

## PFO or UFO

### How Good Is Transesophageal Echocardiography in Identifying Patent Foramen Ovale as the Cause of a Cryptogenic Stroke?

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Patent foramen ovale (PFO), which has been reported to be present in about one quarter of the adult population, is generally a hemodynamically insignificant interatrial communication.<sup>1</sup> Since the advent of contrast echocardiography (echo), a strong association has been reported between cryptogenic stroke (CS) and PFO in patients <55 years of age.<sup>1,2</sup> Although several studies have reported the association of PFO with CS in older patient populations, the association of atrial septal abnormalities and stroke in an older age group was not confirmed by a meta-analysis.<sup>1,3</sup> Among 1100 stroke-free subjects (mean age, 69 years) in the Northern Manhattan Study evaluated by contrast transthoracic echo, PFO was detected in 164 (15%). After adjustment for demographics and risk factors, PFO was not found to be significantly associated with stroke.<sup>4</sup>

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#### Article see p 125

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In an enlightening article titled “Is Patent Foramen Ovale a Modifiable Risk Factor for Stroke Recurrence?” Kent and Thaler<sup>5</sup> note that, “The evidence suggests that many patients with CS and PFO...have strokes that are unrelated to their PFO.” They introduced the concept of PFO propensity, defined as “the patient-specific probability of finding a PFO in a patient with CS on the basis of age and other risk factors”—including the absence of diabetes mellitus, hypertension, smoking history, coronary artery disease, and previous history of stroke or transient ischemic attack (TIA). The probability that a stroke is attributable to the PFO in a patient with a CS and a PFO is related nonlinearly to PFO propensity. The authors note that, “There is substantial heterogeneity in both PFO propensity and recurrence risk among patients with PFO and CS...”<sup>5</sup>

Transesophageal echocardiographic contrast study is probably the most sensitive diagnostic test for detecting a PFO, followed by transcranial Doppler and contrast transthoracic echo.<sup>1</sup> Of note, the detection of microbubbles in the cerebral circulation by transcranial Doppler does not necessarily confirm the presence of a PFO. Furthermore, transcranial Doppler

cannot identify the intracardiac site of a right-to-left shunt. Factors reportedly associated with paradoxical embolus across a PFO, potentially causing a CS, include the size of a PFO and of its right-to-left shunt<sup>1</sup>; anomalies such as atrial septal aneurysm, Eustachian valve, and Chiari network<sup>2</sup>; elevated right atrial pressure (relative to left-sided pressure)<sup>3</sup>; and a potential source of embolization—for example, a venous thrombus or a hypercoagulable state.<sup>4</sup>

#### Current Study

In this issue of *Circulation: Cardiovascular Imaging*, Wessler et al<sup>6</sup> report on an analysis from the Risk of Paradoxical Embolism (RoPE) study database, a large multicenter observational database formed by combining, and attempting to align as much as practical, data elements in 12 component databases of patients with CS and known PFO status. An important overall goal of the RoPE study was to determine what features associated with a PFO, as diagnosed by transesophageal echocardiography (TEE), can predict that a PFO is likely causally related to a CS. In another recent article, the authors report on a score derived from clinical and neuroimaging features, which stratifies patients with PFO and CS by the probability that their CS is attributable to a PFO.<sup>7</sup> In particular, the authors report that the absence of a history of hypertension, diabetes mellitus, smoking, stroke, or TIA; the presence of a cortical infarct on brain imaging; and younger age are associated with a high RoPE score, specifically >6 on a 10-point scale, making it more likely that a CS is causally related to a PFO. In the current report, the authors examine whether 3 TEE features reportedly associated with a PFO, that is, large physiological shunt size, associated hypermobile septum, and presence of a right-to-left shunt at rest, are predictive of a high RoPE score, suggesting that a CS is likely caused by an accompanying PFO. In comparing 637 patients with presumed PFO-attributable stroke (based on a RoPE score >6) to 657 most likely not to have had a PFO-attributable stroke, the authors found that neither the presence of a large shunt size (ie, >10 microbubbles detected in the left atrium ≤3 cardiac cycles after right atrial opacification), a hypermobile septum (ie, ≥10 mm excursion from the midline), or a right-to-left shunt at rest were more often detected in either group.<sup>6</sup>

#### Importance of Findings

This is a large multicenter study from a group of experienced investigators who have devoted significant time and thought to the association of PFO and CS. Their observation that TEE features such as PFO shunt size, associated hypermobile septum, and presence of a right-to-left shunt at rest are not predictive

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circ Cardiovasc Imaging*. 2014;7:5-7.)

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*Circ Cardiovasc Imaging* is available at  
<http://circimaging.ahajournals.org>

DOI: 10.1161/CIRCIMAGING.113.001361

of a clinical/neuroimaging risk index, which has been shown to predict the association of PFO with CS, is important. These negative findings involving TEE-detected parameters suggest that one should apply caution in using these as predictors of probable PFO-attributable CS—or, perhaps, that if one wants to use  $\geq 1$  of these 3 parameters, one needs to be better able to standardize them. One must also consider other possible mechanisms by which a PFO may cause a CS, for example, in situ thrombus formation in a tunnel-like PFO or, possibly, atrial arrhythmias associated with intra-atrial thrombus formation.<sup>1</sup>

### Limitations

It is somewhat difficult to judge the quality of the data included in these analyses because TEE variables were collected at multiple sites under independent research protocols. The authors had to do their best post hoc in standardizing definitions for their 3 key TEE variables among component databases that did not use the same definitions. In this regard, the authors did a good job in citing the nonstandardized definitions, for example, of atrial septal aneurysm or shunt size—not only in the 12 component databases they have amalgamated as part of the RoPE study database but also in the published literature. Furthermore, exploratory analyses (shown in the Data Supplement I in their article) failed to identify trends relating the 3 TEE measures of interest to PFO-attributable CS when data were evaluated from sites with uniform measurement protocols. In addition, the authors had to exclude >600 of 1925 cases with a PFO from the RoPE database for a variety of reasons. The authors defend these limitations by stating in their conclusion that, “[O]ur results can also be seen as reflecting the limitations of TEE measurements as they are usually performed in routine clinical practice.” However, this approach may not have helped answer the questions their study has sought to answer. Other limitations of the study include lack of an absolute gold standard for the diagnosis of a CS attributable to a PFO; poor kappa statistics for inter-reader reliability, especially in the PFO in Cryptogenic Stroke Study (PICCS; hypermobile septum,  $\kappa=0.33$ ; large PFO shunt size,  $\kappa=0.14$ ; shunt at rest,  $\kappa=0.33$ ); and absence of TEE data on the presence of Eustachian valves/Chiari network and for contrast injections performed via the femoral vein.

### Effective Therapy

Assuming that we were able, with reasonable reliability, to detect a PFO that was likely the cause of a CS, how effective are the current therapies in preventing a recurrent stroke or TIA? In patients on medical therapy, either warfarin or aspirin, the presence of a PFO in a CS does not seem to increase the chance of recurrent ischemic stroke or death regardless of PFO size or the presence of an atrial septal aneurysm.<sup>8</sup> In the PICCS cohort, there was no significant difference in time to this primary end point between those with and without a PFO in the overall population. In patients with a PFO, there was no significant difference in time to these end points between those treated with warfarin and those treated with aspirin.<sup>8</sup>

The first prospective, randomized, independently adjudicated PFO device closure trial, CLOSURE-1 (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke

and/or transient ischemic attack due to the Possible Passage of a Clot of Unknown Origin through a Patent Foramen Ovale), was designed to test whether PFO closure using the STARFlex device plus medical therapy of 6 months of aspirin and clopidogrel, followed by 18 months of aspirin was superior to medical therapy alone (24 months of warfarin or aspirin, or the combination) in preventing a recurrent stroke or TIA in patients with a CS or a TIA and a PFO. Results showed the 2-year stroke rate to be essentially identical in both treatment arms (3%), with no significant benefit in the STARFlex arm associated with the presence of an atrial septal aneurysm or the degree of initial shunting.<sup>9</sup> Three recent meta-analyses of randomized controlled trials comparing PFO device closure with medical therapy have reported differing results. These meta-analyses have included trials with both STARFlex (CLOSURE-1) and AMPLATZER (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment [RESPECT] and Percutaneous Closure of PFO Versus Medical Management in Patients with Cryptogenic Stroke [PC-Trial]) PFO closure systems. One of the meta-analyses concluded that, “Currently-available randomized data do not support the use of PFO closure for secondary stroke prevention in patients with cryptogenic stroke and PFO.”<sup>10</sup> A second meta-analysis concluded that although there was no statistically significant difference between device closure and medical therapy, there was a trend toward overall improvement in outcomes in the device closure group.<sup>11</sup> Yet a third meta-analysis suggested that there was a marginally beneficial effect in the device closure group.<sup>12</sup> Currently ongoing randomized trials should add more clarification of this treatment issue. However, it seems at this time that current PFO closure devices are not a panacea for preventing recurrent stroke or TIA in patients with a CS and PFO.

In conclusion, this interesting article adds to the evidence that TEE has significant limitations in identifying in a patient with a CS that the cause of the stroke was likely to be a PFO, as opposed to a UFO (unidentified flying object).

### Disclosures

None.

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KEY WORDS: Editorials ■ cryptogenic stroke ■ patent foramen ovale ■ transesophageal echocardiography

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*Circ Cardiovasc Imaging.* 2014;7:5-7

doi: 10.1161/CIRCIMAGING.113.001361

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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