Interleukin 18 in acute myocardial infarction

Interleukin 18 (IL-18), which is a recently cloned cytokine synthesised by Kupffer cells, has been shown to activate macrophages. Macrophages and T cells have been reported to be activated in patients with acute myocardial infarction (MI). IL-18 is postulated to play a role in the development of myocardial dysfunction through activation of immune cells. However, the circulating concentration of IL-18 has not been reported in patients with acute MI.

To elucidate the changes in the release of IL-18 in patients with coronary artery disease, we examined the correlation between IL-18 concentrations and the serum activities of myocardial enzymes, estimating myocardial necrosis or atrial natriuretic peptide (ANP). Our goal was to determine whether measurement of IL-18 could be used as a new indicator of myocardial damage in patients with acute MI.

We evaluated 24 patients with acute MI (19 men and five women aged 39–79 years). Patients diagnosed with acute MI had to have been admitted within six hours of the onset of symptoms. The diagnosis of acute MI was based on the presence of typical chest pain which persisted for at least 30 minutes, ST segment elevations > 0.2 mV in at least two contiguous leads, and an increase in serum creatine kinase activity to twice the upper limit of normal (> 250 IU/L). The diagnosis of congestive heart failure was based on a history of dyspnoea and symptomatic exercise intolerance with signs of pulmonary congestion or peripheral oedema at clinical examination, and following usual investigations. As a control group, we included 12 age and sex-matched patients who had no evidence of coronary stenosis or coronary spasm on coronary angiography. No patient had evidence of septicaemia, collagen vascular disease, advanced liver disease, renal failure, malignancy or infectious disease.

Blood was sampled immediately after admission and at 1, 2, 3, 6, and 9 hours after admission and then every 12 hours until five days after admission. Blood was drawn from the antecubital vein into silicone tubes (4.5 ml of blood and 0.5 ml of 0.13 M sodium citrate), and centrifuged for 15 minutes at 1600 g at 4°C. The plasma was stored at −80 °C.

Exercise-induced myocardial ischaemia does not cause increase in C-reactive protein concentration

High plasma concentrations of C-reactive protein (CRP), which are predictive of a poor prognosis in patients with acute coronary syndromes, might reflect an inflammatory pathogenic component to ischaemia. However, however, that short periods of ischaemia are powerful inflammatory stimuli sufficient to induce the synthesis of acute phase reactants. Therefore, the acute phase response in acute coronary syndrome may reflect the extent and severity of myocardial ischaemia. To establish whether myocardial ischaemia is an adequate stimulus to induce an increase in CRP, its plasma concentrations were evaluated in a group of patients with chronic stable angina and normal baseline values of CRP in whom myocardial ischaemia was induced by exercise.

Fifteen patients (10 men, mean (SD) age 60 (9) years) with chronic stable angina and reproducible positive exercise testing for myocardial ischaemia participated in this study. No patient had suffered a previous myocardial infarction and mean left ventricular ejection fraction was 62 (5)%. All patients had at least one critical stenosis in the proximal two thirds of one major epicardial coronary artery. The control group consisted of nine healthy subjects (six men, mean (SD) age 61 (9) years) without evidence of ischaemic heart disease and normal physical examination, rest ECG, and echocardiogram. After pharmacological washout, treadmill exercise testing was performed following the Bruce protocol. The level of the ST segment, 80 ms after the J point, was calculated after signal averaging by means of a computer analysed system in all 12 leads.

For CRP, venous blood samples were obtained immediately before (T0), at the end of the exercise test (T1), and 6 (T2), 24 (T3), and 48 (T4) hours after the exercise test. CRP concentration was immunologically determined by immunoturbidimetric method (Roche Unimate 3 CRP, Milan, Italy). The normal upper reference value for CRP with this method is up to 5 mg/L. Data on CRP are expressed as median values and interquartile ranges and were analysed by using two way analysis of variance (ANOVA) for repeated measures. Differences between groups were considered to be significant at a probability value of p < 0.05.

All patients with chronic stable angina had positive exercise tests and reached ST segment depression > 0.2 mm with a mean (SD) value of 2.9 (0.3) mm at 80 (13)% of the predicted heart rate. Ten patients complained of typical chest pain during exercise testing. All controls had negative exercise test and none experienced chest pain. The mean value of ST segment depression was 0.53 (0.18) at 96 (3)% of the predicted heart rate.

### Table 1

<table>
<thead>
<tr>
<th>Marker</th>
<th>Initial rise (hours)</th>
<th>Maximal rise (hours)</th>
<th>Maximal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-18</td>
<td>2.2 (0.9)</td>
<td>13 (8)</td>
<td>82 (17) pg/ml</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>4.2 (1.2)</td>
<td>10 (3)</td>
<td>12900 (2000) mm/L</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>4.0 (1.3)</td>
<td>12 (1)</td>
<td>165 (1.9) IU/L</td>
</tr>
<tr>
<td>CK-MB</td>
<td>4.1 (1.2)</td>
<td>11.0 (3.7)</td>
<td>143 (1.3) IU/L</td>
</tr>
<tr>
<td>LDH</td>
<td>6.2 (1.7)</td>
<td>46 (19)</td>
<td>1723 (455) IU/L</td>
</tr>
</tbody>
</table>

Baseline values of CRP were similar in patients and controls (table 1). At the end of exercise testing and 6, 24, and 48 hours after the testing the values of CRP did not change significantly in both groups.

CRP concentration is a sensitive marker for underlying systemic inflammation. 1 Recently, its prognostic role in a variety of cardiovascular conditions has been repeatedly emphasised. Baseline concentrations of CRP in apparently healthy persons, in subjects with cardiovascular risk factors, and in patients with stable angina represent an independent risk factor for future cardiovascular events. Furthermore, high concentrations of CRP in patients with unstable angina and myocardial infarction are associated with a worse prognosis independently of the extent and severity of myocardial ischaemia or cell injury. Finally, persistently raised plasma concentrations of CRP after coronary surgery have been shown to be predictive of postoperative complications, and in patients with coronary artery disease undergoing successful coronary artery angioplasty or stent implantation, pre- and postprocedural high plasma concentrations of CRP are independent predictors of cardiac events at follow-up. 2

A potential flaw of our study is that the duration and severity of transient exercise induced myocardial ischaemia might not have been sufficient to produce an adequate stimulus to induce the production of CRP. Yet, in a previous study, no increase in CRP plasma concentrations was observed in patients with variant angina despite the longer duration of the single ischaemic episodes (> 10 minutes) and total ischaemic burden (> 40 minutes). 3 Furthermore, although the number of patients and controls was small, the statistical power of the study in the assessment of CRP changes within and between groups was sufficiently high (> 80% for pairwise comparisons); thus it is unlikely that significant changes in CRP were not detected.

In conclusion, the results of the present study, showing that exercise induced severe myocardial ischaemia does not induce an increase in CRP, support the concept that myocardial ischaemia “per se” is not an adequate stimulus to cause an increase in CRP serum concentrations, and that the increase observed in patients with acute coronary syndromes is unlikely to be related to myocardial ischaemia but is rather a marker of an underlying inflammatory process which may contribute to the pathogenesis of myocardial ischaemia.

Table 1  C-reactive protein plasma concentrations before and after exercise testing at the different sampling points

<table>
<thead>
<tr>
<th>Sample</th>
<th>Stable angina</th>
<th>95% CI</th>
<th>Controls</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>3.18 (2.6–3.9)</td>
<td>2.7 to 3.8</td>
<td>2.04 (1.6–3.4)</td>
<td>1.7 to 3.3</td>
</tr>
<tr>
<td>T1</td>
<td>3.46 (2.8–4.0)</td>
<td>2.9 to 4.0</td>
<td>2.34 (1.4–3.7)</td>
<td>1.6 to 3.5</td>
</tr>
<tr>
<td>T2</td>
<td>3.36 (2.6–4.1)</td>
<td>2.6 to 4.0</td>
<td>2.25 (1.8–3.4)</td>
<td>1.9 to 3.4</td>
</tr>
<tr>
<td>T3</td>
<td>3.18 (2.4–3.9)</td>
<td>2.3 to 3.7</td>
<td>2.25 (1.5–3.3)</td>
<td>1.5 to 3.2</td>
</tr>
<tr>
<td>T4</td>
<td>2.98 (2.3–3.8)</td>
<td>2.3 to 3.5</td>
<td>3.24 (1.9–3.2)</td>
<td>2.0 to 3.4</td>
</tr>
</tbody>
</table>

Values are expressed in mg/l and represent medians and interquartile ranges. Differences are not significant. See text for explanation of T0–T4. CI, confidence interval.

Interleukin 18 in acute myocardial infarction

YUKIHIRO SETA, TSUGIYASU KANDA, TORU TANAKA, MASASHI ARAI, KENICHI SEKIGUCHI, TOMOYUKI YOKOYAMA, MASASHI KURIMOTO, JUN'ICHI TAMURA and MASAHIKO KURABAYASHI

Heart 2000 84: 668-669
doi: 10.1136/heart.84.6.668

Updated information and services can be found at:
http://heart.bmj.com/content/84/6/668.1

These include:

References
This article cites 6 articles, 2 of which you can access for free at:
http://heart.bmj.com/content/84/6/668.1#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Drugs: cardiovascular system (8842)
- Acute coronary syndromes (2742)
- Heart failure (565)
- Clinical diagnostic tests (4779)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/