Mean platelet volume in acute myocardial infarction: a case-controlled study

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Introduction

The burden of cardiovascular diseases (CVD) is high in South Asian countries [1-3]. Among the CVD, hard coronary heart disease events including acute myocardial infarction (AMI) and coronary death tend to strike at an earlier age in comparison to that in the Western countries. All the common CVD risk factors are more prevalent in developing countries. There are many modifiable and nonmodifiable risk factors for AMI like age, sex, smoking, hypertension, diabetes mellitus etc. However, alcohol consumption does not act as a protective factor for AMI in South Asian natives in previous studies [4]. Diagnosis of myocardial infarction is based on signs and symptoms supported with electrocardiography and cardiac biomarkers like troponin and CPK-MB. Wherever available, coronary angiography and primary percutaneous coronary intervention (PCI) is the main stay of management.

Electrocardiogram (ECG) is an important tool to diagnose myocardial ischemia but the sensitivity of 12 lead ECG in diagnosing AMI was found to be very low [5,6]. The American College of Cardiology guidelines recommend taking serial ECGs at 5-10 minute interval or continuous monitoring if initial ECG is not diagnostic [7]. Sometimes, even serial ECGs need the help of an expert in ECG interpretation in cases of left bundle branch block (LBBB) or when features are suggestive of early repolarization. Myocardial infarction can occur in young adults and may be without a known risk factor.

Pathophysiological involvement of platelets in the atherosclerotic process has already been established. Aspirin, an antiplatelet agent is essential in most of the situations whether it is thrombolytic approach or PCI or pharmacoinvasive (thrombolysis followed by PCI) approach. It is well known that platelet rich thrombus is central to the pathology of MI and acute coronary syndrome. Platelet activation and aggregation ignite the process of coagulation and inflammation. It has been observed that larger platelets are more reactive [8]. High mean platelet volume (MPV) has been shown to be associated with AMI [8], acute ischemic stroke [9], preeclampsia [10], acute mesenteric ischemia [11]. We propose that MPV may be an important adjunct in the management of AMI. However, studies have shown conflicting results [12,13]. The present study
was undertaken to evaluate the MPV in patients with AMI in comparison to healthy controls.

Materials and methods
The study was initiated after obtaining Institutional Ethics Committee (IEC) approval of the protocol. The patients admitted in the Emergency department or Intensive Coronary care Unit with the diagnosis of AMI were included for study. The diagnosis of AMI was as per criteria laid down in consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction (Table 1) [14]. Fifty consecutive cases of MI and equal number of age (+/−5 years) and sex matched controls from the same population who did not have a past history of stroke or MI were enrolled for this study. Informed written consent was obtained from each participant. The exclusion criteria included inflammatory diseases (like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease etc.) severe liver disease, renal disease, myeloproliferative disorder, thrombotic thrombocytopenic purpura (TTP) and idiopathic thrombocytopenic purpura. Only newly diagnosed cases were included in the study. Patients suspected to have AMI were assessed and investigated immediately on arrival to the ER. Samples for MPV estimation and other blood investigations were collected. Blood samples were collected in ethylene diamine tetraacetate (EDTA) vacutainer for MPV and processed within 30 minutes of venesection. Platelet size tends to increase at room temperature on storage in first two hours and subsequently remain relatively stable for up to eight hours [15]. Dastjerdi et al., assured that MPV measurement can be accurate if sample is analysed within one hour of collection [16]. The resident physician involved in the study was assigned to adhere to the time frame to minimize in vitro increase in platelet volume. All patients were managed according to the standard treatment guidelines under the physician in charge of the case. MPV was analyzed in Melet Schloesing MS9-5 hematology analyser. The mean difference in the subgroups was compared using Students T-test. Receiver operating characteristic (ROC) curve analysis was performed on the MPV values to find a cut-off with maximum sensitivity and specificity. The statistical analysis was performed using the software SPSS v 16.0.

Results
The study cohort consisted of 50 patients diagnosed with MI and 50 healthy volunteer controls. The mean age of controls was 54.0±13.3 and that in cases was 55.0±13.6. There were 38 males in either group. The clinical features are given in Table 2. Among the patients, 17 were hypertensive, 28 were smokers and 10 had diabetes mellitus. In the control group, 9 were hypertensive, 26 were smokers and 8 had diabetes mellitus. Forty one of the patients had ST-segment elevation MI (STEMI) and nine had Non-STEMI. The mean MPV in case group was 11.0±2.2fl and in control group 7.8±1.3fl (p=0.000). The mean MPV in patients with STEMI was 11.1±2.2fl and in those with Non-STEMI was 11.0±2.3fl which showed no significant difference between groups.

Comparison between patients and controls of each subgroup showed consistent results that patients had significantly elevated MPV. ROC (receiver operating characteristic) analysis of the MPV values revealed the area under the curve (AUC) to be 88.7% (95% CI 82.5-94.9%) with a p=0.000. Diagnostic test evaluation with a cut-off of 9.15 MPV gives a sensitivity of 76%, specificity of 90% with a positive predictive value of 88.37%.

In subgroup analysis within the patients, it was found that MPV in those with diabetes was significantly greater than that in patients without diabetes (p=0.023) (Table 2). The correlation was not observed in control subjects with and without diabetes (p=0.664). Subgroup analysis of smokers vs non-smokers and hypertensives vs non-hypertensive also did not reach statistical significance in neither cases nor controls (Figure 1).

Discussion
MPV is a platelet marker which can be obtained as a part of complete blood count(CBC) using an automated hematology counter which measures the average size of platelets present in the blood. In this study MPV was significantly higher in patients with AMI in comparison to the control subjects. There was no significant difference in MPV values between ST elevation and non-ST elevation myocardial infarction. This finding was in accordance with the observation by Yekelar et al [17]. AMI occurs due to coronary atherosclerosis and thrombus formation. Platelets play a significant role in atherosclerosis as well as thrombosis [18, 19]. When atherosclerotic plaque ruptures
or erodes platelets are recruited to the exposed subendothelial region and partially occluded vessel becomes completely occluded with the newly formed thrombus. Larger platelets have greater prothrombotic potential and are biologically more potent. Increased platelet volume have been shown to be more reactive with greater production of thromboxane A2, and serotonin. There are other mechanisms by which platelets contribute to development of myocardial infarction via platelet mediated vasoconstriction and inflammation. Chu et al., opined high MPV as a cardiovascular risk factor in a meta-analysis [8].

There are various studies where higher MPV has been correlated with metabolic syndrome, hypertension, increasing age, and hyperlipidemia [20-23] but contradictory studies also exist [24]. In the present study risk factors like smoking and hypertension did not show correlation with MPV in either cases or controls.

Platelets have been implicated in the micro and macrovascular complications of diabetes mellitus [25]. Hendra et al., in their study found that MPV was higher in patients with diabetes and AMI when compared to those with diabetes but without AMI [26]. Similarly Tuzcu et al., had reported MPV to be higher in patients with diabetes complicated with retinopathy than those without retinopathy [27]. Subgroup analysis of patients with AMI in present study revealed that MPV was significantly higher in patients with diabetes than those without diabetes. Diabetes, due to Insulin deficiency and/or insulin resistance, is considered a prothrombotic state. There are various ways by which diabetes can increase platelet activity [28]. Prolonged hyperglycemia leads to nonenzymatic glycation of platelet surface proteins. Moreover glycoprotein Ib/IIa is reported to be overexpressed in diabetic individuals [29].

Martin et al., had meticulously evaluated volume and density of platelets in myocardial infarction and suggested that platelet changes were secondary to megakaryocyte abnormalities and these changes preceded myocardial infarction [30]. They also seemed to have increased expression of procoagulant surface adhesion molecules like P-selectin and GPIIb/IIIa. In fact Huczek

Figure 1. Box-plots depicting the MPV in different groups of patients who have Diabetes mellitus, Hypertension or are smokers. The patients having diabetes are found to have a significantly higher MPV (p=0.023).

| Characteristic | Feature | Controls | Cases | P-value |
|---------------|---------|----------|-------|---------|
|               | n MPV in fl (Mean±SD) | n MPV in fl (Mean±SD) |       |         |
| Total cohort  | -       | 50 7.81±1.28 | 50 11.04±2.2 | 0.000   |
| Sex           | Male    | 38 7.68±1.12 | 38 11.29±2.30 | 0.000   |
|               | Female  | 12 8.15±1.31 | 12 10.52±1.94 | 0.001   |
| Hypertension  | No      | 41 7.90±1.22 | 33 9.70±2.24 | 0.000   |
|               | Yes     | 9 7.10±1.28 | 17 11.70±1.99 | 0.000   |
| Smoker        | No      | 24 7.97±1.38 | 22 10.70±2.19 | 0.000   |
|               | Yes     | 26 7.65±1.21 | 28 11.41±2.16 | 0.000   |
| Diabetes Mellitus | No   | 42 7.80±1.80 | 40 10.7±2.20 | 0.000   |
|               | Yes     | 8 7.70±1.68 | 10 12.5±1.47 | 0.000   |
| MI            | STEMI   | --          | 41 11.12±2.18 | --     |
|               | Non-STEMI | --        | 9 11.01±2.28 | --     |
et al., observed that abciximab (GPIIb/IIIa antagonist) reduced mortality significantly only in patients of myocardial infarction who had high MPV [31]). They further observed that high MPV also carried worse prognosis in terms of poor angiographic reperfusion and higher six months mortality following primary percutaneous coronary intervention (PCI). Martin et al., also found that greater MPV correlated with subsequent mortality and nonfatal myocardial reinfarction [32]. Peregr et al., revealed that thrombolysis (in STEMI) failure rate was significantly higher in patients with high MPV [33]. Slavka et al., in their study concluded that increased MPV may carry increased risk of mortality due to ischemic heart disease which was as much as that due to smoking or obesity [34].

Conclusion
MPV is a very low cost investigation and can be obtained easily in most health care settings. This study corroborates others observations that MPV is higher in patients with AMI. It is not yet clear whether increase in MPV is the cause or effect of coronary artery occlusion. However we propose that it may be useful as a marker of myocardial infarction in an appropriate clinical situation. Further study may be tested in a larger cohort of patients with AMI to confirm its use as an adjunct to diagnosis.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Usha Agrawal, Bimal K Agrawal, N C Mahajan- Study plan and protocol designing, manuscript writing, Bimal K Agrawal, Bharatveer Manchanda, Akash Garg, Abhishek Mittal- Informed consent, acquisition of data
Usha Agrawal- Statistical analysis.

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