Ultrasonic Evaluation of Early Carotid Atherosclerosis

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We investigated the prevalence of carotid atherosclerosis, including mild early lesions, and its association with cervical bruits and various risk factors (age, male sex, hypertension, hyperlipidemia, diabetes mellitus, obesity, and cigarette smoking) in 232 consecutive Japanese patients. High-resolution real-time B-mode ultrasonography was performed to determine the extent of atherosclerosis, and it was quantified by using a scoring system. The prevalence of carotid atherosclerosis was 49%, 59%, and 41% in all 232 patients, the 100 symptomatic patients, and the 132 asymptomatic patients, respectively. Although carotid lesions were detected frequently (87%) in the 30 patients with cervical bruits, bruits were noted in only 30% of the 88 examined patients with carotid atherosclerosis. Independent risk factors for carotid atherosclerosis in these patients were found to be age, male sex, and hyperlipidemia; diabetes mellitus was a possible risk factor for carotid atherosclerosis. Our study did not show a close association between hypertension and carotid atherosclerosis, and this might be caused by the high prevalence of hypertension in our patients. Our findings suggest an increasing prevalence of carotid atherosclerosis in the Japanese, though this should be confirmed in a population-based study. Our study demonstrates the clinical usefulness of high-resolution B-mode ultrasonography for the evaluation of early carotid atherosclerosis. (Stroke 1990;21:1567-1572)

Extracranial carotid atherosclerosis is one of the major causes of cerebrovascular disease. Atherosclerotic lesions must be moderately or severely advanced before they can be detected by clinical signs and symptoms. Moreover, the presence of asymptomatic carotid stenosis is considered to be a powerful indicator of the likelihood of cardiovascular disease. To prevent further progression of such cardiovascular disease, the detection of early carotid atherosclerosis by noninvasive and quantitative methods is desirable. Among the noninvasive methods, high-resolution B-mode ultrasonography is one of the best for direct visualization of the carotid arteries. This method provides real-time information about both lumen and vessel wall characteristics. During the last few years, this method has become able to detect even mild early lesions and vessel wall irregularities of the extracranial carotid arteries.

Several studies assessing carotid atherosclerosis with ultrasonography have been carried out. However, most of the studies observed the prevalence only in middle-aged Caucasians, and only a few investigators focused on hemodynamically nonsignificant mild-to-moderate lesions. No such data are available for the Japanese population. We used ultrasonography to assess carotid lesions, including mild early lesions, in symptomatic and asymptomatic Japanese patients at risk of developing atherosclerosis.

Subjects and Methods

The investigation consisted of a validity study and a survey of carotid lesions. The former was a sensitivity/specificity study to compare findings among ultrasonography, angiography, and pathologic diagnosis. Intraobserver and interobserver reproducibilities were also examined. The survey was an ultrasonographic assessment of the carotid arteries in 232 Japanese patients, which was carried out from May 1988 to March 1989 at Osaka University Medical School Hospital.

For the validity study, we examined 33 healthy persons as controls to determine the properties of
normal carotid arteries. The controls were free from recognized risk factors for atherosclerotic disease, except cigarette smoking. Their ages ranged from 24 to 74 years. In 36 stroke patients, the findings of B-mode ultrasonography were compared with those of corresponding contrast angiography. Ultrasonographic findings in five patients who underwent carotid endarterectomy were directly compared with the specimens obtained at endarterectomy, and three patients who died during follow-up were also evaluated for the correlation between ultrasonographic findings (wall lesion thickness, lesion size, and ulceration) and the pathologic findings at autopsy.

After the validity study was finished, the survey of carotid lesions was performed prospectively. From May 1988 to March 1989, ultrasonography of the carotid arteries in 300 consecutive patients was carried out by three physicians. We excluded from this consecutive series 20 patients with Takayasu's arteritis and 48 patients who had no risk factors for atherosclerosis. In total, 232 patients were examined to evaluate the prevalence of carotid lesions. Of these 232 patients, 100 had chronic-stage ischemic cerebrovascular disease (CVD); 34 had transient ischemic attack, 56 had minor stroke, and 10 had major stroke. The remaining 132 patients without CVD had at least one of five recognized risk factors for atherosclerosis (hypertension, hyperlipidemia, diabetes mellitus, obesity, or cigarette smoking).

The age, sex, and prevalence of the five risk factors in these 232 patients are shown in Table 1. The prevalence of carotid lesions, the relation between cervical bruises and carotid lesions, and the relation between risk factors and carotid lesions were assessed.

In all subjects in both studies, carotid B-mode imaging was performed with a 7.5-MHz transducer having an axial resolution of <0.4 mm (SSD-125, Aloka, Tokyo, Japan and EUB-450, Hitachi Medico, Tokyo). The subject was seated comfortably, and scanning of the extracranial carotid arteries in the neck was performed bilaterally in three different longitudinal projections and the transverse projection, as follows. First, with the subject sitting with the head upright, the common carotid artery (CCA) was examined in the anterior-oblique plane. Second, the CCA and the internal carotid artery (ICA) were examined in the lateral plane. Third, with the head bowed slightly forward and turned to the side under examination, both the CCA and ICA were examined in the posterior-oblique plane. Fourth, with the head upright again, the CCA and the ICA plus the external carotid artery were examined in the transverse plane. All these images were recorded on videotape and photographed.

The severity of carotid atherosclerosis in each subject was evaluated by using two indexes: plaque score and maximum percentage stenosis. The plaque score was computed by summing the maximum thickness of the intima-media complex (plaque thickness) measured in millimeters on the near and far walls at each of four divisions of both sides of the carotid arteries (Figure 1). This scoring system is a modification of the method of Crouse et al. Stenosis of the carotid arteries was measured on sonograms and

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TABLE 1. Prevalence of Risk Factors for Atherosclerosis in 232 Japanese Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yr) (mean±SD)</th>
<th>Male sex</th>
<th>Hypertension</th>
<th>Hyperlipidemia</th>
<th>Diabetes mellitus</th>
<th>Obesity</th>
<th>Cigarette smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>CVD</td>
<td>100</td>
<td>61±14</td>
<td>76 76</td>
<td>69 69</td>
<td>46 46</td>
<td>37 37</td>
<td>28 28</td>
<td>44 44</td>
</tr>
<tr>
<td>Non-CVD</td>
<td>132</td>
<td>58±14</td>
<td>88 67</td>
<td>83 63</td>
<td>71 54</td>
<td>39 30</td>
<td>30 23</td>
<td>54 41</td>
</tr>
<tr>
<td>Total</td>
<td>232</td>
<td>59±13</td>
<td>164 71</td>
<td>152 66</td>
<td>117 50</td>
<td>76 33</td>
<td>58 25</td>
<td>98 42</td>
</tr>
</tbody>
</table>

CVD, cerebrovascular disease.

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**Figure 1.** Diagram of carotid bifurcation and measurements obtained from B-mode ultrasonography. Plaque score was computed by summing maximum thickness in millimeters of plaques in each segment on both sides (a+b+c+ contrastralateral plaques). S1, region of internal carotid artery (ICA) <15 mm distal to its bifurcation from common carotid artery (CCA); S2, region of ICA and CCA <15 mm proximal to bifurcation; S3, region of CCA >15 mm and <30 mm proximal to bifurcation; S4, region of CCA >30 mm proximal to bifurcation below flow divider. Length of individual plaques was not considered in determining plaque score.
angiograms, if available, according to the method given by Ricotta et al., and the maximum percentage stenosis was computed by measuring the residual lumen diameter and the original diameter at the site of maximal stenosis and dividing the difference by the original diameter.

To compare the findings between ultrasonography and contrast angiography in the 36 stroke patients, the severity of carotid atherosclerosis was evaluated by the maximum percentage stenosis as no lesion, mild stenosis (<25%), moderate stenosis (25–50%), severe stenosis (≥50%), or occlusion. All cerebral angiograms were evaluated by two physicians blindly and in a double-checking manner.

To compare the findings between ultrasonography and pathologic examination, the carotid arteries were removed at autopsy ≤2 hours after death from the three men who died during follow-up. These specimens and the endarterectomy specimens from the five patients who underwent ultrasonography before surgery were longitudinally opened and photographed using 35 mm transparency film. Atherosclerotic lesions were evaluated for thickness, length, ulceration, and other histologic characteristics. Intraobserver reproducibility was evaluated in 15 patients between two different examinations. Interobserver reproducibility was evaluated in the same 15 patients by three different examiners in a single day.

Age, sex, and the five other risk factors for atherosclerosis together with symptoms of CVD were evaluated in all 232 patients in the survey. Patients were considered hypertensive if they were taking antihypertensive agents and/or if the blood pressure measured in the hospital was >160 mm Hg systolic and/or >95 mm Hg diastolic. Patients were considered diabetic if they were being treated for diabetes with oral hypoglycemic agents or insulin, and/or the fasting blood glucose level in the hospital exceeded 110 mg/dl, and/or the glycosylated hemoglobin (HbA) level in the hospital exceeded 6.4%. Patients were considered hyperlipidemic if they were taking antihyperlipidemic agents and/or if the serum cholesterol level exceeded 220 mg/dl. Patients were considered obese if the body mass index exceeded 25. Patients were categorized as being either nonsmokers (never smoked cigarettes or quit >10 years ago) or smokers (recent past cigarette smokers and current cigarette smokers). Cervical bruits were evaluated in 180 patients by a physician in the outpatient department using a stethoscope. Physicians diagnosed CVD based on the clinical history and the results of x-ray computed tomography.

The extent of atherosclerosis was related to candidate risk factor variables in univariate analysis by linear regression. The χ² test was used to evaluate differences in the prevalence of carotid lesions and risk factors. Multivariate linear regression analysis was used to assess the correlation between carotid lesions and risk factors and was carried out using the HALBAU statistical package for personal computers (PC-9801 NEC, Tokyo, Japan). Only variables significant at p<0.05 were retained in the equation.

Results
There was a significant positive linear correlation between thickness of the intima–media complex and age in 33 healthy control subjects (Figure 2). Mean±SD thickness of the intima–media complex was 0.59±0.15 mm, and maximum thickness of the intima–media complex was <1 mm. Carotid atherosclerotic lesions were defined on the basis of these findings in the controls.

In the 36 stroke patients (72 vessels) who were examined by both angiography and ultrasonography, occlusion was found in eight, severe stenosis in three, mild or moderate stenosis in 20 vessels, and no lesion in 40 vessels; one vessel could not be evaluated due to angiographic technical problems. The sensitivity and specificity of ultrasonography were 88% and 90%, respectively; the overall accuracy was 89%.

The characterization of plaque and artery walls by ultrasonography was also confirmed by comparison with pathologic specimens. Carotid artery wall thickness measured by ultrasonography correlated significantly with that measured at pathologic examination (Y=1.33X−0.36, r=0.96, P<0.01). There was also a significant correlation between plaque size measured by ultrasonography and that measured by pathologic examination (r=0.72, P<0.01). The typical ultrasonographic appearance of plaque is shown in Figure 3. Thickness of the intima–media complex and heterogeneous plaques were clearly identified by ultrasonography, as in the pathologic specimen, and the two methods of assessment were in good agreement.

The mean coefficient of variation for the difference between plaque scores obtained in repeated examinations performed by the same examiner was only 7%. The mean coefficient of variation for differences among the three different examiners was 8.9%.

As presented in Table 2, 113 (49%) of all 232 patients had detectable atherosclerotic lesions. The prevalence of carotid lesions was significantly higher in the CVD group (59%) than in the non-CVD group (41%). Severe stenosis was significantly
more frequent in the CVD group than in the non-CVD group, and occlusion was noted only in the CVD group ($p<0.01$).

The prevalence of carotid lesions increased with age. In the 113 patients with lesions, a significant positive correlation was found between age and plaque score ($r=0.302$, $p<0.01$). The prevalence of carotid lesions was higher in men (91 of 164, 55%) than in women (22 of 68, 32%). The prevalence of carotid lesions increased markedly in male patients in their 50s and in female patients in their 60s.

In the 180 patients evaluated, cervical bruits were detectable in 30 (17%). Although carotid plaques were detected frequently in the patients with cervical bruits (26 cases, 87%), bruits were audible in only 26 of the 88 patients (30%) with carotid plaques. Although the incidence of cervical bruits increased with the severity of carotid atherosclerosis, 26% of the 72 patients who had mild or moderate stenosis also had cervical bruits.

The occurrence of risk factors for carotid atherosclerosis was compared between patients with and without lesions. Multivariate analysis indicated significant correlations with plaque score for age, male sex, and hyperlipidemia (Table 3), and diabetes mellitus appeared as an age-dependent positive risk

<table>
<thead>
<tr>
<th>TABLE 3. Relation Between Risk Factors and Plaque Score by Multivariate Analysis</th>
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</thead>
<tbody>
<tr>
<td>Risk factor</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>All seven risk factors</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Multiple</td>
</tr>
<tr>
<td>Six risk factors (excluding age)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Multiple</td>
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</table>


<table>
<thead>
<tr>
<th>Group</th>
<th>Absent</th>
<th>Present</th>
<th>&lt;25</th>
<th>25-50</th>
<th>≥50</th>
<th>Occlusion</th>
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<tbody>
<tr>
<td>CVD ($n=100$)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>41</td>
<td>59</td>
<td>22</td>
<td>22</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>41%</td>
<td>59%</td>
<td>22%</td>
<td>22%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Plaque score</td>
<td>0</td>
<td>6.3±5.3</td>
<td>2.9±2.0</td>
<td>6.0±4.6</td>
<td>12.2±6.0</td>
<td>10.1±6.9</td>
</tr>
<tr>
<td>Non-CVD ($n=132$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>78</td>
<td>54</td>
<td>20</td>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>59%</td>
<td>41%</td>
<td>20%</td>
<td>30%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Plaque score</td>
<td>0</td>
<td>4.8±4.0</td>
<td>2.9±1.9</td>
<td>5.5±4.3</td>
<td>9.7±4.5</td>
<td>...</td>
</tr>
</tbody>
</table>

CVD, cerebrovascular disease; values of plaque score are mean±SD.

*p < 0.01 and 0.05, respectively, different from non-CVD group by $\chi^2$ test.
factor (Table 3). Hypertension, obesity, and cigarette smoking were not significantly associated with carotid atherosclerosis.

**Discussion**

This study shows that detectable atherosclerotic extracranial carotid lesions, including early phases of atherosclerosis, are present in both symptomatic (59%) and asymptomatic (41%) patients. As for the prevalence of mild or moderate stenosis, there was no significant difference between symptomatic and asymptomatic patients. The prevalence in our asymptomatic patients was similar to that in eastern Finland (49%), which Salonen et al reported on by means of high-resolution ultrasonography.

Recent advances in ultrasonic technology have allowed the measurement of carotid artery wall thickness in both healthy and diseased subjects. Thickness of the intima–media complex as defined by Pignoli et al is considered to represent the artery wall thickness. From analysis of the pathologic specimens, we also confirmed the results of Pignoli's group. Salonen et al defined an abnormal thickness of the intima–media complex as a distance of more than 1.1–1.2 mm between the lumen–intima interface and the media–adventitia interface. In our evaluation of healthy Japanese subjects, the maximum thickness of the intima–media complex was <1.0 mm. Therefore, we defined carotid atherosclerosis as an intima–media complex thickness of >1.0 mm.

To obtain good reproducibility, several criteria for the measurement of carotid lesions have been used. We used two indexes to evaluate carotid atherosclerosis: plaque score and maximum percentage stenosis. The plaque score is a set of criteria for the quantification of carotid lesions that allows reproducible and accurate assessment. However, lesions in only part of the cervical carotid artery were assessed using the original plaque score. Accordingly, we increased the length of the segment of interest from 5 to 15 mm (Figure 1). We consider the plaque score to be a useful index for evaluating nonsignificant lesions and total carotid atherosclerosis.

A cervical bruit is an important sign of a possibly significant carotid lesion. In our study, 87% of the patients with carotid bruits had carotid atherosclerosis. However, 41% of the patients without bruits also had carotid atherosclerosis. Lo et al reported a similar incidence of carotid lesions in asymptomatic patients with bruits. For detecting early carotid atherosclerosis, cervical bruits appear to be an insensitive marker. Therefore, ultrasonography of high-risk patients is necessary whether they have cervical bruits or not.

Of all known risk factors, age has the strongest association with atherosclerotic lesions of all arteries, including the carotid artery. Our univariate and multivariate analyses show that both the prevalence of carotid atherosclerosis and the plaque score strongly correlate with age. Although hypertension is undoubtedly the most important risk factor for atherosclerosis, we failed to confirm this relation. It is difficult to draw any conclusions about the relation between hypertension and carotid atherosclerosis from our results because of our selection of subjects and their backgrounds. Our patients had a high prevalence of hypertension, and this makes evaluation of its influence on carotid atherosclerosis difficult.

Tell et al suggested in their review that hyperlipidemia is a stronger risk factor for cerebrovascular atherosclerosis with advancing age in Caucasians. In Japanese patients, our multivariate analysis showed that hyperlipidemia (hypercholesterolemia) is also a risk factor for carotid atherosclerosis. The relation between diabetes mellitus and atherosclerosis has been reported by several investigators. Crousse et al showed a positive correlation between diabetes and carotid atherosclerosis evaluated by ultrasonography in a univariate analysis, but this relation disappeared in stepwise multiple linear regression analysis. From our results, we consider that diabetes mellitus is a possible risk factor for carotid atherosclerosis in the Japanese.

The relation between cigarette smoking and cerebral atherosclerosis in the Japanese is still uncertain. Many studies in Caucasians have shown that cigarette smoking has a significant positive association with atherosclerosis in the coronary and peripheral arteries and the aorta. Cigarette smoking has also been found to be a significant risk factor for carotid atherosclerosis. However, we found no significant difference in the prevalence of carotid atherosclerosis between smokers and nonsmokers.

High-resolution B-mode ultrasonographic assessment of carotid artery wall thickness has become a standard technique for visualizing atherosclerotic lesions, and many crossover studies using this technique have been reported. In spite of the inherent shortcomings in using hospital-based registry data, our study is the first to present information on carotid atherosclerosis in the Japanese by using this technique. A high prevalence of early carotid atherosclerosis was found, and a significant relation was observed between carotid lesions and age, male sex, and hyperlipidemia. From these hospital-based results, we suppose that the "racial" differences in the pattern of cerebrovascular atherosclerosis might be decreasing gradually with changes in diet and other environmental factors. However, to confirm this supposition population-based studies should be carried out. On the basis of this study, the natural history of carotid atherosclerosis and intervention for treatment are currently being investigated in the Japanese.

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References

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