Abstract

Objective  Purpose was to assess the stroke mechanism in patients with patent foramen ovale (PFO).

Methods  We reviewed the medical records of 111 stroke patients with PFO and sinus rhythm (PFO-S group), 25 with PFO and atrial fibrillation (AF) (PFO-AF group) and 67 with AF but not PFO (AF group), who had received contrast transesophageal echocardiography. The clinical and neuroradiological findings were then compared among the three groups. Deep vein thrombosis was investigated in 93 patients with PFO. We determined the number of patients with definite paradoxical embolism who met three criteria: deep vein thrombosis, neuroradiological features indicating embolic stroke, and the absence of other sources of emboli. We also evaluated those with probable paradoxical embolism who met two of the three criteria.

Results  The PFO-S group more frequently exhibited hypercholesterolemia (p<0.0001) and lesions limited to the posterior circulation (p<0.0004), and less frequently exhibited large or cortical lesions in the anterior circulation (p=0.0008, p<0.0001, respectively), than the PFO-AF and AF groups. In the PFO-S and PFO-AF groups, other sources of emboli such as a cardiac source of emboli, cerebral artery stenosis ≥50%, or complicated atheroma in the aortic arch were identified in 72 cases (52.9%). In the 93 patients with examination for deep vein thrombosis, the definite and probable criteria of paradoxical embolism were fulfilled only in three (3.2%) and 33 cases (35.5%), respectively.

Conclusion  In stroke patients with PFO, not only paradoxical brain embolism through the PFO but also other causes of stroke may contribute to the development of stroke.

Key words: stroke, patent foramen ovale, atrial fibrillation, paradoxical brain embolism

Introduction

Patent foramen ovale (PFO) is found in about 30% of autopsies and may be associated with paradoxical brain embolism (1). The prevalence of PFO in patients with stroke is higher than in control subjects and PFO is more frequently detected in cryptogenic stroke than in stroke of known etiology (2·4). Contrast transesophageal echocardiography (TEE) enables the detection of PFO with a higher degree of sensitivity, which has contributed to the diagnosis of paradoxical brain embolism (5).

Typical patients with paradoxical brain embolism through PFO demonstrate a venous thrombus as the direct source of emboli and neuroradiological features of cerebral embolism. However, numerous stroke patients with PFO do not have a venous thrombus or neuroradiological findings of brain embolism. Therefore, the contribution of paradoxical embolism through PFO to the development of stroke may be smaller than previously thought. Although clarifying the causes of stroke in patients with PFO is important, the clinical characteristics of stroke patients with PFO have not been fully elucidated. Thus, we retrospectively reviewed the medical records of stroke patients having PFO with or without atrial fibrillation (AF) and those of stroke patients with AF but not PFO, and compared their clinical and neuroradiological findings. In addition, we proposed definite and probable criteria for paradoxical brain embolism and determined how many stroke patients with PFO met the criteria.

For editorial comment, see p 401.
Medical factors. Patients taking antihypertensive medicine and with a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg were considered hypertensive, while diabetic patients were defined as those taking insulin or oral antidiabetic agents, and exhibiting a fasting plasma glucose level of ≥ 126 mg/dl or plasma glucose at any time of ≥ 200 mg/dl. Patients taking antihypercholesterolemic medicine, or with a plasma total cholesterol of ≥ 220 mg/dl were defined as having hypercholesterolemia.

We investigated the circulation territory, either anterior or posterior circulation, responsible for the infarction, whether the lesions involved cortical areas, and whether the lesions were larger than 3.0 cm in diameter in patients with infarctions of the anterior circulation (9–11).

We also compared the incidence of cervical or cerebral artery stenosis ≥ 50% demonstrated by carotid ultrasonography, MRA, or cerebral angiography, in the major artery proximal to the responsible infarction, intraluminal filling defect indicating an embolus on angiogram, reopening of the previously occluded artery confirmed by MRA, and atherosclerotic lesions thicker than 4.0 mm at the aortic arch among the three groups. We reviewed medical records for other sources of emboli, such as arterial dissection, ulcerative plaque at the carotid artery, and cardiac and cerebral catheter manipulation.

In the 136 patients having PFO with or without AF, we investigated underlying heart diseases by electrocardiography, TEE and transthoracic echocardiography. Thrombus in lower leg veins was investigated by ultrasonography in 86 patients, by RI scintigraphy in 46 patients, and by either procedure in 93 patients. Using the diagnostic criteria given in Table 1, we ascertained the number of patients who met the definite or probable criteria for paradoxical embolism.

Continuous data were expressed as mean ± SD. We used the Chi squared test for analysis of discrete variables and analysis of variance with the multiple comparison test with Scheffe’s test for analysis of continuous variables.

Results

Patients in the PFO-S, PFO-AF, and AF groups were 63.5±11.7 years old, 68.0±11.7 years old, and 70.7±7.8 years old, respectively (ANOVA, p<0.0001). Patients in the PFO-S were significantly younger than those in the AF group (multi comparison test with Scheffe, p<0.0001, Table 2). Hypercholesterolemia was noted in 54.1%, 20.0%, and 38.8% of patients taking antihypertensive medicine and with a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, respectively. Patients in the PFO-S were significantly younger than those in the AF group (multi comparison test with Scheffe, p<0.0001).

Hypercholesterolemia was noted in 54.1%, 20.0%, and 38.8% of patients taking antihypertensive medicine and with a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, respectively. Patients in the PFO-S were significantly younger than those in the AF group (multi comparison test with Scheffe, p<0.0001).

Hypercholesterolemia was noted in 54.1%, 20.0%, and 38.8% of patients taking antihypertensive medicine and with a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, respectively. Patients in the PFO-S were significantly younger than those in the AF group (multi comparison test with Scheffe, p<0.0001).
Table 1. Diagnostic Criteria for Paradoxical Brain Embolism

1) Brain infarction demonstrated by CT or MRI.
2) Patent foramen ovale diagnosed by TEE.
3) Intravenous thrombus demonstrated by ultrasonography or RI venography.
4) Neuroradiological features of brain embolism, such as cortical infarction demonstrated by CT or MRI and angiographic findings of intraluminal filling defect (embolus shadow) or reopening of previously occluded arteries.
5) Absence of other sources of embolism, such as heart disease (atrial fibrillation, prosthetic valves, rheumatic heart disease, dilated cardiomyopathy, sick sinus syndrome, acute myocardial infarction, ventricular aneurysm), atherosclerotic plaque at the aortic arch thicker than 4.0 mm, and arterial stenotic lesion (≥50%) proximal to the lesion.

Diagnosis of paradoxical brain embolism.
Definite 1)+2)+3)+4)+5)
Probable 1)+2)+3)+4)
1)+2)+3)+5)
1)+2)+4)+5)

Table 2. Demographics

<table>
<thead>
<tr>
<th>Number of patients with infarction located in the anterior circulation.</th>
<th>PFO-S group 111</th>
<th>PFO-AF group 25</th>
<th>AF group 67</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.5±11.7</td>
<td>68.0±11.7</td>
<td>70.7±7.8*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, male</td>
<td>84 (75.7)</td>
<td>22 (88.0)</td>
<td>47 (70.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71 (64.0)</td>
<td>11 (44.0)</td>
<td>45 (67.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>42 (37.8)</td>
<td>6 (24.0)</td>
<td>24 (35.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>60 (54.1)</td>
<td>5 (20.0)</td>
<td>14 (20.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Territoriality of the infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>76 (68.5)</td>
<td>21 (84.0)</td>
<td>53 (79.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>35 (31.5)</td>
<td>2 (8.0)</td>
<td>8 (11.9)</td>
<td>0.0018**</td>
</tr>
<tr>
<td>Both</td>
<td>0 (0)</td>
<td>2 (8.0)</td>
<td>6 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Stenotic lesion***</td>
<td>31 (22.8)</td>
<td>2 (8.0)</td>
<td>5 (7.5)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Aortic arch atheroma</td>
<td>10 (9.0)</td>
<td>10 (40.0)</td>
<td>20 (30.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Number of patients with cerebral angiography.

<table>
<thead>
<tr>
<th>Embolic shadow</th>
<th>28</th>
<th>13</th>
<th>19</th>
<th>0.71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial artery occlusion</td>
<td>14 (50.0)</td>
<td>11 (84.6)</td>
<td>16 (84.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>Follow-up MRA</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reopening on MRA</td>
<td>0</td>
<td>8 (88.9)</td>
<td>7 (100)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

(%) *multi comparison test with Scheffe p<0.0001 vs. PFO-S group, **vs. anterior circulation, ***at the artery proximal to the infarction. +PFO-S group vs. PFO-AF and AF groups.
In patients with infarction in the anterior circulation, lesions larger than 3.0 cm in diameter were seen in 27.6%, 56.5%, and 61.8% (p=0.0002), and cortical lesions were observed in 46.0%, 95.7%, and 83.6% (p<0.0001) of the PFO-S, PFO-AF and AF groups, respectively. Large infarcts and cortical lesions were significantly less frequent in the PFO-S group than in the PFO-AF and AF groups (p=0.0008, p<0.0001, respectively).

We performed carotid ultrasonography in all patients, MR angiography (MRA) in 77 (69.4%) of the PFO-S group, in 20 (80.0%) of the PFO-AF group, and in 50 (74.6%) of the AF group. Cerebral angiography was carried out in 28 (25.2%), 13 (52.0%), and 19 (28.4%) of the PFO-S, PFO-AF, and AF groups, respectively. The incidence of arterial stenotic lesion proximal to the infarction was 22.8%, 8.0%, and 7.5% of the PFO-S, PFO-AF, and AF groups, respectively (p=0.0011). The stenotic lesions were significantly more commonly complicated in the PFO-S group than in the PFO-S and AF groups (p=0.0002, Table 2).

The incidence of intracranial arterial occlusion demonstrated by cerebral angiography was 50.0%, 84.6%, and 84.2% (p=0.017), and reopening of a previously occluded artery detected by follow-up MRA was demonstrated in 0%, 88.9%, and 100% (p<0.0001) of the PFO-S, PFO-AF and AF groups, respectively. The incidence of intracranial arterial occlusion and reopening phenomenon was significantly less frequent in the PFO-S group than in the PFO-AF and AF groups (p<0.0043 and p<0.0001, respectively, Table 2). The incidence of embolic shadow was low in all three groups (p<0.0043 and p<0.0001, respectively, Table 2). All patients with findings of intraluminal filling defect or reopening phenomenon had cortical infarction.

TEE revealed complicated atheroma at the aortic arch in 9.0%, 40.0%, and 30.0% of the PFO-S, PFO-AF, and AF groups, respectively (p=0.0001). In the 136 patients with PFO, an underlying heart disease was demonstrated in 26 patients (19.1%); non-valvular atrial fibrillation in 25 and sick sinus syndrome in one. Other sources of emboli in the PFO group were ulcerative carotid plaque (n=1), arterial dissection (n=2), and cardiac catheter manipulation (n=1). In total, sources of emboli including a cardiac source of emboli (n=26), cerebral artery stenosis ≥50% (n=33), complicated atheroma (n=20), and other sources mentioned above (n=4) except for PFO and deep vein thrombosis were demonstrated in 72 (52.9%) of the 136 patients with PFO (eight had both AF and aortic atheroma, one had both AF and stenotic lesion, and one had AF, stenotic lesion and aortic atheroma). Deep vein thrombosis was found in 25 of the 93 patients (26.9%) who were examined by ultrasonic examination or RI scintigraphy. Of these 93 patients, the definite and probable criteria for paradoxical brain embolism were fulfilled in only 3 (3.2%) and 33 cases (35.5%), respectively.

Discussion

Several studies have revealed that paradoxical embolism through PFO is an important stroke mechanism (2–4). However, in the present study, we found that 3.2% and 35.5% of stroke patients with PFO fitted the criteria for definite and probable paradoxical brain embolism, respectively. We also found that a considerable number of stroke patients with PFO had other sources of emboli (52.9%) and risk factors of atherosclerosis. Neuroradiological features of embolic stroke such as large or cortical infarction, or reopening of a previously occluded artery were less common in the PFO-S group than in the PFO-AF and AF groups. On the other hand, the clinical and neuroradiological features in the PFO-AF group were similar to those in the AF group. These distinguishing characteristics of the PFO-S and PFO-AF groups suggest that a considerable number of patients developed stroke not only by paradoxical embolism through PFO but also by other embolic mechanisms from a cardiac source, proximal arterial stenosis, atherosclerotic lesions in the aortic arch, or thrombotic or hemodynamic mechanisms in the large or small arteries. Therefore, the risk of stroke and other sources of emboli in stroke patients with PFO must be investigated to determine if they meet the criteria for paradoxical embolism, which requires anticoagulant therapy against recurrent attacks. The present study was retrospective, and thus prospective studies examining consecutive stroke patients are required to obtain an accurate prevalence rate for paradoxical embolism in stroke.

PFO is an important mechanism by which stroke develops in the young (2, 3), whereas in the elderly, non-valvular atrial fibrillation (NVAF) is the most frequent embolic source of brain infarction (12). Recent population-based surveys have revealed that 10% of people over 80 have AF (13). Thus, the differences in several features of stroke patients among the PFO-S, PFO-AF, and AF groups may be reflected by a difference in age.

Infarction in the posterior circulation was common in the PFO-S group. Small emboli passing through the PFO may enter the vertebral arteries more easily than the common carotid arteries. Otsubo et al reported that aortogenic infarction tends to occur at the posterior circulation (14). Therefore, emboli from atherosclerotic lesions in the aortic arch may play an important role in developing stroke in the PFO-S group, although aortic atherosclerotic lesions were also reported to play an important role in the development of stroke in patients with NVAF (15).

Exploration for deep vein thrombus is essential for proper diagnosis of paradoxical embolism. The detection rate of thrombus was 26.9% among the cases investigated in the present study. Recently, echo examination was applied to small veins for detecting thrombi. The more widely the echo examination is applied, the higher the detection rate of venous thrombi in stroke patients with PFO. If thrombi are detected, anticoagulant therapy should be applied and if not, antiplatelet treatment may achieve prevention to the same extent as the anticoagulant therapy (16).

In conclusion, the clinical features of patients having PFO with sinus rhythm appear to differ from those of patients
with AF. Other causes of stroke should be considered in stroke patients with PFO because not only paradoxical brain embolism through the PFO but also other causes of stroke may contribute to development of the stroke.

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

References