The central role of platelet activation in determining the severity of acute coronary syndromes

S Kennon, C P Price, P G Mills, M Macey, J Cooper, H Clarke, A D Timmis

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Recent observational studies in acute coronary syndromes have shown that factors influencing the degree of platelet activation also influence the mode of presentation. Prior aspirin treatment and smoking—with directionally opposite effects on platelet function—were found to be independently associated with unstable angina and myocardial infarction, respectively. However, the few studies involving direct measurement of activation parameters in acute coronary syndromes have not provided a consensus regarding this. To clarify whether there is differential activation in unstable angina and acute myocardial infarction we have prospectively assessed platelet activation in a cohort of patients presenting with acute coronary syndromes by using a light scattering technology to determine mean platelet component, a marker of platelet degranulation.

METHODS

Consecutive patients admitted to an east London hospital with acute coronary syndromes were recruited. Myocardial infarction was diagnosed if two of the following criteria were fulfilled: (a) cardiac chest pain lasting at least 30 minutes; (b) >0.1 mV ST elevation in at least one standard lead or >0.2 mV ST elevation in two or more contiguous chest leads; and (c) creatine kinase concentration >400 IU/l (upper limit of reference range 200 IU/l). ECG criteria were not required for the diagnosis of unstable angina; however, patients were recruited only if they fulfilled criteria for Braunwald class 3B unstable angina. Patients admitted with acute coronary syndromes within the previous 21 days were excluded, as were those who had undergone percutaneous coronary intervention in the previous six months. Blood was taken on admission—before antithrombotic treatment—for platelet activation status (mean platelet component) and troponin I determination.

Whole blood samples were taken into vacutainers (Becton Dickinson) containing EDTA. Samples were analysed, between 30–240 minutes after venesection, for determination of mean platelet component with the ADVIA 120 haematology system (Bayer Corporation, Tarrytown, New York, USA). Troponin I concentrations were measured with a commercially available assay (Bayer Immuno 1 Analyser, Bayer Plc, UK) and a cut off point of 0.1 µg/l.

Variables significant (p ≤ 0.05) on univariate analysis were selected for testing in a stepwise multiple logistic regression model. In view of the relatively small sample size exact logistic regression analysis was used to check the ordinary analysis.

RESULTS

The study group comprised 89 patients, 25 with acute myocardial infarction and 64 with unstable angina. The groups were similar as regards age and sex distribution. A previous history of acute coronary syndromes or revascularisation was recorded more commonly in patients with unstable angina whose admission medication was significantly more likely to include drugs for secondary prevention. Pretreatment with aspirin was less frequent and smoking more frequent in acute myocardial infarction than in unstable angina (table 1). Mean (SD) platelet component was lower in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Univariate predictors of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Unstable angina</td>
</tr>
<tr>
<td></td>
<td>(n=64)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.5 (12.6)</td>
</tr>
<tr>
<td>Men</td>
<td>50 (78.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (14.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (48.4%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (28.1%)</td>
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<tr>
<td>Family history</td>
<td>19 (29.7%)</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>44 (68.8%)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.40 (1.40)</td>
</tr>
<tr>
<td>Glucose* (mmol/l)</td>
<td>1.84 (0.32)</td>
</tr>
<tr>
<td>Creatinine* (µmol/l)</td>
<td>4.73 (0.29)</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
</tr>
<tr>
<td>Mean platelet volume (fL)</td>
<td>9.1 (1.2)</td>
</tr>
<tr>
<td>Mean platelet count (&lt;10^12/l)</td>
<td>242.3 (66.7)</td>
</tr>
<tr>
<td>MPC (g/l)</td>
<td>258.6 (1.38)</td>
</tr>
<tr>
<td>Admission medication</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>44 (68.8%)</td>
</tr>
<tr>
<td>β Blocker</td>
<td>26 (40.6%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>18 (28.6%)</td>
</tr>
<tr>
<td>Statin</td>
<td>26 (40.6%)</td>
</tr>
</tbody>
</table>

Data are numbers (%) except for continuous variables where data are mean (SD).

*Glucose and creatinine are log transformed.

ACE, angiotensin converting enzyme; MPC, mean platelet component.
acute myocardial infarction than in unstable angina (246.7
(15.8) v 258.6 (13.8) g/l, p = 0.001), reflecting significantly
greater platelet activation. This difference persisted when the
unstable angina cohort was limited to 48 patients at high risk
of future cardiac events defined by troponin I concentration
> 0.1 µg/l or ischaemic ST/T changes on the presenting ECG
(246.7 (15.8) v 258.1 (14.4) g/l, p = 0.016).

In logistic regression analysis, the odds of presenting with
acute myocardial infarction were reduced by 91% (odds ratio
(OR) 0.09, 95% confidence interval (CI) 0.02 to 0.32,
p < 0.0001) by pretreatment with aspirin and by 64% (OR
0.36, 95% CI 0.18 to 0.72, p = 0.004) for an increase in mean
platelet component by one standard deviation. A history of
acute myocardial infarction was reduced by 91% (odds ratio
(OR) 0.26, 95% CI 0.06 to 1.02, p = 0.05), was the
only other variable with independent predictive power. The
exact logistic regression for the model gave similar results
though the effect of hypertension was weaker (data not
shown). If the time between venesection and analysis of blood
was forced into the logistic regression analysis, mean platelet
component remained a significant predictor of clinical
presentation (OR 0.48, 95% CI 0.27 to 0.86, p = 0.01).

DISCUSSION
Our finding that mean platelet component is lower in acute
myocardial infarction than in unstable angina, reflecting
greater platelet activation, confirms the central role of throm-
bogenicity in the pathogenesis of acute coronary syndromes.
Indeed, platelet activation was an independent predictor of
the mode of presentation and, even in the subgroup of
patients with unstable angina at high risk of future events,
platelet activation was significantly lower in those with
myocardial infarction.

Some studies have not found a difference in platelet activa-
tion between unstable angina and myocardial infarction.
However, Garlichs and colleagues’ found greater expression of
the CD40 ligand in unstable angina than in myocardial infarct-
 This appears counterintuitive but may reflect greater
hydrolysis and release of the ligand in myocardial infarction.
Mathur and colleagues’ found a greater expression of P selec-
tin in myocardial infarction than in unstable angina but also
found that mean platelet volume, which is directly related to
platelet activity, was greater in unstable angina than in
myocardial infarction. Fundamental differences in platelet biology
between patients with unstable angina and those with
myocardial infarction were proposed as an explanation for
these findings because platelets are anucleate and their size
is predetermined at the time of thrombopoiesis. In the
 current study platelets were larger in those with acute myocardial
infarction than in those with unstable angina. However, this dif-
ference was not significant, and it is unclear whether the
diagnosis specific differences in mean platelet component
were predetermined or reactive. Studies in apparently healthy
volunteers have shown greater platelet activation in those
with a strong family history of coronary artery disease’ and in
those who subsequently die from cardiac causes.¹ This is con-
sistent with the degree of platelet activation being causally
related to outcome. Certainly, we identified no factors that
accounted for the differences in platelet activation that were
independent of smoking habit and pretreatment with cardiac
drugs that are known to influence platelet function.

Mean platelet component, as determined by the ADVIA 120
haematology system, is derived by using a laser source and
light scattering technology. It reflects the granularity of plate-
lets and is inversely related to the expression of CD62P.
Because the assay measures granularity, it has the advantage
over standard flow cytometric techniques of avoiding the need
for sample preparation with antisera, which is complex, time
consuming, expensive, and a source of error.

This study has shown diagnosis specific differences in
platelet activation in acute coronary syndromes. The data
therefore provide direct evidence to support the hypothesis
that platelet activation at the time of plaque disruption is a
major determinant of clinical presentation.

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