Altered CD18 leucocyte integrin expression and adhesive function in patients with an acute coronary syndrome

The adhesion of leucocytes to vascular endothelium is fundamental to the pathogenesis of atherothrombosis and the acute coronary syndromes. CD11b/CD18 receptor is particularly important in this process. This molecule is expressed on both neutrophils and monocytes. In common with other integrin receptors it consists of α and β subunits (CD11b and CD18, respectively), which allow binding of leucocytes to the endothelial surface.

The aims of our study were: (1) to compare the expression of CD11b and CD18 on peripheral neutrophils and monocytes in patients with an acute coronary syndrome, patients with stable coronary artery disease, and healthy controls; and (2) to assess any functional change in neutrophil adhesion in the acute coronary syndrome.

Twenty-two consecutive patients with an acute coronary syndrome were studied. None had received thrombolytics or glycoprotein IIb/IIIa inhibitors and none had undergone coronary revascularisation. All were on maintenance aspirin (n = 19) or had received >12 hours of such treatment in hospital (n = 3). Twelve patients with stable coronary artery disease were also studied. All had a >50% stenosis of at least one major coronary artery, had stable cardiac symptoms over the past six months, and were taking maintenance aspirin. The third group consisted of 12 healthy volunteers with no cardiac history or symptoms. These subjects were asked to take aspirin for three days before blood sampling. None of the patients or volunteers studied had conditions known to affect leucocyte adhesion molecule expression or function. Cell surface expression of the CD11b and CD18 subunits was determined by flow cytometry. Functional changes in neutrophil adhesion were assessed using a well validated technique that relies on their ability to adhere to nylon columns. The assay determines percentage neutrophil adherence, with 98% of this adhesion mediated by CD18. In our laboratory it has a coefficient of variation of 5.4%.

Table 1 CD18 and CD11b expression on leucocytes plus percentage neutrophil adhesion in patients with an acute coronary syndrome (with and without concurrent cardiac troponin I concentrations > 0.1 ng/ml), patients with stable coronary artery disease, and healthy controls

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Monocytes</th>
<th>CD11b</th>
<th>CD18</th>
<th>CD11b</th>
<th>CD18</th>
<th>% Neutrophil adhesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome (n=22)</td>
<td>4.02 (0.45)</td>
<td>1.89 (0.19)*</td>
<td>5.74 (0.57)*</td>
<td>4.92 (0.41)‡</td>
<td>9.5 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Positive cTnI (n=10)</td>
<td>4.34 (0.73)</td>
<td>2.01 (0.29)</td>
<td>6.45 (0.80)</td>
<td>5.17 (0.62)</td>
<td>8.7 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Negative cTnI (n=12)</td>
<td>3.76 (0.58)</td>
<td>1.49 (0.20)</td>
<td>5.15 (0.80)</td>
<td>4.71 (0.57)</td>
<td>10.3 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Stable coronary artery disease (n=12)</td>
<td>2.83 (0.32)</td>
<td>1.64 (0.17)</td>
<td>3.33 (0.27)</td>
<td>3.72 (0.27)</td>
<td>15.3 (2.1)‡</td>
<td></td>
</tr>
<tr>
<td>Healthy controls (n=12)</td>
<td>3.43 (0.32)</td>
<td>1.20 (0.15)</td>
<td>3.77 (0.27)</td>
<td>3.08 (0.25)</td>
<td>15.5 (2.5)§</td>
<td></td>
</tr>
</tbody>
</table>

Results expressed as mean (SEM) fluorescence intensity.

*p < 0.05 v healthy controls; †p < 0.01 v healthy controls; ‡p < 0.01 v acute coronary syndrome; §p < 0.05 v acute coronary syndrome.

Results are presented as mean (SE) unless otherwise stated. Kruskal–Wallis and Mann–Whitney U tests were used to compare groups, with a double sided p value < 0.05 considered significant.

Among the 22 patients with an acute coronary syndrome the mean duration of symptoms before blood sampling was 15.4 (2.2, range 1–36) hours. Fourteen patients were ultimately diagnosed as having unstable angina, five had a non-Q wave myocardial infarction, and three sustained a Q wave myocardial infarction.

Expression of CD11b and CD18 was similar on neutrophils and monocytes from patients with stable coronary artery disease and healthy controls (table 1). However, monocytes from patients with an acute coronary syndrome had higher expression of CD11b and CD18. Neutrophil CD18 expression was also higher in unstable patients, when compared with healthy controls, through neutrophil adhesion (table 1). There was no difference in CD18 mediated neutrophil adhesion in healthy subjects and patients with stable coronary artery disease (table 1). In contrast, CD18 mediated neutrophil adhesion was lower among patients with an acute coronary syndrome than either of these control populations. Neutrophil adhesion was lowest among patients with an acute coronary syndrome who had evidence of myocardial damage at the time of blood sampling (concurrent cTnI concentrations > 0.1 ng/ml). Conversely, the expression of CD11b and CD18 was highest among patients with positive cTnI. The numbers in these subgroups are, however, small.

Patients with an acute coronary syndrome in whom cTnI is negative lie between those with stable symptoms (who have lower CD11b and CD18 expression but greater CD18 mediated neutrophil adhesion) and patients with positive cTnI (who have higher cell surface expression of CD11b and CD18 but reduced neutrophil adhesion). This trend is particularly pronounced in the case of CD11b expression by monocytes (p < 0.01), and to a lesser extent for CD18 mediated neutrophil adhesion (p = 0.06) and expression of this molecule by monocytes (p = 0.07).

This small study provides further evidence for our findings.

In addition to the small sample size, the current study has several limitations. Aspirin reduces the adherence of neutrophils and lymphocytes, and we therefore controlled for such treatment. It is, however, uncertain what influence other agents might have on CD18 expression and function. Similarly, patients with an acute coronary syndrome had a higher prevalence of cardiovascular risk factors and this could represent an alternative explanation for our findings.

In conclusion, the current study reports increased CD11b/CD18 expression on leucocytes from patients with acute coronary syndrome. This is associated with reduced CD18 mediated neutrophil adhesion in vitro. Further work is required to clarify the reasons for this paradox and to assess whether the observed changes in leucocyte CD18 biology represent a cause or an effect of the event.

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Progressive ECG changes before the onset of atrial flutter in adult congenital heart disease patients

Atrial flutter is a frequent complication in patients with adult congenital heart disease either during natural history or after surgical repair. 1 The incidence of such an arrhythmia increases postoperatively with time and is usually associated with complex atrial surgery. 1 When it occurs, atrial flutter compromises haemodynamics, reduces exercise tolerance, and is often resistant to medical treatment. The P wave has been found to change its electrical characteristics before atrial fibrillation supervenes in patients with coronary artery disease. 2 We sought to study the same hypothesis in 39 adult congenital heart disease patients, 31% of them with Mustard or Fontan surgery, who developed atrial flutter long after surgical repair, and compare them with 30 diagnosis matched controls who had never developed atrial arrhythmias. All the patients studied had undergone at least three consecutive annual ECG recordings before the onset of flutter, which were compared with those recorded similarly over the three years in controls. P wave amplitude and duration were measured using an electronic “digimetric” caliper (Mitutoya) and a magnifier to confirm reproducibility.

We studied 39 patients with complex congenital heart disease following loss of atrioventricular synchrony and inductively coupled plasma atomic emission spectroscopy (ICP-MS; VG Elemental PlasmaQuad II Turbo+) and inductively coupled plasma atomic emission spectroscopy (ICP-AES; Spectro-Flame–BOP) after pressure dissolution of the coil with HF, HNO₃, H₂O₂, HCIO₃ at 37–200°C and by use of wavelength dispersive x ray spectrometry (WDS). To avoid interference with surface contaminants, the coils were embedded in a conductive embedding medium and ground to achieve representative cross sections.

Coil embolisation has been the standard technique for occlusion of pathologic vessels, aneurysms, and fistulae for more than three decades. Tungsten is an attractive material for use as an endovascular coil, because of its high radiopacity and thrombogenicity. 7 Recently, decreasing radiopacity has been reported in patients after implantation of tungsten coils (MDS, Balt).
In 21 patients who received tungsten coils a mean follow up of 97 months (two days to 38 years) was achieved. Fluoroscopy performed in 14/21 patients revealed a decreased radiopacity in 9/14 patients (fig 1). Repeat angiography performed in 7/21 patients demonstrated recanalisation of 1–4 of the previously MDS occluded vessels in 5/7 patients; in all patients with recanalised vessels a decreased radiopacity of the coils was observed. Serum concentrations for tungsten were greatly increased in 8/8 patients, ranging from 2.0 µg/l to 14.4 µg/l (mean 6.43 µg/l, normal value < 0.2 µg/l). No unexplained clinical symptoms were reported (mean 6.43 µg/l, normal value < 0.2 µg/l). No unexplained clinical symptoms were reported during follow up examination. The MDS coils we examined are produced from > 99.9 mas.% tungsten.

Dissolution and device failure of a “permanent” medical implant caused by recanalisation of a previously occluded vessel can occur along with raised serum concentrations of the degradation products. It may be speculated that minimal residual shunting was present in our patients early after coil implantation, thereby accelerating the degradation of tungsten by keeping the pH at a level > 7.4. However, no adverse clinical effects were identified during follow up of the patients. Although there are no reports published on toxicity or unexplained clinical symptoms in patients receiving tungsten coils, there is a lack of concise data on the toxicity and clearance of tungsten in humans. Our own analysis shows that MDS coils are produced from pure tungsten (> 99.9 mas.%). We assume that the analysis performed by others was undertaken with an energy dispersive x ray spectrometer (EDX) and the deviation may be caused by incidental superposition of the energy of ultimate and subordinate lines; adequate results can only be obtained with a wavelength dispersive spectrometer because of its superior specificity.

We conclude that tungsten coils can dissolve leading to implant failure and greatly increased serum tungsten concentrations. The clinical use of these coils can no longer be recommended. Although there is lack of evidence for in vitro or in vivo toxicity of tungsten, patients with MDS coils should be followed thoroughly with tests for serum tungsten, patients with MDS coils should be followed thoroughly with tests for serum tungsten concentrations, and liver and renal function. Repeat angiography may be warranted if decreased radiopacity is observed.