Level of High-Sensitivity C-Reactive Protein Is Predictive of 30-Day Outcomes in Patients With Acute Myocardial Infarction Undergoing Primary Coronary Intervention*

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Background: C-reactive protein (CRP) has been well recognized as a strong independent predictor of short-term and long-term mortality after non–ST-segment elevation acute coronary syndromes. However, limited studies have been conducted correlating CRP levels within 6 h following the onset of ST-segment elevation (ST-se) acute myocardial infarction (AMI) to mortality. The purpose of this study was to evaluate the predictive value of CRP measured by high-sensitivity CRP assay (hsCRP) on 30-day clinical outcomes in patients with ST-se AMI of onset < 6 h undergoing primary percutaneous coronary intervention (PCI).

Methods and results: We conducted a prospective cohort study in 146 consecutive patients with ST-se AMI of onset < 6 h who were undergoing primary PCI. Blood samples for hsCRP were obtained in the catheterization laboratory before coronary angiography. Patients were classified into high (group 1: hsCRP > 2.37 mg/L, n = 73) and low (group 2: hsCRP ≤ 2.37 mg/L, n = 73) hsCRP groups according to the median value of hsCRP after AMI. Univariate analysis demonstrated that the 30-day composite major adverse cardiac events (MACE) [death, recurrent ischemia, and re-occlusion] were significantly higher in group 1 than in group 2 (23.3% vs 4.1%, p = 0.0008). Multiple stepwise logistic regression analysis demonstrated that high hsCRP (p = 0.001), cardiogenic shock (p = 0.0003), and low left ventricular ejection fraction (p = 0.032) were independent predictors of 30-day MACE.

Conclusions: Prospective evaluation of the hsCRP in ST-se AMI of onset < 6 h allows accurate risk stratification of individuals at risk of 30-day MACE after primary PCI.

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Key words: acute myocardial infarction; high-sensitivity C-reactive protein

Abbreviations: AMI = acute myocardial infarction; BMI = body mass index; CRP = C-reactive protein; hsCRP = high-sensitivity C-reactive protein; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; ST-se = ST-segment elevation; TIMI = Thrombolysis in Myocardial Infarction

Inflammation plays a crucial role in all stages of atherosclerosis, from initiation, through to progression, and finally acute coronary syndromes.1−4 Accumulating evidence suggests that C-reactive pro-tein (CRP) contributes to inflammation in atheroma and also actively participates in the atherosclerotic process.2−7 Numerous investigations8−10 have shown that CRP represents one of the most important predictors of vascular death in various settings. Studies11,12 have demonstrated that CRP is related to adverse outcomes in patients with non–ST-segment elevation acute coronary syndromes. Even after early aggressive coronary intervention, the serum level of CRP remains a strong independent predictor of short-term and long-term mortality in these patients.12 CRP, an acute-phase reactant, is synthesized and secreted in the liver 6 h after an acute inflam-
The synthesis of CRP starts 6 h after the onset of acute myocardial infarction (AMI) and reaches a peak level after approximately 50 h. Therefore, it is not surprising that the peak level of CRP reflects the severity of myocardial damage in much the same way as creatine phosphokinase and correlates with the prognosis of patients with AMI. Hence, it is important to clarify whether the level of high-sensitivity CRP (hsCRP), which would appear to have important prognostic value, is already elevated before the onset of AMI. Surprisingly, there are limited data correlating CRP value, is already elevated before the onset of AMI. Which would appear to have important prognostic value, is already elevated before the onset of AMI. Hence, it is important to clarify whether the level of high-sensitivity CRP (hsCRP), which would appear to have important prognostic value, is already elevated before the onset of AMI. Consequently, the purpose of this study was to investigate the link between serum CRP levels measured by high-sensitivity CRP assay (hsCRP) and short-term clinical outcomes in patients with onset of AMI < 6 h undergoing primary percutaneous coronary intervention (PCI).

**Materials and Methods**

**Primary End Point**

The primary end point of the study was the 30-day composite occurrence of major adverse cardiac events (MACE), including death, recurrent ischemia, or re-occlusion of the infarct-related artery (IRA).

**Inclusion and Exclusion Criteria**

In our hospital, all patients with AMI were considered eligible for primary PCI. For the purpose of this study, the serum levels of hsCRP of all patients who underwent primary PCI were prospectively measured. Blood samples were drawn after vascular puncture before coronary angiography was performed in the cardiac catheterization room. To avoid other variables that could influence the serum levels of hsCRP, we excluded patients with a history of recent surgery or trauma within the preceding 2 months, renal insufficiency (creatinine > 1.5 mg/dL), malignancy or liver cirrhosis, febrile disorders, acute or chronic inflammatory disease at study entry or history of recent infection, as well as those with AMI onset of ≥ 6 h. Patients were also excluded if fever (body temperature > 37.5°C) was observed in the emergency department. Patients were classified into one of two groups (the high or low hsCRP groups) based on extent of hsCRP level. The median value of hsCRP was used to classify patients into these two groups.

**Definitions of Control Groups**

Thirty subjects who underwent PCI due to angina matched with respect to age, gender, hypertension, diabetes mellitus, current smoking, and hypercholesterolemia served as coronary artery disease subjects. We also studied 30 age- and gender-matched healthy volunteers. Informed consent was obtained from all study subjects. The study protocol was approved by the Institutional Review Committee on Human Research of our institution.

**Procedure and Protocol**

Stent implantation was strongly encouraged except in cases involving IRA with heavy calcification or reference lumen diameter < 2.5 mm, or after coronary angioplasty with stent-like result on the treatment site. Tirofiban therapy (loading dosage, 20 μg/kg of body weight) was administered to patients on presentation in the emergency department, followed by a maintenance infusion of 0.15 μg/kg/min for 18 to 24 h at the beginning of this study. However, tirofiban therapy was subsequently withdrawn, as this therapy was found not to provide an additional benefit to patients with AMI undergoing primary PCI. From May 2002, the PercuSurge GuardWire device (Medtronic AVE; Santa Rosa, CA) was utilized in consecutive patients presenting with AMI (< 12 h in duration) in our hospital. The enrollment and exclusion criteria, and procedural method have been described previously in detail. Clopidogrel (loading dose of 300 mg after stenting then 75 mg/d) was administered for at least 4 weeks to patients who underwent primary stenting, and aspirin (100 mg/d po) was administered to each patient indefinitely.

**Blood Sampling Laboratory Investigations**

Blood samples were obtained once in both healthy volunteers and angina control subjects (in the catheterization laboratory after vascular puncture). WBC counts, biochemical measurements, and electrolytes were determined by standard laboratory methods.

The hsCRP was measured by immunonephelometry (BN system; Dade Behring; Newark, DE). The lower detection limit of this test is < 0.15 mg/L. We assessed the intra-individual variability of serum hsCRP levels in study patients, angina subjects, and healthy subjects. The mean intra-assay coefficients of variance were 2.92%, 2.79%, and 2.96%, respectively.

**Definitions and Data Collection**

AMI was defined as typical chest pain lasting for > 30 min with ST-segment elevation (ST-se) > 1 mm in two consecutive precordial or inferior leads. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters.

Detailed in-hospital and follow-up data were obtained including age, sex, coronary risk factors, Killip score on hospital admission, preinfarction angina, BMI, body temperature on hospital admission, WBC counts, creatinine level, serum level of hsCRP, angiographic findings, and number of diseased vessels. These data were collected prospectively and entered into a computerized database.

**Statistical Analysis**

Data were expressed as mean ± SD. Categorical variables were compared using χ² test or Fisher exact test. Univariate analyses were performed using Student t test. Continuous variables were compared using Wilcoxon rank-sum test. Continuous variables among three groups were compared using one-way analysis of variance for parametric data and Kruskal-Wallis test for nonparametric data. Repeated measures of analysis of variance were used for comparison of age among the three groups. Statistical analysis was performed using statistical software (SAS for Windows version 8.2; SAS Institute; Cary, NC); p < 0.05 was considered statistically significant.
RESULTS

Between November 2002 and January 2004, we prospectively investigated and recruited 228 consecutive patients of any age who presented with AMI undergoing primary PCI in our hospital. Eighty-two of the 228 patients (40.0%) were subsequently excluded due to onset of AMI ≥ 6 h (65 patients), fever (3 patients), infection (3 patients), malignancy (2 patients), liver cirrhosis (1 patient), or renal function impairment (8 patients). Therefore, the remaining 146 patients constituted the study population.

Baseline Characteristics of Study Patients, Angina Patients, and Healthy Control Subjects

There were no significant differences among the three groups with regard to age, gender, body temperature, BMI, or creatinine level (Table 1). There were also no significant differences between study patients and angina subjects in terms of coronary artery disease risk factors or multiple-vessel disease. However, the incidences of previous myocardial infarction and previous stroke were significantly higher in the study patients than in the angina subjects. Laboratory investigation demonstrated WBC counts were significantly higher in the study patients than in the angina patients and healthy control subjects. Furthermore, serum levels of hsCRP did not differ between angina patients and healthy control subjects. Angiographic results demonstrated that there was no significant difference in multiple vessel disease between study patients and angina subjects.

Comparison of Baseline Characteristics Between High and Low hsCRP Groups in Study Patients

Patients with an hsCRP level ≤ 2.37 mg/L were classified into the low hsCRP group, and those with an hsCRP level > 2.37 mg/L were placed in high hsCRP group (Table 2). The two groups were similar with respect to gender, cardiovascular risk factors, previous stroke, previous myocardial infarction, cardiogenic shock, preinfarction angina, body temperature on admission, BMI, and duration from onset of chest pain to time of blood sampling. There were also no significant differences in the two groups in terms of WBC counts and serum creatinine. Furthermore, angiographic findings demonstrated that there were no significant differences in terms of anterior wall infarction, multiple vessel disease, pre-PCI Thrombolysis in Myocardial Infarction (TIMI) flow grades, and intercoronary collateral circulation. The rates of successful reperfusion, stent implantation, and adjunctive tirofiban therapy or adjunctive utilization of the PercuSurge GuardWire device did not differ between group 1 and group 2 patients. However, left ventricular angiogram demonstrated that the high hsCRP group had significantly lower left ventricular ejection fraction (LVEF) than the low hsCRP group.

Thirty-Day Clinical Outcomes and Independent Predictors of Composite End Points

The 30-day MACE occurred in 23.3% of group 1 patients and 4.1% of group 2 patients (p = 0.0008) [Tables 3, 4]. Each component of the primary end point was more prevalent in group 1 than in group 2 (Table 3). Four group 1 patients who underwent primary stenting with acute in-stent occlusion due to

Table 1—Baseline Characteristics of Study Patients, Angina Patients, and Healthy Control Subjects*

<table>
<thead>
<tr>
<th>Variables</th>
<th>AMI Patients (n = 146)</th>
<th>Angina Patients (n = 30)</th>
<th>Normal Control (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>60.0 ± 10.8</td>
<td>61.4 ± 9.5</td>
<td>61.0 ± 8.2</td>
<td>0.703</td>
</tr>
<tr>
<td>Male gender</td>
<td>126 (86.3)</td>
<td>24 (80.0)</td>
<td>24 (80.0)</td>
<td>0.489</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (50.7)</td>
<td>16 (53.3)</td>
<td>11 (36.7)</td>
<td>0.792</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>54 (37.0)</td>
<td>11 (36.7)</td>
<td>17 (56.7)</td>
<td>0.974</td>
</tr>
<tr>
<td>Current smoking</td>
<td>83 (56.8)</td>
<td>15 (50)</td>
<td>15 (50)</td>
<td>0.631</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>66 (45.2)</td>
<td>15 (50)</td>
<td>15 (50)</td>
<td>0.631</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>12 (8.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>11 (7.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>25.2 ± 3.6</td>
<td>25.3 ± 4.4</td>
<td>24.8 ± 5.3</td>
<td>0.110</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>36.3 ± 0.6</td>
<td>36.4 ± 0.4</td>
<td>37.0 ± 0.4</td>
<td>0.120</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.2</td>
<td>0.23</td>
</tr>
<tr>
<td>WBC counts, × 10^9/mL</td>
<td>10.6 ± 2.3</td>
<td>5.8 ± 1.2b</td>
<td>5.5 ± 0.8b</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>2.95 ± 2.37a</td>
<td>1.35 ± 0.74b</td>
<td>1.03 ± 0.58b</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Anterior wall infarction</td>
<td>78 (53.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple-vessel disease</td>
<td>73 (50.0)</td>
<td>13 (43.3)</td>
<td></td>
<td>0.506</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD or No. (%) of patients.
†Means with different letters (a, b) indicate significant difference (at 0.05 level) by Kruskal-Wallis test.

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thrombosis, and two group 1 patients who underwent balloon angioplasty with recurrent angina due to acute recoil at the treatment site required emergency target vessel revascularization. Therefore, target vessel revascularization at 30 days was significantly higher in group 1 than in group 2 patients: 8.2% (6 of 73 patients) vs 0% (0 of 73 patients), p = 0.024. These six patients were all discharged uneventfully.

Baseline variables (Table 2) and both the high and low hsCRP groups were used to assess the independent predictors of 30-day MACE. Multiple stepwise logistic regression analysis (Table 4) demonstrated that high hsCRP was an independent predictor of 30-day MACE, along with cardiogenic shock and low LVEF. Additionally, continuity of WBC count was used as the variable during multivariable analysis (Table 4). Although WBC count was not an independent predictor related with 30-day MACE, it had a tendency to statistical significance.

### DISCUSSION

This study on the levels of hsCRP in patients with onset of AMI < 6 h undergoing primary PCI provided two striking clinical implications. First, hsCRP levels within 6 h of the onset of AMI were markedly higher compared to those for angina patients and healthy subjects. Second, a high level of hsCRP is strongly associated with 30-day MACE.

Recently, we demonstrated that old age, unsuccessful or delayed reperfusion, multivessel disease, and cardiogenic shock are independently associated with poor clinical outcomes.\(^\text{20,21}\) In the present study, we found that besides these conventional risk factors related to MACE in patients with AMI undergoing primary PCI, hsCRP, which appears to be as a novel inflammatory mediator, was also an independent predictor for 30-day MACE. Our finding is of clinical importance because it provides a new direction for predicting untoward clinical outcomes. Therefore, we encourage the use of this powerful parameter for the risk stratification of patients in the clinical setting of AMI. Furthermore, patients with an hsCRP level > 2.37 mg/L should receive particular attention because they have a 5.7-fold increase in 30-day MACE.

In the present study, we found that the serum level of hsCRP was significantly higher in patients with AMI of onset < 6 h than in patients with angina without coronary plaque rupture. Our results highlight the important role of this novel inflammatory marker in the clinical setting of AMI, which results in the development of new therapeutic strategies.
from plaque rupture and thrombus formation. Our findings corroborate a previous study\textsuperscript{17} suggesting that CRP levels within 6 h after the onset of AMI reflect the vulnerability of culprit coronary lesions. The suggestion from previous study\textsuperscript{17} and our clinical observations are further supported by a recent autopsy study\textsuperscript{22} that demonstrated that there appears to have a positive correlation between hsCRP levels and increased numbers of thin cap atheromas in the coronary tree that are vulnerable to rupture. This might be due to the fact that CRP not only reflects an underlying inflammatory process in the atherosclerotic plaque lesion,\textsuperscript{2,4} but also directly participates in the promotion of atherosclerotic processes and endothelial cell inflammation.\textsuperscript{3,5} Furthermore, it also has a direct effect by stimulating endothelial-1 and interleukin-6 release, up-regulating adhesion molecules, and stimulating monocyte chemoattractant protein-1 while facilitating macrophage low-density lipoprotein uptake.\textsuperscript{5–7}

WBC count is a simpler and universally available marker of inflammation.\textsuperscript{23} Patients with higher baseline WBC have a heightened inflammatory process.\textsuperscript{24} Studies\textsuperscript{23,25,26} have shown that elevation of WBC count during AMI is associated with adverse outcomes. In the present study, we also found an association between high WBC count and 30-day MACE, although it just failed to reach statistical significance (p = 0.059). Therefore, this finding is clinically important and encourages the use of this parameter for the risk of stratification of patients with AMI.\textsuperscript{24}

Our study has limitations. First, it would be difficult to evaluate the exact duration from onset of chest pain to blood sampling. Therefore, the effect of myocardial injury on stimulation of synthesis and release of hsCRP from the liver could not be completely eliminated in the present study. Second, although the striking impact of the serum level of hsCRP on 30-day clinical outcomes was recognized, the correlation between hsCRP level and long-term clinical outcomes was not evaluated in the present study. Therefore, future studies should be prospectively established to evaluate this relationship. Third, abciximab, one of the platelet glycoprotein IIb/IIIa receptor inhibitors, has been demonstrated to improve clinical outcomes of patients with AMI undergoing primary PCI.\textsuperscript{27} However, abciximab was not administered in the present study. Furthermore, tirofiban, another glycoprotein IIb/IIIa receptor inhibitor, had no effect on 30-day MACE in the present study. Therefore, whether the combined therapy with primary PCI and abciximab can ameliorate the relationship between high hsCRP level and 30-day MACE remains uncertain.

In conclusion, high hsCRP is strongly associated with 30-day MACE in patients with AMI treated with primary PCI. Its striking impact on 30-day untoward clinical outcomes was not ameliorated by primary PCI. Therefore, we suggest that hsCRP should be viewed as an important biomarker in daily clinical practice, and suggest that prospective evaluation of hsCRP in ST-se AMI of onset < 6 h allows more accurate risk stratification of individuals at risk of 30-day MACE after primary PCI.

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