Cryptogenic stroke (CS) represents up to 40% of all ischemic strokes. It is a diagnosis by exclusion, based on thorough investigation of other established causes of stroke. Patent foramen ovale (PFO) is a remnant of the fetal circulatory system that provides a passage between the two atria in adult life, resulting in transient right-to-left shunting of blood when the right atrial pressure exceeds that of the left atrium. PFO has been implicated in the pathogenesis of CS, the most likely mechanism being paradoxical embolization through the PFO. Other possible hypotheses, such as the formation and release of thrombus from within the PFO tunnel and the passage of vasoactive humoral substances that are normally degraded in the pulmonary circulation, have also been suggested. However, the common culprit remains the presence of abnormal interatrial communication, and this represents an obvious target for therapy.

PFO AND CS

The passage of embolus through a PFO has been well documented in a number of case reports. More recently, a study with diffusion-weighted magnetic resonance imaging brain scanning in patients (n = 60) with nonmajor acute pulmonary embolism showed that up to 33% (n = 5/15) of the patients with a PFO had silent brain infarcts at admission. This is significantly more common than in patients without a PFO, which was reported at 2% (n = 1/45; P = .003). Although the sample size is small and focused on a high-risk group of patients, the findings are intriguing and further confirm the pathological relationship of PFO, paradoxical embolization, and cerebral infarcts.

Numerous retrospective case-control studies have also shown a higher prevalence of PFO in patients with CS. A meta-analysis of these studies showed that CS patients younger than 55 years are six times more likely to have a PFO compared to patients with a known cause of stroke. A recent study also reported that, in patients older than 55 years (n = 372), PFO was significantly more common in CS patients (28.3%) than in patients with a known cause of stroke (11.9%; P < .001). In the Patent Foramen Ovale In Cryptogenic Stroke Study (PICSS) involving 601 stroke patients, PFOs were present in 39.2% of CS patients as opposed to 29.9% of patients with a known cause of stroke (P < .02).

Despite the higher prevalence of PFO in CS patients seen in observational studies, prospective epidemiological studies have reported conflicting results. The Northern Manhattan Study (NOMAS) involving 1,100 stroke-free patients (mean age, 68.7 ± 10) failed to show a significant difference between the presence of PFO and the risk of first stroke. Similarly, the Stroke Prevention: Assessment of Risk in a Community (SPARC) study, which involved 585 patients (average age, 66.9 ± 13.3), showed that PFO is not an independent predictor of stroke over a mean follow-up of 5.1 years. In patients with previous CS, a recent meta-analysis also showed that the presence of a PFO did not increase the relative risk of recurrent ischemic events.

SEGREGATING THE “BYSTANDER” PFO

Given that PFO can be found in up to one-quarter of the general population, it is likely that some of the PFOs detected are unrelated to the index cerebral event. However, it is difficult to differentiate a “bystander” PFO from a “pathological” PFO. Some studies have attempted to address this issue and have suggested that PFOs that are larger in size, those with longer tunnels, those that produce a greater right-to-left shunt, and those that coexist with atrial septal aneurysm are more associated with CS. However, these findings are not consistently found across different studies.

Limitation in the lack of standardization of PFO detection and determination of their pathological significance is a common problem with these epidemiological studies. To date, most studies have used a transesophageal echocardiogram (TEE) and have considered...
the presence of any bubbles in the left atrium as a positive contrast study. However, there are two potential problems with this definition. First, it can be difficult to elicit a sufficient Valsalva maneuver under conditions of the TEE, which can lead to false-negative results. Second, the improved echocardiographic image quality and technique has allowed a much higher rate of shunt detection compared to previous contrast echo studies.

Although the presence of a PFO is uncontested, even if a few bubbles are seen shunting across, one must question the significance of such a small shunt in the context of CS.

The concept of a bystander PFO has also been illustrated by a recent study involving surgical closure of incidental PFO. A systematic review of 22 clinical trials on the role of PFO closure in patients with CS showed no survival benefit.

### TABLE 1. CLINICAL TRIALS ON THE ROLE OF PFO CLOSURE IN PATIENTS WITH CS

<table>
<thead>
<tr>
<th>Trial</th>
<th>PFO Closure Device Used</th>
<th>Comparison Groups</th>
<th>Primary Endpoints</th>
<th>Start Date</th>
<th>Sites</th>
<th>Estimated Enrollment</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOSURE Ia</td>
<td>StarFlex septal closure system (NMT Medical Inc., Boston, MA)</td>
<td>PFO closure + aspirin against best medical treatment</td>
<td>Incidence of stroke and hard TIA, all-cause mortality at 30 days/discharge, neurological mortality on follow-up</td>
<td>2003</td>
<td>United States</td>
<td>900</td>
<td>Enrollment completed in 2008, pending results</td>
</tr>
<tr>
<td>RESPECTb</td>
<td>Amplatzer PFO occluder (AGA Medical, Plymouth, MN)</td>
<td>PFO closure against best medical treatment</td>
<td>Recurrence of nonfatal stroke, postrandomization mortality, or fatal ischemic stroke</td>
<td>2003</td>
<td>United States</td>
<td>500</td>
<td>Ongoing, estimated completion date not available</td>
</tr>
<tr>
<td>CLOSEc</td>
<td>Any device</td>
<td>Aspirin, anticoagulation, and PFO closure</td>
<td>Fatal and nonfatal stroke</td>
<td>2007</td>
<td>France</td>
<td>900</td>
<td>Ongoing, estimated completion by 2012</td>
</tr>
<tr>
<td>Gore REDUCEd</td>
<td>Helex septal occluder (W. L. Gore &amp; Associates, Flagstaff, AZ)</td>
<td>PFO closure + antiplatelet therapy against antiplatelet therapy alone</td>
<td>Recurrent ischemic stroke, image-confirmed TIA, or death due to stroke</td>
<td>2008</td>
<td>United States</td>
<td>664</td>
<td>Ongoing, estimated completion by 2014</td>
</tr>
<tr>
<td>PC-Triale</td>
<td>Amplatzer PFO occluder</td>
<td>Antithrombotic therapy against PFO closure</td>
<td>Death, nonfatal cerebrovascular event, peripheral embolism</td>
<td>2000</td>
<td>Europe and Australia</td>
<td>500</td>
<td>Ongoing, estimated completion by 2011</td>
</tr>
</tbody>
</table>

Abbreviations: TIA, transient ischemic attack.

*a* Evaluation of the StarFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a PFO.

*b* Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

*c* Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence.

*d* Gore Helex Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients.

*e* Patent Foramen Ovale and Cryptogenic Embolism.

Currently, there are no published randomized data with regard to PFO closure and the recurrence of stroke. Available nonrandomized data seem to favor PFO closure over best medical therapy. A systematic review of
transcatheter PFO device closure and medical therapy showed the 1-year recurrent neurological thromboembolism rate was 0% to 4.9% for PFO closure and 3.8% to 12% for medical therapy.\textsuperscript{19} The major and minor complications associated with PFO closure occurred in 1.5% and 7.9% of patients, respectively. A recent nonrandomized study involving 103 patients with more than one cerebrovascular event at baseline reported that percutaneous PFO closure had a lower risk of recurrent stroke or transient ischemic attack compared to medical treatment alone (7.3% vs 33.2%; hazard ratio = 0.26; \(P = 0.01\)).\textsuperscript{20}

Several randomized trials comparing PFO closures and medical treatment are ongoing (Table 1). The CLOSURE I trial with the StarFlex septal closure system completed enrollment in 2008. The results will likely be available by the third quarter of 2010 and should provide some of the first randomized data on the role of PFO closure in CS patients. Four other trials, including CLOSE, Gore REDUCE, RESPECT, and PC-Trial, are ongoing, albeit with a slow rate of patient recruitment. However, debates over issues such as the significance of trivial residual shunts after closure and the imaging requirements for neurological endpoints will continue.

Given the lack of randomized trial data, the American Heart Association and American Stroke Association current guidelines on the prevention of stroke have no recommendations on the role of PFO closure in patients with first stroke. In patients with recurrent CS despite optimal medical therapy, the guidelines consider PFO closure as a possible option (class IIb, level of evidence C).\textsuperscript{21} Although the current guidelines may allow physicians to select the most appropriate therapy on an individual basis, they also serve to remind us of the importance of completing ongoing randomized controlled trials to facilitate better decision making.

**CONCLUSION**

Similar to many other areas of interventional cardiology, enthusiasm in PFO closure, together with improvements in percutaneous technologies, have altered referral patterns and, to some extent, driven utilization worldwide.\textsuperscript{22,23} Current developments in minimalistic PFO closure technologies with bioabsorbable materials and deviceless techniques have made this an even more attractive treatment option. Although many observational studies and nonrandomized treatment trials support the role of PFO closure in stroke prevention for patients with CS, it is crucial that more robust data be made available for a wider acceptance.

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