C-Reactive Protein and Lesion Morphology in Patients With Acute Myocardial Infarction

Toshihiko Sano, MD; Atsushi Tanaka, MD; Masashi Namba, MD; Yoshiharu Nishibori, MD; Yukio Nishida, MD; Takahiko Kawarabayashi, MD; Daiju Fukuda, MD; Kenei Shimada, MD; Junichi Yoshikawa, MD

Background—Elevated serum C-reactive protein (CRP) is of clinical significance in the management of acute coronary syndromes, but there have been few in vivo studies detailing the relation between lesion morphology and elevated CRP in the setting of acute myocardial infarction (AMI). In this study, we investigated the relation between lesion morphology as seen under preintervention intravascular ultrasound (IVUS) and CRP in the acute phase of AMI.

Methods and Results—Our patient population comprised 90 consecutive patients with AMI who underwent preintervention IVUS within 6 hours of the onset of symptoms. We divided our patient population into an elevated CRP group (≥3 mg/L) or a normal CRP group on the basis of serum CRP levels. There were no differences in patient characteristics or angiographic findings. We observed significantly more plaque rupture in the elevated CRP group than in the normal CRP group (70% versus 43%, P=0.01). A multivariate logistic regression model revealed that the presence of ruptured plaque alone correlated with elevation of serum CRP (P=0.02; odds ratio, 3.35; 95% CI, 1.22 to 9.18).

Conclusions—Elevated CRP may be related to the presence of ruptured plaque. Our results suggest that in the setting of AMI, elevated CRP levels may reflect the inflammatory activity of a ruptured plaque. (Circulation. 2003;108:282-285.)

Key Words: inflammation • plaque • myocardial infarction • ultrasonics

A growing number of studies report that C-reactive protein (CRP) levels are elevated within 6 hours of the onset of acute myocardial infarction (AMI).1,2 Elevation in CRP levels is associated with poor prognosis in acute coronary syndromes,3–5 whereas elevated serum CRP is a predictor of future risk of myocardial infarction.6,7 Elevated serum CRP therefore has an important role to play in the management of an acute coronary syndrome.

To the best of our knowledge, however, few in vivo studies have dealt with the relation between lesion morphology and elevated CRP in patients with AMI. We have previously reported that preintervention intravascular ultrasound (IVUS) can accurately identify lesion morphology, including the features of plaque rupture, in the acute phase of AMI.8–10 In this study, our aim was to investigate the relation between lesion morphology, as observed under preintervention IVUS, and CRP in the acute phase of AMI.

Methods

Our study population comprised 90 consecutive patients with AMI who underwent preintervention IVUS within 6 hours of the onset of symptoms. Diagnosis of AMI was determined from the presence of >30 minutes of continuous chest pain, ST-segment elevation >2.0 mm on at least 2 contiguous ECG leads, and more than a 3-fold increase in serum creatine kinase levels. We excluded from our population 2 patients who had had prior myocardial infarction, 2 patients with coronary artery bypass failure, 4 patients with subacute thrombosis or restenosis after percutaneous coronary intervention (PCI), and 3 patients in whom adequate IVUS images could not be obtained.

The Ethics Committee of Baba Memorial Hospital approved the protocol for the study. We also obtained written informed consent from all participants before initial coronary angiography.

Study Protocol

First, blood samples were taken from a peripheral vessel in the Emergency Room before the administration of any medical agents. In all patients, coronary angiography was performed with the use of a 6F Judkins-type catheter through the femoral approach. All patients received an intravenous bolus injection of 10 000 IU of heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. After completion of diagnostic coronary angiography and before any intervention, all patients were evaluated with IVUS. The IVUS catheter (3.2F Ultra cross, CVIS, Boston Scientific) was carefully advanced distal to the lesion under fluoroscopic guidance. It was then pulled back automatically from the distal portion at 0.5 mm/s, facilitating observation of the lesion. IVUS images were recorded on S-VHS videotape for off-line analysis. While pulling back the catheter, we manually infused a contrast medium suitable for IVUS imaging, carefully observing the lesion.
Typical preintervention IVUS image of AMI lesion. A, Typical preintervention IVUS image of ruptured plaque. This eccentric plaque ruptured at the shoulder (white arrow). B, Preintervention IVUS image with no visible features of plaque rupture. Image shows a concentric lesion with several highly echoic layers, one on top of the other, like the rings of a tree.

CRP, Troponin T, and CK-MB Analysis

The blood samples were centrifuged, and serum was removed and stored at −80°C until assay could be performed. CRP was analyzed turbidimetrically with sheep antibodies against human CRP with the use of a commercially available testing kit (TIA CRP-S, Nittobo K.K.). We defined elevated CRP as ≥3 mg/L in accordance with the definition previously adopted elsewhere. Using this benchmark, we divided our 90 subjects into either a normal CRP group or an elevated CRP group.

Similarly, we used commercially available testing kits to measure CK-MB (Shikarikid CK-MB, Kantoukagaku K.K.) and Troponin T (Troponin T III STAT, Roche Diagnostics K.K.).

Analysis of IVUS Images

The morphological features detected in our IVUS images were interpreted by two independent experienced observers who were unfamiliar with the angiographic and clinical data. Evaluation of lesion morphology and other measurements during IVUS was done according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, and Reporting of Intravascular Ultrasound Studies. Fissure was defined as an abrupt, focal, superficial break in the linear continuity of the plaque, extending in a radial direction. Dissection was defined as rupture of the plaque creating one or more neolumina. A lipid pool–like image was defined as a pooling of low-echoic material or echolucent material covered with a high-echoic layer. The Figure shows a preintervention IVUS image typical of one of the AMI lesions in the study.

Computer planimetry (TapeMeasure, Indec Systems) was used to measure the culprit lesion site, including the morphometric parameter external elastic membrane cross-sectional area (EEM-CSA). The mean time required for preintervention IVUS was 3.5 minutes. Our preintervention IVUS findings are summarized in Table 3. IVUS identified plaque rupture in 50 patients with IVUS without serious procedural complications.

Angiographic Analysis

Coronary angiograms were reviewed separately by two independent observers who were unaware of the IVUS findings. Perfusion degree was evaluated according to TIMI criteria, and collaterals were graded according to the Rentrop classification, with good collateral flow defined as grade 2 or 3. Angiographic thrombus was defined as a filling defect seen in multiple projections surrounded by contrast in the absence of calcification and >10 mm in length.

Statistical Analysis

Results are expressed as mean±SD values for continuous variables. Qualitative data are presented as numbers (%). Continuous variables have been compared by means of the Student’s t test and categoric data by Fisher’s exact test.

A multivariate logistic regression model was used to determine predictors of elevated CRP. Independent variables included in the model were age, sex, a history of systemic hypertension, a history of diabetes mellitus, a history of hypercholesterolemia, obesity (defined as a body mass index ≥25 kg/m²), positive remodeling, deep calcium, plaque rupture, and lesion EEM-CSA. A probability value <0.05 was considered statistically significant.

Results

Patient Characteristics and Angiographic Findings

Elevated serum CRP levels were observed in 43 (48%) patients. Patient characteristics and clinical results for all patients in the study are summarized in Table 1. There were no differences in clinical characteristics between the two groups. Similarly, there were no differences in serum levels of CK-MB, in the prevalence of elevated Troponin T at admission, or in the angiographic findings between the groups. The latter are summarized in Table 2.

IVUS Results

Coronary artery lesions were successfully observed in all patients with IVUS without serious procedural complications. The mean time required for preintervention IVUS was 4.8±3.5 minutes. Our preintervention IVUS findings are summarized in Table 3. IVUS identified plaque rupture in 50 (56%) patients. Fissure/dissection was observed in 41 of these 50 patients. Fissure/dissection was observed significantly more frequently in the elevated CRP group (58% versus 34%, P=0.03). Injection of saline or contrast medium confirmed communication between the lumen and plaque in 9 of these 50 patients. All of these 9 patients also had a lipid pool–like image. Also, plaque rupture was observed significantly more
frequently in the elevated CRP group than in the normal CRP group (70% versus 43%, P=0.01).

Adjusting for age, sex, coronary risk factors, and IVUS morphology, a multivariate logistic regression model showed that the presence of ruptured plaque alone correlated with elevated serum CRP (Table 4).

**Discussion**

**CRP and Lesion Morphology**

Despite the importance of CRP in the management of acute coronary syndromes, very few in vivo studies have addressed the relation between lesion morphology and CRP. Our results in this in vivo study suggest that the presence of ruptured plaque is only related to elevated CRP in patients with AMI.

CRP is mainly synthesized and secreted by hepatocytes 6 hours after an acute stimulus and shows rapid turnover (with a half-life of 19 hours).14 It is already known that myocardial necrosis promotes the synthesis of CRP. In this study, we only included patients with AMI treated within 6 hours of the onset of symptoms. There were no differences in CK-MB or Troponin T at admission, which suggests that our elevated CRP levels may reflect coronary lesions just before rupture but are unlikely to reflect myocardial necrosis. Plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam cells. These rupture-related macrophages are activated, indicating ongoing inflammation at the site of plaque disruption. Macrophages are capable of degrading the extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and the family of matrix metalloproteinases that may weaken the fibrous cap, predisposing it to rupture.15

Our results suggest that elevated CRP may reflect the activity of these activated macrophages. One pathological study, using immunohistochemical staining for CRP, into patients who had sudden death associated with severe coronary artery disease has reported that CRP may correlate with the number of thin-capped atheromas that can be considered vulnerable plaques.16 These pathological findings may lend support to our own conclusions.

It has also been suggested that CRP is elevated in the setting of “active” angina17 and that elevated CRP may be a predictor of a future risk of the onset of AMI.6,7 Our results may help to explain why elevated CRP may predict the future onset of AMI or why CRP levels are elevated in patients with “active” angina.

Also, recent studies have suggested that CRP may play a direct role in promoting inflammatory atherosclerosis,18,19 Our results raise the possibility that CRP is not only a marker of vascular inflammation but also plays an important key role in plaque disruption.

It has also been reported that coronary calcium deposition may be a feature of atherosclerosis and plaque rupture20,21 and may predict future coronary events.21,22 This has led to speculation that coronary calcium deposition may be related to CRP. However, the evidence for a relation between coronary calcium and CRP on electron beam computerized tomography studies is controversial.23-25 A recent study showed that both coronary calcium and CRP independently contribute risk stratification toward the incidence of cardiovascular events.26 We believe that neither superficial nor deep calcium deposition, as identified by IVUS, is associated with CRP elevation and suspect rather that elevated CRP and calcium deposition reflect a different pathological status in patients with AMI.

**TABLE 2. Angiographic Findings**

<table>
<thead>
<tr>
<th></th>
<th>Elevated CRP Group (n=43)</th>
<th>Normal CRP Group (n=47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left descending artery</td>
<td>24 (56)</td>
<td>28 (60)</td>
<td>0.94</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>3 (7)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>16 (37)</td>
<td>16 (34)</td>
<td></td>
</tr>
<tr>
<td>TIMI flow grade 0 at initial angiogram</td>
<td>24 (56)</td>
<td>24 (51)</td>
<td>0.68</td>
</tr>
<tr>
<td>Good collateral flow</td>
<td>13 (30)</td>
<td>11 (23)</td>
<td>0.49</td>
</tr>
<tr>
<td>Large thrombus on angiogram</td>
<td>5 (12)</td>
<td>2 (4)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stent use</td>
<td>31 (72)</td>
<td>18 (74)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Data presented are mean±SD or numbers (%). EEM indicates external elastic membrane; CSA, cross-sectional area.

**TABLE 3. Preintervention IVUS Findings**

<table>
<thead>
<tr>
<th></th>
<th>Elevated CRP Group (n=43)</th>
<th>Normal CRP Group (n=47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS images</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccentric</td>
<td>30 (70)</td>
<td>24 (51)</td>
<td>0.09</td>
</tr>
<tr>
<td>Plaque rupture</td>
<td>30 (70)</td>
<td>20 (43)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fissure/dissection</td>
<td>25 (58)</td>
<td>16 (34)</td>
<td>0.03</td>
</tr>
<tr>
<td>Confirmed by IVUS contrast</td>
<td>5 (12)</td>
<td>4 (9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Lipid pool–like image</td>
<td>22 (51)</td>
<td>14 (30)</td>
<td>0.05</td>
</tr>
<tr>
<td>Superficial calcium</td>
<td>19 (44)</td>
<td>18 (38)</td>
<td>0.67</td>
</tr>
<tr>
<td>Deep calcification</td>
<td>13 (30)</td>
<td>21 (45)</td>
<td>0.19</td>
</tr>
<tr>
<td>Positive remodeling</td>
<td>13 (30)</td>
<td>7 (15)</td>
<td>0.13</td>
</tr>
<tr>
<td>Distal reference EEM-CSA, mm²</td>
<td>13.3±5.2</td>
<td>13.1±4.9</td>
<td>0.88</td>
</tr>
<tr>
<td>Distal reference lumen-CSA, mm²</td>
<td>6.7±3.2</td>
<td>6.6±3.3</td>
<td>0.80</td>
</tr>
<tr>
<td>Lesion EEM-CSA, mm²</td>
<td>15.1±5.7</td>
<td>13.2±4.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Proximal reference EEM-CSA, mm²</td>
<td>16.3±5.0</td>
<td>15.5±4.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Proximal reference lumen-CSA, mm²</td>
<td>7.9±3.2</td>
<td>8.1±2.9</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Data presented are mean±SD or numbers (%). EEM indicates external elastic membrane; CSA, cross-sectional area.

**TABLE 4. Multivariate Logistic Regression Model for Elevated CRP**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Hypercholesterolemia &gt;220 mg/dL</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Obesity, body mass index &gt;25kg/m²</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Plaque rupture</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Deep calcium</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Positive remodeling</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Lesion EEM-CSA</td>
<td></td>
<td>0.62</td>
</tr>
</tbody>
</table>
In our normal CRP group, 44% were non–rupture-type lesions. Pathological evaluation showed AMI caused not only by plaque rupture but also cases in which plaques did not rupture, such as in plaque erosion, which is a major substrate for coronary thrombosis in AMI.27,28 A recent and separate pathological study reported that eroded proteoglycan-rich and smooth muscle cell–rich plaques lack a superficial lipid core, are less likely to see plaque rupture, and have fewer foci-containing macrophages.29 Nonruptured lesions are thought to cause a less inflammatory response compared with ruptured lesions in vivo. Serum CRP levels may reflect lesion characteristics in the setting of AMI.

Study Limitations
There can be said to be a number of limitations associated with this study. Not all plaque rupture cases may present with fissure/dissection or plaques with communications to the lumen when observed under preintervention IVUS. Lesions with small ruptured plaques may be misread as nonruptured plaques. Our study may therefore contain some ruptured lesions misclassified as nonruptured lesions. Also, an occluded artery is devoid of pressure and undergoes elastic recoil with a marked reduction in all dimensional measurements. Therefore, positive remodeling and its assessment can be substantially influenced by either the presence of physiological pressure in the artery or its absence.

Clinical Implications
Although CRP is a nonspecific acute-phase reactant, our results may contribute to identifying plaques at high risk of rupture and disruption and high-risk lesion characteristics in patients with AMI.

It has previously been reported that elevated CRP is a predictor of adverse outcomes after PCI.2–5 Recently, we have reported that lesion characteristics such as a lipid pool–like image, which are often associated with plaque rupture, may affect the results of primary angioplasty and may cause the no-reflow phenomenon or acute occlusion after angioplasty.9,10 We recommend that the results of this current study should be borne in mind when forming strategies for PCI, such as the use of distal protection devices.

References
27. van der Wal AC, Becker AE, van der Loos CM, et al. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994;89:36–44.
C-Reactive Protein and Lesion Morphology in Patients With Acute Myocardial Infarction
Toshihiko Sano, Atsushi Tanaka, Masashi Namba, Yoshiharu Nishibori, Yukio Nishida, Takahiko Kawarabayashi, Daiju Fukuda, Kenei Shimada and Junichi Yoshikawa

Circulation. 2003;108:282-285; originally published online June 30, 2003;
doi: 10.1161/01.CIR.0000079173.84669.4F

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/3/282