Echolucent Carotid Plaques as a Feature in Patients With Acute Coronary Syndrome

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Background Carotid arterial ultrasound examination may be helpful for screening populations at high risk for acute coronary syndrome (ACS), so the present study was designed to identify the carotid arterial characteristics of patients with ACS.

Methods and Results Carotid ultrasound examinations were performed in 172 patients with ACS, 166 patients with stable coronary artery disease (CAD), and 96 control subjects. Common carotid arterial structures were assessed by the intima-media thickness (IMT), interadventitial diameter (IAD), lumen diameter (LD), the IMT to LD ratio (IMT/LD), and the plaque burden based on the plaque score. Plaque morphology was assessed by the echogenicity based on the gray-scale median (GSM). IMT, IAD, IMT/LD, and plaque score did not differ between the ACS and stable CAD groups. The GSM in the ACS group was lower (47.5±25.3, p<0.001) than in the control (70.1±22.5) and stable CAD (73.7±23.4) groups. Multiple logistic regression analysis showed that the presence of carotid echolucent plaques (GSM ≤60) was an independent predictor of ACS.

Conclusions Echolucent carotid plaques were strongly associated with ACS and may be a surrogate marker of high-risk patients. (Circ J 2006; 70: 1629–1634)

Key Words: Acute coronary syndrome; Carotid arteries; Coronary disease; Plaque; Ultrasonics

Coronary plaque rupture with subsequent thrombosis is the major recognized pathogenic event in acute coronary syndrome (ACS), a term encompassing unstable angina pectoris (AP), acute myocardial infarction (AMI), and sudden coronary death. Identification of plaques prone to rupture might, therefore, help to define a population at high risk for future occurrence of ACS. However, reliable noninvasive methods for clinical screening and diagnosis for ACS have not been established.

Plaque instability might occur systemically in not only the coronary arteries, but also in peripheral arteries. This hypothesis has been investigated angiographically in a large scale cohort study, the European Carotid Surgery Trial, which reported that patients with an angiographically irregular carotid plaque surface are at an increased risk of future AMI and sudden cardiac death. Noninvasive, high-resolution ultrasonographic examinations of the carotid arteries have been performed to assess atherosclerosis in terms of characteristics such as carotid plaque burden, arterial structures, and plaque morphology. The carotid arterial intima-media thickness (IMT) is an established surrogate measure of generalized atherosclerosis. Previous studies have shown an association between the degree of carotid IMT and the presence of coronary artery disease (CAD), and the IMT has been identified as an independent predictor of future coronary events. Other studies have shown the importance of carotid arterial remodeling pattern associated with ACS and future cardiovascular diseases. In addition, previous studies have sought to identify carotid plaques prone to rupture, based on features such as plaque echolucency, which has been associated with histologic features indicating an increased risk for cardiovascular disease. Therefore, we hypothesized that carotid arterial ultrasound examination might be helpful for screening populations at high risk for ACS, and we designed this study to identify the relevant carotid arterial characteristics.

Methods

Study Population The present study was performed from November 2002 to September 2005 in 2 Japanese centers: University of Tsukuba Hospital and Ibaraki Seinan Medical Center Hospital. We prospectively studied 338 patients with CAD (260 men, 78 women, 64±10 years), including 172 patients with ACS and 166 with stable CAD, and age- and sex-matched control subjects without manifestation or history of cardiovascular disease (72 men, 24 women, 63±7 years). All CAD patients underwent coronary angiography and significant coronary stenosis was diagnosed by detection of stenosis ≥50% in 1 or more major epicardial arteries. In the ACS group, only patients experiencing a first ACS event were included, which excluded those with a history of CAD. The diagnosis of ACS included all patients with acute or rapidly worsening symptoms thought to result from CAD at the time of hospitalization, and included patients with ST- and non-ST-elevation AMI, or with unstable AP. AMI was diagnosed by the presence of the following 3 criteria: persistent chest pain lasting >20min; elevation of

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serum total creatine kinase concentration to more than twice the upper limit of normal, together with significant elevation of the serum troponin T concentration; and changes in the electrocardiogram consistent with either ST-elevation AMI (ST segment elevation ≥1 mm in at least 2 standard leads or ≥2 mm in at least 2 contiguous precordial leads) or non-ST-elevation myocardial infarction (ST segment depression >1 mm in 2 contiguous leads or inversion of the T waves of ≥1 mm in at least 3 contiguous leads). Patients with unstable AP were classified according to the Braunwald classification, based on new onset or a changed pattern of AP over the previous 2 months. Other patients with obstructive CAD in at least 1 coronary segment were diagnosed as having stable CAD. All patients gave informed consent before participation.

Ultrasound Examination
Duplex carotid artery ultrasonography, using either the Toshiba SSA 390A with a 7.5-MHz linear array multifrequency transducer (Toshiba Medical, Tokyo, Japan) at the University of Tsukuba Hospital or the Vivid 7 system with a 7-MHz linear array multifrequency transducer (GE Vingmed Ultrasound, Horten, Norway) at the Ibaraki Seinan Medical Center Hospital, was performed by well-trained sonographers or physicians who were unaware of the results of the coronary angiography. In patients with ACS, carotid artery duplex ultrasonography was performed 10±4 days (range: 2–18 days) after admission. B-mode and corresponding color Doppler images were digitized onto a 3.5-inch magneto-optical disk. All appropriate images were stored in and processed by a computer (VAIO PCG-VGN-ASOB; Sony, Tokyo).

We assessed the common carotid arterial structures at a point 1 cm proximal to the carotid bifurcation bulb region using longitudinal images. We identified 2 interfaces on each wall. On the near wall, the 1st interface was the adventitial–medial boundary, and the 2nd was the intima–lumen boundary. On the far wall, the 1st interface was the lumen-intima boundary, and the 2nd was the media–adventitia boundary. The distance from the 1st interface of the near wall to the 2nd interface of the far wall was defined as the interadventitial diameter (IAD); the distance from the 2nd interface of the near wall to the 1st interface of the far wall as the lumen diameter (LD); and the distance between the 1st and the 2nd interfaces of the far wall as the IMT. The IAD, LD, and IMT were calculated as the mean value of both sides. The ratio of IMT to LD ratio (IMT/LD) was calculated to assess carotid arterial structures. The plaque score was used to estimate the total carotid plaque burden. Plaque was defined as an area within which the IMT exceeded 1.10 mm on the longitudinal images. Plaque score was the sum of the maximum IMT measured at each of 3 locations: the distal common carotid region 2 cm proximal to the bifurcation bulb region; the bifurcation bulb region; and the proximal internal carotid artery region 1 cm distal to the bifurcation bulb region, including both near and far sides of the carotid arteries. Gain setting of the B-mode image was carefully set, using the time gain compensation, to obtain a noiseless vessel lumen area and an echo-dense area of adventitia in the vicinity of the plaques. Carotid plaque morphology was assessed objectively by computer-assisted quantification of echogenicity using a parameter gray-scale medium (GSM). Echogenicity of the B-mode images was standardized using Adobe Photoshop software (Adobe Systems, version 5.0, San Jose, CA, USA), with a gray scale from 0 to 255 (0 as the darkest and 255 as the brightest tone). First, the GSM of 2 echo-anatomic reference points (blood and adventitia) were measured based on the histogram property of the software (input value). Second, algebraic (linear) scaling of the image was performed with the curve capability of the software so that the gray-scale value of all pixels in the image was adjusted according to the input value (ie, the GSM obtained in the original images) and the output value of the 2 reference points: output value of blood in the range of tones 0–5, and that of adventitia in the range of tones 185–195. This yielded a standardized GSM that could be used to quantify the echogenicity of plaque. Because we used 2 different ultrasound systems, differences in the GSM values of the standardized images derived from each system were investigated in 30 plaques, and a strong correlation of the GSM values between the systems was found (Y =1.01X–0.47, R²=0.938, p<0.001). We investigated intra- and interobserver variability of the GSM values in 100 plaques; these were 5.1±2.3% and 6.2±2.5%, respectively. In cases in which there were multiple plaques, the plaque with the lowest GSM was considered representative.

Statistical Analysis
Results are expressed as the mean±SD. A p-value<0.05 was considered statistically significant. One-way analysis of variance was used to compare variables among the 3 groups. When significant differences between groups were present, Sheffe’s test was used to compare individual groups. The chi-squared test was used for categorical variables. Multivariate logistic analysis was performed to assess independent predictors for patients with ACS. All clinical variables with a value of p<0.05 in the univariate analysis were tested. Receiver-operating characteristic (ROC) analysis was used to determine the optimal cutoff value of the GSM for identifying patients with ACS. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity. The area under the ROC curve was used to quantify the ability of the GSM to predict patients with ACS. All calculations were performed using the Dr SPSS II for Windows statistical program (SPSS Inc, Chicago, IL, USA).

Results
Characteristics of the Study Population
The clinical characteristics of the 3 groups are summarized in Table 1. Of the patients with ACS, 133 had AMI and 39 had unstable AP. In the stable CAD group, 41 patients (25%) had a prior myocardial infarction, 40 (24%) had a previous history of percutaneous coronary intervention, and 15 (9%) had undergone coronary artery bypass grafting. Risk factors for atherosclerosis did not differ significantly between the ACS and stable CAD groups. In the stable CAD group, a larger proportion of patients took β-blockers or aspirin than in the ACS group.

Carotid Ultrasound Examinations
The common carotid arterial structures of the 3 groups are summarized in Table 2. The IAD, IMT, and IMT/LD in the control group were smaller than in both the ACS and stable CAD groups. However, these variables did not differ significantly between the ACS and stable CAD groups. In contrast, the LD did not differ between the 3 groups. The plaque score in the control group was lower than in that for patients with CAD, although it did not differ significantly.
between the ACS and stable CAD groups.

A larger proportion of subjects in the control group (34 subjects, 35.4%) had no plaques than in the ACS (14 patients, 8.1%) and stable CAD groups (14 patients, 8.4%, Fig 1). After these subjects excluded, the GSM in the ACS group was lower (47.5±25.3) than in the control (70.1±22.5) and stable CAD groups (73.7±23.4, Fig 2).

Univariate logistic regression analysis revealed that serum low-density lipoprotein-cholesterol concentration, serum high-density lipoprotein-cholesterol (HDL-C) concentration, IMT, plaque score, and GSM were predictors.

### Table 1 Clinical Characteristics of Patients With ACS or Stable CAD

<table>
<thead>
<tr>
<th></th>
<th>Control (n=96)</th>
<th>ACS (n=172)</th>
<th>Stable CAD (n=166)</th>
<th>p value across groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63±7</td>
<td>63±11</td>
<td>65±10</td>
<td>–</td>
</tr>
<tr>
<td>Male, %</td>
<td>75</td>
<td>77</td>
<td>77</td>
<td>–</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.0±3.3</td>
<td>24.9±3.1</td>
<td>25.1±4.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>32</td>
<td>63</td>
<td>69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus %</td>
<td>10</td>
<td>33</td>
<td>35</td>
<td>0.002</td>
</tr>
<tr>
<td>FBS, mg/dl</td>
<td>101.7±16.2</td>
<td>121.7±47.5</td>
<td>118.2±37.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>5.2±3.4</td>
<td>6.0±1.4</td>
<td>6.1±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>193.3±37.0</td>
<td>195.2±43.5</td>
<td>196.0±42.8</td>
<td>0.12</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>123.0±33.7</td>
<td>124.3±37.4</td>
<td>131.4±37.5</td>
<td>0.09</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>56.3±14.3</td>
<td>46.4±11.9</td>
<td>49.0±13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>128.8±63.2</td>
<td>124.1±67.3</td>
<td>133.8±70.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>30</td>
<td>60</td>
<td>53</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>– – 25</td>
<td>– – –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>–</td>
<td>–</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Medications %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>0</td>
<td>4</td>
<td>15*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>11</td>
<td>42</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>5</td>
<td>29</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>5</td>
<td>13</td>
<td>17</td>
<td>0.03</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>2</td>
<td>20**</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CAD, coronary artery disease; FBS, fasting blood sugar; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

*p=0.02 vs ACS group, **p<0.001 vs ACS group.

### Table 2 Common Carotid Arterial Structure and Plaque Score of the 3 Groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ACS</th>
<th>Stable CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAD, mm</td>
<td>7.88±0.91</td>
<td>8.27±0.92*</td>
<td>8.28±0.88*</td>
</tr>
<tr>
<td>LD, mm</td>
<td>6.45±0.85</td>
<td>6.70±0.80</td>
<td>6.60±0.84</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.71±0.12</td>
<td>0.79±0.14*</td>
<td>0.78±0.13*</td>
</tr>
<tr>
<td>IMT/LD, mm</td>
<td>0.11±0.02</td>
<td>0.12±0.03*</td>
<td>0.12±0.03*</td>
</tr>
<tr>
<td>Plaque score</td>
<td>2.42±2.33</td>
<td>6.33±4.26*</td>
<td>6.84±4.24*</td>
</tr>
</tbody>
</table>

IAD, interadventitial diameter; LD, lumen diameter; IMT, intima-media thickness. Other abbreviations see in Table 1.

*p=0.001 vs control, **p<0.05 vs control.

### Fig 1
Comparison of the prevalence of subjects without plaques, and representative plaques to measure the gray-scale medium (GSM), echolucent plaques and echogenic plaques among control, acute coronary syndrome (ACS), and stable coronary artery disease (CAD) groups.

*p<0.001 vs other groups; **p<0.001 vs ACS; §p=0.006 vs control.

### Fig 2
Comparisons of the gray-scale medium between control subjects (n=62) and patients with acute coronary syndrome (ACS; n=158) or with stable coronary artery disease (CAD; n=152). (Open circle) Individual gray scale medium values, (Bar with closed circle) mean ± SD. *p<0.001 vs ACS group.

between the ACS and stable CAD groups.

A larger proportion of subjects in the control group (34 subjects, 35.4%) had no plaques than in the ACS (14 patients, 8.1%) and stable CAD groups (14 patients, 8.4%, Fig 1). After these subjects excluded, the GSM in the ACS group was lower (47.5±25.3) than in the control (70.1±22.5) and stable CAD groups (73.7±23.4, Fig 2).

Univariate logistic regression analysis revealed that serum low-density lipoprotein-cholesterol concentration, serum high-density lipoprotein-cholesterol (HDL-C) concentration, IMT, plaque score, and GSM were predictors.
for patients with ACS (Table 3). In the multiple logistic regression analysis, GSM was identified as an independent predictor for ACS, as was the serum HDL-C concentration (Table 3, multivariate analysis model I).

The ROC analysis revealed that a cutoff value for GSM \(< 60.5\) provided the best separation between subjects with and without ACS (sensitivity: 0.68, specificity: 0.76, Fig 3). Based on that result, carotid plaques with GSM \(\leq 60\) were defined as echolucent, and those with GSM \(> 60\) defined as echogenic. A larger proportion of patients in the ACS group (45 patients, 26.2\%) had echolucent plaques than in the stable CAD (100 patients, 60.2\%) and control groups (47 subjects, 49.0\%). Univariate logistic regression analysis revealed that presence of an echolucent plaque was a predictor for ACS (Table 3). In the multiple logistic regression analysis model in which the presence of an echolucent plaque was adopted instead of GSM, it was identified as an independent predictor for ACS (Table 3, model II).

In a subanalysis of a study population composed of the patients with ACS and control subjects, univariate logistic regression analysis revealed that serum HDL-C concentration, hemoglobin A1c, presence of hypertension, current smoking, IAD, IMT, plaque score, and presence of echolucent plaque were predictors for ACS (Table 4). In the multiple logistic regression analysis, presence of echolucent plaque, plaque score, and serum HDL-C concentration were identified as independent predictors for ACS.

**Discussion**

The present study showed a higher prevalence of echolucent carotid plaques in patients with their first ACS event, compared with those with stable CAD and the control subjects. Carotid echolucent plaques were an independent predictor for ACS.

**Echolucent Carotid Plaques and Plaque Vulnerability**

The present study used the GSM to assess carotid plaque echogenicity. In previous studies, various subjective or objective methods have been used to assess carotid plaque echogenicity. The lack of a uniform method is an important problem because it can affect the results of studies. However, the GSM is a reliable and objective measure of carotid echogenicity.\(^\text{13}\) In the recent study by Ito et al,\(^\text{16}\) an integrated backscatter analysis was also used as an objective method of assessing carotid plaque characterization. They examined
the effects of statin therapy on the arterial wall using integrated backscatter ultrasound, and showed that the quantification of plaques tissue characterization was could objectively identify the effect of the therapy. Therefore, the objective assessment of carotid plaque morphology is an advantage of the present study.

The present study showed that there was a lower echogenicity of carotid plaques in patients with ACS. Recently, Honda et al. showed a lower echolucency of carotid plaques, which was identified by an integrated backscatter method in patients with ACS, compared with patients with stable CAD. Furthermore, they showed that carotid echolucent plaques could predict future coronary complications in patients with stable CAD. In another cohort study of patients undergoing carotid endarterectomy, echolucent carotid plaques identified subjectively were associated with future cardiovascular events, including AMI as well as recurrent carotid stenosis.11

In the present study, because most carotid ultrasound examinations were performed within 2 weeks after the first ACS event, the results could reflect the carotid characteristics before the ACS event, and might correspond to the findings of the cohort studies. Vulnerable carotid plaques have common histologic features with those of the coronary arteries; namely, a thin fibrous cap, large lipid core, and high macrophage content.8,9 Such histologic features tend to be found in echolucent carotid plaques. Therefore, carotid plaque morphology based on echolucency might predict coronary plaque instability. Recently, it has been shown that complex carotid plaque, defined as having an irregular surface and/or heterogeneous echogenicity, is more prevalent in patients with unstable AP compared with those with stable CAD.17 Those researchers found that the C-reactive protein concentration was independently associated with complex carotid plaques. Therefore, systemic inflammatory responses play an important role in the vulnerability of both the coronary and carotid arteries.18

**Carotid Plaque Burden in ACS**

The present study showed that the plaque score was independently associated with ACS in the subanalysis of the ACS and control groups. We evaluated not only the common carotid IMT, but also the plaque score as a marker of the total carotid plaque burden. Measuring only the far wall of the common carotid artery within a specified distance of the carotid bifurcation might risk missing important information in other parts of the vessel, as it has been demonstrated that the common carotid IMT is weakly correlated with coronary atherosclerosis.19 Therefore, estimation of the total carotid plaque burden is a more specific predictor of atherosclerosis, as it has been demonstrated that the combined measurement of the common carotid and internal carotid IMT at the far and near walls of the arteries is a better predictor of cardiovascular events than the thickness measurement taken from the common carotid IMT alone.15 and that the total plaque cross-sectional area measured on longitudinal images of the common, internal, and external carotids is a better predictor of acute coronary events.16 In contrast, the plaque score was not an independent predictor for ACS in the total study population, which might be related to the increased plaque score in patients with stable CAD. The results suggest that the total carotid plaque burden has the potential to predict populations at high risk for ACS, but it might represent the extent of atherosclerosis rather than arterial vulnerability.

**Carotid Arterial Structures and ACS**

The present study did not demonstrate a difference in carotid arterial structure between patients with ACS and those with stable CAD. Kato et al. recently demonstrated an association between angiographically complex coronary plaques, which may represent vulnerable coronary plaques, in patients with ACS and progression of expansive (positive) carotid artery remodeling.9 The Cardiovascular Health Study showed an association between carotid arterial hypertension with increased vascular mass and development of new cardiovascular disease. Those studies suggest that coronary plaque vulnerability can be estimated from carotid arterial remodeling patterns. In contrast, the present study showed that the common carotid LD did not differ between control subjects and patients in the CAD groups, corresponding to the result that was reported in a comparison between patients with stable CAD and disease-free control subjects.15 Recently, it has been demonstrated that the common carotid LD does not affect the magnitude of the association of common carotid IMT to the risk of AMI.22 These results suggest that common carotid remodeling, which mainly depends on the increased IMT, occurs commonly in patients with CAD and partially represents the increased plaque burden.

**Study Limitations**

The present study had a cross-sectional design, but the usefulness of carotid plaque echolucency assessment in identifying populations at high risk of future cardiovascular events should be determined by longitudinal evaluation. However, the ACS group in the present study consisted of patients with their first ACS event, and the patients were studied early after the occurrence of ACS. Therefore, the carotid arterial characteristics in this ACS group may represent those in populations at high risk for ACS.

In the control group, we did not perform coronary angiography to confirm the presence of coronary atherosclerosis, which may have affected our results. Carotid plaque characterization by GSM canceled the heterogeneity of gray-density images in the plaques. Based on pathologic studies, this heterogeneity carries important information concerning plaque vulnerability.17 In heterogeneous regions, the value of GSM analysis may be increased by analyzing pixel distribution over the echogenic regions within the plaque of interest. Therefore, the GSM of plaques in the present study may have underestimated the prevalence of vulnerable carotid plaque.

The present study did not evaluate serum C-reactive protein concentrations, although that may have provided additional information.17,18 In patients with AMI, C-reactive protein concentrations are often increased at the time of admission, probably because of inflammatory responses by the myocardium at risk of infarction. Therefore, it was difficult to determine the representative value for C-reactive protein. In addition, Choi et al. showed that C-reactive protein concentrations were not associated with carotid atherosclerosis in patients with hypertension. Thus, the relationship between carotid atherosclerosis and C-reactive protein concentrations has not been identified and needs to be confirmed in large population-based studies.

**Conclusion**

The present study demonstrated a higher prevalence of carotid echolucent plaques in patients with their first ACS,
compared with those with stable CAD and control subjects. Carotid arterial structure and plaque burden differed between patients with their first ACS and control subjects, but not between patients with ACS and stable CAD. Because the presence of echolucent carotid plaque was independently associated with first ACS, it may be a surrogate marker for identifying patients at high risk for ACS.

References