PFO Closure for Prevention of Recurrent Cryptogenic Stroke

The evidence base is here.

BY JOHN F. RHODES, JR, MD

Patent foramen ovale (PFO) is composed of overlapping portions of septum primum and septum secundum, acting as a trap door that can flap open throughout the cardiac cycle. After birth, although the septum primum should fuse to the septum secundum, 25% of adults may have incomplete fusion leading to a PFO.[1] This trap door physiology in the atrial septum cannot be detected by a routine physical examination, and most often, because it is not standard to perform agitated saline injection with Valsalva maneuver, it is not appreciated by chest-wall echocardiography. Consequently, the PFO (be it large or small, long- or short-tunnel, aneurysmal or not) will often go undiagnosed until the patient has an event, such as a stroke. This carries a potential implication that the right-to-left shunt of the PFO is a risk factor for future similar events.

BACKGROUND

Stroke is the third leading cause of death and the leading cause of disability in young patients.[2] Cryptogenic stroke, defined as stroke without an identifiable source despite a systematic investigation, occurs in 40% of all ischemic stroke cases.[3] When this cryptogenic stroke patient population is assessed for the presence of a PFO, there is a higher prevalence (40%–75%) compared to the noncryptogenic stroke population (5%–30%).[4,5] Because the incidence of new or recurrent stroke in the US is approximately 700,000 annually,[4] this would result in approximately 280,000 cryptogenic strokes per year and 140,000 that could be attributed to the PFO. If the treatment cost for transcatheter closure of a PFO is approximately $15,000 per case, the annual cost for PFO device closure would be approximately $2.1 billion for patients with PFO-related strokes. Although this number is tremendous, the current national cost of >$67 billion resulting from recurrent stroke patients requiring hospitalization, chronic medications, and the loss of work days, is without any reasonable doubt also enormous.[4]

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THE DEBATE

The debate of whether we should close a PFO for recurrent stroke prevention is nearly 20 years old and going strong. During this time, many physicians have been closing PFOs through humanitarian device exemption pathways or "off-label" use in patients to prevent recurrent stroke, as well as to avoid the need for long-term anticoagulation therapy. Although we have been considering PFO device closure as an option for preventing recurrent stroke since the late 1980s,[6] we also have been treating young cryptogenic stroke patients with medications that prevent thrombus and platelet aggregation for even longer. Despite this, we still do not have convincing evidenced-based data to support this practice. That being said, it appears that evidence is beginning to shift toward the PFO finally being implicated for its involvement in the cryptogenic stroke patient.

The current prospective randomized trials in the US are still awaiting follow-up, but enrollment is finishing. Thus, evidence-based data are finally close to being presented. Meanwhile, there is still a considerable amount of data available to implicate PFO in a relationship to the young cryptogenic stroke patient population. For us to assume that thrombus or platelet abnormalities in the venous system are involved in recurrent cryptogenic stroke, we must also assume the involvement of a "door" for them to cross to the arterial side. This is a critical distinction because there is clearly no consensus within the physician community regarding whether PFO should be implicated, and there is also no consensus about the type of treatment (oral anticoagulation or antiplatelet therapy) or duration of medical therapy after a cryptogenic stroke.

EVIDENCE TO IMPLICATE PFO

Prevalence

In general, many data are available to confirm a strong association between the presence of a PFO and the cryptogenic stroke patient population. Many publications since 1897 have confirmed the prevalence of PFO in the general population to be approximately 25%.[1] On the other hand, more recent publications have shown a significantly higher prevalence of PFO in young cryptogenic stroke patients (between 40% and 75%).[4,7] For example, Lamy and colleagues[8] investigated the prevalence of PFO in 581 cryptogenic stroke patients aged 18 to 55 years. All patients underwent transesophageal echocardiography (TEE) with agitated saline evaluation during rest and Valsalva maneuver. The overall prevalence of PFO was 46%, with these patients being younger, less likely to have traditional risk factors for stroke, and on average having a less severe stroke event. In this study, features consistent with paradoxical embolism were generally not found more frequently in patients with PFO and cryptogenic stroke, such as Valsalva maneuver-provoking activity within 30 minutes of stroke, history of deep venous thrombus, or pulmonary embolic events. Although circumstances predisposing to deep venous thrombus were also found not to be associated, they suggest a possible trend because the *P* value was .05.

In 2000, Overell and colleagues[9] showed that patients with a cryptogenic stroke younger than 55 years of age have a consistently higher likelihood of PFO. When comparing patients with cryptogenic stroke to control patients, the odds ratio was 3.1 for PFO, 6.1 for atrial septal aneurysm, and 15.6 for PFO and atrial septal aneurysm, implying PFO should be sought in these patients (younger than 55 years) and, if found, should not be regarded as incidental.

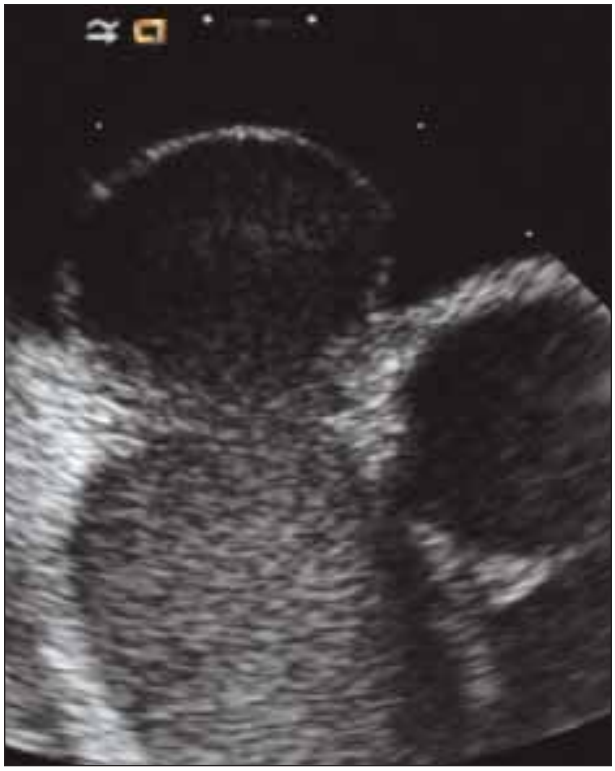

Figure 1. Intracardiac echocardiography shows the right atrium at the top, aorta to the right, and left atrium at the bottom with a large atrial septal aneurysm.

In November 2007, Handke and colleagues[10] reported on 503 patients (227 having cryptogenic stroke, 276 with a known cause for stroke) and found that 131 patients were younger than 55 years and 372 patients were 55 years of age or older. They reported that the prevalence of PFO and PFO with concomitant atrial septal aneurysm among patients with cryptogenic stroke and those of stroke with a known cause were significantly different for both age populations. In addition, the odds ratio for the presence of PFO among patients with cryptogenic stroke as compared to those with stroke of known cause also revealed a positive association for both age groups.

Anatomy and Shunt Size

The anatomy of PFO has been studied and discussed extensively in the recent literature. De Castro and colleagues[11] studied 350 patients with acute stroke and described a "high-risk" PFO group for recurrent stroke as patients presenting with right-to-left shunt at rest, as well as higher septal membrane mobility. This high-risk PFO group had a significantly higher recurrent stroke risk compared to the low-risk group, as determined at 3-year follow-up (range, 4–58 months). The recurrent

TABLE 1. CURRENT US RANDOMIZED CLINICAL TRIALS FOR PFO CLOSURE VERSUS MEDICAL THERAPY FOR RECURRENT STROKE MANAGEMENT

	CLOSURE I	RESPECT	REDUCE
Subjects	900	710	664
Randomization	1:1	1:1	2:1
Entry criteria	Stroke or TIA	Abnormal MRI	Abnormal MRI
Screening window	6 months	9 months	6 months
Medical therapy	Clopidogrel, aspirin, or warfarin	Best medical therapy	Antiplatelet only
Endpoint	Stroke, TIA, or death	Stroke or death	Stroke or death

stroke risk in the low-risk PFO group was 4.3% and was 12.5% in the high-risk PFO group (*P*=.05). When looking specifically at cryptogenic stroke patients, the recurrent risk at 3-year follow-up was as high as 16.3%.

Another interesting evaluation was published by Schuchlenz and colleagues[12] who studied 121 stroke patients and 123 control patients (60 years of age or older). Stroke patients were found to be more likely to have a large PFO compared to the controls (*P*<.001). More specifically, the stroke group was found to have an average PFO diameter of 4±2 mm compared to the control group at 2±1 mm. Consequently, the conclusion was that the diameter of the PFO was specifically associated with the severity of injury; thus, concluding that the diameter of the PFO was an independent risk factor for recurrent strokes (*P*<.001). More specifically, they found that a PFO diameter >4 mm was associated with an odds ratio of 3.4 for transient ischemic attacks (TIAs), 12 for stroke, and 27 for two or more strokes. In contrast, a PFO of <4 mm was specifically associated only with TIA having an odds ratio of 1.5. PFO characteristics have also been examined in regard to the degree of shunting. Stone and colleagues[13] studied 34 patients with an average age of 56 years and followed them for 21 months. The patient populations were divided into large and small shunts based on the agitated saline injections into a peripheral IV. In the large shunt group, 31% of the patients had a recurrent adverse neurologic event compared to none in the small shunt group (*P*=.03).

The other association that has been extensively looked at with PFO is atrial septal aneurysm (Figure 1). Atrial septal aneurysm is a septal excursion of ≥10 mm into one or the other atrium, with a base diameter excursion of ≥15 mm. Although the incidence of atrial septal aneurysm in the general population is between 1% and 2%, there is a higher incidence reported in the stroke population (between 8%–48%),[14] which tends to be associated with the larger shunt as well as the larger-diameter PFO.[12] There is considerable evidence that the presence of PFO and atrial septal aneurysm is likely to increase the risk of recurrent cryptogenic stroke. Mass and colleagues[14] studied 581 patients aged 18 to 55 years who had experienced a cryptogenic stroke. All of these patients were treated with aspirin, and the average follow-up was 39 months. PFO with atrial septal aneurysm was found in 48% of the patients. Patients with septal abnormalities tended to be younger and less likely to have hypertension, hypercholesterolemia, or to be cigarette smokers. At 4 years of follow-up, the risk of recurrent stroke was 4.2% in the group with no PFO or atrial septal aneurysm, 2.3% in the PFO-only group, and 15.2% in the atrial septal aneurysm and PFO group. Therefore, the presence of atrial septal aneurysm in PFO was thought to be a significant predictor of an increased risk of recurrent stroke. Other anatomical structures of importance for these patients include the eustachian valve and Chiari's network. The prevalence of Chiari's network is approximately 1.3% to 4%; anatomically, it is a web-like network in the right atrium.[15] There may be connections with this to the eustachian valve as well as direct attachments to the interatrial septum or anterior wall of the right atrium. These networks may be associated with movement of

the lower extremity venous return across the PFO in a right to left direction and can be cumbersome during the transcatheter closure procedure.

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In 1995, Schneider and colleagues[16] retrospectively reviewed 1,437 TEE images and found Chiari's network in 2%. They reported that 83% of the patients with Chiari's network had a PFO compared to 24% in the control group. Also, for the patients with Chiari's network, the indication for the TEE was a suspected cardiac source of arterial embolism in 83% of patients, and 54% of these patients had already had recurrent embolic events. In addition, if a patient had a history of stroke and the TEE revealed a Chiari's network, the prevalence of PFO was 96%, with a 55% chance of "intense" right-to-left shunt compared to a control group with 12% intense shunt. In summary, these data are evidence that PFO is likely a significant cause of stroke, and PFO size, anatomy, and degree of shunting are important. Atrial septal aneurysm does increase the risk of stroke and the recurrent stroke risk. In addition, there is a significant role in the original stroke, as well as the recurrent stroke, with regard to Chiari's network when found in the right atrium.

Management Options

Currently, management options for patients with recurrent PFO include medical or transcatheter device closure. Traditional medical therapy has been either antithrombotic with warfarin (which requires monitoring the international normalized ratio) or antiplatelet, including aspirin, dipyridamole, or clopidogrel. These are often life-long therapies and are associated with bleeding side effects that can be catastrophic, as well as lifestyle restrictions. The published major bleeding risk for warfarin is approximately 2% to 13% per year,[17] which is higher than the <1% procedural risk for device closure of a PFO.[18] Also, many studies have shown a higher recurrence risk for patients treated medically. Schuchlenz[19] studied 280 cryptogenic stroke patients and demonstrated an annual recurrent neurologic event rate of 13% for antiplatelet therapy, 5.6% for anticoagulation therapy, and 0.6% for PFO device closure (P<.001). In general, studies do not favor one medical treatment regimen over another in the cryptogenic stroke patient population. PICSS (PFO Cryptogenic Stroke Study) was a prospective multicenter study involving 630 patients (265 with PFO and 365 without PFO).[5] Patients were subdivided by age, and aspirin versus warfarin treatments were utilized in patient populations both with and without PFO. With multivariate analysis, PFO associated with interatrial atrial septal aneurysm and patient age 65 years or older was more likely to result in a recurrent stroke compared to patients without PFO.

Current Clinical Trials

In general, PFO closure for strokes is a topic in the literature with no consensus. There are currently no occluder devices approved in the US for PFO, and there are currently three clinical trials underway assessing patients for closure with catheter-placed devices versus medical management to prevent recurrent stroke (Table 1). The first clinical trial is CLOSURE 1 by NMT (Boston, MA). CLOSURE 1 includes 900 subjects with 1:1 randomization in an entry criterion of stroke or TIA. The medical therapy in the test arm is 6 months of clopidogrel and 24 months of aspirin. Medical therapy in the control arm is 24 months of aspirin or warfarin, or both. The primary endpoint for CLOSURE 1 is stroke or a TIA. CLOSURE 1 has currently completed enrollment, and we are awaiting follow-up data prior to the reported results. The second clinical trial is RESPECT and is currently underway by AGA Medical (Minneapolis, MN). RESPECT initially included 500 subjects, although enrollment has been extended to more than 700 subjects. The randomization is 1:1, with entry criteria of stroke or TIA if the MRI is abnormal. The screening window was extended to 9 months to help with enrollment, and the medical therapy is "current standard of care." The primary endpoint for RESPECT is stroke or death. Problems with both of these trials are that they are randomized to medical versus PFO closure and many subjects are having difficulty with the treatment preference. Some patients prefer to have the PFO closed, and some prefer life-long medical therapy. These issues have resulted in slow enrollment, although both trials are finally reaching completion. A third clinical trial that is starting enrollment is the Gore REDUCE Study (Gore & Associates, Flagstaff, AZ). Gore REDUCE is a prospective, randomized, multicenter, and multinational study comparing antiplatelet medical therapy versus device closure using the Gore Helex Septal occluder device (Figure 2). What makes the Gore REDUCE study unique are the 2:1 randomization scheme, standardized antiplatelet medical therapy

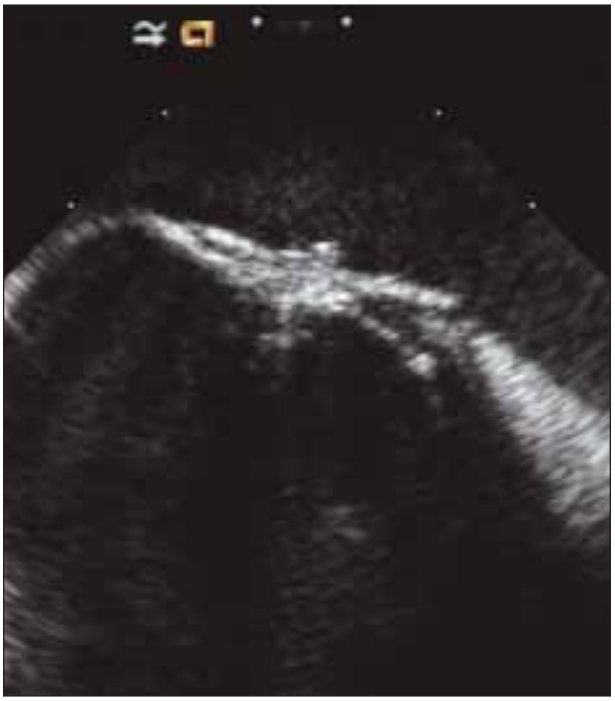

Figure 2. The Gore Helex Septal occluder device by intracardiac echocardiography 6 months after implantation.

across both treatment arms, MRI evaluation of all subjects at recurrent event as well as at 24 months, and the use of US and Nordic sites for participation in the trial. The primary endpoint is freedom from recurrent ischemic stroke, image-confirmed TIA, or death due to stroke through 24 months after randomization. Secondary endpoints include safety and efficacy. All available subjects will have an MRI at 24 months after randomization, as well as a TEE to assess the results in the device arm group.

SUMMARY

Is there an evidence base for a "relationship" between PFO and recurrent stroke? Without argument, 25% of people have a PFO. Without argument, paradoxical embolism, defined as an arterial embolic event without evidence of a left-sided source, is one possible etiology for cryptogenic stroke. Without argument, PFO is a potential source for transient right-to-left intracardiac shunting and subsequent embolization to the brain. Without argument, the clinical syndrome of PFO and recurrent cerebrovascular events has been extensively studied in patients younger than 60 years. If a patient has an initial cerebrovascular event at this age, the likelihood of no etiology for this event is high, and therefore, the diagnosis of cryptogenic stroke is often implicated. Finally, without argument, the association between PFO as the etiology of paradoxical embolism will always be presumptive, and if we do not produce evidenced-based data through randomized clinical trials for this patient population, the debate on this topic may persist for years to come. ■

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