Release of interleukin-6 in acute myocardial infarction: apparent difference between myocardial necrosis and stunning

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Background: Elevated plasma levels of C-Reactive Protein (CRP) and Interleukin-6 (IL-6; the cytokine mainly responsible for CRP synthesis by the liver) have been demonstrated in patients with acute myocardial infarction (AMI). Plasma CRP has been correlated with infarct size, whilst plasma IL-6 has been associated with myocardial stunning.

Methods: To assess whether CRP and IL-6 are related to Infarct size, myocardial stunning or both, we measured the cumulative release of CRP and IL-6 during the first 24 hours in 44 patients with first AMI. Infarct size was assessed enzymatically (72-hours cumulative LDH release) and by 2D-echocardiography using wall motion score (WMS) at admission and at 3 months. Myocardial stunning was defined as change in WMS and number of segments showing recovery from baseline to 3-months follow-up. Patients were divided in 2 groups of 22 patients by median release values of CRP (66 mg/L) and IL-6 (208 µg/L).

Results:

<table>
<thead>
<tr>
<th>Release in 48 hours (n = 44):</th>
<th>CRP (mg/L)</th>
<th>IL-6 (µg/L)</th>
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<tbody>
<tr>
<td>≤66</td>
<td>≥56</td>
<td>≤208</td>
</tr>
<tr>
<td>Mean WMS (admission)</td>
<td>7.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean WMS (3 months)</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Change WMS (adm-3 months)</td>
<td>3.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Recovery (mean # segments)</td>
<td>3.3</td>
<td>3.3</td>
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</tbody>
</table>

Furthermore, IL-6 release correlated with cumulative LDH (r = 0.38; p = 0.01), CRP release (r = 0.47; p < 0.001) and 3-months WMS (r = 0.44; p = 0.003), CRP release correlated with cumulative LDH (r = 0.40; p = 0.007) and 3-months WMS (r = 0.49; p = 0.001).

Conclusion: IL-6 and CRP release in first AMI are positively correlated with infarct size. Myocardial stunning is more apparent in both the low IL-6 and CRP release groups.

Decreased levels of beta-endorphin in circulating mononuclear leukocytes from patients with acute myocardial infarction

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Objectives: Beta-adrenergic stimulation and interleukin-1 activate lymphocytes to release opioids that subsequently occupy opioid receptors on sensory nerves and result in antinociception. Since both catecholamines and cytokines have been found on admission and are associated with an increased risk of myocardial infarction, we measured IL-1 Ra levels in 43 patients with severe angina.

Methods: From 11 patients with acute myocardial infarction forearm venous blood samples were taken on admission and at 24 and 48 hours, thereafter. Blood samples were taken on admission, and at 24 and 48 hours, thereafter.

Results: IL-1Ra data are presented as median and range. Patients were grouped according to the presence of in-hospital events (death, myocardial infarction or refractory angina); 26 patients had in-hospital events (G1) and 17 had an uneventful course (G2). In G1, IL-1ra was 0.357 (0.058-0.854) ng/ml on admission and rose to 0.426 (0.08-1.234) ng/ml at 48 hours (P = 0.011). Conversely, in G2, IL-1ra on admission was 0.184 (0.012-1.308) ng/ml (P = 0.009 vs G1) and did not change significantly at 48 hours (0.176, range 0.006-0.816).

Conclusion: Our study demonstrates that levels of IL-1Ra, a reliable marker of IL-1 and TNFα production, are elevated on admission, and increase further at 48 hours in spite of full medical therapy, in patients with unstable angina and in-hospital events. Conversely, in patients with no uneventful in-hospital course have significantly lower levels of IL-1ra. Our data may open new avenues to novel therapeutic approaches in unstable angina.

Can C-reactive protein or troponins T and I predict outcome in patients with intractable unstable angina?

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C-reactive protein, a sensitive marker of inflammation, has previously been reported to be elevated in unstable angina. Recently, levels of both troponin I and T, which are sensitive and specific markers of myocardial injury, have been shown to correlate with outcome in acute coronary syndromes. We measured these 3 markers in 72 patients (54 male; mean age 62.9 yrs (range 36.0-72.4)) transferred to this centre with refractory chest pain in whom acute myocardial infarction was excluded by absence of ≥ twofold rise in creatine kinase. Presence of transient myocardial ischaemia (TMI) (detected by continuous ST segment monitoring) and coronary anatomy (angiographic analysis by two blinded observers) were also assessed.

Results: Median levels for CRP, troponin T and troponin I were 8.7 mg/dl (4.8-203.9), 0.0 µg/ml (0-2.51), 0.05 µg/ml (0-7.1) respectively. T (10%) patients had normal coronaries and 1, 2, 3 had 1, 2, 3 vessel disease respectively. 19 (26%) had TMI, 33 (46%) had complex lesion morphology and 6% had intracoronary thrombus. Of the 3 markers, troponin T alone was higher in patients with multivessel disease (p < 0.05) and those with TMI (p < 0.05), but there was no significant relationship between CRP, troponin T or I and coronary morphology or thrombus.

Conclusion: In patients transferred to a tertiary centre with intractable chest pain, CRP and troponin I are not predictive of TMI or lesion morphology, both of which are surrogate markers of outcome. Troponin T is, however, elevated in those patients with multivessel disease and also those with TMI.

Vascular endothelial growth factor mRNA synthesis by peripheral blood mononuclear cells in patients with acute myocardial infarction

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Vascular endothelial growth factor (VEGF) is an angiogenic glycoprotein that is upregulated in cardiac myocyte subjected to ischemia. Serum levels of VEGF are reportedly elevated in the subacute phase of acute myocardial infarction (AMI). However, there is no direct evidence that VEGF mRNA is expressed in patients with AMI. To investigate whether VEGF mRNA is expressed in AMI, we measured levels of VEGF mRNA in peripheral blood mononuclear cells (PBMC) obtained from patients with AMI using competitive polymerase chain reaction (PCR).

Materials and methods: Fifteen patients with AMI and 15 healthy controls were enrolled. In this study, PBMC were isolated from all patients on day 14 after onset, and from all controls. Total RNA was extracted from PBMC and reverse transcribed into cDNA. We performed competitive PCR by co-amplifying serial dilutions of GAPDH mutant templates containing a unique Eco RV site. Next, to measure VEGF cDNA semiquantitatively in the samples containing identical amount of GAPDH, we performed competitive PCR similarly by co-amplifying serial dilutions of VEGF mutant templates containing a unique Eco RI site. Lastly, to measure VEGF mRNA semiquantitatively in the samples containing identical amount of GAPDH, we performed competitive PCR similarly by co-amplifying serial dilutions of VEGF mutant templates containing a unique Eco RI site. We measured VEGF mRNA by Southern blot and densitometry. Sera were also obtained from the same patients on day 14 after onset, and the serum concentration of VEGF was measured by ELISA method.

Results: Higher levels of VEGF mRNA in the PBMC were observed in the AMI patients (3.0 ± 1.55 ng/gt/gAPDH) than in healthy controls (1.8 ± 0.4 ng/gt/gAPDH) (p < 0.05). Serum levels of VEGF were significantly correlated with the amount of VEGF mRNA in the PBMC (p < 0.05).

Conclusions: Levels of VEGF mRNA in PBMC were elevated in the subacute phase of AMI and significantly correlated with serum VEGF concentration. Results suggest that VEGF in PBMC is overexpressed in response to some signals during the subacute phase of AMI for the purpose of angiogenesis and healing.