Predictive value of basal C-reactive protein levels for myocardial salvage in patients with acute myocardial infarction is dependent on the type of reperfusion treatment

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Introduction

Growing evidence shows that inflammation plays an important role in the development and progression of coronary artery disease (CAD). In many studies, increased levels of different markers of inflammation have been associated with either an augmented risk of developing CAD in apparently healthy individuals or with poor prognosis in patients with known CAD.\textsuperscript{1,2}

C-reactive protein (CRP), a marker of low-grade systemic inflammation, has been studied in
different subsets of patients with CAD. In patients with acute myocardial infarction (AMI), peak levels of CRP have been associated with infarct size and clinical outcomes.\(^3\),\(^4\) However, the peak of CRP levels is often attained after reperfusion therapy had been applied and cannot serve for guiding selection of initial treatment strategy in patients with AMI. The prognostic value of CRP measured on admission in patients with AMI treated with mechanical or pharmacological reperfusion approaches is not known. Considering the negative impact of inflammation on the reperfusion efficacy and microcirculatory function, it is of interest to know whether CRP level on admission is predictive of myocardial salvage achieved with reperfusion and whether there are treatment specific differences in the possible predictive value.

The objective of our study was to evaluate the correlation between CRP values measured on admission and myocardial salvage assessed by technetium (Tc)-99\(^m\) sestamibi scintigraphy in patients with AMI treated with either coronary stenting or thrombolysis.

Methods

Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOPAMI) 1 and 2 were two randomized trials that compared stenting with thrombolysis in patients within 12 h from symptoms onset and detailed study protocols have been published previously.\(^5\),\(^6\) Briefly, abciximab was used as adjunct therapy during stenting and thrombolysis with alteplase. Alteplase was used as a full-dose therapy or as a half-dose therapy combined with abciximab.

Baseline CRP values were available in 288 of the 302 patients included in both STOPAMI trials. Paired scintigraphic studies necessary for the calculation of myocardial salvage were available in 250 patients (125 patients treated with stenting and 125 patients treated with thrombolysis [thrombolysis alone in 54 patient and thrombolysis plus abciximab in 71 patients]); they constituted the study population. Of the 38 patients excluded due to incomplete scintigraphic data, 19 patients belonged to the stent group and 19 patients to the thrombolysis group (nine patients to thrombolysis alone and 10 patients to thrombolysis plus abciximab). Follow-up at 18 months was done by phone contact.

Measurement of CRP

Venous blood samples were collected on admission for each patient and were immediately analysed. CRP was measured by a high sensitivity assay (Tina-quant®). Its analytic sensitivity (lowest measurable CRP concentration that can be distinguished from zero) is 0.03 mg/l. The functional sensitivity, i.e. the lowest CRP concentration that can be reproducibly measured with an interassay coefficient of variation <10%, is 0.11 mg/l.

Scintigraphic evaluation

All patients received an intravenous injection of 27 mCi (1000 MBq) of Tc-99\(^m\) sestamibi before initiation of reperfusion therapy. Single-photon emission computed tomography was done within 6–8 h of injection of the radionuclide to calculate the initial perfusion defect representing the area at risk. A second scintigraphic study was performed at 7 to 14 days after reperfusion treatment for the calculation of infarct size. Salvage index was then calculated as the proportion of the initial perfusion defect that was salvaged by reperfusion.

Statistical analysis

Continuous variables are expressed as mean±SD and discrete variable are expressed as proportions (percentages). The differences between groups were assessed using t test for continuous data and \(\chi^2\) test or Fisher’s exact test for categorical data. The relationship between CRP values and myocardial salvage (continuous response variable) was adjusted for other covariates including reperfusion strategy, in a multivariate model based on multiple linear regression analysis. Survival analysis was performed applying the Kaplan–Meier method. For all statistical analysis a p-value of less than 0.05 was considered to indicate a significant difference.

Results

A CRP value of 12 mg/l (the threshold for the upper quartile in this population) was used to divide the patients into two groups: 60 patients with high CRP levels (>12 mg/l) and 190 patients with low CRP values (≤12 mg/l).

Baseline characteristics

As shown in Table 1, patients with high CRP values were significantly older than those with low CRP values. Regarding infarct characteristics, there was a trend for a longer time to admission interval in patients with high CRP. In addition, baseline creatine kinase (CK)-MB was 39.6±36.4 IU/l in the high CRP group and 38.2±48.6 IU/l in the low CRP group (p=0.84). In the high CRP group, 55% of the patients...
were treated with thrombolysis and 45% with stenting; in the low CRP group, 48% of the patients were treated with thrombolysis and 52% with stenting (p=0.37).

**CRP, myocardial salvage and clinical outcome**

Patients with high CRP levels had a significantly lower salvage index (0.35±0.42 vs 0.48±0.34) and higher 18-month mortality (11.7 vs 3.2%; Fig. 1) than those with low CRP. The independence of the correlation between CRP values and myocardial salvage was assessed by the use of multiple linear regression analysis including age, gender, diabetes, high blood pressure, smoking, hypercholesterolaemia, history of myocardial infarction, history of coronary bypass graft surgery, Killip class, anterior localization of myocardial infarction, time to admission interval and initial perfusion defect (variables shown in Table 1) as well as the type of reperfusion therapy (stenting or thrombolysis) as potential confounders. Both CRP (independent variable) and myocardial salvage (response variable) were entered into the model as continuous variables to avoid possible bias associated with the use of cut-off values. After adjustment, there was a significant relationship between CRP values and myocardial salvage, with higher CRP values associated with less myocardial salvage (p=0.008). Additional independent factors associated with reduced myocardial salvage were: reperfusion therapy with thrombolysis (p<0.001), previous myocardial infarction (p=0.002) and male gender (p=0.02). The remaining factors of the model including age (p=0.48), time to admission interval (p=0.13) and initial perfusion defect (p=0.82), did not correlate significantly with myocardial salvage.

**CRP, myocardial salvage and type of reperfusion therapy**

In the group of stenting plus abciximab, basal CRP levels were not significantly associated with myocardial salvage: salvage index was 0.55±0.32 in the group with higher CRP values and 0.56±0.28 in

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**Table 1** Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRP &gt;12 mg/l n=60</th>
<th>CRP ≤12 mg/l n=190</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.5±12.7</td>
<td>60.0±12.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Women</td>
<td>20 (33)</td>
<td>45 (24)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (23)</td>
<td>36 (19)</td>
<td>0.46</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>40 (67)</td>
<td>117 (62)</td>
<td>0.48</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30 (50)</td>
<td>88 (46)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>39 (65)</td>
<td>143 (75)</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>5 (8)</td>
<td>25 (13)</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous coronary bypass graft surgery</td>
<td>2 (3)</td>
<td>10 (5)</td>
<td>0.54</td>
</tr>
<tr>
<td>Killip class &gt;2</td>
<td>4 (7)</td>
<td>6 (3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>29 (48)</td>
<td>87 (46)</td>
<td>0.73</td>
</tr>
<tr>
<td>Time to admission interval, min</td>
<td>241±184</td>
<td>197±156</td>
<td>0.07</td>
</tr>
<tr>
<td>Initial perfusion defect, % of LV</td>
<td>31.8±19.2</td>
<td>32.0±19.3</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Data are presented as mean±standard deviation or as numbers (percentages). LV=left ventricle

**Fig. 1** Mean salvage index (left) and 18-month mortality (right) according to C-reactive protein (CRP) level on admission in patients with acute myocardial infarction.
the group with lower CRP values (p=0.89, Fig. 2). Eighteen-month mortality was 3.7% among patients with high CRP levels and 3.1% among those with lower CRP values (p=0.80). In the group of thrombolysis, basal CRP levels were significantly associated with myocardial salvage: salvage index was 0.19±0.42 in the group with higher CRP values and 0.40±0.38 in the group with lower CRP values (p=0.007). Eighteen-month mortality was 18.2% among patients with high CRP levels and 3.3% among those with lower CRP values (p=0.02). When we divided the latter patients in two subgroups, those treated with thrombolysis plus abciximab and those with thrombolysis alone, we observed a different impact of the baseline CRP levels. In the subgroup treated with the combination thrombolysis plus abciximab, a higher CRP level was associated with a salvage index of 0.30±0.33 and a lower CRP level with a salvage index of 0.38±0.38 (p=0.43, Fig. 2). In the subgroup treated with thrombolysis alone, a higher CRP level was associated with a salvage index of 0.09±0.48 and a lower CRP level with a salvage index of 0.42±0.37 (p=0.006, Fig. 2).

**Discussion**

In this study, we analysed the relationship between CRP levels measured on admission and myocardial salvage achieved in patients with AMI treated with three different reperfusion strategies. CRP is an acute phase reactant synthesised by the liver when stimulated by cytokines, primarily interleukin-6 released from inflamed tissue. It has been used as a marker of low grade systemic inflammation and the development of high-sensitivity C-reactive assays has enabled its use for the detection of micro-inflammation at vascular level. CRP values on admission in patients with AMI may reflect pre-existent inflammation and/or the response to the extent of myocardial necrosis.

A heightened inflammatory state has been associated with resistance to thrombolytic therapy as well as increased thrombus burden and impaired microvascular perfusion in patients treated for AMI. Neumann et al. found that interleukins 6 and 8 caused an increased expression of tissue factor-a potent procoagulant on the surface of monocytes. Additionally, it has been shown that CRP may directly promote thrombosis by activating complement and inducing monocytes to produce tissue factor. So, while being used as markers of inflammation, the protagonists of inflammatory response such as CRP, can contribute to thrombus formation and its stability; both of them can have an impact on the efficacy of reperfusion therapy in patients with AMI.

Our study population consisted in patients with AMI treated with primary coronary stenting plus abciximab or thrombolysis without or with abciximab. We found that high CRP levels on admission were associated with reduced myocardial salvage. A more detailed analysis showed, however, that baseline CRP levels were not predictive of myocardial salvage in patients treated with stenting. The predictive value of CRP was confined to patients treated with thrombolysis and was particularly evident in those who did not receive abciximab. Therefore, the results of the present study suggest that patients presenting with AMI and increased CRP levels particularly benefit from a primary reperfusion strategy based on coronary artery stenting and/or addition of abciximab.

Abciximab is a glycoprotein IIb/IIIa inhibitor that possesses antithrombotic and anti-inflammatory properties. The anti-inflammatory profile might counterbalance the negative effects related to a heightened inflammatory state as reflected by
high CRP values. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) V trial no significant clinical benefit was observed in patients with AMI when abciximab was added to the thrombolytic therapy. However, this study did not address the potential of a beneficial effect of adjunctive abciximab in the particular subset of patients with AMI who present with an enhanced inflammatory state as reflected by high CRP levels.

No correlation was found between CRP levels on admission and myocardial salvage achieved with stenting in the present study. As all the patients in this group received abciximab as adjunctive therapy, we are not able to say whether the lack of a CRP-related difference in myocardial salvage is attributable to stenting or abciximab. A recent study found also no correlation between baseline CRP levels and final infarct size in 34 patients with AMI treated with primary balloon angioplasty but without abciximab. However, only patients with full restoration of angiographic flow were included and a different method for infarct size determination was used in the latter study.

Three additional points deserve special consideration. First, this study has insufficient power to address the endpoint of mortality and patients who died before the second scintigraphic study was performed (required for calculation of myocardial salvage) were excluded. Therefore, the concordant prognostic value of CRP levels with respect to myocardial salvage and survival in the groups with different reperfusion strategies needs confirmation from larger studies. Second, there was a trend for a longer time to admission interval in patients with high CRP compared to those with low CRP. Longer intervals are expected to have a more unfavourable impact on the efficacy of thrombolysis. We cannot fully exclude a certain contribution of this parameter to the relationship observed between CRP levels and myocardial salvage in the group of thrombolysis, although the relationship remained independent after appropriate adjustment in the multivariate model. Third, patients with high CRP values on admission were older compared to those with low CRP values. European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study reported that CRP levels were increased with age. In this case, too, we cannot fully exclude that an older age might have contributed to the observed association between a high CRP level and decreased myocardial salvage, despite respective adjustment in the multivariate model. Although the exact underlying mechanisms remain unknown, it is important to note that the use of coronary artery stenting and administration of abciximab in patients with AMI blunt the unfavourable relationship between CRP and myocardial salvage.

References

