A Review of Transcatheter Closure of Patent Foramen Ovale

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ABSTRACT: A patent foramen ovale (PFO) is a common variant in cardiac anatomy found in 25% to 30% of U.S. adults. While PFOs are a normal part of fetal development and commonly seen in asymptomatic adults, they have been implicated in a variety of pathophysiologic conditions. The most clinically important of these is paradoxical embolization of venous thrombus resulting in stroke or systemic embolism. Various devices can be used to close PFOs via a transcatheter approach to prevent recurrent stroke. Data regarding the safety and effectiveness of these devices is rapidly evolving, with recent long-term results suggesting efficacy in preventing secondary stroke in carefully selected patients. This review discusses historical data on PFO occurrence and treatment, a risk score that can assess the likelihood of a stroke being attributable to a PFO, a variety of other conditions that may be linked to PFOs, and current research regarding the role transcatheter closure plays in their treatment.

INTRODUCTION

Patent foramen ovale (PFO) is a variant in cardiac anatomy found in up to 30% of adults[1] and often resulting in intracardiac shunt. A necessary part of normal fetal development, the PFO was first found to be associated with a higher rate of cryptogenic strokes in retrospective studies, especially in those with a history of complex migraines.[2] This, coupled with case reports of thrombus-in-transit crossing the septum through the PFO,[3,4] led some clinicians to postulate that percutaneous closure might prevent recurrent cryptogenic strokes. PFO closure for this indication has been evaluated in four randomized controlled trials, and in October 2016, efficacy data finally led to premarket approval by the U.S. Food and Drug Administration (FDA) for transcatheter PFO closure. Additionally, PFOs have been implicated in a variety of other conditions such as platypnea-orthodeoxia,[5] decompression illness,[6] and migraines,[7] and closure has been explored with varying degrees of success in the treatment of these conditions. This review discusses results of these studies, evaluation strategies for PFO and PFO closure, and additional indications for PFO closure.

CASE

A 34-year-old man presented for evaluation after his second stroke. His first cerebral infarction had occurred while traveling, and he had recovered with no residual deficits. No overt venous thromboembolic disease or hypercoagulable disorder had been identified. His evaluation at that time had revealed only a PFO detected by transesophageal echocardiogram (TEE) and transthoracic echocardiogram. The patient was otherwise healthy, with an active lifestyle and no atherosclerotic risk factors. As a result, he was enrolled 1 year later in the REDUCE Trial, a randomized study evaluating the efficacy of the GORE CARDIOFORM Septal Occluder (W. L. Gore & Associates) in PFO closure to prevent recurrent stroke. The patient was randomized to medical therapy, which consisted of full-dose aspirin.

Months after randomization, he presented with left hemiplegia, dysarthria, and facial droop and was treated emergently with systemic thrombolysis and successful transcatheter thrombus extraction. He recovered well with no residual deficits. Since he had met the trial end point of recurrent cerebral vascular embolism, he was offered compassionate off-label transcatheter PFO closure. After multidisciplinary evaluation and extensive discussion with the patient, he was taken to the catheterization lab to undergo closure of his PFO with a GORE CARDIOFORM Septal Occluder (Figure 1). He was placed on aspirin and clopidogrel for 1 month followed by aspirin alone thereafter. Repeat echocardiogram with bubble showed no evidence of residual shunt. Since that time, he has returned to his previous active lifestyle with no further events after more than 3 years of follow-up.

CRYPTOGENIC STROKE AND PFO

Stroke is a major cause of morbidity and mortality in the United States and throughout the world, with approximately 795,000 people experiencing new or recurrent cerebrovascular events each year.[8] Although prevention, diagnosis, and acute treatment have advanced significantly in the contemporary era, approximately 25% of strokes have no identifiable etiology[9]; thus, prevention of these so-called cryptogenic strokes remains elusive. Nevertheless, a number of potential etiologies–for example, paroxysmal atrial fibrillation, hypercoagulable states (genetic or acquired),[10] autoimmune or inflammatory

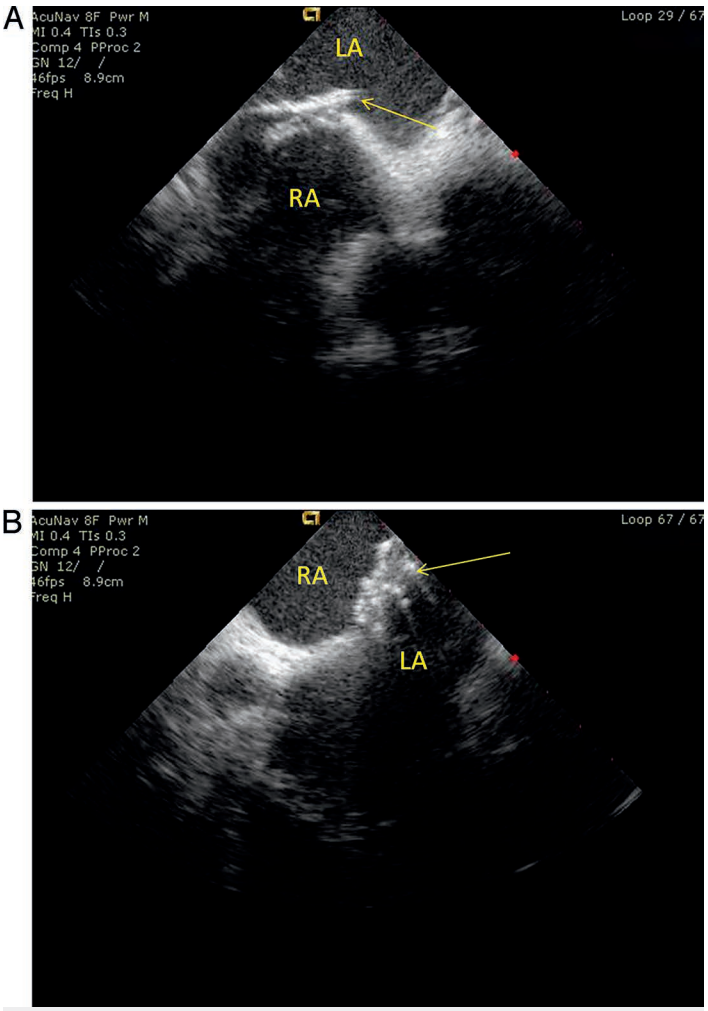

Figure 1.
Closure device delivery. Intracardiac echocardiography showing (A) a delivery catheter placed across the PFO and (B) the Gore Helex Septal Occluder (W. L. Gore & Associates, Inc.) in appropriate position within the interatrial septum, sealing the PFO. RA: right atrium; LA: left atrium

vasculitides, or aortic arch plaque—may be present yet difficult to detect in many of these cases.

Another potential etiology is paradoxical embolization of venous thrombus through intra- and extracardiac shunts, such as atrial septal defect, ventricular septal defect, pulmonary arteriovenous malformations, or PFO. The PFO is by far the most common of these, thought to occur in between 25% and 30% of adults; however, it is important to note that a PFO represents a normal variant anatomy rather than a true pathology. In the developing fetus, relatively oxygenated blood from the placenta is delivered to the fetus via the umbilical vein, which returns to the right atrium. The blood is thought to be diverted from the right atrium to left atrium preferentially via the Eustachian ridge through the foramen ovale. This prioritizes oxygen delivery to the ascending aorta and therefore the coronary arteries and cerebral circulation, whereas the patent ductus arteriosus diverts flow from the pulmonary arteries to the descending aorta.[11] After birth, the pulmonary vascular resistance falls, resulting in a rapid increase in pulmonary blood flow and left atrial volume and pressure; this in turn causes the flap-like foramen ovale to close and ultimately seal over with endocardial tissue in most individuals. However, in up to one-third of individuals, there remains a residual potential communication with a varying degree and direction of shunting.[1]

DIAGNOSIS/EVALUATION

Evaluation for right-to-left shunting through a PFO is typically performed using echocardiography (echo) to look for the early appearance of bubbles in the left atrium after agitated saline is injected through an intravenous catheter.[12] On transthoracic echo, bubbles appearing on or before the third cardiac cycle are highly suggestive of an intracardiac shunt, although anything less than six cycles may still be consistent with intracardiac shunt. Longer periods of time may be suggestive but are not definitively related to intrapulmonary or other noncardiac sources of shunting. Additionally, having the patient perform the Valsalva maneuver during agitated saline injection can increase sensitivity.[5] Transesophageal echo, which is considered the gold standard, can often allow for direct visualization of bubbles crossing the foramen ovale (Figure 2) as well as visualization of flap valve motion. It is important to note, however, that other sources of shunting can result in positive bubble studies. These include atrial septal defects (e.g., unroofed coronary sinus with persistent left-sided superior vena cava, ostium secundum, ostium primum, or sinus venosus), ventricular septal defect, and other congenital or acquired shunts.

While this residual shunt across a PFO is common in the general population, the prevalence may be up to 50% in those with true cryptogenic strokes as seen in observational studies.[2] Additionally, a number of case reports have demonstrated in vivo and postmortem "thrombus-in-transit," in which a thrombus is seen intact within the PFO itself (Figure 3).[3,4] Taken together, these observations are consistent with a syndrome of venous thrombus embolizing to the right atrium, through the PFO, and into the systemic circulation, causing cerebrovascular embolic infarct or other systemic embolic events. In this same manner, paradoxical embolism through a PFO is thought to contribute in part to these cryptogenic strokes.

Given the high prevalence of PFO in the general population and the fact that it is rarely possible to prove beyond doubt that a stroke was PFO related, risk stratification of patients

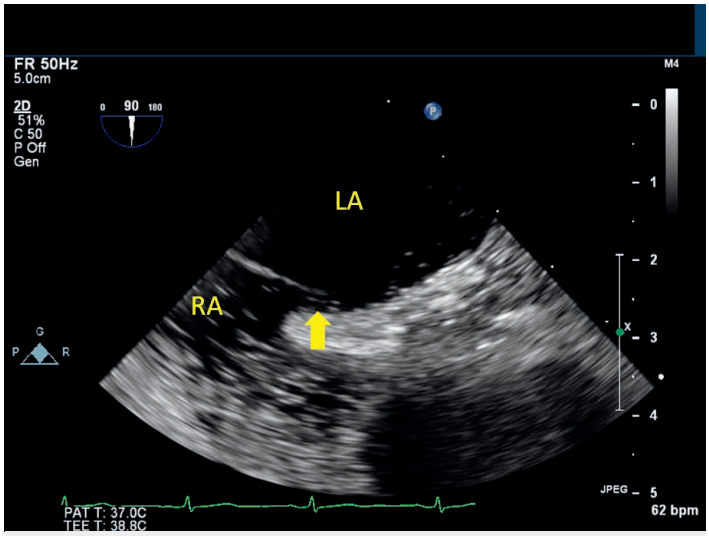

Figure 2.
Transesophageal echocardiogram (TEE) bubble study. Agitated saline bubbles directly visualized crossing the interatrial septum from right to left via a patent foramen ovale (arrow) using TEE in the bicaval view. LA: left atrium; RA: right atrium

with cryptogenic stroke and PFO is necessary. To that end, the Risk of Paradoxical Embolism (RoPE) score was developed based on pooled data from several cryptogenic stroke databases (Table 1). The RoPE score balances traditional vascular risk factors (diabetes, hypertension, smoking, prior stroke, or transient ischemic attack) against age and cortical infarct identified on imaging to estimate the probability that a cryptogenic stroke was attributable to PFO (Table 2).[13] The score was developed using 12 databases of patients suffering cryptogenic stroke to determine which ones were most likely to have a PFO. With this information and the probability of having a PFO in a control group, researchers used the Bayes' theorem to calculate how much of an individual's future stroke risk was attributable to having a PFO. The RoPE score can therefore be used to estimate the odds of a stroke being attributable to a PFO in a patient presenting with cryptogenic stroke. Of note, though patients with a high RoPE score have a higher probability of further PFO-attributable strokes than those with a low RoPE score, their overall risk of recurrent stroke is quite low (between 2% and 4% annually); however, they are more likely to have further cryptogenic events. To further stratify the benefit of PFO closure, more research is needed to determine which anatomical or patient characteristics could place patients with higher RoPE scores at increased risk of recurrent stroke.

PFO CLOSURE TRIALS

Whether transcatheter PFO closure reduces the risk of recurrent cryptogenic stroke has been the subject of three prospective clinical trials: CLOSURE I, RESPECT, and PC. In CLOSURE I, patients aged 18 to 60 years old with either a prior transient ischemic attack (TIA) or stroke and a PFO were randomized to PFO closure with a STARFlex device (NMT Medical) or to medical therapy with either aspirin, warfarin, or both at the discretion of the local trial physicians. The composite end point of CLOSURE I was stroke, TIA, or death from any cause within 30 days or from neurologic cause from 31 days to 2 years.[14] Although there was a trend toward benefit from closure, it did not meet statistical significance.

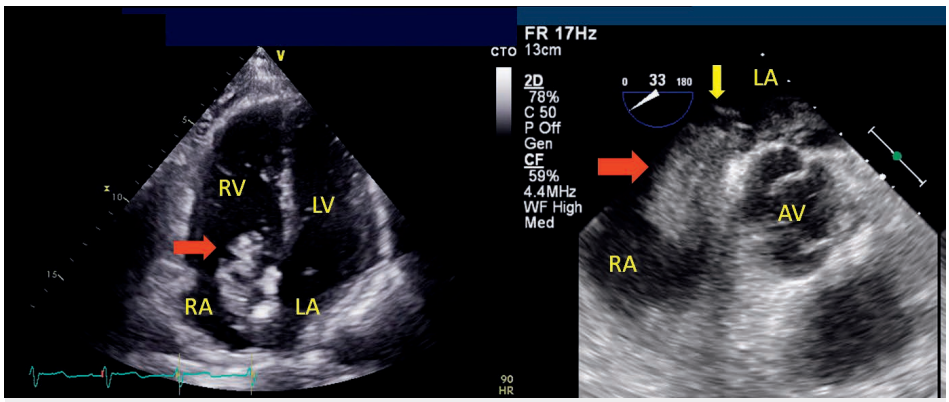

Figure 3.
Patent foramen ovale (PFO) with thrombus in transit. Intraoperative transesophageal echocardiogram showing a thrombus (red arrow) crossing the interatrial septum from right atrium (RA) to left atrium (LA) through a patent foramen ovale (yellow arrow). RV: right ventricle; LV: left ventricle; AV: aortic valve

This was followed by the PC trial,[15] in which patients aged 18 to 60 years with ischemic strokes, TIAs, or peripheral emboli and PFO were randomized to PFO closure with the AMPLATZERTM PFO Occluder device (St. Jude Medical) plus 1 to 6 months of dual antiplatelet therapy or to medical therapy with either aspirin or anticoagulation. In this trial, the composite end point was death, stroke, TIA, or systemic embolism. Again, there was a trend toward benefit from closure without achieving statistical significance.

Finally, the RESPECT trial enrolled subjects aged 18 to 60 years who had both a prior stroke and PFO. The end point in this trial was fatal stroke, stroke, or early death from any cause. In data presented at the Transcatheter

CHARACTERISTIC	POINTS
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or transient ischemic attack	+1
Nonsmoker	+1
Cortical infarct on imaging	+1
Age 18-29	+5
30-39	+4
40-49	+3
50-59	+2
60-69	+1
> 70	+0

Table 1.
Risk of Paradoxical Embolism calculator (RoPE). The above table shows the RoPE risk calculator for probability of paradoxical embolism as the etiology of cerebral infarction. The score ranges from 0 to 10, with higher scores indicating higher likelihood.[13]

ROPE SCORE	PFO PREVALENCE (%)	PFO ATTRIBUTABLE FRACTION (%)
0-3	23	0
4	35	38
5	34	34
6	47	62
7	54	72
8	67	84
9-10	73	88

Table 2.
Patent foramen ovale (PFO) attributable risk percentage.[13] RoPE: Risk of Paradoxical Embolism

Cardiovascular Therapeutics meeting in 2016, there was a 45% relative risk reduction in stroke at a mean follow-up of 5.9 years in the arm treated with transcatheter device closure.[16] The positive long-term data from RESPECT ultimately led to premarket FDA approval of the AMPLATZER PFO Occluder for prevention of recurrent stroke. A fourth trial, the REDUCE trial, is currently completing follow-up. In REDUCE, patients with imaging-confirmed stroke were randomized 2:1 to PFO closure using the Gore HELEX or CARDIOFORM septal occluder versus medical therapy (Figures 4, 5). The end point is recurrent ischemic stroke or imaging-confirmed TIA at 2 years, with data collection ending in February 2017. Further information is available at clinicaltrials.gov (Table 3).

In each of these trials, closure was compared to medical therapy,[14-16] which entailed either antithrombotic or anticoagulant therapy at the discretion of the treating physicians. Aspirin was the most commonly used antithrombotic therapy. A propensity-score–adjusted meta-analysis of 2,385 patients (1,582 in the antiplatelet group, 803 in the anticoagulant group) comparing

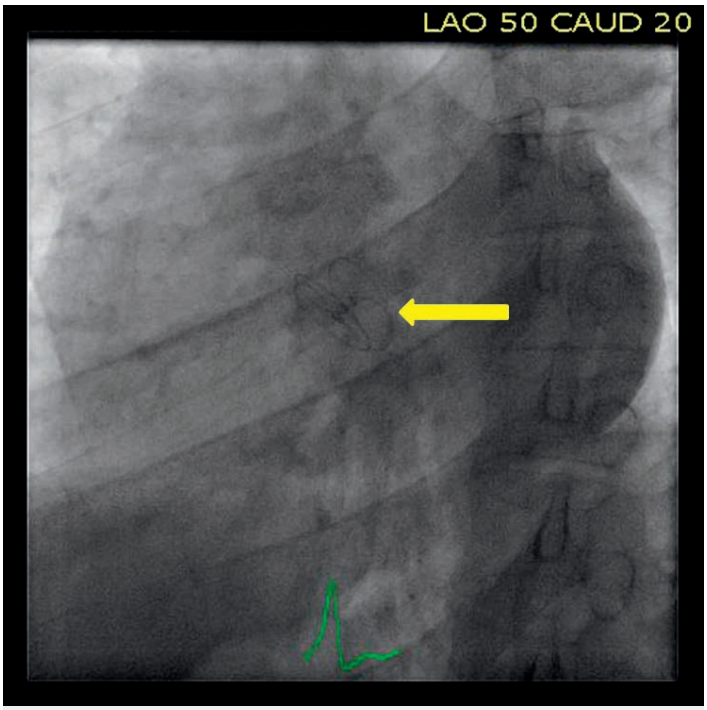

Figure 4.
This fluoroscopic image demonstrates the GORE CARDIOFORM Septal Occluder (yellow arrow) (W. L. Gore & Associates, Inc.) after deployment in the atrial septum.

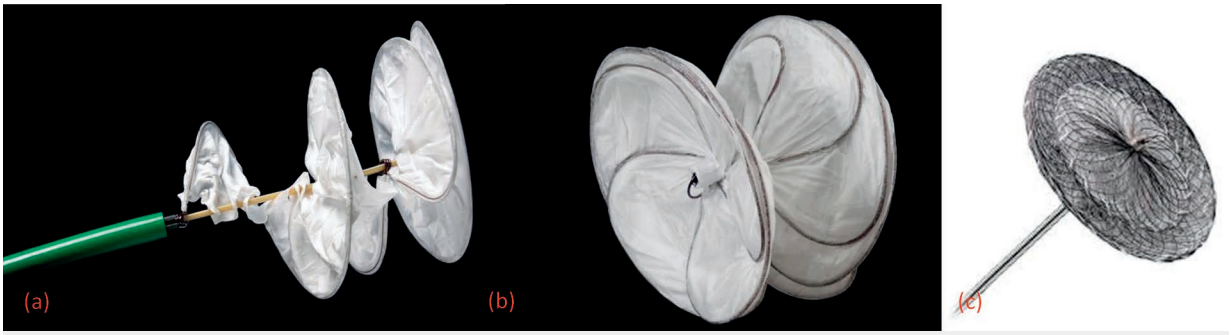

Figure 5.
Patent foramen ovale (PFO) occluder devices. This image shows (a) the GORE HELEX Septal Occluder (W. L. Gore & Associates, Inc.), (b) the GORE Cardioform Septal Occluder, and (c) the AMPLATZER PFO Occluder (St. Jude Medical).

antithrombotic to anticoagulant therapy found no significant difference between the two in a composite end point of stroke, TIA, or death, although warfarin conferred an increased risk of bleeding. Therefore, it seems that both are potentially appropriate treatments for secondary prevention.[17]

DEVICE SAFETY

In addition to demonstrated efficacy, procedural success in trials using the AMPLATZER device was greater than 95% across the RESPECT and PC trials; it may be even higher in clinical practice since this represented early experience for many of these centers.[14,15] Once in place, device erosion or embolization has been rare, with one series of 1,000 consecutive patients showing only two instances of either.[18] Device thrombosis is similarly rare when patients are placed on appropriate antithrombotic regimens after implant. Vascular access complications are seen in up to 3.2% of patients. Atrial fibrillation occurred two to five times more frequently in patients after device implantation than in those who received medical therapy[14-16] and was more common in the CLOSURE I study, which employed the StarFLEX device versus the AMPLATZER device used in PC and RESPECT. In the final RESPECT data, atrial fibrillation occurred 0.25% in 3,141 patient-years after

TRIAL	DEVICE	POPULATION	END POINT	OUTCOME
CLOSURE1	STARFlex PFO occluder	Cryptogenic TIA or stroke and PFO (ages 18-60)	Stroke, TIA, death from any cause at 30 days or neurologic cause 31 days to 2 years	HR 0.78 (CI 0.45-1.35), *P* = .37
PC TRIAL	AMPLATZER PFO occluder	Cryptogenic TIA, stroke, or systemic embolism and PFO (ages 18-60)	Death, TIA, stroke, or systemic embolism	HR 0.63 (CI 0.24-1.62), *P* = .34
RESPECT	AMPLATZER PFO occluder	Cryptogenic stroke and PFO (ages 18-60)	Fatal stroke, stroke, early death from any cause	HR 0.55 (CI 0.305-0.999), *P* = .046
REDUCE	Gore HELEX septal occluder and CARDIOFORM septal occluder	Cryptogenic stroke or imaging-confirmed TIA and PFO (ages 18-60)	Recurrent ischemic stroke or imaging-confirmed TIA	Ongoing

Table 3.
Comparison and results of the four major randomized trials evaluating closure of patent foramen ovale (PFO) for stroke prevention. TIA: transient ischemic attack

device implantation in contrast to 0.15% in 2,669 patient-years in patients treated with medical therapy ($P = .37$).[16]

CLOSURE TECHNIQUE AND CONSIDERATIONS

As noted above, transcatheter PFO closure can typically be done effectively with a low complication rate. The first step is to introduce a sheath into the common femoral vein. A bolus of heparin is given, and a catheter is advanced to the right atrium and across the PFO with guidance from a combination of fluoroscopic and either TEE or intracardiac echocardiography.[19] Use of a variety of catheters has been described, but a 7Fr Arrow wedge catheter (Teleflex Incorporated) works well—with the back end of a J wire shaped to create an MPA curve—and offers the ability to perform hemodynamic assessment at the time of the procedure. Next, an Amplatz Super Stiff Guidewire (Boston Scientific) can be placed into the left upper pulmonary vein through the catheter, which will act as a rail for positioning the delivery system. A sizing balloon (if needed to measure the length of the PFO tunnel) is advanced over the wire and across the defect and inflated with a diluted contrast mixture. The balloon is then exchanged for the delivery catheter, which is loaded with the appropriately sized device, and positioned across the PFO. The left atrial disk is deployed first, and the system is retracted until it is well apposed against the interatrial septum; the right atrial disk is then deployed. Stability and placement of the device is confirmed using both fluoroscopy and echocardiography while gently placing traction on the device prior to its release.

Although the procedure can generally be done safely and effectively, there are several anatomical characteristics that can add a layer of complexity. In so-called "tunnel PFOs," there is significant overlap of the ostium primum and secundum; this can lead to malposition and incomplete deployment of the right atrial disk because the linking segment between the disks has a fixed length.[20] In turn, a poorly seated device can lead to incomplete occlusion or increased risk of device embolization. Several techniques have been developed to deal with this. including balloon angioplasty (often using a peripheral balloon), balloon pull-through, "detunnelisation" with a sizing balloon, or transseptal puncture, in which the device is placed through the iatrogenic defect with the disks anchoring the septum together.[20-23] Lipomatous hypertrophy of the interatrial septum may cause a similar issue in which incomplete apposition of the disks lead to residual shunt or device embolization. Techniques using devices with longer waists such as VSD occluders have been described.[24] Several anatomic characteristics have been associated with residual shunting, including atrial septal aneurysm, large shunt degree, and large PFO size. Special care is required to ensure appropriate device sizing and placement in such cases.[25]

Surgical closure is an alternative for patients who are ineligible for percutaneous closure due to anatomic or patient-level characteristics or for patients with another indication for surgical intervention. The technique typically requires one or several sutures to tack the two layers of the interatrial septum together and eliminate the communication. The surgery is most commonly performed through a median sternotomy[26] and requires cardiopulmonary bypass with all the attendant risks. There is also a risk of postpericardiotomy syndrome and postoperative atrial fibrillation, and it typically involves a significantly longer recovery than transcatheter closure.[26] Additionally, very little data is available comparing surgical closure to medical therapy.

GUIDELINE RECOMMENDATIONS

After initial data from the CLOSURE I, PC, and RESPECT trials failed to demonstrate statistically significant efficacy by intention-to-treat analysis, the American Heart Association/ American Stroke Association made class III recommendations in 2014 for PFO closure to prevent stroke, level of evidence A. Importantly, the class III recommendation for this guideline was amended to state "available data does not support benefit for PFO closure" rather than the standard "recommend against" language.[27] Furthermore, the American Academy of Neurology (AAN) recommended against PFO closure for routine treatment of cryptogenic stroke outside of research settings unless episodes were recurrent without other clear etiology.[28] Since the October 2016 FDA approval of the AMPLATZER PFO Occluder for prevention of recurrent cryptogenic stroke based on the long-term RESPECT data, new guidelines have not been provided by either organization. At present, clinicians are left in the awkward position of either ignoring guidelines or denying a select group of patients access to a therapy that is of benefit to them based on the most recent clinical data. It remains to be seen how the AAN will respond to the most recent data and subsequent FDA device approval.

MISCELLANEOUS CLOSURE INDICATIONS

In addition to cerebrovascular events, PFO closure has been explored in the treatment of several other disease states or high-risk populations. For example, it is safe, effective, and typically resolves symptoms in patients with platypnea-orthodeoxia and documented right-to-left shunt across a PFO.[5,29]Additionally, patients with symptomatic decompression illness (DCI) are more likely to have PFOs,[6] and closure of these PFOs has been correlated with a decreased incidence of recurrence and a decrease in arterial bubbles.[30,31] Patients who have symptomatic DCI after diving within normal rates of ascent—especially those with neurologic sequelae—and a demonstrated PFO should be considered for device closure if they plan to continue diving

at deeper depths. Even in the setting of a PFO, diving at a depth of less than 30 m is very rarely associated with symptomatic DCI, so avoiding depths greater than 15 to 20 m is an alternative.[5]

Given the rarity of DCI, divers considering closure for this indication should likely be seen by a cardiologist experienced with both PFO closure and dive medicine.

PFO CLOSURE FOR MIGRAINE

People with severe migraines and aura have been shown to have an increased prevalence of PFO with right-to-left shunt.[7] Three randomized controlled trials—PRIMA, MIST, and PREMIUM—evaluated the effect of PFO closure on reducing migraine symptoms.[32] However, none of these trials met primary outcome, which was reduction in migraine-free days (PRIMA), migraine cessation (MIST), and 50% reduction in migraine days (PREMIUM). Both MIST and PREMIUM demonstrated a statistically significant reduction in migraine days per month on secondary analyses. Additionally, this reduction tended to be greater in patients who have auras associated with their migraines.[32] Whether or not the risk/benefits ratio favors invasive procedure and permanent intracardiac device implantation remains unclear. At this time, further studies are evaluating the role of closure in this condition.

CONCLUSION

The role of PFO closure in preventing recurrent cryptogenic stroke is rapidly evolving since the advent of the long-term RESPECT data. While risk stratification using the RoPE score calculator may provide some objective guidance, multidisciplinary evaluation by vascular neurologists and structural interventional cardiologists may be beneficial. Given the vast prevalence of PFO, further investigation is necessary to elucidate which populations and anatomic characteristics are associated with the greatest benefit from closure. PFO closure in patients with platypnea-orthodeoxia and decompression illness appears to be beneficial based on small case series and case reports; however, its role in migraine prevention remains unclear. Since many patients being treated with PFO closure devices are young, large multicenter long-term registries will be required to understand the effect of low-frequency adverse events.

KEY POINTS

- Patent foramen ovale (PFO) is a part of normal embryological development but remains persistently patent as a variant anatomy in up to 25% to 30% of the general population.
- Patent foramen ovale is commonly overrepresented in several disease states.
- Transcatheter closure of PFO to prevent stroke from paradoxical embolism can be safely done and offers benefit in people who are appropriately selected using tools such as the Risk of Paradoxical Embolism score.
- Transcatheter closure can be used successfully to treat other conditions in which PFOs play a role, including platypnea-orthodeoxia and decompression illness in divers.
- Patent foramen ovale with right-to-left shunt is seen more frequently in people suffering from migraines, especially when accompanied by aura. The role of transcatheter closure for this condition remains under investigation.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:
patent foramen ovale, intracardiac shunt, cryptogenic stroke, transcatheter PFO closure

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