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REVIEW ARTICLE

Understanding the No-Reflow Phenomenon in Coronary Interventions: A Comprehensive Review

Ahmed Saeid Eldamanhory[1], Tarek A. AbdelAziz[1], Mohamed AbdelAziz Attia Mohamed[1], Nader Talat Kandeel[1], Islam Elsayed Shehata[1*]

***Correspondence author:**
Dr. Islam Elsayed Shehata

E-mail:
iemshehata@zu.edu.eg

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ABSTRACT

Background: The no-reflow phenomenon, a complex complication arising post-successful coronary revascularization, presents a big challenge in the management of acute myocardial infarction. This comprehensive review explores the complex aspects of this condition, exploring its incidence, pathophysiology, predictors, clinical impact, diagnosis, and management strategies. Despite advancements in investigative and therapeutic approaches, a comprehensive understanding of the precise mechanisms in humans remains elusive.

Methods: The article addresses the varied incidence of no-reflow across clinical settings, ranging from 2% in elective native coronary interventions to 26% in primary percutaneous coronary interventions for acute myocardial infarction. Notably, up to 60% of ST-elevation myocardial infarction patients undergoing primary PCI experience no-reflow even after optimal coronary vessel reperfusion. Pathophysiology encompasses ischemia-reperfusion injury, distal microthromboembolism, and endothelial dysfunction, which are categorized into structural and functional types. Predictors, including age, reperfusion time, blood pressure, thrombus burden, and vessel diameter, emphasize the importance of tools for assessing risks.

Results: No-reflow significantly impacts left ventricular function and remodeling, leading to prolonged hospitalization durations and heightened long-term mortality. Diagnosis relies on crucial modalities such as coronary angiography and cardiac magnetic resonance imaging.

Management strategies encompass prevention through optimizing door-to-balloon time, blood glucose, and blood pressure control, along with various treatment options like thrombus aspiration, glycoprotein IIb/IIIa inhibitors, nitroprusside, calcium channel blockers, and adenosine.

Conclusions: This review provides a detailed viewpoint on the complex nature of the no-reflow phenomenon, emphasizing the persistent need for research to enhance outcomes in patients undergoing coronary interventions.

Keywords: No-Reflow Phenomenon; Coronary Interventions; Acute Myocardial Infarction; Pathophysiology; Management Strategies

INTRODUCTION

In the contemporary landscape of immediate reperfusion strategies for patients experiencing acute myocardial infarction, the primary focus revolves around minimizing the duration of coronary occlusion and myocardial ischemia to mitigate myocardial necrosis. Despite rigorous efforts in this direction, a residual risk of myocardial ischemia persists, manifesting as a no-reflow phenomenon (1). This phenomenon denotes inadequate myocardial perfusion within a patent epicardial coronary artery, typically attributed to microvascular obstruction resulting from diverse mechanisms (2). Various definitions of the no-reflow phenomenon exist in the literature, with a classical definition dating back to 2001 by Eeckhout and Kern, characterizing it as insufficient myocardial perfusion through a specific coronary

circulation segment during primary percutaneous coronary intervention (PPCI) without angiographic evidence of mechanical vessel obstruction (3). More recently, a detailed perspective considers no-reflow in the context of diminished antegrade blood flow (Thrombolysis In Myocardial Infarction [TIMI]) flow (0 or 1) following stent deployment, not attributable to abrupt closure, spasm, or significant stenosis of the original target lesion (4).

INCIDENCE

The occurrence of the no-reflow phenomenon exhibits variability based on the clinical context, with rates as low as 2% in elective native coronary percutaneous coronary interventions (PCI), escalating to 20% in saphenous venous graft (SVG) interventions, and reaching up to 26% in primary PCI for acute myocardial infarction (AMI) (5). A noteworthy observation, highlighted in a European Heart Journal article, reports the manifestation of no-reflow in up to 60% of ST-elevation myocardial infarction (STEMI) patients undergoing primary PCI, even following optimal reperfusion of coronary vessels (6).

PATHOPHYSIOLOGY

Since the initial description of the no-reflow phenomenon in 1974, various mechanisms have been proposed for its development (7). The pathophysiology of no-reflow is intricate and multifaceted, with several theories offering partial explanations:

A) Ischemia Injury: The onset of no-reflow begins with myocardial ischemia, defined as myocardial tissue blood flow less than 40 mL/min for 100 g of tissue, resulting in irreversible damage to cardiomyocytes and endothelial cells. At the endothelial level, the formation of blebs and protrusions obstruct the microcirculation. Additionally, phenomena such as microvascular hemorrhage, fibrin deposits, platelet clumping, white blood cell aggregation, and rouleaux formation of red blood cells may occur. Endothelial cell necrosis leads to a loss of vascular integrity, causing extravascular accumulation of fluid and blood cells, further compressing the microvessel lumen (8, 9).

B) Reperfusion Injury: Reperfusion injury arises from the restoration of normal blood supply to the damaged microcirculation, accelerating myocardial swelling, tissue edema, endothelial disruption, and inflammation. Activated neutrophils release oxygen-free radicals and pro-inflammatory mediators, contributing to sustained vasoconstriction of coronary microcirculation. Autonomic dysfunction, specifically alpha-adrenergic receptor-mediated vasoconstriction of coronary microcirculation, also plays a role in no-reflow development (10).

C) Endothelial Injury: Endothelial integrity, regulated by growth factors such as vascular endothelial growth factor (VEGF), is compromised during myocardial ischemia. This increases endothelial permeability, a factor observed in experimental models as a significant contributor to no-reflow development (11).

D) Distal Atherothrombotic Embolization: Primary percutaneous coronary intervention (PCI) is often performed in the presence of a high thrombus burden, and manipulations during the procedure can lead to the distal embolization of microthrombi and plaque components. Distal embolization stands out as a major contributing factor to the development of no-reflow. As a protective measure, aspiration catheters and thrombectomy devices are advocated, especially in the presence of a high thrombus burden (12, 13).

Based on these underlying mechanisms, no-reflow can be classified into two main categories: structural and functional no-reflow. Structural no-reflow involves irreversible damage to microcirculation within the necrotic myocardium, characterized by endothelial swelling, edema, and microvascular obstruction. On the other hand, functional no-reflow is reversible and occurs when microvasculature patency is compromised due to alpha-adrenergic-related vasoconstriction, spasm, microthrombotic embolization, and reperfusion injury, with the accumulation of neutrophils and platelets, presenting a relatively better prognosis (Figure 1) (14, 15).

PREDICTORS OF NO-REFLOW PHENOMENON

Numerous studies have sought to identify risk factors and predictors for the development of the no-reflow phenomenon (16). One study revealed that independent predictors of the no-reflow phenomenon included age over 65 years, reperfusion time exceeding 6 hours, systolic blood pressure on admission less than 100 mmHg, intra-aortic balloon pump (IABP) use before percutaneous coronary intervention (PCI), a low initial Thrombolysis In Myocardial Infarction (TIMI) flow (≤1), a high thrombus burden, and a long target lesion (16). A comprehensive meta-analysis in 2018, pooling data from 27 studies, identified several factors associated with an increased risk of no-reflow, such as advanced age,

male gender, family history of coronary artery disease, smoking, diabetes mellitus, hypertension, delayed reperfusion, Killip class ≥2, elevated blood glucose at the time of the procedure, elevated serum creatinine, increased heart rate, decreased left ventricular function, long lesion length, multivessel disease, initial TIMI flow ≤1, and high thrombus burden (17).

In a more recent study in 2020, a risk scoring system was proposed as a predictor for the development of no-reflow during primary PCI. Parameters included in the model were age, absence of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) use, collateral circulation, thrombus burden, diameter of the target lesion, and blood glucose levels (18). Activation of the renin-angiotensin system leads to increased production of angiotensin II, subsequently raising vascular resistance and myocardial oxygen demand. The use of ACEIs and ARBs inhibits these downstream hazardous pathways (19).

Concerning the relationship between the culprit vessel and the incidence of the no-reflow phenomenon, extensive research has been conducted, yet no significant correlation between the culprit vessel and the development of no-reflow has been conclusively identified to date (20).

CLINICAL IMPACT

A substantial number of patients with ST elevation experience impaired myocardial reperfusion despite the opening of the culprit's vessel, restoration of epicardial blood flow, and the absence of in-situ thrombosis or vasospasm (21). The persistence of systolic dysfunction, even after opening the epicardial vessel and establishing Thrombolysis In Myocardial Infarction (TIMI) 3 flow through pharmacological and/or mechanical intervention for acute myocardial infarction, may be attributed to irreversible injury (myocardial necrosis), reversible injury (myocardial stunning), or a combination of both (22).

The development of the no-reflow phenomenon carries a poor prognosis and is associated with depressed left ventricular (LV) ejection fraction and adverse LV remodeling (21). In short-term follow-up, the no-reflow phenomenon has been linked, in various studies, to an increased duration of hospitalization compared to patients without no-reflow (6). A large study involving 1140 patients reported that no-reflow after primary PCI was associated with reduced myocardial salvage, a larger infarct size, worse left ventricular ejection fraction at six months, and an increased risk of 1-year mortality (23). On long-term follow-up, the development of the no-reflow phenomenon during primary PCI has been identified as a strong predictor of 5-year mortality (23).

DIAGNOSIS OF NO-REFLOW

Diagnosing no-reflow begins with the clinical scenario and involves various diagnostic modalities. The clinical presentation of the no-reflow phenomenon varies widely depending on the situation. In the catheterization laboratory, the clinical presentation is often sudden and dramatic, with the patient experiencing severe chest pain and hemodynamic instability (24).

A) Coronary Angiography: The suspicion of no-reflow arises in any situation of impaired TIMI flow after ruling out similar conditions. Spasms of the epicardial coronary arteries should be ruled out by administering intracoronary nitroglycerine boluses (25). The term "no-reflow phenomenon" originated from the observation of the absence of coronary flow despite the deployment of a coronary stent and the opening of the occluded coronary vessel. The TIMI flow scale is utilized to evaluate different coronary flow grades during PCI procedures, classifying flow into Grades 0 (no flow), 1 (penetration without perfusion), 2 (partial perfusion), and 3 (complete perfusion) (2).

B) Cardiac Magnetic Resonance Imaging (CMR): CMR with gadolinium administration is the gold standard non-invasive technique for assessing microvascular obstruction (MVO) (26). While no specific guideline recommendations exist for the best timing or type of sequence to assess MVO by CMR, studies often perform CMR assessment after ST-elevation myocardial infarction (STEMI) between 2 and 9 days post-primary PCI, as the extent of both MVO and infarction significantly increases in the first 48 hours post-reperfusion. Gadolinium contrast, used in first-pass-perfusion imaging and late MVO, reflects the state of coronary microcirculation (27). CMR T2 weighted sequences additionally provide crucial data about tissue edema and intramyocardial hemorrhage (28). Late MVO has been identified as the most powerful predictor of regional and global left ventricular functional recovery in homogenous studies among STEMI patients treated with primary PCI (29).

C) Other Techniques: Other diagnostic techniques, including the electrocardiogram, contrast echocardiography, and nuclear imaging, may be used to confirm the diagnosis of no-reflow. However, due to their low sensitivity, these methods

are rarely employed in clinical practice for diagnosing no-reflow (Table 1).

MANAGEMENT

Numerous studies and meta-analyses have explored therapeutic approaches for managing the no-reflow phenomenon. However, there is currently no universal consensus on a specific approach for its management. Euro Intervention has proposed an algorithm for dealing with the no-reflow phenomenon in the catheterization lab (Figure 2). The 2011 American guidelines for percutaneous coronary intervention (PCI) are the only guidelines that have provided specific recommendations for managing this catastrophic complication (30).

A) Prevention of No-Reflow:

B) Preventing the no-reflow phenomenon involves undertaking precautions. Achieving a shorter door-to-balloon time, maintaining optimal blood glucose levels, and managing optimal blood pressure are initial steps in preventing the occurrence of no-reflow (32).

B) *Treatment of No-Reflow:*

1- Thrombus Aspiration: Thrombus aspiration has been considered a potential solution to reduce the risk of distal embolization involved in the pathophysiology of no-reflow. Studies suggested a reduction in the incidence of no-reflow with thrombus aspiration before PCI, resulting in improved clinical outcomes. However, routine use of thrombus aspiration is no longer recommended based on the 2017 European Society of Cardiology (ESC) guidelines for ST-elevation myocardial infarction (STEMI), citing limited crossover and evidence from trials like TASTE and TOTAL (34). In cases of large residual thrombus burden post-vessel opening, thrombus aspiration may be considered (35).

2- Glycoprotein IIb/IIIa Inhibitors: Glycoprotein IIb/IIIa inhibitors, antiplatelets that inhibit platelet aggregation, were investigated in the INFUSE-AMI trial on STEMI patients undergoing primary PCI. Intracoronary injection of abciximab significantly reduced infarct size at 30 days post-MI. However, due to the high bleeding risk, the use of these inhibitors should be carefully considered. The 2017 ESC guidelines recommended their consideration for bailout if there is evidence of no-reflow or a thrombotic complication (37).

3- Nitroprusside: Intracoronary vasodilators, including adenosine, calcium channel blockers, or nitroprusside, are recommended by the 2011 ACC PCI guidelines to treat PCI-related no-reflow during primary or elective PCI (38). Nitroprusside, activating guanylate cyclase, induces smooth muscle relaxation and vasodilation. Local distal administration usually improves coronary flow and myocardial blush without affecting systemic blood pressure. Studies comparing nitroprusside and nicorandil in treating no-reflow demonstrated lower TIMI frame counts with nitroprusside. A meta-analysis in 2014 showed that intracoronary sodium nitroprusside reduces TIMI frame count, improves left ventricular function, and significantly reduces major adverse cardiac events (MACE) incidence (40).

4- Calcium Channel Blockers: Studies, including a recent meta-analysis, demonstrated the potential benefit of intracoronary verapamil injection in reducing major adverse events in patients undergoing PCI. However, further research is needed to establish calcium channel blockers as a standard treatment for no-reflow (42).

5- Adenosine: Adenosine, recommended by ACC guidelines for managing no-reflow, induces smooth muscle relaxation in the coronary microcirculation and possesses antiplatelet properties. Evidence from the AMISTAD-II trials showed a significant reduction in infarct size with high-dose adenosine. The REOPEN-AMI trial found improved ST-segment resolution at 90 minutes with adenosine compared to intracoronary nitroprusside (28, 21).

DILEMMA ABOUT THE NEED FOR A NEW AGENT

Despite the efficacy of adenosine in managing no-reflow, its short half-life poses a limitation. Recent data from animal models have suggested that a 2-hour intracoronary adenosine infusion is more effective than an adenosine bolus in ameliorating no-reflow. However, a significant concern with adenosine use is the potential for inducing atrioventricular block when infused into the arterial bed supplying the conduction system. Therefore, adenosine cannot be employed in situations of heart block, sinus bradycardia, and junctional rhythm, which are not uncommon during ST-elevation myocardial infarction (STEMI) and primary percutaneous coronary intervention (PCI) (32).

Moreover, despite the use of various agents, refractory no-reflow—defined as no-reflow that persists even after employing at least two agents such as adenosine, verapamil, and glycoprotein IIb/IIIa inhibitors—remains a challenge in a substantial percentage of primary PCI patients.

In light of these challenges, there is a growing interest in exploring new agents for the management of refractory no-reflow and situations where adenosine is contraindicated. Epinephrine, traditionally used in clinical settings to treat cardiopulmonary arrest, has emerged as a potential candidate. Despite its established clinical use, there is a limited amount of published data regarding the effectiveness of epinephrine in coronary no-reflow (44). This opens up a dilemma regarding the necessity for innovative agents that can address the shortcomings associated with current therapeutic options and provide effective solutions in challenging clinical scenarios.

Table 1: Other diagnostic modalities for no-reflow phenomenon:

Diagnostic Modalities for diagnosis of No-reflow phenomenon	**Findings**
Electrocardiography post-intervention	Persistent ST-segment elevation
Dual Myocardial scintigraphy	Uptake perfusion mismatch
Myocardial Tc-99m sestamibi scintigraphy	No-reflow zone
Myocardial contrast echocardiography	Echocardiograms are obtained after IV or IC injection of sonicated microbubbles. The lingering microbubbles within the myocardium indicate no reflow.

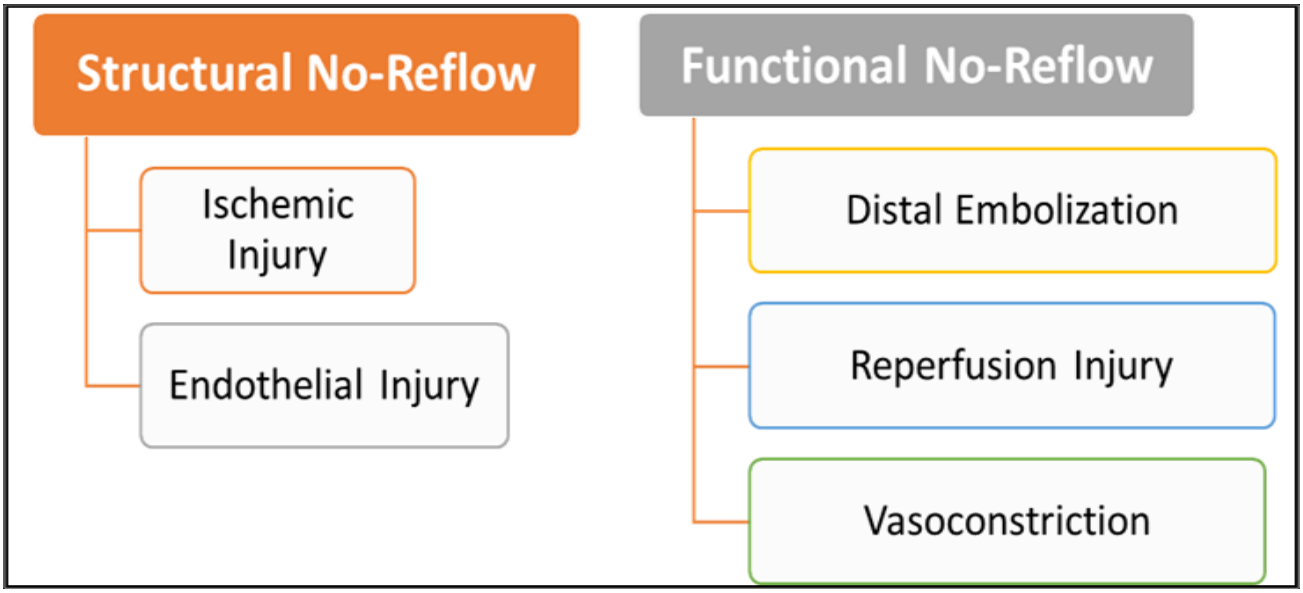

Figure 1: Classification of different types of no-reflow **(15)**

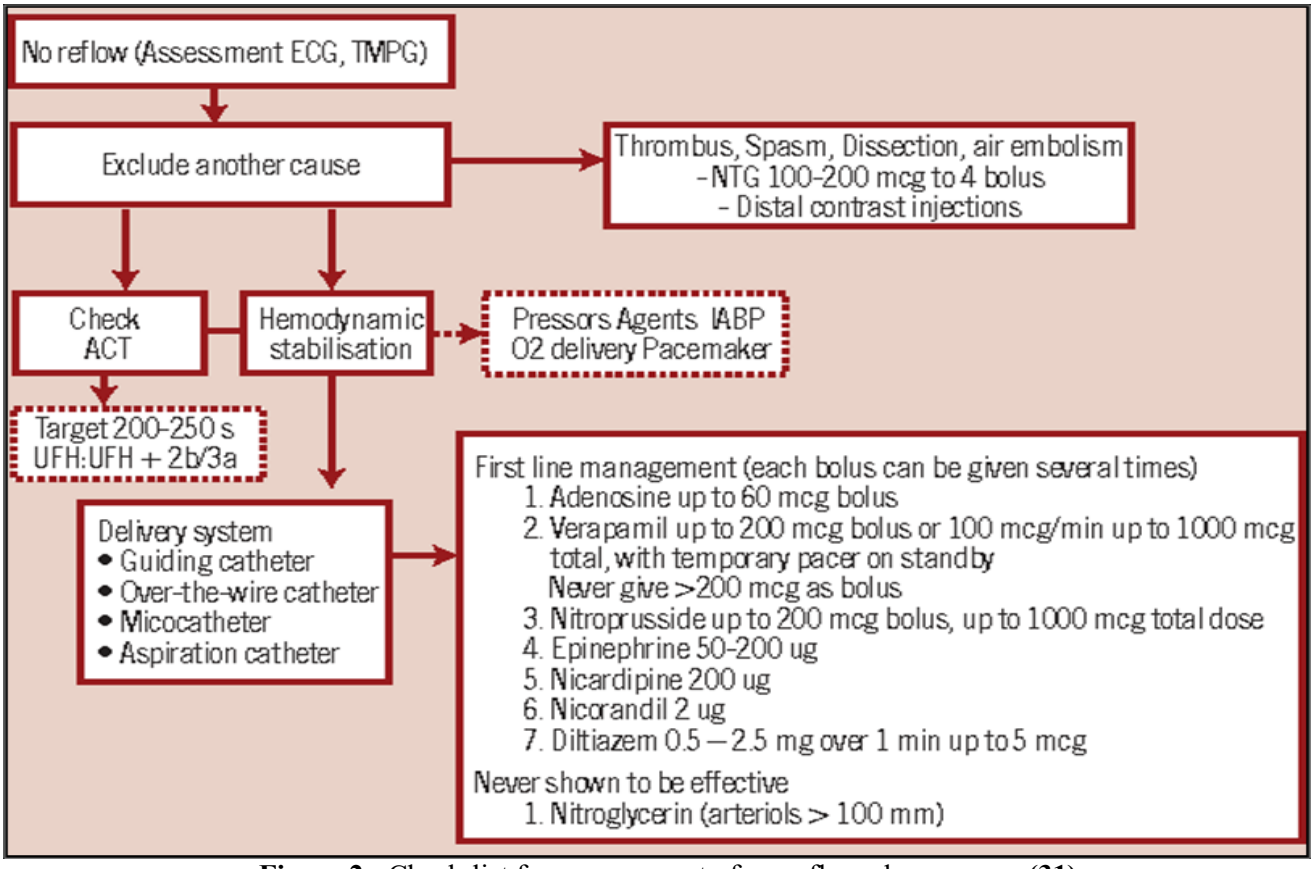

Figure 2: Check-list for management of no-reflow phenomenon **(31)**

CONCLUSION

This review offers a comprehensive overview of the no-reflow phenomenon, addressing its incidence, pathophysiology, predictors, clinical impact, diagnosis, and management (9). The complexities surrounding no-reflow necessitate ongoing research for improved outcomes in patients undergoing coronary interventions.

DECLARATIONS

Ethics approval and consent to participate: The protocol was approved by our University Institutional Review Board (ZU-IRB#10006/25-12-2022), which confirmed that all methods were performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

***Consent for publication*:** Not applicable.

Availability of data and material: Our comparative cross-sectional study data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions: AE wrote the review and did statistical analysis. TA collected data and acquisition analysis and was the major contributor to writing the manuscript. IS did the statistical analysis, drafted and revised the article. NK collected tables and figures and revised the article. IS interpreted the patient data and critically revised the article. All authors read and approved the final review article.

Conflict of interest: None

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