Mobile Aortic Plaques Are a Cause of Multiple Brain Infarcts Seen on Diffusion-Weighted Imaging

Yuji Ueno, MD; Kazumi Kimura, MD; Yasuyuki Iguchi, MD; Kensaku Shibazaki, MD; Takeshi Inoue, MD; Nobutaka Hattori, MD; Takao Urabe, MD

Background and Purpose—Multiple brain infarcts are often seen on diffusion-weighted images in cardioembolic stroke patients. Recently, mobile aortic plaques (MAPs) have been proposed as embolic sources. However, the clinical characteristics of patients with MAPs are unclear.

Methods—We prospectively studied patients with acute ischemic stroke who underwent transesophageal echocardiography. The patients were classified into 3 groups based on transesophageal echocardiography findings: atheromatous aortic plaques <4 mm, atheromatous aortic plaques ≥4 mm without mobility, and MAPs. Based on their diffusion-weighted image findings, the patients were divided into 3 subgroups: (1) single lesion; (2) multiple lesions in a single vascular territory; and (3) multiple lesions in multiple vascular territories. We assessed the clinical characteristics and the diffusion-weighted image findings of stroke patients with MAPs.

Results—One hundred sixty-seven patients (age, 70 ±12 years; 98 males) were enrolled; 128 (77%) had atheromatous aortic plaques <4 mm, 27 (16%) had atheromatous aortic plaques ≥4 mm, and 12 (7%) had MAPs. Older age, male gender, coronary artery disease, and cerebral arterial stenotic lesions were seen most frequently in patients with MAPs. On diffusion-weighted image findings, patients with MAPs were most frequent in the multiple lesions in multiple vascular territories group (P = 0.001). On multiple logistic regression analysis, the National Institutes of Health Stroke Scale score (OR: 1.11; 95% CI: 1.01 to 1.22; P = 0.039), arterial stenotic lesions (OR: 4.71; 95% CI: 1.35 to 16.41; P = 0.015), and mobile aortic plaques (OR: 14.44; 95% CI: 2.87 to 72.66; P = 0.001) were significantly associated with the multiple lesions in multiple vascular territories group.

Conclusions—MAPs were not uncommonly observed in patients with acute ischemic stroke. MAPs could cause multiple brain infarcts on diffusion-weighted images. (Stroke. 2007;38:2470-2476.)

Key Words: diffusion-weighted image ■ embolic stroke ■ mobile aortic plaques ■ multiple brain infarction ■ transesophageal echocardiography

Since the last decade, atheromatous aortic plaques (AAPs) in the thoracic aorta have been considered to be associated with ischemic stroke.1–6 In particular, AAPs ≥4 mm in thickness have been recognized as advanced atherosclerotic lesions and have been linked with cryptogenic ischemic stroke, stroke recurrence, and all vascular events.7,8

Mobile aortic plaques (MAPs) can also be potential embolic sources in patients with cerebral ischemic strokes of unknown etiology.2,4,5,9–15 Even in patients diagnosed with advanced AAPs >5 mm in thickness, the incidence of embolic events is higher in those who have mobile components than in those who do not have mobile components.4 Transesophageal echocardiography (TEE) is widely accepted as a useful modality for identifying not only cardiac abnormalities, but also MAPs, which have mobile components that move with the pulsatile aortic flow.15 On the other hand, it is not uncommon that cardioembolic brain strokes have characteristic topographic lesion patterns such as multiple brain infarction.16–18

To date, the clinical characteristics, including the topographic lesion patterns of ischemic stroke, associated with MAPs have not been fully elucidated. The aim of the present study was to identify MAPs using TEE and to elucidate the clinical features of patients with acute stroke with MAPs. We compared the characteristics of patients with stroke with and without MAPs.

Materials and Methods
From September 2004 to January 2006, we prospectively enrolled patients with acute ischemic stroke within 7 days of onset who underwent TEE. Ischemic stroke was diagnosed as an acute neurological event that lasted more than 24 hours, which was associated with focal hyperintensity on MRI, including diffusion-weighted imaging (DWI). The patients’ age, gender, risk factors, National Institutes of Health Stroke Scale (NIHSS) score, TEE findings, and brain MRI findings were assessed. We compared these clinical

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characteristics according to the degree of AAPs: (1) patients with AAPs <4 mm in thickness; (2) patients with AAPs ≥4 mm without mobility; and (3) patients with MAPs. The patients and their families gave their written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

Risk Factors
We assessed the vascular risk factors based on the following: (1) hypertension was defined as a history of using antihypertensive agents, a systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg 14 days after the stroke; (2) diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, a fasting blood glucose level >126 mg/dL, or a glycosylated hemoglobin >6.4%; (3) hyperlipidemia was defined as the use of antihyperlipidemic agents or a serum cholesterol level >220 mg/dL; (4) current smoking status was obtained; (5) a history of alcohol consumption was obtained; and (6) coronary artery disease was defined as a history of angina pectoris or myocardial infarction.

MRI Protocol
Immediately after admission, brain MRI was done. The MRI was acquired with a 1.5-Tesla GE Signa MR scanner equipped with single-shot echoplanar imaging to obtain rapid diffusion images (GE; Excite XI). The MRI studies included a diffusion-weighted sequence, fluid-attenuated inversion recovery, and magnetic resonance angiography, resulting in a total imaging time of approximately 20 minutes. Imaging parameters were as follows: 8000/70.4, (TR/TE); matrix, 128×192; field of view, 240 mm; section thickness, 6 mm; spacing, 1 mm; and field of view, 24 cm. Two b values were used (0 and 1000 s/mm²). Diffusion gradients were applied to successive images in each of the x, y, and z directions, and the DWIs were formed from the mean of these values. The diagnosis of acute infarction on DWI was based on the finding of focal hyperintensity that was judged not to be attributable to normal anisotropic diffusion or magnetic susceptibility artifact. Based on their DWI findings, the patients were divided into three subgroups: (1) those with a single ischemic lesion (S group); (2) those with multiple ischemic lesions in a single vascular territory (MS group) such as unilateral involvement of the anterior circulation or the posterior circulation; and (3) those with multiple lesions in multiple vascular territories (MM group) such as those with unilateral anterior circulation and posterior circulation involvement, those with bilateral anterior circulation involvement, or those with bilateral anterior circulation and posterior circulation involvement (Figure 1). The size of infarcts (<15 mm, 15 to 30 mm, and >30 mm) on DWI was also assessed. In patients with multiple infarcts, the maximum diameter of the largest lesion was evaluated. White matter abnormalities seen on fluid-attenuated inversion recovery were also evaluated according to the Fazekas’ classification. MRI findings were evaluated by two experienced neuroradiologists (K.S. and T.I.).

Echocardiographic Study
The TEE was done using an HDI 5000 (Philips Medical Systems) with a 4- to 7-MHz wideband multiplane probe. The study was performed in patients who were awake and had fasted for at least 4 hours before the examination. Lidocaine spray but no premedication was given. The patients were placed in the left lateral decubitus position during probe insertion. The probe was advanced to the distal esophagus and withdrawn slowly to a location 25 cm from the incisors. The multiplane probe was manipulated to provide appropriate views, including the axial and sagittal images, throughout the aorta.

Figure 1. Four representative DWI slices for a patient who had MAPs showing multiple brain infarcts in the territories of the right middle cerebral artery, the bilateral posterior cerebral artery, and the basilar artery.
The thickness of the plaques located in the aortic arch, which was defined as the portion of the aorta between the curve at the top of the descending aorta and at the upper point of visibility, was determined by measuring the thickness of the intima media complex (Figure 2). To determine the severity of atherosclerosis, the most advanced lesion was evaluated. Large aortic plaques were defined as ≥4 mm in thickness. Aortic lesions were diagnosed as MAPs if they had mobile components that were seen swinging on their peduncles (Figure 3). The examinations were done by an experienced sonographer and recorded on super VHS videotapes. The data were reviewed by experienced sonographers (Y.U., K.K., and Y.I.) who were blinded to the clinical data.

Investigation for Other Potential Embolic Origins and Arterial Stenosis
During the TEE study, the presence of patent foramen ovale, atrial septal aneurysm, intracardiac thrombus, and spontaneous echocontrast was also evaluated. Contrast saline was used to evaluate for the presence of patent foramen ovale. In all patients, 12-lead electrocardiograms and 24-hour electrocardiogram monitoring were done to detect atrial fibrillation. To assess the degree of extra- and intracranial arterial stenosis, all patients also underwent color-flow duplex carotid ultrasonography and/or cerebral angiography. Arterial stenotic lesions were identified based on the presence of a stenosis ≥50%.

Statistical Analysis
Numerical values are reported as mean±SD. Baseline characteristics, vascular risk factors, TEE findings, and brain MRI findings were compared among groups. Statistical analysis was performed using the χ² test for categorical variables and the Kruskal–Wallis test for nonparametric analysis. All variables with a P<0.2 on univariate analysis were entered into the stepwise logistic regression analysis. A 2-sided P<0.05 was considered significantly different. All analyses were performed using the Statistical Package for the Social Science (SPSS 11.0) software for Windows.

Results
Overall, 319 patients with acute ischemic stroke were admitted to Kawasaki Medical School Hospital. Of them, 152 patients were excluded from the study: 47 patients declined to participate, 6 developed congestive heart failure, 5 developed pneumonia, 3 died before an examination could be performed, 2 underwent surgical procedures, 8 developed severe...
dysphagia, 79 had a disturbance of consciousness, and 2 patients had thoracic aortic dissection, which made it impossible to assess the presence of AAPs. Thus, a total of 167 patients (mean age, 70 ± 12 years; male, 98; NIHSS score, 4.3 ± 4.4) were enrolled in the present study. Based on the Trial of Org 10172 in Acute Stroke Treatment criteria (TOAST),20 the patients had the following stroke subtypes: 65 patients had small-vessel disease, 6 had large-artery atherosclerosis, 37 had cardioembolism, 23 had other determined etiology, and 36 had other undetermined etiologies.

### Characteristics of Patients With Mobile Aortic Plaques

Overall, 128 (77%) patients had AAPs <4 mm, 27 (16%) had AAPs ≥4 mm, and 12 (7%) had MAPs (one patient had a long thread-like lesion [Figure 3C] and 11 had MAPs with ulcerations [Figure 3A]); the mean AAP thicknesses were 2.2 ± 0.9 mm, 4.5 ± 1.6 mm, and 8.8 ± 2.9 mm, respectively. In patients with MAPs, stroke of other determined etiology was found in 8 patients and stroke of other undetermined etiologies was found in 36 patients, who had other embolic sources: one patient had atrial fibrillation, one had a patent foramen ovale and an atrial septal aneurysm, and 2 had bilateral carotid stenosis and patent foramen ovale. Table 1 lists the baseline characteristics for all patients and by groups. Of the 3 groups, the patients with MAPs were the oldest (P < 0.001) and had a marked male preponderance (P = 0.002). The mean NIHSS score on admission was lowest in patients with AAPs <4 mm without mobility (P < 0.001). Hypertension was relatively more common in patients with AAPs ≥4 mm and MAPs than in patients with AAPs <4 mm (P = 0.096). Coronary artery disease and arterial stenotic lesions were most frequently seen in patients with MAPs (P < 0.001). On brain MRI, patients with MAPs had the highest frequency of MMs (P < 0.001) (Figure 4). However, no significant differences in the size of infarcts or in white matter abnormalities were seen among the patients with various degrees of AAPs.

### Multiple Brain Infarcts

The S, MS, and MM groups included 127 (76%), 22 (13%), and 18 (11%) patients, respectively. On univariate analysis, the AAP thickness was the highest in the MM group.
Lesion patterns, n (%)

- Single lesion
- Multiple lesions in a single vascular territory
- Multiple lesions in multiple vascular territories

P=0.001

AAPs < 4 mm  AAPs ≥ 4 mm  MAPs

17 (13)  2 (7)  1 (4)  100 (78)  24 (89)  6 (50)

(P=0.036) (Figure 5). Older age, high NIHSS score, and the presence of coronary artery disease were more common in the MM group than in the other groups (P=0.002, P=0.013, and P=0.009). Moreover, among the three groups, the MM group had the highest frequency of arterial stenotic lesions and MAPs (P<0.001). On stepwise logistic regression analysis, 10 variables (age, male gender, NIHSS score, hyperlipidemia, coronary artery disease, arterial stenotic lesion, thickness of AAPs, atrial fibrillation, MAPs, and spontaneous echocontrast) were chosen. The independent factors associated with the MM group included NIHSS score (OR: 1.11; 95% CI: 1.01 to 1.22; P=0.039), arterial stenotic lesions (OR: 4.71; 95% CI: 1.35 to 16.41; P=0.015), and mobile aortic plaques (OR: 14.44; 95% CI: 2.87 to 72.66; P=0.001) (Table 2).

Discussion

We found that the presence of MAPs was not uncommon in patients with acute ischemic stroke. Several studies have previously stated that the frequency of MAPs ranged from 2% to 7% in patients with ischemic stroke.4–6,12,13,15 Morphological analysis has elucidated the structure of MAPs. Studies based on autopsy and surgically removed specimens revealed that MAPs were a residual body of ruptured plaque and that the mobile components were superimposed thrombus.15,21–23 In addition, mobile lesions have also been shown to disappear after anticoagulation or thrombolytic therapy, which could lead to thrombus formation.24,25 Conversely, on pathology, cholesterol crystals alone were found to occlude multiple intracranial small
TABLE 2. Stepwise Regression Analysis Predicting Multiple Brain Infarctions

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a single vascular territory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.00–1.09</td>
<td>0.038</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.69</td>
<td>0.90–8.06</td>
<td>0.077</td>
</tr>
<tr>
<td>In multiple vascular territories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.11</td>
<td>1.01–1.22</td>
<td>0.039</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.14</td>
<td>0.03–0.73</td>
<td>0.019</td>
</tr>
<tr>
<td>Arterial stenotic lesions</td>
<td>4.71</td>
<td>1.35–16.41</td>
<td>0.015</td>
</tr>
<tr>
<td>Mobile aortic plaques</td>
<td>14.44</td>
<td>2.87–72.66</td>
<td>0.001</td>
</tr>
</tbody>
</table>

vessels. Thus, MAPs have been considered to be high-risk sources for cerebral embolism.

In the present study, patients with MAPs were more likely to be older males with coronary artery disease and arterial stenotic lesions. Previous studies identified the characteristics of patients who had advanced AAPs but not MAPs, which include older age, the presence of risk factors for atherosclerosis, and concomitant vascular diseases such as coronary artery disease.27,28 Moreover, the presence of AAPs was found to have a sensitivity of 90% and a specificity of 90% for coronary artery obstruction and could be used as a predictor of cardiovascular events.26,29

Multiple brain infarctions have been frequently observed in patients with acute ischemic stroke, especially in patients with cardiac embolic sources such as atrial fibrillation, intracardiac thrombus, and even patent foramen ovale.17,18 We found that multiple brain infarctions located in multiple vascular territories were significantly associated with MAPs. Thus, MAPs could be a cause of multiple brain infarctions in multiple vascular territories. Various mechanisms have been proposed to explain how MAPs could cause multiple brain infarctions. First, plaque rupture can scatter multiple small emboli that can then occlude cerebral vessels. In a transcranial Doppler study of patients with ischemic stroke, the incidence of high-intensity transient signals was associated with severe AAPs, suggesting that microemboli are derived from advanced aortic lesions.30 Second, a previous TEE study found that aortic flow is retrograde and rotational, and that this could affect the swinging motion of the MAPs’ mobile components. Thus, many detached thrombi could be spread by the aortic flow and pass into various cerebral vessels, resulting in multifocal brain infarctions.15

Our study has some limitations. First, not all patients with stroke had TEE; thus, there may have been a bias in the selection of patients for TEE. Furthermore, the number of patients with MAPs was small. A further study involving a much larger sample size is needed. Second, the thoracic ascending aorta, which is located anterior to the left main bronchus, cannot be seen on TEE. Therefore, MAPs in the ascending aorta might have been missed.

In conclusion, it was identified that the frequency of older age, male gender, and concomitant vascular disease could increase with the advancement of the aortic atherosclerosis. In addition, mobile aortic plaques, which might be the result of plaque rupture, were strongly linked to multiple brain infarctions. Thus, to evaluate for the aortic plaque stages, using TEE could be used to predict the clinical characteristics of patients with stroke. In patients with such characteristics, physicians should be aware of the presence of mobile aortic plaques.

Disclosures

None.

References


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