spasm at acute reperfusion [1]. Simultaneously, ischemia-related acidosis and hyperosmolarity modify erythrocyte membrane, which becomes more rigid. As the final result, deformability of red blood cells is decreased [9].

One of the most commonly suggested mechanisms of no-reflow is embolization of the distal microvascular coronary circulation [9]. Microembolization may be due to defragmentation of an intracornary thrombus (as commonly seen in acute myocardial infarction) as well as due to small particles of atherosclerotic plaque (as seen in stable coronary disease). The association of no-reflow with longer ischemic time and worse initial TIMI flow may indicate the presence of highly organized thrombus burden with higher propensity for distal embolization [2]. Such mechanism is additionally advocated by the results of studies using intravascular ultrasound [10] and intracoronary doppler [4] as well as by reduction of prevalence of no-reflow phenomenon after thrombectomy in acute myocardial infarction as seen in some studies [11].

The equilibrium loss resulting from ischemia, augmented by sudden blood flow restoration, induces a complex inflammatory response, intensity of which may be very diverse. The biological potential of the factors affecting this process is huge and it may markedly increase the reperfusion injury. Activated neutrophils adhere to the endothelium, plug capillars in infarcted myocardium, directly injure endothelium and affect platelets. Endothelial cells can influence leukocytes, platelets and microvascular function by release of adhesion and vasoactive factors. Platelets also actively contribute to the inflammatory reaction by releasing a spectrum of biologically active substances which affect leukocytes, endothelial cells as well as platelets themselves by stimulating their adhesion and aggregation [12]. As a result of the complex interaction mentioned above, no-reflow phenomenon may occur even in the absence of a thrombus or microembolization [13].

One of the earliest morphological changes accompanying reperfusion is myocardial cell swelling with intracellular and interstitial oedema. There-fore, compression of the microvascular bed by tissue oedema is one of potential mechanisms affecting tissue blood-flow, which must be taken under consideration [13]. Moreover, endothelial cells might be even more prone than myocardial cells to damage caused by ischemia followed by reperfusion. Local endothelial swelling and protrusion occluding capillary lumen is a common finding after reperfusion [14].

Undoubtedly, expression of the mechanisms discussed above becomes more evident with prolongation of ischemia, enhancing the probability of no-reflow. On the other hand, maintaining blood flow in the infarct related vessel, even if severely diminished, inhibits the cascade of events which would lead to microcirculation damage [1]. Olszowska et al. [6] proved the prognostic importance of ischemia duration time and restoration of patency of the infarct related artery for no-reflow occurrence risk stratification. It should be noted though, that no differences in the prevalence of no-reflow between patients treated with either primary or facilitated PCI were seen, despite higher incidence of blood flow maintenance in the latter group [6].

Ischemic preconditioning might be capable of reducing the risk for no-reflow by preserving microvascular function and integrity. Some authors suggest that application of short periods of artery reocclusion after ischemia and reperfusion (postconditioning) can also improve vascular function and reduce infarct size [14]. Studies by Olszowska et al. [6] did not confirm the protective role of reccurrent ischemic episodes during the pre-infarction period, though it is important to note that the group of patients presenting with pre-infarction angina was small.

Mechanisms underlying microvascular dysfunction after reperfusion in myocardial infarction are very complex and only partially understood. Studies defining risk factors of no-reflow phenomenon, like study by Olszowska et al. [6] published in this issue of Cardiology Journal, composes an important contribution in our knowledge, however it is only a beginning of the way of prevention and successful treatment of patients saddled with this complication. Numerous and multidirectional attempts to prevent no-reflow phenomenon have not significantly succeeded yet [1]. In several small studies performed in various patients' cohorts adenosine, verapamil, nicardipine, nitroprusside and nicorandil have been shown to improve microvascular perfusion [15]. Nevertheless, no therapy has yet been proven to effectively prevent or to reverse no-reflow in STEMI patients [3]. Promising results

of single device studies, in particular those with use of thrombectomy, have not been confirmed in randomized trials [15]. Perhaps recently published research by Ikeno et al. [16] will be a landmark one [17]. They have demonstrated effectiveness of a novel strategy, targeted inhibition of the δ isoform of protein kinase C (δPCK), to treat post-reperfusion no-reflow in animal models. However, because of complexity of pathophysiological mechanisms of no-reflow phenomenon, this promising method should be explored further.

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