Mean Platelet Volume is Associated with Inadequate Reperfusion Detected by Angiography in Patients with Successful Fibrinolytic Therapy

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Abstract

Background: Higher Mean platelet volume (MPV) is associated with fibrinolysis failure and adverse outcomes in patients with ST elevation myocardial infarction (STEMI). However, there are no data about the effects of MPV on antegrade coronary blood flow and the degree of reperfusion in patients with successful fibrinolysis.

Objective: The aim of our study was to investigate the role of MPV on coronary circulation via thrombolysis in myocardial infarction (TIMI) frame count (TFC) after successful fibrinolytic therapy.

Methods: Among 145 patients treated with fibrinolytics, 123 (84.8%) consecutive patients with successful fibrinolysis determined by electrocardiography criteria were included. The patients were divided into two groups according to TFC. TFC > 40 was accepted as a marker for inadequate reperfusion and TFC ≤ 40 was accepted as an indicator of complete reperfusion.

Results: After coronary angiography, 57 patients had TFC ≤ 40 and 66 patients had TFC > 40. MPV was significantly higher in the inadequate reperfusion group (8.93 ± 0.87 fl vs 7.92 ± 0.80 fl, p < 0.001). Higher MPV was found to be an indicator of inadequate reperfusion and coordinates of the ROC curve indicated a cutoff value of 8.3 fl for MPV.

Conclusion: Higher MPV on admission in STEMI patients treated with successful fibrinolytic therapy was found to be associated with inadequate reperfusion detected by TFC. (Int J Cardiovasc Sci. 2016;29(3):168-174)

Keywords: mean platelet volume; ST elevation myocardial infarction; fibrinolytic therapy; TIMI frame count.

Introduction

Circulating platelets play an essential role in thrombotic complications of atherosclerotic plaques. Mean platelet volume (MPV) is an indicator of systemic inflammation and thrombotic potential of the blood. Younger platelets are larger, and hence more reactive and associated with increased prothrombotic potential. High MPV is common in the elderly population and has been strongly associated with acute coronary syndromes and their complications. MPV is related to insufficient reperfusion in the infarct-related artery and adverse outcomes in patients with ST-elevation myocardial infarction (STEMI) who have undergone primary percutaneous coronary interventions (pPCI). Early treatment with fibrinolytic therapy is effective in recanalization of the infarct-related artery. Resolution of ST elevation, development of terminal T-wave inversion and idioventricular rhythm are electrocardiographic signs of reperfusion in STEMI patients treated with fibrinolytics. Data concerning platelet reactivity and the degree of reperfusion after successful fibrinolytic therapy determined by electrocardiography (ECG) criteria and relief of chest pain are scarce. Thrombolysis in myocardial infarction (TIMI) flow grade and TIMI frame count (TFC) are simple quantitative parameters to evaluate the antegrade coronary blood flow. We investigated the relationship between MPV and reperfusion in the infarct-related artery detected by TFC after successful fibrinolytic therapy, determined by electrocardiography.
Methods

Study Population

Study design and protocol were approved by the local ethical committee. All patients diagnosed with STEMI in the emergency room at night shifts between 2010 and 2011 were screened. There was no pPCI in our hospital during the night shift in the study period. A total of 156 consecutive patients with diagnosis of first acute STEMI, within 12 hours of chest pain, were enrolled. Eleven patients were not included due to contraindications for fibrinolysis (n = 7), previous myocardial infarction (n = 3), and to previous coronary artery bypass graft surgery (n = 1). STEMI was defined according to the criteria recommended by guidelines. Response to fibrinolysis was accepted as relief from chest pain combined with ST segment resolution ≥ 50%.

Informed consent was obtained from all patients before fibrinolytic therapy.

Exclusion criteria

Patients were excluded if they had a contraindication to fibrinolytic therapy (e.g. previous hemorrhagic stroke, ischemic stroke in the previous three months, active bleeding, known malignancy, aortic dissection, systolic blood pressure > 180 mmHg), severe comorbidity, any platelet disorder, history of coronary artery bypass graft or previous myocardial infarction, and patients who had undergone rescue PCI.

Laboratory analyses

Laboratory findings (blood chemistry, complete blood count, etc.), electrocardiographic findings, concomitant medications and risk factors (hypertension, diabetes, etc.) of all patients were recorded. Blood samples were obtained on admission before administration of fibrinolytic therapy, acetylsalicylic acid, clopidogrel and low molecular weight heparin. All samples that were used to measure MPV were collected in tubes containing EDTA and sent to the laboratory within a few minutes. MPV was automatically calculated using the Beckman Coulter LH 780 analyzer. All samples were analyzed within 30 minutes, to avoid the swelling of platelets by EDTA.

Fibrinolytic Therapy

Among the 145 patients treated with fibrinolytic therapy, 141 patients (97%) received alteplase (15 mg IV bolus, 0.75 mg/kg for 30 min, 0.50 mg/kg for 60 min, total maximum dose 100 mg) for 90 minutes and 4 patients (3%) received streptokinase. The choice of fibrinolytic regimen was at the discretion of the physician. ECG at the beginning of fibrinolytic infusion, and at 30, 60 and 90 minutes was recorded. At the end of the infusion, a ST segment resolution > 50% in the derivation with highest initial ST segment elevation, combined with relief from chest pain, was accepted as successful fibrinolytic therapy. After treatment with fibrinolytic therapy, 123 patients had successful fibrinolysis.

TIMI flow grade and TFC calculation

All patients with successful fibrinolysis underwent coronary angiography within 24 hours of hospital admission. Angiograms were evaluated by two independent interventional cardiologists. The degrees of coronary flow and reperfusion were assessed by TIMI flow grade as previously defined, and by TFC. TFC was calculated according to criteria determined by Gibson. Interobserver variability was ≤ 5%, calculated from 15 random patients. The first frame was considered as the first frame in which contrast material extended across at least 70% of the artery with antegrade flow, and the last frame as that in which contrast reached the distal landmark of the artery. The frame difference between the two points was calculated as TFC. TFC for the left anterior descending (LAD) artery was divided by 1.7 and corrected TFC (cTFC) was calculated. TFC of over 40 frames per second (fr/s) was accepted as inadequate reperfusion whereas TFC of equal to or under 40 fr/s was accepted as complete reperfusion. These two groups were analyzed for the relationship between MPV and TFC.

Statistical analysis

The program SPSS 16.0© was used for statistical analysis. Normality of distribution was assessed by the Kolmogrov-Smirnov test. When the values satisfied the conditions of normality, bivariate comparisons for continuous variables were performed using the independent samples t-test, and for non-normal distributions the Mann Whitney-U test was used. Categorical data were evaluated by the chi-square test. The strength of the association between two continuous variables was evaluated by the Spearman correlation test, and if the size of the correlation was between 0.30 to 0.50, the strength was categorized as low positive correlation. ROC curve was used in order to assess the accuracy of MPV for predicting TFC, and the area under the curve (AUC) was calculated by using Med-Calc version 12.0.1©. A p value of under 0.05 was considered statistically significant.
Results

After exclusion criteria, 123 out of 145 consecutive patients treated with fibrinolytics with successful fibrinolysis, determined by ECG criteria and symptoms, were included in the study. All patients underwent coronary angiography within 24 hours of admission. For the infarct-related artery, and TFC ≤ 40 was accepted as an indicator of complete reperfusion. Fifty-seven patients had TFC ≤ 40 and 66 patients had TFC > 40. The clinical features of these two groups are shown in Table 1. No statistically significant differences in gender, risk factors, door to needle time, chest pain duration, infarct-related artery or multivessel disease were detected between these two groups. Also, there was no significant difference regarding left ventricular ejection fraction between the groups. However, patients in the inadequate reperfusion group were significantly older and had lower platelet counts. Correlation analysis revealed a significant positive correlation between TFC and MPV (p < 0.01, r: 0.461). However, the strength of the association was moderate (Figure 1). Mean MPV was significantly higher in the inadequate reperfusion group (8.93 ± 0.87 fl vs. 7.92 ± 0.80 fl, p < 0.001), and a higher MPV was found to be an indicator of inadequate reperfusion after successful fibrinolytic treatment. Coordinate values demonstrated by ROC analysis indicated a cutoff value of 8.3 fl for MPV (sensitivity 75.8%, specificity 68.4%, negative predictive value 70.9% and positive predictive value 73.5%) and AUC was 0.702 (95% CI: 0.576–0.824) (Figure 2).

Discussion

Our results demonstrated that high MPV on admission indicates inadequate reperfusion in STEMI patients treated with successful fibrinolytic therapy, determined by ECG.

Fibrinolytic therapy is one of two methods used to restore coronary perfusion and minimize myocardial damage. It is strongly recommended by various guidelines, especially in patients with a chest pain duration of lower than three hours and an expected PCI related delay of over 60 min.7 Fibrinolytic therapy does not always result in adequate reperfusion. Even though fibrinolytic therapy is widely used in an acute setting, complete reperfusion can be restored in only 50-60% of patients.11 In our study, door to needle time (26.82 ± 9.35 minutes) and time from symptom onset (3.23 ± 1.94 hours) were shorter than in many studies and real-world data. A high successful reperfusion rate (84.8%) may be due to these short time intervals. It has been shown that high MPV on admission is associated with impaired ST segment resolution in STEMI patients treated with fibrinolysis.12 In this study, we aimed to investigate the effect of MPV on antegrade coronary blood flow in patients with relief of chest pain and ST-segment resolution ≥ 50% after fibrinolytic therapy.

There are many angiographic parameters to evaluate successful reperfusion, such as myocardial blush score or TFC. However, in our study, we wanted to determine the correlation of MPV with TFC to avoid confusion between these parameters. TIMI flow grade is another useful and adequate parameter to define coronary reperfusion after fibrinolysis. In our study, incidence of TIMI 3 flow was significantly lower in patients with inadequate reperfusion than in patients with complete reperfusion. However, more than half of the patients had TIMI 3 flow in the inadequate reperfusion group. Antegrade coronary blood flow can also be assessed more accurately by TFC. Hence, we used TFC to evaluate coronary circulation and reperfusion in detail. Higher TFC (> 40) is a marker of inadequate reperfusion and is associated with in-hospital mortality, major cardiovascular events and poor prognosis after fibrinolytic therapy.13 Larger platelet volume corresponds to more active platelets and is correlated with thrombosis. It is well known that patients with acute myocardial infarction have higher MPV than those without myocardial infarction.5,14 However, effects of MPV on coronary circulation after successful fibrinolysis remains unclear. As we detected a correlation between MPV and TFC, our finding reveals that higher MPV continues to cause thrombotic microvascular dysfunction despite successful fibrinolysis. In addition, high MPV correlates with fibrinolysis failure in STEMI patients.15 Previous studies have demonstrated the relationship between MPV and incomplete reperfusion after fibrinolytic therapy.16,17 However, these previous reports did not consider ECG changes, ST segment resolution and symptoms after fibrinolysis. In our study, we excluded the patients with inadequate ST segment resolution and residual symptoms to eliminate the negative effect of high MPV on fibrinolysis. To our knowledge, this is one of the largest studies that have evaluated the relationship of MPV with coronary reperfusion in STEMI patients, and first report that investigated the importance of MPV only in patients with successful fibrinolysis detected by ECG. In our trial, a total of 123 patients with successful fibrinolysis were evaluated with coronary angiography and most of them (77%) had TIMI 3 flow. However, correlation analysis revealed a significant positive correlation between MPV and inadequate reperfusion detected by TFC. Mean MPV was significantly higher in the inadequate reperfusion group.
Table 1
Characteristics of complete and inadequate reperfusion groups

<table>
<thead>
<tr>
<th>Demographic features and risk factors</th>
<th>Complete perfusion (TFC ≤ 40) n = 57</th>
<th>Incomplete perfusion (TFC &gt; 40) n = 66</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.6 ± 9.8</td>
<td>62 ± 11.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender n (%)</td>
<td>43 (75.4)</td>
<td>50 (75.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>9 (15.8)</td>
<td>15 (22.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>28 (49.1)</td>
<td>39 (59.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cigarette smoking n (%)</td>
<td>38 (66.7)</td>
<td>42 (63.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hyperlipidemia n (%)</td>
<td>15 (26.3)</td>
<td>16 (24.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>Family history n (%)</td>
<td>12 (21.1)</td>
<td>13 (19.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.1 ± 1.2</td>
<td>13.8 ± 1.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Platelet count (/mm^3*1000)</td>
<td>237.61 ± 56.22</td>
<td>265.62 ± 59.45</td>
<td>0.03</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>7.92 ± 0.80</td>
<td>8.93 ± 0.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Door to needle time and chest pain duration</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Door to needle time (minutes)</td>
<td>27.22 ± 8.15</td>
<td>26.24 ± 10.40</td>
<td>0.56</td>
</tr>
<tr>
<td>Chest pain duration (hours)</td>
<td>2.7 ± 1.3</td>
<td>3.0 ± 2.0</td>
<td>0.35</td>
</tr>
<tr>
<td>Angiographic features</td>
<td></td>
<td></td>
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<tr>
<td>LAD n (%)</td>
<td>28 (49.1)</td>
<td>30 (45.5)</td>
<td>0.781</td>
</tr>
<tr>
<td>LCX n (%)</td>
<td>7 (12.3)</td>
<td>11 (16.6)</td>
<td></td>
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<tr>
<td>RCA n (%)</td>
<td>22 (38.6)</td>
<td>25 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease n (%)</td>
<td>14 (24.6)</td>
<td>22 (33.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Mean TFC</td>
<td>31.5 ± 5.5</td>
<td>54.2 ± 12.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI 3 flow n (%)</td>
<td>57 (100)</td>
<td>38 (57.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

(MPV: mean platelet volume; TIMI: thrombolysis in myocardial infarction; TFC: TIMI frame count; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery)

than in the complete reperfusion group. Also, patients in the incomplete reperfusion group were significantly older. We found that age and MPV were indicators of poor coronary reperfusion after successful fibrinolytic therapy.

Our study has some limitations. First, this was a single-center study and included a relatively small numbers of patients. Second, it was a cross-sectional study, and thereby patients’ (short term and long term) follow-up data were not obtained. Finally, data of infarct size not identified by ECG or scintigraphy, which might have demonstrated the prognostic clinical benefits of the therapy, were not evaluated.

Conclusion

In the present study, higher MPV was found to be associated with worse antegrade coronary blood flow in STEMI patients treated with successful fibrinolysis. Platelets and their size play a major role in acute coronary syndrome pathogenesis, and they can interact with reperfusion in infarct-related arteries in these patients. Successful fibrinolysis does not always indicate adequate reperfusion. As a rapid, inexpensive and easily accessible method, MPV can be used to predict inadequate reperfusion in patients with STEMI and treated successfully with fibrinolytic therapy.
Figure 1
Correlation analysis of TIMI frame count and mean platelet volume ($r$: 0.461, $p < 0.001$)

Figure 2
ROC curve analysis for mean platelet volume (cutoff point: 8.3 fl). Area Under the Curve 0.702 (95% CI: 0.576-0.824)
Author contributions

Conception and design of the research: Arslan A, Kirimli O. Acquisition of data: Arslan A, Eyuboglu M, Senarslan O, Ekinici MA, Simsek MA. Analysis and interpretation of the data: Arslan A, Eyuboglu M, Senarslan O, Ekinici MA, Simsek MA, Kirimli O. Statistical analysis: Arslan A, Kirimli O. Writing of the manuscript: Arslan A. Critical revision of the manuscript for intellectual content: Arslan A, Eyuboglu M, Senarslan O, Ekinici MA, Simsek MA, Kirimli O.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Abdurrahman Arslan, from Dokuz Eylul University, School of Medicine.

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