MAYO CLINIC

Management of the Patient With Patent Foramen Ovale in 2021: A Spectrum of Cases

Guy S. Reeder, MD; Nathaniel W. Taggart, MD; and Naser M. Ammash, MD

Abstract

Patients with patent foramen ovale can manifest in a variety of ways. These presentations and their resolution are discussed in this article.

 ■ Mayo Clin Proc. 2021;96(5):1356-1362

From the Department of Cardiovascular Medicine (G.S.R., N.M.A.) and Division of Pediatric Cardiology (N.W.T.), Mayo Clinic, Rochester, MN; and the Sheikh Shakbout Medical City, Abu Dhabi, United Arab Emirates (N.M.A.)

Common presentations (Figure 1) and problems in patients with a patent foramen ovale (PFO) are presented in a case management format. The management decisions are those solely of the authors. References are provided when available, and knowledge gaps are identified.

CASE 1

An asymptomatic 27-year-old male patient undergoes transthoracic echocardiography because of a history of hypertrophic cardiomyopathy in a first-degree relative. The echocardiogram shows no evidence of hypertrophic cardiomyopathy, but there is a PFO with bidirectional shunt noted by color imaging. Peripheral vein agitated saline injection (bubble study; Figure 2) shows right-to-left shunt. Should anything further be done regarding these findings?

Longitudinal population-based studies have shown no evidence of an increased risk of stroke or embolism in asymptomatic patients found to have a PFO as an incidental finding. Accordingly, there is no recommendation for treatment with anticoagulant or antiplatelet agents, or consideration of device closure.[1,2] The patient could be counseled about venous thrombosis prevention by staying well hydrated and avoiding prolonged periods of immobilization.

CASE 2

A 37-year-old healthy woman developed sudden onset of aphasia and right hemiparesis after prolonged air travel. Brain imaging showed defects consistent with an embolic process. Her symptoms resolved after intravenous tissue plasminogen activator (tPA). Lower-extremity duplex examination demonstrated evidence of a subclinical deep vein thrombosis. Extensive neurologic workup including magnetic resonance angiography of the extracranial circulation, venous thrombophilia testing, and 30-day ambulatory cardiac monitoring all demonstrated no abnormalities. The patient was taking estrogen-containing oral contraceptive. Transesophageal echocardiography (TEE) demonstrated a PFO with atrial septal aneurysm and a small right-to-left shunt at rest on bubble study, which became large during a Valsalva maneuver. The study results were otherwise normal. How should this patient be managed?

This patient with unexplained ischemic stroke most likely had paradoxical embolization of a thrombus through the PFO. This presumptive diagnosis is supported by the presence of deep vein thrombosis on duplex scanning, the "high-risk" finding of atrial septal aneurysm, and the lack of demonstration of other potential causes of stroke in an otherwise healthy young patient.[3] Suggested testing for PFO device closure is shown in Table 1.

Recent randomized trials of PFO device closure versus antiplatelet therapy have demonstrated the superiority of device closure for prevention of recurrent stroke after a first event in patients under the age of 60 who had undergone a comprehensive assessment for more common causes of stroke, such as atherosclerotic disease involving the cervical vessels, spontaneous arterial dissection, and

Mayo Clin Proc. ■ May 2021;96(5):1356-1362 ■ https://doi.org/10.1016/j.mayocp.2020.12.018
www.mayoclinicproceedings.org ■

overt or subclinical atrial fibrillation as detected on cardiac monitoring.[4-7] In a recent meta-analysis comparing device closure of PFO versus antiplatelet therapy, the absolute reduction in the incidence of recurrent stroke was 8.7% over 5 years of follow-up (10% vs 1.3%).[8]

The US Food and Drug Administration has approved 2 devices for closure of PFO: the Amplatzer PFO occluder and the Gore Cardioform septal occluder (Figure 3A-C). Risks of device closure are low, with less than a 1% chance of serious procedural complication in experienced centers, such as stroke, myocardial infarction, or cardiac tamponade, and less than a 2% long-term risk of persistent atrial fibrillation.[8]

Guideline recommendations published in 2020 by the American Academy of Neurology recommend device closure of PFO over antiplatelet therapy for secondary prevention of recurrent stroke, in carefully evaluated patients without another demonstrated stroke etiology.[9] This recommendation has been endorsed by the Society for Cardiac Angiography and Intervention, American Heart Association, and American Stroke Association.

This patient underwent device closure as an outpatient procedure and returned to work 3 days later. She has had no complications and no recurrence of neurologic symptoms.

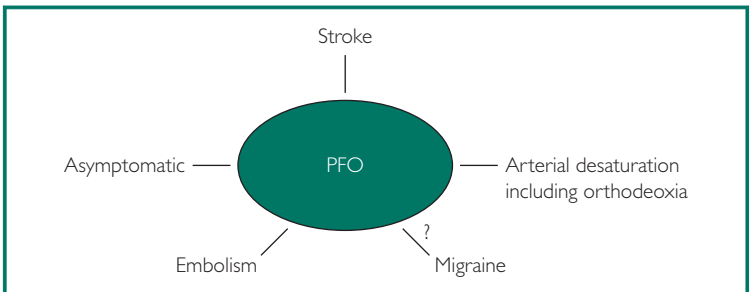

FIGURE 1. While the majority of individuals with PFO have no symptoms, a variety of complications related to PFO may occur. PFO, patent foramen ovale.

CASE 3

A 26-year-old man with transient left-sided weakness had a transthoracic echocardiogram as part of an evaluation for possible source of embolism. This demonstrated a right-to-left shunt by bubble study, but the exact location of the shunt could not be determined. Subsequently, TEE showed no evidence of intracardiac or intrapulmonary shunting (Figure 4). What is the explanation for this discrepancy?

The patient required heavy intravenous sedation for TEE because of a prominent gag reflex. He was unable to perform a satisfactory Valsalva maneuver during the TEE, and his PFO and related atrial level shunt went undetected. Later the same day, he underwent a repeated transthoracic bubble study that showed a large right-to-left atrial shunt after Valsalva release (Figure 5). Intracardiac echocardiography performed at the time of PFO device closure, confirmed the presence of a large PFO.

Intravenous sedation interferes with adequate performance of the Valsalva maneuver in some patients,[10] and it can cause a false-negative TEE examination result for right-to-left shunting. For patients referred to our echocardiographic laboratory, we perform transthoracic bubble study before sedation for a TEE examination, to improve the sensitivity of detecting a PFO with shunting. In all patients undergoing TEE bubble study for possible right-to-left shunting, it is important to localize the exact

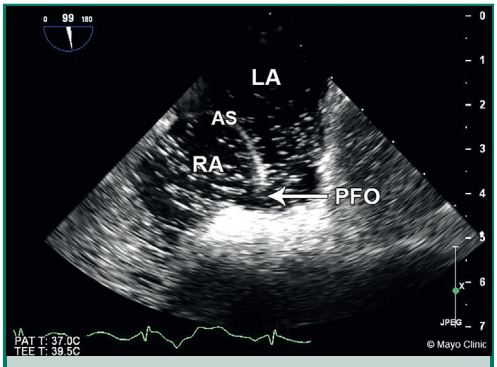

FIGURE 2. Bubble study demonstrating right-to-left shunt on an transesophageal echocardiogram. Microbubbles have crossed from RA to LA, indicating right-to-left shunt across a PFO. AS, atrial septum; LA, left atrium; PFO, patent foramen ovale; RA, right atrium.

TABLE 1. Patent Foramen Ovale Closure for Unexplained Stroke

The following are required:

- Ischemic (embolic) stroke etiology confirmed by neurology consultation/imaging
- PFO with right-to-left shunting documented by echocardiography bubble study
- Absence of other cardiac embolic sources (eg, PFE, LAA thrombus)
- Negative venous thrombophilia screen including lupus anticoagulant and anticardiolipin antibodies
- MRA or CT angiogram of the extracranial arterial circulation negative for embolic source including dissection
- Cardiac rhythm monitoring (30-120 days) negative for atrial fibrillation

CT, computed tomography; LAA, left atrial appendage; MRA, magnetic resonance angiography; PFE, papillary fibroelastoma; PFO, patent foramen ovale.

location of the shunt. If microbubbles appear in the left atrium but cannot be seen crossing the atrial septum (through a PFO or atrial septal defect), then careful examination of pulmonary veins must be performed to detect an intrapulmonary shunt—for example, owing to pulmonary arteriovenous malformation.

CASE 4

A 57-year-old man presented to the General Cardiology Clinic with a complaint of intermittent dyspnea. There was no history of cardiac disease. He had a history of farmer's lung, but no recent pulmonary symptoms. His physical examination was unrevealing. When asked more specifically to describe his symptoms, he noted that they could occur at any time, and that he had learned that by walking around or otherwise exercising for a few minutes, his dyspnea would often improve. His symptoms had been attributed to farmer's lung.

Evaluation in the pulmonary function laboratory demonstrated resting hypoxemia with an O_2 saturation of 97% in supine position and as low as 84% in the sitting and standing positions. There was no correction with nasal cannula oxygen at 2, 4, and 6 L/min. However, after the patient had walked on a treadmill for a few minutes while breathing room air, his oxygen saturation increased to 96% (Table 2). What is the explanation for these findings?

Echocardiography demonstrated a PFO with intermittent right-to-left shunting that increased in the upright position, as demonstrated by bubble study injections. Pulse oximetry confirmed normal supine arterial O_2 saturation with a fall in saturation in the upright position. Grade 1 left ventricular diastolic dysfunction was also noted. A diagnosis of platypnea-orthodeoxia was made, and he subsequently underwent uncomplicated device closure of a large PFO. His symptoms and the associated intermittent arterial desaturation resolved.

The finding of resting arterial desaturation that improves with exercise is unusual. We hypothesized that at rest in the upright position, right atrial pressure was higher than the left atrial pressure for some portion

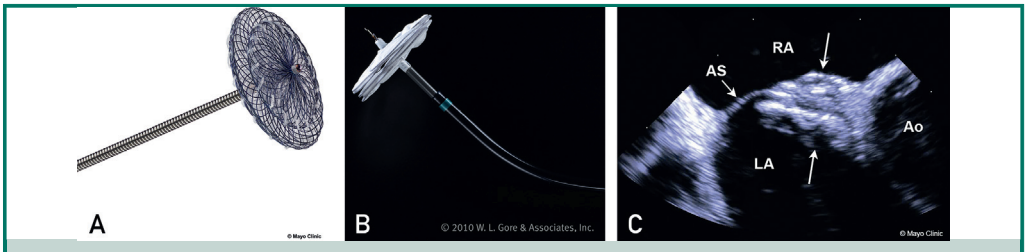

FIGURE 3. (A) Amplatzer PFO occluder. (B) Gore cardioform septal occluder. (C) Intracardiac echocardiogram showing Gore cardioform septal occluder after deployment. Arrows indicate the septal occluder device. Ao, aortic; AS, atrial septum; LA, left atrium; PFO, patent foramen ovale; RA, right atrium.

Mayo Clin Proc. ■ May 2021;96(5):1356-1362 ■ https://doi.org/10.1016/j.mayocp.2020.12.018
www.mayoclinicproceedings.org

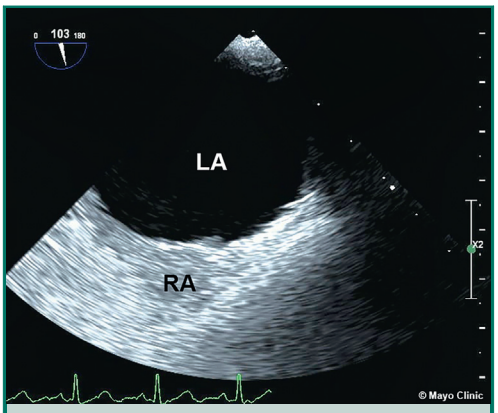

FIGURE 4. Transesophageal echocardiogram, bubble study case 3. No microbubbles seen in LA, indicating no right-to-left shunting present. LA, left atrium; RA, right atrium.

of the cardiac cycle, perhaps related to abnormal pulmonary resistance from the patient's pre-existing lung disease. Right-to-left shunting would occur at this time. With exercise, the left atrial pressure increased because of left ventricular diastolic dysfunction, thus reducing or eliminating the right-to-left shunting by increasing the left-to-right atrial pressure gradient. As a result, symptoms and desaturation would diminish with exercise. PFO device closure is an effective treatment for patients with platypnea-orthodeoxia, and most will have prompt resolution of symptoms after device placement.[11] Arterial blood gases and shunt studies in different body positions are key to diagnosing this treatable condition.

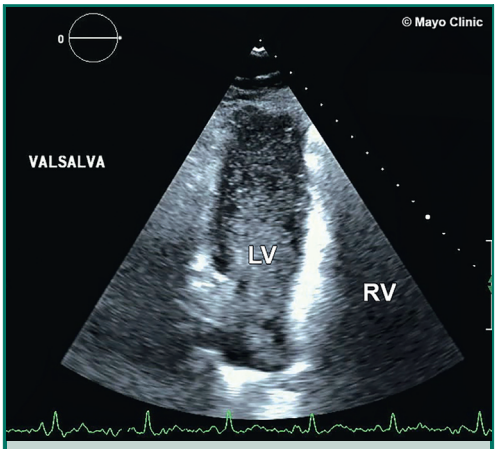

FIGURE 5. Transthoracic echocardiogram, bubble study case 3. Large number of microbubbles in LV, indicate large right-to-left shunt is present. LV, left ventricle; RV, right ventricle.

CASE 5

A 63-year-old woman was referred for consideration of PFO device closure because of progressive exertional dyspnea and an abnormal echocardiogram. The echocardiogram demonstrated a PFO with no shunting at rest, but a large right-to-left shunt induced with Valsalva release. Grade 1 diastolic filling abnormality was also present. An exercise test showed limiting dyspnea at about 6 METs of activity, and this was accompanied by arterial desaturation as measured by fingertip pulse oximetry. There was no evidence of ischemia on imaging. It was believed that the PFO could be contributing to the patient's exertional dyspnea, and the patient was referred for consideration of device closure. How should this patient be managed?

A second upright exercise test was performed using a forehead pulse oximeter. This test did not show any arterial desaturation despite reproduction of the patient's symptoms of breathlessness. Again, there was no indication of myocardial ischemia. Subsequently, right heart catheterization with supine bicycle exercise was performed; it reproduced the patient's symptoms of dyspnea and was characteristic of heart failure with preserved ejection fraction. The resting pulmonary capillary wedge pressure of 14 mm Hg increased to 28 mm Hg at peak exercise, with reproduction of severe dyspnea. At this time, arterial O_2 saturation measured by oximetry and blood gas analysis was 96%. This patient's symptoms were due to heart failure with preserved ejection fraction. The Valsalva-induced right-to-left shunt appeared to be an incidental finding, and PFO device closure was not recommended. The arterial desaturation during initial exercise testing was not duplicated with forehead oximetry and was attributed to poor contact of the fingertip probe. This has also been noted in patients with Raynaud disease. The significance of inducible right-to-left

TABLE 2. Oxygen Titration Study From Case 4 Demonstrating Arterial Desaturation Unresponsive to Oxygen, Self-Correcting With Exercise

Inspired gas	Activity	Time (min)	SpO_2 (%)	Heart rate (beats/min)
Room air	Rest	7.0	87	58
4 L/min	Rest	2.0	86	91
6 L/min oxymizer	Rest	3.0	87	85
8 L/min oxymizer	Rest	2.0	84	92
Room air	2.5 mph, 4.5% grade	3.0	97	109
Room air	2.5 mph, 6% grade	2.0	96	114
Room air	2.5 mph, 7.5% grade	3.0	96	116
Total exercise time		16		

shunting in patients with dyspnea and arterial desaturation has been evaluated in small numbers of patients.[12,13] PFO closure may be appropriate if other causes of arterial desaturation are carefully excluded. In patients with dyspnea, PFO and inducible right-to-left shunt, but without arterial desaturation at rest or with exercise, PFO closure is not of proven benefit. However, this subset of patients has not been systematically studied. Many of these patients might have an alternative explanation for dyspnea, as did the patient in this case.

CASE 6

A 70-year-old man is scheduled to undergo dual-chamber pacemaker implantation for symptomatic bradycardia. He has a known asymptomatic PFO previously documented by echocardiography. His referring physician questions whether the PFO should be closed to prevent the possibility of right-to-left embolization of potential pacemaker thrombus in the future. What should you tell her?

The data here are discordant. In one study of patients with intracardiac device leads, those who had a documented PFO showed a higher incidence of stroke compared with those who did not have a PFO documented.[14] In a separate case control series of patients, all of whom had PFO, the presence of intracardiac device leads did not confer an additional risk of stroke. In fact, most strokes could be related to the occurrence of atrial fibrillation in this latter population.[15]

PFO closure was not recommended in this patient. On the other hand, for patients with obvious device lead thrombus or vegetations, and large right-to-left shunt through a PFO, device closure of PFO or anticoagulation therapy should be considered. PFO closure can be especially important in those undergoing device lead extraction, to prevent paradoxical embolization. In younger patients with genetically mediated malignant arrhythmias and PFO requiring lifelong implantable cardioverter defibrillator for sudden death prevention, shared decision making would be recommended to address the concerns raised regarding the potential for paradoxical embolism over ensuing decades.

CASE 7

A 24-year-old medical student plans to take sport scuba diving lessons. She has just finished the cardiovascular physiology section and questions whether she should have an echocardiogram to rule out a PFO as a risk for decompression illness during her dives. What is the appropriate response?

Screening for PFO is not currently recommended to reduce the chance of decompression illness for sport scuba divers.[16] Decompression illness is extremely uncommon, under 0.1% in the overall population of sport divers, and it is unlikely to be reduced further by routine PFO closure. In all patients, safe scuba diving behavior is recommended to prevent decompression illness. On the other hand, in commercial divers, or those with prior episodes of decompression illness, examination for and

Mayo Clin Proc. ■ May 2021;96(5):1356-1362 ■ https://doi.org/10.1016/j.mayocp.2020.12.018
www.mayoclinicproceedings.org

closure of PFO may be indicated. In a registry of divers with a history of decompression illness and documented PFO, closure of PFO eliminated recurrent episodes of decompression illness, whereas those not closed had a continuing risk of future events.[17]

CASE 8

A 36-year-old woman with frequent migraines has been found to have PFO on an echocardiogram. Should PFO closure be considered to reduce the occurrence of her migraines?

The prevalence of PFO is 20%-25% in the general population; the prevalence of migraine is approximately 12%. Thus, a large number of individuals will have both conditions by chance alone. The transatrial passage of vasoactive substances, such as serotonin or microemboli that are normally filtered by the lungs, into the brain circulation has been proposed as a cause of migraine attack, and observational studies have suggested a benefit of PFO closure among migraineurs. Three prospective randomized trials have examined this question.[18-20] None met their primary endpoints for efficacy. The most recent of these, the Premium trial,[20] was double blinded and sham controlled. The primary endpoint was defined as a 50% reduction in migraine attacks. This endpoint was not met. However, individuals randomized to the treatment arm did experience a reduction in headache days per month (about 1.4 fewer) and were more likely to have complete remission of migraine (8.5% vs. 1%). In a nonprespecified subgroup analysis of patients having predominantly migraine with aura, there was a statistically significant reduction in headache frequency. Of note, the placebo response rate was 31% in the sham treatment group, indicating a strong placebo effect of the procedure. PFO closure was not recommended for this individual. Further investigations into the potential relationship of migraine and PFO are underway.

CONCLUSION

PFO is common, with a prevalence in the general population of approximately 20%-25%. PFO closure is indicated in carefully selected patients with otherwise unexplained stroke after a comprehensive evaluation performed by a dedicated team of cerebrovascular and cardiovascular specialists or well documented platypnea-orthodeoxia. Though closure is most commonly performed through a percutaneous approach, there may be a role for surgical closure, often semi-robotic, in select patients with other coexisting cardiac defects or anatomy unsuitable for device placement.

In the absence of arterial desaturation, otherwise unexplained dyspnea is unlikely to be improved by PFO device closure, but this question needs more study. For most patients undergoing pacemaker implantation, sport divers, or those with migraine, there are currently no guideline indications for routine PFO closure. An individualized approach incorporating expert advice and shared decision making will be needed in some patients.

Abbreviations and Acronyms: **PFO** = patent foramen ovale; **TEE** = transesophageal echocardiogram; **tPA** = tissue plasminogen activator

Potential Competing Interests: The authors report not competing interests.

Correspondence: Guy S. Reeder, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (reeder.guy@mayo.edu).

REFERENCES

1. Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: Innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol*. 2006;47(2):440-445.
2. Petty GW, Khandheria BK, Meissner I, et al. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc*. 2006;81(5):602-608.
3. Elgendy AY, Saver JL, Amin Z, et al. Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale—associated stroke. *JAMA Neurol*. 2020;77(7):878-886.
4. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: The DEFENSE-PFO Trial. *J Am Coll Cardiol*. 2018;71(20):2335-2342.
5. Mas J-L, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med*. 2017;377(11):1011-1021.
6. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. 2017;377(11):1022-1032.
7. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2017;377(11):1033-1042.

8. Mir H, Siemieniuk RAC, Ge L, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: A systematic review and network meta-analysis incorporating complementary external evidence. *BMJ Open*. 2018;8(7):e023761.
9. Messé SR, Gronseth GS, Kent DM, et al. Practice advisory update summary: Patent foramen ovale and secondary stroke prevention. *Neurology*. 2020;94(20):876-885.
10. Thanigaraj S, Valika A, Zajarias A, Lasala JM, Perez JE. Comparison of transthoracic versus transesophageal echocardiography for detection of right-to-left atrial shunting using agitated saline contrast. *Am J Cardiol*. 2005;96(7):1007-1010.
11. Tobis JM, Abudayyeh I. Platypnea-orthodeoxia syndrome: An overlooked cause of hypoxemia. *JACC Cardiovasc Interv*. 2016;9(18):1939-1940.
12. Fenster BE, Nguyen BH, Buckner JK, Freeman AM, Carroll JD. Effectiveness of percutaneous closure of patent foramen ovale for hypoxemia. *Am J Cardiol*. 2013;112(8):1258-1262.
13. Mojadidi MK, Ruiz JC, Chertoff J, et al. Patent foramen ovale and hypoxemia. *Cardiol Rev*. 2019;27(1):34-40.
14. DeSimone Christopher V, Friedman Paul A, Noheria A, et al. Stroke or transient ischemic attack in patients with transvenous pacemaker or defibrillator and echocardiographically detected patent foramen ovale. *Circulation*. 2013;128(13):1433-1441.
15. Poddar KL, Nagarajan V, Krishnaswamy A, et al. Risk of Cerebrovascular events in patients with patent foramen ovale and intracardiac devices. *JACC Cardiovasc Interv*. 2014;7(11):1221-1226.
16. Sykes O, Clark JE. Patent foramen ovale and scuba diving: A practical guide for physicians on when to refer for screening. *Extrem Physiol Med*. 2013;2(1):10.
17. Honěk J, Šrámek M, Honěk T, et al. Patent foramen ovale closure is effective in divers: Long-term results from the DIVE-PFO Registry. *J Am Coll Cardiol*. 2020;76(9):1149-1150.
18. Dowson A, Mullen Michael J, Peatfield R, et al. Migraine intervention with STARFlex Technology (MIST) Trial. *Circulation*. 2008;117(11):1397-1404.
19. Mattle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. *Eur Heart J*. 2016;37(26):2029-2036.
20. Tobis JM, Charles A, Silberstein SD, et al. Percutaneous closure of patent foramen ovale in patients with migraine: The PREMIUM Trial. *J Am Coll Cardiol*. 2017;70(22):2766-2774.