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REVIEW

The no-reflow phenomenon: State of the art

Le no-reflow *: état de l'art*

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Summary Primary percutaneous coronary intervention (PCI) is the best available reperfusion strategy for acute ST-segment elevation myocardial infarction (STEMI), with nearly 95% of occluded coronary vessels being reopened in this setting. Despite re-establishing epicardial coronary vessel patency, primary PCI may fail to restore optimal myocardial reperfusion within the myocardial tissue, a failure at the microvascular level known as no-reflow (NR). NR has been reported to occur in up to 60% of STEMI patients with optimal coronary vessel reperfusion. When it does occur, it significantly attenuates the beneficial effect of reperfusion therapy, leading to poor outcomes. The pathophysiology of NR is complex and incompletely understood. Many phenomena are known to contribute to NR, including leukocyte infiltration, vasoconstriction, activation of inflammatory pathways and cellular oedema. Vascular damage and haemorrhage may also play important roles in the establishment of NR. In this review, we describe the pathophysiological mechanisms of NR and the tools available for diagnosing it. We also describe the

Abbreviations: AMI, acute myocardial infarction; ANGPTL4, angiopoietin-like 4; ATP, adenosine triphosphate; CMR, cardiac magnetic resonance; ce-CMR, contrast-enhanced cardiac magnetic resonance; IV, intravenous; MBG, myocardial blush grade; MVO, microvascular obstruction; NR, no-reflow; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; VE, vascular endothelial; VEGF, vascular endothelial growth factor.

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microvasculature and the endothelial mechanisms involved in NR, which may provide relevant therapeutic targets for reducing NR and improving the prognosis for patients.

MOTS CLÉS
No-reflow ;
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Ischémie ;
Reperfusion ;
Angioplastie coronaire primaire ;
Perméabilité vasculaire

Résumé L'angioplastie coronaire primaire en urgence est la méthode de choix de reperfusion coronarienne pour les patients présentant un infarctus du myocarde. Le taux de succès angiographique de l'angioplastie coronaire est actuellement de 95 %. Cependant, malgré la restauration du flux épicardique, l'angioplastie peut ne pas entraîner de reperfusion réellement efficace du tissu myocardique profond. Ce défaut de reperfusion de la microcirculation myocardique correspond au phénomène de *no-reflow*. Selon les études, celui-ci est retrouvé chez 10 à 60 % des patients ayant pourtant bénéficié d'une reperfusion angiographique optimale. Le *no-reflow* atténue le bénéfice de la reperfusion et est un facteur de mauvais pronostic clinique à la phase aiguë et à long terme avec alteration de la fraction d'éjection ventriculaire gauche, insuffisance cardiaque clinique et survenue d'événements rythmiques ventriculaires. La physiopathologie du *no-reflow* et sa cinétique sont complexes et mal comprises. Plus que l'embolisation distale de débris athéro-thrombotiques, de nombreux phénomènes tels que la vasoconstriction, l'œdème intra- et extra-cellulaire, l'inflammation avec infiltration leucocytaire et libération de signaux cytotoxiques, participent au no-reflow. De plus, des données récentes démontrent un rôle important des dommages endothéliaux et de l'hémorragie intramyocardique. La perte d'integrité de la barrière endothéliale lors de la reperfusion brutale du myocarde ischémié entraîne une hyperperméabilité vasculaire qui semble être un acteur majeur du *no-reflow*. Dans cette revue, nous analyserons les mécanismes physiopathologiques impliqués dans le *no-reflow*, nous décrirons les outils diagnostiques disponibles, les éléments du pronostic et les différentes thérapeutiques à l'essai. Nous porterons une attention particulière à la protection de l'endothélium microvasculaire, qui pourrait constituer une nouvelle cible thérapeutique pour diminuer le *no-reflow*.

Background

Primary percutaneous coronary intervention (PCI) is the best available reperfusion strategy in patients with acute ST-segment elevation myocardial infarction (STEMI) [1]. Up to 95% of occluded coronary vessels can be reopened in the setting of STEMI [2—5]. However, despite re-establishing the epicardial coronary vessel patency, primary PCI may fail to restore optimal myocardial reperfusion within the myocardial tissue in patients with STEMI. This reperfusion failure at the microvascular level is a condition known as no-reflow (NR) [6—10]. NR has been described in up to 60% of STEMI patients with optimal coronary vessel reperfusion [3,11—19]. When NR occurs, it significantly attenuates the beneficial impact of reperfusion therapy, resulting in poor clinical and functional outcomes [6,20—22]. But do we really know what the NR phenomenon is? The pathophysiology of NR is complex and is not fully understood; it involves much more than just distal embolization of thrombotic debris. Indeed, many phenomena contribute to NR: leukocyte infiltration, vasoconstriction, activation of inflammatory pathways and cellular oedema [23,24] (Fig. 1). Recently, experimental data demonstrated the important roles played by vascular damage and haemorrhage in the establishment of NR. Vascular permeability at the endothelial level appears to be a major factor in NR.

In this state-of-the-art review, we will cover all the described pathophysiological mechanisms and the tools available for diagnosing NR in clinical settings. We will also focus further on the microvasculature and the endothelial mechanisms involved in NR, which may provide relevant therapeutic targets to reduce NR and improve patient prognosis.

Pathophysiological mechanisms and predictive factors

The NR phenomenon was described for the first time by Kloner et al. in 1974 [25], in a canine experimental model of myocardial ischaemia-reperfusion.

Ischaemia injury

NR starts with the initial severe ischaemic insult. Lethal ischaemia, defined by a myocardial tissue blood flow < 40 mL/min for 100 g of tissue, causes irreversible cardiomyocyte and endothelial damage. At the endothelial level, bleb formation and endothelial protrusion are observed, and obstruct the microcirculation. Endothelial cell necrosis leads to destruction of tight and adherens