Characteristics of Patent Foramen Ovale Associated With Cryptogenic Stroke
A Biplane Transesophageal Echocardiographic Study

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Background and Purpose Patent foramen ovale is associated with ischemic stroke in patients without a clearly identifiable etiology for stroke (cryptogenic stroke). Paradoxical embolization is thought to be a potential mechanism. However, patent foramen ovale is also found in patients with known cause of stroke. Therefore, using contrast transesophageal echocardiography, we characterized the patent foramen ovale in patients with cryptogenic stroke patients to assess morphological factors that may contribute to paradoxical embolization.

Methods Contrast transesophageal echocardiographic studies of 74 consecutive patients referred for ischemic stroke were reviewed. Twenty-three patients with patent foramen ovale were identified. These patients were classified as having strokes of determined origin or cryptogenic strokes according to criteria developed for the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke. Separation of septum primum from secundum and the number of microbubbles appearing in left atrium were then quantitated. These parameters were compared between patients with cryptogenic stroke and those with known cause of stroke.

Results The patent foramen ovale dimension was significantly larger in patients with cryptogenic stroke compared with patients with an identifiable cause of stroke (2.1 ±1.7 mm versus 0.57±0.78 mm [mean±SD]; P<.01). The number of microbubbles was also greater in patients with cryptogenic stroke compared with patients with an identifiable cause of stroke (13.9±10.7 versus 1.6±0.8 [mean±SD]; P.<.0005).

Conclusions Patients with cryptogenic stroke have larger patent foramen ovale with more extensive right-to-left interatrial shunting than patients with stroke of determined cause. Transesophageal echocardiographically identifiable characteristics of patent foramen ovale may be important in defining the clinical significance of individual patent foramina. (Stroke. 1994;25:582–586.)

Key Words • echocardiography • embolism • foramen ovale, patent

Subjects and Methods

Patient Population

From October 1991 to December 1992, from the group of 383 patients referred to the Echocardiography Service for transthoracic echocardiography for assessment of potential cardiac embolic source, 74 patients with documented ischemic stroke were referred for transesophageal echocardiography either from the Neurovascular Unit of the Neurological Institute or as outpatients. The decision to refer patients for transesophageal study was made individually by the responsible neurologist (attending or house staff physicians), and no set criteria applied. All patients underwent either a computed tomographic scan (CT) or magnetic resonance imaging (MRI) of the head. In addition to transthoracic echocardiography, diagnostic workup in all 74 patients included carotid ultrasound and transcranial Doppler. Twenty-six of the 74 patients also underwent cerebral angiography. Workup for procoagulant state (protein S, protein C, and anticardiolipin antibodies) was not routinely performed in all patients. When clinically indicated, the patients underwent Doppler examination of the lower extremities to locate venous thrombi.

Transesophageal Echocardiography

After undergoing routine transthoracic echocardiography, all patients underwent biplane transesophageal echocardiography (Hewlett-Packard Sonos 1000) with saline contrast injection. Contrast material was prepared by mixing 10 mL of normal saline with 1.0 mL of air through a three-way stopcock. This is known to produce 152 ±79 microbubbles per cubic millimeter with diameter of 30 to 100 μm measured by microscopy. Saline contrast injection was performed at rest and with Valsalva maneuver. A PFO was judged to be present

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if at least one microbubble was seen in the left atrium within three cardiac cycles after maximum opacification of the right atrium. If PFO was judged to be present, further imaging of the fossa ovalis area was undertaken in the vertical view to maximize the separation between the septum primum and secundum. This imaging plane, not available on monoplane probe, is necessary for the assessment of size (Fig 1). Images were recorded on a 1/2-inch VHS tape for subsequent analysis.

Infarct Subtyping
An infarct subtype diagnosis was made by a neurologist aware of the findings of noncontrast transthoracic echocardiography but not transesophageal contrast echocardiography. Diagnoses were based on criteria developed for the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke. An atherosclerotic infarction was attributed to perfusion failure distal to the site of severe stenosis or occlusion of a major intracranial or extracranial vessel or represented cases in which an extracranial lesion was insufficient in itself to account for stroke on hemodynamic grounds but possibly served as an embolic source. Lacune was diagnosed in the case of a lacunar syndrome with a small, deep infarct or no lesion found on CT or MRI. A cardioembolism was diagnosed when a cardiac source was recognized: atrial fibrillation or flutter, bacterial endocarditis, significant valvular pathology including mitral valve prolapse, mitral annular calcification, myocardial infarction within the previous 6 weeks, intracardiac thrombus, atrial myxoma, or pulmonary venous thrombosis. Patients with aortic or mitral valvular vegetation or left-sided chamber thrombus detected by transesophageal echocardiography were reclassified in the cardioembolic category. Patients who could not be classified into one of the above determined categories who had no clear cause of infarction were labeled as having cryptogenic infarcts. Because a hematologic workup for procoagulant state was not consistently performed in all patients, this information was not used in infarct subtyping.

Echocardiographic Study Analysis
On transthoracic echocardiography, the dimensions of right atrium and ventricle were qualitatively assessed. Echocardiographic evidence for elevated right ventricular systolic pressure such as pulmonic valve notching and flat interventricular septum was sought. When feasible, tricuspid regurgitation velocity was measured using continuous-wave Doppler to assess for right ventricular systolic pressure.

On transesophageal echocardiography, the maximum distance between the septum primum and secundum was measured from a frozen video image during normal respiration using commercially available quantitative software in the echocardiography equipment (Fig 2). The maximum number of microbubbles seen in the left atrium within three cardiac cycles after maximum right atrial opacification was also counted (Fig 2). When the number of microbubbles counted was equal to or more than 25, the number was taken as 25. PFO size determination and microbubble count were performed by an echocardiographer unaware of stroke subtype and blinded to other transesophageal echocardiographic findings. Atrial septal aneurysm (ASA) was defined as the motion of interatrial septum with base width 1.5 cm or greater and with at least 1.1 cm excursion into either the left or the right atrium or a sum of the total excursion into the left or right atrium of 1.1 cm or greater.

Statistical Analysis
For comparison of proportions the $x^2$ test was used; this was replaced by Fisher's exact test in cases in which the cell frequency was less than 5. Unpaired $t$ test was used to compare the mean PFO size and the number of microbubbles between the group with cryptogenic stroke and that with known cause of stroke. Linear regression analysis was used to assess the relation between PFO size and the number of microbubbles appearing in the left atrium. Data are shown as mean±1 SD.

Results
Diagnostic subtypes of the 74 patients were as follows: 36 with cryptogenic stroke, 9 with atherosclerotic infarction, 10 with lacunar infarction, 18 with cardioembolism, and 1 other (vertebral dissection). Of the 74 patients undergoing transesophageal echocardiography, 23 (31%) had PFO: 16 (44%) of 36 cryptogenic stroke patients and 7 (18%) of 38 patients with known cause of stroke. Cryptogenic stroke patients (5 men and 11 women; mean age, 46.7±17.1 years) were significantly younger than the
patients with known cause of stroke (5 men and 2 women; mean age, 62.9±19.1 years) (P<.05). The PFO prevalence in cryptogenic stroke patients was significantly higher than that in patients with known cause of stroke (P<.05). The stroke subtypes of the 7 patients with known cause of stroke were as follows: 4 with cardioembolism (1 mitral annular calcification, 1 valvular vegetation, 1 mitral valve prolapse, and 1 left atrial thrombus), 1 with atherosclerotic infarction, 1 with lacunar stroke, and 1 with other (vertebral dissection). Patients in our study did not undergo systematic search for deep venous thrombosis or for pulmonary embolism. However, 1 patient in the cryptogenic stroke group had evidence for pulmonary embolism documented by ventilation/perfusion scan.

On transthoracic echocardiography, all patients with PFO had normal right atrial and ventricular dimensions. No pulmonary valve notching, systolic flattening of interventricular septum, or Doppler tricuspid regurgitant velocity indicative of pulmonary hypertension was noted. Transesophageal echocardiographically diagnosed ASA was present in 9 (12%) of 74 patients. It was seen in 6 (17%) of 36 with cryptogenic stroke and in 3 (8%) of 38 with known cause of stroke (P=NS). Of the 9 patients with ASA, 5 (56%) had associated PFO. The PFO size ranged from 0 to 5.0 mm in cryptogenic stroke patients and from 0 to 2.0 mm in those with determined cause of stroke. PFO size was significantly larger in patients with cryptogenic stroke compared with those with known cause of stroke (2.1±1.7 mm versus 0.57±0.78 mm; P<.01). The number of microbubbles seen in the left atrium ranged from 1 to 25 or more in cryptogenic stroke patients and from 1 to 3 in those with determined cause of stroke. The number of microbubbles was significantly greater in patients with cryptogenic stroke compared with those with known cause of stroke (13.9±10.7 versus 1.6±0.8; P<.0005). When the size of PFO was plotted against the number of microbubbles, there was a good direct correlation between the size and the number of microbubbles (R²=.65; Fig 3).

Discussion

In patients aged younger than 55 years, Lechat et al² found the PFO prevalence to be 54% in cryptogenic stroke patients compared with 10% in control subjects. In those aged younger than 40 years, Webster et al³ reported a prevalence of 56% in cryptogenic stroke patients compared with 15% in control subjects. However, stroke is predominantly a disease of the elderly, and less than 3% of all stroke patients are aged younger than 40 years.¹⁷

Most recently, we reported the association of PFO with cryptogenic stroke in patients of all age groups.⁴ Contrast transthoracic echocardiography was performed in 146 consecutive patients with ischemic stroke unselected for age. Overall, PFO was found in 42% of cryptogenic stroke patients compared with 7% in patients with known cause of stroke. This difference was observed in both the younger and older age subgroups. Therefore, the association of PFO with cryptogenic stroke encompassed all age groups rather than being limited to just a small segment of
the ischemic stroke population. Using contrast transesophageal echocardiography, the current study also demonstrates that the prevalence of PFO is higher in patients with cryptogenic stroke (44%) than in patients with known cause of stroke (18%).

Patent foramen ovale is thought to possibly act as a conduit for paradoxical embolization. Using transesophageal Doppler and saline contrast injection, several studies have demonstrated the delivery of contrast material to the cerebral circulation in patients with PFO detected by contrast transthoracic echocardiography. A recent study by Stöllberger et al demonstrated the high prevalence of deep venous thrombosis in patients with cryptogenic stroke, and a case report documented a thrombus lodged in PFO in a patient with stroke. However, Ranoux et al failed to observe a greater tendency for stroke patients with PFO to have factors presumably associated with paradoxical embolization such as deep venous thrombosis or Valsalva maneuver at the onset of stroke. Therefore, the source of thrombus for paradoxical embolization remains unclearly defined.

Atrial septal aneurysm is associated with stroke. In the present study it was found in 17% of cryptogenic stroke patients and in 8% of patients with known cause of stroke. The difference did not reach statistical significance. Fifty-six percent of patients with ASA were found to have PFO. This prevalence is comparable to the 70% prevalence reported by Pearson et al.

Patent foramen ovale is found with high frequency in the general population. Two autopsy studies indicate that the prevalence of PFO is approximately 27% and 29%. Using contrast transthoracic echocardiography, prevalence of 10% to 18% is reported in patients without stroke. With the use of transesophageal echocardiography, which is more sensitive than transthoracic echocardiography, a prevalence of 22% to 28% is reported. Furthermore, great variability exists in the degree of shunting through a PFO in patients with ischemic stroke and PFO. PFO characteristics associated with paradoxical embolization are unknown. It is therefore possible that a proportion of the detected PFOs may be incidental findings without clinical significance. Webster et al noted that on transthoracic contrast echocardiography, when the appearance of microbubbles in young stroke patients was compared with that seen in control subjects, the stroke patients with PFO appeared to have more microbubbles entering the left-sided chambers. Using contrast transesophageal echocardiography, Cosyns et al noted that the degree of shunting was greater in cryptogenic stroke patients with PFO compared with the control group. However, no study has quantitatively assessed the size and the degree of shunt through a PFO to clearly define the characteristics associated with cryptogenic stroke.

Transesophageal echocardiography allows for a detailed visualization of the fossa ovalis area. With the use of a biplane transesophageal probe, imaging can also be performed in an orientation to clearly visualize the separation of septum primum from secundum, which are the boundaries of PFO. Furthermore, using transesophageal echocardiography the number of microbubbles that cross the atrial septum can be counted to assess the degree of shunt. Therefore, biplane transesophageal echocardiography allows for sizing and quantitation of right-to-left shunting through PFO.

We found that patients with cryptogenic stroke had a larger PFO than those with known cause of stroke. The number of microbubbles seen in patients with cryptogenic stroke was also larger than that seen in patients with known cause of stroke. When the stroke had a determined etiology, the size and the degree of shunt through a PFO were markedly smaller. The size of a PFO directly correlated with the degree of shunt. Larger PFOs allowed an increased amount of embolic material to enter the systemic circulation. Therefore, the size of a PFO and the degree of shunting through it may be the major determinants for PFO to act as a conduit for paradoxical embolization. Right-sided chamber dimensions were normal in cryptogenic patients with PFO. Therefore, these PFOs were not associated with volume overload of the right-sided chambers. Also, no echocardiographic evidence for pulmonary hypertension was noted in cryptogenic stroke patients with PFO. Accordingly, despite the larger size and increased shunting, the PFOs in cryptogenic stroke patients did not appear to have any hemodynamic significance.

For the patients with cryptogenic stroke and PFO, the stroke recurrence rate may vary depending on the PFO characteristics. Because larger PFOs can transmit more paradoxical embolic material, patients with large PFOs may be at a higher risk for recurrence than patients with smaller PFOs. As a result, future studies on stroke recurrence need to incorporate the information on PFO characteristics rather than to regard all patients with PFO as a single group. Furthermore, the role of other factors associated with paradoxical embolization such as deep venous thrombosis needs to be defined. It is also possible that patients with propensity for forming peripheral venous thrombus may be at a higher risk for paradoxical embolization by providing potentially embolic material.

A variety of therapeutic options for cryptogenic stroke patients with PFO exists, including conventional medical therapy with aspirin or warfarin, percutaneous closure, and even surgical closure. Treatment trials using any one of these modalities will also need to take into account the PFO characteristics because they may influence the therapeutic efficacy of various treatment options. The best treatment option may depend on the morphological characteristics of PFO.

There are clear limitations associated with our study. In performing a transesophageal echocardiographic study, only those referred at the discretion of the neurologists underwent the test, and no consistent criteria for its performance were set. Thus, the patients that underwent transesophageal study represented a selected population. Although of great interest, the relation of hematologic abnormality to the presence of PFO was not clarified in this study because of lack of complete procoagulant workup in all patients.

In analyzing the size of PFO, we analyzed the dimension in a single plane. Therefore, the exact dimension of the communicating channel between the left and the right atra may be different from that indicated by the measurements we made. With the use of an omniplane probe, more information on the dimension of the communicating channel may become available. This probe will allow viewing of the fossa ovalis in multiple planes from the same transducer location; this is not
possible with a biplane probe unless the probe is repositioned within the esophagus.

Finally, because we counted the microbubbles in only one plane, it is possible that in another plane the number might have been different. Also, the microbubbles counted will vary depending on the number delivered to the right atrium. Although we mixed the saline with air in as uniform a fashion as possible and used similar injection sites, the number of microbubbles and the rate at which they were injected may have varied. However, there is no reason to believe that systematic differences were introduced in the injection modalities between patients with cryptogenic stroke and those with known cause of stroke that could affect our findings.

References
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