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Association between platelet volume indices and ST segment elevation myocardial infarction (STEMI)

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Abstract

ST-elevation myocardial infarction (STEMI) is a leading cause of mortality and morbidity in the Egyptian population. In this regard, different biomarkers became indicators in the diagnosis, assessment, and risk stratification of STEMI patients. Platelets play a crucial role in thrombus formation with a high count of abnormal large platelets. That is enzymatically and metabolically more active than normal platelets. A correlation between platelet size and function was investigated. Therefore, mean platelet volume (MPV) is a potential diagnostic biomarker of platelet activity. Platelet distribution width (PDW) represents this variability and heterogeneity in platelet size and is considered a marker of platelet activation and a more specific parameter than MVP.

Keywords: Mean Platelet volume; platelet width distribution; thrombus burden; primary percutaneous coronary intervention; ST-elevation myocardial infarction.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide, with myocardial infarction as the leading cause of death in developing and developed countries. Moreover, almost 50% of deaths occur before arrival at the hospital [1]. According to the World Health Organization (WHO) estimation, cardiovascular diseases account for 46.2% of all deaths among the Egyptian population. The American Heart Association (AHA) estimates a person has a heart attack every 41 seconds, with chest pain being among the top reasons for emergency department visits [2].

Worldwide, the epidemiology of patients with STEMI continues to change. According to the Global Registry of Acute Coronary Events (GRACE), STEMI represented about 36% of ACS cases [3]. There is no definitive data about the percentage of STEMI patients among those presenting to Emergency departments with Acute coronary syndromes (ACS) in Egyptian Hospitals.

Natural History of atherosclerosis and the development of atherosclerotic plaque

Atherosclerosis is a lipoprotein-mediated chronic inflammatory disease of arteries that leads to the accumulation of fibrotic, necrotic, and calcified tissue in the arterial intima, described as atherosclerotic lesions or plaques [4]. These plaques cause clinical disease by luminal narrowing or sudden precipitation of arterial thrombi that obstruct

blood flow to the heart (coronary heart disease (CHD), brain (ischemic stroke), or legs (peripheral artery disease (PAD). CHD is the most common of these manifestations, such as stable angina pectoris and acute coronary syndrome (ACS), including acute myocardial infarction (AMI) [3].

Atherosclerosis is a progressive disease that begins early in life, but the speed of progression is highly dependent on vascular localization and varies markedly among different individuals. Even under the most facilitating conditions, developing symptomatic lesions usually takes several decades. The abdominal aorta, coronary arteries, iliofemoral arteries, and carotid bifurcations are typically the most heavily affected [5]. The mechanisms leading to atherosclerotic plaque development are complex, involving lipoprotein retention, inflammatory cell recruitment, foam cell formation, apoptosis and necrosis, smooth muscle cell (SMC) proliferation and matrix synthesis, calcification, angiogenesis, arterial remodeling, fibrous cap rupture, and thrombosis [6].

Most people in developed countries die from progressive atherosclerotic lesions, but only a minority die because of them. The aforementioned advanced lesions are usually asymptomatic throughout life; however, some lesions end up being obstructive to blood flow, and a few elicit life-threatening thrombotic complications. Severe stenosis, which may present as stable angina, is often caused by a fibroatheroma or fibrous plaque. The plaque may be substantially calcified, and the local vessel segment is often negatively remodeled. The obstruction is rarely fatal, except in cases in which scarring of the myocardium may predispose to fatal arrhythmia [7]. MI and other types of ACS are predominantly caused by a luminal thrombus imposed on an atherosclerotic plaque. Three types of lesions have been described in the pathophysiology of acute coronary syndromes: plaque rupture, erosion, and calcified nodules [8].

Plaque rupture is the most frequent mechanism precipitating thrombosis. In plaque rupture, a structural defect (i.e., a gap) in the fibrous cap of a fibroatheroma exposes the highly thrombogenic core to the blood and circulating coagulation factors. That results in a thrombus on the ruptured plaque [4]. If the thrombus occludes the coronary vessel completely, the aerobic metabolism in the affected myocardium stops, resulting in rapid depletion of ATP as well as accumulation of metabolic products such as lactate [9]. Subsequently, these metabolic effects cause electrolyte changes, including a potassium shift to the extracellular space and a reduction in the action potential duration and amplitude. Within seconds, these processes lead to reduced contractility of the cardiac muscles. Although these effects are completely reversible, if blood flow was restored rapidly, animal models have shown that a 20–30-minute time interval of sustained ischemia is sufficient to cause irreversible damage to cardiomyocytes. Necrosis occurs first in the endocardium, which is most distal to the blood flow before it progresses into the subepicardial layers [10].

Myocardial cell death leads to the release of creatinine kinase (CK) into plasma. CK has different isoenzymes, of which CK-MB has its greatest activity in the heart muscle. Thus, the elevation of CK can occur with damage to tissues other than the myocardium, especially skeletal muscle, whereas CK-MB is more specific for myocardial necrosis; levels of both markers are assessed in patients with STEMI to confirm the diagnosis [11].

In addition, the pathological degeneration of the actin and myosin filaments of the heart muscle results in troponin release. Both skeletal and cardiac muscle contract via a

troponin-dependent mechanism and different isoforms of the troponin subunits (troponin I, T, and C) exist. Unlike troponin C, troponin I and T have distinct cardiac and skeletal isoforms. Therefore, cardiac troponin I (cTnI; known as TNNI3) and cardiac troponin T (cTnT; known as TnTc) are specific for myocardial injury and can be used as biomarkers for early diagnosis of MI and evaluation of prognosis [12].

Platelets and their role in thrombus formation

Human adults have nearly one trillion blood platelets in circulation. The non-activated platelet is a small 2-4 μm in diameter and 0.5-1 μm in thickness. Platelets are non-nucleated multifunctional cells, of which two-thirds are present in the general circulation with the remaining third reversibly sequestered in the spleen. Platelets originally derive from the hematopoietic lineage via the megakaryocyte (up to 8 x 103 of platelets from one cell) and function primarily in blood hemostasis forming a platelet plug at the site of vascular injury [13]. The production of platelets from megakaryocytes is a systematic regulated process that is thought to occur in the bone marrow or the lung, as has been shown more recently [14].

The platelet is a complex multifunctional cell. However, the primary function of the platelet is thought to be hemostasis, thrombosis, and wound healing, other physiological roles for the platelet exist; including immunity, angiogenesis regulation as well as communication with other cells and tissue in the vessel. The non-traditional functions of the platelets are considered now a field of extensive research that will help identify the expansive regulatory role that platelets play in the body [15]. In addition, these non-traditional functions have multiple emerging evidence of contribution to the development of inflammatory and immunological conditions as with neurological disorders such as stroke and multiple sclerosis [16].

Platelet plug formation

It is the primary process through which platelets play their primary role in maintaining hemostasis in the vessel under normal conditions. The primary response of hemostasis includes local vasospasm and platelet activation at the site of vascular injury. In contrast to the centrally accumulating RBCs in the blood vessel and to maintain its function, platelets flow within the blood vessel near the wall due to the biophysical nature of the blood constituents and shear forces within the vessel. Proximity to the vessel wall allows for a rapid response when a vascular insult or injury occurs [17]. That rapid response includes four processes of platelet activation; platelet adhesion (deposition of platelets on the damaged sub-endothelial matrix), platelet aggregation (platelet-platelet binding and inter-action), secretion (release of platelet granules), and procoagulant activity (enhancement of thrombin generation and coagulation cascade) [18]. Despite being described sequentially, these steps occur almost simultaneously.

Thrombus burden in STEMI patients

Angiographic evidence of thrombus can be seen in the high incidence of STEMI patients [19]. Massive intracoronary thrombus has been reported in 16.4% of patients with the acute coronary syndrome (ACS). Despite the availability of potent antiplatelet and anticoagulant regimens, intracoronary thrombus remains a risk factor for distal embolization, no reflow, stent thrombosis, and long-term adverse cardiovascular events [20]. There is no ideal management strategy.

Angiography is commonly used for quantification of the thrombus burden. Angiographically, intracoronary thrombus is defined as the presence of a filling defect with reduced contrast density or haziness. Six angiographic morphologic features indicated "high-burden thrombus formation" were suggested [21]. That included a cut-off pattern of occlusion, an accumulated thrombus proximal to the occlusion, a reference lumen diameter of the infarction-related artery (IRA) > 4.0 mm^2, an incomplete obstruction with an angiographic thrombus with the greatest linear dimension more than three times the reference lumen diameter, the presence of floating thrombus proximal to the lesion, a persistent dye stasis distal to the occlusion.

The most widely used TIMI scale depends on the relative estimated size of the thrombus and the affected vessel, using a score ranging from grade 0 to grade 5. It is a more objective and quantitative method developed by Dr. C. Michael Gibson of the TIMI study group. It presents the following grading system for a thrombus [22]:

- Grade 0: No angiographic evidence of thrombus.
- Grade 1: Possible thrombus: decreased contrast density or haziness, irregular lesion contour, a smooth convex meniscus at the site of a total occlusion, suggestive but not firmly diagnostic of thrombus.
- Grade 2: Definite thrombus presents with multiple angiographic characteristics defined by marked irregular lesion contour with a filling defect, the greatest dimension of thrombus is less than half vessel diameter.
- Grade 3: Definite thrombus appears in multiple angiographic views with the greatest dimension from more than half and less than double the vessel diameters.
- Grade 4: Definite large-size thrombus presents with greatest dimension more than two vessel diameters.
- Grade 5: Complete thrombotic occlusion of a vessel.

Sianos *et al.* (2007), suggested that when a grade 5 thrombus is encountered, either a guide wire or a 1.25-1.5 mm balloon is used to recanalize the artery [23]. As soon as the ante-grade flow is restored, underlying residual thrombus can be further categorized as grade 0 (no residual thrombus), grade 1 to 3 (small residual thrombus), and grade 4 to 5 (large residual thrombus) [20].

Factors that favor a high thrombus burden

A high thrombus burden during acute coronary syndrome is favored by various factors related to the patient, lesion, vessel, disease (MI), or PCI [24]. That includes:

- Patient-related factors include hypercoagulability, hypercholesterolemia, hyperhomocysteinemia hyperglycemia, Leucocytosis, smoking, substance abuse (cocaine and methamphetamine), vasculitis, and male sex.
- Lesion-related factors include acute plaque rupture and complex morphology.

- Vessel-related factors include slow coronary flow, morphology; large artery >4 mm, ectasia, aneurysm, old SVG, and right coronary artery (RCA tends to have a large burden of thrombus probably because of proximal propagation of thrombus related to fewer branch points).
- Disease-related (MI-related) factors include late presentation (>12 h), established Q-wave MI with ongoing ischemia, cardiogenic shock, and failed thrombolysis.
- PCI-related factors include triggering the thrombus formation with a guide wire, balloon, or stent known as the "angry clot" phenomenon, inadequate anticoagulation, inadequate dual antiplatelet, and heparin-induced thrombocytopenia. It is important to mention that these factors are intervention-related factors and are not related to all patients with ACS.

STEMI management and reperfusion therapy

Early reperfusion therapy is the mainstay of treatment for patients presenting with an acute STEMI. Options for reperfusion therapy include primary PCI, fibrinolytic therapy, or urgent coronary artery bypass grafting (CABG) [25]. The benefit of reperfusion is greatest early in the course of infarction. The first 2-3 hours represent the most critical time-dependent period with the highest mortality benefit for those treated in the 1st hour [26]. According to ECS Recent guidelines, primary PCI is the therapy of choice for patients with STEMI presented within 12 h of symptom onset, if it can be performed in a timely fashion (i.e. 120 min from STEMI diagnosis) by a skilled operator [27]. For patient treated with primary PCI, approximately 95% of them got restoration of Thrombolysis in Myocardial Infarction TIMI III flow compared with 54% of patients in those treated with thrombolysis and this explain the superiority of PPCI and PTCA over fibrinolytic therapy in numerous clinical trials with a reduction in mortality, reinfarction, and stroke. PCI is also associated with a reduction in the incidence of intracerebral hemorrhage, as compared with fibrinolytic therapy [28]. For a patient who presents to a PCI-capable hospital, primary PCI should be accomplished within 90 minutes of presentation. For patients who present to a hospital that is not PCI capable, Immediate transfer to a PCI-capable one is recommended if the door-to-device time can be achieved within 120 minutes. If primary PCI is unavailable within 120 minutes of diagnosis, then fibrinolysis should be performed 10 min after the diagnosis of STEMI is established unless contraindicated [5, 27].

Thrombolysis has the advantage of being widely available, in contrast to the limited PCI center in any health care system, easily administered, and relatively cheap. However, fibrinolysis therapy has important contraindications that are mostly related to the risk of bleeding including the risk for the development of intracranial hemorrhage (ICH) that estimated to be 0.5:0.7 % according to the user agent. Notably, major risk factors for intracranial hemorrhage are age above 75 years, hypertension, low body weight, female gender, and coagulopathy [25]. The presence of one or more of that absolute or relative contraindication would favor mechanical reperfusion, even if this means a delay of the reperfusion [27].

Platelet indices; mean platelet volume (MPV) and platelet distribution width (PDW) in atherosclerotic coronary artery disease (ASCAD)

It is important to know that these indices have been studied in several cardiovascular diseases, other than coronary artery disease (CAD) including, atrial fibrillation (AF), risk of development of ischemic stroke, and development of venous thromboembolism. In addition, other than cardiovascular disease, investigations were done in other diseases to assess the role of these markers as a prognostic/diagnostic tool including TB, Crohn's disease, ulcerative colitis, renal cell carcinoma, primary gastric carcinoma, and colorectal carcinomas [29].

Mean Platelet volume (MPV)

MPV is a precise assessment tool for platelet size, being measured using automated hematological analyzers. It is a routine part of a complete blood cell count. MPV normal values range between 7.5 and 12.0 fl, the percentage of large platelets should amount to 0.2-5.0% of the whole platelet population [30]. A correlation between platelet size and function has been found. Larger platelets, with more dense granules, are more active enzymatically and metabolically with a higher thrombotic potential which increases thrombus formation [31]. In addition, the larger size of platelets is associated with other markers of activity that include increased platelet aggregation, thrombomodulin release, thromboxane A2 synthesis, and expression adhesion molecules (glycoprotein Ib and glycoprotein IIb/IIIa receptors) [32]. Therefore, mean platelet volume (MPV) is a potentially useful biomarker of platelet activity. Based on that, MPV was investigated as a predictor of different diseases including cardiovascular, inflammatory, and malignant conditions. Numerous studies support the use of MPV as a biomarker/parameter of risk assessment and prognosis in different cardiovascular diseases with different suggested cut-off values [29].

Mean platelet volume (MPV) and acute myocardial infarction (AMI)

As a marker of activity, MPV increases during the onset of myocardial infarction and continues to be elevated weeks after. In MI survivors in the era of reperfusion, elevated MPV was proved as an indicator of poor clinical outcomes with an impaired response to thrombolysis therapy [33]. In those treated with primary PCI, elevated MPV is considered a strong independent factor that predicts impaired microvascular reperfusion, a poor post-intervention myocardial blush grade, the in-hospital major adverse cardiovascular events (MACE), and the 30-day, 1-year, and 2-year mortality [34-35]. In addition, MPV turned out to be an independent factor in the development of slow coronary flow (SCF) and its degree of 35. Moreover, it was found that MPV can predict the development of in-stent restenosis (ISR) In patients post PCI [36]. MPV seems to play a role in mediating the reperfusion injury which may help in deciding which patients may benefit from adjuvant therapy during PPCI [37].

MPV and residual platelet reactivity in patients on dual antiplatelet therapy

The availability of primary percutaneous coronary intervention (PPCI) facilities and the development of local protocols for the management of ACS increased worldwide with a subsequent increase in the proportion of patients that are on dual antiplatelet medications after implantation of drug-eluting stents (DES). Antiplatelet therapy reduces the incidence of complications during the procedure and ischemic cardiovascular events after PCI [38-39]. Interindividual variation in the pharmacodynamic response to antiplatelet medications was observed with their wide use, especially for clopidogrel, which increased attention to monitoring their effect for adequate platelet inhibition [40]. High platelet residual activity can attenuate the efficacy of antiplatelet therapy and increase the risk of the development of CVS events during follow-up. In a large randomized open-label trial, there was no significant improvement in clinical outcome was observed in cases of standard antiplatelet therapy compared to monitoring and adjustment using platelet function tests (PFTs) [41]. In addition, PFTs as aggregation tests are time-consuming, expensive, and technically complex. MPV, as routinely measured before PCI, was a suggested parameter for this monitoring. In one study, high MPV was associated with reduced responses to aspirin and clopidogrel [42]. Moreover, an increase in MPV post PCI was associated with high platelet reactivity [43]. Based on that, MPV can be used to predict MACE in the post PCI follow-up and risk-stratify patients for more intense follow-up and medical therapy.

Platelet distribution width (PDW)

The red cell distribution width (RDW) for RBCs, indicates a varied size of platelets. Platelet activation and aggregation during thrombotic events lead to increased release of large, reticulated platelets from bone marrow (thrombocytopoiesis) [32, 44]. This, in addition to the increased size of activated platelets, increases the variance in platelet size in circulation. Platelet distribution width (PDW) represents this variability and heterogeneity in platelet size and is calculated as the platelet distribution width measured at 20% relative height of the total height of the curve depicting their distribution [45].

An increased PDW is an indication of the anisocytosis of platelets with a normal range for PDW of 9-14 fL [6]. PDW is considered a marker of platelet activation and a more specific parameter than MVP because it is not affected by simple platelet swelling [44, 46]. Just like mean platelet volume (MPV); platelet distribution width (PDW) can be obtained by simple hematology analyzers.

As an available cheap biomarker, it was studied as a prognostic tool in multiple cardiovascular conditions. As in the case of MPV, a greater level of PWD was found in patients with STEMI than those with stable CAD [31]. In addition, increased PDW can predict the development of HF in patients with ACS [47]. In another study, increased PDW was related to the severity of CAD, assessed by the Gensini score, in patients presenting with ACS [48]. Moreover, it can be used as a useful prognostic factor for long-term mortality after AMI [32, 46].

Conclusion

ST-elevation myocardial infarction (STEMI) is a leading cause of mortality and morbidity in the Egyptian population. As a simple and cheap procedure, MPV and PDW have the potential to be used as a test to identify those who are at high risk for myocardial infarction. Moreover, these markers can be used as a prognostic tool as different studies had found their associations to impaired microvascular reperfusion, in-hospital major adverse cardiovascular events (MACE) and the 30-day, 1-year, 2-year mortality, the development of HF in a patient with ACS, slow coronary flow (SCF) and its degree and in-stent restenosis (ISR). Additionally, MPV is a potential pre-angiography independent predictor of thrombus burden in patients with STEMI undergoing primary PCI, who might require more potent antiplatelet therapy.

Conflict of interest: The authors declare no conflict of interest.

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