No-Reflow in STEMI Patients Undergoing Primary PCI: Insights and Interventions

Baher Nabil Nashy; **Tarek Ahmed Naguib**; **Mohamed Taha Elsayed ***; **Ahmed S. Eldamanhory**

Cardiology Department, Faculty of Medicine, Zagazig University, Egypt.

*Corresponding author: **Mohamed Taha Elsayed**; Email: Mtd010151610@gmail.com

Received: 15-09-2024, Accepted: 21-10-2024, Published: 13-11-2024

ABSTRACT

Background: The no-reflow phenomenon is a significant complication during primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). It is characterized by inadequate myocardial perfusion despite successful epicardial coronary artery recanalization and is associated with increased infarct size, adverse ventricular remodeling, and higher mortality. **Objective:** This review aims to provide an updated overview of the pathophysiological mechanisms, risk factors, diagnostic modalities, and current evidence-based strategies. **Methods:** A comprehensive literature review was conducted using databases such as PubMed, Scopus, and Google Scholar. Recent clinical trials, meta-analyses, and guideline-based recommendations related to the prevention and treatment of no-reflow in the context of primary PCI were analyzed and summarized. **Results:** The development of no-reflow is multifactorial, involving distal embolization, ischemia-reperfusion injury, endothelial dysfunction, and microvascular obstruction. Several predictors have been identified, including high thrombus burden, delayed reperfusion, and certain procedural factors. Preventive strategies include optimal antithrombotic therapy, aspiration thrombectomy in selected cases, vasodilator use (e.g., adenosine, nitroprusside, verapamil), and emerging pharmacological agents. Novel techniques aimed at minimizing microvascular injury are also under investigation. **Conclusion:** Early identification of at-risk patients and implementation of targeted preventive strategies are crucial to improving clinical outcomes.

Keywords: No-reflow, STEMI, Primary PCI, Myocardial Perfusion, Reperfusion Injury

Introduction

ST-segment elevation myocardial infarction (STEMI) remains a leading cause of morbidity and mortality worldwide. Primary percutaneous coronary intervention (PCI) has emerged as the preferred reperfusion strategy due to its superiority in restoring epicardial blood flow, reducing infarct size, and improving clinical outcomes when performed promptly. However, despite successful reopening of the culprit coronary artery, myocardial tissue perfusion may remain suboptimal in a considerable number of patients a phenomenon known as the no-reflow phenomenon **(1,2)**.

The no-reflow phenomenon is a serious and frequently encountered complication in patients undergoing primary PCI for STEMI. It refers to inadequate myocardial perfusion at the microvascular level, despite successful opening of the epicardial coronary artery. Although the main coronary vessel may appear patent post-PCI (TIMI 3 flow), perfusion at the tissue level is compromised. This condition can result from a combination of

microvascular obstruction, endothelial injury, distal embolization, and reperfusion injury, all contributing to poor myocardial recovery **(3)**.

No-reflow has been identified as a strong independent predictor of adverse outcomes, including larger infarct size, left ventricular dysfunction, heart failure, and increased mortality. As such, prevention, early recognition, and timely intervention are crucial for improving both short-term and long-term prognosis in STEMI patients **(4)**.

Incidence and Predictors

No-reflow occurs in approximately 10–30% of STEMI patients undergoing primary PCI, although this varies depending on the definition used and the diagnostic tools available **(5)**. Advanced imaging modalities such as cardiac MRI may detect even higher rates of microvascular obstruction. Several predictors have been consistently associated with an increased risk of no-reflow. These include older age, longer ischemic time (especially >6 hours), diabetes mellitus, anterior wall infarction, high thrombus burden, and poor pre-procedural TIMI flow (0 or 1) **(6)**.

High blood glucose levels on admission and lack of robust collateral circulation also contribute to increased vulnerability. Additionally, angiographic features, such as a large reference vessel diameter, proximal lesion location, and long lesion length, are associated with an elevated risk of microvascular complications. Numerous predictive models have been developed to stratify patients based on these clinical and angiographic parameters; however, many lack external validation, and their application in daily clinical practice remains limited **(7,8)**.

Pathophysiology

The pathogenesis of no-reflow is complex and multifactorial. One major mechanism is ischemic injury to the microvascular endothelium, which leads to capillary swelling, microvascular collapse, and interstitial edema, all of which physically obstruct blood flow. Another key factor is distal embolization of thrombus or atheromatous debris during PCI, which can occlude small arterioles and capillaries **(9)**.

Reperfusion injury also plays a critical role: when blood flow is restored after a period of ischemia, the sudden influx of oxygen and inflammatory cells causes oxidative stress, neutrophil activation, and further endothelial damage **(Fig. 1)**. Other contributors include microvascular vasoconstriction, platelet aggregation, and impaired vasodilation due to endothelial dysfunction. The culmination of these events results in poor tissue perfusion and contributes to adverse ventricular remodeling and heart failure development **(10)**.

Clinical Impact and Management Strategies

The presence of no-reflow has profound prognostic implications. Numerous studies have demonstrated that patients with no-reflow experience larger infarct sizes, lower left ventricular ejection fraction (LVEF), and higher in-hospital and long-term mortality **(2-4)**.

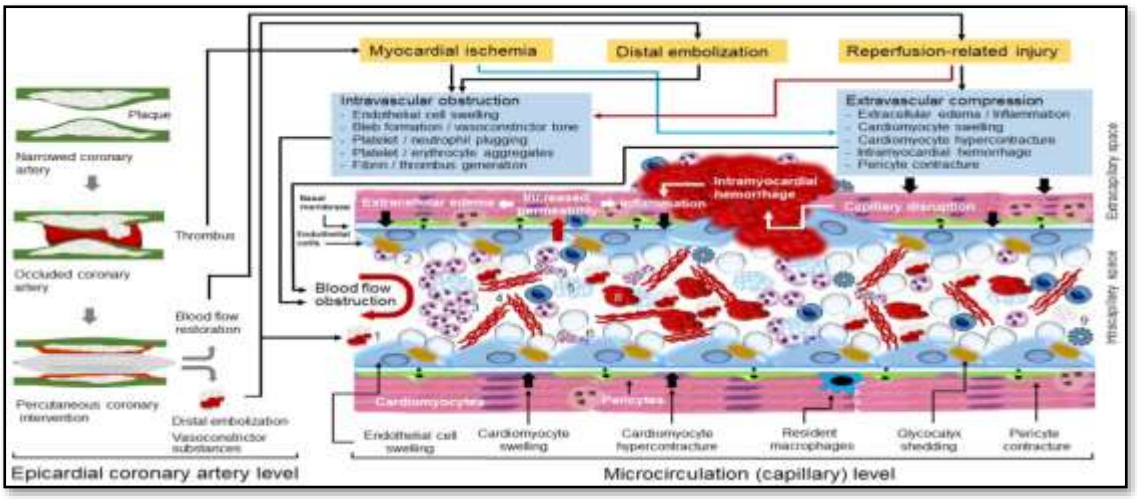

Figure (1): Pathophysiological events of microvascular obstruction and coronary no-reflow.

In some studies, no-reflow was associated with a two-fold increase in 1-year mortality, even after adjusting for other risk factors. Furthermore, these patients are more likely to develop heart failure, experience ventricular arrhythmias, and have higher rates of repeat revascularization. Thus, early identification and effective treatment of no-reflow are critical to improving clinical outcomes **(11)**

Procedural strategies play a significant role. Prevention of no-reflow begins with minimizing ischemic time, as the duration of coronary occlusion directly correlates with microvascular injury **(Fig. 2)**. Early reperfusion, ideally within 90 minutes of first medical contact, significantly reduces the risk of microvascular damage. Pharmacologically, high-dose statin pre-treatment (e.g., atorvastatin 80 mg) has shown consistent benefit in reducing no-reflow, likely through anti-inflammatory and endothelial-stabilizing effects. Antiplatelet therapy, especially with more potent agents like ticagrelor or prasugrel, is preferred over clopidogrel in STEMI settings due to faster and more consistent platelet inhibition. In high-risk patients, glycoprotein IIb/IIIa inhibitors such as tirofiban may be administered, particularly when high thrombus burden is present **(12)**.

Direct stenting, without prior balloon predilatation, minimizes mechanical manipulation of the thrombus and reduces the risk of distal embolization. Manual thrombus aspiration has shown mixed results in large trials but may still be considered in selected patients with a large visible thrombus. Some centers have explored deferred stenting, where the stent is implanted several hours after initial reperfusion to allow for thrombus resolution, although this approach requires careful patient selection due to the risk of reinfarction **(13,14)**.

Once no-reflow is identified, prompt intracoronary therapy is essential**.** A variety of agents have been studied for their ability to improve microvascular perfusion **(Fig. 2)**.. Intracoronary adenosine, a vasodilator and anti-inflammatory agent, can improve flow and reduce reperfusion injury. Verapamil and nicardipine, calcium channel blockers, are used to relieve microvascular spasm. Nitroprusside and nicorandil are also effective,

particularly for their combined vasodilatory and cardioprotective effects. If standard agents fail, intracoronary epinephrine has emerged as a promising rescue therapy, demonstrating high rates of restored TIMI 3 flow in recent small studies **(15,16)**.

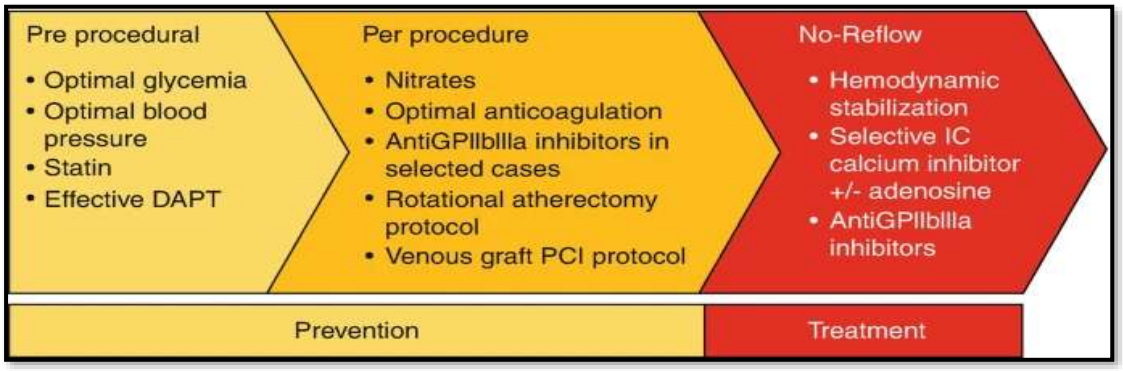

Figure (2): Scheme of No-reflow prevention and treatment

Mechanical interventions may include repeat thrombus aspiration or distal protection devices, though their use is limited in native vessel PCI. The SALINE technique, involving intracoronary bolus saline injection, has shown promise in small trials, possibly through mechanical flushing and reduction of endothelial swelling. Supportive care, including hemodynamic stabilization, oxygenation, and blood pressure optimization, is critical during and after PCI in patients with no-reflow **(17)**.

Several recent studies and meta-analyses have provided new insights. The CHANGE trial demonstrated that IV nicorandil administered before PCI significantly reduced the incidence of no-reflow and improved left ventricular function. Meta-analyses have confirmed the benefits of high-dose statins, direct stenting, and intracoronary vasodilators in both flow restoration and long-term clinical outcomes. A network meta-analysis ranked anisodamine and nicorandil as among the most effective drugs for treating no-reflow, although larger trials are needed. The role of intracoronary alteplase (low-dose fibrinolytic) is also being explored as a prophylactic strategy in high-risk cases, with early results showing promise **(18,19)**.

Challenges and Future Directions

Despite advances, several challenges persist. Definitions of no-reflow vary across studies, complicating interpretation and comparison of results. Many trials are small or underpowered, and there is a lack of high-quality, multicenter randomized trials assessing long-term clinical outcomes rather than just angiographic endpoints. Prediction models, though abundant, often lack external validation and are not widely used in real-world practice. Additionally, interventions that improve flow do not necessarily translate to better survival or reduced heart failure **(20,21)**.

Conclusion:

No-reflow remains a challenging complication in the management of STEMI with primary PCI. Early identification of at-risk patients and implementation of targeted preventive strategies are crucial to improving clinical outcomes.

A combination of early recognition, preventive strategies, procedural technique, and timely pharmacologic intervention is critical to minimize its impact. While considerable progress has been made in understanding the pathophysiology and management of no-reflow, gaps remain in terms of prediction, prevention, and definitive treatment.

Ongoing research into novel therapeutic approaches holds promise for more effective prevention and treatment of this phenomenon.

Recommendations

To prevent the no-reflow phenomenon in STEMI patients undergoing primary PCI, clinicians should first identify high-risk individuals by assessing factors such as high thrombus burden, delayed presentation, and comorbidities like diabetes. Optimal antithrombotic therapy, including dual antiplatelet agents and anticoagulants, is essential, and glycoprotein IIb/IIIa inhibitors may be considered in select cases. Intracoronary vasodilators such as adenosine, verapamil, or nitroprusside can improve microvascular perfusion when no-reflow is detected. Procedural strategies like direct stenting and avoiding aggressive pre-dilation can help minimize distal embolization. Manual aspiration thrombectomy may be used selectively in patients with a large thrombus burden, though not routinely recommended. Maintaining hemodynamic stability and considering mechanical circulatory support in severe cases are also crucial. Post-procedure monitoring and continuation of guideline-directed medical therapy, including DAPT and heart failure management, support long-term outcomes. Emerging pharmacological agents and imaging technologies hold promise for better prevention and real-time detection of no-reflow

Conflict of interest: The authors declare no conflict of interest.
Author contribution: Authors contributed equally in the study.

References:

1- **Ndrepepa, G., Kastrati, A. (2023).** Coronary no-reflow after primary percutaneous coronary intervention—current knowledge on pathophysiology, diagnosis, clinical impact and therapy. *Journal of clinical medicine*, *12*(17), 5592.
2- **Annibali, G., Scrocca, I., Aranzulla, T. C., Meliga, E., Maiellaro, F., Musumeci, G.** (2022). "No-reflow" phenomenon: a contemporary review. *Journal of clinical medicine*, *11*(8), 2233.
3- **Bouleti, C., Mewton, N., & Germain, S. (2015).** The no-reflow phenomenon: state of the art. *Archives of cardiovascular diseases*, *108*(12), 661-674.
4- **Pantea-Roșan, L. R., Pantea, V. A., Bungau, S., Behl, T., Diaconu, C. C. (2020).** No-reflow after PPCI a predictor of short-term outcomes in STEMI patients. *Journal of clinical medicine*, *9*(9), 2956.

5- **Gupta, S., & Gupta, M. M. (2016).** No reflow phenomenon in percutaneous coronary interventions in ST-segment elevation myocardial infarction. *Indian heart journal*, *68*(4), 539-551.

6- **Ndrepepa, G., Tiroch, K., Keta, D., Fusaro, M., Seyfarth, M., Pache, J., ... & Kastrati, A. (2010)**. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. *Circulation: Cardiovascular Interventions*, *3*(1), 27-33.

7- **Eeckhout, E., & Kern, M. J. (2001).** The coronary no-reflow phenomenon: a review of mechanisms and therapies. *European heart journal*, *22*(9), 729-739.

8- **Pelliccia, F., Niccoli, G., Zimarino, M., Andò, G., Porto, I., Calabrò, P., Filardi, P. P. (2023)**. Pathophysiology and treatment of the no-reflow phenomenon in ST-segment elevation myocardial infarction: focus on low-dose fibrinolysis during primary percutaneous intervention. *Reviews in Cardiovascular Medicine*, *24*(12), 365.

9- **Pantea-Roșan, L. R., Pantea, V. A., Bungau, S., Tit, D. M., Behl, T., Vesa, C. M., ... & Diaconu, C. C. (2020).** No-reflow after PPCI—a predictor of short-term outcomes in STEMI patients. *Journal of clinical medicine*, *9*(9), 2956.

10- **Aggarwal, P., Rekwal, L., Sinha, S. K., Nath, R. K., Khanra, D., Singh, A. P. (2021, June**). Predictors of no-reflow phenomenon following percutaneous coronary intervention for ST-segment elevation myocardial infarction. In *Annales de Cardiologie et d'Angéiologie* (Vol. 70, No. 3, pp. 136-142). Elsevier Masson.

11- **Pelliccia, F., Niccoli, G., Zimarino, M., Andò, G., Porto, I., Calabrò, P., ... & Filardi, P. P. (2023)**. Pathophysiology and treatment of the no-reflow phenomenon in ST-segment elevation myocardial infarction: focus on low-dose fibrinolysis during primary percutaneous intervention. *Reviews in Cardiovascular Medicine*, *24*(12), 365.

12- **Niccoli, G., Cosentino, N., Spaziani, C., Minelli, S., Fracassi, F., & Crea, F. (2011).** New strategies for the management of no-reflow after primary percutaneous coronary intervention. *Expert Review of Cardiovascular Therapy*, *9*(5), 615-630.

13- **Refaat, H., Tantawy, A., Gamal, A. S., & Radwan, H. (2021).** Novel predictors and adverse long-term outcomes of No-reflow phenomenon in patients with acute ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Indian heart journal*, *73*(1), 35-43.

14- **Aitmokhtar, O., Paganelli, F., Benamara, S., Azaza, A., Bonello, L., Hamza, O., ... & Benkhedda, S. (2017)**. Impact of platelet inhibition level on subsequent no-reflow in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Archives of cardiovascular diseases*, *110*(11), 626-633.

15- **Ashmawy, M. M., Elsaid, A. M., Sheikh, R. G. E., Guindy, E. A. E., & Setiha, E. A. E. H. E. (2022)**. Incidence and predictors of no reflow phenomenon in patient undergoing primary percutaneous coronary intervention. *Journal of Advances in Medicine and Medical Research*, *34*(22), 437-449.

16- **El Hefnawi, A. O., Abdullah, R. M., Mostafa, T. M., & El Maghawary, L. M. (2021).** Slow flow and No Reflow Post Primary Percutaneous Coronary Intervention: Prediction and Short term Impact. *Eur J Mol Clin Med*, *8*(2), 2640.

17- **d'Entremont, M. A., Alazzoni, A., Dzavik, V., Sharma, V., Lemaire-Paquette, S., Jolly, S. S. (2023)**. No-reflow after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction: an angiographic core laboratory analysis of the TOTAL Trial. *EuroIntervention*, *19*(5), e394.

18- **Galasso, G., Schiekofer, S., D'Anna, C., Gioia, G. D., Piccolo, R., Niglio, T., ... & Trimarco, B. (2014)**. No-reflow phenomenon: pathophysiology, diagnosis, prevention,

and treatment. A review of the current literature and future perspectives. *Angiology*, *65*(3), 180-189.

19- **Dogan, N. B., Ozpelit, E., Akdeniz, S., Bilgin, M., Baris, N. (2015).** Simple clinical riskscore for no-reflow prediction in patients undergoing primary percutaneous coronary intervention with acute STEMI. *Pakistan journal of medical sciences*, *31*(3), 576.

20- **Mazhar, J., Mashicharan, M., & Farshid, A. (2016)**. Predictors and outcome of no-reflow post primary percutaneous coronary intervention for ST elevation myocardial infarction. *IJC Heart & Vasculature*, *10*, 8-12.

21- **Del Turco, S., Basta, G., De Caterina, A. R., Sbrana, S., Paradossi, U., Mazzone, A. (2019)**. Different inflammatory profile in young and elderly STEMI patients undergoing primary percutaneous coronary intervention (PPCI): its influence on no-reflow and mortality. *International journal of cardiology*, *290*, 34-39.