Relationship of C-Reactive Protein to Adverse Cardiovascular Events in Patients Treated by Percutaneous Coronary Intervention for Stable Angina Pectoris

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SUMMARY

Low-grade inflammation as detected by increased C-reactive protein (CRP) levels predicts the risk of cardiovascular events. However, there is still controversy over the mid-term predictive value of CRP in patients referred for elective percutaneous coronary revascularization (PCI) for stable angina pectoris. The aim of this study was to assess the relationship between baseline CRP level and mid-term outcome of patients undergoing PCI.

Two groups of patients with stable angina pectoris were prospectively studied. Group A consisted of 150 consecutive patients with a CRP level ≤ 3 mg/L, and group B consisted of 150 consecutive patients with a CRP level > 3 mg/L undergoing PCI at our institution.

Comparing both groups of patients, the analysis confirmed a significant difference between medians of the CRP levels (0.5 versus 8 mg/mL; \( P < 0.001 \)). A higher level of CRP in group B was associated with a lower presence of male gender (\( P < 0.05 \)) and history of myocardial infarction (\( P < 0.05 \)). On the other hand, in group B there was higher occurrence of smoking (\( P < 0.001 \)), hypertension (\( P < 0.05 \)), hypertriglyceridemia (\( P < 0.001 \)), and diabetes mellitus (\( P < 0.01 \)). The incidence of myocardial infarction based on postinterventional release of TnI > 1.5 ng/mL reached 12% in group A and 14% in group B (\( P = 0.73 \)). Analyses were repeated with adjustment for significant baseline variables, which did not change our findings. The incidence of adverse cardiovascular events during a six month follow-up was 13% in both groups (NS).

Increased CRP serum prior to PCI was not associated with the risk and extent of procedure-related myocardial injury measured by TnI release and does not portend heightened cardiovascular risk at six months after percutaneous revascularization. On the other hand, a CRP level > 3 mg/L was associated with a higher occurrence of cardiovascular risk factors (smoking, hypertension, hypertriglyceridemia, and diabetes mellitus). (Int Heart J 2005; 46: 195-204)

Key words: C-reactive protein, Inflammation, Angioplasty, Stent
Based on evidence from vascular biology and clinical research, it has been shown that inflammatory mechanisms play a key role in the pathogenesis of atherosclerosis and acute cardiovascular events. C-reactive protein (CRP) is a non-specific but sensitive marker of inflammation that has been shown to aid cardiovascular risk prediction in a variety of clinical settings even in apparently healthy persons. Recent data indicate that a higher CRP level is a reliable marker of cardiovascular risk if its level is only slightly increased (CRP > 3 mg/L). Most authors have accepted that CRP measurements should be seriously evaluated as a part of a strategy in assessing the global cardiovascular risk of an individual.

Emerging evidence links an elevated baseline inflammatory status to adverse outcomes among patients undergoing percutaneous coronary revascularization (PCI). However, there is still controversy over the predictive value of CRP in patients referred for elective PCI for stable angina pectoris. The primary purpose of this analysis was to evaluate the immediate association between the pre-PCI CRP value in patients with stable angina pectoris and postinterventional myocardial injury. Additionally, we evaluated the relationship between CRP and the 6-month occurrence of adverse cardiovascular events in patients after percutaneous coronary revascularization.

Methods

Study population: Four hundred and ninety patients with coronary artery disease were treated by PCI between January 2002 and November 2002 in our catheterization lab. Two groups of treated patients were prospectively studied. Group A consisted of 150 consecutive patients with a CRP level ≤ 3 mg/L, while group B consisted of 150 consecutive patients with a CRP level > 3 mg/L undergoing PCI at our institution. Clinical data are summarized in Table I. Patients suffering from acute coronary syndrome in the last month as well as patients after cardiac surgery or patients with other diseases that increase CRP (infection, inflammation, trauma or tumor) were excluded. Patients taking corticosteroids or immunosuppressive drugs were also excluded. At the time of interventional procedure, all patients were scheduled for a six-month follow-up. All patients provided written informed consent before participation.

Blood analysis: The blood samples for CRP measurement were taken in the morning of the intervention day. CRP was assayed in the plasma using high-sensitivity nephelometry (high-sensitivity CRP, nephelometer Analysator II, Behring Diagnostics; Westwood, Massachusetts, USA). The lower limit for detection was 0.1 mg/L.
The blood samples for TnI measurements were taken 24 hours after PCI. TnI was assayed in the plasma using an immunometric assay (IMMULITE Turbo Troponin I, Diagnostic Products Corporation, Los Angeles, CA, USA). The cut-off value of TnI was 1.5 ng/mL and the lower detection limit was 0.5 ng/mL.

**Coronary angiographic findings and PCI procedure:** Only patients with *de novo* stenotic lesions were treated. Stenoses were visually assessed independently by two examiners. Quantitative analysis was used only in borderline cases or when the assessment of both examiners was controversial. Stenosis that reduced the lumen diameter by 50% or more was considered significant. The coronary artery tree was divided into three compartments (left anterior descending artery, left circumflex artery, and right coronary artery) to diagnose from one to three coronary artery diseases.

PCI procedures were performed by standard technique using monorail balloon catheter systems and premounted stents. A femoral approach with 5-7 F guiding catheters was used for all patients. The number of treated lesions, inflations, and inflation pressures was determined by the operators (J.V. and D.T.). Stent delivery was routinely followed by high-pressure balloon inflations (> 16 atm). In selected cases, direct coronary stenting was used. Atherectomy devices were not used. Angiographic success was defined as residual diameter stenosis < 20% determined by visual estimation and the ultimate achievement of thrombolysis in myocardial infarction (TIMI) flow grade 3.
Heparin (100 IU/kg) was administered intravenously at the beginning of the procedure in order to maintain the clotting time > 250 seconds. The activated clotting time was measured 10 minutes after heparin injection. All patients were treated with intracoronary injections of 1 mg of isosorbide dinitrate during PCI. Neither glycoprotein IIb/IIIa inhibitors nor drug eluting stents were used.

A complete clinical examination, including an ECG, was performed on the day after the procedure. The cutoff level for diagnosis of acute MI suggested by the manufacturer and biochemical laboratory of our institution is a TnI level > 1.5 ng/mL. This level was adopted for the analysis. MI was defined as symptoms of ischemia with new electrocardiographic changes and a rise in CK-MB and/or troponin. Therapy with statins was started in all patients after PCI (simvastatin 20-40 mg in 85% of patients, atorvastatin 10-20 mg in 8% of patients, fluvastatin 20-80 mg in 6% of patients, and pravastatin 20 mg in 1% of patients.)

All patients were contacted by telephone, or mail (questionnaire) or visited the physician six months after the procedure. The occurrence of major late clinical events (death, acute myocardial infarction, repeat coronary revascularization) was recorded. Events were subsequently source-documented.

**End points:** The primary end point was the incidence of myocardial infarction (MI) based on the postinterventional release of troponin I (TnI). The cutoff level for a diagnosis of acute MI suggested by both the manufacturer and the biochemical laboratory of our institution is TnI > 1.5 ng/mL at 24 hours following PCI. The secondary end point was the 6-month composite incidence of death (all-cause), myocardial infarction (MI), and target vessel revascularization (surgery or percutaneous revascularization). The end points of death, MI or target vessel revascularization were assessed as the time to the first event, without double counting of clinical events within the same patient.

**Statistics:** Microsoft Excel with Analyse-It (Analyse-it Software, Ltd.) was used for the study database and its analysis. Continuous variables are expressed as the mean ± SD, and discrete variables as counts and percentages. To determine a reasonable sample size and the power of study for secondary end point we used the website www.stat.uiowa.edu/~rlenth/Power/index.html (test equality of two proportions: \( P_1 = 0.12, P_2 = 0.24, n_1 = 150, n_2 = 150, \alpha = 0.05, \text{power} = 0.782 \)). Because the CRP and troponin I data were skewed, these values are expressed as the median and interquartile range (IQR). Differences between medians of both CRP and troponin I in groups A and B were analyzed using the Kruskal-Wallis one-way ANOVA test. The degree of association between CRP and continuous variables was calculated using the Spearman rank correlation. The chi-square test was used for analysis of the postprocedural study end point and occurrence of postprocedural myocardial infarction based on troponin I release. Groups were compared by means of the chi-square test (categorical variables), Student’s \( t \) test
(continuous variables), and one-way ANOVA test (continuous versus binary variables). Analyses were repeated with additional adjustment for age, history of myocardial infarction, cholesterol level > 5 mmol/L, triglyceride level > 2 mmol/L, presence of smoking, and diabetes mellitus by way of logistic regression analysis. A \( P \) value of 0.05 was considered statistically significant.

**RESULTS**

**Acute results:** An analysis comparing the two groups of patients confirmed a significant difference between the median CRP levels (0.5 versus 8 mg/mL; \( P < 0.001 \)) (Figure). There were statistically significant differences in most clinical characteristics: sex (male gender 73% versus 65%; \( P < 0.05 \)), history of myocardial infarction (61% versus 53%; \( P < 0.05 \)), smoking (31% versus 53%; \( P < 0.001 \)), hypertension (67% versus 77%; \( P < 0.05 \)), hypertriglyceridemia (35% versus 50%; \( P < 0.001 \)) and diabetes mellitus (25% versus 35%; \( P < 0.01 \)) (Table I). In all treated patients, there was a weak correlation between triglyceridemia and CRP level (\( r = 0.17; 95\% \) CI 0.05 to 0.28; \( P = 0.007 \)). Other risk factors were not significantly related to CRP level (\( P = 0.12 \) for diabetes mellitus, \( P = 0.06 \) for history of myocardial infarction, \( P = 0.38 \) for smoking and \( P = 0.55 \) for cholesterol). Both groups of patients were similar in a majority of baseline angiographic and interventional characteristics; the only difference was the number of stents used (85% versus 76%; \( P < 0.05 \)) (Table II).

![Figure](image). Scatter diagram of CRP dispersion.
There were no statistically significant correlations between the postprocedural TnI level and baseline CRP values in either group ($r = -0.04; 95\% \text{ CI } -0.19$ to $0.13; P = 0.66$ for group A and $r = 0.07; 95\% \text{ CI } -0.09$ to $0.23; P = 0.40$ for group B). Similarly, there was no statistically significant difference in the median of the postprocedural TnI level ($0.5 \text{ ng/mL versus } 0.5 \text{ ng/mL}; P = 0.13$). The incidence of myocardial infarction based on the postinterventional release of TnI $>1.5 \text{ ng/mL}$ was $12\%$ in group A and $14\%$ in group B ($P = 0.73; 95\% \text{ CI } 0.61$ to $2.34$). Of the patients experiencing a post-PCI troponin elevation $>1.5 \text{ ng/mL}$, the elevation of those in group A was not significantly different from those in group B (median: $4.5 \text{ ng/mL [2.2 -11.5]}$ versus $5.1 \text{ ng/mL [3.1-9.4]}; P = 0.45$). Also, analyses were repeated with adjustment for significant baseline variables, which did not change our findings.

**Follow-up:** Out of 300 patients treated by PCI, a mid-term follow-up (28 ± 10 weeks in both groups) was available in 298 patients (99%). Among 149 patients followed-up in group A, 20 (13%) experienced a primary end point (all-cause death, revascularization, or myocardial infarction). Among 149 patients (99%) followed-up in group B, a primary end point occurred in 20 (13%). There was no statistically significant difference in the secondary end point occurrence in the two groups. The data are summarized in Table III.
DISCUSSION

We investigated whether measurement of preprocedural CRP was able to predict immediate myocardial injury after elective PCI and subsequently, the clinical outcome at six months in stable angina patients. The results of this study demonstrate that in patients undergoing PCI for stable coronary disease, a higher level of CRP is neither a cardiovascular risk factor for post-PCI period nor mid-term follow-up. The implications of these findings to the cardiologist appear to be 3-fold: 1) elevated CRP, as an inflammatory marker in stable angina pectoris subjects undergoing PCI, is not associated with a higher occurrence of postprocedural myocardial injury measured by TnI release, 2) in patients with an established diagnosis of postprocedural myocardial infarction, there is no difference in the extent of necrosis related to baseline CRP level; a finding not previously reported, and 3) elevated baseline CRP in stable angina patients does not portend heightened cardiovascular risk at six months after percutaneous revascularization. Adjustment for possible confounding baseline factors did not alter these results.

CRP and PCI: Recently, the usefulness of inflammatory markers for predicting ischemic events among patients with coronary artery disease has been recognized. Among these inflammatory markers CRP is probably the most useful because it is easy and inexpensive to measure with commercial assays. Several studies examining the relationship between baseline CRP and adverse cardiovascular events have been performed. In a series of 121 PCI patients, preprocedural CRP > 3 mg/L was associated with a greater early adverse outcome. Similarly, an increase in periprocedural death or MI was observed at 72 hours among patients with elevated baseline CRP in the CAPTURE trial, reaching statistical significance by 30 days and 6 months. It is noteworthy that both studies enrolled patients with acute coronary syndromes. Higher than normal CRP levels

<table>
<thead>
<tr>
<th>End point</th>
<th>Group A CRP ≤ 3 mg/L</th>
<th>Group B CRP &gt; 3 mg/L</th>
<th>P value for difference [OR; 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (n/%)</td>
<td>1/1</td>
<td>2/1</td>
<td>1 [2.01; 0.18-22.45]</td>
</tr>
<tr>
<td>Revascularization (n/%)</td>
<td>15/10</td>
<td>14/9</td>
<td>1 [0.93; 0.43-1.99]</td>
</tr>
<tr>
<td>Myocardial infarction (n/%)</td>
<td>4/3</td>
<td>4/3</td>
<td>1 [1;0.25-4.08]</td>
</tr>
<tr>
<td>Total (n/%)</td>
<td>20/13</td>
<td>20/13</td>
<td>1 [1; 0.51-1.95]</td>
</tr>
</tbody>
</table>
(CRP > 3 mg/L) appear to be linked to an increased risk of death or myocardial infarction following PCI but a recent study suggests they are not associated with the need for repeat revascularization. Unfortunately, this study enrolled patients with acute coronary syndromes as well. Similarly, in another recent study, 56% of patients suffered from unstable angina pectoris and the authors reported that an elevated baseline CRP level is independently predictive of early adverse outcome after PCI. Interestingly, the highest cardiovascular risk was observed only in patients with acute coronary syndrome. Thus, we can hypothesize that CRP is a predictor of adverse cardiovascular risk after PCI for acute coronary syndromes. However, it is not a reliable predictor of restenosis per se, but rather a strong, consistent predictor of native coronary artery-related events. Thus, increased CRP as a marker of inflammation is probably a reflection of pathologic processes that play a role in native coronary artery disease (and result in acute coronary syndromes) but not of restenosis. Since the mid-term event-free survival in patients undergoing PCI for stable angina is determined mainly by restenosis per se, it seems in this group of patients that the six-month predictive ability of CRP is rather limited. Of course, this theory is not in contradiction with the proven role of CRP in the prediction of long-term cardiovascular risk.

We do not have a clear explanation for the significant difference in the use of stents in the two groups of patients. However, it is worth noting that the difference was just borderline and there were no other differences in angiographic and interventional data, including the presence, extent, and complexity of atherosclerosis (Table II).

CRP and atherosclerosis: The association of upper-body obesity, hypertriglyceridemia, low HDL, hypertension, and elevated glucose with increased levels of CRP was confirmed by Ridker, et al. They also documented that at all levels of severity of the metabolic syndrome, CRP added important and independent prognostic information in terms of future cardiovascular risk. In the present study, we have illustrated the association of elevated levels of CRP with smoking ($P < 0.001$), hypertension ($P < 0.05$), hypertriglyceridemia ($P < 0.001$), and diabetes mellitus ($P < 0.01$). On the other hand, it is interesting there is no correlation between the baseline CRP level and hypercholesterolemia. However, from the clinical point of view, baseline levels of both showed strong and linear correlations with the incidence of cardiovascular events over the long-term. Since metabolic syndrome is probably associated with a systemic inflammatory response, we have demonstrated, like many others, a weak positive correlation between serum CRP and triglyceridemia ($r = 0.17$; $P = 0.007$).

As we demonstrated in our previous study, the CRP level is not related to the extent or presence of coronary atherosclerosis assessed by coronary angiography, history of MI, or class of stable angina pectoris. Recently, Arroyo-Esp-
liguero, et al.,\textsuperscript{20} have also demonstrated that serum CRP does not correlate with the severity or extent of coronary atherosclerosis in patients with stable angina pectoris. Their findings showing a correlation between CRP levels and both cardiovascular events and complex coronary stenoses suggest that CRP is mainly a marker of coronary atherosclerosis activity. Thus, our as well as similar observations\textsuperscript{20-24} confirm the hypothesis that CRP is not related directly to the extent of coronary atherosclerosis, but to some mechanism influencing plaque vulnerability. The low-grade inflammation detected by CRP is most likely an indirect marker of an increased cytokine response to inflammatory stimuli that is critical for atherosclerotic plaque vulnerability and plaque rupture.\textsuperscript{1)}

**Limitations:** There are some limitations to this study. Clearly, more prospective data are needed because the number of patients followed-up is too small to determine the ultimate value of baseline CRP in assessing the mid-term cardiovascular prognosis of patients after PCI. The present data were collected merely by relying on patient interviews and a standardized questionnaire. On the other hand, this methodology is common to most prospective clinical studies and it is believed that this study design is able to reflect the incidence of adverse coronary events during the follow-up. Finally, only a borderline statistically significant difference was detected in the secondary clinical outcome measures.

**Conclusions:** Increased CRP serum prior to PCI is not associated with the risk and extent of procedure-related myocardial injury as measured by TnI release. Furthermore, elevated baseline C-reactive protein does not portend heightened cardiovascular risk at six months after percutaneous revascularization. An elevated CRP level (> 3 mg/L) is associated with a higher occurrence of cardiovascular risk factors (smoking, hypertension, hypertriglyceridemia, and diabetes mellitus).

**References**