Title

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Developing a treatment strategy guided by clinical data.

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It is estimated that the prevalence of stroke in the US is 5.8 million. In 2008 alone, the total healthcare cost is projected to be $68 billion.[1] A significant proportion of these strokes are cryptogenic (ie, without an identifiable source), which is estimated to be from 8% to 44%.[2,3] Patent foramen ovale (PFO) has been documented to occur in up to one fourth of the general population.[4] Several studies have identified PFO as a potential pathway for thrombus to cross from the venous to the arterial circulation and then embolize to the brain or peripheral circulation. This hypothesis has prompted cardiologists and neurologists to suggest closing the PFO as primary therapy to prevent recurrent strokes. This article summarizes the available clinical data and outlines an approach to patients presenting with cryptogenic stroke.

THE ROLE OF PFO AND CRYPTOGENIC STROKE

The foramen ovale can be considered as an anatomical trapdoor and represents an evolutionary design to shunt blood from the right atrium to the left atrium to ensure that the neonatal brain will receive sufficient oxygenated blood from the mother's placenta during fetal development. During the first year of life, the septum primum and septum secundum fuse in the vast majority of people to produce the foramen ovale. Failure of the fusion of septal components results in the adult having a foramen ovale that remains patent. Only recently has the PFO been implicated in the pathogenesis of disease. Large thrombus trapped by the PFO straddling the interatrial septum has been described in autopsies, at surgery, or during echocardiographic examination.[5] Although the exact mechanism by which a PFO causes cryptogenic stroke is impossible to prove during the clinical event, the "paradoxical embolism" hypothesis postulates that small thrombi formed in the veins of the pelvis and lower extremities bypass the pulmonary circulation through the PFO under certain conditions. Valsalva release, straining, and coughing create a pressure gradient from the right-to-left atrium, producing blood flow that carries the microemboli across the PFO.

Mounting evidence implicating the role of PFO in cryptogenic stroke coincided with the widespread use of transesophageal echocardiography (TEE). An early case-control study showed that the prevalence of PFO was higher (40% vs 10%; $P<.001$) in 60 patients <55 years old with ischemic stroke compared to a control group of 100 patients.[6] A larger meta-analysis of multiple studies confirmed the increased prevalence of PFO in this age group (odds ratio [OR], 6; 95% confidence interval [CI], 3.72–9.68).[7] Recently, the role of PFO in cryptogenic stroke has been revisited in older patients. In a prospective study examining 503 consecutive patients with stroke, Handke et al concluded that the presence of PFO was independently associated with cryptogenic stroke in patients >55 years old (OR, 3; 95% CI, 1.73–5.23).[8] The authors suggested that this is due to the fact that the incidence of venous thromboembolism increases with age.[9]

TREATMENT OPTIONS: MEDICAL THERAPY AND PFO CLOSURE

Despite strong data linking cryptogenic stroke and PFO, there is a lack of consensus on which secondary prevention strategy—medical therapy or PFO closure—is superior to prevent recurrent stroke. A French study prospectively followed 581 cryptogenic stroke patients treated with aspirin for 4 years and reported a recurrence rate of 2.3%.[10] In patients with concomitant PFO and atrial septal

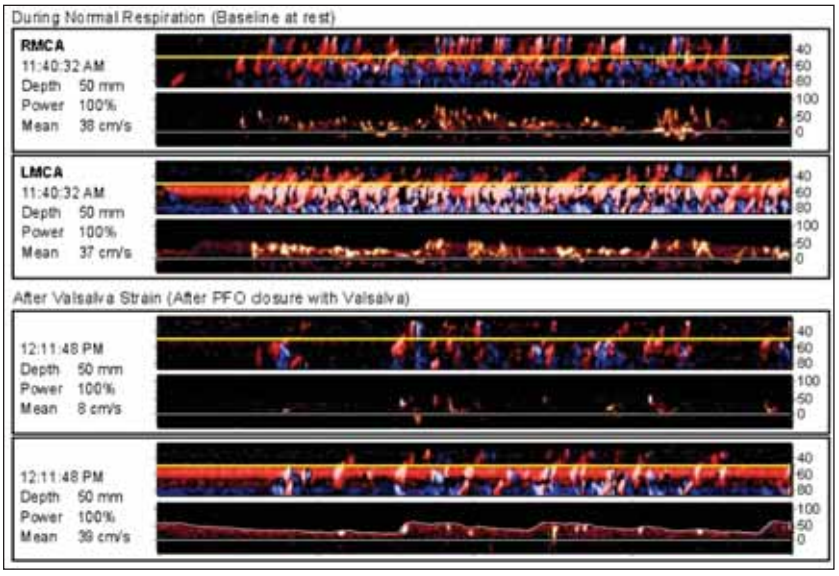

Figure 1. TCD of a patient undergoing percutaneous closure of PFO. Right-to-left shunting is graded according to the number of embolic tracks visualized on the color Doppler signal. Before implantation, there was a grade 4 right-to-left shunt at rest (top tracing). After PFO closure, there was no shunt at rest (not shown), and during Valsalva release, the right-to-left shunt is quantified as grade 2 (bottom tracing).

aneurysm, the recurrence rate was 15.1%. Data supporting full anticoagulation with warfarin are less clear. Meta-analysis of five retrospective cohort studies showed that warfarin was superior to antiplatelet therapy in preventing recurrent strokes (OR, 0.37; 95% CI, 0.23–0.6) and equivalent to surgical closure (OR, 1.19; 95% CI, 0.62–2.27).[11] However, there was no difference between treatment with warfarin and aspirin in both the Cryptogenic Stroke Study (CSS) and the Warfarin and Aspirin for Prevention of Recurrent Ischemic Stroke Study (WARSS).[12,13]

In the past, open heart surgical closure represented the only viable option for the closure of PFO. The Mayo Clinic series consisted of 91 patients who had cryptogenic stroke and underwent surgical closure of a PFO; 92.5±3.2% remained free from transient ischemic attack (TIA) at 1 year and 83.4±6% at 4 years.[14] Unfortunately, a significant proportion of patients experienced major postoperative complications including atrial fibrillation (n=11), pericardial drainage (n=4), exploration for bleeding (n=3), and wound infection (n=1). As catheter-based techniques became more refined, percutaneous closure of PFO for cryptogenic stroke was realized and advocated in 1992 by Bridges et al based on their experience using the Bard Clamshell Septal Occluder (C.R. Bard, Inc., Murray Hill, NJ) in 36 patients.[15] Windecker et al studied 80 patients with percutaneous PFO closure after cryptogenic stroke. The combined recurrent rate of thromboembolic events was 3.4% after a mean follow-up of 1.6±1.4 years, which was less than the recurrence rate of 4.9/100 patient-years in a meta-analysis of nine studies with medical therapy.[16] Residual shunt was a risk factor for recurrent paradoxical embolism (relative risk 4.2; 95% CI, 1.1–1.7, *P*=.03). There were a total of eight procedural complications, which were appropriately managed and resulted in two deployment failures. These pilot studies established percutaneous PFO closure as a relatively safe and effective alternative for surgery. Long-term data are slowly becoming available. Harms et al evaluated 237 patients in a single-center study. During a mean follow-up period of 568±364 days, the cumulative event rate for recurrent stroke was 3.4%.[17] In a large single-center cohort of 525 consecutive patients after percutaneous closure, Wahl et al reported freedom from clinical events of stroke, TIA, or peripheral emboli of 96% at 10 years.[18]

How Does Device Closure of PFO Compare to Anticoagulation or Antiplatelet Medical Therapy?

Currently, the only available published data are in the form of observational studies. In a single-center study comparing percutaneous PFO closure versus medical therapy at 4-year follow-up, Windecker et al reported a nonsignificant trend toward decreased combined risk of stroke, TIA, and death (8.5% vs 24.3%; *P*=.05).[19] A meta-analysis encompassing 10 transcatheter trials and six medical treatment trials showed that recurrent neurologic thromboembolism was 0% to 4.9% after 1 year in patients with device closure versus 3.8% to 12% in medically treated patients.[20] Because of the variability in the studies, no

TABLE 1. HYPERCOAGULABLE CONDITIONS THAT PROMOTE THE FORMATION OF VENOUS THROMBI

Genetic	Acquired
• Protein C deficiency	• Exogenous estrogen
• Protein S deficiency	• Pregnancy
• Factor V Leiden	• Prolonged travel
• Increased factor VIII activity	• Antiphospholipid antibodies
• Prothrombin 20210A mutation	• Anticardiolipin antibodies
• Antithrombin III deficiency	• β2-glycoprotein antibodies
	• Lupus anticoagulant

definite conclusion could be drawn that favored one treatment strategy over the other. Again, residual shunt after implantation was a risk factor for recurrent events (hazard ratio, 3.4; 95% CI, 1.3–9.2). In our experience of PFO closure in 150 patients, there has been no recurrent thromboembolic event in up to 6 years of follow-up.[21]

Randomized clinical trials remain the standard of evidence-based medicine. Success with these percutaneous closure devices has led to two randomized trials in the US. CLOSURE-1 (Evaluation of the StarFlex Septal Closure System in Patients with a Stroke or TIA due to the Possible Passage of Clot of Unknown Origin through a Patent Foramen Ovale) (StarFlex, NMT Medical, Inc., Boston, MA) plans to enroll a total of 900 patients to compare standard medical treatment versus device closure. The RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) uses the Amplatzer PFO Occluder (AGA Medical Corporation, Plymouth, MN) in the treatment arm compared to medical therapy.[22] It is estimated that the results of these randomized clinical trials will be completed by the end of 2009.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CRYPTOGENIC STROKE

A detailed history is necessary in the evaluation of patients with suspected cryptogenic stroke. Physicians should investigate potential hypercoagulable conditions, both genetic and acquired, that favor the formation of venous thrombi (Table 1). Questions should be asked regarding family history of PFO or atrial septal defects and coexisting illnesses, such as migraine headaches, scotomas, and decompression illness, which are often found in patients with PFOs.[23,24]

Imaging studies to investigate the presence of a PFO may include both transcranial Doppler (TCD) and TEE. TCD is an excellent initial screening test that uses small ultrasound probes mounted on a headset to visualize the middle cerebral artery by pulsed wave Doppler.[25] Agitated saline is given through an intravenous line, and the right-to-left shunting is graded by automated counting of the embolic tracks visualized in the arterial tracing (Figure 1). The advantages of TCD are the ease of use and interpretation, patient comfort, and high sensitivity in detecting right-to-left shunts.[26] However, TCD is not specific for a

Figure 2. A PFO visualized during right atrial angiography in the left anterior oblique projection (arrow), performed during normal respiration with contrast injection at the inferior vena cava right atrial border through a pigtail catheter at 15 mL/second for 3 seconds.

PFO. Pulmonary shunts through an arteriovenous malformation in the lung will also yield a positive TCD.

TEE has been described as the gold standard for detecting PFOs.[27] The advantages of TEE are the ability to visualize the anatomy of the PFO, evaluate the presence of atrial septal aneurysm, and rule out other potential sources of cardiac emboli, such as left atrial or ventricular apical thrombus and myxomas. If a patient has a positive TCD and negative TEE, two possibilities may occur: the patient may have a pulmonary shunt, or the TEE was inconclusive due to the patient's lack of cooperation with the Valsalva maneuver from oversedation or the inability to generate enough transthoracic pressure with the TEE probe inserted. In patients with inconclusive TEEs and a high clinical suspicion of PFO, we advocate cardiac catheterization with right atrial angiography combined with mechanical probing of the interatrial septum using a guidewire to provide definitive confirmation of whether a PFO exists (Figures 2 and 3).

Some physicians have advocated the percutaneous closure of all PFOs in patients who have symptoms; however, it is important to balance this enthusiasm with the recognition that complications during and after the procedure can occur. Major device-related complications are rare at experienced centers and range on the order of 0.3% to 1.3%.[17,18,21] The incidence and type of complication that may occur depends on the type of device that is used. Thrombus formation on the device is more frequently associated with the CardioSeal/StarFlex design (CardioSeal, NMT Medical, Inc.) and usually is treated with anticoagulation with warfarin. Potential device complications that may require surgical removal include device migration, erosion of the device through the wall of the atrium (reported in five out of 30,000 Amplatzer PFO implantations), thrombus refractory to anticoagulation, large residual shunt, and severe intractable chest pain. One recent study reported a 9% to 10% incidence of new mild-to-moderate aortic regurgitation after a mean follow-up of 27±15 months with the Amplatzer or Cardia, Inc. devices.[28] The investigators suggested that scarring and inflammation over the closure device may have resulted in retraction of the noncoronary cusp.

Although clinical trials are ongoing, specific recommendations regarding treatment of PFO in the setting of cryptogenic stroke remain controversial. Current guidelines recommend using aspirin in patients with PFO.[29] In 2006, the FDA withdrew the human device exemption for both the CardioSeal and Amplatzer PFO

Figure 3. Left anterior oblique cranial view of an Amplatzer PFO occluder device successfully deployed across the interatrial septum.

Occluder for cryptogenic stroke because the review panel determined that the potential population exceeded the 4,000-patients-per-year restriction.[30] Participation in clinical trials is the only modality to receive these devices; however, recruitment has been slow primarily due to fear of recurrent stroke resulting in unwillingness of patients to be randomized to the medical treatment arm. Off-label use of septal occluders approved for other indications, such as atrial septal defect closure, represents a significant proportion of devices implanted for cryptogenic stroke. Although it may be reasonable to offer PFO closure in patients who do not meet the inclusion criteria of the randomized clinical trials, physicians and patients need to understand that the results of these randomized trials are crucial to show if device closure is preferable to medical treatment. Emphasis on education is pivotal in assisting patients to weigh the short- and long-term risks of medical therapy versus percutaneous closure.

CONCLUSION

Strokes resulting from paradoxical emboli may encompass a much wider population than previously appreciated. The causal role of PFO in cryptogenic stroke is supported by several observational studies. Improvement in device design coupled with low complication rates presents percutaneous closure of PFOs as a promising solution. In the next few years, as data from randomized clinical trials are completed, we will discover if percutaneous closure of PFOs lives up to its potential. ■

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