Clinical Implications of Carotid Artery Remodeling in Acute Coronary Syndrome

Ultrasonographic Assessment of Positive Remodeling

Masaya Kato, MD, Keigo Dote, MD, Seiji Habara, MD, Hiroaki Takemoto, MD, Kenji Goto, MD, Koichi Nakaoka, MD

Hiroshima, Japan

OBJECTIVES
We investigated the relationship between ultrasonographic features of the carotid artery and the angiographic features of coronary plaques in acute coronary syndrome (ACS).

BACKGROUND
The carotid intima-media thickness (IMT) may be a marker of advanced coronary artery disease.

METHODS
Consecutive ACS patients (N = 125) underwent B-mode ultrasonography within one week of the acute coronary event. Using a 7.5-MHz linear array transducer, the common carotid IMT, interadventitial diameter, and luminal diameter were examined. Carotid plaques were also assessed. Then patients were divided into two groups based on the number of complex plaques identified by coronary angiography.

RESULTS
The carotid IMT of 75 patients with multiple complex coronary plaques was significantly larger than that of 50 patients with solitary plaques (p < 0.0003). The prevalence of soft and hard carotid plaques was higher in the group with multiple coronary plaques than in those with single plaques (28% vs. 12%, p < 0.04 and 13% vs. 0%, p < 0.008, respectively). Additionally, the carotid interadventitial diameter was larger in the patients with multiple plaques than in those with single plaques (7.93 ± 0.97 mm vs. 7.48 ± 0.88 mm, p < 0.01), and a significant correlation was observed between the carotid IMT and interadventitial diameter (R = 0.54, p < 0.0001).

CONCLUSIONS
In ACS, multiple complex coronary plaques are associated with positive carotid remodeling, suggesting that plaque vulnerability may be a systemic phenomenon. (J Am Coll Cardiol 2003;42:1026–32) © 2003 by the American College of Cardiology Foundation

High-resolution B-mode ultrasonography has proved to be a valid and reliable method of detecting initial structural atherosclerotic changes of the arterial walls. The carotid intima-media thickness (IMT) may be clinically useful as a marker of the development of atherosclerosis in the setting of various risk factors, as well as a marker of the response to therapy for atherosclerosis, a predictor of events, and a marker of advanced vascular disease in the peripheral, carotid, and coronary circulations (1–5). An increased IMT has been shown to prospectively predict myocardial infarction (MI) and stroke (3). Although rupture of coronary artery plaques and subsequent thrombotic occlusion is implicated in the pathogenesis of acute MI, many investigators (6–8) have reported that coronary occlusion and MI most frequently evolve at sites of mild to moderate stenosis. This has given rise to the notion that less obstructive plaques are more lipid-rich and vulnerable to rupture than larger plaques. Recent studies (9–12) have demonstrated that ruptured and adjacent non-ruptured plaques in patients with acute coronary syndrome (ACS) are usually associated with compensatory vascular enlargement (13) and with a large plaque burden, and that there is frequently a disease-free arc of the vessel wall. The aim of this study was to assess whether there was any relationship between the ultrasonographic features of the carotid arteries and the angiographic morphology of coronary plaques in ACS patients.

METHODS

Study population. This study included 125 consecutive ACS patients who were admitted to the Coronary Care Unit of Hiroshima City Asa Hospital. The patients had ischemic chest discomfort with ST-segment elevation or depression of >0.5 mm or T-wave inversion in two or more leads. Among them, 112 patients had acute MI diagnosed on increased serum levels of creatine kinase (CK) (more than twice the upper limit of normal) and creatine kinase-MB fraction (CK-MB) (>10% of total CK). Thirteen patients showed no CK-MB elevation, and these patients were classified as having unstable angina. All patients underwent angiography to document the culprit coronary lesions within 24 h after the onset of chest pain. Patients with a history of MI, coronary artery bypass grafting, or carotid surgery were excluded. Informed consent was obtained from all patients after an explanation of the study, and the study was approved by the institutional ethics committee.

Coronary angiography. Coronary angiography was performed by the standard Judkins technique and was analyzed as previously described, with substantial lesions (which

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narrowed the vessel diameter by 50% or more) being measured quantitatively (14). Complex coronary plaques were identified according to the following previously used criteria (15–17): an intraluminal filling defect consistent with thrombus, defined as abrupt vessel cutoff with persistence of contrast or an intraluminal filling defect in a patent vessel within or adjacent to a stenotic region with surrounding homogeneous opacification by contrast; plaque ulceration, defined as the presence of contrast and a hazy contour beyond the vessel lumen; plaque irregularity, defined as irregular margins or overhanging edges; and impaired flow. Lesions were considered complex if there was >50% luminal narrowing and two or more of these morphologic features, whereas lesions characteristic of chronic total occlusion or more than 50% luminal narrowing without plural these morphologic features were considered simplex.

The location of the culprit plaque was determined by correlating the presence of a complex plaque with electrocardiographic and wall motion abnormalities. In each patient, the coronary vasculature was reviewed to identify cardiographic and wall motion abnormalities. In each patient, correlating the presence of a complex plaque with electrocardiographic and wall motion abnormalities, these morphologic features were considered simplex.

leading edge of the first echogenic line to the leading edge of the second echogenic line, as defined by Pignoli et al. (18). The first line represented the luminal-intimal interface and the collagen-containing upper layer of the tunica adventitia formed the second line. The distance from the first line of the near wall to that of the far wall was defined as the luminal diameter, and the distance from the second line of the near wall to that of the far wall was defined as the interadventitial diameter (Fig. 1). Using longitudinal images, the maximum and minimum IMT values of the far wall, the average of the maximum and minimum IMT values, and the maximum luminal diameter and interadventitial diameter were determined by the same operator (M.K.), who was blinded to the results of coronary angiography. All measurements were made using electronic calipers. High echoic segments of the carotid wall were identified as calcified atherosclerotic segments. The morphology of common carotid artery with the mean value of maximum and minimum carotid IMT >1.1 mm and the interadventitial diameter >8.0 mm was defined as the positive remodeling. The reproducibility of measuring the IMT and the interadventitial diameter was examined in 20 patients who underwent scanning twice at an interval of two weeks. Ultrasound was performed by two trained sonographers each time. The mean difference of the maximum IMT and the interadventitial diameter between the two determinations was 0.01 and 0.03 mm, and the standard deviation was 0.02 and 0.04 mm, demonstrating good reproducibility of the measurements.

Carotid plaques were assessed as follows. A plaque was defined as a distinct area with an IMT 50% thicker than the neighboring sites on visual assessment. Plaques were divided into two types. Soft plaques were defined as low echoic or isoechoic structures without any high echoic region indicating calcification, whereas hard plaques contained a high echoic area of atherosclerotic calcification.
Table 1. Clinical Characteristics of ACS Patients With Single and Multiple Coronary Plaques

<table>
<thead>
<tr>
<th></th>
<th>Single-Plaque Group</th>
<th>Multiple-Plaque Group</th>
<th>p Values</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>63 ± 10</td>
<td>64 ± 9</td>
<td>0.76</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>39/11</td>
<td>60/15</td>
<td>0.79</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 ± 7</td>
<td>160 ± 8</td>
<td>0.65</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>59 ± 8</td>
<td>61 ± 9</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>56</td>
<td>69</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>30</td>
<td>51</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>62</td>
<td>56</td>
<td>0.50</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>52</td>
<td>40</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemic family history (%)</td>
<td>12</td>
<td>11</td>
<td>0.82</td>
</tr>
<tr>
<td>Oral drug therapies (%)</td>
<td>Calcium channel blockers 18</td>
<td>17</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Antiplatelet agents</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Nitrates</td>
<td>8</td>
<td>8</td>
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Values are the mean ± SD.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome.

Statistical analysis. Results are presented as the mean ± SD. Univariate analysis was performed using Student’s t test. Categorical data were compared against a chi-squared distribution. Linear regression analysis was used to determine the relationship between continuous variables, and p < 0.05 was considered statistically significant. Clinical and coronary angiographic variables were entered into a multivariate logistic regression model of carotid positive remodeling to test for their independent effects. Age, gender, and the presence of MI, hypertension, diabetes, hyperlipidemia, current smoking, and ischemic family history (only including coronary artery disease [CAD]) represented the independent clinical variables, and the presence of multiple complex plaques, simplex plaques, multivessel disease, and the culprit vessel represented the independent coronary angiographic variables. Odds ratios and 95% confidence methods were calculated to assess predictive value.

RESULTS

The clinical characteristics of the two groups are shown in Table 1. There were no significant differences between the groups, except for the prevalence of diabetes mellitus. Half of patients in the multiple-plaque group had diabetes mellitus. Seventy-two percent of diabetic ACS patients had multiple coronary plaques. Coronary angiographic findings in the patients with solitary and multiple coronary plaques are shown in Table 2. Acute MI showed a similar incidence in both groups.

B-mode ultrasonographic features of the common carotid artery are shown in Table 3. In ACS patients with multiple complex coronary plaques, the carotid IMT was significantly larger than in patients with solitary plaques. Although the carotid luminal diameter was similar in the two groups, the patients with multiple complex plaques had a significantly greater carotid interadventitial diameter than did the patients with solitary complex plaques. The frequency of soft plaques and carotid calcification was also higher in the multiple-plaque group. Furthermore, no patient from the single-plaque group had hard carotid plaques (Fig. 2). There was a significant positive correlation between the carotid IMT and the interadventitial diameter ($r = 0.54$, p < 0.0001), and the carotid IMT and the ratio of the interadventitial diameter to the luminal diameter ($r = 0.58$, p < 0.0001) (Fig. 3).

The strongest independent predictor of the carotid positive remodeling was the presence of multiple complex coronary plaques (Table 4). The presence of coronary simplex plaques had no significant influence on carotid positive remodeling (p = 0.75). Among the clinical variables, the presence of hypertension and diabetes mellitus was a strong predictor of carotid positive remodeling.

DISCUSSION

This is the first study to show that ACS patients with multiple complex coronary plaques have a larger carotid IMT and also a larger common carotid diameter when compared with ACS patients who have solitary plaques. Glagov et al. (13) demonstrated a positive correlation between arterial size and plaque area, which was particularly strong for segments of the coronary arteries with ≤20% stenosis, and showed that a decrease of the luminal area only became evident for stenosis >40%. Because the carotid...
luminal diameter was similar in the two patient groups and a significant positive correlation existed between carotid IMT and interadventitial diameter, carotid wall thickness and vascular enlargement might be associated with positive vascular remodeling. Multiple complex coronary plaques might imply the progression of positive carotid remodeling. The various carotid ultrasonographic features of the ACS patients are shown in Figure 4. Most of the patients with solitary discrete plaques had a normal IMT and little vascular enlargement. However, the patients with multiple or diffuse coronary plaques showed carotid enlargement, an increase of the IMT, an increase of soft plaques, and calcified hard plaques, indicating more advanced coronary atherosclerosis.

Although many investigators have reported about the carotid artery morphology, few studies have quantified the association between carotid plaques and risk of subsequent stroke. The Cardiovascular Health Study (19) and the Rotterdam Study (20) are the only two population-based cohort studies that have investigated carotid plaques in relation to subsequent stroke in asymptomatic subjects. The Cardiovascular Health Study focused on characteristics of the most prominent plaque in the bifurcation or internal carotid artery and concluded that hypoechoic but not hyperechoic plaques increased the risk of ischemic stroke. The Rotterdam Study (20) also reported a relation between number of sites affected with plaques and risk of stroke, but no differences in risk associated with plaques located at different sites in the carotid arteries. These results suggest that the hypoechoic carotid plaques might be vulnerable and sources of thromboembolism. Therefore, positive remodeling of carotid artery also could be a marker of cerebrovascular disease, as well as coronary vascular disease.

Several investigators (6–8) have reported that acute coronary events most frequently evolve at sites of mild to moderate stenosis, giving rise to the notion that less

<table>
<thead>
<tr>
<th>Table 3. Ultrasonographic Measurements of the Common Carotid Arteries</th>
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<tr>
<td><strong>Single-Plaque</strong></td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>IMT&lt;sub&gt;mean&lt;/sub&gt; (mm)</td>
</tr>
<tr>
<td>IMT&lt;sub&gt;min&lt;/sub&gt; (mm)</td>
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<tr>
<td>IMT&lt;sub&gt;max&lt;/sub&gt; (mm)</td>
</tr>
<tr>
<td>IMT&lt;sub&gt;mean&lt;/sub&gt; &gt; 1.1 mm (%)</td>
</tr>
<tr>
<td>IAD (mm)</td>
</tr>
<tr>
<td>IAD &gt; 8.0 mm (%)</td>
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<tr>
<td>LD (mm)</td>
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Values are the mean ± SD. 
IAD = interadventitial diameter; IMT<sub>max</sub> = maximum carotid intima-media thickness (IMT); IMT<sub>mean</sub> = mean value of maximum and minimum IMT; IMT<sub>min</sub> = minimum carotid IMT; LD = luminal diameter.

Figure 2. Frequency of soft plaques, hard plaques, and calcification in the common carotid artery. Acute coronary syndrome patients with multiple coronary plaques had more carotid plaques and calcification compared with patients who only had a single coronary plaque. Open bars = single-plaque group; closed bars = multiple-plaque group.

Figure 3. Relationship between the mean of the maximum and minimum common carotid intima-media thickness values (IMT<sub>mean</sub>) and the inter-adventitial diameter (IAD) (top panel), and IMT<sub>mean</sub> and the ratio of IAD to the luminal diameter (LD) (bottom panel) in acute coronary syndrome patients. A significant positive correlation exists between IMT<sub>mean</sub> and IAD, and IMT<sub>mean</sub> and the ratio of IAD to LD.
Obstructive plaques are more lipid-rich and vulnerable to rupture than more stenotic plaques. Angiography cannot be used to predict events induced by the rupture of plaques that are only associated with mild to moderate stenosis. Previous histopathological (9,10) and intravascular ultrasound (IVUS) studies (10–12) have demonstrated that ruptured plaques and adjacent non-ruptured plaques were predominantly associated with compensatory vascular enlargement, a large plaque burden, and a disease-free arc of the vessel wall. These findings suggest that positive vascular remodeling and eccentric plaque distribution may be important triggers of acute coronary events. On the other hand, negative remodeling associated with a circumferential plaque distribution and adventitial thickening are more common in patients with stable symptoms (9–12). Our present results suggest that plaque vulnerability might be a systemic phenomenon, rather than a regional one. The presence of multiple complex coronary plaques was reported to be associated with an increased incidence of recurrent ACS (17,21). Furthermore, a recent study (22) demonstrated that neutrophil myeloperoxidase counts were significantly lower in patients with ACS than in those with chronic stable angina, suggesting the systemically widespread inflammatory process. Also, the vulnerability of solitary discrete coronary plaques could not be predicted by B-mode ultrasonographic observation of the carotid artery without a direct observation by coronary angioscopy or IVUS (10–12,23).

Our definition of positive remodeling of the carotid arteries is based on absolute measurements of IMT and interadventitial diameter rather than comparison to a reference site. However, the reference site could not be set because the vascular remodeling may be a systemic phenomenon. Therefore, we defined the carotid positive remodeling as the mean carotid IMT >1.1 mm and the interadventitial diameter >8.0 mm based on previous observational findings (24–26). Our results of significant independent predictors of the defined carotid positive remodeling suggest that systemic positive vascular remodeling might be more common in hypertension and diabetes mellitus. Previous studies (27,28) demonstrated that the vascular remodeling of carotid artery in patients with untreated hypertension was associated with compensatory carotid enlargement. This vascular remodeling might be associated with circulating neurohormonal factors, as well as high blood pressure. On the other hand, Haffner et al. (29) have reported that type 2 diabetics without clinical CAD had a slightly larger IMT than nondiabetics with CAD. Furthermore, Yamazaki et al. (30) demonstrated that progression of carotid IMT was associated with a high incidence of CAD in type 2 diabetics. Our results suggest that the carotid interadventitial diameter as well as carotid IMT could be an additional predictor of acute coronary events by demonstrating systemic plaque vulnerability in diabetics.

Recent studies (31–33) have demonstrated that lowering of lipid levels with statin therapy could reduce inflammation and stabilize vulnerable coronary plaques, leading to a lower incidence of cardiac events. Furthermore, inhibition of angiotensin II by angiotensin–converting enzyme inhibitors or angiotensin II receptor blockers might have an anti-inflammatory effect and stabilize vulnerable plaques (34,35). It is possible that positive remodeling of the carotid artery might indicate the efficacy of such treatments for preventing the rupture of vulnerable plaques in ACS patients. Further
investigations may provide useful information for the management of patients with positive carotid arterial remodeling.

**Study limitations.** In the present study, we did not include a control group without ACS, especially with stable coronary syndromes. Because carotid IMT and the other ultrasonographic findings in ACS patients were not compared with these parameters in control group without ACS, it was uncertain whether positive remodeling in carotid arteries was proper to ACS. Based on the previous studies (9–12, 22), patients with stable coronary syndromes would have a lower incidence of plaque instability and might have demonstrated different carotid ultrasonographic findings compared with ACS patients. However, the carotid plaque morphology of these patients could not be simply compared with that of ACS patients because patients with stable coronary syndromes would be divided into more subgroups based on the clinical features and coronary angiographic findings. Further investigations seem to be needed to set a suitable control group.

As the recent Rotterdam study (20), we defined a distinct area with an IMT 50% thicker than the adjacent segments as a carotid plaque. The evaluation was made by “eyeballing” judgement without measuring the thickness of the lesions or of the adjacent structure and a diffusely diseased artery may not have any plaque. Alternatively, several studies defined a localized thickening >1.1 mm as a common carotid plaque. However, the differences in the definition did not affect our results because more patients in the multiple-plaque group had diffuse carotid plaques using this definition.

As an alternative to IMT, a recent review (36) demonstrated the use of ultrasound measurements of plaque area and plaque volume as surrogate outcomes for CAD. Previous histopathological and IVUS studies in human coronary arteries (9–12) have demonstrated the importance of eccentric plaque distribution for the triggers of acute events. Because we measured the ultrasonographic variables using carotid longitudinal images, the eccentricity of lesions could not be fully recognized.

**Conclusions.** Our study demonstrated that multiple complex coronary plaques in ACS patients are associated with the progression of positive carotid arterial remodeling, thus suggesting that plaque vulnerability may be a systemic phenomenon.

**Reprint requests and correspondence:** Dr. Masaya Kato, Department of Cardiology, Hiroshima City Asa Hospital, 2-1-1 Kabeiminami, Asakita-ku, Hiroshima 731-0293, Japan. E-mail: ms-katou@ASA-HOSP.CITY.HIROSHIMA.JP.

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