Frequency of Atrial Septal Aneurysms in Patients With Cerebral Ischemic Events

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Background—Atrial septal aneurysm (ASA) is a putative risk factor for cardioembolism. However, the frequency of ASA in the general population has not been adequately determined. Therefore, the frequency in patients with cerebral ischemic events, compared with the frequency in the general population, is poorly defined. We sought to determine the frequency of ASA in the general population and to compare the frequency of ASA in patients with cerebral ischemic events with the frequency in the general population.

Methods and Results—The frequency of ASA in the population was determined in 363 subjects, a sample of the participants in the Stroke Prevention: Assessment of Risk in a Community study (control subjects), and was compared with the frequency in 355 age- and sex-matched patients undergoing transesophageal echocardiography in search of a cardiac source of embolism after a focal cerebral ischemic event. The proportion with ASA was 7.9% in patients versus 2.2% in control subjects ($P < 0.002$; odds ratio of ASA, 3.65; 95% CI, 1.64 to 8.13, in patients versus control subjects). Patent foramen ovale (PFO) was detected with contrast injections in 56% of subjects with ASA. The presence of ASA predicted the presence of PFO (odds ratio of PFO, 4.57; 95% CI, 2.18 to 9.57, in subjects with versus those without ASA). In 86% of subjects with ASA and cerebral ischemia, transesophageal echocardiography did not detect an alternative source of cardioembolism other than an associated PFO.

Conclusions—The prevalence of ASA based on this population-based study is 2.2%. The frequency of ASA is relatively higher in patients evaluated with transesophageal echocardiography after a cerebral ischemic event. ASA is frequently associated with PFO, suggesting paradoxical embolism as a mechanism of cardioembolism. In patients with cerebral ischemia and ASA, transesophageal echocardiography did not detect an alternative source of cardioembolism other than an associated PFO.

Key Words: aneurysm ▪ cerebral ischemia ▪ echocardiography

A n association between atrial septal aneurysm (ASA) and focal cerebral ischemic events (stroke and transient ischemic attack) has been suggested. Nevertheless, the role of ASA as a risk factor for cerebral ischemia is poorly defined. This is the result of variable echocardiographic definitions of ASA and the lack of adequate nonselected control groups in previously published studies. Specifically, the frequency of ASA in a large nonselected population has not been determined. Therefore, the relative frequency of ASA in patients with cerebral ischemic events is unknown.

The Stroke Prevention: Assessment of Risk in a Community (SPARC) study is a community-based study evaluating the prevalence of potential risk factors for stroke in the population. The purpose of the present study was to compare the frequency of ASA in the SPARC population, assessed with transesophageal echocardiography (TEE), with its frequency in a group of patients undergoing TEE after a cerebral ischemic event. An association between ASA and cerebral ischemia was established. Possible mechanisms of cardioembolism are considered.

Methods

Study Populations

SPARC Study

The SPARC study was designed to estimate the prevalence of potential risk factors for cerebral ischemia in the population. The resources of the Rochester Epidemiology Project were used to enumerate the Olmsted County population ≥45 years old. The SPARC sampling process was designed to randomly select 580 subjects, stratified by sex and 5 age subgroups (45 to 54 years, 55 to 64 years, 65 to 74 years, 75 to 84 years, ≥85 years). Of the 1475 Olmsted County residents selected, 230 were ineligible according to predefined exclusion criteria (terminal illness, dementia, significant functional disability, or esophageal disease precluding TEE) and 609 refused to participate in the study. In all, 636 subjects participated in...
a home interview, 48 of whom dropped out of the study. The final SPARC study sample consisted of 588 subjects (47% of those eligible) who were evaluated with TEE, carotid ultrasonography, and ambulatory blood pressure monitoring. TEE was performed successfully in 581 of the SPARC participants.

Control Group
The control group of the present study consisted of 363 subjects randomly selected for review from the SPARC TEE database.

Patient Group
The patient group consisted of 355 patients in whom TEE was performed in search of an embolic source after a focal cerebral ischemic event (stroke or transient ischemic attack) clinically compatible with cerebral embolism. These patients were identified through the Mayo Clinic Echocardiography Laboratory computerized database and were matched with the control group by age and sex.

Transesophageal Echocardiography
All TEE studies (control and patient groups) were performed during the same 2-year period (June 1993 to August 1995). TEE was performed according to standard practice guidelines. Briefly, esophageal intubation was performed with the patient in the fasting state and in the left lateral decubitus position, after premedication with topical anesthesia (lidocaine) and sedation (intravenous midazolam and meperidine, as clinically indicated). Commercially available ultrasonographic instruments (Acuson XP-128 equipped with a biplane 5-MHz transesophageal probe and Hewlett Packard Sonos 1500/2500 with an OmniPlane probe) were used for cardiac imaging. The heart and thoracic aorta were scanned for the presence of potential embolic sources. The interatrial septum (IAS) was viewed primarily in the transverse midesophageal 4-chamber view and the longitudinal biatrial/bicaval view.

Echocardiographic Definitions
Atrial Septal Aneurysm
ASA was defined according to criteria previously published by Hanley et al: (1) diameter of the base of the aneurysmatic portion of the IAS measuring ≥15 mm and either (2) protrusion of the IAS, or part of it, ≥15 mm beyond the plane of the IAS or (3) phasic excursion of the IAS during the cardiorespiratory cycle ≥15 mm in total amplitude (Figure 1).

Patent Foramen Ovale
A patent foramen ovale (PFO) was defined as a right-to-left interatrial shunt diagnosed by intravenous injections of agitated saline with the patient at rest and with provocative maneuvers (cough or release of Valsalva or both).

For the present study, all TEEs were reviewed systematically by an observer blinded to the initial diagnoses, with offline measurements of ASA dimensions. Any discrepancies between the initial and review diagnoses were settled by a third observer blinded to all previous diagnostic data.

Statistical Analysis
The frequency of ASA in each group and the frequency of PFO among those with or without ASA were estimated and studied by multivariate logistic models. An estimate of the ratio of the odds of ASA among the patients to that among the control subjects and associated 95% CI, adjusted for age and sex, was obtained from the multivariate logistic model. Similarly, the ratio of the odds of PFO among those with ASA to the odds among those without ASA with associated 95% CI, adjusted for group, age, and sex, was also estimated from a multivariate logistic model. If the CIs failed to include the integer 1, there was a significant association (P≤0.05).

Results
Prevalence of ASAs
The proportions with ASA in the patient and control groups and in the various age subgroups are shown in Figure 2. Overall, 7.9% of the patient group (28 of 355 patients) and 2.2% of the control group (8 of 363 subjects) had ASA (P=0.002). The odds of ASA were 3.65 greater (95% CI, 1.64 to 8.13) in patients than in control subjects after adjustment for minor age and sex differences between study groups.

Additional Cardiac Sources of Embolism
Right-to-left interatrial shunting through a PFO was detected in 56% of subjects with ASA. The presence of ASA was a predictor of the presence of PFO. The odds of PFO were 4.57 greater (95% CI, 2.18 to 9.57) in subjects with ASA than in those without ASA. Among subjects with ASA, nearly the same proportions of patients and control subjects had PFO (P=0.70). TEE did not identify thrombi in any of the ASAs. Alternative potential cardiac or aortic sources (or both) of embolism in patients with ASA are presented in the Table. Importantly, in 24 of the 28 patients with ASA (86%), no alternative cardiac source of embolism was identified.

Discussion
The present study demonstrated a significantly higher proportion of ASA in patients referred for TEE after a cerebral ischemic event than is present in the general population. This finding suggests that ASA is a risk factor for cerebral ischemia. ASA is frequently associated with right-to-left interatrial shunting. Therefore, paradoxical embolism is a probable mechanism of cardioembolism in a large subgroup of patients with ASA.
Additional Sources of Embolism in 28 Patients With Cerebral Ischemia and Atrial Septal Aneurysm

<table>
<thead>
<tr>
<th>Embolism Source</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intradacrical thrombus</td>
<td>1</td>
</tr>
<tr>
<td>Prosthetic valve†</td>
<td>2</td>
</tr>
<tr>
<td>Aortic atherosclerosis‡</td>
<td>2</td>
</tr>
<tr>
<td>Left ventricular dysfunction§</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrilation∥</td>
<td>1</td>
</tr>
</tbody>
</table>

*More than 1 source of embolism was identified in some patients.
†Mitrail mechanical prosthesis in 1 patient and aortic mechanical prosthesis in another.
‡Complex atherosclerosis (plaque thickness ≥5 mm and/or mobile plaque elements) in ascending aorta or aortic arch.
§Left ventricular systolic dysfunction (ejection fraction <40%).
∥Atrial fibrillation during the TEE examination.

Frequency of ASA
The rate of ASA detection with echocardiography varies from 0.22% in consecutive transthoracic studies to significantly higher rates by TEE, the diagnostic technique of choice. The frequency of ASA is highly variable among TEE studies, reflecting differences in study populations as well as in ASA definition. Although any cutoff in ASA definition is arbitrary, the 15-mm cutoff adopted in the present study provides relatively high specificity for ASA diagnosis. According to this definition, the proportion of ASA in the general population is low (2.2%) and similar to a 1% proportion noted in a large autopsy series. This figure is lower than those of smaller population-based studies, which reported frequencies of 4.5% (no quantitative definition of ASA) and 13% (15-mm ASA definition).

ASA and Cerebral Ischemia
A possible relationship between ASA and cerebral ischemia was suggested initially by retrospective observations of the high frequency of preceding cerebral ischemic events in patients with an echocardiographic diagnosis of ASA. This was confirmed subsequently in 2 multicenter studies. In addition, studies comparing the proportion of ASA in patients with cerebral ischemia with its proportion in those undergoing TEE for miscellaneous clinical indications have found a relatively high prevalence of ASA in association with cerebral ischemia. However, the control groups of such studies were highly prone to selection bias. Our study allowed an estimation of the relative frequency of ASA in patients with cerebral ischemia in comparison with a sample of the general population undergoing TEE.

Right-to-left shunting through a PFO (permitting paradoxical embolism), thrombus formation in the ASA, associated mitral valve prolapse, and supraventricular arrhythmias are the potential mechanisms of cardioembolism associated with ASA. Our data support only the first mechanism, although undiagnosed transient atrial arrhythmias as well as small or rapidly resolving thrombi in ASAs cannot be excluded.

Clinical Implications
Clinical follow-up data have suggested that ASA is associated with an increased risk of stroke recurrence. However, the optimal therapeutic regimen for secondary prevention and possibly primary prevention of stroke in subjects with ASA remains to be determined.

In summary, our study estimated the frequency of ASA in the general population, confirmed an association between ASA and cerebral ischemic events, and suggested that paradoxical embolism is a mechanism of cardioembolic stroke in patients with ASA.

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References
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