Mean Platelet Volume on Admission Predicts Impaired Reperfusion and Long-Term Mortality in Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

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

BACKGROUND
Mean platelet volume is predictive of unfavorable outcome among survivors of STEMI when measured after the index event. No data are available for the value of admission MPV in patients with STEMI treated with primary PCI.

METHODS
Blood samples for MPV estimation, obtained on admission in 398 consecutive patients presenting with STEMI, were measured before primary PCI. Follow-up up to six months was performed.

RESULTS
No-reflow was significantly more frequent in patients with high MPV (>10.3 fl) compared with those with low MPV (<10.3 fl) (21.2% vs. 5.5%, p < 0.0001). The MPV was correlated strongly with corrected Thrombolysis In Myocardial Infarction frame count (CTFC) (r = 0.698, p < 0.0001). Kaplan–Meier survival analysis showed six-month mortality rate of 12.1% in patients with high MPV versus 5.1% in low MPV group (log rank = 6.235, p = 0.0125). After adjusting for baseline characteristics, high MPV remained a strong independent predictor of no-reflow (odds ratio [OR] 4.7, 95% confidence interval [CI] 2.3 to 9.9, p < 0.0001), CTFC >40 (OR 10.1, 95% CI 5.7 to 18.1, p < 0.0001), and mortality (OR 3.2, 95% CI 1.1 to 9.3, p = 0.0084). Abciximab administration resulted in significant mortality reduction only in patients with high MPV values (OR 0.02, 95% CI 0.01 to 0.48, p < 0.0165).

CONCLUSIONS
Mean platelet volume is a strong, independent predictor of impaired angiographic reperfusion and six-month mortality in STEMI treated with primary PCI. Apart from prognostic value, admission MPV may also carry further practical, therapeutic implications.

Platelets play an important role in pathogenesis of acute coronary syndromes. It has been shown that platelet size, measured as mean platelet volume (MPV), correlates with their reactivity (1). Mean platelet volume is positively associated with indicators of platelet activity including expression of glycoprotein Ib and glycoprotein IIb/IIIa receptors (2–6). Higher values of MPV characterize patients with myocardial infarction and unstable angina as compared to those with stable angina or noncardiac chest pain, and elevated MPV has been recognized as an independent risk factor for myocardial infarction and stroke (7–10). An elevated MPV is associated with poor clinical outcome among survivors of myocardial infarction (11,12). Lately, it has also been proved that there is a positive relationship between MPV and the severity of acute ischemic cerebrovascular events (13).

To our knowledge, there are no reports on the predictive value of MPV in the era of primary percutaneous coronary intervention (PCI), which is currently the treatment of choice in acute ST-segment elevation myocardial infarction (STEMI). In our study we sought to determine whether MPV, measured on admission, can be used in determining the risk of impaired reperfusion and six-month mortality in STEMI patients treated with primary PCI.

METHODS

Patient population. Three hundred and ninety-eight consecutive patients admitted with diagnosis of STEMI, within 12 h from the onset of symptoms, were primarily enrolled in the study. Patients with cardiogenic shock within 24 h were also included; STEMI was defined as typical chest pain lasting for >30 min, with ST-segment elevation >1 mm in two consecutive precordial or inferior leads. In seven patients with no significant stenosis of the culprit lesion from the *1st Department of Cardiology, The Medical University of Warsaw, Warsaw, Poland; †Department of Medical Informatics, The Medical University of Warsaw, Warsaw, Poland; and the ‡Department of Cardiology, Swiss Cardiovascular Center, Bern, Switzerland. Supported by grants from the State Committee for Scientific Research (KBN 3 PO5B 122 23 and KBN 2 PO5C 045 26).

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The glycoprotein IIb/IIIa inhibitors (abciximab) were administered during PCI, at the discretion of the operator, as a 0.25 mg/kg bolus and a 0.125 μg/kg/min 12-h infusion.

**Study end points.** The angiographic end point of the study was the occurrence of no-reflow or CTFC ≥40. The clinical end point was all-cause mortality at six months.

**Statistical analysis.** Patients were divided into tertiles based on MPV values estimated on admission. Continuous data are presented as means ± SD. Differences in continuous variables between groups were determined by t test or Mann-Whitney test, for variables with or without normal distribution, respectively. To test the normal distribution, the Kolmogorov-Smirnov test was used. For all continuous variables apart from hematocrit values, the test rejected normality. Categorical variables were summarized as percentages and compared with the chi-square test. The Spearman correlation coefficient was computed to examine the association between two continuous variables. Survival curves were constructed by the Kaplan-Meier method, and differences in survival were assessed using the log-rank test. The impact of MPV value on no-reflow phenomenon, CTFC ≥40, and mortality were evaluated using multivariate logistic regression model. Stepwise selection procedure with 0.1 level for staying in the model was used to select important predictors. The final models were evaluated by using a concordance (C) index. Positive troponin I (TnI) on admission was defined as any value above upper range (>0.1 ng/ml; Dimension, Dade Behring, Newark, Delaware). A p value (two-tailed) <0.05 was considered statistically significant and confidence intervals (CI) were 95%. All analyses were performed using 8.02 Version SAS statistical software (SAS Institute Inc., Cary, North Carolina).

**RESULTS**

**Baseline characteristics.** No-reflow phenomenon was observed in 42 (10.8%) and CTFC ≥40 in 91 patients (23.5%). At six-month follow-up, 29 patients had died (7.5%). After the determination of baseline MPV values, the study population was divided into tertiles (first tertile: <9.7 fl [n = 130]; second tertile: 9.7 to 10.2 fl [n = 126]; third tertile: ≥10.3 fl [n = 132]). A high MPV (n = 132) was defined as a value in the third tertile (≥10.3 fl), and a low MPV (n = 256) was defined as a value in the lower two tertiles (<10.3 fl).

Demographic, clinical, and procedural characteristics in individual groups are listed in Table 1. Patients with high MPV values were older, had also significantly longer mean time to reperfusion, and were more likely to have hypertension as compared with patients with low MPV (Table 1).

**Correlation of MPV with other biomarkers.** There was a weak, although significant, negative correlation between MPV and platelet count (r = −0.211, p < 0.0001). Slight, but significant, positive correlation was also observed between MPV and leukocyte count (r = 0.116, p = 0.002). Platelet and leukocyte counts were not significantly associated with no-reflow, CTFC ≥40, or six-month mortality.
Apart from MPV, in our data set, presence of multivessel disease on pre-PCI angiogram (OR = 3.5, 95% CI 1.7 to 7.1, p = 0.0007) and admission positive TnI (OR = 4.8, 95% CI 1.6 to 14.3, p = 0.004) were also independent predictors of no-reflow. However, MPV maintained an independent contribution to risk assessment of no-reflow, regardless of TnI status on admission. High admission MPV was associated with significantly higher risk of developing no-reflow in patients with positive (p < 0.0001) as well as negative TnI (p = 0.0027) (Fig. 2).

Patients with high MPV had significantly higher mean CTFC than those with low MPV (48.4 ± 23.5 vs. 30.3 ± 16.7, p < 0.0001); MPV determined at the time of admission was correlated strongly with CTFC (r = 0.698; p < 0.0001). The higher the MPV value, the greater the number of cine frames needed to reach the distal part of the IRA after primary PCI (Fig. 3). High MPV on admission was an independent predictor of impaired reperfusion defined as CTFC ≥40 in univariate as well as multivariate analysis (Table 3).

To evaluate the prognostic power of multivariate models, we compared two models: before and after incorporation of MPV. The C-index for no-reflow and CTFC ≥40 models before incorporation of MPV were 0.71 and 0.65, respectively. After incorporation of MPV, the C-index values increased to 0.78 and 0.82, respectively.

**MPV and long-term mortality.** The mean MPV was significantly higher in the 29 patients who died (10.40 ± 1.85 fl) as compared with the 359 survivors (9.96 ± 0.90 fl, p = 0.0134). Figure 4 shows the Kaplan-Meier curves for six-month all-cause mortality in patients with low MPV versus those with high MPV. The all-cause mortality rate at six-month follow-up was significantly higher in patients with high MPV values as compared to those with low MPV (12.1% vs. 5.1%, p = 0.0125). After adjusting for baseline characteristics, high MPV remained an independent predictor of six-month mortality (Table 3). The performance of multivariate model after incorporation of MPV showed improvement with the C-index increase from 0.82 to 0.86.

Moreover, the prognostic association between MPV and six-month mortality was even stronger in patients with STEMI complicated with cardiogenic shock on admission. Cardiogenic shock cases were well balanced between low MPV (6.6%) compared with the high MPV group (9.1%, p = 0.385). Eight of 12 patients with high MPV died in cardiogenic shock (66.7%) as compared to only 3 of 17 with low MPV (17.7%, p = 0.0074). Using logistic regression, high MPV appeared to be a strong and independent predictor of mortality in cardiogenic shock (OR = 9.3, 95% CI, 1.7 to 52.7, p = 0.011).

### Table 1. Baseline Characteristics According to Mean Platelet Volume

<table>
<thead>
<tr>
<th>MPV Low (n = 256)</th>
<th>MPV High (n = 132)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, %</td>
<td>71.9</td>
<td>72.7</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>59.2 ± 11.2</td>
<td>61.5 ± 11.4</td>
</tr>
<tr>
<td>Time to reperfusion, h</td>
<td>4.7 ± 3.6</td>
<td>6.1 ± 4.6</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76.7 ± 16</td>
<td>79.1 ± 17.3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130.2 ± 21.5</td>
<td>127.5 ± 16.1</td>
</tr>
<tr>
<td>Systemic hypertensin, %</td>
<td>58.2</td>
<td>71.2</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>14.8</td>
<td>19.7</td>
</tr>
<tr>
<td>Active smokers, %</td>
<td>57.8</td>
<td>50.0</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>43.8</td>
<td>38.6</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>22.7</td>
<td>15.2</td>
</tr>
<tr>
<td>Prior aspirin use, %</td>
<td>32.0</td>
<td>30.3</td>
</tr>
<tr>
<td>Anterior wall MI, %</td>
<td>45.3</td>
<td>40.9</td>
</tr>
<tr>
<td>Killip class, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>75.8</td>
<td>75.8</td>
</tr>
<tr>
<td>II</td>
<td>14.5</td>
<td>12.1</td>
</tr>
<tr>
<td>III</td>
<td>3.1</td>
<td>3.0</td>
</tr>
<tr>
<td>IV</td>
<td>6.6</td>
<td>9.1</td>
</tr>
<tr>
<td>IRA, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>39.5</td>
<td>48.5</td>
</tr>
<tr>
<td>LCx</td>
<td>14.5</td>
<td>9.8</td>
</tr>
<tr>
<td>LAD</td>
<td>46.1</td>
<td>41.7</td>
</tr>
<tr>
<td>Vein graft</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>22.7</td>
<td>22.7</td>
</tr>
<tr>
<td>Baseline TIMI flow grade 0/1, %</td>
<td>80.9</td>
<td>83.3</td>
</tr>
<tr>
<td>Stent utilization, %</td>
<td>84.8</td>
<td>79.5</td>
</tr>
<tr>
<td>Abciximab administration, %</td>
<td>50.0</td>
<td>56.1</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD (p values for Mann-Whitney test) or percentage of patients (p values for chi-square test).

Aspirin = acetylsalicylic acid; IRA = infarct-related artery; LAD = left anterior descending artery; LCx = left circumflex artery; MI = myocardial infarction; MPV = mean platelet volume; RCA = right coronary artery; SBP = systolic blood pressure; TIMI = Thrombolysis In Myocardial Infarction.

We did not observe any significant correlation between MPV and other markers measured on admission (Table 2).

### Table 2. Correlation Between Mean Platelet Volume and Other Laboratory Measurements

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>−0.211</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>0.116</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.013</td>
<td>0.766</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.029</td>
<td>0.575</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.015</td>
<td>0.766</td>
</tr>
<tr>
<td>Troponin I</td>
<td>0.048</td>
<td>0.346</td>
</tr>
</tbody>
</table>
MPV and abciximab use. Abciximab was administered in 202 patients (52.1%) at the discretion of the operator—in clinically assessed higher risk patients. Therefore, older age (mean age, 60.9 ± 11.3 years vs. 59 ± 11.2 years, p = 0.092), longer time to reperfusion (mean time, 6.4 ± 4.4 h vs. 3.8 ± 2.9 h, p < 0.0001), diabetes (22.8% vs. 9.7%, p = 0.0005), hypertension (66.8% vs. 58.1%, p = 0.074), history of myocardial infarction (27.7% vs. 11.7%, p < 0.0001), anterior wall STEMI (55.9% vs. 30.6%, p < 0.0001), heart failure on admission (Killip class 1, 35.2% vs. 12.4%, p < 0.0001), and no-reflow (17.8% vs. 3.2%, p < 0.0001) were more frequent among abciximab-treated patients as compared with abciximab-untreated patients. Otherwise, both groups were well balanced.

Six-month mortality rates in abciximab-treated patients were as follows: 8.6% in MPV low group and 10.8% in MPV high group. In abciximab-untreated patients, the clinical end point occurred in 1.6%, and 13.8%, respectively. After adjusting for baseline characteristics and occurrence of no-reflow phenomenon, it appeared that abciximab administration resulted in significant mortality reduction only in patients with high MPV values (OR = 0.02, 95% CI 0.01 to 0.48, p = 0.0165). Based on stepwise selection in multivariate logistic regression model for predicting mortality in this study, abciximab did not influence significantly the six-month mortality neither in the low MPV subgroup, nor in all patients.

**DISCUSSION**

Predictive value of MPV for no-reflow, CTFC, and six-month mortality. Failure to achieve TIMI flow grade 3 after successful opening of the artery without angiographic evidence of mechanical obstruction, observed in 5% to 20% of patients treated with primary PCI and defined as no-reflow phenomenon, is associated with more extensive myocardial necrosis, worse segmental and global contractility of the left ventricle, malignant arrhythmias, and increased mortality (16–18). Pathophysiology of no-reflow is believed to be multifactorial (19,20). Higher (slower) CTFC values after reperfusion therapy have also been found to be associated with poor clinical outcome (21). In the present study, we demonstrated that no-reflow as well as calculated CTFC ≥40 occur significantly more frequently in patients with higher baseline values of MPV. Moreover,
MPV correlated with coronary blood flow expressed as continuous variable (CTFC), which further strengthens the findings of this study. We assume that the presence of larger, more reactive platelets or platelet aggregates may be associated with intravascular plugging on both epicardial and tissue level of the IRA, thus resulting in no-reflow and slower CTFC after primary PCI. Higher MPV may correspond with the increased number of both platelet-leukocyte and platelet-platelet aggregates (22). Correlations between MPV and platelet count and MPV and leukocyte count observed in the present study might support this hypothesis.

Several clinical and angiographic predictors of abnormal reperfusion have been recently identified, although simple, preprocedural biochemical markers are still searched for (23–25). Results from the present study support the idea that platelets play an important role in the pathophysiology of no-reflow (20) and suggest that MPV may be considered as a useful, independent, hematological marker allowing for early and easy identification of patients who are at a higher risk of impaired reperfusion after primary PCI.

We also showed that measuring of MPV helps to select a subgroup of patients (MPV ≥10.3 fl) with significantly higher mortality in six-month follow-up. Martin et al. (11) proved previously that greater MPV, when measured six months after myocardial infarction, is associated with increased risk of death and reinfarction in two-year follow-up. However, differently from the study mentioned above, we measured MPV directly on admission. Although MPV was correlated with age, hypertension, and longer time to reperfusion, it provided prognostic information that was independent of these variables. Our findings support and extend the data from Pabon et al. (12), who found positive correlation between admission MPV and the in-hospital incidence of major acute coronary events.

**MPV status and potential benefit from abciximab administration.** Administration of abciximab during primary PCI resulted in significant reduction of six-month mortality in patients with high MPV values. Interestingly, four large clinical trials in the setting of primary PCI failed to show a significant mortality reduction with glycoprotein IIb/IIIa inhibitor administration when compared to placebo, and one analysis from a recently published registry showed an even higher rate of cardiovascular events with glycoprotein IIb/IIIa blockade (26,27). Thus, the method for better selection of patients who benefit from glycoprotein IIb/IIIa inhibitor use is needed.

The results of the present study suggest that patients with high MPV on admission represent the group with higher risk for thrombosis. To that end, the higher the risk for thrombosis, the greater the benefit from abciximab administration. Apart from that, there is another possible explanation for major abciximab benefits in patients with high MPV. In this paper we concentrated on platelet-mediated effects; however, it is known that phospholipid constituents of the platelet membrane as well as platelet granules, microparticles, and other receptors appear to be increased among patients who have greater MPV (2–5). As such, the potential mechanisms for heightened adverse events among patients with larger platelets may be also related to increased inflammatory triggers, not evaluated precisely in this study. Therefore, the abciximab benefits would be also greater in this situation. It has been shown that heterotypic monocyte-

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**Figure 3.** Correlation between admission mean platelet volume (MPV) and corrected TIMI frame count (CTFC) assessed on final angiogram.

**Figure 4.** Kaplan-Meier curves for all-cause mortality according to mean platelet volume (MPV). The six-month all-cause mortality was 12.1% in high MPV versus 5.1% in low MPV.
platelet aggregates are a target for abciximab, which suppresses monocyte tissue factor because of a reduction of monocyte-platelet cross talk (28,29).

Study limitations. There are several limitations of this study. Previous studies have reported that MPV increases in a time-dependent manner when EDTA is used as anticoagulant (30). However, a recently published study proved that when the measurement is performed within 2 h after venipuncture, the anticoagulation with EDTA accounts for less than 0.5 fL increase in MPV (9). It is alleged that platelet swelling may be associated with different amounts of EDTA in sample tubes (13). To minimize the effect of EDTA on platelet size in the present study, standardized sample tubes were used, and all samples were processed early (at 30 min) after blood collection.

We could not exclude the presence of heterotypic platelet aggregates in the high MPV group. We may assume—on the basis of correlations between MPV and other laboratory measurements—that such aggregates could be present (Table 2). However, such phenomenon would only be determined by flow cytometry, the method that is currently costly, time-consuming, and needs specialized equipment (21). Therefore, MPV still remains an easy, useful tool for indirect monitoring platelet activity in different situations (31,32).

Adjustment for mortality according to abciximab treatment should be treated with caution because of the small sample size. Especially in the high MPV arm, larger cohort of patients would be required for a more meaningful analysis. Thus, our data concerning the potential MPV-guided approach to the selection of patients that may benefit from abciximab use in acute myocardial infarction treated with primary PCI must be evaluated in larger-scale, randomized trials.

An important practical limitation to the current data deals with the availability of the MPV in the setting of PCI for STEMI, when with a rapid door-to-balloon time this information may not be available. However, if the strong prognostic value of MPV is confirmed, the different types of automatic, rapid platelet function analyzers may resolve this problem in the future.

Conclusions. Admission MPV is a strong and independent predictor of impaired reperfusion and mortality in STEMI treated with primary PCI. Apart from prognostic value, measuring of MPV may also carry further practical, therapeutic implications.

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REFERENCES


