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No Reflow during primary PCI: Pathophysiology and Predictors

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Abstract

The no-reflow phenomenon occurs in about one third of the patients treated with primary PCI for acute ST segment elevation myocardial infarction. Our understanding of its pathophysiology has expanded considerably: in addition of the effect of prolonged ischaemia also reperfusion injury contributes significantly to the microvascular damage in the perfusion territory of the infarct-related coronary artery. Lethal reperfusion injury to both the endothelial cells and the cardiomyocytes is mainly related to the effects of oxidative stress and the energy paradox. Paradoxical vasoconstriction caused by endothelial dysfunction, plugging of the capillaries by endothelial blebs and by packed neutrophils and mechanical compression by myocardial oedema all related to the reperfusion injury lead to microvascular obstruction. Iatrogenic embolization of thrombus and/or plaque material during coronary intervention adds further to the development of the no-reflow phenomenon. New insights in the pathophysiology open the way to a new therapeutic approach of the no-reflow phenomenon: preventing embolization during primary coronary intervention by using adjunctive thrombus aspiration before stent deployment and reducing the reperfusion injury by post-conditioning.

Keywords: Myocardial infarction, reperfusion, oxidative stress.

Introduction:

Coronary artery disease (CAD) most of the time refers to coronary atherosclerotic disease that results in severe coronary artery narrowing, leading to inadequate blood supply to the heart muscle (myocardium). Acute coronary syndromes (ACSs) comprise the acute manifestations of CAD. (**1**).

ACS is the leading cause of death worldwide and it refers to any condition attributed to obstruction of the coronary arteries, which reduces blood flow to the heart, and includes unstable angina and myocardial infarction (MI). **(2).**

STEMI is the most acute manifestation of CAD, with substantial morbidity and mortality. Early reperfusion (re-establishing the blood flow in the occluded artery) is the most effective way to preserve the viability of the ischemic myocardium and limit infarct size. Early diagnosis of STEMI is crucial to initiate appropriate treatment and should ideally be made within 10 minutes of first medical contact. **(3)**

Primary percutaneous coronary intervention (PCI) is the gold standard for treating ST-segment elevation myocardial infarction (STEMI) patients due to its ability to re-establish epicardial arterial flow. However, primary PCI is still associated with poor clinical outcomes in some patients, many of whom have severe coronary microvascular obstruction or dysfunction after the procedure. **(4).**

Although PCI is successful in most cases, up to 40% of the patients do not have complete myocardial reperfusion despite successful treatment of the culprit lesion as evidenced by poor myocardial blush grade (MBG)**. (5)**.

No-reflow is the term used to describe the inadequate myocardial reperfusion of a given coronary segment without angiographic evidence of epicardial vessel obstruction, flow-limiting dissection, conduit vessel spasm or apparent in situ thrombosis.**(6)**

Clinically, no-reflow is important, because of its independent association with increased in-hospital mortality, malignant arrhythmias, and cardiac failure. Furthermore, it is related to a poor long-term prognosis due to post procedural myocardial infarction (MI) or extension of MI. The pathophysiology of no-reflow is likely multifactorial, thus requiring several strategies to counteract this phenomenon. **(7)**.

Pathophysiological Mechanisms of no reflow:

No reflow is related to a functional and structural alteration of the coronary microcirculation and we can list four main pathophysiological mechanisms: distal atherothrombotic embolization, ischemic damage, reperfusion injury, and individual susceptibility to microvascular Damage. (**8)**

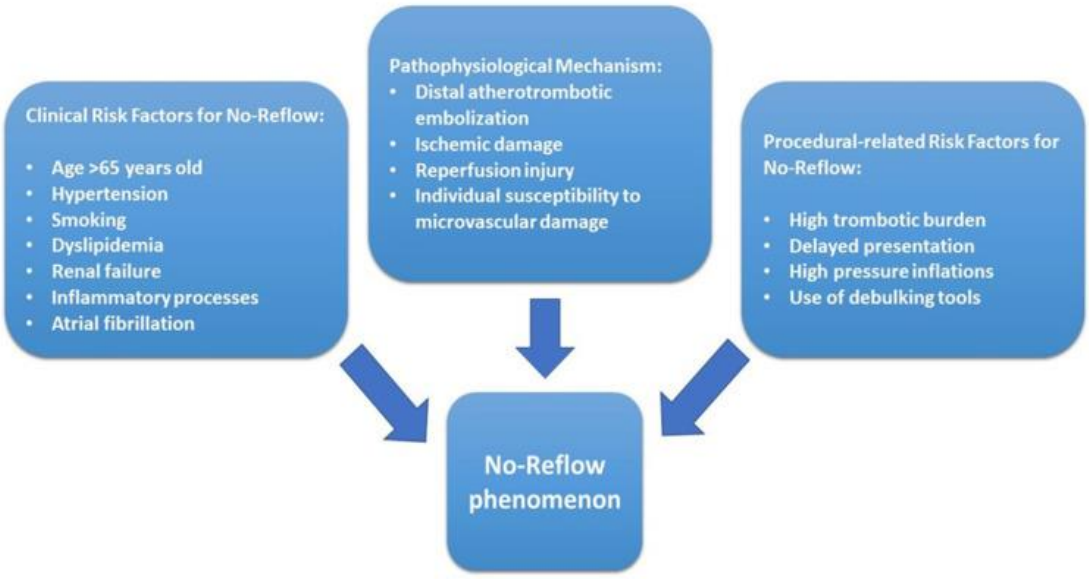

Fig (1): Summary of all the different factors involved in the genesis of the No-Reflow phenomenon. (**8)**

1-Distal atherothrombotic embolization:

A complex atherosclerotic plaque can lead to distal embolization phenomena both during the acute and procedural phases, leading to increased distal vascular resistance and additional microinfarcts that promote the release of pro-inflammatory and vasoconstrictive substances. (**9)**

2- Ischemic damage:

The severity of ischemic injury is directly proportional to the duration of ischemia time. Ischemic damage results in the death of cardiomyocytes, endothelial cells, and formation of interstitial edema with impaired nitric oxide production and subsequent microcirculation obstruction favored by vascular endothelial growth factors (VEGF) release that increase vascular permeability (**10)**

3- Reperfusion injury:

Reperfusion injury, is caused by the abrupt restoration of blood flow at the level of the damaged microcirculation, causes direct cardiomyocyte damage with an influx of inflammatory neutrophils during reperfusion that promotes the production of inflammatory cytokines, free oxygen radicals, vasoactive substances, and proteolytic enzymes. (**11)**

4- Individual susceptibility to microvascular damage:

The presence of preexisting endothelial dysfunction or genetic mutations, such as the 1976TC polymorphism of the gene for adenosine receptors and various ion channels, increases the susceptibility to microvascular dysfunction and no-reflow (**12**)

Predictors of No-Reflow Phenomenon:

Many of the novel therapeutic strategies aim to prevent the development of the No-Reflow phenomenon or to limit its severity. It is thus essential to be able to identify patients at increased risk of the No-Reflow phenomenon during PPCI. Predisposing factors and predictors of the No-Reflow phenomenon may be classified as: clinical, anatomical, physiological or a composite of these**(13)**.

They are described below and are summarized in figure (2)

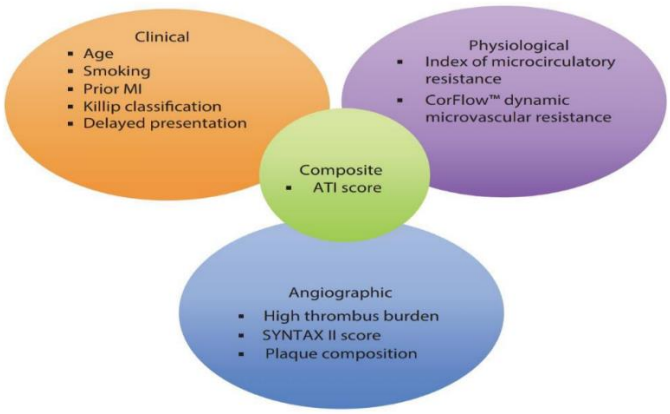

Figure (2): Summary of predictive indices. **(13)**

These indices can be assessed prior to primary percutaneous coronary intervention for ST-segment elevation myocardial infarction to predict post procedural coronary no-reflow.

1-Clinical predictors:

Older patients with delayed presentation to treatment facilities have been repeatedly identified as a high-risk group with longer time to reperfusion associated with higher prevalence and a larger region of the No-Reflow phenomenon.**(14)**

Furthermore, smoking, prior myocardial infarction and Killip class at presentation were additionally identified as predictors of the No-Reflow phenomenon and there is also evidence supporting female gender, hyperglycemia, hypercholesterolemia, hypertension and mild-to-moderate renal dysfunction as further risk factors. The combination of clinical risk factors into the CHA2DS2-VASc score has also been shown to predict the No-Reflow phenomenon in patients presenting with both STEMI and non-STEMI.**(15)**

2-Angiographic predictors:

It is well established that distal embolization of athero-thrombotic debris is one of the main contributors to the No-Reflow phenomenon pathogenesis. The thrombotic burden and thrombus composition are thus important determinants for the risk of distal embolization. It has been shown that higher thrombus burden predicts the No-Reflow phenomenon and clinical outcomes.**(16)**

Similarly, the **SYNTAX** score, which is a measure of the extent and complexity of coronary artery disease, has also been shown to predict the No-Reflow phenomenon. This has been further supported by a study showing that high thrombus burden, high SYNTAX score, late presentation and anterior MI are all independent predictors of no reflow. **(14)**

3-Physiological predictors:

The pathogenic mechanisms contributing to the No-Reflow phenomenon are complex and multitudinous, yet coronary microvascular dysfunction is the final common outcome. Hence it is unsurprising that, in addition to being useful for diagnosing post-PCI microvascular dysfunction, elevated index of microcirculatory index measurements prior to stent insertion have also been shown to predict final the No-Reflow phenomenon. A cut-off value of >40 is usually considered prognostically significant in patients presenting with STEMI.**(14)**

4-Composite predictors:

No individual predictive marker has proven valuable enough for 'stand-alone' clinical use and thus there has been recent interest in developing a composite score that combines information from several domains, reflecting in this way the multifactorial pathogenesis of the No-Reflow phenomenon. One of the most recent ones, with the merit of integrating clinical, anatomical and physiological factors is the age-thrombotic burden-IMR (ATI) score **(17)**

It was shown that an ATI score ≥4 predicts a 95.1% risk of final IMR ≥40 GL**.** An ATI score > 4 was associated with larger infarct size and MVO both acutely and at 6 months follow-up.**(18)**

Table (1): Age-thrombotic burden-index of microcirculatory resistance score. **(18)**

Parameter	**Strata**	**Score**
Age (years)	< 50	0
	≥ 50	1
Thrombus score	0–3	0
	4	1
	5	3
Pre-stenting IMR	≤40	0
	> 40 and < 100	1
	≥100	2

Summary of age, thrombus burden and index of microcirculatory resistance score.

Maximum score is 6. A score ≥4 predicts a 95.1% risk of post-primary PCI IMR ≥40. IMR: Index of microcirculatory resistance.

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