International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Strategies to Prevent the No-Reflow Phenomenon in Primary PCI: A Comprehensive Review

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: 21 May 2024; **Accepted**: 08 June 2024; **Published**: 19 August 2024

ABSTRACT

The no-reflow phenomenon, defined as inadequate myocardial tissue perfusion despite successful epicardial coronary artery recanalization during primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), remains a significant clinical challenge associated with increased infarct size, adverse ventricular remodeling, and higher morbidity and mortality. Its multifactorial pathophysiology involves distal embolization of thrombotic and atheromatous debris, ischemia-reperfusion injury, endothelial dysfunction, microvascular spasm, and capillary plugging by inflammatory cells. A complication associated with increased morbidity and mortality due to impaired myocardial salvage and adverse left ventricular remodeling. This comprehensive review aims to synthesize current evidence on the pathophysiology, risk factors, and preventive strategies for no-reflow during primary PCI. Pharmacological interventions such as intracoronary vasodilators, antiplatelet agents, and novel therapies are examined alongside mechanical approaches including thrombus aspiration and distal protection devices. Additionally, the role of procedural techniques, such as optimized stent deployment and ischemic conditioning, is discussed. Emphasis is placed on early identification of high-risk patients and tailored therapeutic strategies to minimize no-reflow incidence. Future directions focusing on emerging biomarkers and advanced imaging techniques to predict and monitor no-reflow are also explored. By consolidating existing knowledge and highlighting evolving practices, this review seeks to guide clinicians in optimizing outcomes in primary PCI by effectively preventing no-reflow.

Keywords: No-Reflow Phenomenon; Primary PCI; Risk factors; Strategies

Introduction

Primary percutaneous coronary intervention (PCI) has become the gold standard treatment for acute ST-segment elevation myocardial infarction (STEMI), significantly improving survival by restoring epicardial coronary artery patency. However, despite successful mechanical reperfusion, a substantial subset of patients experience inadequate myocardial perfusion at the microvascular level a condition known as the no-reflow phenomenon. This paradoxical complication is characterized by the failure to achieve optimal tissue-level blood flow despite the absence of angiographic evidence of mechanical obstruction **(1)**.

According to the most recent ESC Guidelines, PPCI is currently considered the standard of care for patients with ST elevation myocardial infarction **(2)**. Randomized clinical trials have clearly shown that primary PCI is superior than thrombolytic therapy in reducing the incidence of stroke, re-infarction, and death when treatment delays are similar **(3)**.

As stated in the European guidelines, primary PCI is the preferred reperfusion strategy in following situations **(Figure 1)**. Patients with STEMI occurring within 12 hours of symptom onset, provided the intervention can be performed within 120 minutes of STEMI diagnosis (Class I). Patients with STEMI and symptoms lasting >12 h in the presence of **(4).**

Ischemic symptoms must continue despite the lack of ST-segment elevation, and there must be one of the

following conditions as haemodynamic instability or cardiogenic shock, recurrent or on-going chest pain refractory to medical treatment, life-threatening arrhythmias or post resuscitation of cardiac arrest, mechanical complications of MI, acute heart failure, and recurrent dynamic ST-segment or T wave changes, especially in setting of intermittent ST-segment elevation **(5)**. Regarding late comers who present 12-48 hours from onset of chest pain , primary PCI should be considered and is given class IIa recommendations in the last ESC guidelines **(6).**

In stable patients with sustained blockage of the IRA 3–28 days post- MI, the OAT demonstrated no therapeutic advantage of routine coronary intervention compared to medical care alone. Consequently, regular PCI of an occluded IRA in asymptomatic individuals more than 48 hours after symptom onset is contraindicated **(7).**

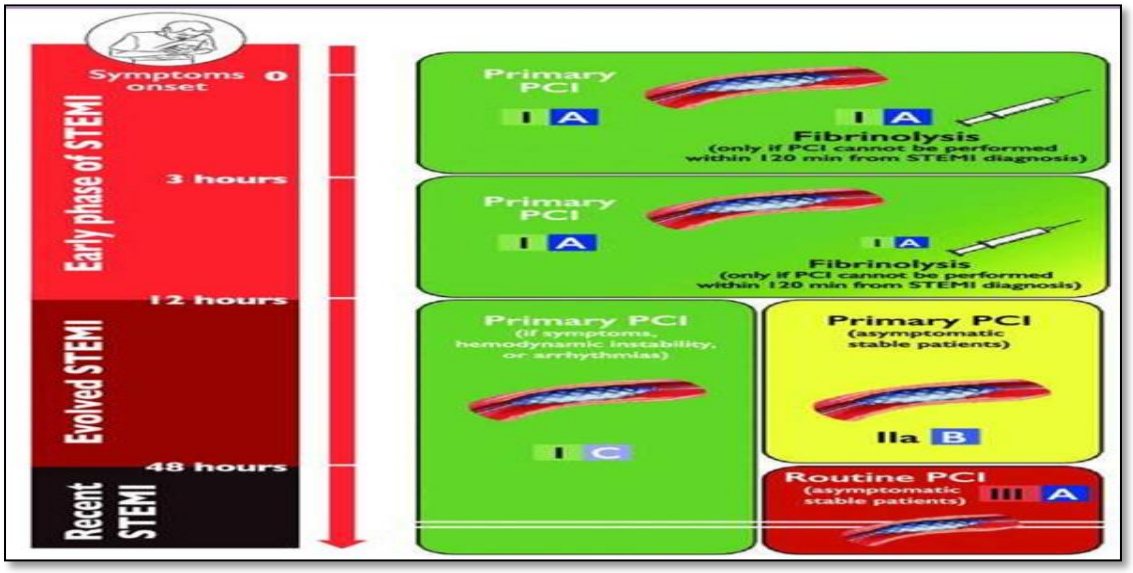

Fig.1: Selection of best reperfusion strategies according to time frame from symptoms onset. PCI= percutaneous coronary intervention; STEMI=ST-segment elevation myocardialinfarction **(4)**

Procedural aspects during primary PCI

A. Access

Over recent years, there has been a debate regarding radial and femoral access and superiority of one over the other. Radial access has been shown in numerous studies to be the most effective technique for acute coronary patients receiving primary PCI from skilled radial operators. Radial access was linked to lower risks of vascular problems and bleeding, according to the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX (MATRIX) experiment, which included 8404 patients with acute coronary syndrome (48% STEMI). Following initial PCI, the RIVAL investigation showed a significant mortality benefit for the radial access group over the femoral access group **(7).**

Accordingly , ESC guidelines in 2017 gave a clear class I recommendation for superiority of radial over femoral access during primary PCI provided it's done by experienced operator **(8)**.

B. Stenting vs. PTCA only

Percutaneous trans-luminal coronary angioplasty (PTCA) was the first interventional technique to show up as a solution for patients with STEMI. Later on, coronary stenting became the technique of choice during primary PCI **(9)**.

Stenting with a BMS was associated with a lower risk of re-infarction and target vessel revascularization when compared to balloon angioplasty alone, but no mortality benefit has been proven **(10)**.

New-generation drug-eluting stents have proven superior to bare-metal stents in patients with acute myocardial infarction, especially in terms of re-intervention rates, in two large published trials: the Everolimus-Eluting Stents Versus Bare-Metal Stents in ST Segment Elevation Myocardial Infarction (EXAMINATION) trial and the Effect of Biolimus-Eluting Stents with Biodegradable Polymer versus Bare-Metal Stents on Cardiovascular Events among Patients with Acute Myocardial Infarction (COMFORTABLE AMI) trial **(11)**.

Deferring stenting as a way to diminish microvascular obstruction (MVO) was recommended as a solution to increased no-reflow development during primary PCI **(12)**.

The primary clinical outcome, which included all-cause mortality, non-fatal myocardial infarction, and revascularization of non-infarct-related artery lesions, was unaffected by deferred stenting (48 hours post-index procedure) in the Deferred versus Conventional Stent Implantation in Patients with ST-Segment Elevation Myocardial Infarction (DANAMI 3-DEFER) trial. As a result, postponed stenting is no longer recommended for normal use **(13)**.

C. Thrombus aspiration

Potentially reducing the likelihood of distal embolization including no-reflow pathophysiology, thrombus aspiration has been proposed. In different studies, thrombus aspiration before PCI resulted in reduction of no-reflow incidence and as a result better clinical outcomes **(14)**.

As a result, thrombus aspiration was routinely performed in primary PCI operations until the 2017 ESC guidelines for STEMI, which advised against its routine usage (Class III). This suggestion was derived from the outcomes of the Taste and TOTAL studies, which indicated that merely 1–5% of randomized patients transitioned from PCI alone to thrombus aspiration; thus, routine thrombus aspiration is no longer advised. Thrombus aspiration may be warranted in instances of substantial residual thrombus burden or no-reflow following the recanalization of the occluded artery **(15)**.

D. Culprit versus Complete Revascularization

A large debate is still going on the concept of culprit versus complete revascularization with conflicting evidence in the last few years. An important issue to consider is the hemodynamics of the patients which could greatly affect the strategy of revascularization. Before being released from the hospital, STEMI patients with multivessel disease should consider revascularization of non-IRA lesions, per the PRAMI, DANAMI-3-PRIMULTI, and Compare-Acute trials **(16)**.

Revascularization of non-culprit lesions should not be done immediately, according to recent results from the Culprit Lesion Only PCI vs. Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) investigation. At the 30-day follow-up, only the PCI of the responsible vessel significantly reduced the need for renal replacement therapy and all-cause death in CULPRIT-SHOCK. Based on that, culprit vessel revascularization during index procedure and staged other vessels intervention during index hospitalization became the strategy of choiceAs a result, head CT scans were performed to assess any potential brain injury. The CT scans were read by skilled on-site radiologists. The initial brain CT revealed signs of increased ICP, such as sulci effacement, substantial edema, midline displacement, and ventricle collapse. Based on the findings of the head CT scan, osmotic treatment was determined to be necessary **(17)**.

No-reflow phenomenon

The no-reflow phenomenon in a number of ways. After PPCI, Eeckhout and Kern characterized the no-reflow phenomenon as inadequate myocardial perfusion in a particular segment of the coronary circulation without angiographic evidence of mechanical arterial obstruction **(18)**.

Reduced antegrade blood flow (TIMI) after stent implantation that was not caused by sudden closure, spasm, or significant stenosis of the original target lesion has recently been studied in relation to no-reflow **(19)**.

Clinical Impact of no-reflow phenomenon

Despite the culprit arterial's patency, the restoration of epicardial blood flow, and the absence of in situ thrombosis or vasospasm, a considerable percentage of patients with ST elevation have impaired myocardial reperfusion. After pharmacological and/or mechanical intervention for acute myocardial infarction, systolic dysfunction may persist even after the epicardial vessel is opened and TIMI 3 flow is achieved. This could be due to irreversible injury (myocardial necrosis), reversible injury (myocardial stunning), or a combination of both **(20).**

Development of no-reflow carries a poor prognosis and is associated with depressed LV ejection fraction and adverse LV remodelling **(21)**.

Short-term follow-up studies have linked the no-reflow phenomena to prolonged hospitalization compared to patients without this condition. A comprehensive study involving 1140 patients revealed that no-reflow following primary PCI correlated with diminished myocardial salvage, greater infarct size, poorer left ventricular ejection fraction at 6 months, and heightened risk of mortality at one year **(22)**.

On long term follow up, development of no-reflow phenomenon during primary PCI has been found to be a strong predictor of 5-years mortality **(23)**.

Management of No-reflow phenomenon

Numerous studies and meta-analyses have examined various therapeutic strategies for the management of the no-reflow phenomena. To date, there is no consensus on a definitive strategy for the handling of the no-reflow problem. Euro Intervention has presented an approach to address the no-reflow situation in the catheterization laboratory **(Figure 2)**. The 2011 American guidelines for percutaneous coronary intervention are the sole guidelines that provide explicit advice for the management of this devastating event **(24)**.

A) Prevention of no-reflow

The management of no-reflow begins with preventive measures rather than therapeutic interventions. Reducing door-to-balloon time, achieving ideal blood glucose levels, and maintaining optimal blood pressure are essential first measures to prevent the no-reflow occurrence **(25)**.

B) Treatment of no-reflow

Local vasodilator therapy and local antiplatelet therapy were the main focuses of pharmacotherapy for the treatment of no-reflow.

1. **Thrombus Aspiration**

One effective strategy to reduce the risk of distal embolization linked to no-reflow pathophysiology is thrombus aspiration. In different studies, thrombus aspiration before PCI resulted in reduction of no-reflow incidence and as a result better clinical outcomes. Consequently, thrombus aspiration became a routine step in primary PCI procedures until 2017 ESC guidelines for STEMI which showed that Routine use of thrombus aspiration is not recommended (Class III). The Taste and TOTAL trials' findings, which showed that only 1–5% of randomized patients switched from PCI alone to thrombus aspiration, served as the basis for this advice **(26)**.

As a result, regular thrombus aspiration is no longer recommended. Thrombus aspiration could be necessary if there is a substantial amount of residual thrombus load after vascular opening using a guide wire or balloon **(27)**.

2.Glycoprotein IIb/IIIa inhibitors

Antiplatelet drugs known as glycoprotein IIb/IIIa inhibitors prevent thrombotic events by blocking platelet aggregation and vascular coagulation. Cardiac MRI at 30 days after myocardial infarction revealed that intracoronary injection of abciximab significantly reduced infarct size in the INFUSE-AMI trial, which was performed on STEMI patients after initial PCI. The administration of Glycoprotein IIb/IIIa inhibitors, on the other hand, needs to be weighed against its benefits and hazards due to the increased risk of bleeding. According

to the 2017 ESC guidelines for STEMI, GP IIb/IIIa inhibitors should be taken into consideration for bailout in cases of thrombotic complications or no-reflow (Class IIa recommendation) **(28)**.

3.Nitroprusside

In order to treat PCI-related no-reflow that occurs following primary or elective PCI, the 2011 ACC PCI recommendations offer a class IIa recommendation for the use of an intracoronary vasodilator, specifically adenosine, a calcium channel blocker, or nitroprusside **(29)**.

In treating no-reflow in patients with acute myocardial infarction, a brief research comparing the effects of nitroprusside and nicorandil revealed that the TIMI frame count was statistically substantially lower in the nitroprusside group **(30)**.

Intracoronary sodium nitroprusside decreases corrected TIMI frame count, improves left ventricular function, and considerably decreases incidence of myocardial infarction (MACE), according to a 2014 meta-analysis **(31)**.

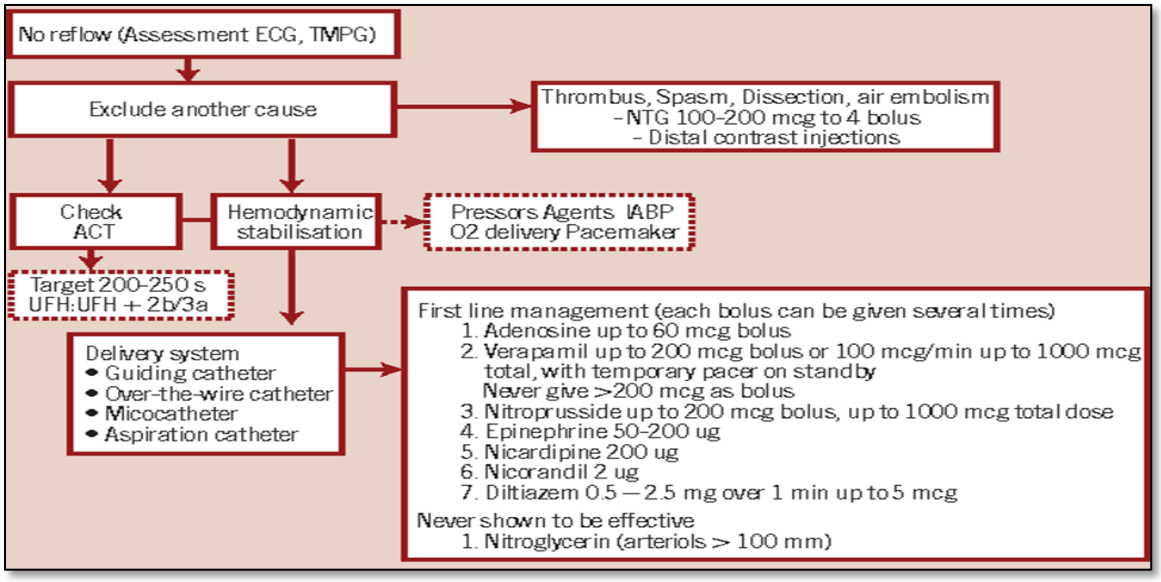

Fig. 2: Check-list for management of no-reflow phenomenon (24). ECG: Electrocardiography, TMBG : TIMI myocardial blush grade, ACT: Activated clotting time**.**

4. Calcium channel blockers

In 1982, Kloner et al. demonstrated that verapamil treatment effectively restored coronary perfusion in animal models of myocardial ischemia. A recent meta-analysis demonstrated that intracoronary verapamil injection decreased the two-month incidence of significant adverse events in patients who underwent PCI **(32).**

Specifically, nicardipine proved advantageous in preventing no-reflow following rotational atherectomy and percutaneous treatments in venous grafts. Nevertheless, to date, the available data are inadequate to substantiate the use of calcium channel blockers as a conventional treatment for no-reflow, and bigger randomized controlled trials remain necessary **(33)**.

5. Adenosine

Adenosine is among the medicines endorsed by ACC recommendations for the management of the no-reflow phenomena. It achieves its action by inducing smooth muscle relaxation in the coronary microcirculation, in addition to possessing antiplatelet characteristics. The advantageous effect extended beyond vasodilation to a reduction in neutrophil count in the ischemic region and relative maintenance of endothelial integrity in those locations **(34)**.

The AMISTAD-II studies, which showed a significant reduction in infarct size with high-dose adenosine (70 mg/kg/min given over 3 hours), provide the justification for using adenosine in the treatment of no-reflow **(34)**.

Conclusion:

The no-reflow phenomenon remains a significant complication of primary PCI, particularly in the setting of STEMI, and is strongly associated with adverse clinical outcomes, including increased infarct size, heart failure, and mortality.

Prevention requires a multifaceted, patient-tailored approach that combines early recognition of high-risk features, optimized pharmacologic therapy, and refined procedural techniques. Strategies such as minimizing total ischemic time, using potent antiplatelet and antithrombotic agents, judicious thrombus aspiration, direct or deferred stenting, and intracoronary vasodilators have shown varying degrees of efficacy. Emerging approaches like intracoronary fibrinolysis and advanced device-based interventions offer additional promise but require further validation.

Recommendation

Although the utilization of several medications, refractory no-reflow characterized as no-reflow that persists despite the administration of at least two medicines, including adenosine, verapamil, and glycoprotein IIb/IIIa inhibitors remains prevalent among a significant proportion of primary PCI patients.

The necessity for a novel drug to address refractory no-reflow phenomena, particularly in cases when adenosine is contraindicated, prompted numerous researchers to examine the effects of epinephrine on no-reflow. Despite the therapeutic application of epinephrine for treating cardiac arrest, there is a scarcity of published data concerning its efficacy in coronary no-reflow

References:

1- **Vogel, B., Claessen, B. E., Arnold, S. V., Chan, D., Cohen, D. J., Mehran, R. (2019).** ST-segment elevation myocardial infarction. Nature reviews Disease primers, 5(1), 39.

2- **Fernández-Bergés, D., Degano, I. R., Fernandez, R. G., Marrugat, J. (2020)**. Benefit of primary percutaneous coronary interventions in the elderly with ST segment elevation myocardial infarction. Open heart, 7(2), e001169.

3- **Buller, C. E., Fu, Y., Mahaffey, K. W., Todaro, T. G., Adams, P., Armstrong, P. W. (2008)**. ST-segment recovery and outcome after primary percutaneous coronary intervention for ST-elevation myocardial infarction: insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. Circulation, 118(13), 1335-1346.

4- **Zuccarelli, V., Andreaggi, S., Walsh, J. L., Vibhishanan, J., De Maria, G. L. (2024)**. Treatment and care of patients with ST-segment elevation myocardial infarction what challenges remain after three decades of primary percutaneous coronary intervention?. Journal of Clinical Medicine, 13(10), 2923.

5- **Keeley, E. C., Hillis, L. D. (2007)**. Primary PCI for myocardial infarction with ST-segment elevation. New England Journal of Medicine, 356(1), 47-54.

6- **Borgia, F., Goodman, S. G., Halvorsen, S., Piscione, F., Di Mario, C. (2010)**. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. European heart journal, 31(17), 2156-2169.

7- **Wang, P., Ye, X., Yan, D., Zhang, Z. (2022)**. Incidence and risk factors of left ventricular thrombus in acute ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: a meta-analysis. Medical Principles and Practice, 31(5), 415-423.

8- **Werner, N., Nickenig, G., Sinning, J. M. (2018)**. Complex PCI procedures: challenges for the

interventional cardiologist. Clinical Research in Cardiology, 107(Suppl 2), 64-73.

9- **Chiang, A., Gada, H., Kodali, S. K., Lee, M. S., Pinto, D. S., Kirtane, A. J. (2014)**. Procedural variation in the performance of primary percutaneous coronary intervention for ST-elevation myocardial infarction: A SCAI-based survey study of US interventional cardiologists. Catheterization and Cardiovascular Interventions, 83(5), 721-726.

10- **Corones, K., Coyer, F. M., Theobald, K. A. (2009)**. Exploring the information needs of patients who have undergone PCI. British Journal of Cardiac Nursing, 4(3), 123-130.

11- **Magro, M., Räber, L., Heg, D., Taniwaki, M., Kelbaek, H., Ostojić, M., (2014)**. The MI SYNTAX score for risk stratification in patients undergoing primary percutaneous coronary intervention for treatment of acute myocardial infarction: a substudy of the COMFORTABLE AMI trial. International journal of cardiology, 175(2), 314-322.

12- **Vink, M. A., Amoroso, G., Dirksen, M. T., Van der Schaaf, R. J., Tijssen, J. G., Slagboom, T. (2011)**. Routine use of the transradial approach in primary percutaneous coronary intervention: procedural aspects and outcomes in 2209 patients treated in a single high-volume centre. Heart, 97(23), 1938-1942.

13- **Kelbæk, H., Høfsten, D. E., Køber, L., Helqvist, S., Kløvgaard, L., Engstrøm, T. (2016)**. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. The Lancet, 387(10034), 2199-2206.

14- **Hoffman, S. J., Routledge, H. C., Lennon, R. J., Mustafa, M. Z., Rihal, C. S., Gulati, R. (2012)**. Procedural factors associated with percutaneous coronary intervention-related ischemic stroke. JACC: Cardiovascular Interventions, 5(2), 200-206.

15- **Fanaroff, A. C., Zakroysky, P., Dai, D., Wojdyla, D., Rao, S. V. (2017)**. Outcomes of PCI in relation to procedural characteristics and operator volumes in the United States. Journal of the American College of Cardiology, 69(24), 2913-2924.

16- **Ozaki, Y., Hara, H., Onuma, Y., Katagiri, Y., Amano, T., Kobayashi, Y., Task Force on Primary Percutaneous Coronary Intervention (PCI) of the Japanese Cardiovascular Interventional Therapeutics (CVIT). (2022)**. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) update 2022. Cardiovascular intervention and therapeutics, 37(1), 1-34.

17- **Armstrong, P. W., Gershlick, A. H., Goldstein, P., Wilcox, R., Danays, T., Lambert, Y., Van de Werf, F. (2013)**. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. New England Journal of Medicine, 368(15), 1379-1387.

18- **Ito, H. (2009)**. No-reflow phenomenon in patients with acute myocardial infarction: its pathophysiology and clinical implications. Acta Med Okayama, 63(4), 161-168.

19- **Bouleti, C., Mewton, N., Germain, S. (2015)**. The no-reflow phenomenon: state of the art. Archives of cardiovascular diseases, 108(12), 661-674.

20- **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.

21- **Caiazzo, G., Musci, R. L., Frediani, L., Umińska, J., Navarese, E. P. (2020)**. State of the art: no-reflow phenomenon. Cardiology clinics, 38(4), 563-573.

22- **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.

23- **Allencherril, J., Jneid, H., Atar, D., Alam, M., Levine, G., Kloner, R. A., & Birnbaum, Y. (2019)**.

Pathophysiology, diagnosis, and management of the no-reflow phenomenon. Cardiovascular drugs and therapy, 33(5), 589-597.

24- **Rezkalla, S. H., Stankowski, R. V., Hanna, J., Kloner, R. A. (2017)**. Management of no-reflow phenomenon in the catheterization laboratory. JACC: Cardiovascular Interventions, 10(3), 215-223.

25- **Butler, M. J., Chan, W., Taylor, A. J., Duffy, S. J. (2011)**. Management of the no-reflow phenomenon. Pharmacology & therapeutics, 132(1), 72-85.

26- **Lim, S. Y. (2016)**. No-reflow phoenomenon by intracoronary thrombus in acute myocardial infarction. Chonnam Medical Journal, 52(1), 38-44.

27- **Li, H., Fu, D. G., Liu, F. Y., Li, X. M. (2018)**. Evaluation of related factors, prediction and treatment drugs of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction after direct PCI. Experimental and therapeutic medicine, 15(4), 3940-3946.

28- **Adjedj, J., Muller, O., Eeckhout, E. (2018)**. A handbook of primary PCI: no-reflow management. Primary Angioplasty: A Practical Guide, 223-235.

29- **Su, Q., Li, L., Naing, K. A., Sun, Y. (2014)**. Safety and effectiveness of nitroprusside in preventing no-reflow during percutaneous coronary intervention: a systematic review. Cell biochemistry and biophysics, 68(1), 201-206.

30- **Wei, P. A. N., Ying, F. A. N., Shu-sen, Y. A. N. G., Yue, L. I., Wei-min, L. I. (2009)**. Intracoronary nitroprusside in the prevention of the no-reflow phenomenon in acute myocardial infarction. Chinese medical journal, 122(22), 2718-2723.

31- **Tesic, M. B., Stankovic, G., Vukcevic, V., Ostojic, M. C. (2010)**. The use of intracoronary sodium nitroprusside to treat no-reflow after primary percutaneous coronary intervention in acute myocardial infarction. Herz, 35(2), 114-118.

32- **Oikonomou, E., Mourouzis, K., Vogiatzi, G., Siasos, G., Deftereos, S., Papaioannou, S., Tousoulis, D. (2018)**. Coronary microcirculation and the no-reflow phenomenon. Current pharmaceutical design, 24(25), 2934-2942.

33- **Shahri, B., Vojdanparast, M. (2020)**. Coronary No-reflow Phenomenon: A Review of Therapeutic Pharmacological Agents. Razavi International Journal of Medicine, 8(1234).

34- **Darwish, A., Frere, A. F., Abdelsamie, M., Awady, W. E., Gouda, M. (2022)**. Intracoronary epinephrine versus adenosine in the management of refractory no-reflow phenomenon: a single-center retrospective cohort study. Annals of Saudi medicine, 42(2), 75-82.