Transesophageal Echocardiography for Quantifying Size of Patent Foramen Ovale in Patients With Cryptogenic Cerebrovascular Events

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Background and Purpose—Patent foramen ovale (PFO) is a risk factor for paradoxical embolism, and severe shunting and wide opening of PFO are risk factors for severe and recurrent cerebrovascular events. Neither contrast echocardiography nor 2-dimensional (2D) measurement of PFO size have been validated or compared with invasive balloon sizing.

Methods—We performed transesophageal echocardiography (TEE) in 100 patients with cryptogenic stroke and catheter closure of PFO. The amount of contrast shunting through the PFO during cubital and femoral contrast delivery and the PFO size measured by 2D TEE were compared with balloon sizing.

Results—There was a significant correlation \( r^2 = 0.8; P < 0.0001 \) between 2D TEE measurement and invasive balloon sizing. Mean balloon-sized PFO diameter was significantly larger than mean PFO diameter measured by 2D TEE (8.3 ± 2.6 versus 5.2 ± 1.7 mm). Semiquantitative contrast TEE correlated with PFO size \( r^2 = 0.7; P < 0.0001 \) only if the contrast agent was administered through a femoral vein. Correlation was poor when the contrast agent was administered via a cubital vein.

Conclusions—We conclude that 2D TEE measurement of a PFO size is more accurate than the traditionally used contrast technique. (Stroke. 2002;33:293-296.)

Key Words: cerebral ischemia ■ contrast media ■ echocardiography, transesophageal ■ embolism, paradoxical ■ foramen ovale, patent

The prevalence of patent foramen ovale (PFO) is higher in patients with unexplained cerebrovascular events than in the general population (up to 75% versus 25% to 30%).1–3 Additionally, patients with PFO carry risk for recurrent cerebrovascular events in the range of 1.7% to 4.7% per year.4 Recent studies have demonstrated that the size of a PFO as estimated by 2-dimensional (2D) transesophageal echocardiography (TEE) affects the risk of stroke.5,6 Mean PFO diameter was significantly larger (4 ± 2 mm) in patients with cryptogenic cerebrovascular events than in controls (2 ± 1 mm) or in patients with strokes of defined cause.3,6 These data emphasize the importance of 2D measurements of PFO size. Thus far, neither 2D measurement of PFO size by TEE nor semiquantitative assessment by contrast echocardiography has been compared with invasive balloon sizing. Usually, PFO size is assessed semiquantitatively by transthoracic echocardiography, by TEE, or by transcranial Doppler ultrasonography on the basis of the number of contrast microbubbles appearing in the left atrium or cerebral circulation after injection of contrast agent into a cubital vein. However, in addition to the size of a PFO, the magnitude of the contrast shunt is influenced by the position of the patient; the choice, dosage, and route of administration of the contrast agent; the provocative maneuvers used; and patient compliance in performing provocative maneuvers.7–10 Furthermore, anatomic and functional variations of the right atrial inflow area11 and pathological conditions influence the amount of contrast shunting through a PFO.11 Nonetheless, semiquantitative grading systems of PFO size are used for diagnosis, clinical decision making, and treatment recommendations.4,12–15 Direct evaluation of the PFO size may be more independent of these factors and was shown to be an independent indicator of stroke.3 The purpose of this study was to investigate the diagnostic accuracy of TEE for assessing PFO size by 2D measurement or semiquantitative contrast echocardiography.

Subjects and Methods
We studied 100 consecutive patients (mean age, 37.4 ± 11.7 years; range, 13 to 69 years; 62 males and 38 females) with a PFO and a presumed paradoxical cerebrovascular event who were undergoing cardiac catheterization for closure of the PFO with a transcatheter device. The indications for intervention were recurrent presumed
paradoxical cerebrovascular events despite medical treatment, complications or contraindications for anticoagulation, or patient preference for this treatment.

Transesophageal Echocardiography
TEE was performed with a 5-MHz phased multiplane probe (Sonos 2500, Hewlett Packard, or Vingmed System Five, General Electric). In addition to the standard views, the region of the fossa ovalis was studied to detect a separation between the septum primum and the septum secundum. The maximum opening diameter of the communicating channel was measured at the entrance into the left atrium, online and offline, by 2 different observers using the equipment software. Two contrast studies (D-galactose, Echovist, Shering Berlin) were performed in each patient, administered into an antecubital vein, during normal inspiration and with a Valsalva maneuver.

Right-to-left shunting was graded as minimal if only a few bubbles passed through the PFO, moderate if a cloud of contrast bubbles was documented in the left atrium, or severe if there was opacification of the left atrium (Figure 1).

Cardiac Catheterization (Intervention)
The right femoral vein was accessed with a standard 7F introducer, and the echo contrast agent was administered through this port. A Radiofocus guidewire (Terumo Corporation) was used to cross the PFO. Thereafter, the PFO was passed under TEE and fluoroscopic guidance with a 6F Lehman right heart catheter (Cook). Pressures were recorded in the right heart and the left atrium. An extra-stiff Amplatz exchange guidewire (Cook) was placed in the left upper pulmonary vein, and an occlusion balloon catheter (MEDI-TECH, Boston Scientific) was passed over the guidewire and inflated with dilute contrast material. The maximum volume that could be passed from right to left was calibrated with a sizing template. The observers who estimated PFO size by the invasive technique were blinded to PFO size measured by TEE.

Statistical Analysis
Correlations between PFO diameters determined invasively and by TEE were assessed with linear regression analysis; differences were compared with the paired Wilcoxon test. Semiquantitative contrast studies and PFO diameter measured by TEE or by balloon sizing were compared with nonparametric ANOVA (Kruskal-Wallis). Agreement of contrast TEE studies (femoral versus cubital contrast administration and interobserver variability) was analyzed by Cohen’s weighted \( k \). A value of \( P<0.05 \) was considered statistically significant. The relative influence of variables, including age, weight, size, sex, atrial septal aneurysm, cubital or femoral contrast TEE, and left or right atrial pressure, on PFO diameter measured by 2D TEE was analyzed with multiple linear regression.

Results
There was a strong correlation between 2D TEE measurements and balloon sizing (\( r^2=0.8; \ P<0.0001 \) by linear regression). The 2D TEE measurement of PFO size was related to semiquantitative contrast TEE via the femoral route (\( r^2=0.75; \ P<0.0001 \)) (Figure 2A) but not to semiquantitative contrast TEE via the cubital route (Figure 2B). The mean PFO diameter measured by 2D TEE (5.2±1.7 mm; range, 2 to 10 mm) was significantly smaller than that measured by balloon (8.3±2.6 mm; range, 4 to 14 mm; \( P<0.0001 \), Wilcoxon test). Multiple linear regression analysis showed a

Figure 1. Semiquantitative contrast echocardiography in the same patient. Minimal right-to-left contrast shunting during cubital contrast agent administration (top) and severe shunting during femoral contrast agent administration (bottom) are shown. LA indicates left atrium; RA, right atrium.

Figure 2. The corresponding severity of right-to-left shunting (shunting was graded as minimal [1] if only a few bubbles passed through the PFO, moderate [2] if a cloud of contrast bubbles was documented in the left atrium, or severe [3] if there was opacification of the left atrium) in 100 patients with various PFO diameters determined by 2D TEE during cubital contrast agent administration (A) (\( P=0.15 \), ANOVA) and during femoral contrast agent administration (B) (\( P<0.0001 \), ANOVA).

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significant association between PFO diameter measured by 2D TEE, atrial septal aneurysm ($r^2=0.6; P<0.0001$), and femoral contrast TEE ($r^2=0.75; P<0.0001$). There was no significant association between PFO size as measured with 2D TEE or balloon sizing and cubital contrast TEE, left or right atrial pressure, age, weight, or body size. Mean right atrial pressure was significantly lower than mean left atrial pressure ($5.4\pm2.7$ mm Hg; range, 0 to 14 mm Hg versus $7.6\pm2.9$ mm Hg; range, 2 to 16 mm Hg).

Interobserver agreement for evaluation of PFO size was 0.9 for 2D TEE and 0.8 for semiquantitative contrast echocardiography (weighted $\kappa$ correlation coefficient).

**Discussion**

We found a significant correlation between PFO size measured by 2D TEE and measured by balloon sizing. There was no correlation between the results of these 2 modalities and the results obtained by the traditional semiquantitative contrast echo method. A significant correlation between the amount of right-to-left contrast shunting and PFO diameter was found only if the contrast agent was administered through a femoral vein.

Some investigators have stated that the opening diameter and the volume shunted through this valvelike structure are related mainly to an increase in right atrial pressure. This is consistent with the increased prevalence of PFO in patients with chronic obstructive lung disease and pulmonary hypertension. However, elevated right heart pressures were not present in our study population. Our observations confirm that the mode of administration is a major determinant of contrast agent shunting through a PFO. Because blood flow from the inferior vena cava is directed against the fossa ovalis and blood from the superior vena cava is directed primarily through the tricuspid valve, contrast agent entering the right atrium from the superior vena cava can bypass the interatrial septum or a PFO, thus causing a false-negative or weak contrast study.

However, the methods we used (2D TEE and balloon sizing) also have their limitations. The patent foramen is a flaplike valve that is formed by overlapping of the relatively thick septum secundum and the relatively thin, mobile, and compliant septum primum. These 2 septa form a tunnel-like ellipsoidal communication between the right and the left atrium. Measurement of this complex 3-dimensional oval channel by 2D TEE is usually performed in the shorter axis because it is difficult to obtain the long axis of this oval communication with this technique. Because of this limitation, the true orifice may be underestimated by 2D TEE. Invasive measurements of PFO and atrial septal defects with the use of relatively stiff guidewires and sizing balloons have demonstrated significant compliance of the septum primum and resolution of the overlap. This technique makes the oval defect more circular, causing an elongation of the shorter axis and a foreshortening of the longer axis. As a result of the softness and distensibility of the septum primum, there is a potential of overestimating the size of the PFO by the balloon sizing technique. Recently, 3-dimensional echocardiography has been shown to be superior to 2D echocardiography in measurement of atrial septal defects. It remains to be seen whether this technique can provide additional information on PFO quantification.

Most studies have used saline contrast with transthoracic echocardiography, transcranial Doppler, and transmural Doppler to detect or quantify right-to-left shunts. A limitation of saline contrast is that bubble size is not standardized. Backscattered signal power is dependent on bubble size, which for agitated saline contrast varies from 24 to 144 $\mu$m, and its value for shunt quantification is questionable. If bubble size is not standardized, there is no simple relationship between returned signal power and bubble number. Moreover, the large bubbles of the widely used air/saline mixture entail a risk of adverse effects in patients with a right-to-left shunt because bubbles as small as 10 $\mu$m can obstruct the microcirculation. We performed the contrast studies with a commercially available contrast agent with an exactly defined bubble size ($99% <12$ $\mu$m, $95% <8$ $\mu$m). Therefore, we do not know whether the results of the correlation between PFO size and the contrast agent we used are pertinent to saline.

Our study probably has a selection bias toward patients with large PFOs. The mean PFO diameter measured by 2D TEE in our series was 5.2 mm, which is more than twice the diameter found in control subjects without presumed paradoxical cerebrovascular events.

In conclusion, multiplane 2D TEE sizing of PFO is as reliable as femorally administrated semiquantitative contrast TEE or balloon sizing. Because balloon sizing or femoral contrast administration is invasive and not applicable in routine practice, 2D TEE should be used to quantify a PFO. A small contrast shunt does not rule out a large PFO if the contrast agent is administrated through a cubital vein. Further studies of the risk of PFO or of treatment strategies in patients after presumed paradoxical embolism should include PFO diameter determined by 2D TEE instead of the traditionally used contrast method.

**References**


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