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The Association of Patent Foramen Ovale Morphology and Stroke Size in Patients With Paradoxical Embolism

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Background**—**Patent foramen ovale (PFO) has been implicated in the pathogenesis of cryptogenic stroke through paradoxical embolization to the cerebral circulation. This study evaluated the relationship between the morphological and functional size of the PFO by echocardiography compared with cerebral infarct volume identified on MRI.

Methods and Results**—**Patients who were referred to interventional cardiology with the diagnosis of cryptogenic stroke were included and had either a transesophageal echocardiogram or an intracardiac echo and a brain MRI at the time of stroke. Transesophageal echocardiogram or intracardiac echo was used to obtain PFO measurements. MRI of the brain with 3 sequences (T2, diffusion-weighted imaging, and fluid-attenuated inversion recovery) was used to diagnose acute stroke and measure the infarct volume. In the 72 patients studied, the median measured stroke volume was 4.3 cm^3 on diffusion-weighted imaging, 4.1 cm^3 on T2, and 3.5 cm^3 on fluid-attenuated inversion recovery. There was no significant correlation between the PFO height, length, septum secundum thickness, or echo bubble grade and the infarct volume measured from the 3 MRI sequences. There was a significant correlation between septal excursion distance and infarct volume (r=0.35; P=0.005), but the 12 patients with atrial septal aneurysm did not have the largest strokes.

Conclusions**—**This analysis revealed that septal excursion distance correlates with stroke size by MRI. However, smaller PFO size without the presence of atrial septal aneurysm may still be associated with significant strokes. There was no significant association between PFO height, length by echo, or shunt grade by transcranial Doppler study and brain infarct volume. Therefore, PFO size or morphology should not be the only criteria to decide whether a PFO should be closed. **(*Circ Cardiovasc Interv*. 2010;3:506-510.)**

Key Words: echocardiography ■ embolism ■ stroke ■ foramen ovale patent

Of the 795 000 strokes that occur annually in the United States, ≈87% are classified as ischemic.[1,2] Despite extensive evaluation, >40% of all ischemic strokes have no clear identifiable cause and are classified as cryptogenic.[3] Approximately 50% of patients aged <55 years with cryptogenic stroke are found to have a patent foramen ovale (PFO).[4] Autopsy studies indicate that the prevalence of PFO in the general population is ≈25%.[5] PFO is created by the failure of fusion between the septum primum and septum secundum, resulting in a potential communication between the right and left atriums.[6] There is increasing interest in the association of PFO and cryptogenic stroke through the presumed mechanism of paradoxical embolization.[7–9] It is hypothesized that a small venous thrombus reaches the arterial circulation, leading to cerebral infarction via a right-to-left shunt through the PFO, which bypasses the pulmonary capillary filter.[10] Although this mechanism has not been proven, 3 randomized clinical trials currently are evaluating whether percutaneous closure of PFO can prevent recurrence of cryptogenic stroke compared with anticoagulation or antiplatelet therapy. There has been intense speculation of potential predictors of stroke in these patients, including the size of the PFO, degree of right-to-left shunt, presence of atrial septal aneurysm (ASA), or predisposition with hypercoagulable states.[11,12] Knowledge of these factors could have important clinical significance by allowing clinicians to identify those patients most susceptible to initial or recurrent cryptogenic stroke and then to stratify them to more aggressive therapy.[13] This retrospective analysis evaluated the association between PFO morphology and the size of cerebral infarct in patients with cryptogenic stroke.

Clinical Perspective on p 510

Methods

Patient Population

Of the 227 patients with cryptogenic stroke who were seen at the UCLA Interventional Cardiology Program between 2001 and 2009, 72 had an adequate brain MRI and a cardiac echo examination. The

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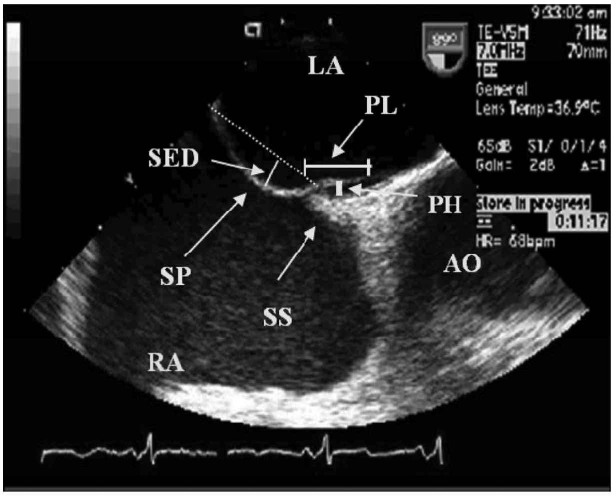

Figure 1. TEE measurements of PFO parameters. TEE in the vertical plane at the level of the interatrial septum demonstrates how the PFO was measured. AO indicates aorta; LA, left atrium; PL, PFO length; PH, PFO height; RA, right atrium; SED, septal excursion distance; SP, septum primum; SS, septum secundum.

remaining 155 patients had their transesophageal echocardiogram (TEE), MRI, or both performed at an outside hospital, which made the retrieval of these studies difficult, or the MRI was not performed at the time of the acute stroke, which precluded the accurate assessment of diffusion-weighted imaging (DWI). (Supplemental Table 1 provides the comparison between the 72 and 155 patients.) Cryptogenic stroke was defined by the presence of a transient or permanent neurological deficit, with MRI evidence of an ischemic lesion in the absence of a clear etiology.[14] Patients underwent diagnostic imaging, including carotid ultrasound, magnetic resonance angiography, 24-hour cardiac monitoring, hypercoagulable workup, and echocardiography to exclude other potential etiologies of stroke. A prothrombotic state was determined based on a positive hypercoagulable laboratory workup or a clinical predisposition such as malignancy or hormone replacement therapy.[15] TEE and MRI data were used to determine the presence of an association between structural and functional PFO parameters and cerebral infarct volume. The institutional board review approved all protocols, and each patient gave informed consent to participate in clinical follow-up.

Echocardiography

TEE was obtained using a 7.0-MHz multiplane vector array probe (Acuson TE-V5 mol/L; Mountain View, Calif). Studies were reviewed on the Kinet-X echocardiography imaging station (Siemens, Inc; Munich, Germany), and measurements were made using the caliper ruler included on the images. Outside-hospital TEE studies (n=22) were loaded into the Kinet-X system and analyzed in the same manner. TEE images that optimally demonstrated the presence and length of the PFO were chosen. The caliper software was used to measure the height of the PFO opening in diastole and systole; the maximal and minimal PFO lengths were defined by the overlap of the septum primum and septum secundum as well as the thickness of the septum secundum (Figure 1). The excursion of the atrial septum into the right and left atriums was measured, and the presence of an ASA was identified if the septum primum excursion into either atrium exceeded 10 mm or the total excursion distance was >15 mm.[16] To ensure consistency in the echocardiographic measurements, an interobserver variability analysis was performed on 30 patients; the Pearson correlation coefficient and Bland-Altman limits of agreement were determined for all PFO measurements.

An agitated saline bubble study was conducted to evaluate the degree of right-to-left shunt. Patients received an agitated saline injection into an antecubital vein, and the number of bubbles seen in the left atrium after 3 cardiac cycles was recorded. The International Consensus Criteria were used to classify bubble grade.[17] Absence of bubbles was classified as grade 0. A positive study was classified as 1 to 9 bubbles (grade I), 10 to 20 bubbles (grade II), and >20 bubbles (grade III) appearing in the left atrium.

MRI

Adequate MRI studies were available for analysis in 72 patients who had evidence of an embolic stroke. The area of stroke was identified on the DWI, fluid-attenuated inversion recovery (FLAIR), and T2-weighted sequences and was confirmed by a stroke neurologist. Acute strokes were identified initially on the DWI sequence, and older lesions appeared on T2 and FLAIR but were absent on DWI. The vascular distribution of infarcts also were identified and recorded. The distribution was determined based on the origin of the culprit vessel involved in the cerebral infarction. The anterior circulation was defined as the area supplied by the internal carotid arteries, which include the anterior and middle cerebral arteries. The posterior circulation arose from the vertebral arteries and was defined as the posterior cerebral artery, vertebral arteries, and basilar artery. Using Medical Image Processing, Analysis, and Visualization software, the area of the stroke was outlined at each brain section level using volume of interest image segmentation, which is the process of identifying connected regions of images as members of a common group. The area of the stroke was summed over the depth of the MRI levels to calculate the stroke volume in cm^3.

Transcranial Doppler

Data were collected on patients who had transcranial Doppler (TCD) studies to determine whether a PFO was present. TCD studies with agitated saline were performed in 26 patients. During the TCD procedure, the patients were asked to perform a spontaneous Valsalva maneuver, and the bubble grade was measured. In 15 (58%) patients, there was an increase in bubble grade during the Valsalva maneuver. The Spencer Logarithmic Scale was used for grading of TCD right-to-left shunt as follows: Grade 1 (1 to 10 embolic tracks) and grade 2 (11 to 30 embolic tracks) were considered negative for a significant shunt; grade 3 (31 to 100 embolic tracks), grade 4 (grade 101 to 300 embolic tracks), and grade 5 (>301 embolic tracks) were indicative of the presence of right-to-left shunt.[17]

Statistical Analysis

Continuous data are presented as mean±SD or median and interquartile range (IQR), as appropriate. The association of PFO size and other structural parameters and MRI stroke volume was conducted using the Spearman correlation coefficient for continuous and ordinal categorical variables. The 2-sample *t* test or the Wilcoxon rank sum test was used to compare PFO morphology and stroke volume among patients with anterior and posterior cerebral infarction. The Pearson correlation and agreement limit[18] were calculated to assess the agreement of echo parameters measured by 2 observers. Analysis was conducted using SPSS version 11.5 software, and a $P<0.05$ was considered statistically significant.

Results

The clinical variables of the 72 patients with acute cryptogenic stroke are shown in Table 1. The average age of the group was 49.0±16.0 years, with 43 (60%) male patients. Hypercoagulable conditions were observed in 13 (18%) patients. The vascular territory involved in the infarct was distributed between the anterior circulation in 46 (64%), posterior circulation in 20 (28%), or both in 6 (8%).

Echocardiographic data of the structural components of the PFO are shown in Table 2. The average PFO height, defined as the distance between the septum primum and septum secundum, was 2.6±1.7 mm. The maximum PFO length, defined by the maximum distance of overlap between the septum primum and septum secundum, was 11.2±4.0 mm, and the minimum PFO length was 6.5±2.6 mm. The maxi-

Table 1. Clinical Characteristics of the Cohort

	Cryptogenic Stroke (n=72)
Age, y	49.0±16.0
Male sex	43 (60)
Hypertension	19 (26)
Cigarette smoking*	11 (15)
Dyslipidemia†	25 (35)
Diabetes mellitus	4 (6)
Hypercoagulable state‡	13 (18)
Vascular distribution§	
Anterior circulation	46 (64)
Posterior circulation	20 (28)
Both	6 (8)

Data are presented as n (%) or mean±SD. Clinical characteristics are of patients with PFO and cryptogenic stroke.

*Current or prior history of cigarette smoking.

†Based on the National Cholesterol Education Program guidelines.

‡Hypercoagulable state is determined based on laboratory workup (protein C, protein S, antithrombin III, factor V Leiden, prothrombin 20210A, factor VIII, homocysteine, anticardiolipin antibodies, β2-glycoprotein antibodies, dilute Russell viper venom test) or clinical predisposition, including malignancy or hormone replacement therapy.

§Anterior circulation refers to cerebral blood supply that originates from the internal carotid arteries, and the posterior originates from the vertebral arteries.

mum overlap of the septum primum and septum secundum also is described as the tunnel length of the PFO. The mean thickness of the septum secundum was 7.6±2.6 mm, and the average total septal excursion distance was 5.6±5.2 mm. The median bubble grade used to quantify the degree of right-to-left shunting was 2.0 with IQR between 1 (Q1) and 3 (Q3). The criterion for atrial septal aneurysm was met in 12 (16.7%) patients from the 72 studies. At rest on Doppler imaging, left-to-right shunt through the PFO was observed in 53 (74%) patients. On agitated saline bubble study, right-to-left shunt at rest was identified in 32 (45%) patients, which increased to 89% during the Valsalva maneuver.

Three MRI sequences (DWI, T2, and FLAIR) were used to calculate the infarct volume. The median stroke volume calculated by DWI was 4.3 cm^3 (IQR, 1.3, 14.4), 4.1 cm^3 (IQR, 1.0, 19.6) by T2, and 3.5 cm^3 (IQR, 0.9, 14.1) by FLAIR. The correlations of the structural components of PFO versus the volume of cerebral infarct measured on MRI are listed in Table 3 and plotted in Figure 2. There was no

Table 2. Echocardiographic PFO Parameters

	Cryptogenic Stroke (n=72)
PFO height, mm	2.6±1.7
Maximum PFO length, mm	11.2±4.0
Minimum PFO length, mm	6.5±2.6
Septum secundum thickness, mm	7.6±2.6
Total septum excursion distance, mm	5.6±5.2
Median bubble grade (IQR)	2.0 (1, 3)

Data are presented as mean±SD, unless otherwise indicated. Structural and functional parameters of the PFO measured on TEE in patients with cryptogenic stroke are shown. No bubbles was classified as grade 0, 1 to 9 bubbles as grade I, 10 to 20 bubbles as grade II, and >20 bubbles as grade III.

Table 3. Summary Spearman Correlation Coefficients and *P* Values Among PFO Parameters, TCD Bubble Grade, and Infarct Volume on MRI

	MRI Technique		
	DWI	T2	FLAIR
PFO height	0.032	0.028	0.055
P	0.81	0.83	0.69
Maximum PFO length	−0.048	−0.088	0.035
P	0.71	0.49	0.81
Minimum PFO length	−0.023	−0.063	0.039
P	0.86	0.62	0.78
Septum secundum thickness	−0.058	−0.107	−0.031
P	0.65	0.39	0.82
Total septum excursion	0.292	0.346	0.252
P	0.02	0.005	0.06
PFO bubble grade	0.120	−0.009	0.075
P	0.36	0.95	0.59
TCD bubble grade (rest)	0.164	0.117	0.026
P	0.43	0.56	0.91
TCD bubble grade (Valsalva)	−0.208	−0.086	−0.088
P	0.34	0.68	0.70
Median stroke volume, cm^3	4.3	4.1	3.5
IQR	1.3, 14.4	1.0, 19.6	0.9, 14.1

Correlation coefficients (*r*) and *P* values comparing the structural components of the fossa ovalis and the cerebral infarct volume calculated from the 3 MRI sequences in patients with cryptogenic stroke are shown. Negative values represent inverse correlation.

significant correlation between the PFO height, maximum and minimum PFO length, septum secundum thickness, or bubble grade and the stroke volume as measured on DWI, FLAIR, or T2 MRI.

The PFO morphology was compared between patients in the anterior and posterior infarct cohorts (supplemental Table 2). There was no significant difference in the PFO height, maximum and minimum PFO length, septum secundum thickness, or bubble grade between the 2 cohorts of vascular distribution. In addition, the average cerebral infarct volume was compared in patients with cryptogenic stroke involving anterior versus posterior cerebral circulation. For the MRI sequences in the anterior circulation, the median stroke volume by DWI was 6.9 cm^3 (IQR, 1.6, 17.2), 5.6 cm^3 (IQR, 1.2, 21.6) by T2, and 7.0 cm^3 (IQR, 1.4, 18.6) by FLAIR. For posterior circulation, DWI was 1.1 cm^3 (IQR, 0.7, 2.6), T2 was 1.0 cm^3 (IQR, 0.7, 8.7), and FLAIR was 1.0 cm^3 (IQR, 0.7, 4.4). There was a statistically significant difference between stroke volume and territory for each MRI sequence (DWI, $P=0.04$; T2, $P=0.02$; FLAIR, $P=0.05$). This analysis implies that paradoxical embolization produces larger-volume strokes in the anterior circulation territory compared with the posterior circulation. TCD bubble grade at rest and on release of Valsalva strain also was compared with stroke volume. The median baseline TCD Spencer Logarithmic Scale bubble grade was 2, and the median TCD grade increased to 4 with Valsalva maneuver. There was no correlation between TCD grade and stroke volume by MRI (Figure 2).

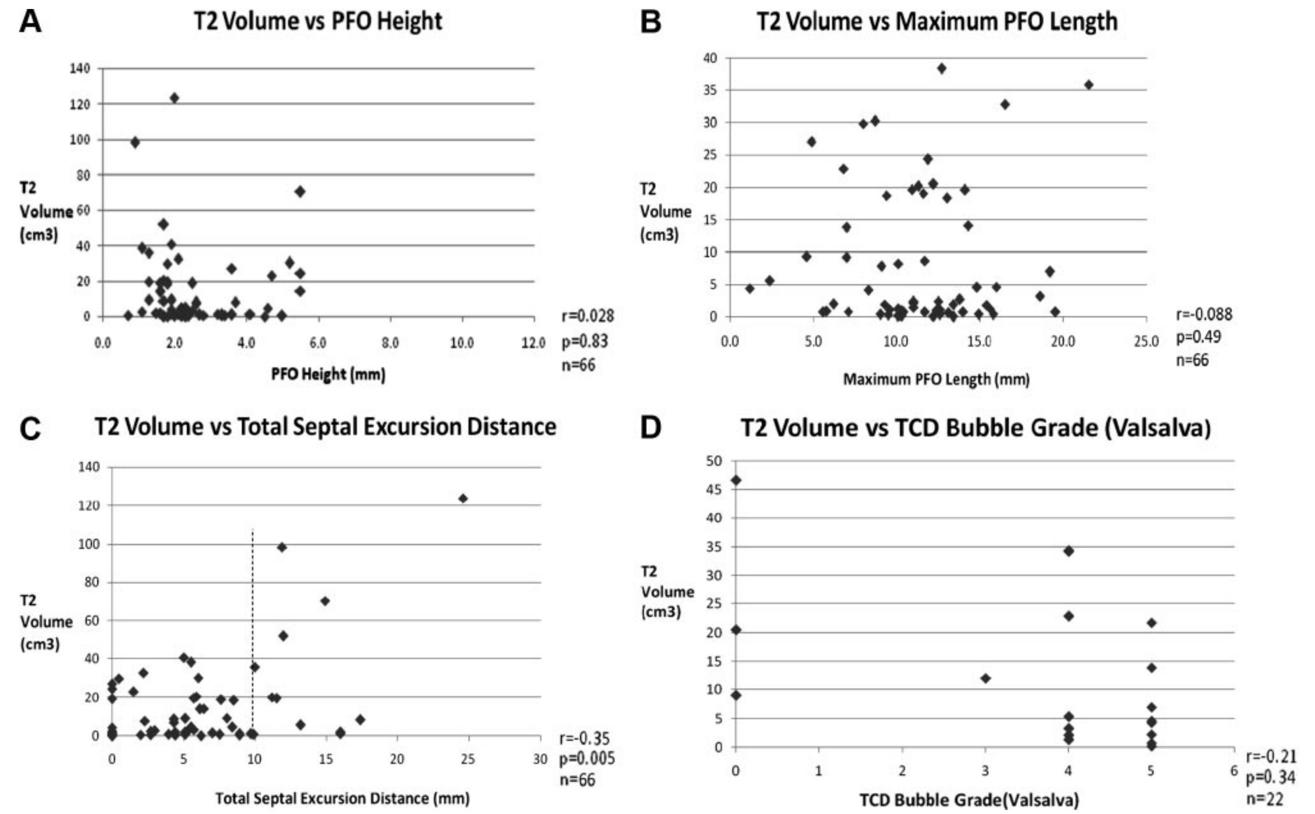

Figure 2. Scatter plots of PFO height (A), maximum length (B), total septal excursion distance (C), and TCD bubble grade (D) versus calculated cerebral infarct volume on T2-weighted MRI.

The interobserver analysis showed good correlations for all echo parameters, and the agreement limits demonstrated reasonable agreement (supplemental Table 3) as follows: septum secundum maximum thickness (r=0.63; P<0.001), septum secundum minimum thickness (r=0.54; P=0.002), PFO height (r=0.78; P<0.001), maximum PFO length (r=0.75; P<0.001), minimum PFO length (r=0.84; P<0.001), and septal excursion distance (r=0.90; P<0.001).

Discussion

The main finding of this study is that there was a significant correlation between total septum excursion distance by TEE compared with stroke volume on DWI and T2 MRI sequences. Previous studies have shown that a large total septal excursion distance with the presence of ASA increases the anatomic size of a right-to-left shunt and increases the risk of recurrent embolic events,[11,19–21] but to our knowledge, this study is the first to demonstrate that the size of the stroke corresponds to the size of the PFO as measured by septal excursion. There was no significant correlation between PFO height, PFO length, and septum secundum thickness as measured by TEE and the size of the stroke as measured on MRI. The functional degree of right-to-left shunt estimated by the amount of bubbles seen in the left atrium during an agitated saline injection during TEE or by TCD also failed to demonstrate an association with the size of the infarcted territory.

Previous studies have demonstrated a relationship between the PFO height, presence of ASA, and the degree of right-to-left shunt and the incidence of cryptogenic stroke.[6–8] Large defects between the right and left atriums may facilitate paradoxical passage of thrombi from the venous system into the arterial circulation.[9] However, the likelihood of a cryptogenic stroke is a different question than the potential size of the stroke. To our knowledge, only 1 study has evaluated the correlation between PFO structural parameters and stroke size. Bonati et al[16] demonstrated a positive trend between PFO size and the infarct lesion diameter (P=0.06) in 48 patients. However, that study used the infarcted brain lesion diameter as a surrogate for stroke size, which does not account for the 3D contour of a stroke. One hypothesis is that a larger PFO would allow embolization of a larger thrombus that occludes more proximal cerebral vessels, inducing larger infarcts.[22] However, paradoxical embolization does not rely solely on the size of the tunnel between the septum primum and septum secundum; presumably, it is the interplay of morphological and functional parameters and the size and frequency of venous thrombosis that determine the dynamics of embolization through the PFO.[23] The observation that the frequency and size of the strokes were larger for anterior circulation than for posterior circulation stroke volume was not expected based on other reports that cryptogenic stroke predominantly affects the posterior circulation.[24] These observations support the concept that the size of the stroke is determined more by the size of the thrombus than by the morphology of the PFO or cerebral blood flow patterns.

Study Limitations

All observational studies of PFO are subject to methodological difficulties. This study is retrospective, and cases were selected based on adequacy and availability of both the TEE and the acute MRI studies.

Conclusions

This comparison between PFO morphology by echocardiography and stroke size as measured by MRI revealed a correlation between septal excursion distance and stroke volume. PFO length, height, and septum secundum thickness did not correlate with stroke volume. In addition, measures of right-to-left shunt flow by TCD or echo did not demonstrate an association with stroke volume. Although large septal excursion distances correlate with stroke size, there is considerable overlap, and it is possible to have a large stroke with a small PFO. Other factors such as the size of the thrombus are also likely to influence the volume of infarcted brain in addition to any quantitative measure of the PFO pathway. These results suggest that PFO size and morphology should not be used as the only criteria for whether a PFO should be closed.

Disclosures

Dr Tobis is a consultant for AGA Medical Inc, W.L. Gore Inc, and Coherex Inc. He is an investigator in the RESPECT and PREMIUM clinical trials.

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CLINICAL PERSPECTIVE

In evaluating patients with known patent foramen ovale (PFO) and cryptogenic strokes, healthcare providers often question whether percutaneous closure of PFO can prevent recurrence of cryptogenic stroke as compared with anticoagulation or antiplatelet therapy. This retrospective study looked at the relationship between cerebral infarction volume and parameters of PFO size and function in patients who have had cryptogenic stroke. Our analysis revealed that septal excursion distance correlates with stroke size by MRI. However, PFO length, height, septum secundum thickness, and right-to-left shunt flow by transcranial Doppler do not correlate with stroke volume. Smaller PFO size without the presence of atrial septal aneurysm may still be associated with significant strokes. Therefore, PFO size should not be used to decide whether a PFO should be closed.