Significance of Earlier Carotid Atherosclerosis for Stroke Subtypes

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Background and Purpose—In addition to advanced stenosis, earlier stages of carotid atherosclerosis are associated with the risk for stroke. However, the significance has not been established for specific stroke subtypes. This study examines the association of earlier carotid atherosclerosis with stroke subtypes.

Methods—The subjects comprised 1059 patients (mean SD age, 62 ± 11 years) with <60% carotid stenosis. With the use of ultrasound, carotid atherosclerosis was evaluated by the plaque score, as defined by the sum of all plaque heights in bilateral carotid arteries. On the basis of neurological signs and symptoms, medical history, and brain MRI, we diagnosed stroke and its subtypes as follows: no stroke (n = 738), atherothrombotic infarction (AI) (n = 56), lacunar infarction (LI) (n = 117), cardioembolic infarction (n = 65), cerebral hemorrhage (n = 26), and other or unclassified stroke (n = 57).

Results—The plaque score was higher in AI (10.5 ± 5.9) and LI (6.0 ± 5.1) groups than in the no-stroke group (4.3 ± 4.9) (both P < 0.05), although it was similar between other stroke groups and the no-stroke group. Each 1 SD greater plaque score was associated with 2.5-fold (95% CI, 2.0 to 3.2) higher risk for AI and 1.4-fold (95% CI, 1.2 to 1.7) higher risk for LI compared with the no-stroke group. When we adjusted for cardiovascular risk factors, plaque score remained significantly associated with AI but not with LI. By receiver operating characteristic curve analyses, the receiver operating characteristic area for AI (0.81 to 0.86) was greater than that for LI (0.62 to 0.67) when we used plaque score either alone or in combination with cardiovascular risk factors.

Conclusions—Although evaluation of carotid atherosclerosis may aid in the risk assessment for AI and LI, the benefit appears to be greater for AI. (Stroke. 2001;32:1780-1785.)

Key Words: atherosclerosis ■ carotid arteries ■ risk assessment ■ ultrasonography

Development of ultrasound technology has allowed for a noninvasive evaluation of atherosclerosis in the carotid arteries. The initial manifestation is characterized by a subtle increase in vascular intima-media thickness (IMT), whose progression leads to plaque formation and vascular narrowing. Because advanced carotid stenosis often impairs cerebral blood flow and becomes the nest for emboli, carotid ultrasound examination is most often performed for the diagnosis and risk assessment of stroke. With the use of ultrasound, studies have shown that carotid stenosis ≥70% increases the incidence of future stroke, whereas the risk is limited when the stenosis is ≤60%.1 Thus, carotid stenosis, as the result of advanced atherosclerosis, is a well-defined risk factor for stroke.

In addition to such advanced lesions, earlier carotid atherosclerosis, without direct threat to the brain, has been linked to an elevated risk for stroke. The linkage is supported by an association between carotid and systemic atherosclerosis.2-5 As a reflector of systemic atherosclerosis, increased carotid artery IMT has been associated with a higher risk for stroke. In the Rotterdam Study6 and the Cardiovascular Health Study,7 each 1 SD change in IMT increased the incidence of future stroke by approximately 30%, independent of traditional cardiovascular risk factors. In addition, existence of carotid artery plaques was associated with transient ischemic attack (TIA),8 and the enlargement increased the risk for future neurological events.9 On the basis of these findings, carotid atherosclerosis, even in the absence of advanced stenosis, appears to be associated with the risk for stroke.

However, stroke is a heterogeneous disease that comprises several subtypes with different etiologies. Because atherosclerosis is a precursor of atherothrombotic infarction (AI), carotid atherosclerosis is a reasonable risk factor for this stroke subtype. This rationale is reinforced by an association between carotid and major cerebral artery atherosclerosis.2 By contrast, lacunar infarction (LI) is most often the result of
lipohyalinosis, fibrinoid necrosis, or microatheroma in intracerebral small arteries, diluting the significance of carotid atherosclerosis for this stroke subtype. Moreover, atherosclerosis is not likely to play a direct role in cardioembolic infarction (CE), intracerebral hemorrhage, and subarachnoid hemorrhage. Nevertheless, associations between carotid atherosclerosis and the specific stroke subtypes have not been established. Knowledge of these associations would refine the utility of carotid ultrasound evaluation for the risk assessment of stroke.

Given the recent debates regarding whether IMT represents focal atherosclerosis, Ebrahim et al have shown that carotid artery plaques are more strongly associated with elevated cardiovascular risk than a diffuse increase in IMT. To quantitatively evaluate plaques, Handa et al used a scoring system that is currently known as the plaque score (PS). PS is defined as the sum of all plaque heights in bilateral extracranial carotid arteries. PS is associated with traditional cardiovascular risk factors and is higher in subjects with stroke and silent cerebral infarction. We have shown a utility of PS for the prediction of future stroke in a population at higher cardiovascular risk.

This study examines the association of PS with specific stroke subtypes.

Subjects and Methods

Subjects

The subjects for this cross-sectional study were enrolled from patients of the Department of Internal Medicine and Therapeutics at Osaka University Hospital who had undergone carotid ultrasound examination between January 1996 and August 2000. Many of them had a history of stroke and/or cardiovascular risk factors such as hypertension, hyperlipidemia, and diabetes. In addition, they included patients with nonspecific neurological complaints such as dizziness, vertigo, headache, and memory disturbances. The majority of patients had been referred from other hospitals or departments for the assessment of cerebral circulation, for the secondary prevention of stroke, or for perioperative risk assessment before surgery. Because of the high prevalence of stroke and its risk factors, carotid ultrasound examinations were performed for the screening of carotid atherosclerosis and stenosis or, in some cases, for the assessment of vertebrobasilar circulation.

To mitigate direct threats to cerebral circulation and to focus on atherosclerosis per se, patients with the following characteristics were excluded: (1) patients with carotid stenosis ≥60% or occlusion by duplex ultrasound; (2) patients who had had carotid endarterectomy; (3) patients with collagen diseases, including Takayasu’s arteritis and systemic lupus erythematosus; (4) patients with TIA, because TIA is highly heterogeneous and often very similar to stroke but not classified as stroke; and (5) patients with stroke within the preceding 2 weeks, because of the hemodynamic and metabolic modulations often observed after the events.

During the study period, 1197 patients had undergone carotid ultrasound examination, of whom 138 patients met any of the above criteria and were excluded. As a consequence, the subjects for this investigation comprised 1059 patients (mean±SD age, 62±11 years), including 593 men and 466 women.

The protocols for the carotid ultrasound examinations were approved by the Osaka University Institutional Review Board, and informed consent was obtained from all subjects after the nature of the procedures had been fully explained. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Carotid Ultrasonography

Duplex carotid ultrasonography was performed as previously described with the use of linear array 7.5-MHz transducers (EUB-525, Hitachi, Inc; SSA-260A, Toshiba, Inc). In accordance with our previous studies, severity of carotid atherosclerosis was evaluated by PS.

Briefly, the subject lay in the supine position in a dark room, and the examinations were done with the head held in the midline position or slightly tilted to either side. Initially, the common and internal carotid arteries were scanned cross-sectionally and longitudinally, whereby distribution of atheromatous plaques was roughly evaluated. During the initial scanning, optimal insonation angles were determined for the estimation of respective plaque heights, and the measurements were performed on the frozen frame, perpendicular to the vascular walls. Bilateral carotid arteries were examined by the same procedures. Thereafter, PS was computed by summing the maximum thickness of all plaques (local increases in IMT ≥1.1 mm) located in bilateral carotid arteries. Length of individual plaques was not considered for the calculation of this score. Carotid stenosis/occlusion was diagnosed by the commonly used criteria.

All measurements were performed by 5 strokologists (stroke neurologists/cardiologists) skilled in carotid ultrasound examinations (Y.N., Y.S., M.S., H.H., H.Y.), who were unaware of the patients’ cardiovascular data. To achieve higher consistency of imaging procedures and readings, the examiners held a meeting twice a year, during which the ultrasound protocols were reconfirmed. When interobserver reproducibility of PS was assessed for 65 subjects with carotid plaques, the interrater correlation of PS was 0.86, with similar averages between the arbitrary pairs of examiners (10.2±8.5 versus 11.2±8.2; P=NS; average interval, 3.0±2.0 months).

Diagnoses of Stroke and Stroke Subtypes

Neurological signs and symptoms were evaluated by the strokologists of our department when patients visited and/or were admitted to the hospital. Histories of neurological episodes were carefully obtained from the patients and/or their families. On the basis of neurological signs and symptoms and medical history, patients were classified into either stroke or no-stroke groups. The diagnosis of stroke included patients with an acute disturbance of focal neurological function resulting in either signs or symptoms of presumed vascular origin that persisted for >24 hours.

Patients diagnosed as having stroke underwent brain MRI scans (1.5-T Signa Horizon; GE Medical Systems; 1.5-T Magnetom Vision; Siemens, 5.0 mm slice thickness), including T1- and T2-weighted spin-echo images. On the scans, the existence and distribution of intracranial ischemic or hemorrhagic lesions were investigated. Infarction was defined as a focal area showing low and high signal intensity on T1- and T2-weighted images, respectively. Because the appearance of hemorrhagic lesions changes depending on their age, hematomas and their scars were identified in accordance with common criteria. For several patients in whom MRI was contraindicated, surrogate CT scans were performed. All scans were read by neuroradiologists outside the department and thereafter by the strokologists of our department.

On the basis of neurological signs and symptoms, medical history, and brain scans, stroke and its subtypes were diagnosed. Because all evaluations were done as part of routine clinical work, the strokologists involved in diagnoses were not completely blinded to the carotid findings. Thus, to reinforce the diagnostic objectivity, the subtypes were always diagnosed by ≥1 strokologist, with the final diagnoses made by consensus. Stroke subtypes were as follows.

No Stroke

Th diagnosis of no stroke was made when neurological abnormalities or history of cerebrovascular accidents was not identified.

Atherothrombotic Infarction

AI was defined as infarction presumably due to intracranial major artery occlusion with MRI evidence of a large infarction (>15 mm) in areas such as the cortex, semioval center, or watershed area. The lesion had to be in a distribution consistent with the patient’s signs.
TABLE 1. Baseline Characteristics by Stroke Subtype

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>No Stroke</th>
<th>AI</th>
<th>LI</th>
<th>CE</th>
<th>CH</th>
<th>Other*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1059</td>
<td>738</td>
<td>56</td>
<td>117</td>
<td>65</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td>62±11</td>
<td>66±8†</td>
<td>63±8</td>
<td>64±13</td>
<td>60±8</td>
<td>61±15</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>56</td>
<td>49</td>
<td>79†</td>
<td>68†</td>
<td>69†</td>
<td>69</td>
<td>77†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23±3</td>
<td>24±3</td>
<td>23±2</td>
<td>23±3</td>
<td>23±3</td>
<td>24±3</td>
<td>23±3</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>139±20</td>
<td>139±20</td>
<td>147±20</td>
<td>139±18</td>
<td>131±21†</td>
<td>147±21</td>
<td>133±24</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>81±12</td>
<td>81±13</td>
<td>83±11</td>
<td>82±12</td>
<td>77±13</td>
<td>87±12</td>
<td>79±11</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.8±1.4</td>
<td>5.8±1.3</td>
<td>6.8±2.2†</td>
<td>6.0±1.5</td>
<td>5.6±1.4</td>
<td>5.9±1.2</td>
<td>5.8±1.6</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.3±1.0</td>
<td>5.3±1.0</td>
<td>5.1±0.8</td>
<td>5.3±1.0</td>
<td>5.1±1.0</td>
<td>4.9±0.7</td>
<td>5.1±1.0</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>47</td>
<td>41</td>
<td>79†</td>
<td>60</td>
<td>57</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>Hypertension medication use, %</td>
<td>58</td>
<td>59</td>
<td>64</td>
<td>69</td>
<td>31†</td>
<td>85†</td>
<td>39</td>
</tr>
<tr>
<td>Diabetes mellitus medication use, %</td>
<td>12</td>
<td>11</td>
<td>30†</td>
<td>18</td>
<td>9</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Hyperlipidemia medication use, %</td>
<td>27</td>
<td>26</td>
<td>41</td>
<td>34</td>
<td>17</td>
<td>8†</td>
<td>33</td>
</tr>
</tbody>
</table>

For continuous variables, values indicate mean and SD. BP indicates blood pressure.

*Other or unclassified stroke.
†P<0.05 vs no-stroke group (differences are shown only between no-stroke group and each stroke group).

and symptoms and without strong evidence of a separate cardioembolic source. To improve diagnostic accuracy, MR angiography was performed in the majority of these patients.

**Lacunar Infarction**
LI was defined as stroke with consciousness and higher cerebral function maintained in the setting of one of the typical lacunar syndromes: pure motor, pure sensory, pure sensorimotor, ataxic hemiparesis, dysarthria–clumsy hand, pure hemiballismus, or pure hemichorea. The patient had to have an MRI scan after the events that demonstrated a small (<15 mm) deep infarction in the territories supplied by the perforating branches of major cerebral arteries.

**Cardioembolic Infarction**
CE was defined as stroke with a recognized cardioembolic source without definite evidence of large-artery occlusive disease. The embolic source included left atrial thrombus, persistent or paroxysmal atrial fibrillation/flutter, myocardial infarction, prosthetic heart valve, and right-to-left intracardiac shunt with right-sided source of embolism. Percutaneous and/or transesophageal echocardiography was performed in all these patients.

**Cerebral Hemorrhage**
Cerebral hemorrhage (CH) was defined as cerebral, cerebellar, or brain stem hemorrhage as evidenced by the existence of hematoma or its scar. The lesions had to be in a distribution consistent with the patient’s signs and symptoms. This category did not include hemorrhagic infarction occurring after embolic stroke.

**Other or Unclassified Stroke**
This category included cerebral infarction occurring in close temporal relationship to an invasive catheter or surgical procedure other than endarterectomy or due to a rare cause, including vertebral artery dissection, fibromuscular hyperplasia, and moyamoya disease. This category also included definite cerebral infarction not meeting one of the aforementioned criteria or cases in which there was >1 possible explanation for stroke. There could not have been an obvious cardioembolic source or a normal MRI scan. Patients with history of subarachnoid hemorrhage were also included in this category because there were only a few such patients. In addition, scans in which the interpretation would not allow for a reliable classification of traditional stroke subtypes fit into this category.

**Data Analyses**
Cardiovascular risk factors and PS were compared between the no-stroke group and each stroke group by 1-way ANOVA, followed by Tamhane’s multiple comparison test. The risk factors considered in this study were age, male sex, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, serum total cholesterol, their respective medications, and smoking. Blood pressure was measured by sphygmomanometer when neurological evaluations were performed. Smoking status was categorized defined on the basis of self-reports, with a smoker defined by current or past smoking ≥10 cigarettes per day for ≥1 year. Because of the well-known association between carotid atherosclerosis and cardiovascular risk factors, PS was further compared between the no-stroke group and each stroke group by adjusting for age and sex and subsequently by adjusting for all the aforementioned risk factors. The ability of PS to stratify specific stroke subtypes was examined by logistic regression analyses, followed by receiver operating characteristic (ROC) curve analyses.

Data are presented as mean±SD unless otherwise specified. A 2-tailed P value <0.05 was considered statistically significant. All analyses were performed with the use of SPSS 9.0 (SPSS Japan Inc).

**Results**

**Baseline Characteristics**
Baseline characteristics of the study sample are shown in Table 1. Stroke was diagnosed in 321 of 1059 subjects, including 56 AI (17% of total stroke), 117 LI (36%), 65 CE (20%), 26 CH (8%), and 57 other or unclassified stroke (18%). In the no-stroke group and the specific stroke groups, average levels of systolic blood pressure and use of hypertensive medication were relatively high, although the mean values for body mass index and serum total cholesterol were within normal limits. Compared with the no-stroke group, the percentages of men and smokers were generally higher in the stroke groups. Of note, cardiovascular risk factors were most prevalent in the AI group.

**PS in Patients With Specific Stroke Subtypes**
As a measure of carotid atherosclerosis, PS was higher in the AI and LI groups than in the no-stroke group, whereas significant differences were not found between other stroke groups and the no-stroke group (Figure, Table 2). However, the magnitude of PS may be influenced by cardiovascular risk factors in each group. When we adjusted for age and sex, PS continued to be higher in the AI and LI groups than in the
no-stroke group. After further adjustments for cardiovascular risk factors, the difference in PS persisted between the AI and no-stroke groups but diminished between the LI and no-stroke groups.

**PS for Stratifying Specific Stroke Subtypes**

If PS is higher in AI and LI patients, it may be of value for risk assessment. To examine the contribution of PS to stratify these stroke subtypes, we performed logistic regression analyses with either AI or LI as an end point (Table 3). Because the risk for the respective end points appeared to increase log-linearly with PS (data not shown), we computed the odds ratios associated with 1 SD increase in PS (1 SD = 5.3 for all subjects). In univariate analyses (model 1), each 1 SD greater PS was associated with 2.5-fold higher risk for AI and 1.4-fold higher risk for LI compared with the no-stroke group. Adjustments for age and sex modified these associations only slightly (model 2). After additional adjustments for other risk factors (model 3), PS remained independently associated with AI but not with LI. Given these results, the ability of PS to stratify AI and LI was further examined by ROC curve analyses. Although the area under ROC curves was >0.5 for both AI and LI (Table 3, models 1 to 3), the ROC area for AI was greater than that for LI in all models.

**Discussion**

In addition to advanced stenosis, earlier stages of carotid atherosclerosis have been associated with the risk for stroke.

### Table 3. Stratification of AI and LI by PS

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS-associated OR*</td>
<td>2.5 (2.0–3.2)†</td>
<td>2.2 (1.7–2.9)†</td>
<td>1.8 (1.3–2.4)†</td>
</tr>
<tr>
<td>ROC area</td>
<td>0.81 (0.76–0.86)†</td>
<td>0.81 (0.75–0.86)</td>
<td>0.86 (0.82–0.91)</td>
</tr>
<tr>
<td>LI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS-associated OR*</td>
<td>1.4 (1.2–1.7)†</td>
<td>1.3 (1.0–1.6)†</td>
<td>1.2 (0.9–1.5)</td>
</tr>
<tr>
<td>ROC area</td>
<td>0.62 (0.56–0.67)†</td>
<td>0.64 (0.58–0.69)</td>
<td>0.67 (0.62–0.72)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI. In model 1, only PS is included in the model; model 2, PS + age + sex; model 3, PS + age + sex + cardiovascular risk factors.

*Odds ratio (OR) associated with 1 SD change in PS.

†P<0.05.

However, the significance for specific stroke subtypes has not been established. As a measure of earlier carotid atherosclerosis, the present study demonstrated higher PS in the AI and LI groups than in the no-stroke group. When we adjusted for traditional cardiovascular risk factors, the difference in PS persisted between the AI and no-stroke groups but diminished between the LI and no-stroke groups. Additionally, although PS was associated with the risk for both AI and LI, risk assessment by PS appeared to be more effective for AI.

Because the study sample comprised patients of our department, the prevalence of cardiovascular risk factors and stroke was generally high (Table 1), with 1 of 3 patients having a diagnosis of stroke. The percentages of major stroke subtypes were similar to those reported for the Japanese cohort, although the proportion of LI was higher than in Western countries. Compared with the no-stroke subjects, cardiovascular risk factors were more prevalent in the specific stroke groups, with the highest prevalence in the AI group, supporting the association between stroke and such risk factors.

As a measure of earlier carotid atherosclerosis, PS was higher in AI and LI patients than in no-stroke subjects (Figure, Table 2), with the differences only slightly modified by age and sex. These findings suggest increased severity of atherosclerosis in such patients. Although the average PS also appeared to be higher in the CH and other or unclassified stroke groups, the differences did not reach statistical significance. However, the number of CH patients was relatively small, limiting our power to detect the difference. After further adjustment for traditional cardiovascular risk factors,
PS continued to be higher in AI patients than in no-stroke subjects. Although such earlier carotid lesions per se would not explain the etiology of AI, this finding further supports an involvement of atherosclerotic process in the evolution of AI. By contrast, the difference between LI and no-stroke subjects diminished after the risk factor adjustments. On the basis of this result, the higher PS found in LI patients appears to be induced by cardiovascular risk factors prevalent in such patients.

Given the higher PS observed for AI and LI patients, PS may be of aid in the risk assessment of these stroke subtypes. Compared with the no-stroke subjects, each 1 SD greater PS was associated with 2.5-fold higher risk for AI and 1.4-fold higher risk for LI (Table 3, model 1), and the associations were only slightly modified by age and sex (model 2). These findings suggest the potential value of evaluating PS for risk assessment of AI and LI. However, when the risk is assessed in the clinic, other cardiovascular data may also be taken into account. After adjustment for traditional cardiovascular risk factors, PS remained significantly associated with AI but not with LI (model 3). Thus, even when other clinical data are available, carotid evaluation appears to convey an additional benefit for risk assessment of AI. Conversely, the benefit in the stratification of LI may be limited in such conditions. To further compare PS in the stratification of AI and LI, we performed ROC curve analyses. When PS alone (model 1) and in combination with other risk factors (models 2 and 3) was used, the ROC area for AI was greater than that for LI. On the basis of these results, evaluation of carotid atherosclerosis appears to be more effective in the risk assessment for AI than in that for LI.

Many studies, including ours, have shown associations of earlier carotid atherosclerosis with coronary artery disease. However, studies relating it to stroke have been limited, and even infarction and hemorrhage were not distinguished in these studies. Recently, Touboul et al have examined carotid atherosclerosis and even infarction and hemorrhage were not distinguished in studies. By contrast, the difference between LI and no-stroke subjects found in this study, in contrast to the present study, the differences in IMT were not modified by cardiovascular history. They measured IMT at plaque-free regions and defined cardiovascular risk factors as binary variables, whereas we quantified plaques and included some risk factors as continuous variables. Such methodological differences could have yielded the different results between this study and theirs.

Certain limitations exist for the present study. Given the difficulty of performing cerebral angiography on all stroke patients, the subtypes were diagnosed in a noninvasive manner, potentially allowing for misdiagnoses. As an example, small deep infarction, which we classified in the LI group, could be the result of major cerebral artery occlusion or occult cardiogenic emboli. However, we have included all equivocal diagnoses in the other or unclassified stroke group, probably reducing the chance for misclassification of major stroke subtypes. Additionally, because of the high prevalence of cardiovascular risk factors in no-stroke subjects, the results of this study cannot be directly transferred to the general population. However, carotid ultrasonography is most often performed for cardiovascular patients in hospitals, supporting the clinical value of our findings.

In summary, this study demonstrated increased severity of carotid atherosclerosis in AI and LI patients compared with no-stroke subjects. Although evaluation of carotid atherosclerosis may be beneficial in the risk assessment for AI and LI, the benefit appears to be greater for AI. Large prospective studies are necessary to establish the link between earlier carotid atherosclerosis and the future risk for specific stroke subtypes.

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References


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