INTRODUCTION

Platelets are well known to have a significant role in the pathogenesis of acute coronary syndromes. Mean platelet volume (MPV); a measure of the platelet size, has been showed to correlate with platelets' reactivity [(1)]. MPV has been demonstrated to be directly associated with indicators of platelet activity in the terms of expression of glycoprotein Ib and glycoprotein IIb/IIIa receptors [(2–6)].

Patients who experienced myocardial infarction or unstable angina showed higher values of MPV compared with those who had stable angina or non-cardiac chest pain. In addition, elevated MPV value has been identified as an independent risk factor for the development of myocardial infarction and stroke [(7–10)]. Among survivors of myocardial infarction, an elevated MPV has been correlated with poor clinical outcome [(11, 12)]. An additional clue about the MPV contribution to thrombotic events is that MPV showed a positive relationship with the severity of acute ischemic cerebrovascular events [(13)].

Failure to restore the blood flow to the coronary microcirculation after successful opening of the occluded culprit vessel and restoration of the epicardial blood flow without angiographic evidence of mechanical obstruction is defined as No-Reflow phenomenon (NRP). NRP is perceived in 5% to 20% of patients with myocardial infarction undergoing primary PCI (PPCI).

No-reflow should never be underestimated as it is associated with adverse clinical and functional outcomes in the forms of malignant arrhythmias, extensive myocardial necrosis, worse segmental and global left ventricular contractility, and higher mortality rates [14–16]. Pathophysiology of no-reflow is assumed to be multifactorial in nature [17–19].

In the present study, we are trying to determine in the setting of ST-elevated myocardial infarction (STEMI) if patients with higher baseline MPV values may have higher chances of experiencing no-reflow after PPCI compared to those who have lower values.

We have an assumption that the existence of larger and more reactive platelets may be associated with larger platelet aggregates and subsequently intravascular plugging of the culprit vessel on both the epicardial and tissue level, therefore lead to impaired reperfusion after primary PCI. Higher MPV may correlate with the increased number of aggregates of both platelet-platelet and platelet-leukocyte [20].

Although many clinical and angiographic predictors of impaired reperfusion have been determined, several studies are still underway in search of simple preprocedural biochemical markers in order to tailor the appropriate management strategies before, during, and after the procedure [21–23].

Results from the present study may come out with two high yield concepts. Firstly, it may support the concept that platelets play a significant role in the pathophysiology of no-

reflow [18]. Secondly, MPV may contribute as an independent marker to the early recognition of patients in the setting of STEMI who are at a higher risk of experiencing impaired reperfusion after primary PCI.

Although MPV will be correlated with other variables such as age, hypertension, and cardiac biomarkers, we anticipate detecting prognostic information that will be independent of these variables.

AIM OF THE WORK

We seek to determine the prognostic value of mean platelet volume (MPV) for angiographic reperfusion in patients with acute ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Chapter 1
NO REFLOW PHENOMENON: PATHOGENESIS AND PREDICTORS

Definition of No-Reflow:

In the current management of ST-segment elevation myocardial infarction (STEMI), mechanical reperfusion by urgent primary percutaneous coronary intervention (PPCI) represents the substantial strategy [(24)]. However, in a fairly large proportion of patients PPCI is only able to restore epicardial coronary artery patency but not myocardial reperfusion, a condition known as no-reflow phenomenon [(25)].

Optimal reperfusion is defined as a rapid, sustained, and complete coronary recanalization with adequate myocardial tissue perfusion [(26)]. On the contrary, "No-reflow phenomenon" is defined as impaired coronary flow; TIMI (Thrombolysis in Myocardial infarction grade) flow < 3 despite restoration of epicardial coronary artery patency in the absence of any spasm or dissection [(27)].

No-reflow phenomenon incidence was a matter of debate until it has been clearly identified as a consequence of reperfusion in a significant number of clinical and experimental studies. Incidence of no-reflow after mechanical reperfusion has a variable prevalence, ranging from 5% up to 50%, according to population under study and methods used to assess the phenomenon [(25, 27, 28)].

Clinical implications of No-reflow:

No-reflow has been obviously shown to be associated with adverse clinical and functional outcomes [29-35] including increased incidence of:

a. Early post-infarction complications (arrhythmias, early congestive heart failure, pericardial effusion, and cardiac tamponade).
b. Adverse left ventricular structural remodeling.
c. Late repeat hospitalization for heart failure.
d. Death.

Therefore, every effort should be pursued to detect, prevent, and treat no-reflow, in order to avoid its negative potential and to make the most effective outcome of PPCI.

Reversibility of No-Reflow

No-reflow can be classified into either sustained or reversible. Sustained no-reflow is possibly due to irreversible anatomical changes of coronary microcirculation, whereas reversible no-reflow is supposed to be a consequence of reversible functional changes of microcirculation.

Several studies using different methods were conducted to identify reversibility of No-reflow and its impact;

Niccoli et al. [36], with repeat in-hospital coronary angiography showed that patients with no reflow found to have

an improvement of TIMI and/or MBG leading to a final TIMI 3 and MBG $\geq$ 2 were classified as reversible no reflow; the remaining patients were classified as sustained no reflow.

Galiuto et al. [37], with myocardial perfusion sequential measurement by myocardial contrast echocardiography (MCE) demonstrated that No-reflow detected 24 h after successful PCI spontaneously improves over time in almost 50% of patients. Additionally, whereas patients with reversible no-reflow were noted to have their LV volumes unchanged over time, patients with sustained no-reflow experienced unfavorable left ventricle (LV) structural remodeling.

Hoffman et al. [38] by determining myocardial blush grade (MBG) changes over time detected similar findings. Interestingly, the evolution of MBG was an influential predictor of LV structural remodeling.

We can conclude from the previous studies that no-reflow is potentially reversible to some extent in some patients; therefore anticipated understanding of the mechanisms of reversibility may lead to tailored strategies for reversal of no reflow phenomenon.

Pathogenesis of No-Reflow

4 pathogenetic components are implicated in the occurrence of no-reflow phenomenon **(figure 1)**:

1) Distal atherothrombotic embolization**.**
2) Ischemic injury**.**

3) Reperfusion injury**.**

4) Susceptibility of coronary microcirculation to injury**.**

Based on the understanding of these components, appropriate strategies should be presumed to prevent or treat each of them in order to decrease the incidence and prevalence of sustained no-reflow.

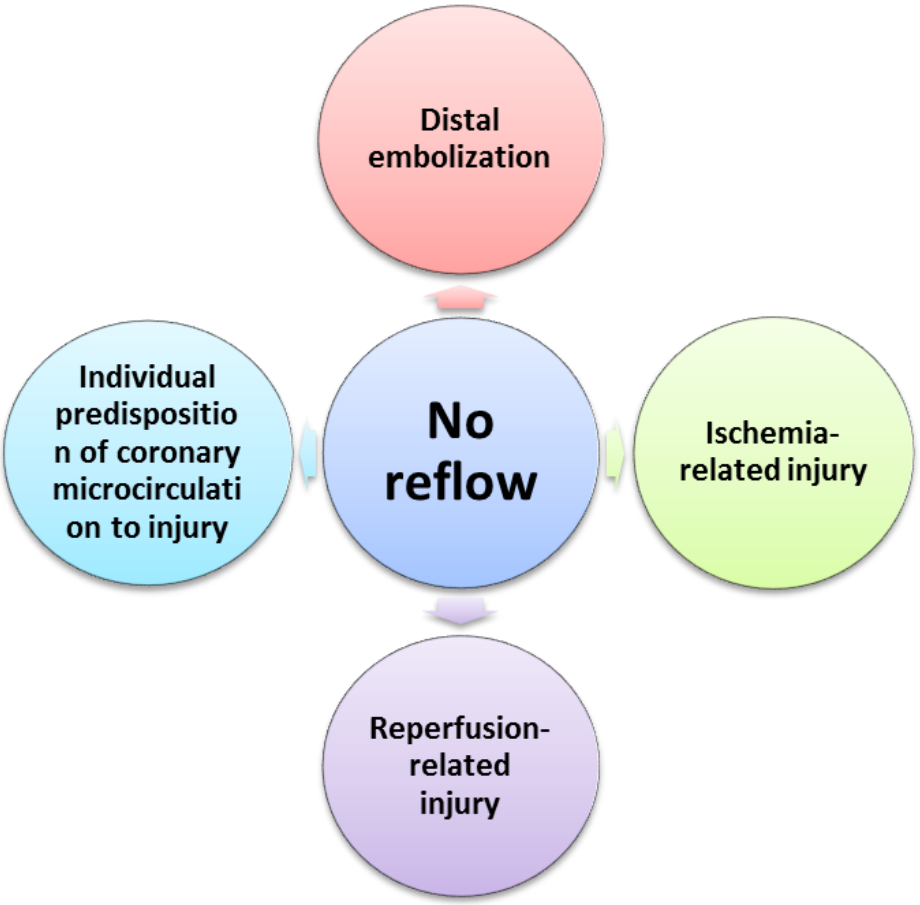

Figure (1): Pathogenesis of NO-reflow phenomenon**.**

a. Distal embolization

Spontaneous distal embolization of thrombus or fissured atheromatous plaque from the epicardial culprit lesion is common and might be further triggered by percutaneous coronary interventions (PCIs) [(39)]. It has been shown that when microspheres occlude more than 50% of coronary capillaries, myocardial blood flow irreversibly decreases [(40)].

Okamura et al. [(41)] was able to count the number of embolic particles using a Doppler guidewire to recognize the high-intensity transient signals. Throughout PPCI, the approximate number of emboli was 25. Based on that, such small number of emboli is unlikely to affect coronary blood flow. Yet, large emboli defined as >200-µm in diameter can obstruct pre-arterioles, causing infarctlets.

b. Ischemia-related injury

After prolonged ischemia, endothelial cells undergo morphological change leading to obliteration of the lumen of capillaries. Furthermore, erythrocytes emigration through endothelial gaps occurs [(42)]. More reduction in the blood flow to the regional myocardium typically ensues. [(43)]. In addition, interstitial edema and myocardial cell swelling may lead to microvascular compression [(44)].

c. Reperfusion-related injury

Platelets and neutrophils aggressively infiltrate coronary microcirculation at the time of reperfusion [42, 45]. Once neutrophils are advanced into post-ischemic myocardium, they will be activated with successive adhesion to the endothelium and migration in the surrounding tissue. Activated neutrophils lead to endothelial and tissue damage through release of oxygen free radicals, proteolytic enzymes, and pro-inflammatory mediators. Platelets and neutrophils make aggregates that plug capillaries and eventually obstructing the blood flow [46, 47].

Neutrophils, platelets, and endothelial cells release potent vasoconstrictors that may lead to adverse sustained vasoconstriction of the microcirculation [48].

Inflammatory mediators represent interplay between platelets, neutrophils, and endothelium;

- Tumor necrosis factor-alpha is expressed by reperfusion, and it can blunt coronary flow reserve. [49]
- Interleukin-1β has been demonstrated to play a role in ischemia-reperfusion (IR) injury. [50]
- Selectin expression on endothelia cell surfaces contributes to mechanical plugging of the coronary microcirculation. [51]

- Superoxide predominates over nitric instantly after reperfusion of ischemic tissues which aggravates the inflammatory state. [52]

Reperfusion may irreversibly damages myocytes [53]. Intracellular content of sodium (Na+) usually increases at times of ischemia and subsequently calcium overload (through sarcolemmal Na+/Ca++ exchanger) that induces uncontrolled hypercontraction and triggers opening of the mitochondrial permeability transition pore (m-PTP). Moreover, Na+ and Ca++ accumulation leads to myocyte cell swelling. Once extracellular osmolality is rapidly normalized by reperfusion, rupture of the cell membrane directly ensues. Interestingly, cyclosporine [54] and ischemic pre-conditioning [55] block the m-PTP which represents a potential for the management of no reflow as will be discussed later.

Natriuretic peptides may modulate IR injury. Atrial natriuretic peptide (ANP) is believed to inhibit the renin-angiotensin-aldosterone system and endothelin (ET-1) that enhance microvascular obstruction (MVO), infarct size, and myocardial remodeling [56]. **Hayashi et al.** [57] demonstrated that ANP infusion in patients, who experienced anterior myocardial infarction for the first time, resulted in lower levels of ET-1, angiotensin-II, and aldosterone. In addition, B-type natriuretic peptide administration before and during coronary occlusion, showed a reduction in the infarct size [58].

ET-1 contributes to tissue injury and edema through exerting its potent vasoconstrictive properties on small coronary arteries, enhancement of neutrophil adhesion to the endothelium, and stimulation of elastase release. [59]

d. *Individual predisposition of coronary microcirculation to injury*

Genetic and/or acquired predisposition may occur. Diabetes mellitus principally has been related to impaired microvascular reperfusion after PPCI [60]. Hypercholesterolemia was assessed in the animal model and showed exacerbation of reperfusion injury by augmenting endothelial oxidative stress [61]. On the other hand, pre conditioning apparently improves microvascular function [62].

Predictors of the Pathogenetic Components of No-Reflow

a. *Predictors of distal embolization*

It has been speculated that heavy thrombus burden could be considered as a predictor of distal embolization and consequently incidence of No reflow. Yip et al. [63] conducted a study on 800 patients with STEMI and concluded a score to assess thrombus burden based on the following characteristics:

1. An angiographic thrombus with the greatest linear dimension more than 3 times the reference lumen diameter.

2. Cutoff pattern (lesion morphology with an abrupt cutoff without taper before the occlusion)**.**
3. Presence of accumulated thrombus (>5 mm of linear dimension) proximal to the occlusion**.**
4. Presence of floating thrombus proximal to the occlusion**.**
5. Persistent contrast medium distal to the obstruction**.**
6. Reference lumen diameter of the infarct-related artery (IRA) >4.0 mm.

These features were concluded to be independent predictors of no-reflow. **Limbruno et al.** [(64)] conducted a study on 46 patients with acute MI underwent PPCI using a filter-based distal protection device and showed the value of heavy thrombus burden as a predictor of distal embolization at the culprit vessel. In addition, they demonstrated that Yip's score was an independent predictor of total debris volume captured in the filter's basket.

Moreover, **Yip et al.** [(63)] suggested that in large coronary arteries stent placement triggers distal embolization of thrombotic debris, but in small coronary vessels stent deployment may fix the thrombus to the vessel wall, in particular if the thrombus is no longer fresh.

b. Predictors of ischemia-related injury

Longer intervals to reperfusion lead to a higher incidence of No reflow and a larger region of No-reflow [(65)]. **Turschner et al.** [(66)] demonstrated that prolonged ischemia followed by reperfusion results in tissue edema which increases the myocardium thickness. No-reflow consequently occurs that believed to be due to mechanical factors.

The extent of the ischemic region is considered a significant determinant of the incidence of No-reflow. The extent of ischemic region determined by ECG (QRS score) and by echocardiography (wall motion score index) showed an association with the prevalence of no reflow [(67, 68)]. When the IRA is LAD, there is a higher prevalence of no-reflow as compared with other epicardial coronary arteries which supports the theory that a larger extent of the ischemic region is a relevant predictor of no-reflow [(68)].

c. Predictors of reperfusion-related injury.

There are several indices that we could rely on to assess the possibility of Reperfusion injury and indeed no reflow including the following clinical predictors.

Platelet count is a clinical predictor of No reflow as it is associated with microvascular injury after PPCI [(69)]. Platelet reactivity measured on admission by the Platelet Function

Analyzer–100 (Dade Behring, Milan, Italy), was correlated to higher prevalence of No reflow and adverse remodeling [(70)].

Plasma levels of **thromboxane-A2 (TxA2)** have also been shown to be a useful predictor no-reflow [(71)].

Matsumoto et al. [(72)] demonstrated the protective effect of **natural antioxidants**. Patients who experienced no-reflow had lower levels of vitamin C, vitamin E, and glutathione peroxidase retrieved from coronary sinus before PPCI than those who exhibited myocardial reperfusion.

ET-1 levels on admission have been recently demonstrated as an independent predictor of no-reflow [(73)]. Selective ET-1 antagonist showed a beneficial effect in animal models of ischemia-reperfusion which may support it as a therapeutic target [(74)].

d. Predictors of individual susceptibility to microvascular injury

Genetic and acquired factors play a role in individual susceptibility to microvascular injury, therefore higher incidence of no-reflow. Therefore, several studies have been conducted to demonstrate such susceptibility either genetic or acquired.