Serum Amyloid A is a Better Predictor of Clinical Outcomes than C-Reactive Protein in Non-ST-Segment Elevation Acute Coronary Syndromes

Masami Kosuge, MD; Toshiaki Ebina, MD; Toshiyuki Ishikawa, MD; Kiyoshi Hibi, MD; Kengo Tsukahara, MD; Jyun Okuda, MD; Noriaki Iwahashi, MD; Hiroyuki Ozaki, MD; Hideto Yano, MD; Ikuyoshi Kusama, MD; Tastuya Nakati, MD; Satoshi Umemura, MD; Kazuo Kimura, MD

Background Elevated C-reactive protein (CRP) is associated with adverse outcomes in non-ST-segment elevation acute coronary syndromes (NSTE-ACS); however, the prognostic significance of serum amyloid A (SAA), also an important inflammatory marker, remains unclear.

Methods and Results The ability of SAA, in combination with CRP, to predict clinical outcomes was evaluated in 277 patients with NSTE-ACS. Patients were classified according to the presence or absence of elevated SAA (>0.8 mg/dl) and elevated high-sensitivity CRP (>0.200 mg/dl) on admission: group 1, both SAA and CRP normal (n=133); group 2, SAA normal, but CRP elevated (n=30); group 3, SAA elevated, but CRP normal (n=28); and group 4, both SAA and CRP elevated (n=86). In groups 1, 2, 3, and 4, the rates of combined endpoints including death, (re)infarction, or urgent target-vessel revascularization at 30 days were 8%, 3%, 25%, and 23%, respectively (p=0.002). Multivariate analysis showed that as compared with group 1, the odds ratios for combined endpoints in groups 2, 3, and 4 were 0.50 (p=0.30), 1.95 (p=0.038), and 1.86 (p=0.044), respectively.

Conclusions Regardless of the level of CRP, elevated SAA is associated with adverse 30-day outcomes in patients with NSTE-ACS, so SAA is a better predictor of clinical outcome than CRP in these patients. (Circ J 2007; 71: 186–190)

Key Words: Acute coronary syndromes; Inflammation; Prognosis

Inflammation plays an important role in the pathogenesis of coronary artery disease. Elevated levels of C-reactive protein (CRP), the prototypical acute-phase protein, are associated with adverse outcomes in healthy individuals, as well as in patients with stable angina or acute coronary syndromes (ACS).

Serum amyloid A (SAA), also an important acute-phase reactant protein, has a wider dynamic range and a more rapid response with different kinetics, as compared with CRP. Previous studies have suggested that SAA is a more useful and sensitive indicator of inflammation in some noncardiovascular inflammatory conditions. However, SAA has not been as thoroughly examined as CRP in ACS, so in the present study we evaluated the ability of SAA, in combination with CRP, to predict clinical outcomes in patients with non-ST-segment elevation ACS (NSTE-ACS).

Methods

Patients We studied 277 consecutive patients (mean age 67±10 years, range 38–94; 192 men, 85 women) who were admitted to the coronary care unit and fulfilled the following criteria: (1) typical chest discomfort attributed to cardiac ischemia, lasting at least 5 min and occurring within 24 h of hospital admission and involving an unstable pattern of pain; (2) no conditions precluding the evaluation of ST-segment changes on the ECG (left or right bundle branch block, left ventricular hypertrophy, or ventricular pacing); (3) fully assessable ECG on admission; (4) simultaneous measurement of plasma SAA and CRP levels on admission; (5) no conditions known to modify plasma SAA or CRP levels; and (6) fully assessable angiographic data during hospitalization. Patients with nonischemic or atypical pain, persistent new ST-segment elevation, or a Q-wave myocardial infarction on presentation were excluded. All patients gave informed consent and the study protocol was approved by the hospital’s Internal Review Boards.

Patients were classified into 4 groups according to the presence or absence of elevated SAA (>0.8 mg/dl, the upper limit of normal) or elevated high-sensitivity CRP (>0.200 mg/dl, the upper limit of normal) on admission: Group 1 (n=133): both SAA and CRP normal; Group 2 (n=30): SAA normal, but CRP elevated; Group 3 (n=28): SAA elevated, but CRP normal; and Group 4 (n=86): both SAA and CRP elevated.

Electrocardiographic Evaluation A 12-lead ECG was recorded on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. All ECGs were examined by 1 cardiologist who was unaware of all other clinical data. ST-segment shifts were measured...
Serum amyloid A (SAA), high-sensitivity C-reactive protein (CRP), and creatine kinase MB isoenzyme (CK-MB) levels are expressed as medians (25th, 75th). All other data are presented as means ± SD or percentages of patients.

Normal SAA, SAA level in normal range; Elevated SAA, SAA level ≥0.8 mg/dl; Normal CRP, CRP level in normal range; Elevated CRP, CRP level >0.200 mg/dl; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; HMG CoA, hydroxymethylglutaryl-coenzyme A reductase inhibitor; SBP, systolic blood pressure; HR, heart rate; LAD, left anterior descending coronary artery; RCA, right coronary artery; LMT, left main coronary artery.

80 ms after the J point for ST-segment depression, using the preceding TP segment as baseline.5 ST-segment depression of ≥0.5 mm was defined as clinically significant.5,16

Analysis of Biochemical Markers

Blood samples for measurement of plasma CRP and SAA levels were taken on admission. SAA levels were measured by latex-enhanced nephelometric immunoassay, performed on a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan). High-sensitivity CRP levels were simultaneously measured by N Latex CRP Mono tests, performed on a Behring BN II Nephelometer (Behring Diagnostics, Tokyo, Japan) using polystyrene microbeads coated with monoclonal mouse antibodies.17 In addition, a qualitative assay for cardiac-specific troponin T (TnT; Roche Diagnostics, Tokyo, Japan; detection limit, 0.1 ng/ml of cardiac-specific TnT) was performed. A TnT level of ≥0.1 ng/ml was defined as positive. In patients who were negative within 6 h of the onset of symptoms, the test was repeated at 8–12 h.

Angiographic Analysis

All patients underwent cardiac catheterization a median of 3 days after admission. All coronary angiograms were evaluated by 1 cardiologist who was unaware of all other clinical data. Stenosis ≥75% in any projection was considered clinically significant. In patients with 1 defined culprit lesion, the details of the lesion (morphologic characteristics18 and presence of thrombus) were examined.

Data Analysis

The study endpoint was a composite of death, myocardial (re)infarction, or refractory angina leading to urgent target-artery revascularization within 30 days of admission. Myocardial (re)infarction was diagnosed on the basis of either cardiac enzyme levels or ECG evidence. Enzyme-based evidence of re-infarction was defined as a re-elevation of the myocardial bound fraction of creatine kinase (CK-MB) to higher than the upper limit of normal if the previous CK-MB level was in the normal range, or 50%
above the previous level if the previous level was above the normal range.

**Statistical Analysis**

Because SAA, CRP, and CK-MB levels do not follow normal distributions, comparisons between groups were carried out using the Mann-Whitney test. The Pearson’s correlation analysis was performed to estimate correlations between SAA and CRP. The remaining continuous variables were compared with the use of t-tests. Proportions were compared with the use of chi-squared tests. SAA, CRP, and CK-MB levels are expressed as medians; the remaining variables are expressed as means±SD. Differences were considered statistically significant at p<0.05. Multiple logistic regression analysis was used to examine determinants of the combined endpoint of death, myocardial (re)infarction, or urgent target-vessel revascularization, because of instability (repeated episodes of angina or hemodynamic instability despite aggressive drug therapy) within 30 days. Variables used for analysis included age, sex, prior infarction, hypertension, diabetes mellitus, TnT, ST-segment depression, and SAA and CRP status on admission. The strength of associations with SAA and CRP status was assessed by comparing patients who had normal SAA and CRP levels with those who had elevated levels of SAA, CRP, or both. Odds ratios and 95% confidence inter-
irrespective of the presence or absence of elevated CRP were independent predictors of adverse events at 30 days, irrespective of the presence or absence of elevated CRP. In patients with elevated SAA levels but normal CRP levels, but this did not reach statistical difference.

Clinical Outcomes

Fig 2 shows outcomes at 30 days. Patients with elevated SAA levels had higher rates of adverse events (death, myocardial infarction, or urgent target-vessel revascularization) at 30 days, irrespective of whether CRP was elevated. This relation persisted among the 153 patients who had negative TnT tests. Multivariate analysis showed that positive TnT test, ST-segment depression, and elevated SAA level (groups 3 and 4) were independent predictors of adverse events at 30 days, irrespective of the presence or absence of elevated CRP. In patients with negative TnT tests, ST-segment depression and elevated SAA level (groups 3 and 4) were independent predictors of adverse events at 30 days, irrespective of the presence or absence of elevated CRP levels (Table 2).

Discussion

This study showed that elevation of SAA on admission is associated with adverse outcomes at 30 days in patients with NSTE-ACS, irrespective of the presence or absence of elevated CRP levels and, in contrast, elevated CRP levels with normal SAA normal levels were not associated with adverse outcomes at 30 days. These findings suggest that SAA is more strongly related to 30-day outcomes than CRP alone and may thus provide important prognostic information.

Both CRP and SAA are routinely used clinically as inflammatory markers. These proteins usually respond in parallel to a given stimulus; however, the magnitude of the SAA response has been found to be greater than that of CRP.8–10 Some studies have shown that SAA levels increase with higher degrees of inflammation, whereas CRP levels remain normal.5,11,12,14 Thus, SAA is considered more sensitive and useful than CRP as a marker of acute inflammatory response.11–14

There is growing evidence that elevated CRP levels have prognostic value in patients with NSTE-ACS.4–7 but data supporting the prognostic value of SAA are more limited. Liu et al reported that elevated SAA on admission was associated with higher rates of revascularization, myocardial infarction, and death in patients with unstable angina without evidence of myocardial necrosis. Morrow et al found that a marked baseline elevation of SAA was predictive of increased mortality at 14 days in patients with unstable angina and non-Q wave myocardial infarction.19 In those studies, the prognostic roles of SAA and CRP were found to be similar. To our knowledge, however, no previous investigation has assessed the prognostic value of combining the CRP and SAA levels in patients with NSTE-ACS. Our study demonstrated that patients with NSTE-ACS who had elevated SAA levels but normal CRP levels were more likely to have adverse clinical outcomes. Perhaps these patients had low-grade inflammation associated with detectable elevation of SAA, but not of CRP. In contrast, an elevated CRP level with normal SAA level was unrelated to adverse outcomes. Nakayama et al showed that elevated SAA levels tend to disappear more quickly than elevated CRP levels during viral and bacterial infections.10 Elevated CRP levels with normal SAA may thus reflect the early stage of the resolution of inflammation. Because the biosynthesis of SAA and CRP is controlled by different combinations of cytokines,20 the clinical implications of these proteins to the acute-phase response may differ.

The exact reasons why elevated SAA levels are related to adverse clinical outcomes remain unclear. Myocardial cell necrosis leads to substantial increases in inflammatory markers in NSTE-ACS. However, the relationship between elevated SAA levels and adverse outcomes persisted even

### Table 2 Multivariate Analysis of Factors Associated With 30-Day Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Patients with negative troponin T tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95%CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Group 1</td>
<td>1.00 (→)</td>
<td>–</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.50 (0.24–2.55)</td>
<td>0.301</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.95 (1.10–5.49)</td>
<td>0.038</td>
</tr>
<tr>
<td>Group 4</td>
<td>1.86 (1.14–4.69)</td>
<td>0.044</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (0.99–1.11)</td>
<td>0.115</td>
</tr>
<tr>
<td>Sex</td>
<td>0.62 (0.20–1.88)</td>
<td>0.396</td>
</tr>
<tr>
<td>Prior infarction</td>
<td>2.25 (0.64–7.98)</td>
<td>0.207</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.06 (0.38–2.91)</td>
<td>0.174</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.10 (0.41–2.92)</td>
<td>0.856</td>
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<tr>
<td>Positive troponin T on admission</td>
<td>6.83 (1.54–30.2)</td>
<td>0.048</td>
</tr>
<tr>
<td>ST depression on admission</td>
<td>8.69 (1.17–78.2)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Group 1, both SAA and CRP in normal range; Group 2, SAA in normal range, but CRP elevated; Group 3, SAA elevated, but CRP in normal range; Group 4, both SAA and CRP elevated.

CI, confidence interval. See other abbreviations see in Table 1.
among patients with negative TnT tests, suggesting that elevated levels of SAA do not necessary reflect myocardial cell necrosis. SAA has a number of immunomodulatory roles, including induction of chemotaxis of polymorphonuclear cells, monocytes, and T lymphocytes and promotion of the release of tumor necrosis factor-α, interleukin (IL)-1, and IL-8 from polymorphonuclear cells.23-25 SAA can also induce the production of collagenases, which contribute to remodeling of the extracellular matrix in areas of inflammation and weakening of the fibrous cap of plaque, leading to its rupture.26-28 CRP has been reported to have similar effects, but differences between CRP and SAA remain unclear.29-31 Our study showed a trend toward higher incidences of multivessel disease, severe stenosis, and complex culprit lesions in patients with elevated SAA levels. Johnson et al showed that SAA levels, but not CRP levels, are related to the severity of coronary artery disease as assessed by coronary angiography in women with a suspected diagnosis of ischemia.32 The association of elevated SAA levels with adverse outcomes may in part be related to the severity of coronary artery disease. If confirmed in larger studies, our findings have important therapeutic implications because patients with elevated SAA levels at admission are likely to have increased risks of morbidity and mortality, even in the absence of positive TnT tests or elevated CRP levels. Such patients may benefit from more aggressive treatment.

Study Limitations
The results of this study should be considered in the light of following limitations. First, we used strict inclusion entry criteria to ensure a homogeneous group of patients. Therefore, our study group was small. Second, the frequency of following limitations. First, we used strict entry criteria to ensure a homogeneous group of patients. Therefore, our study group was small. Second, the frequency of coronary artery disease was assessed by coronary angiography in women with a suspected diagnosis of ischemia. The association of elevated SAA levels with adverse outcomes may in part be related to the severity of coronary artery disease. If confirmed in larger studies, our findings have important therapeutic implications because patients with elevated SAA levels at admission are likely to have increased risks of morbidity and mortality, even in the absence of positive TnT tests or elevated CRP levels. Such patients may benefit from more aggressive treatment.

References


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