The role of immature platelet fraction in acute coronary syndrome

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Dear Sir,

Activated platelets play a crucial role in the pathogenesis of acute coronary syndrome (ACS) (1), and platelet size can be a determinant of platelet function. Thus, large platelets are metabolically more active than small platelets and have greater pro-thrombotic potential (2). However, the clinical influence of platelet size, measured as mean platelet volume (MPV), is controversial (3–6).

An alternative to MPV measurement is the analysis of immature platelet fraction (IPF). Newly formed platelets can be distinguished from mature platelets that are poor in RNA by flow cytometric quantification using fluorescent dyes that bind RNA (7). However, this method produces high intra-assay reproducibility coefficients of variation (8) and requires specialist personnel to perform it.

A new, rapid and fully automated method for the measurement of reticulated platelets, expressed as the immature platelet fraction (IPF), using the Sysmex XE-2100 blood cell counter has been under development. Recently, Grove et al showed the importance of IPF and both MPV and age were detected. Furthermore, IPF showed a significant negative correlation with platelet count (9), although further studies were required. Therefore, the aim of this study is to examine the relationship between IPF and ACS in a case-control study.

A total of 404 individuals were enrolled in the study. A total of 202 patients with a documented first episode of ACS were prospectively recruited upon admission to the Coronary Unit. The diagnosis of ACS included ST segment elevation myocardial infarction (STEMI, n = 129) and non-ST segment elevation ACS (NST ACS, n = 73). The latter group included non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) patients. Diagnosis of STEMI, NSTEMI and UA was made according to the new ESC/ACC consensus definition (10). The control group for our study included 202 unrelated healthy persons without a history of vascular or thromboembolic disease and a normal electrocardiogram. All subjects gave their informed consent to enter the study.

Blood was collected from the antecubital vein at 08:00 a.m. on day 1 or 2 after admission. IPF was calculated as the ratio of immature platelets to the total number of platelets in a fully automated haematology analysis system (Sysmex XE-2100; Sysmex, Kobe, Japan), as described previously (11). Chi² contingency tests were used to examine associations between categorical variables and continuous data were checked for normality of distribution and subsequently analyzed as appropriate using unpaired t-tests (normally distributed data) or Mann-Whitney tests (non-normally distributed data). Adjustments for well-known cardiovascular risk factors (CVRFs) were made by developing logistic regression models. A level of p < 0.05 was considered significant for all tests.

The study cohort demographics are shown in Table 1. The average coefficient of variation for IPF (10 consecutive analyses) in 10 samples from healthy subjects was 8.9%. ACS cases had a significantly higher IPF level than age- and sex-matched controls (median ± interquartile range, 5.1 ± 4.3% vs. 3.9 ± 3.2%, p < 0.001) (Fig. 1). After adjustment for the established CVRFs the difference in IPF between ACS and controls remained significant (p = 0.01). In addition, the elevated IPF levels were more apparent for ACS patients with STEMI cases than those who had an NSTEMI ACS (5.5 ± 4.7% vs. 4.6 ± 3%, respectively: univariate analysis, p = 0.011; multivariate analysis, p = 0.004).

We also investigated the associations of IPF with haematological parameters and conventional CVRFs in the whole group. Significant positive correlations between IPF and both MPV and age were detected. Furthermore, IPF showed a significant negative correlation with platelet count.

Table 1. Characteristics of subject controls and patients. SD, standard deviation; NSTE ACS, non-ST segment elevation acute coronary syndrome; ACS, acute coronary syndrome. Values in parentheses are percentages.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 202)</th>
<th>NSTE ACS (n = 73)</th>
<th>STEMI (n = 129)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>67.5 ± 11.3</td>
<td>68.28 ± 12.6</td>
<td>66.7 ± 12.4</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151 (74.8)</td>
<td>58 (79.5)</td>
<td>93 (72.1)</td>
<td>0.512</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (13.4)</td>
<td>18 (24.7)</td>
<td>26 (20.2)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67 (32.2)</td>
<td>40 (54.8)</td>
<td>66 (51.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>25 (12.3)</td>
<td>17 (23.3)</td>
<td>27 (20.9)</td>
<td>0.039</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>6 (2.9)</td>
<td>9 (12.3)</td>
<td>17 (13.2)</td>
<td>0.096</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22 (10.9)</td>
<td>18 (24.7)</td>
<td>32 (24.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet count (x10⁹/l) mean ± SD</td>
<td>212.6 ± 60</td>
<td>193.9 ± 52</td>
<td>183.3 ± 59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean platelet volume (fl) mean ± SD</td>
<td>10.7 ± 0.8</td>
<td>11 ± 0.8</td>
<td>11.1 ± 0.9</td>
<td>0.012</td>
</tr>
</tbody>
</table>

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Received: February 25, 2009
Accepted after major revision: October 8, 2009
Prepublished online: November 13, 2009
doi:10.1160/TH09-02-0124
Thromb Haemost 2010; 103: 247–249

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Thrombosis and Haemostasis 103.1/2010
and haemoglobin levels. By contrast, IPF was not statistically associated with sex, hypertension, hypercholesterolaemia, hypertriglyceridaemia, diabetes or smoking.

Our results show that IPF levels are associated with ACS and are consistent with two previous case-control studies of arterial thrombosis (12–13). Nevertheless these two studies were based on a flow cytometry analysis with poor reproducibility. The current results parallel the recent report by Grove et al., in which IPF measured with the Sysmex XE-2100 was significantly higher in patients with ACS, especially in STEMI (9), which would support its implementation in routine clinical practice. In addition, our age- and sex-matched case control reduced the potential bias arising from these confounders.

There is an association between IPF and the presence of ACS. The higher IPF in ACS patients suggests the consumption of platelets and a compensatory production of larger reticulated platelets in the bone marrow (14–15). However, the role of IPF in the diagnosis and prognosis of ACS is not well established. To propose a high IPF as a criterion for making a diagnosis of ACS cannot be recommended. According to our results, the sensitivity curves and specificity of high IPF (7%) for discriminating between controls and patients are very limited. However, the effect of high IPF on prognosis in terms of rethrombosis is much more promising. Immature platelets are hyperreactive, prothrombotic and associated with the diminished antiplatelet effects of aspirin (16–18).

In conclusion, IPF values measured with the Sysmex XE-2100 are higher among patients with a first episode of ACS than in controls. Prospective studies to evaluate the predictive value of IPF and the potential benefit of antithrombotic prophylaxis in these patients are warranted.

Acknowledgement
We would like to thank Phil Mason and the Hemostasis & Thrombosis Unit and the Coronary Unit Staff for their excellent technical assistance.

References