Is Elevated Mean Platelet Volume Associated With a Worse Outcome in Patients With Acute Ischemic Cerebrovascular Events?

S. Greisenegger, MD; G. Endler, MD; K. Hsieh, MD; S. Tentschert, MD; C. Mannhalter, PhD; W. Lalouschek, MD, PhD

Background and Purpose—Increased mean platelet volume (MPV), indicating higher platelet reactivity, is associated with an increased risk of myocardial infarction. Higher levels of MPV have been found in patients with acute ischemic stroke than in control subjects. Data from smaller studies regarding an association between MPV and stroke severity and outcome have been controversial. If such an association exists, MPV might help to identify patients at increased risk of a severe course of acute cerebrovascular disease.

Methods—Within a multicenter, cross-sectional study nested in a cohort, we analyzed the relation between MPV and stroke severity as determined by the modified Rankin Scale after 1 week in 776 patients with acute ischemic stroke or transient ischemic attack. By multivariate logistic regression modeling, we determined the influence of MPV on stroke severity, adjusting for potential confounding factors.

Results—Patients within the highest quintile of MPV had a significantly higher risk of suffering a severe stroke, defined as modified Rankin Scale score of 3 to 6, compared with patients within the lowest quintile (odds ratio=2.6; 95% confidence interval, 1.6 to 4.1; P<0.001). This association remained significant after adjustment for possible confounding factors (odds ratio=2.2; 95% confidence interval, 1.2 to 4.0; P=0.013).

Conclusions—Our results indicate that an elevated MPV is associated with a worse outcome for acute ischemic cerebrovascular events independent of other clinical parameters. (Stroke. 2004;35:1688-1691.)

Key Words: stroke • platelets • stroke outcome

Platelets play a crucial role in the pathogenesis of atherosclerotic complications, contributing to thrombus formation or apposition after plaque rupture. Mean platelet volume (MPV) is a marker of platelet function, ie, large platelets contain more dense granules and produce more thromboxane A₂. Increased MPV has been associated with greater in vitro aggregation in response to ADP and collagen.

Elevated MPV levels have been identified as an independent risk factor for myocardial infarction in patients with coronary heart disease and for death or recurrent vascular events after myocardial infarction. Moreover, increased platelet size has been reported in patients with vascular risk factors such as diabetes, hypercholesterolemia, and smoking and in patients with renal artery stenosis. Previous studies have demonstrated higher levels of MPV in patients with acute ischemic stroke than in control subjects. In contrast, data regarding the association between MPV and stroke severity or stroke outcome have been controversial.

The aim of our study was to investigate whether MPV is associated with the severity and outcome of acute ischemic cerebrovascular events in a large white population of systematically documented patients.

Subjects and Methods

We performed a cross-sectional study nested in a prospective stroke registry of patients admitted to 8 neurological departments in Vienna, Austria. Patients with stroke or transient ischemic attack (TIA) who were admitted to 1 of the participating centers between October 1998 and June 2001 were prospectively documented. During that period, 2400 patients with an acute TIA/ischemic stroke were admitted to 1 of the participating centers. A total of 1078 patients from 3 centers in which MPV was not routinely determined were excluded. Of the remaining 1322 patients, MPV was determined in 846 cases (64%), whereas in the other 476 patients (36%), MPV was not determined on admission. The modified Rankin Scale (mRS) was available in 776 (92%) of those patients with an MPV value on admission. We compared patients with an MPV value on admission and patients without an MPV value on admission with respect to age, sex, and stroke severity, and we found no significant differences between these groups (ie, [1] we compared the patients with an MPV value on admission [n=846] with the entire other group [n=1554], including the patients from those departments in which an MPV was not determined, and [2] we compared the patients with an MPV value on admission [n=846]...
with the patients without an MPV value on admission from those departments in which MPV was eventually determined (n=476). The r2 score 1 week after the event of the patient group included in our study was classified as independent (score 0 to 2) or dependent/dead (score 3 to 6).

All patients underwent cranial CT or MRI, laboratory investigations for vascular risk factors, duplex sonography of the carotid and vertebral arteries, and a thorough cardiac investigation. Stroke etiology was classified according to predefined criteria into large-artery disease, small-vessel disease, cardioembolism, and undetermined.12

EDTA blood samples, drawn at admission, were analyzed by flow cytometry in automated hematology analysis systems (Sysmex 5000, Sysmex XE-2100, Sysmex SE 9500/SE 9000, Beckman Coulter GenS). The samples were processed within a maximum of 2 hours after venipuncture (in most cases within <1 hour). During the time between venipuncture and processing, the samples were stored at room temperature. The same blood tubes were used in all departments. Daily quality controls showed an intraassay coefficient of variation of 2.5% and interassay coefficient of variation of 3.0%.

Statistical Analysis
Statistical analyses were performed with the χ2 test for binary and categorical data and the Mann–Whitney U test for continuous variables. The severity of the cerebrovascular event was classified according to predefined criteria into large-artery disease, small-vessel disease, cardioembolism, and undetermined.12

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All patients had given informed consent to participate in the study. Permission for the study was obtained by the local ethics committees.

Results
Patients with a severe stroke were significantly older, were more often female, had a prior history of stroke or TIA more often, and showed a higher white blood cell count on admission than patients with a mild stroke. Furthermore, patients with mRS score 3 to 6 more often suffered atrial fibrillation and, probably as a consequence of this, cardioembolic stroke.

Three hundred seventy-seven (49%) of the 776 patients were taking antihypertensive drugs before admission; 210 (27%) were taking aspirin; 31 (4%) were taking clopidogrel; 12 (1.5%) were taking aspirin/extended-release dipyridamole; 37 (5%) were on oral anticoagulation; and 111 (14%) were taking lipid-lowering medication. There was no significant association between use of antiplatelet drugs before admission and stroke severity (Table 1).

We observed a slight but significant negative correlation between MPV on admission and stroke severity (r = −0.262, P < 0.001) and with blood glucose on admission (r = 0.125; P = 0.001). Platelet count was not significantly associated with stroke severity. Blood glucose levels on admission were available in only 711 of 776 patients. However, we also performed multivariate logistic regression including blood glucose levels, which did not influence the association between MPV on admission and stroke severity. We did not find significant correlations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mRS 0–2 (n=447)</th>
<th>mRS 3–6 (n=329)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>177 (40)</td>
<td>179 (54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, median (25/75 percentile), y</td>
<td>65 (56/75)</td>
<td>74 (63/81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>280 (63)</td>
<td>224 (68)</td>
<td>0.116</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>104 (23)</td>
<td>93 (28)</td>
<td>0.114</td>
</tr>
<tr>
<td>Current cigarette smoking, n (%)</td>
<td>140 (31)</td>
<td>58 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke/TIA, n (%)</td>
<td>63 (14)</td>
<td>64 (20)</td>
<td>0.046</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>126 (28)</td>
<td>102 (31)</td>
<td>0.395</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>219 (49)</td>
<td>126 (38)</td>
<td>0.003</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>64 (14)</td>
<td>111 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocyte count, median (25/75 percentile), G/L</td>
<td>7.9 (6.5/9.6)</td>
<td>8.4 (6.9/10.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Platelet count, median (25/75 percentile), G/L</td>
<td>222 (186/266)</td>
<td>218 (181/260)</td>
<td>0.371</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>51 (11)</td>
<td>34 (10)</td>
<td>0.636</td>
</tr>
<tr>
<td>Antiaggregant before index event, n (%)</td>
<td>145 (32)</td>
<td>110 (33)</td>
<td>0.770</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>7 (1.6)</td>
<td>15 (4.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery disease</td>
<td>57 (13)</td>
<td>62 (19)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>104 (23)</td>
<td>128 (39)</td>
<td></td>
</tr>
<tr>
<td>Small-artery disease</td>
<td>126 (28)</td>
<td>54 (16)</td>
<td></td>
</tr>
<tr>
<td>No determined etiology</td>
<td>160 (36)</td>
<td>85 (26)</td>
<td></td>
</tr>
</tbody>
</table>

Categorical variables were analyzed by χ2 test; continuous variables were analyzed by Mann–Whitney U test.
between MPV on admission and serum cholesterol, triglyceride, serum creatinine, sodium, potassium, leukocyte count, and C-reactive protein levels on admission.

Patients with a severe stroke had significantly more often MPV on admission in the highest quintile (Table 2; \( P=0.002 \)). Compared with patients with MPV in the lowest quintile, those within the highest quintile had a 2.6-times unadjusted risk of suffering a severe stroke (95% CI, 1.6 to 4.1; \( P<0.001 \)).

After we controlled for all factors associated with stroke severity (\( P<0.2 \)) in the logistic regression model, the association between MPV in the highest quintile and a worse outcome was still significant (Table 3).

The MPV values in the department with the Coulter analyzer (n=132) were significantly lower than those in the other departments (n=644). Therefore, we adjusted for different departments in the multivariate analysis, which had no effect on the association between MPV and stroke severity (Table 3). Adjustment with regard to the MPV measurement method gave similar results. To further confirm our results, we also performed an analysis with method-specific MPV quintiles, which gave similar and significant results with regard to the association between MPV and stroke severity.

We also sought to determine a possible association between MPV and outcome 3 months after the event. However, the mRS after 3 months was available in only 455 of the 776 patients (59%). After we controlled for age and sex, MPV was associated with a worse outcome (mRS score 3 to 6) in this subgroup of patients in a logistic regression model (odds ratio=2.2; 95% CI, 1.2 to 4.5; \( P=0.001 \)).

<table>
<thead>
<tr>
<th>MPV Quintiles</th>
<th>mRS 0–2 (n=447)</th>
<th>mRS 3–6 (n=329)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6.7–9.2 fl)</td>
<td>113 (25%)</td>
<td>48 (15%)</td>
<td></td>
</tr>
<tr>
<td>2 (9.3–9.9 fl)</td>
<td>79 (18%)</td>
<td>61 (19%)</td>
<td></td>
</tr>
<tr>
<td>3 (10.0–10.6 fl)</td>
<td>99 (22%)</td>
<td>76 (23%)</td>
<td>0.002</td>
</tr>
<tr>
<td>4 (10.7–11.2 fl)</td>
<td>85 (19%)</td>
<td>66 (20%)</td>
<td></td>
</tr>
<tr>
<td>5 (11.3–15.3 fl)</td>
<td>71 (16%)</td>
<td>78 (24%)</td>
<td></td>
</tr>
</tbody>
</table>

*\( \chi^2 \) test.

Table 2. Association Between MPV and Stroke Severity According to mRS Score 1 Week After Admission

In this study increased MPV was associated with a worse outcome in patients suffering an acute ischemic cerebrovascular event. Patients within the highest quintile of MPV had a >2-fold risk of suffering a severe stroke compared with patients within the lowest quintile. The association of high MPV with severe stroke remained significant after adjustment for confounding factors.

Currently available studies report controversial results regarding MPV and stroke outcome. Recently, Butterworth and Bath11 described increased platelet size in patients with worse stroke outcome after 3 months, whereas 2 earlier studies9,10 did not find any significant relation between MPV and stroke outcome. Possible reasons for these divergent results could be small numbers of patients and the use of different outcome measures in these studies.

One might argue that increased MPV and higher platelet reactivity simply reflect a marker for a more severe stroke event and a more pronounced acute-phase reaction. In the Vienna Stroke Registry, only patients who were submitted to the center a maximum of 72 hours after symptom onset were included. For the present data we included only patients whose MPV was determined on admission. Given the average life span of a platelet of 8 days,2,10 it is unlikely that the platelet size at the time of measurement was affected by the acute vascular event. More likely, our results suggest that patients who then suffered a severe stroke already had an increased MPV, reflecting higher platelet reactivity, before the stroke occurred.

Platelet size is determined at the level of the progenitor cell (ie, the megakaryocyte), and recent studies reported that cytokines such as interleukin-3 or interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets.5,14,15 It is therefore reasonable to speculate that a proinflammatory state before the cerebrovascular event may confer a higher MPV and a prothrombotic condition.

Previous studies reported that MPV values increase because of platelet swelling when EDTA is used as anticoagulant;6,17 however, a recent study demonstrated that this increase of platelet size amounts to approximately <0.5 fl when the analysis is performed within 2 hours after venipuncture.5 Probably the reported platelet swelling in EDTA was due to different amounts of EDTA in the blood tubes. In our study every participating hospital used the same standardized blood tubes, and all blood samples were analyzed within 2 hours after blood sampling.

Little is known about effects of various drugs on platelet size. Previous in vitro studies found no effect of aspirin on platelet size.18,19 However, it was shown that clopidogrel significantly inhibits the ADP-induced increase in MPV in vitro.20 Clinical data on a possible association of MPV with various platelet inhibitors in patients do not exist. Furthermore, previous studies reported effects of losartan,21 doxazosin,22 and lipid-lowering drugs23 on platelet size in vitro. Interestingly, in our study patients with prior aspirin medication had significantly higher MPV values, possibly because of a higher vascular premorbidity (data not shown). Unfortunately, there were too few patients treated with other prior

Discussion

\[ \text{Univariate and Multivariate}^* \text{ Analysis of Association Between MPV and Stroke Severity According to mRS Score 1 Week After Admission} \]

\[ \begin{array}{llllll}
\text{MPV Quintiles} & \text{Univariate} & \text{Multivariate} \\
               & \text{OR (95% CI)} & \text{OR (95% CI)} & \text{P} & \text{OR (95% CI)} & \text{P} \\
1† (6.7–9.2 fl) & 1 & — & 1 & — & 1 & — \text{Reference category.} \\
2 (9.3–9.9 fl) & 1.8 (1.1–2.9) & 0.014 & 1.5 (0.8–2.6) & 0.173 \\
3 (10.0–10.6 fl) & 1.8 (1.2–2.8) & 0.010 & 1.5 (0.8–2.6) & 0.181 \\
4 (10.7–11.2 fl) & 1.8 (1.2–2.9) & 0.011 & 1.5 (0.8–2.8) & 0.156 \\
5 (11.3–15.3 fl) & 2.6 (1.6–4.1) & <0.001 & 2.2 (1.2–4.0) & 0.013 \\
\end{array} \]

*Adjusted for sex, age (quintiles), diabetes, hypertension, smoking, atrial fibrillation, hyperlipidemia, etiology, leukocyte count (quintiles), previous stroke/TIA, thrombolysis, and participating stroke center.
antiplatelet medications to achieve sufficient statistical power for a meaningful analysis. Whether patients with an increased MPV represent a subgroup with a particularly high risk of cerebrovascular events and whether targeted interventions with platelet inhibitors or other drugs, such as antihypertensives or lipid-lowering agents, might be beneficial in such patients remains to be evaluated.

We describe for the first time a relation between MPV and clinical severity of acute ischemic cerebrovascular events using a validated outcome scale in a large, multicenter evaluation. Measurement of MPV is easy to establish and therefore might serve as a valuable predictor of a worse outcome in patients with acute ischemic cerebrovascular events. Prospective studies investigating the effects of various drugs, including non-antiplatelet drugs (eg, statins, angiotensin II antagonists), in acute stroke on platelet size and reactivity and treatment effect should follow.

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