Mean platelet volume as diagnostic and therapeutic marker of risk and prognosis of heart disease

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ABSTRACT

Increased mean platelet volume (MPV) is associated with platelet reactivity and is a predictor of cardiovascular risk and unprovoked nervous thromboembolism. Mean platelet volume is a precise measure of platelet size. Studies have reported the use of MPV as a biomarker for predicting ischemic stroke in atrial fibrillation patients as well as in anticoagulant prescription and rhythm-control therapy. Moreover, MPV may predict cardiovascular event outcome following percutaneous coronary intervention in patients with coronary artery disease. MPV may predict residual platelet reactivity in dual antiplatelet therapy. Factors influencing MPV result were discussed. This review centered on the reports that MPV may be a biomarker of risk and prognosis of prevalent heart diseases.

Introduction

Platelets are small anucleated cytoplasmic bodies circulating in the blood stream. These cellular fragments are derived from megakaryocytes in the bone marrow.[1] In a steady state, megakaryocytopoiesis supplies about 10^{11} platelets per day with a new turnover every 8-9 days. However, this process is influenced by various environmental changes. Platelets normally circulate at concentration of $150\text{-}400\times10^9$/L.[2,3]

Platelets contain many organelles, a microtubular

system, a metabolically active membrane and consist mainly of three types of granules: α-granules contain the von Willebrand factor, platelet-derived growth factor, platelet factor 4 and β-thrombomodulin. They are the most abundant granules in platelets and are rapidly exocytosized upon activation to enhance hemostasis and inflammation. The dense bodies contain adenosine nucleotides [adenosine diphosphate (ADP) and adenosine triphosphate (ATP)], calcium and serotonin, which induce platelet aggregation, vasoconstriction, cytokine production and modulators of inflammation. The lysosomes contain glycohydrolases and proteases that can aid in pathogen clearance, breakdown of extracellular matrix and contribute in clearance of platelet thrombi and degradation of heparin.[1-5]

Platelets play critical roles in the progression of thrombosis, atherosclerotic lesions and plaque destabilization; they express and secrete many substances that are crucial mediators of coagulation, inflammation and atherosclerosis.[3,4] Larger platelets are metabolically and enzymatically more active than smaller ones and exhibit greater thrombotic potential.[6-8] More so, increased platelet size is associated with other markers of activity such as platelet aggregation, enhanced thromboxane synthesis and β-thromboglobulin release and increased expression of adhesion molecules.[7] Hence, platelet volume is thought to be predictive of cardiovascular diseases.[9] Mean platelet volume (MPV) has been preferentially explored as marker of platelet reactivity and various diseases partly due to its inexpensive nature. It is part of the component of the complete blood count routinely run with automated hemo analyzers. This review sets off to illuminate the role of mean platelet volume as a biomarker of the risk and prognosis of cardiovascular disease and cardiac events.

Mean platelet volume as a biomarker of the risk and prognosis of coronary artery disease

Mean platelet volume has been reported as potential tool in predicting patients who may develop coronary artery disease after primary percutaneous intervention.[10] Diverse studies have centered on the role of MPV in predicting cardiovascular events, prediction of clinical outcome of patients undergoing dual antiplatelet therapy.

Mean platelet volume as a biomarker for acute myocardial infarction

Acute myocardial infarction occurs due to coronary atherosclerosis as well as thrombosis.[11] When atherosclerotic plaque ruptures or erode, platelets are recruited to the exposed subendothelial region and the partially occluded vessels become completely occluded with the new formed thrombus. Large platelets have greater thrombotic potential and are biologically more potent.[12] Increased platelet volume has been shown to be more reactive with greater production of thromboxane A_2 and serotonin. Studies have reported platelet volume to be significantly higher among acute myocardial infarction patients than control subjects.[13,14] An elevated MPV correlates with poor clinical outcomes among survivors of myocardial infarction in the era of thrombolysis and an impaired response to thrombolysis in those with ST segment elevated myocardial infarction.[15] Elevated MPV has also been reported has also been reported to carry worse prognosis in terms of poor angiographic reperfusion and higher six months mortality following primary percutaneous coronary intervention (PCI) and also correlates with subsequent mortality and nonfatal myocardial reinfarction.[16]

Mean platelet volume as prognostic tool in percutaneous coronary intervention outcome

MPV has been reported as a useful biomarker in early identification of patients with stable coronary artery disease at high risk of post-PCI low-reflow. Studies have shown that pre-procedural elevated MPV is associated with the incidence of major adverse cardiac event and restenosis following PCI.[17] The study submitted that MPV is a potential marker of restenosis after PCI. Another study reported that MPV independently predicted post-PCI-corrected thrombolysis in myocardial infarction frame count.[18] It was suggested that monitoring MPV after PCI might aid in risk classification.

Mean platelet volume and residual platelet interference in dual antiplatelet therapy

Antiplatelet therapy is used to reduce the incidence of procedural-related complication as well as ischemic cardiovascular events in patients undergoing PCI.[19] High on-treatment platelet reactivity is associated with 2-9-fold increased risk of recurrent ischemic events among patients receiving dual anti-platelet therapy for coronary artery disease.[20] The high residual platelet reactivity can limit the overall utility of antiplatelet therapy.

Mean platelet volume as a biomarker of ischemic stroke in atrial fibrillation patients

Mean platelet volume has been identified as a biomarker of adverse cardiovascular events in atrial fibrillation (AF). These could be viewed in the role as predictor of ischemic stroke, guide towards rhythm or rate control tools in AF patients as well as guide in anticoagulant therapy.

Mean platelet volume predictor of stroke risk

Several studies have reported significant higher MPV in AF patients than in the control subjects.[21,22] There is a positive association between MPV and the severity of acute ischemic stroke[23] and in predicting the risk of ischemic stroke in patients with atrial fibrillation.[24-26] Butterworth and Bath[27] reported that platelet volume is increased in patients with acute ischemic stroke. O'malley et al.[28] reported high values of MPV in all subtypes of ischemic stroke. Greisenegger et al.[29] observed that an elevated MPV is associated with worst outcome for acute ischemic cerebral events independent of other clinical parameters. Another case-control study reported that stroke patients with AF had higher MPV than AF patients without stroke history.[23] The exact mechanism underlying this supposed relationship is not yet clearly understood. However, it has been suggested to be due to the association between MPV and markers of left atrial stasis, reinforcing the notion that cardioembolic mechanism may be in play when AF is associated with stroke.[29]

Mean platelet volume as a guide in therapy selection in atrial fibrillation treatment

There are two approaches to the treatment of atrial fibrillation; cardioversion and treatment with antiarrhythmic drugs to maintain sinus rhythm and use of rate-controlling drugs, allowing atrial fibrillation to persist.[30] Although studies on difference in mortality in the two methods were reported to have no difference.[30-32] However, Hong et al.[33] demonstrated that MPV and the rate control strategy for treatment of AF were predictive markers for stroke.

Mean platelet volume as anticoagulant therapy guide in atrial fibrillation

Anticoagulant therapy and antiplatelet agents reduce stroke by 60% and 20%, respectively in patients

with atrial fibrillation. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation.[34] In view of this, identifying patients with high risk of ischemic stroke is important in the management of AF patients. Mean platelet volume has been shown to enhance predictive value of the clinical variables employed when calculating $CHAD_2$ or CHA_2DS_2VASc scores.[24] Ha *et al.*[24] reported that patients with high MPV who were not on anticoagulation therapy had poorer stroke-free survival than did others, even for those with $CHAD_2$ score of <2. It was suggested that anticoagulation therapy was required by patients with high MPVs.[24]

Possible mechanisms of action of mean platelet volume in cardiovascular diseases

Although the exact mechanism by which elevated MPV influences the progression of cardiovascular diseases is not completely clear, multiple mechanisms may be involved. However, some postulations have been offered. Larger platelets are metabolically and enzymatically more active than smaller ones, containing more prothrombotic materials, with increased thromboxane A_2 and B_2 and glycoprotein IIb-IIIa receptor expression.[35,36] They show decreased inhibition of aggregation by prostacyclin and greater aggregability in response to ADP *in vitro*.[37] Larger platelets are denser and contain more α-granules which release thrombotic substances including platelet factor 4,[38] P-selectin[35] and platelet derived growth factor,[39] a chemotactic and mitogenic factor contributing to vascular neointimal proliferation.[40] More so, larger platelets are more often reticulated and this is an independent predictor of poor response to dual antiplatelet therapy.[41]

Factors influencing mean platelet volume results

Certain preanalytical factors can affect the result of MPV if not properly followed.

Venipuncture, filling and mixing

Careful and non-prolonged venipuncture is required for sample meant for MPV. Inaccurate venipuncture, filling of tube and mixing may result in platelet activation and produce clumping, hence, giving wrong result.

Choice of anticoagulant

To inhibit coagulation of blood for hematological samples before analysis, anticoagulants are used. EDTA or sodium citrate are standard substances. Both

bind calcium in an irreversible (EDTA) or reversible (sodium citrate) manner. Platelets will swell and continue to do so due to anticoagulants.[42]

Specifically, EDTA causes ultra-structural morphological changes in platelets.[43] Na-EDTA as an anticoagulant, results in less pronounced swelling than K-EDTA.[44] More so, sodium citrate results in more distinct swelling in *low concentration* (0.12 mmol/mL, ratio 9:1, blood to citrate) and almost no swelling in *high concentration* citrate (0.12 mmol/mL, ratio 4:1, blood to citrate).[45]

Time interval of measurement

Time interval is negligible in high concentration Na_3-citrate (1:4, citrate to blood) anticoagulated sample whereas low concentration of Na_3-citrate (1:9, citrate to blood), and K-EDTA samples are best analyzed between 60 and 90 min, respectively, from the time of collection.[45,44] Some studies recommend measurement within 1 hour regardless of anticoagulant used.[46]

Sample storage temperature

Some studies have reported that cooling citrate blood sample tubes from 37°C to 4°C increases mean platelet volume results by 18%.[47,48]

Limitations

Some limitations of this review are that the literature search was limited to association of MPV with cardiovascular disease. This might be a limitation. Moreover, most relevant studies reported have been retrospective in nature and involved small number of patients.

Conclusions

Several researchers have reported correlation between the risk of ischemic stroke in atrial fibrillation patients and elevated MPV following PCI in coronary heart diseases. MPV value can guide the physician on the risk of restenosis following PCI. MPV as a marker can provide an insight on therapy selection in AF patients as well as residual platelet reactivity in dual platelet therapy.

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