Diffusion-Weighted Imaging in Stroke Attributable to Patent Foramen Ovale
Significance of Concomitant Atrial Septum Aneurysm

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Background and Purpose—Patent foramen ovale (PFO) is an established cause of stroke in young patients without other determined etiologies (ie, cryptogenic stroke). The additional presence of atrial septum aneurysm (ASA) possibly increases stroke risk, but it remains undetermined which factors best predict thromboembolism in patients with PFO. Diffusion-weighted imaging (DWI) may help to distinguish the characteristics of cerebral embolism associated with different features of the interatrial septum in PFO stroke.

Methods—In a stroke databank–based cohort study, DWI and transthoracic/transesophageal echocardiography findings were assessed in 48 consecutive patients with cryptogenic ischemic stroke associated with PFO. The number, size, and distribution of acute ischemic lesions on DWI were correlated with PFO size, degree of interatrial right-to-left shunt (RLS), and the presence of ASA.

Results—Patients with PFO plus ASA combined more often had multiple acute DWI lesions (16 of 30, 53%) than those with PFO alone (3 of 18, 17%; \( P = 0.01 \)). This association remained significant after correction for PFO size, degree of RLS, and vascular risk factors in a logistic-regression analysis (\( P = 0.04 \)). No significant associations between DWI lesion characteristics and PFO size or degree of RLS were found.

Conclusions—The presence of concomitant ASA is independently associated with multiple cerebral ischemic lesions in PFO stroke, which may indicate an increased embolic risk. (Stroke. 2006;37:2030-2034.)

Key Words: atrial septum aneurysm ■ foramen ovale, patent ■ magnetic resonance imaging, diffusion-weighted ■ stroke, ischemic

Patent foramen ovale (PFO) is an established cause of stroke in young patients without other determined etiologies (ie, cryptogenic stroke). Patients with PFO and atrial septum aneurysm (ASA) combined may be at higher risk for stroke than patients with PFO alone, yet results from prospective studies were not unequivocal. There is ongoing uncertainty about which feature of the interatrial septum—anatomic size of the defect, degree of interatrial right-to-left shunt (RLS), or concomitant ASA—best predicts the risk of thromboembolism in PFO stroke.

Advanced neuroimaging techniques may provide additional insight into features of cerebral embolism associated with interatrial septum abnormalities. Besides its high sensitivity and specificity in detecting acute ischemic brain lesions, diffusion-weighted (DWI) magnetic resonance imaging (MRI) has been shown to be useful in distinguishing different stroke mechanisms. To date, this method has not been used to characterize embolic brain lesions in PFO stroke. We performed an exploratory study on DWI lesion characteristics in patients with cryptogenic stroke associated with PFO. We examined whether the number, distribution, and size of acute ischemic lesions on DWI differed depending on PFO size, degree of interatrial RLS, and the presence of concomitant ASA.

Subjects and Methods

Study Population

Based on our prospectively ascertained hospital stroke databank, all patients admitted from May 1999 (the time DWI entered routine application in our institution) to April 2005 (6 years) were selected after fulfilling the following inclusion criteria: (1) acute first ischemic stroke, ie, presence of a single episode of focal neurological deficit lasting \( >24 \) hours, with exclusion of intracerebral hemorrhage or other structural brain disease on cranial computer tomography (CCT) or MRI; (2) age \( \geq 60 \) years; (3) the presence of PFO as detected by transesophageal echocardiography (TEE) as the most likely stroke etiology (see next sections); (4) the absence

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2030
of any other determined stroke etiologies according to TOAST criteria after a complete diagnostic workup; (5) lacunar syndromes were included only when conventional MR sequences (ie, T1, T2, FLAIR) revealed no signs of cerebral microangiopathy; and (6) evaluation by standard stroke MRI protocols, including DWI. Patients with prior stroke were excluded. Patients with hypercoagulable states were not excluded a priori, taking into account the high prevalence of these disorders in PFO patients reported in the literature.14,15

Demographic data, date and time of symptom onset, vascular risk factors (including oral contraceptive use, hormone replacement therapy, and history of coagulopathy), clinical stroke syndrome according to the Oxfordshire Community Stroke Project criteria,16 and stroke severity at the time of presentation measured by the National Institutes of Health Stroke Scale17 were assessed from our database.

Ancillary testing besides echocardiography to exclude other stroke etiologies comprised neurovascular extracranial and intracranial Doppler sonography and extracranial color duplex sonography; chest x-ray; and a 12-lead ECG in all patients. Twenty-four–hour ECG, venous duplex sonography; and (6) evaluation by standard stroke MRI protocols, (ie, T1, T2, FLAIR) revealed no signs of cerebral microangiopathy; and (6) evaluation by standard stroke MRI protocols, including DWI. Patients with prior stroke were excluded. Patients with hypercoagulable states were not excluded a priori, taking into account the high prevalence of these disorders in PFO patients reported in the literature.14,15

Cardiac Assessment
All patients underwent both transthoracic echocardiography and TEE with a 5-MHz multiframe transducer, with contrast injection, at rest and during provocative maneuvers (Valsalva maneuver and coughing), performed by 7 experienced cardiologists. PFO was assessed in the left lateral position. Serving as the contrast agent, an aerated colloid solution was produced by mixing 5 mL of gelatin solution (Physiogel; B. Braun Medical), 10 mL of 0.9% NaCl, and 5 mL of air with two 20-ML syringes over a 3-way stopcock. Initially, 10 mL of this mixture was injected into a newly applied or pre-existing antecubital or forearm intravenous catheter. With this mixture, good opacification of the right atrium can be achieved even with small (0.9-mm) intravenous catheters. PFO was diagnosed if ≥3 microbubbles were observed passing through the foramen ovale from the right to the left atrium, either spontaneously or after provocative maneuvers.3 If no RLS was visible after a minimum of 3 contrast injections at rest, the procedure was first repeated with the Valsalva maneuver and then with coughing, according to published guidelines.18 In turn, if RLS was already visible at rest, no further contrast injections were performed. To ensure maximum cooperation, the Valsalva maneuver was practiced by the patient before the start of echocardiography and performed under mild sedation with preserved responsiveness.

Echocardiography tapes and/or digital recordings were reviewed by consensus readings of 2 experienced sonographers (A.K.-S., A.Z.L.), who were blinded to the patients’ clinical data and neuroimaging findings. PFO was characterized by the following parameters: (1) PFO size was measured by the maximum separation of the septum primum and septum secundum in millimeters. PFO size was classified as large when the separation was ≥2 mm and small when the separation was <2 mm.4 (2) The degree of interatrial RLS was determined on the basis of the numbers of microbubbles (MBs) passing through the PFO from the right to the left atrium. Because we expected a limited number of such patients in a single-center setting, RLS was assessed in a dichotomous manner by modifying a published grading system.3 RLS with >30 MBs was graded as large,2,19 and RLS with 3 to 30 MBs was graded as small. (3) The presence of ASA was diagnosed if the rightward and leftward protrusions of the interatrial septum combined were at least 15 mm. The base of the aneurysm had to be at least 15 mm in diameter.19

Diffusion-Weighted Imaging
DWI was performed on a 1.5-T MRI system (Siemens Magnetom Symphony) with a single-shot, multislice spin-echo, echoplanar imaging sequence. Diffusion gradients were applied in 3 orthogonal directions to generate isotropic DWI with the following parameters: repetition time/echo time, 4741/105 ms; field of view, 230; matrix 128X128 mm; b-values, 0, 500, and 1000 s/mm2; and thickness/gap, 5/2 mm.

Two experienced observers, 1 stroke neurologist (S.T.E.) and 1 neuroradiologist (S.G.W.), who were blinded to the patients’ clinical data and echocardiography findings analyzed the images. Discrepancies were resolved by consensus readings. Acute ischemic brain lesions were assessed and defined as hyperintense signal alterations on DWI, appearing isointense/hypointense on corresponding apparent diffusion coefficient maps. The number and vascular territories (anterior, middle, and posterior cerebral artery; infratentorial arteries) of all acute ischemic lesions were noted according to previously published templates.20 Topographically separate DWI lesions were assumed when no continuity was detectable between lesions in 1 slice as well as in adjacent slices.7,11,21 In each patient, the size of the largest DWI lesion was assessed by its largest axial diameter.11,21 Based on the vascular territories, the following lesion patterns were distinguished: (1) single lesion; (2) multiple lesions confined to 1 vascular territory; and (3) multiple lesions involving ≥1 vascular territory.

Statistical Analysis
First, DWI lesion characteristics were compared with PFO parameters in univariate comparisons. The Mann-Whitney test was used to compare ordinal variables (eg, lesion number) and continuous variables (eg, lesion diameter in millimeters). Nominal variables (eg, multiple versus single lesions) were compared with Fisher’s exact test. Second, multivariate analyses were performed to detect the influence of each PFO parameter (PFO size, presence of ASA, degree of RLS) on the occurrence of multiple brain lesions (logistic regression) and on lesion diameter (ANCOVA) independently. Lesion diameter was logarithmically transformed to achieve a normal distribution. The regression models were corrected for the presence of cerebrovascular risk factors. A probability value <0.05 was considered statistically significant. Data are indicated as mean and interquartile range (IQR), unless stated otherwise.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
Between May 1999 and April 2005, 1327 patients with ischemic stroke were admitted to our stroke unit. Forty-eight patients with stroke attributable to PFO (3.6%) met the study inclusion criteria. The mean age was 48 years (IQR, 41 to 54 years), and two thirds were male (n = 32). Vascular risk factors were present in 28 patients (58%).

The mean National Institutes of Health Stroke Scale score at the time of presentation was 6.1 (IQR, 2 to 9), half of the patients (n = 24) presented with partial anterior circulation syndrome. Venous duplex sonography of the lower extremities was performed in two thirds of patients (n = 32) and revealed deep vein thrombosis in 5 cases (10% of all sonograms). Details on risk factors and stroke syndromes are summarized in Table 1.

### Results

#### Patient Characteristics

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### TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>48</td>
</tr>
<tr>
<td>Age, y*</td>
<td>48 (IQR, 41–54; range, 24–59)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>32 (67)</td>
</tr>
<tr>
<td>Cerebrovascular risk factors, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥1 risk factor</td>
<td>28 (58)</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (35)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hormone replacement therapy or oral contraception</td>
<td>2 (13% of female patients)</td>
</tr>
<tr>
<td>NIHSS*</td>
<td>6.1 (IQR, 2–9; range, 1–21)</td>
</tr>
<tr>
<td>Stroke syndrome, n (%)†</td>
<td></td>
</tr>
<tr>
<td>PACS</td>
<td>24 (50)</td>
</tr>
<tr>
<td>POCS</td>
<td>17 (35)</td>
</tr>
<tr>
<td>LACS</td>
<td>5 (10)</td>
</tr>
<tr>
<td>TACS</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Severity scale.

†Stroke syndromes according to the Oxfordshire Community Stroke Project criteria: PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome; and TACS, total anterior circulation syndrome.

### PFO Characteristics

PFO was classified as large in two thirds of patients (n = 32) and small in one third. ASA was present in 30 patients (62.5%). Two thirds of patients (n = 32) had a large interatrial RLS, and one third had a small RLS. Twenty-five patients (52%) had both large PFO and ASA. Thus, large PFO size was significantly associated with ASA (P = 0.002).

### DWI Lesion Characteristics

DWI was performed after a mean of 2.8 days (IQR, 1 to 3) after stroke onset. Disagreement on DWI findings between the 2 readers occurred in 5 patients (10%) and was resolved by consensus: a missed single small DWI lesion (n = 2), a 10-mm deviation in measurement of lesion diameter (n = 1), disagreement on lesion signal intensity on the apparent diffusion coefficient maps (n = 1), and lesion location in the posterior cerebral artery as opposed to the middle-posterior cerebral artery border zone territory (n = 1).

Hyperintense lesions on DWI with an isointense/hypointense appearance on the apparent diffusion coefficient maps were present in all but 1 patient (n = 47), yielding a detection rate of 98% (95% CI, 89% to 100%). The patient with a negative DWI had acute isolated internuclear ophthalmoplegia, suggesting a small pontine infarct. Twenty-eight patients (58%) had single ischemic lesions, and 19 patients (40%) had multiple lesions. The middle cerebral artery territory was involved most frequently in 26 patients (54%). Three patients (6%) had anterior cerebral artery territory involvement. Lesions in the posterior cerebral artery territory were found in 10 patients (21%), and infratentorial lesions occurred in 12 patients (25%). Nine patients (19%) had multiple lesions involving >1 vascular territory. The mean number of acute DWI lesions in the entire study population was 2.6 (IQR, 1.0 to 3.8; range, 0 to 13). The mean diameter of the largest DWI lesion was 31 mm (IQR, 9 to 44 mm; range, 3 to 138 mm).

### Univariate Analysis

#### PFO Size

Patients with a large PFO did not differ significantly from patients with a small PFO with respect to the number of DWI lesions, and maximum lesion diameter (Table 2).

### Atrial Septum Aneurysm

Patients with a PFO plus ASA had more DWI lesions (3.1; IQR, 1.0 to 5.0) than did those with PFO alone (1.7; IQR, 1.0...
These reports main and novel result of our study was that concomitant ASA without assessment of RLS and the presence of ASA. The focused on the impact of PFO size on neuroimaging features, characteristics. Second, we did not determine total DWI lesion volume, which would be a more adequate marker of lesion size than diameter. The occurrence of multiple lesions is likely to result in a higher total lesion volume but not necessarily in a greater diameter of the largest lesion. However, lesion diameter was chosen in analogy to previous DWI studies.11,21 Finally, longitudinal follow-up examinations with PFO were not performed. In serial DWI studies, new ischemic lesions may serve as a surrogate marker of recurrent cerebral ischemia.

### Table 3. Logistic-Regression Analysis Showing Effect on Occurrence of Multiple Cerebral Lesions

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vs small PFO size</td>
<td>1.3</td>
<td>0.2</td>
<td>9.1</td>
<td>0.77</td>
</tr>
<tr>
<td>ASA vs no ASA</td>
<td>5.3</td>
<td>1.1</td>
<td>25.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Large vs small RLS</td>
<td>1.00</td>
<td>0.2</td>
<td>6.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Presence vs absence of cerebrovascular risk factors</td>
<td>1.2</td>
<td>0.3</td>
<td>4.5</td>
<td>0.78</td>
</tr>
</tbody>
</table>

For each variable, the effect is indicated by the odds ratio (OR), lower and upper limits of the 95% CI, and the P value, corrected for all other variables.

### Table 4. ANCOVA Showing Effect on Lesion Diameter

<table>
<thead>
<tr>
<th>Variable</th>
<th>GMR</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vs small PFO size</td>
<td>2.27</td>
<td>1.00</td>
<td>5.26</td>
<td>0.06</td>
</tr>
<tr>
<td>ASA vs no ASA</td>
<td>0.90</td>
<td>0.47</td>
<td>1.75</td>
<td>0.76</td>
</tr>
<tr>
<td>Large vs small RLS</td>
<td>0.55</td>
<td>0.26</td>
<td>1.19</td>
<td>0.13</td>
</tr>
<tr>
<td>Presence vs absence of cerebrovascular risk factors</td>
<td>0.82</td>
<td>0.45</td>
<td>1.47</td>
<td>0.51</td>
</tr>
</tbody>
</table>

For each variable, the effect is indicated by the geometric mean ratio (GMR), lower and upper limits of the 95% CI, and the P value, corrected for all other variables.

Discussion

Our study is the first to assess embolic brain lesions in PFO stroke by DWI. The combination of PFO plus ASA was associated with a higher likelihood of multiple ischemic lesions than PFO alone. Size of PFO and degree of RLS were not associated with significant differences in DWI lesion characteristics.

Earlier studies on neuroimaging findings in PFO stroke included patients with noncryptogenic stroke22 and relied on CCT or conventional MRI without DWI.22,23 These reports focused on the impact of PFO size on neuroimaging features, without assessment of RLS and the presence of ASA. The main and novel result of our study was that concomitant ASA was associated with the occurrence of multiple ischemic brain lesions in PFO stroke, even after correction for PFO size and degree of RLS. In the univariate analysis, the absolute number of lesions was significantly higher in patients with PFO and ASA combined compared with those with PFO alone.

Because the presence of multiple acute ischemic lesions is thought to arise from multiple emboli or the break-up of a single large embolus,10 our findings may suggest a higher embolic risk associated with concomitant ASA in patients with PFO. Increased interatrial septum mobility is believed to enhance the probability of paradoxical embolism by mechanically directing blood flow from the inferior vena cava through the PFO into the left atrium.24 Other postulated mechanisms of increased embolic risk include the association of ASA with larger PFO size, a prominent eustachian valve, and right atrial filamentous strands.25 Our findings are supported by a large, prospective, cohort study of 581 young patients with cryptogenic stroke in whom the simultaneous presence of PFO and ASA was associated with a significant increase in recurrent strokes compared with PFO alone.3 This finding was not confirmed in a subpopulation of the Warfarin-Aspirin Recurrent Stroke Study, but outcome data were not provided for patients with cryptogenic stroke separately.4
Summary

In conclusion, our findings show that the presence of concomitant ASA is independently associated with multiple cerebral ischemic lesions in stroke attributable to PFO, suggesting an increased embolic risk.

Acknowledgment

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Disclosures

None.

References

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