Aortic Arch Atherosclerotic Lesions and the Recurrence of Ischemic Stroke

Shigeru Fujimoto, MD; Masahiro Yasaka, MD; Ryoichi Otsubo, MD; Hiroshi Oe, MD; Kazuyuki Nagatsuwa, MD; Kazuo Minematsu, MD

Background and Purpose—Aortic arch atherosclerotic lesions are often associated with embolic brain infarction. We investigated the relationship between stroke recurrence and the characteristics of aortic arch atherosclerotic lesions.

Methods—Among 487 stroke patients who underwent transesophageal echocardiography, 283 patients with brain embolism diagnosed without significant occlusive lesions (≥50%) in their cerebral arteries were included in this study. We measured the intima-media thickness (IMT) and evaluated the extension and mobility of the aortic arch atherosclerotic lesions. During a mean follow-up period of 3.4 years, we investigated the relationship between stroke recurrence and the various characteristics of the aortic arch atherosclerotic lesions.

Results—An IMT ≥4.0 mm was found in 67 patients (25.3%). In 51 of these patients, the aortic lesions extended to the origin of the branches of the arch. Recurrences of cerebral ischemic events were found in 32 patients (recurrence group) and not in the other 251 (nonrecurrence group). Aortic atheroma ≥4.0 mm (41% versus 22%), aortic atheroma extending to the branches (63% versus 39%), and both (38% versus 16%) were more frequently seen in the recurrence group than in the nonrecurrence group (P<0.05, P<0.1, P<0.01, respectively). After adjustment for age and the presence of hypertension, an aortic atheroma that was ≥4.0 mm as well as extending to the branches was found to be an independent predictor of ischemic stroke recurrence (hazard ratio 2.42, P<0.05).

Conclusions—Stroke recurrence is associated with the severity of the atheroma (IMT ≥4.0 mm) and plaque extension to the branches. (Stroke. 2004;35:1426-1429.)

Key Words: aorta ▪ stroke ▪ recurrence ▪ echocardiography

Several studies using transesophageal echocardiography (TEE) reported that severe atherosclerotic lesions are frequently observed in the aortic arch in patients with brain infarction of unknown cause.1-9 In these studies, a wall thickness ≥3 to 5 mm, the presence of ulceration, or the presence of a mobile aortic arch plaque was found to be associated with embolic brain infarction. Amarenco et al8 found that ulcerated plaques at the aortic arch are independently associated with brain infarction of unknown cause. They also reported that the association between aortic plaques and ischemic stroke is particularly strong when the plaques are ≥4 mm in thickness.9 Moreover, a previous study demonstrated that atherosclerotic plaques ≥4 mm thick at the aortic arch are significant predictors of recurrent brain infarction and other vascular events.10 Jones et al demonstrated that a complex aortic atheroma ≥5 mm or an atheroma with mobile elements is an independent risk factor for ischemic stroke.11 However, no study has yet evaluated the relationship between the extent of aortic arch atherosclerotic lesions and the occurrence of brain infarction.

Several studies reported the characteristics of aortogenic brain embolism. Otsubo et al12 suggested that the size of brain infarction in aortogenic brain embolism was smaller than that in cardiogenic brain embolism. Mentel et al13 reported that aortogenic brain embolism tends to occur relatively more commonly in the vertebrobasilar system. However, in addition to their aortic atheroma, many patients with embolic brain infarction also have heart disease or an occlusive disease in their cerebral arteries that can be an embolic source for their brain infarction. Therefore, it is difficult to determine the actual role of an aortic atheroma on an embolic brain infarction, especially in patients with other potential sources of emboli.

The purpose of the present study was to evaluate the relationship between the characteristics of aortic arch atherosclerotic lesions and brain infarction in a longitudinal follow-up study in patients both with and without heart disease as possible sources of emboli.

Materials and Methods

TEE studies were performed in 487 ischemic stroke patients from January 1995 to December 1998. Based on 4 vessel cerebral angiography, magnetic resonance angiography, and duplex carotid ultrasonography, 283 patients with brain embolism diagnosed and
without significant occlusive lesions (≥50% in the cerebral arteries were included in this study. There were 194 men and 89 women, with a mean age of 63.2 ± 25 (mean ± SD) years. Of the 283 patients, 239 had a completed ischemic stroke and 40 had transient ischemic attacks. The remaining 4 patients were admitted to our hospital because of headache, vertigo, dizziness, or head injury, and computed tomography revealed a silent territorial cortical infarction in all of them. TEE studies were performed for an embolic source. In addition to the TEE studies, electrocardiography or transthoracic echocardiography, or both, were performed to evaluate the heart for possible embolic sources, such as atrial fibrillation, sick sinus syndrome, mitral valve stenosis, prosthetic valves, cardiomyopathy, old myocardial infarction, atrial septal defect, patent foramen ovale, pulmonary arteriovenous fistula, and infectious endocarditis. At least 1 such heart disease was observed in 162 patients; the remaining 121 patients had no heart disease. The following cerebrovascular risk factors were investigated: hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg), diabetes mellitus (fasting plasma glucose ≥ 126 mg/dL or plasma glucose at any time ≥ 200 mg/dL), and hypercholesterolemia (plasma total cholesterol ≥ 220 mg/dL).

We used a commercially available real-time 2-dimensional echocardiography system (model SSD-2200; Aloka) equipped with a 5.0-MHz phased array biplane or omniplane transesophageal transducer. We observed the aortic arch with both transverse and sagittal views. Focal increases in intima-media thickness (IMT) ≥ 1.1 mm were regarded as atheromatous plaques. We evaluated the maximum IMT, extension of the aortic lesions, and presence of any mobile plaque at the arch. We observed the aortic arch from the distal to the proximal portion with a sagittal view and tried to identify the origin of the 3 branches. We carefully evaluated to which branches the atheroma reached. When all 3 branches were visible, they were labeled the left subclavian artery, left common carotid artery, and innominate artery, respectively, from the distal portion. When the atheromatous plaque of ≥ 1.1 mm extended to at least 1 origin of the branch, we defined it as an extending atheroma.

Patients were treated with antiplatelet therapy (114 patients), anticoagulant therapy (149 patients), or both (5 patients). In all 283 patients, we observed the recurrence of ischemic stroke and all death through the outpatient clinic until July 2000. The mean follow-up period was 3.4 ± 1.4 (mean ± SD) years and the minimum follow-up period was 1.4 years. When a patient could not go to our hospital regularly because of some circumstances such as removal, discontinue visits to our outpatient clinic, and so on, we searched the status by phone. We investigated the relationship between the characteristics of the aortic arch atherosclerotic lesions and stroke recurrence.

We used 2-tailed $t$ tests and $\chi^2$ tests to compare proportions. A 2-tailed $P<0.05$ was considered to indicate statistical significance. The data were analyzed using Statview software. The incidence of stroke recurrence was expressed per 100 person-years of follow-up. We used the Kaplan–Meier method to evaluate the distribution of time to events. Kaplan–Meier curves were compared using the log-rank test to detect a trend. We also constructed a proportional hazards model, which included risk factors of cerebrovascular disease and the characteristics of the aortic atheroma. The characteristics of the aortic atheroma included: model 1, IMT ≥ 4 mm; model 2, extension to at least 1 branch (extending atheroma); and model 3, both of these.

**Results**

A wall thickness ≥ 4.0 mm was found in 67 (25.3%) of the 283 patients. In 51 of these 67 patients (76%), the aortic lesions were both ≥ 4.0 mm and extending to the origin of at least 1 branch. An aortic atheroma ≥ 4.0 mm was found to be statistically significantly more likely to extend to branches compared with an atheroma < 4 mm ($P<0.01$). A mobile plaque was observed in 5 patients and all of them had an aortic atheroma that was both ≥ 4.0 mm and extending to at least 1 branch. The baseline characteristics according to the IMT are shown in Table 1. Patients with an aortic atheroma ≥ 4.0 mm were significantly older ($P<0.001$) and had hypertension more frequently ($P<0.0001$). There was no significant difference in follow-up period between patients with and without an aortic atheroma ≥ 4.0 mm.

Using TEE, we were able to identify all 3 branches of the aortic arch in 87 (31%) patients, 2 branches in 114 (40%), 1 branch in 78 (28%), and no branch was detected in 4 (1%) patients. Among the 87 patients in whom we were able to evaluate the origins of all 3 branches, heart disease as a possible embolic source was present in 48 patients. In the other 39 patients without heart disease, 14 (36%) patients had an aortic atheroma ≥ 4.0 mm. The initial ischemic lesions were shown to be in the vascular territories of the branch to whose origin the aortic atheroma extended in 10 (71%) of the 14 patients.

We observed 32 patients with stroke recurrence during the follow-up period. Of these 32 patients, 13 had an aortic atheroma ≥ 4.0 mm and 20 had an extending atheroma. In the 13 patients with an atheroma ≥ 4.0 mm and stroke recurrence, 12 patients had an extending atheroma and 2 of these patients also had a mobile plaque. Patients who had stroke recurrence had an aortic arch atheroma ≥ 4.0 mm or atheroma that was ≥ 4.0 mm as well as extending to at least 1 branch more frequently than those who had not ($P<0.05$, $P<0.01$, respectively). Patients with stroke recurrence were significantly older than those without stroke recurrence ($P<0.01$) (Table 2). No other significant differences in baseline characteristics were observed between these patients. Four patients died during the follow-up period, 1 because of stroke recurrence, 1 because of subarachnoid hemorrhage, and the other 2 because of heart attacks.

Of the 33 patients who had an atheroma ≥ 4.0 mm without any heart disease as a possible embolic source, 6 had a recurrent stroke and all of them were treated with antiplatelet therapy without anticoagulant therapy. The aortic arch atherosclerotic lesions in these 6 patients extended to at least 1 branch. In the 3 patients in whom we were able to evaluate all

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Patients According to the Thickness of the Aortic Atheroma</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Males (%)</td>
</tr>
<tr>
<td>Observation period (y)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
</tr>
<tr>
<td>Heart disease (%)</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Antiplatelet (%)</td>
</tr>
<tr>
<td>Anticoagulant (%)</td>
</tr>
<tr>
<td>Follow-up period (y)</td>
</tr>
</tbody>
</table>

NS indicates not significant.
the branches at the aortic arch by TEE, all the recurrent ischemic lesions occurred in the territory of the branch to whose origin the aortic atheroma extended. Five of the 6 recurrent ischemic lesions were observed in the same vascular territory as the initial lesion. One patient had a mobile plaque.

The incidence of stroke recurrence was 9.1% per person-year in patients with an aortic atheroma ≥4.0 mm in comparison with 2.3% per person-year in patients with an atheroma <4 mm. The incidence of stroke recurrence was 9.8% per person-year in patients with an aortic atheroma extending to at least 1 branch, compared with 2.9% per person-year in patients without an aortic atheroma extending to at least 1 branch.

Age and the presence of hypertension that showed P<0.1 in the univariate analysis for predicting stroke recurrence (Table 2) were included into the multivariate analysis with the characteristics of the aortic atheroma. After adjusting for age and hypertension, the multivariate analysis revealed that the presence of an aortic atheroma that was ≥4.0 mm or extending to at least 1 branch was not an independent predictor of stroke recurrence (models 1 and 2 in Table 3). However, the presence of an aortic atheroma that was both ≥4.0 mm and extending to at least 1 branch was an independent predictor of stroke recurrence (hazard ratio=2.42; 95% CI: 1.12 to 5.21; P<0.05) (model 3 in Table 3). Age was an independent predictor of stroke recurrence in all these multivariate analyses. Kaplan-Meier curve analysis revealed a significant difference in the recurrence-free survival between patients with an atheroma ≥4.0 mm and patients with an atheroma <4 mm, both in patients with and without heart disease as a possible embolic source (P<0.05 by log-rank test in both).

### Discussion

The present results show that an aortic atheroma ≥4.0 mm can be a significant predictor for recurrent ischemic stroke and are similar to those of The French Study of Aortic Plaques in Stroke Group. Our incidence of stroke recurrence was 9.1% per person-year in patients with an aortic atheroma ≥4.0 mm compared with 2.9% per person-year in patients with an atheroma <4.0 mm.

In univariate regression, an aortic atheroma ≥4.0 mm can be a significant predictor for recurrent ischemic stroke. We also evaluated the extension of the aortic atheroma using TEE. An association between the extension of the aortic atheroma to the branches and ischemic stroke has not previously been demonstrated. Our multiple regression analysis showed that an aortic atheroma ≥4.0 mm that also extended to at least 1 branch was a more significant predictor than an

### Table 2. Comparison Between Patients With and Without Stroke Recurrence

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stroke Recurrence (+) (n=32)</th>
<th>Stroke Recurrence (-) (n=251)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>68.6±8.9</td>
<td>62.5±11.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Males (%)</td>
<td>22 (69)</td>
<td>172 (69)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>26 (81)</td>
<td>161 (64)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>7 (22)</td>
<td>47 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>9 (28)</td>
<td>72 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td>21 (66)</td>
<td>141 (56)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet (%)</td>
<td>13 (41)</td>
<td>101 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Anticoagulant (%)</td>
<td>16 (50)</td>
<td>133 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic atheroma (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4≤4 mm (%)</td>
<td>13 (41)</td>
<td>54 (22)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Extending atheroma (%)</td>
<td>20 (63)</td>
<td>98 (39)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Both (%)</td>
<td>12 (38)</td>
<td>39 (16)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<4 mm, both in patients with and without heart disease as a possible embolic source (P<0.05 by log-rank test in both).

### Table 3. Multivariate Analyses for Predicting Stroke Recurrence According to the Characteristics of Aortic Arch Atheroma

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atheroma ≥4 mm</td>
<td>1.98</td>
<td>0.94–4.15</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00–1.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.44</td>
<td>0.57–3.68</td>
<td>NS</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atheroma extending to at least 1 branch</td>
<td>1.59</td>
<td>0.76–3.33</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00–1.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.53</td>
<td>0.60–3.85</td>
<td>NS</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic atheroma both ≥4 mm and extending to at least 1 branch</td>
<td>2.42</td>
<td>1.12–5.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00–1.08</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.37</td>
<td>0.53–3.52</td>
<td>NS</td>
</tr>
</tbody>
</table>
atheroma that did not extend to the branches. Kaplan–Meier curve analysis revealed a significant difference in the recurrence-free survival between patients with and without an atheroma both $\geq 4.0$ mm and extending to at least 1 branch. We could observe all 3 branches at the aortic arch only in 31%, although at least 1 branch in 99%. This low value of 31% in detection rate of all 3 branches is a limitation of our study, which may cause difficulty in analysis of relationship between the extending atheroma and vascular territory of recurrence. However, it seems that our results showed some relationship between the extending atheroma and vascular territory of recurrence. Our 33 patients who had an atheroma $\geq 4.0$ mm without any heart disease as a possible embolic source were diagnosed clinically as having a definite aorto- genetic brain embolism. Of these patients, 6 had a recurrent stroke. In these 6 patients, their aortic atheroma extended to at least 1 branch, and in 5 of these 6 patients, a recurrent stroke was observed in the same vascular territory as the initial stroke. Furthermore, in the 3 patients in whom we could evaluate all branches at the aortic arch with TEE, all the recurrent ischemic lesions were in the territory of the branch to whose origin the aortic atheroma extended. The vascular territory of aorto- genetic brain embolism could be related to which branch the aortic atheroma extended. Our results suggest that extension of the aortic atheroma to the branches is an important factor for stroke occurrence.

In the present study, no significant difference in the type of medical treatment (antiplatelet agents or anticoagulant agents) was observed between patients with and without stroke recurrence (Table 2). However, the incidence of stroke recurrence was 9.1% per person-year in patients with an aortic atheroma $\geq 4.0$ mm and this incidence rate was lower than that found by The French Study of Aortic Plaques in Stroke Group (11.9% per person-year). Our study included more patients that were being treated with anticoagulant agents (45% versus 20%). In fact, 30 of the 67 patients with aortic atheroma $\geq 4.0$ mm were treated with anticoagulant agents. This difference was likely caused by the fact that more patients with heart disease as a possible embolic source were included in the present study than in The French Study of Aortic Plaques in Stroke Group. These factors could effectively explain the difference in the rate of stroke recurrence. The difference in the use of anticoagulants between the studies is interesting, but our study was not designed as a therapeutical trial.

Even in patients with heart disease as a possible embolic source, the presence of an aortic atheroma $\geq 4.0$ mm was a significant predictor of stroke recurrence. Otsubo et al \(^{14}\) suggested that an atherosclerotic lesion in the aortic arch is associated with a hypercoagulable state and that this might play an important role in the development and pathophysiology of thromboembolism. Thus, although an aortic atheroma itself is a possible embolic source, it might further increase the risk of intracardiac thrombus formation caused by the hypercoagulable state with which it is associated.

The present study revealed that a severe aortic atheroma has a significant association with ischemic stroke in patients with or without heart disease. Both the thickness and the extension of the aortic atheroma were found to be important factors for the occurrence of ischemic stroke. The optimal medical therapy (antiplatelet agents or anticoagulant agents) for patients with severe aortic atheroma remains to be determined by randomized trials.

**Acknowledgments**

This study was supported in part by a research grant for cardiovascular diseases 15C-1 from the Ministry of Health, Labor, and Welfare of Japan.

**References**


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Stroke. 2004;35:1426-1429; originally published online April 29, 2004;
doi: 10.1161/01.STR.0000127788.32550.d4
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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