

Device Closure for PFO

The data and devices associated with percutaneous PFO closure.

BY GERALD YONG, MBBS (HONS), FRACP; MICHAEL H. SALINGER, MD, FACC, FSCAI;
AND TED E. FELDMAN, MD, FACC, FSCAI

In 1877, Cohnheim, a German anatomist, performed an autopsy on a young woman with a patent foramen ovale (PFO) who had died from a nonhemorrhagic stroke. He hypothesized that a clot passing through the PFO must have caused the patient's demise and thus provided the first description in the medical literature of a paradoxical embolism.¹ In the 130 years since Cohnheim's original description of paradoxical embolism, there has been a great deal of study on the association between PFO and stroke. Clinical diagnostic techniques have been developed to permit the antemortum diagnosis of PFO. In addition to stroke resulting from presumed paradoxical embolism, other diseases that are associated with PFO currently include migraine, decompression illness in divers, and platypnea-orthodeoxia syndrome. Multiple therapeutic options have been developed and explored for closure of PFO to potentially reduce the risk of these diseases.

The foramen ovale represents a central location in the interatrial septum where the septum primum and the septum secundum overlap. *In utero*, these tissues grow to overlap but remain unfused, allowing ongoing communication between the right atrium and left atrium. This communication allows venous blood to return from the placenta to re-enter the systemic circulation without traversing the pulmonary circulation. Shortly after birth, the septum primum and septum secundum fuse, and the communication between the right and left atrium closes in the majority of cases.² Failure of the septum primum and the septum secundum to

fuse results in a PFO. In a large autopsy study performed at the Mayo Clinic involving 965 hearts, the incidence of PFO was found to be 27%.³ Pooled autopsy studies have demonstrated a similar 26% incidence of PFO, with a range of 17% to 35%.

DIAGNOSIS OF PFO

Clinically, the antemortum diagnosis of PFO is best made using bubble contrast echocardiography. Transthoracic echocardiography (TTE) has limited ability to detect PFO, and the incidence of PFO detected by TTE in large active laboratories has been 10% to 18%. Failure to demonstrate a PFO on TTE does not exclude the potential of a PFO. Properly performed, trans-

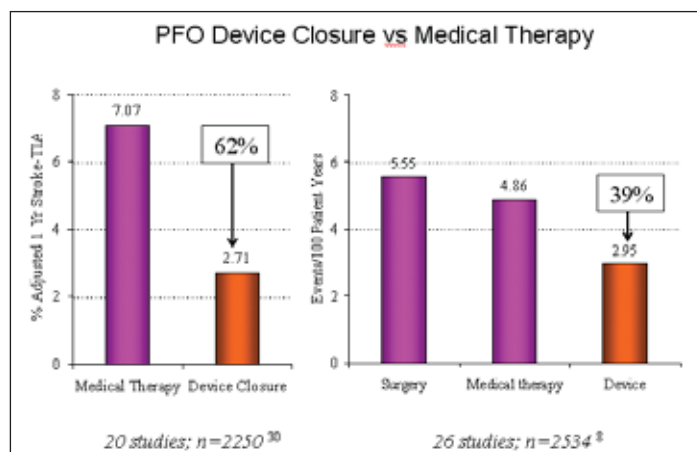


Figure 1. A pooled analysis of multiple trials shows a decrease in recurrent episodes of stroke and transient ischemic attack (TIA) after device closure for PFO. Adapted from *Circulation*. 2005;112:1063-1072 and *Ann Intern Med*. 2003;139:753-760.

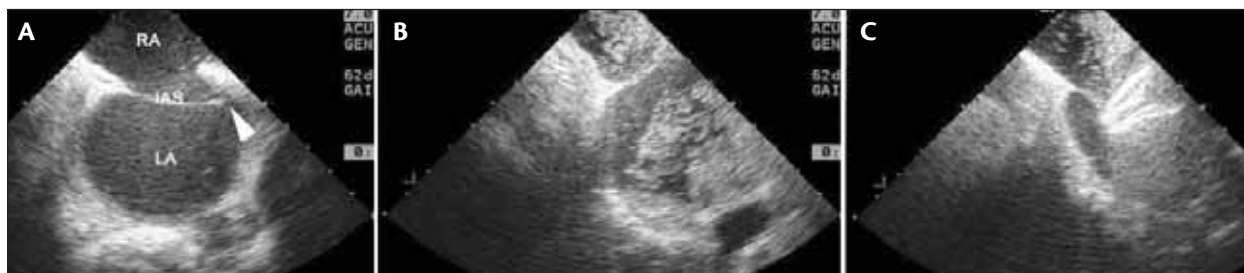


Figure 2. Intracardiac echo (ICE) images. The PFO tunnel is seen from the right atrium (RA). The left atrium (LA) is in the far field, and the arrowhead marks the PFO tunnel (IAS = interatrial septum) (A). Hand-agitated saline is used for bubble contrast. The RA is filled with contrast, and a large number of bubbles have immediately entered the LA, forming a dense cloud of contrast (B). After placement of an AGA Medical closure device (Plymouth, MN), there is complete closure of the shunt. The device creates shadowing in the LA, but no bright echoes from bubbles are seen in the LA (C).

esophageal echocardiography (TEE) in large active laboratories has detected PFO in 18% to 33% of patients studied.⁴ The incidence of PFO detected by TEE very closely approximates the incidence of PFO in pooled autopsy data and has led to the position that a properly performed TEE is the clinical gold standard for ante-mortum detection of PFO. To be properly performed, the TEE study should include Doppler flow interrogation and imaging with intravenous injection of agitated saline or echo imaging contrast agent during a Valsalva maneuver, or with external abdominal compression to demonstrate right-to-left flow across the interatrial septum.⁵ A PFO is judged to be present if any microbubble is seen in the left-sided cardiac chambers within three cardiac cycles from maximal right atrial opacification. TEE also provides potentially important information regarding atrial septal morphology, the presence of an atrial septal aneurysm, and the presence or absence of intra-atrial thrombus or masses. Later appearance of bubbles on the left side of the circulation may indicate an extracardiac shunt, such as a pulmonary arteriove-

nous malformation, which can be found in approximately 10% of the population.

More recently, intracardiac echo has been used as both a diagnostic imaging modality as well as to direct transcatheter therapeutic maneuvers. Less-invasive screening has also been recently advocated using intravenous contrast and transcranial Doppler imaging.⁶ Intravenous bubble contrast is administered, and early appearance of high-intensity transient Doppler signals in the cerebral circulation demonstrates the presence of a shunt. A positive screen would establish the presence of a right-to-left shunt, although it would be unable to specify the level of the shunt. The sensitivity (78%-93%) and specificity (92%-100%) of this noninvasive approach appears quite promising.^{4,7,8}

CLINICAL SYNDROMES ASSOCIATED WITH PFO

PFO and Cryptogenic Stroke

Incidence of PFO in cryptogenic stroke compared to stroke with known causes. Cryptogenic stroke is an ischemic

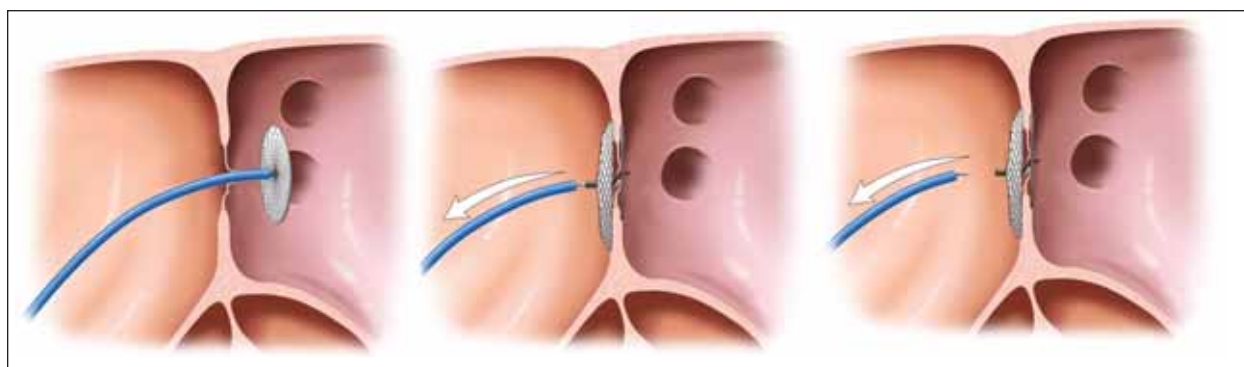


Figure 3. The AGA Medical PFO closure device. The left panel shows the guide catheter placed across the PFO. The LA disk has been opened. The system is pulled back until the LA disk engages the interatrial septum, and the RA disk is exposed as seen in the middle panel. Finally, the delivery cable is unscrewed, and the device is released, as shown in the right panel.

(Courtesy of AGA Medical)

(Courtesy of NMT Medical)

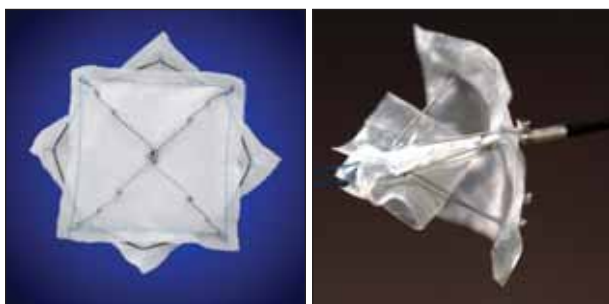


Figure 4. The NMT Medical double-disc closure device (Boston, MA). On the left is a front view of the two discs of the StarFlex device, made of polyester. On the right is the Bio-Star device, with discs made of bioabsorbable material. The RA disc has been pulled back in preparation for loading into a delivery catheter.

stroke with no clearly defined etiology. It is seen in up to 40% of acute ischemic stroke and is more common in younger patients.⁹ Over the years, multiple case-control studies have demonstrated a significantly higher prevalence of PFO in patients with cryptogenic stroke compared to nonstroke patients or patients who have stroke with known cause. This relationship is most apparent when evaluating patients younger than 55 years. In a meta-analysis of these case-control studies,¹⁰ the prevalence of PFO in patients younger than 55 years with cryptogenic stroke is 55%, which is significantly higher than a prevalence of 17% in either patients having stroke with known cause or nonstroke controls. One recent population study suggested no increased risk for stroke among patients with PFO, but surveyed only 1,072 patients, for an event with an incidence of <1/5,000, and was thus underpowered.¹¹

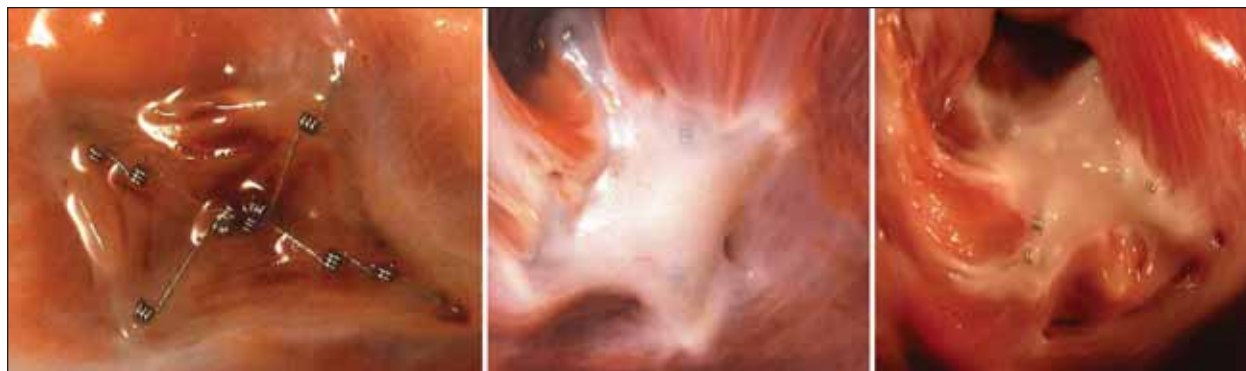
Potential mechanism of PFO causing cerebrovascular events. The main hypothesis of the potential mechanism of stroke caused by a PFO is paradoxical embolism of venous emboli to the arterial circulation. After the first description of paradoxical embolism by Cohnheim, there are multiple case reports of thrombi seen traversing a PFO on echocardiography.¹²⁻¹⁴ Additionally, there are reports from the operating room of thrombus directly visualized traversing a PFO, and thrombus has also been observed within PFOs in autopsies. An alternative hypothesis for the origin of these thrombi is *in situ* formation within the PFO.

Risk of stroke in patients with PFO. In one study of stroke-free patients in Northern Manhattan, in which the prevalence of PFO as detected by TTE was 15%, there was no significant difference in the incidence of

stroke on follow-up to 5 years between patients with and without a PFO. The annualized stroke rate was 1.22 per 100 person years in patients with PFO compared to 0.89 per 100 person years ($P=NS$) in those without a PFO.¹⁵ A smaller population study in a largely stroke-free population in Minnesota also demonstrated a similar incidence of cerebrovascular events with no difference between those with a PFO as detected by TEE and those without a PFO (annualized death/stroke/TIA rate, 1.4% vs 1.8%; $P=NS$).¹⁶ This study excluded patients younger than 45 years, who represent the very population at risk for PFO-related stroke.

In patients with a stroke who have a PFO, there is a much higher incidence of recurrent cerebrovascular events. In one small study, 33 patients with apparent PFO-related paradoxical embolism were followed for 18 months without medical or surgical therapy. The annualized 1-year recurrent event rate in this small group was found to be 16%.¹⁷ Konstantinides et al reported rates of stroke and death of 13% and 10%, respectively, among patients with pulmonary embolism and PFO versus 2.2% and 6.8%, respectively, when pulmonary embolism was not associated with PFO.¹⁸ Despite this, a number of subsequent prospective follow-up studies in patients with stroke have failed to demonstrate a significant increase in risk of recurrent stroke in patients with PFO compared to non-PFO controls.^{19,20} The PFO in Cryptogenic Stroke Study (PICSS) incorporated 603 patients with a recent (<30 days) ischemic stroke who were treated with either aspirin or warfarin and who underwent TEE; PFO was identified in 203 patients (33%). The 2-year incidence of recurrent stroke or death was 14.8% in the patients with a PFO and 15.4% in those without a PFO.¹⁹

Subgroups with increased risk. Atrial septal aneurysm is a hypermobile atrial septum extending at least 10 mm into the right or left atrium; it occurs in 2.2% of the general population and is associated with a PFO in 56% of cases.²¹ Concurrent PFO and atrial septal aneurysm have been suggested to be associated with a significantly higher risk of recurrent events.^{20,22} Mas et al studied 581 patients aged 18 to 55 years with ischemic stroke of unknown origin (treated with either aspirin or warfarin) and found that the risk of recurrent stroke over a 4-year period was 15.2% in patients with concurrent PFO and atrial septal aneurysm compared to 4.2% in patients with neither of these abnormalities.²⁰ Potential mechanisms for the increased risk of recurrent events with presence of both abnormalities include enhancement of preferential flow orientation from the inferior vena cava toward the PFO promoting paradoxical embolism,²²



(Courtesy of NMT Medical)

Figure 5. Healing of the Bio-Star device in an animal model (left: after implantation; center: after 90 days; right: after 1 year).

and *in situ* thrombi formation within the atrial septal aneurysm.²³ In the PICSS study, however, there was no demonstrable increased risk of recurrent event with PFO and atrial septal aneurysm, possibly related to older population compared to the other studies.¹⁹ Device closure of PFO associated with atrial septal aneurysm has been shown to have comparable success rates compared to device closure of PFO alone.²⁴

Thrombophilias, or hypercoagulable states, may potentially increase the risk of paradoxical embolism in patients with PFO and also complicate device closures by causing device thrombosis. Unfortunately, there are very limited data, with most large studies on medical treatments or PFO closures excluding patients with thrombophilias. In a small study by Giardini et al, 72 patients with PFO-associated systemic thrombotic events who were referred for transcatheter device closure were tested for thrombophilias. Thrombophilia was present in 28% of this population. Prior to device closure, 80% of patients with thrombophilia had >1 thromboembolic events compared to 10% of patients without thrombophilia ($P<.001$). After device closure of PFO, recurrent cerebroembolic events after 20 months of follow-up were 4%, with no significant difference between patients with thrombophilias and those without a thrombophilia.²⁵

Medical therapy for stroke associated with PFO. Medical therapies for patients with PFO who experienced a stroke include antiplatelet therapy with aspirin and possibly clopidogrel, or anticoagulant therapy with warfarin. A number of nonrandomized prospective follow-

up studies have suggested no benefit of anticoagulant therapy over antiplatelet therapy.²⁶⁻²⁹ The PICSS study is currently the only randomized controlled trial comparing aspirin to warfarin in medical treatment of PFO-associated stroke. PICSS randomized patients with stroke of all etiology to treatment with aspirin or warfarin. A subgroup that had a PFO diagnosed on TEE was found to have 2-year recurrent stroke and TIA rates that were similar between the warfarin and aspirin cohorts (16.5% vs 13.2%; $P=.65$).¹⁹ This is a high recurrent event rate, which suggests that either both aspirin and warfarin are equally effective, or that they are both ineffective.

Comparison of PFO closure with medical therapy in preventing stroke in patients with PFO. There are multiple nonrandomized trials suggesting a potential benefit in PFO closure in patients with cryptogenic stroke who have a PFO. A number of single-center, nonrandomized trials have compared medical therapy versus PFO closure by either percutaneous means (majority) or surgery.^{26,27,29,31,32} Most have reported at least a trend to lower cerebrovascular events after PFO closure. The largest of these trials by Windecker et al followed 308



(Courtesy of Gore & Associates)

Figure 6. The Gore Helix closure device (Gore & Associates, Flagstaff, AZ). The design creates a low profile for delivery.

(Courtesy of St. Jude Medical)

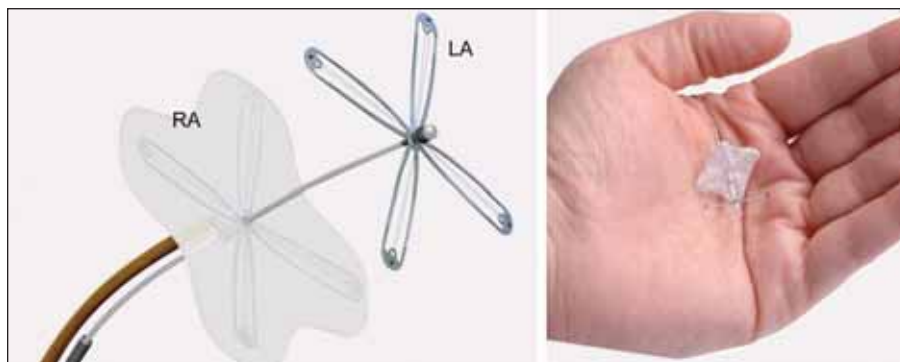


Figure 7. The St. Jude Premier device (St. Paul, MN). The LA element is designed to minimize the amount of material in the LA. The RA and LA elements are connected by a tether, the length of which can be adjusted to the tunnel length.

patients with cryptogenic stroke treated with either percutaneous closure ($n=150$) using a variety of devices or medical treatment ($n=158$; 50% on antiplatelet therapy and 50% on anticoagulant therapy).²⁶ At 4 years of follow-up, there was a trend to a lower incidence of recurrent cerebrovascular event (stroke or TIA) with PFO closure compared to medically treated patients (7.8% vs 22.2%; $P=.08$). This 4-year recurrent cerebrovascular event risk, however, was significantly lower in a cohort of 122 patients with complete closure of PFO at 6 months compared to medically treated patients (6.5% vs 22.2%; $P=.04$). The importance of complete PFO closure on potential efficacy of reducing recurrent cerebrovascular events also has been suggested by a number of other studies.^{27,29,32}

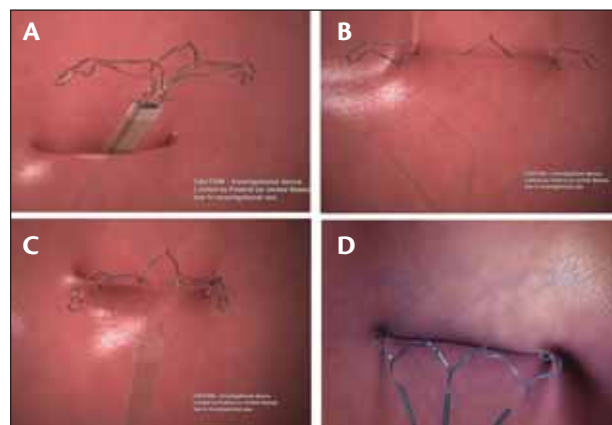
Retrospective reviews have pooled and compared data from multiple series reporting outcomes on either medical treatment or PFO closure in PFO-associated cryptogenic stroke.^{8,30} In one analysis, the annualized incidence of death, stroke, or TIA was 4.86 per 100 patient years from nine studies on medical treatment ($n=943$) and is significantly higher than 2.95 per 100 patient years from 12 studies on percutaneous PFO closure ($n=1,430$).⁸ These analyses are limited by inherent problems with analyzing nonrandomized data across different series with different patient cohorts. Many of the individual experiences in these analyses were completed using older devices. Despite their limitations, these aggregate data are compelling (Figure 1). It is frequently stated that there are no data to support PFO closure for prevention of stroke or TIA; there are no randomized data, but there are numerous published nonrandomized reports. The American Academy of Neurology has concluded that, in the absence of randomized trials, there is insufficient evidence to evaluate the efficacy of surgical or endovascular closure, and this

opinion reflects controversy regarding the indications for PFO closure after stroke or TIA.³³ Figure 1 summarizes nonrandomized data on several thousand patients, supporting a decrease in recurrent events by 40% to 60% from PFO device closure.^{8,30}

PFO AND MIGRAINE HEADACHE

A number of investigators have noted a link between migraine headache and PFO.

The frequency of PFO in the migraine population ranges from 40% to 60%, compared with 15% to 25% in the general population.³⁴⁻³⁸ It has also been observed that shunt-associated migraine responds favorably to atrial septal repair in patients treated with PFO closure for stroke.³⁹⁻⁴⁶ Anzola found a high rate of improvement in migraine during a 1-year period in migraine patients compared to control patients in a nonrandomized study, with a cure rate approaching 50% and an improvement rate of an additional half of the patients treated with PFO closure.³⁹ Subsequent investigators have made similar observations. In a review of six observational trials of PFO closure in patients treated for stroke or TIA, the proportion of patients with migraine improvement was 42%, and more



(Courtesy of Coherex Medical)

Figure 8. The Coherex flat stent (Coherex Medical, Salt Lake City, UT). The device sits within the PFO tunnel, leaving minimal foreign body exposed to the circulation. The stent is passed across the PFO, and the LA arms (called “moose horns”) are opened (A). The LA arms are pulled back to overlap the PFO rim on the LA side (B). The RA side of the stent is unsheathed (C). The delivery catheter is detached (D).

than half of patients reported complete resolution of their migraines.⁴⁷ These trials comprise almost 600 patients and had a mean follow-up generally longer than 1 year. The entire population of patients reviewed in those studies had a migraine prevalence of 35% in this stroke and TIA population.

These observations and retrospective studies led to a prospective, randomized trial of PFO closure versus sham procedure in a non-stroke migraine population.

The MIST trial randomized 73 patients through a sham arm and 74 patients to an implant arm, and then followed them for 1 year.⁴⁸ The primary endpoint to the trial (complete headache resolution) occurred in three patients in each group, and was thus nonsignificant. However, a reduction in headache burden, defined as the product of frequency and duration of headache, occurred in 37% of the implant patients and in only 17% of the sham closure patients ($P=.033$). A secondary endpoint was 50% reduction in migraine headache days, which occurred in 42% of the closure patients and in only 23% of the sham patients ($P<.05$). This 42% response rate in the treatment group is very similar to a response rate to many of the approved pharmacologic agents used for migraine therapy and twice the typical 20% to 25% placebo response rate in drug trials.

The nonrandomized observations in stroke patients undergoing PFO closure and the randomized data in the MIST trial have provided the impetus for a number of randomized larger trials in migraine headache populations without stroke in the US. Migraine patients with aura seem most likely to respond and will comprise the study group in these larger investigations. Trials have been planned using the NMT Medical, Inc. (CardioSeal/StarFlex), AGA Medical Corporation (Amplatzer PFO Occluder), St. Jude Medical, Inc. (Premier), and Intrasept (Cardia Inc., Eagan, MN) devices. Randomization is underway with some of these devices, and there will be an answer regarding the proportion of migraine patients who might respond to PFO closure. In addition, the studies are large enough to likely provide some insight into the character of migraine that might be most amenable to therapy.

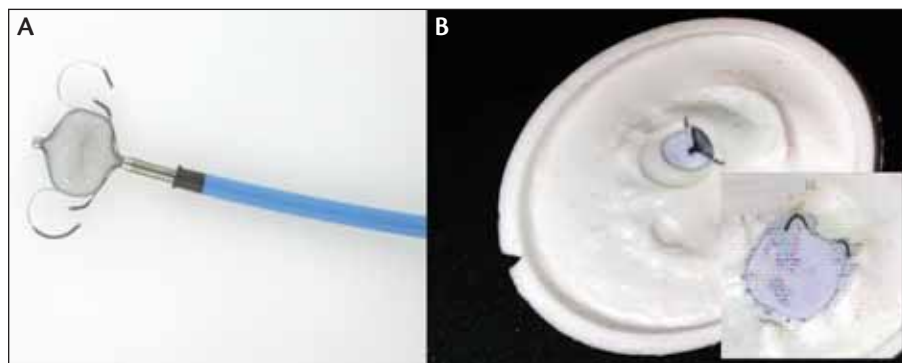


Figure 9. The Intra-tunnel device by NDC Inc. (a Johnson & Johnson company, Miami, FL). The device sits within the PFO tunnel, leaving minimal foreign body exposed to the circulation. The device attached to delivery system (A). In a model of the interatrial septum, the implanted device from an RA view, with the LA view in the inset (B).

(Courtesy of NDC, a Johnson & Johnson Company)

PERCUTANEOUS TRANSCATHETER DEVICE CLOSURE OF PFO

There has been great technological advancement and refinement of percutaneous techniques for PFO and atrial septal defect closure since the first description more than 30 years ago.^{49,50} The relative ease and efficacy of the currently used percutaneous approaches for PFO closure have caused a rapid adoption of these procedures.³⁰ The available PFO closure devices are implanted in a cardiac catheterization suite in an awake patient using local femoral anesthesia. The route of delivery is by femoral venous puncture. No arterial puncture is typically used, so the incidence of vascular complications is low. The procedures are guided by echocardiography. Although TEE has been commonly used during the early development of these approaches, intracardiac echocardiography, also delivered via femoral venous puncture, is now the standard in most catheterization laboratories. The procedure takes less than 1 hour and can be performed on an outpatient or 1-night stay basis. The dramatic change in the ability to achieve closure of these defects compared to surgical approaches via sternotomy or thoracotomy has created a great deal of interest among patients with PFO who seek closure.

The efficacy of the percutaneous approaches has been demonstrated in numerous trials. The vast majority (86%-100%) of defects are completely closed at the time of device implantation (Figure 2).⁵¹ Most of the remainder close as the devices are overgrown by tissue in the few months after implantation. Patients are typically treated with aspirin or aspirin and clopidogrel for 6 months after closure devices are implanted. Endocarditis prophylaxis is recommended for 6 months as well. Major complications occur in approximately 1.5% of

cases and include death, hemorrhage requiring transfusion, need for surgical intervention, cardiac tamponade, and erosion of the device through the free wall of the atria or aorta in rare cases with the AGA Amplatzer devices.³⁰ Device thromboses have been reported in 0% to 7% of cases, depending on the specific device. Device thrombosis has responded to therapy with warfarin or intravenous heparin, but a few cases have required surgical explantation.⁵²

Multiple devices have been designed and developed both in Europe and in the US. The most widely used devices in the US currently are the Amplatzer PFO Occluder from AGA Medical and the CardioSeal/StarFlex devices from NMT Medical (Figures 3-5).⁵³ A variety of new devices are under development. Variations on the double umbrella concept (Figures 6 and 7), modifications aimed at minimizing the amount of implant material, especially on the left atrial side (Figures 8 and 9), and bioabsorbable devices and nondevice or energy-based closure approaches are in various stages of design and trial evaluation. The HeartStitch device (Sutura Inc., Fountain Valley, CA) has been used in a preclinical model for suture-mediated PFO closure. Nondevice approaches include tissue welding with radiofrequency energy (Figure 10), which in pilot trials has been found to be effective in closing as many as 80% of PFO defects <10 mm in diameter.

The Food and Drug Administration (FDA) granted Humanitarian Device Exception (HDE) status to the CardioSeal device in 2000 and the Amplatzer PFO Occluder in 2002. Under this scheme, the devices are available for use under highly restrictive conditions that require that a patient experience a cerebral event despite medical treatment and a therapeutic international normalized ratio. The criterion for HDE requires

that the annual target population for use of the devices be 4,000 or less. In August 2006, upon review, the FDA and the manufactures involved have concluded that the patient population in the US, as described by the approved indication (patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy), is significantly in excess of 4,000 patients per year. This has led to a withdrawal of HDE status for both devices as of August 14, 2006. In a recent statement, the FDA has reaffirmed that results of randomized trials will be necessary for approval of these devices for use in prevention of recurrent stroke and TIA. Thus, the dedicated PFO occluder devices are only available in the US as part of a clinical trial or registry with strict entry restrictions. These require recurrent cerebral events while on medical therapy. Many practitioners, and certainly patients with PFO and stroke, do not wish to wait for a recurrent event prior to closure of the defect.

Currently, there are no completed randomized, controlled trials of primary or secondary prevention of cerebrovascular events with PFO closure compared to medical therapy. Randomized trials comparing device closure of PFO versus medical therapy are now enrolling patients. Recruitment for these trials has been slow. There are multiple factors contributing to the difficulty in enrolling in these trials; young patients with first strokes, especially when these first events are debilitating or accompanied by major neurologic deficits, are unwilling to wait for a second event before being treated, and physicians convinced by the existing body of nonrandomized evidence are biased toward device closure. "Off-label" use of devices for ventricular septal defect (VSD) or atrial septal defect (ASD) closure, which have been granted unrestricted FDA approval, is a

growing practice. The three possible devices currently used in this off-labeled fashion include the NMT VSD device (which differs from their PFO device only by catalogue number); the AGA Amplatzer ASD occluder and a recently approved Amplatzer Cribriform Septal occluder; and the Gore Helex ASD septal occluder device. An important consequence of these factors is the "shunting" of high-risk patients away from the randomized trials. This shunting creates a risk that the trials will randomize only lower-risk patients, and

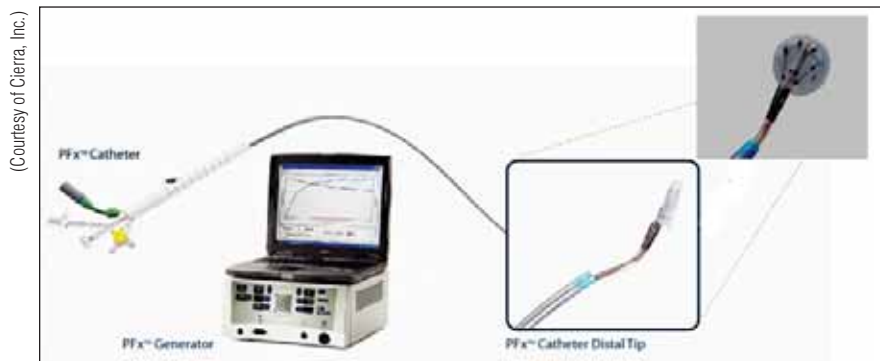


Figure 10. Radiofrequency device for PFO closure using tissue welding. The Cierra PFX closure system (Cierra, Inc., Redwood City, CA) is composed of a radiofrequency generator, a guide catheter, and a therapy catheter with a radiofrequency electrode. The electrode is applied to the septum with a vacuum. No device is left behind after PFO closure.

despite randomization, fail to adequately categorize the treatment effects of device closure versus medical therapy in this population.

CONCLUSION

There are multiple epidemiologic data suggesting a higher prevalence of PFO in patients with cryptogenic stroke and also in patients with migraine. Percutaneous closure is safe, and current nonrandomized trial data suggest it is associated with a reduced rate of recurrent stroke and TIA events in patients who present with first events. Observational data have shown an improved or cured migraine headache after PFO closure for stroke, and a single small, randomized trial has demonstrated reduced headache burden in patients with classic migraine without stroke. Large-scale randomized controlled trials are underway to evaluate the efficacy of PFO closure in secondary prevention of cerebrovascular events and also in improving migraines. A variety of new devices and nondevice PFO closure methods are under development. As noted by Homma et al, "as the complication rate from device implantation decreases and simpler devices are developed, the threshold for percutaneous closure is likely to decline."⁸ Improvement in device technology and a growing body of evidence to define patients who most benefit from the therapy are bringing this forecast to greater realization. ■

Gerald Yong, MBBS (Hons), FRACP, is from the Cardiology Division, Evanston Hospital, Evanston, Illinois. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Yong may be reached at (847) 570-2250; gyong@enh.org.

Michael H. Salinger, MD, FACC, FSCAI, is from the Cardiology Division, Evanston Hospital, Evanston, Illinois. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Salinger may be reached at (847) 570-2250; msalinger@enh.org.

Ted E. Feldman, MD, FACC, FSCAI, is from the Cardiology Division, Evanston Hospital, Evanston, Illinois. He has disclosed that he receives grant/research funding from St. Jude and is a paid consultant to Cordis. Dr. Feldman may be reached at (847) 570-2250; tfeldman@enh.org.

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