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NO-REFLOW PHENOMENON – MECHANISM, PREVENTION AND TREATMENT STRATEGIES

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ABSTRACT

No-reflow phenomenon is a major clinical problem in the treatment of acute myocardial infarction, which happens despite effective recanalization of the epicardial coronary arteries. It is also marked by compromised microvascular blood circulation and it is linked to poor clinical outcome, such as bigger infarct size, left ventricular remodeling and higher mortality rates. The lack of no-reflow pathophysiology is multifactorial in nature and consists of distal microthromboembolization, reperfusion injury, endothelial dysfunction, microvascular spasm, and excessive inflammatory response. The no-reflow diagnosis continues to be difficult. Angiographic techniques such as Thrombolysis In Myocardial Infarction (TIMI) flow grade, which are used widely, are not very effective in evaluating microvascular perfusion. Higher resolution imaging including cardiac magnetic resonance imaging, myocardial contrast echocardiography, among others, offer a more accurate analysis; nevertheless, their application in clinical practice is limited due to their infrequent availability and high cost. No-reflow phenomenon is also a complicated combating mechanism. The existing approaches to therapy are mainly directed at alleviating the burden of thrombus, limiting the area of infarction, and alleviating reperfusion damages. However, the efficacy of these methods is dynamic and inadequately frequently, and no single therapy aimed at the coronary microvascular dysfunction development is determined. This means that more investigations about the mechanism behind no-reflow, the creation of more sensitive diagnostic techniques, and specific treatment of no-reflow have to be taken to enhance microvascular reperfusion and patient outcome.

KEYWORDS

No-Reflow Phenomenon, Acute Myocardial Infarction, Mechanism, Treatment

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Introduction

Acute myocardial infarction remains one of the leading causes of morbidity and mortality worldwide, despite significant progress in reperfusion therapy, in particular percutaneous coronary intervention (PCI) (Ibánez i in., 2017a; Reed i in., 2017). However, effective restoration of flow in the infarct-causing artery does not always lead to adequate myocardial reperfusion at the microcirculation level. This phenomenon, referred to as no-reflow, is a significant clinical problem because it is associated with increased infarct size, adverse left ventricular remodeling, and worsening short- and long-term prognosis (Ito, 2001; Niccoli i in., 2009). Despite its significant clinical significance, the diagnosis of no-reflow remains difficult. Routinely used angiographic methods do not allow for precise assessment of microcirculatory perfusion, and achieving normal epicardial flow does not exclude persistent microcirculatory dysfunction (Celik i in., 2016; Ito, 2001). More advanced imaging techniques, such as cardiac magnetic resonance imaging or contrast echocardiography, enable more accurate assessment of myocardial perfusion, but their availability in routine clinical practice remains limited (Srikanth & Ambrose, 2012; Wu i in., 1998). Treating the no-reflow phenomenon also poses a significant therapeutic challenge. Available therapeutic strategies primarily focus on limiting thrombotic burden, reducing infarct size, and mitigating reperfusion injury, but their effectiveness is variable and often insufficient (Kloner i in., 2017; Niccoli i in., 2016). Despite promising results of experimental and clinical studies on pharmacological interventions targeting microcirculation, there is a lack of clear evidence enabling routine implementation of effective causal therapy (Carrick i in., 2016; Elgendy & Jneid, 2018). Therefore, the no-reflow phenomenon remains the subject of intensive experimental and clinical research. A better understanding of its pathophysiological mechanisms, improved diagnostic methods, and the development of effective therapeutic strategies targeting microcirculation are crucial to further improving the outcomes of patients with acute myocardial infarction (Heusch, 2019; Niccoli i in., 2016). The aim of this paper is to discuss the current state of knowledge regarding the pathogenesis, diagnosis and therapeutic management of the no-reflow phenomenon.

Percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is an invasive treatment method used to treat coronary artery disease, whereby narrowed and/or obstructed coronary arteries are dilated mechanically. This is carried out percutaneously (mainly through radial or femoral arterial access) using catheters which are inserted into the coronary vasculature following fluoroscopic guidance. In PCI, the catheters are transported through the blood vessels into the coronary arteries, where guidewires and balloon or stent devices will be deployed to reestablish luminal patency. This process is based on real-time fluoroscopic visualization of device placement and the proper delivery of therapeutic implants, therefore, reducing the risk of vascular comorbidity (Ahmad i in., 2025; Neumann i in., 2019). The main goal of the percutaneous coronary intervention (PCI) is to normalize the physiological coronary blood flow, which then suppresses myocardial ischemia, increases left ventricular systolic performance, and improves clinical outcomes of patients (Rao i in., 2025). The modern practice of percutaneous coronary intervention (PCI) has made a routine use of coronary stents and especially drug eluting stents (DES) which have shown reduced rate of restenosis, and also less frequent repeat revascularization (Stefanini & Holmes, 2013). This is a commonly used methodology in both stable coronary artery disease and acute coronary syndromes and forms one of the basis methods of reperfusion therapy (Ibánez i in., 2017a).

Indications for percutaneous coronary intervention

Indications for percutaneous coronary intervention include both acute coronary syndromes and chronic coronary syndromes in which mechanical revascularization is of prognostic or symptomatic benefit. PCI is the procedure of first choice in patients with ST segment elevation myocardial infarction (STEMI), provided the procedure is carried out in the recommended time from the moment of the symptoms, since it restores the coronary flow and limits the extension of myocardial necrosis and mortality (Ibánez i in., 2017a). In the context of acute coronary syndromes without ST-segment elevation, i.e., NSTEMI and unstable angina, percutaneous coronary intervention is indicated in patients who have high-risk features. Such features are hemodynamic instability, recurrence of ischemic symptoms despite optimal pharmacologic therapy, significant electrocardiographic abnormalities, or elevated myocardial necrosis biomarkers (Collet i in., 2021). In chronic coronary syndromes, percutaneous coronary intervention is used principally to control the symptoms of angina pectoris in patients who despite an optimal pharmacological treatment still suffer a symptoms persistence, as well as in case of presence of hemodynamically significant coronary artery stenoses demonstrated by functional assessment modalities such as the fractional flow reserve, or in case of identification of a large ischemic area with non-invasive testing of the patient (Knuuti i in., 2020). Additional indications for percutaneous coronary intervention (PCI) include the treatment of in-stent restenosis, the advancement of atherosclerotic lesions following previous revascularization, and select cases of multivessel disease in which the risk profile for cardiac surgery is increased or where the vascular anatomy makes one best suited for a percutaneous approach. The final decision to proceed with PCI must be individualised and must integrate a thorough evaluation of the clinical presentation, coronary anatomy and comorbidities, as well as patient's preferences; this is a decision often made as part of an interdisciplinary consultation with the Heart Team, which is usually performed (Neumann i in., 2019).

PCI Techniques

PCI is carried out in the cath lab, usually under local anaesthesia, following vascular access, usually radial or femoral, following the insertion of a vascular sheath and subsequent introduction of a guiding catheter to the coronary artery ostium under fluoroscopic guidance. Subsequent coronary angiography makes it possible to assess the anatomy; a guidewire is then passed through the narrowed or occluded portion. Depending on the nature of the lesion, balloon pre-dilation and stent deployment (mostly drug eluting stents) are performed, post-dilation may be performed for an optimal angiographic result and to reduce the risk of underexpansion (Neumann i in., 2019). In patients with severely calcified lesions, the classical angioplasty is often not effective or is at risk of incomplete stent expansion, thus, strategies of plaque modification are used (atherectomy, e.g., rotational) and intravascular lithotripsy (IVL). Clinical data from the DISRUPT CAD program supports the effectiveness of IVL to support successful stenting of these challenging lesions (Hill i in., 2020; Kereiakes i in., 2022). In the treatment of bifurcation lesions, the "provisional stenting" strategy (one stent with optional protection of the side branch) is preferred, whereas in selected cases of bifurcations with significant significance of both branches, double-stent techniques are used; in bifurcations of the distal left main coronary artery, the DK crush strategy was shown to be superior to the provisional strategy in the DKCRUSH-V study (Chen i in., 2017). A particularly complex subgroup is chronic total occlusion (CTO), where anterograde, retrograde and subintimate strategies (including controlled entry/re-entry) are employed, and the choice of approach is a component of the management algorithms delineated in expert documents; the principles of technique and the selection of equipment are delineated in the European EuroCTO consensus which also outlines the prerequisites of operator and centre experience (Galassi i in., 2019). Intravascular imaging modalities including intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have an ever growing role in optimization of percutaneous coronary intervention (PCI) procedures. IVUS, which uses ultrasound technology, is useful in assessing luminal dimensions, plaque burden, and calcific involvement, thus helping in stent deployment and apposition. Conversely OCT which uses high resolution optical imaging provides detailed visualization of the superficial coronary anatomy, thrombus, and subtle irregularities of the implants like malapposition or minor dissections, although using OCT requires a brief flushing of the imaging field with blood (Collet i in., 2021; Neumann i in., 2019). Data derived from randomized controlled trials and meta-analytic syntheses show that percutaneous coronary intervention (PCI) based on intravascular imagings has better outcomes as compared to angiography alone such as a significant reduction in treatment site failure rate (Stone i in., 2024), and for the OCT strategy, there is also strong evidence from a randomized clinical trial published in the New England Journal of Medicine (Ali i in., 2023). After finishing the process, the device is extracted, the puncture is sealed and antiplatelet therapy starts depending on the clinical profile and risk of bleeding as is essential for the subsequent prevention of stent thrombosis (Collet i in., 2021).

Classification of PCI complications

Complications of percutaneous coronary intervention encompass a wide spectrum of events related to the procedure itself, the access site, and the circulatory system's response. Literature describes complications related to the vascular access site, coronary complications including acute vessel occlusion, dissection, perforation, no-flow phenomenon, arrhythmias, and stroke. Additionally, analyses highlight bleeding complications and complications related to the use of contrast media and ionizing radiation (Mahilmaran, 2023).

No-reflow phenomenon

No-reflow is the term used to describe a condition in which perfusion of the myocardium to a certain coronary segment is insufficient despite the angiographic demonstration of vessel patency in the presence of no obvious mechanical causes such as stenosis, hypotension, and dissection (Ramjane i in., 2008). This phenomenon is explained by perfusion disturbances within the coronary microcirculation that occur in spite of the successful restoration of epicardial artery patency during percutaneous coronary intervention. Consequently, technical success of revascularization of a large vessel is not always associated with good myocardial perfusion. In contrast with those scenarios characterized by mechanical occlusion of the arteries, the no-reflow phenomenon is mainly representative of functional and structural damage to the small resistance vessels and this scenario is termed microcirculatory microobstruction (Annibali i in., 2022; Jaffe i in., 2010). A well-documented pathophysiological mechanism of the no-reflow phenomenon represents distal microembolization co-existent with intravascular manipulation. Thrombotic fragments, lipid cores of atherosclerotic plaques, and platelet aggregates can embolize to the peripheral micrografts, thus causing mechanical occlusion. This embolic event assays a local inflammatory processes characterized by leukocyte activation and concomitant production of cytokines and reactive oxygen species; these mediators in turn add to vascular resistance and woolen the perfusion deficits (Annibali i in., 2022; Tomaniak i in., 2013). Another vital element involved in the pathogenesis of no-reflow is re-perfusion injury which is a phenomenon arising from the sudden restoration of blood flow to tissues that have been subjected to prolonged periods of ischemia. This event is concomitant with increased oxidative stress, mitochondrial dysfunction, and an unregulated entry of calcium ions in cellular compartments. Consequently, cells of the endothelium and the myocardium encounter edema, which leads to the secondary constigence of the orifice of the microvessels and the further reduction of the tissue perfusion (Jaffe i in., 2010; Ndrepepa i in., 2018). An additional thing that plays a significant part in the development of no-reflow is vascular endothelial dysfunction. Ischemia and subsequent reperfusion cause a loss of balance between vasodilators and vasoconstrictors. Reduced nitric oxide bioavailability coupled with elevated release of the neutrophil-degranulation mediators endothelins and catecholamines causes sustained microvascular constriction and dysfunction in the mechanisms of coronary flow autoregulation (Annibali i in., 2022). The activation of platelets combined with the coagulation cascade has a pivotal influence within the pathogenesis of the no-reflow phenomenon, mostly by formation of microthrombi in the capillary bed. This effect is remarkably increased in persons presenting with acute coronary syndromes carrying an increased thrombotic load, hence providing a partial mechanistic explanation for the higher frequency of no reflow during primary PCI in patients with ST segment elevation myocardial infarction (Ndrepepa i in., 2018; Tomaniak i in., 2013).

No-reflow risk factors

The occurrence of no-reflow phenomenon is highly increased in elder people and patients with chronic comorbidities such as diabetes mellitus, hypertension or chronic kidney disease. These conditions favor endothelial dysfunction and generate both structural and functional derangements in the coronary microcirculation. Severe clinical status upon admission either in terms of high Killip classification or as precondition with cardiogenic shock is also associated with a higher risk of unsuccessful microcirculatory reperfusion. Within the context of myocardial infarction phenotypes, an especially poor prognosis is known in cases of anterior wall infarction, diffuse myocardial necrosis, prolonged ischaemic intervals and the lack of developed collateral circulatory networks. These factors result in significant and extensive microcirculatory injury even before the onset of reperfusion interventions. (Zhang i in., 2024; Ibánez i in., 2017b; Ito, 2001; Jaffe i in., 2010).

No-reflow diagnostics

The diagnostic process usually involves a synthesis of the angiographic changes, electrocardiographic changes, and cardiac enzyme levels in order to determine the existence and the extent of impaired microvascular perfusion (Dawson i in., 2024). Angiographic assessment, which is assessed as usual when doing percutaneous coronary intervention, provides visual confirmation of immediate microvascular blockage, despite the absence of mechanical vessel blockage (Annibali i in., 2022). Electrocardiographic analysis is frequently used in conjunction with this technique; sustained elevation of ST − segments after successful epicardial reperfusion could indicate atrophy of microvascularity, and a rise in cardiac biomarkers, which is a further indication of myocardial injury inherent to the no-reflow phenomenon (Karasu i in., 2024; Li i in., 2018). Some of the highly developed imaging modalities are used to accurately describe no-reflow, which includes Doppler flow velocity, contrast-enhanced echocardiography, cardiac magnetic resonance imaging, and positron emission tomography. However, the flow grade Thrombolysis In Myocardial Infarction (TIMI) is always the easiest and quickest one to use as a diagnostic tool (Lim i in., 2004). Despite the convenience of TIMI flow grade, non-invasive imaging techniques, including myocardial contrast echocardiography and cardiac magnetic resonance imaging, can give a more accurate measurement of myocardial perfusion, therefore, allowing a better assessment of the no-reflow phenomenon after percutaneous coronary intervention (Srikanth & Ambrose, 2012). More specifically, cardiac magnetic resonance imaging of microvascular obstruction is a strong prognostic variable in the detrimental clinical outcomes, such as mortality (Beijnink i in., 2023). Cardiac magnetic resonance imaging with late gadolinium enhancement, though being sensitive when evaluating microvascular obstruction, is still a costly method that is not commonly integrated into clinical practice due to the absence of overall value assessment (Elgendy & Jneid, 2018). The no-reflow definition of thrombolysis of myocardial infarction (TIMI) flow grade as less than or equal to 2 in the absence of macrovascular obstruction or TIMI flow grade 0-2 is a simple and easy-to-departure technique of assessment. However, this method has a shortcoming of not enabling a direct assessment of capillary perfusion (Celik i in., 2016). More refined angiographic definitions of microvascular obstruction also include TIMI flow grades less than 3, a TIMI flow grade 3 and myocardial blush grade or TIMI myocardial perfusion grade of 0 to 1 (Niccoli i in., 2016). Even though TIMI flow classification system is mainly used to evaluate the epicardial macrovascular perfusion, the chronic failure to restore TIMI flow grade III after reperfusion of the culprit vessel suggests the presence of residual deficiency of the microcirculatory network (Tan i in., 2023). To a TIMI grade of 3, thus indicating successful epicardial reperfusion, as many as 60ʻutes of ST-elevation myocardial infarction may however possess no-reflow on cardiac magnetic resonance imaging up to 72 hrs, hence emphasizing the shortcomings of the use of the angiographic method alone (Celik i in., 2016). The observed discrepancy brings out the need to adopt more sensitive and specific diagnostic modalities, like the Index of Microvascular Resistance, against which a direct and quantitative assessment of the microvascular function is obtained (Carrick i in., 2016). Despite this, grades of Thrombolysis In Myocardial Infarction (TIMI) blush fail to evaluate microvascular pathology and poor long-term adverse outcome due to high levels of inter- and intra-observer variability and high levels of special expertise are required to reliably assess the parameter (Carrick i in., 2016). Also, angiography can be performed too soon to fully evaluate the extent of reperfusion injury since complex pathophysiological events occur within hours and days after reperfusion (Celik i in., 2016). Nevertheless, some angiographic parameters, such as, the Thrombolysis in Myocardial Infarction flow score, myocardial blush grade, and the Thrombolysis in Myocardial Infarction myocardial perfusion grade are regularly used to demarcate angiographic coronary microvascular dysfunction and obstruction (Niccoli i in., 2016). The myocardial blush grade, which was first published in 1998, measures the tissue radiopacity after contrast injection of the epicardial coronary arteries and it measures the rate of dissipation of contrast and thus provides a semi-quantitative measure of microvascular perfusion (Khattak i in., 2024). Those with a score of zero would mean there was no myocardial blush, those with a score of one meant a slight blush, those with a score of two meant it was a moderate blush, less than what would be seen in a healthy artery, and those with a score of three means that it was normal blush (Celik i in., 2016; Khattak i in., 2024). Thrombolysis In Myocardial Infarction Thrombolysis In Myocardial Infarction system is a myocardial perfusion grading scale, which grades 0 (no perfusion), 1, 2 and 3 (normal perfusion) (Niccoli i in., 2016). These angiographic parameters are commonly used but it is still imperative to remember that the angiographic assessment of the reperfusion of micro-vessels is often imprecise due to the high discrepancy existing between conventional coronary angiography and arterioles which actually provide a control over the myocardial perfusion level (Doherty i in., 2021). Therefore, successful epicardial reperfusion, indicated by a TIMI 3 flow, does not invariably guarantee effective myocardial perfusion, with 20%-40% of acute coronary syndrome patients still exhibiting impaired

microvascular blood flow (Abdel-Galeel i in., 2021). In fact, impaired microcirculation can manifest despite having TIMI 3 flow which, consequently, results in the emergence of undesirable sequelae like left ventricles remodeling and reduction of ejection fraction (Doherty i in., 2021). The diagnosis of coronary microcirculation disorders, including the no-reflow phenomenon, is subject to significant limitations resulting from the insufficient sensitivity and specificity of commonly used methods. Angiographic assessment of reperfusion, despite its availability and routine use, does not reliably reflect actual microcirculation perfusion and may lead to underestimation of the extent of myocardial damage. Furthermore, the dynamic nature of reperfusion injury and the time lag between intervention and full progression of the pathology complicate the unambiguous interpretation of test results. The limited availability and cost-intensiveness of more precise imaging techniques mean that routine clinical practice still lacks an optimal, readily available tool for the unambiguous assessment of coronary microcirculation function.

No-reflow drug treatment

Interventions that target the no-reflow phenomenon are eclectic with the majority entailing pharmacological interventions, mechanical methods that aim to restore microvascular patency and mitigate myocardial injury downstream. These measures attempt to improve coronary microcirculation, reduce distal embolization and counteract the action of inflammatory and thrombotic cascades triggered by ischemia - reperfusion injury. Pharmacologic techniques often include the use of vasodilators, antiplatelet agent, antithrombotic agent whereas mechanical only include aspiration thrombectomy and distal protection devices (van Kranenburg i in., 2014). Taking into account the complexity of no-reflow pathophysiology, the complex therapeutic approach often involves the combination of various modalities to address the multiple factors. Primary initial pharmacological intervention mainly focuses on prevention and treatment of thrombotic events and inflammatory reactions that play major role as precursors of no-reflow. In this strategy, the use of glycoprotein IIb/IIIa inhibitors has been incorporated and this has been found to be effective in improving microvascular perfusion by inhibiting platelet aggregation and consequently preventing the formation of micro thrombus. However, there are contradicting reports of their uniformly positive outcome in all patient groups, and some studies show no statistically significant change in myocardial perfusion or patient outcome (Kalia, 2023; Kimura i in., 2019). A variety of other pharmacological agents such as adenosine, nitroprusside and nicorandil among others have been studied as vasodilatory and cardioprotective agents in combination with antiplatelet therapy to address microvascular dysfunction (Qi i in., 2018). Adenosine, in particular, has shown promise in improving myocardial perfusion and left ventricular ejection fraction in the acute phase by alleviating microvascular dysfunction (Sucato i in., 2020). The intracoronary administration of adenosine and verapamil has proven to have potential effectiveness in preventing the no-reflow phenomenon under the small scale settings of limited clinical studies (Soukoulis i in., 2014). However, the systematic prophylax use of these vasodilators is limited by the occurrence of adverse events and thus their high usage across all classes of patients is restricted (Jafari Afshar i in., 2023). Other studies have documented a possible benefit of statin pre-primary percutaneous coronary intervention (PCI) in counteracting the occurrence of no-reflow phenomenon. However, in a meta-analysis of a large number of studies it was found that interventions like aspiration thrombectomy, deferred stenting and ischemic pre-conditioning had been linked with positive improvements in angiographic endpoints but never necessarily translated into better clinical outcome (Elgendy & Jneid, 2018). On the other hand, the pre-intervention administration of high-dose atorvastatin has been proven to improve reperfusion and to prevent major adverse cardiac events by 47 percent in high-risk cardiac patients with the acute coronary syndrome who were administered atorvastatin without prior experience of statin treatment (Rangel, 2021). The effectiveness of these agents is often dependent upon when and how they are delivered with intracoronary delivery close to the microvasculature possibly leading to high effective dosages (Beijnink i in., 2023). Further research is needed to determine the effectiveness of novel drug treatments and improved delivery systems to improve microvascular performance and, accordingly, patient outcome.

No-reflow mechanical treatment

Mechanical interventions which are useful to counteract the no-reflow phenomenon, mainly focus on the mechanical debridement of the thrombotic mass and the protection of distal microvascular compartments against embolic material which subsequently prevents later occlusion (Goyal i in., 2017). The above measures include not only manual aspiration thrombectomy, but also using distal protection devices, all of which should eliminate the lumen of the coronary artery and prevent the passage of particulate matter into the microcirculation (Geng i in., 2021). However, the recent usage of the aspiration thrombectomy has been

questioned based on the big-scale randomized controlled trial that has failed to find a uniform decrease in the infarct size, or clinical outcome (Kingma, 2018). In line with this, despite the apparent theoretic value of distal protection devices in preventing embolization, the clinical implications of these devices in either preventative embolization reduction or prognosis improvement of the patient have not been clearly proved so far (Mignatti i in., 2025). Although some mechanical methods have shown only partial success, research still advances to identify new methods, including the pressure-controlled intermittent coronary sinu occlusion to manage this complicated pathophysiology of no-reflow phenomenon (Doherty i in., 2021).

Novel Therapeutic Approaches

In addition to traditional interventions, there are emerging treatment approaches driven by a deeper understanding of the molecular and cellular processes that mediate microvascular dysfunction and ischemia-reperfusion injury and thus continually leading to the revision of therapeutic regimes that relate to the no-reflow phenomenon (Mignatti i in., 2025). There is an investigative interest in the efficacy of fibrinolytic agents and anticoagulant regimens, but the direct effect of these modalities on the incidence of no-reflow, has been moderate with some pilot studies suggesting that intracoronary, low-dose streptokinase after PCI will benefit myocardial reperfusion in patients with ST-segment elevation myocardial infarction (Elgendy & Jneid, 2018). However, microvascular occlusion by microthrombi has caused interests in antithrombotic therapy, which include the drugs like abciximab and tirofiban which have shown a possibility of decreasing the size of infarction and improving the clinical outcome of given patients (Beijnink i in., 2023). Nevertheless, a potential, random, controlled, multicenter study which evaluated distal microcirculatory protection during the percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction showed that despite effective retrieval of embolic debris this practice did not lead to better microvascular circulation or overall prognosis (Basso & Thiene, 2006). This highlights the intricate nature of no-reflow, suggesting that strategies targeting macroscopic embolization alone may be insufficient without addressing the underlying microvascular dysfunction (Xue i in., 2021). Mechanical thrombus aspiration and distal embolic protection devices are preemptive measures that aim to reduce cases of distal embolization and reperfusion injury, although their effectiveness differs significantly depending on the situation, e.g. saphenous vein graft percutaneous coronary intervention, as compared to native coronary artery intervention (Soukoulis i in., 2014). Moreover, the widening field of targeted therapies, in particular, the use of therapeutic biomarkers (including Index of Microcirculatory Resistance) evidence significant potential of personalised medicine in the prevention and treatment of no-reflow (Canu i in., 2022). The therapeutic hypothermia is also discussed as a potential treatment option in present studies and it has been shown that localized cooling of ischemic myocardium can significantly decrease the no -reflow area, regardless of infarct size (Kloner i in., 2017). The cooled saline infusion technique which is administered within the infarct related artery, is currently in the process of investigation, as highlighted by suchTrials as European Intracoronary Cooling Evaluation in Patients With ST-elevation Myocardial Infarction to determine its safety and efficacy (Silva i in., 2022). Considering the multifactorial etiology of the no-reflow phenomenon, further studies concentrating on combinatorial regimes for treatment that simultaneously act on disparate pathophysiological mechanisms, such as microembolization, endothelial dysfunction and inflammatory responses, may engender superior clinical outcomes when compared to monotherapy strategies (Pinelli i in., 2018).

Conclusions

The no-reflow phenomenon remains a significant clinical challenge in the management of acute myocardial infarction, substantially affecting patient prognosis despite successful epicardial reperfusion. Its multifactorial pathogenesis renders both diagnosis and treatment particularly challenging. Current therapeutic strategies primarily focus on reducing thrombus burden and limiting infarct size; however, their efficacy is variable and often limited. Despite promising results from experimental and clinical studies investigating pharmacological interventions, there is a lack of conclusive evidence supporting the routine implementation of effective therapies specifically targeting the coronary microcirculation. Consequently, further research into the underlying mechanisms of the no-reflow phenomenon, as well as the development of more precise diagnostic and therapeutic tools, is required to improve microvascular perfusion and patient outcomes.

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