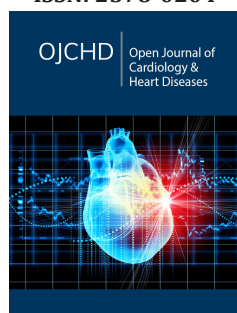


Assessment of Role of Platelet-to-Lymphocyte Ratio in Prediction of Angiographic No-Reflow in Patients Subjected to Primary Percutaneous Coronary Intervention

ISSN: 2578-0204



***Corresponding author:** Ghada Mahmoud Shawkat Ali, Doctor of Cardiology Department, Assuit University, Egypt

Submission: January 02, 2020

Published: January 09, 2020

Volume 3 - Issue 2

How to cite this article: Ghada M S A, Salwa R D, Hatem A R H and Mohamed A A. Assessment of Role of Platelet-to-Lymphocyte Ratio in Prediction of Angiographic No-Reflow in Patients Subjected to Primary Percutaneous Coronary Intervention. Open J Cardiol Heart Dis.3(2). OJCHD.000556.2020. DOI: [10.31031/OJCHD.2020.03.000556](https://doi.org/10.31031/OJCHD.2020.03.000556).

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Ghada Mahmoud Shawkat Ali^{*1}, Salwa Roshdy Dimitry², Hatem Abdel Rahman Helmy² and Mohamed Ashraf Ahmed³

¹Doctor of Cardiology Department, Egypt

²Professor of cardiovascular medicine, Egypt

³Lecturer of cardiovascular medicine, Egypt

Abstracts

Primary Percutaneous Intervention is the most advantageous and rewarding reperfusion strategy available in patients with acute ST-segment-elevation myocardial infarction (STEMI), although it fails to restore optimal myocardial reperfusion in a sizeable portion of patients mostly because of no-reflow phenomenon.

No reflow is defined as suboptimal myocardial reperfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction. Inflammation has a substantial role in the initiation and propagation of the atherosclerotic process. The platelet-lymphocyte ratio (PLR) has been recently proposed to be a marker of thrombotic and inflammatory state, mainly in patients with coronary or peripheral ischemic events.

Abbreviations: PPCI: Primary Percutaneous Coronary Intervention; PCI: Percutaneous Coronary Intervention; STEMI: Segment Elevation Myocardial Infarction; PLR: Platelet to Lymphocyte Ratio; TIMI: Thrombolysis in Myocardial Infarction

Introduction

Myocardial infarction occurs when myocardial ischemia, a diminished blood supply to the heart, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal operating function and homeostasis. Critical myocardial ischemia can occur as a result of increased myocardial metabolic demand, decreased delivery of oxygen and nutrients to the myocardium via the coronary circulation, or both. An interruption in the supply of myocardial oxygen and nutrients occurs when a thrombus is superimposed on an ulcerated or unstable atherosclerotic plaque and results in coronary occlusion [1]. The moment a STEMI is diagnosed, treatment is begun. In addition to administering several drugs to attempt to stabilize the heart muscle - including oxygen, morphine, beta blockers and statin - steps are taken immediately to open up the blocked artery [2,3]. Primary percutaneous coronary intervention (PPCI) is more effective than thrombolytic therapy for the treatment of ST-segment elevation myocardial infarction (STEMI) when delivered by an experienced team soon after the onset of symptoms. However, performance of PCI in a timely fashion can be logistically challenging, and delays in time to reperfusion with primary PCI adversely affect outcome [4].

No reflow is defined as suboptimal myocardial reperfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction. During the last 3 decades, multiple experimental and clinical studies have identified a number of predisposing factors of no-reflow phenomenon and have proposed an array of explanative mechanisms and strategies to overcome it in the clinical setting, however, several aspects of no-reflow phenomenon remain poorly understood [5-7]. Inflammation has a substantial role in the

initiation and propagation of the atherosclerotic process. The platelet-lymphocyte ratio (PLR) has been recently proposed to be a marker of thrombotic and inflammatory state, mainly in patients with coronary or peripheral ischemic events. However, little is known regarding the PLR and its association with adverse outcomes in patients with cardiovascular diseases [8-10]. Thus, it is interesting to assess the predictive value of pre-procedural PLR

Coronary artery plaques and thrombosis

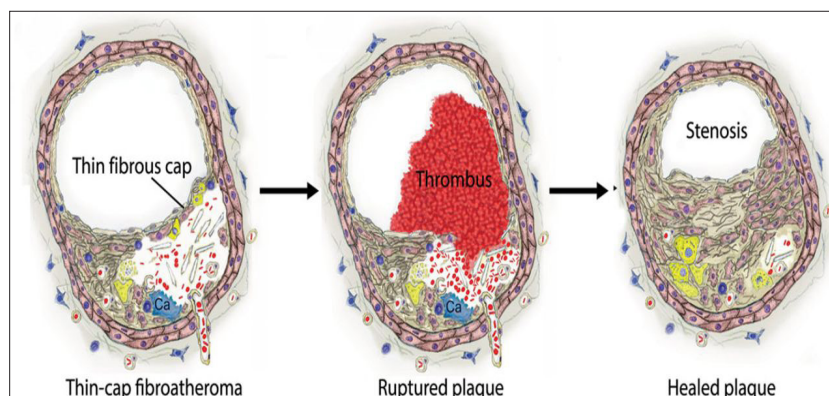


Figure 1: Plaque rupture and healing: Rupture of a thin cap fibroatheroma with nonfatal thrombus and subsequent healing with fibrous tissue formation and constrictive remodeling [11,12].

A. Mechanisms of plaque rupture, erosion, and thrombosis: In plaque rupture, a structural defect—a gap—in the fibrous cap exposes the highly thrombogenic core to the blood. Dislodged plaque material is sometimes found within the thrombus, indicating that rupture and thrombosis coincided and thereby supporting its causal relationship (Figure 1).

B. Mechanisms of plaque rupture: Plaque rupture occurs where the cap is thinnest and most infiltrated by foam cells (macrophages) [11]. In eccentric plaques, the weakest spot is often the cap margin or shoulder region, [12] and only extremely thin fibrous caps are at risk of rupturing. Rupture of a thin cap and subsequent thrombosis may occur spontaneously, but in some cases, a temporary increase in emotional or physical stress provides the final triggering of the event.

C. Thrombosis: The magnitude of the thrombotic response on ruptured or eroded plaques is extremely variable, and only occasionally a major and life-threatening luminal thrombus evolve. Probably the determinants are those of the classic triad of Virchow:

- thrombogenicity of the exposed plaque material
- local flow disturbances
- systemic thrombotic propensity.

With plaque rupture, cap collagen and the highly thrombogenic lipid core, enriched in tissue factor-expressing apoptotic micro particles, are exposed to the thrombogenic factors of the blood [13,14]. Although blood flow continues over the culprit lesion, micro-emboli of plaque material and thrombus may be washed away, leading to distal embolization [15,16] that may cause microvascular obstruction and prevention of myocardial perfusion despite a re-canalized infarct-related coronary artery.

in the development of no reflow in patients undergoing coronary stent implantation for the treatment of STEMI [10].

Role of Thrombosis in STEMI

The most common cause of a heart attack is a blood clot that forms inside a coronary artery, or one of its branches. This blocks the blood flow to a part of the heart.

Myocardial ischemic events

Myocardial injury and myocardial cell death: Myocardial ischemia happens if blood supply to the myocardium does not meet the demand. If this imbalance persists, it triggers a cascade of cellular, inflammatory and biochemical events, leading eventually to the irreversible death of heart muscle cells, resulting in MI.

Evolution of MI and ventricular remodeling: Typical MI initially manifests as coagulation necrosis that is ultimately followed by a healing process characterized by formation of myocardial scarring, known as myocardial fibrosis. This mechanism allows significant architectural changes to the composition, shape and contractile function of the myocardium, especially in the left ventricle, which is the major contributor to the contractile function of the heart. Eventually the left ventricle dilates and changes to a more spherical shape, in a process known as ventricular remodeling. Despite being an irreversible process, ventricular remodeling is a regulated process, therefore, specific treatment strategies and agents should be used in acute MI management in order to reduce the occurrence and severity of ventricular remodeling [17].

Primary Percutaneous Coronary Intervention

Primary percutaneous coronary intervention (PPCI) has been shown to be superior to fibrinolysis in the treatment of acute myocardial infarction with ST-segment elevation in patients admitted to highly experienced angioplasty centers, primary angioplasty is offered only to the limited number of patients admitted directly to hospitals with interventional services. Transportation from the local hospital to an angioplasty centre has been considered to represent a major limitation on the widespread use of primary angioplasty (Figure 2).

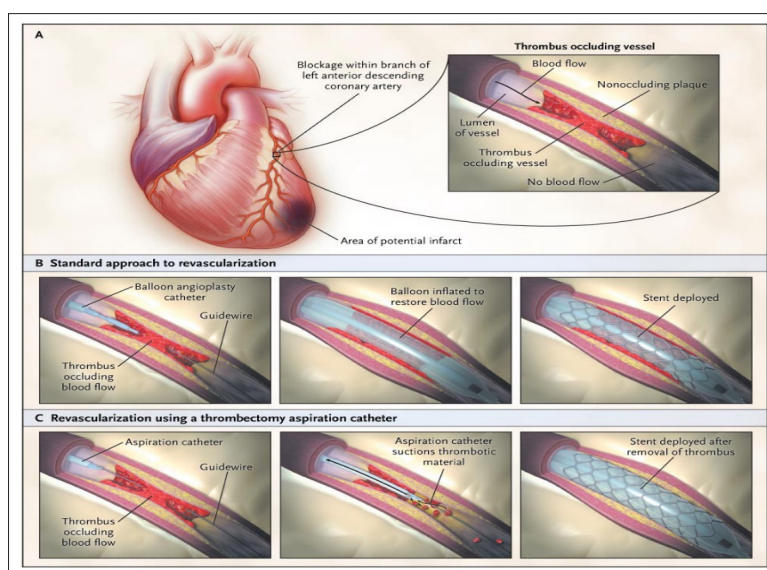


Figure 2: Thrombotic occlusion of an artery associated with acute myocardial infarction and subsequent Percutaneous Coronary Intervention (PCI). In an occluded infarct-related artery (Panel A), reperfusion can be achieved by the standard means of primary PCI (Panel B) or by the new method of thrombus aspiration (Panel C), followed by stenting [18].

No Reflow Phenomenon after Primary PCI

According to Kloner et al. [5] no-reflow is defined as suboptimal myocardial reperfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction. The concept of “no reflow” refers to a state of myocardial tissue hypo perfusion in the presence of a patent epicardial coronary artery. The underlying cause of no reflow is microvascular obstruction, which may be produced by various mechanisms. No reflow occurs after primary PCI may be asymptomatic or may present clinically with continued chest pain and ST-segment elevation. Reperfusion no reflow is preceded by ischemic cell injury, is confined to the irreversibly damaged necrotic zone, and may be exacerbated at the time of reperfusion. Reperfusion no reflow is an independent predictor of adverse clinical outcome after AMI regardless of infarct size and is associated with heart failure and increased mortality [18,19].

Diagnosis of no reflow

a. ECG ST-segment resolution is a readily available marker of tissue-level reperfusion, persistence of ST-segment elevation in an AMI patient may reflect either epicardial artery occlusion or microvascular obstruction.

b. Coronary angiography allows a semi quantitative grading of epicardial coronary flow according to the Thrombolysis in Myocardial Infarction (TIMI) flow grades.

The no-reflow phenomenon is recognized angiographically in >20% of patients undergoing primary angioplasty for AMI and in <2% of elective PCI cases. Reduced coronary flow after primary angioplasty (TIMI flow 0 to 2) is associated with worse outcome than normal (TIMI 3) flow, even when no significant epicardial obstruction remains [19]. The TIMI frame count assesses the

number of angiographic frames required for the contrast medium to reach standardized distal landmarks of the coronary tree, and the myocardial blush grade is a quantitative assessment of myocardial contrast density.

TIMI Flow Grading

TIMI Grade Flow’ is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty [20-23]:

1. TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.
2. TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.
3. TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory.

4. TIMI 3 is normal flow which fills the distal coronary bed completely

c. Myocardial contrast echocardiography has greatly advanced the noninvasive assessment of myocardial perfusion and may demonstrate microvascular no reflow even among patients with angiographic TIMI 3 flow after primary PCI, which predicts worse outcome [24]. Tissue hypo enhancement on contrast-enhanced MRI and CT reflects impaired myocardial perfusion and correlates with histological evidence of microvascular obstruction.

d. A rise in serum cardiac biomarkers after PCI reflects myocardial necrosis secondary to tissue hypo perfusion and ischemia. More than 70% of patients may exhibit elevated troponin values after an otherwise successful elective PCI [25].

Pathophysiology of no reflow

After prolonged cessation of coronary occlusion and restoration of blood flow to the epicardial coronary arteries, there is sufficient structural damage to the microvasculature to prevent restoration of normal blood flow to the cardiac myocytes. This may lead to inadequate healing of the cardiac scar. In addition, it may prevent the development of future collateral flow.

1. It is more pronounced with longer periods of coronary occlusions. No reflow appears to be a process rather than an immediate event that occurs at the moment of reperfusion.

2. Microscopic examination showed that the cardiac cells within the no-reflow area were swollen. The capillary endothelium was damaged and exhibited areas of regional swelling with large intraluminal protrusions that in some cases appeared to plug the capillary lumen [26].

3. Intravascular plugging by fibrin or platelets may also contribute to the no-reflow phenomenon [27-30]. Beneficial effects of ibuprofen, prostaglandin E1, and vascular washout with heparinized saline support the concept that these blood elements may be important [31-33].

4. Leukocyte intravascular plugging appears to play an important role in the pathophysiology of no reflow. Engler et al

showed that the no-reflow areas had evidence of capillary leukocyte plugging [34].

5. Leukocytes may interfere with blood flow by mechanical plugging and perhaps by their release of oxygen free radicals that will add further injury to the capillary endothelium [34-37]. Thus, the no-reflow phenomenon is likely multifactorial. During the ischemic phase, endothelial damage, including endothelial swelling and myocyte edema, led to initial no-reflow zones. With reperfusion, additional edema, myocyte contraction, platelets, fibrin, and leukocyte plugging resulted in expansion of the no-reflow zones over the early hours of reperfusion. Platelet and leukocyte depletion and vasodilators appeared to lessen no reflow [38-41].

An additional mechanism plays a very important role during short-term intervention in acute myocardial infarction. Micro-emboli of atherosclerotic debris, blood clots, and platelet plugs are released into the microcirculation, particularly with restoration of normal blood flow by thrombolysis, angioplasty, stenting, or other percutaneous intervention. Although this is more common in vein graft intervention, it is to be expected in native coronary arteries. A variety of new, innovative devices are now in clinical practice and in the research phase to filter these micro-emboli during the interventional procedure (Figure 3).

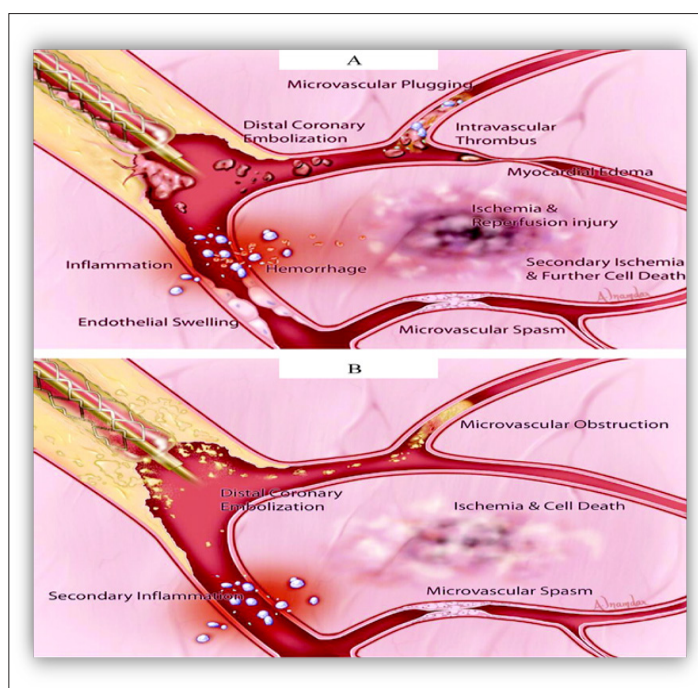


Figure 3: Schematic representation of pathophysiological mechanisms that may contribute to reperfusion no reflow in the setting of primary angioplasty for AMI. The vasculature within the necrotic zone is subjected to additional injury after reperfusion. Microvascular spasm and plugging, intravascular thrombus, endothelial swelling, and capillary compression by edema within the adjacent myocardial tissue may lead to microvascular obstruction. Angioplasty-induced distal coronary embolization of plaque and thrombus may compound the vascular obstruction. An inflammatory response may exacerbate this process, which leads to further myocardial ischemia and cell death. B, Interventional no reflow after no infarct angioplasty is induced by distal coronary embolization of plaque components. Mechanical obstruction of the microvasculature may be accompanied by an inflammatory vascular response that leads to vascular spasm. These mechanisms result in myocardial ischemia and cell death [41].

Platelet - Lymphocyte Ratio (PLR)

Rapid restoration of coronary blood flow to the jeopardized myocardium is the crux of therapy, after acute myocardial infarction. The invention and usage of stents have made PCI a safe, effective, and preferred reperfusion modality for the treatment of STEMI [42]. Nevertheless, even after patency of an infarcted artery was successfully achieved via stent implantation, sufficient myocardial reperfusion was not observed in 2.3% to 29% of patients in the setting of acute myocardial infarction, which is often called the no-reflow phenomenon [5,43-45]. Despite the mechanical opening of the infarct-related artery (IRA), early post infarction complications, adverse left ventricular remodeling, and in-hospital and long-term morbidity and mortality are increased in patients who develop no reflow [46-49]. The platelet-lymphocyte ratio (PLR) has been recently proposed to be a marker of thrombotic and inflammatory state [8,9]. However, little is known regarding the PLR and its association with adverse outcomes in patients with cardiovascular diseases [10].

Significance of PLR

Acute coronary syndrome (ACS) is a leading cause of morbidity and mortality. Inflammation has an important role in the progression and destabilization of coronary atherosclerosis. Several inflammatory biomarkers, such as interleukin (IL)-6, [50] C-reactive protein [51,52], and matrix metalloproteinases [53], have been identified as independent predictors of adverse outcomes in patients with ACS. However, these biomarkers are not used as routine or inexpensive examinations for patients with ACS.

Increased platelet activation has an important role in the initiation and progression of atherosclerosis [54]. Higher platelet counts may reflect increased platelet activation, which has a pivotal role in megakaryocytic proliferation and produces relative thrombocytosis [55]. In addition, low lymphocyte counts indicate a depressed immune response that is associated with adverse outcomes in cardiovascular disorders [56,57]. Therefore, an elevated platelet-to-lymphocyte ratio (PLR) might enhance micro-particle, platelet, monocyte, or neutrophil aggregate production, which results in a state of activated hemostasis, and it will lead to an increased risk of adverse outcomes in ACS. Therefore, PLR is a combined marker of lymphocytopenia and thrombocytosis and may better indicate no-reflow as well as mortality. Increased platelet counts may reflect underlying inflammation as several inflammatory mediators stimulate megakaryocytic proliferation and produce relative thrombocytosis.

Activated platelets release inflammatory and mitogenic substances into the local microenvironment, which would promote the recruitment of more platelets and leukocytes [58,59]. The rush of platelets and neutrophils that follows reperfusion may lead to the formation of neutrophil-platelet aggregates that plug the microcirculation and reperfusion-related injury [60]. A positive correlation was found between the acute phase reactants and pro-inflammatory proteins (CRP, interleukin (IL)-1, IL-6, and tumor necrosis factor α) and an elevated platelet count in nonspecific

inflammatory conditions [61]. In addition, recent studies have shown that patients with CAD have increased platelet and monocyte aggregates in their bloodstream, which was associated with plaque instability, worse in-hospital outcomes, and increased risk of future cardiac events [62,63]. On the other hand, elevated numbers of lymphocytes have also been speculated to be related to an increase in plaque stability [64]. Previous studies reported that lymphocytopenia was independently related to mechanical complications and mortality in patients with acute myocardial infarction.

Conclusion

Although several mechanisms have been proposed to explain the no reflow phenomenon, the pathophysiology of no-reflow has not been fully explained, and its Aetiology appears to be multifactorial. Platelet lymphocyte ratio (PLR) is a novel factor that can predict none-reflow in patients subjected to primary percutaneous intervention and can predict the post interventional adverse cardiac outcomes, complications and mortality. Further large-scale, prospective and multicenter studies are needed to clarify and confirm the association between the PLR and no reflow, which might be promising in identifying patients who need prophylactic treatment.

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