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Some Practical Points About Patent Foramen Ovale Conditions that May Not Be Covered in the Rest of the Book

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KEYWORDS

• Patent foramen ovale • Stroke • Migraine • Altitude sickness

KEY POINTS

- The gold standard for diagnosing a patent foramen ovale (PFO) should be a right heart catheterization with proof that a guidewire or catheter has traversed the atrial septum.
- The PFO-Associated Stroke Causal Likelihood (PASCAL) classification system should be used by neurologists to determine whether the PFO is likely to be causally related to the stroke or an “innocent association.”
- “PFO Associated Stroke” is now considered a separate entity as a cause of stroke, which should facilitate the workup and treatment option for this condition.

INTRODUCTION

The exploration of patent foramen ovale (PFO) as a pathway for multiple disease states has been one of the more fascinating advances in cardiology over the last 25 years. This compendium of articles will describe some of the major clinical conditions and issues surrounding the study of PFO. The authors who wrote these chapters are some of the leading experts in this field. They deserve much credit for helping us understand the sometimes subtle mechanisms associated with PFO. It is our hope that this collection of articles will help educate neurologists and cardiologists who deal with PFO-associated clinical states such as stroke of otherwise unknown etiology, migraine with aura, decompression illness, altitude sickness, and hypoxemia out of proportion to underlying pulmonary disease. We hope that these chapters provide useful information for clinicians, helping them understand some of the nuances of PFO diagnosis, and treatment options for PFO-related conditions.

As with all doctors, I first learned about PFO in medical school embryology and anatomy and then revisited it as a cardiology fellow to understand fetal physiology. But I only learned that a PFO could cause pathologic states when I heard a lecture by Jim Locke, from Boston Children’s Hospital, at the American College of Cardiology meeting around 1998. I was fascinated that a common cardiac structure was only now being associated with stroke in young otherwise healthy individuals. I was hooked by Jim’s magnetic delivery and wanted to get involved in this field to understand it better. In 2001, I was visited by Rudy Davis at University of California, Los Angeles (UCLA), who was working on the development of the CardioSeal device by NMT Medical (Boston, MA). The technology advanced significantly with the Amplatzer PFO occluder (Abbott; Chicago, IL) developed by Kurt Amplatz. Subsequent technological improvements were made by W.L. Gore & Associates (Newark, DE) with the Helix and then the Cardioform devices. Instead of being

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a rare entity, I have seen over 1200 patients with PFO-associated conditions that are described in this book. The fact that patients like these were not identified prior to the 1990s provides a lesson in the history of medical science. It was only with new diagnostic tools such as modern echocardiography, equipped with harmonic imaging and transesophageal echo with injection of contrast that these right-to-left shunts were more readily identified in vivo.

Cryptogenic Stroke Versus Patent Foramen Ovale-associated Stroke: What Is in a Name?

One of the benefits of the isolation imposed by the coronavirus-19 pandemic was that it permitted the virtual convening of a working group of cardiologists and neurologists who were involved in PFO research. The purpose of this group was to recognize the advances that have been made over the last 20 years in identifying the causality of PFO related to many strokes of otherwise unknown etiology. Instead of calling these “cryptogenic strokes,” the group felt confident that there were enough data to assign this category of stroke as “PFO associated stroke.”¹ The nomenclature change is important because it recognizes that a PFO can be pathologically involved as a pathway for stroke, rather than an uncertain consideration when all other causes are ruled out. In addition, naming PFO as a subcategory of stroke has helped to formalize the workup and evaluation of these patients. At UCLA, the stroke neurologists are usually the physicians who first see these patients and evaluate them with a transcranial Doppler (TCD), because this is the most sensitive screening method to identify right-to-left shunt. If that is positive, they obtain a transesophageal echocardiogram (TEE) to identify if there are high-risk aspects of the PFO such as an atrial septal aneurysm. The TCD also quantitates the shunt severity. This information, together with the clinical evaluation, has led to the PASCAL classification which helps to stratify the likelihood that the stroke was due to the PFO pathway.²

Pearls and Pitfalls: Some Practical Points About Patent Foramen Ovale

Although autopsy studies demonstrate a probe patent or larger PFO in 35% of cases, I define a clinically significant right-to-left shunt as a grade 3 or larger shunt on a TCD study. This degree of shunting on TCD corresponds to a moderate size (≥ 6 mm) PFO by balloon sizing during cardiac catheterization. In our control population of 200 unselected people referred to the cardiac catheterization laboratory (excluding known congenital

heart disease or transplant patients), we found this degree of shunting in 20% of subjects. PFO is thus the most common form of congenital heart lesion. There are data to suggest that PFO is hereditary, although it is not a direct autosomal dominant inheritance (Tobis, Gevorgian, and West, unpublished data from UCLA). In a study of 154 patients from 50 families, the incidence of PFO was 63% among first-degree relatives.

A foramen ovale is essential for fetal survival because the amount of oxygen delivered through the placenta is only 67% saturated. If this degree of desaturated blood, coming from the placental veins to the inferior vena cava, was to be pumped through the nonfunctioning fetal lungs, the blood would lose more oxygen and there would be insufficient oxygen delivery for fetal survival. The PFO permits placental blood to pass directly across the atrial septum and enter the arterial circulation. This mechanism is so important that it is preserved throughout evolution. All mammals must have a PFO.

Echocardiographic Bubble Studies and the Best Way to Diagnose a Patent Foramen Ovale

One consideration that is frustrating about this field is the disconnect between echocardiographic assessment of right-to-left shunts and what is observed in the catheterization laboratory. The echocardiography literature is replete with studies comparing transthoracic echocardiography (TTE) with TEE or even TCD. The literature considers TEE to be the gold standard. But the TTE and TEE assessment of the severity of the shunt or the size of the PFO is often misleading when compared to balloon sizing measurements made in the catheterization laboratory.³⁻⁸ The echo report may say that the PFO size is small, with the implication that the PFO would be too small to permit a thrombus to pass through and cause the patient’s stroke. But during cardiac catheterization, the PFO may be an average size (7 mm) or larger. In support of this observation, a pooled analysis of 2 clinical trials of “high-risk” PFO closure for stroke (ie, studies that only closed PFOs of stroke patients with a large shunt or atrial septal aneurysm) found that although an atrial septal aneurysm was a significant predictor of recurrent stroke, a large shunt by echocardiography was not.⁹ I believe that these studies are likely incorrectly categorizing some patients’ PFOs as “small” based on echocardiography data alone.

A similar mistake occurs for the echocardiographic assessment of the timing of agitated saline bubbles arriving to the left atrium. Contrary to most echocardiographic literature statements, delayed arrival does not mean that there is a pulmonary

arterial-venous malformation (AVM) shunt. It may take time for the bubbles to fill the superior aspect of the right atrium near the fossa ovalis and the PFO does not open up in every cardiac cycle. In our experience with over 2000 TCD examinations, a PFO was present 99% of the time in cases where there was a significant shunt (TCD \geq grade 3) versus 1% for a pulmonary AVM. If a patient has hereditary hemorrhagic telangiectasia, then the incidence of pulmonary AVM is 30%, but these cases are infrequent.¹⁰ I would caution physicians who are interested in this field to be skeptical of the echocardiographic data that does not compare the frequency of finding a PFO with evidence based on a right heart catheterization (ie, ability to pass a guidewire across the atrial septum), which should be the correct in vivo gold standard for PFO diagnosis. I hope that the echocardiographic societies will reassess their guideline statements, as TEE (the current accepted gold standard by echocardiographic societies) can miss or misdiagnose a PFO in 10% of cases.⁷

Patent Foramen Ovale-Associated Stroke

Other chapters will focus on the randomized clinical trials which demonstrated that PFO closure is preferable to medical therapy for prevention of recurrent strokes. I will limit my comments to some curious incidental observations about PFO-associated stroke. Based on the number of ischemic strokes of unknown origin and the frequency of PFO in the population, it is estimated that the risk of a PFO-associated stroke is approximately 1 in 1000 patients with a PFO per year. In patients who present with PFO-associated stroke, the recurrence rate increases 10-fold to 1% per year on medical therapy. The longest clinical trials followed patients for 10 years and the repeat incidence of stroke was 10% in the medically treated arm.¹¹ It is likely that these patients self-select for those who have an increased likelihood of developing venous thrombosis, presumably from varicose veins or hemorrhoids.

Some of the patients have a predisposition to form a venous thrombus, usually from a congenital abnormality in the clotting cascade. But the predominant form of thrombophilia is acquired, with the use of estrogen-containing compounds either for birth control or hormone replacement therapy.¹² In one of our series, 50% of women who had a PFO-associated stroke were on estrogen therapy at the time of their event.¹³ These patients stopped the exogenous estrogen but were randomized in the clinical trials. We do not know what the recurrence rate of stroke would be in someone who stops their estrogen administration.

It is possible that these patients would have a much lower chance of recurrent stroke once estrogen therapy is stopped. If so, their inclusion in the randomized clinical trials would make the recurrence rate much lower in the medical treatment arm and would have diminished the apparent effectiveness of the device arm.

Migraine and Stroke

Another fascinating area is the connection between migraine headaches and stroke. In one study of 1200 ischemic stroke patients, among those who had a stroke of unknown origin, the frequency of PFO was 60%. Of patients who had a stroke of unknown etiology and migraine with frequent aura, the frequency of PFO was 93%.¹⁴ When I was in medical school, the teaching was that the increased frequency of stroke in people with migraine was because migraine was due to transient intense vasoconstriction of the cerebral arteries. The blood vessels then dilated, which caused the throbbing sensation of a migraine. The belief was that if vasoconstriction was strong enough, it would cause the ischemic stroke seen in migraineurs. This theory of migraine is now superseded by experimental data, showing that migraine aura is associated with cortical spreading depolarization. In laboratory studies on transgenic mice that are given the gene for human migraine with hemiplegia, it has been demonstrated that a migraine starts with vasodilation and is then followed by mild vasoconstriction. But the degree of vasoconstriction is about 20% diameter reduction, which is not enough to cause an ischemic brain infarct. The current theory is that migraine is due to a complex interaction within several cortical centers that stimulate nociceptive fibers and receptors responsible for the cephalgia. Migraine is no longer thought of as a "vascular headache," but rather a complex central nervous system event with allodynia.¹⁵

What is the connection then between migraine and stroke? We believe that stroke is more prevalent in migraineurs because migraine is the clinical manifestation that a large PFO is likely to be present. Fifty percent of people with migraine with aura have a PFO.¹⁶ The PFO conduit permits some vasoactive substance (perhaps serotonin) to bypass metabolism in the lungs and enter the cerebral circulation to trigger a migraine in susceptible people. The migraine identifies those people who are likely to have a PFO pathway, which later in life could permit a venous thrombus to also enter the cerebral circulation. In those migraineurs who also take estrogen compounds, the risk of stroke is even higher because they now have a stimulant

for venous thrombosis as well as the PFO pathway to the brain. These considerations have led to the following 2 hypotheses. I believe these to be correct based on my observations and I hope that they will be tested someday in a prospective clinical trial.

- Almost all strokes that occur in young patients with migraine are caused by a paradoxical embolus through a PFO. Migraines do not cause stroke from intense vasospasm; they are the clinical clue that a PFO may be present. Corollary: the increased risk of stroke in migraineurs who take estrogen is due to the more likely presence of a PFO in migraineurs.
- Almost all strokes that occur in young women who take birth control pills are caused by a paradoxical embolus through a PFO. Estrogen does not cause arterial cerebral thrombosis, but rather, predisposes to venous thrombosis which then embolizes through the PFO pathway.

Patent Foramen Ovale and Altitude Sickness

The most enjoyable research project with which I have been involved in my 40 years of academic medicine was our study evaluating the connection between a right-to-left shunt through a PFO and the susceptibility to altitude sickness. This project is described more completely in “[OKPFO and Acute Mountain Sickness](#)”. Briefly, to recruit patients who hiked at high altitude, an associate and I backpacked to 12,000 feet on the Mount Whitney trail in the Sierra Nevada, California and stayed at Trail Camp for 1 week. We recruited individuals hiking over Mount Whitney from Whitney Portal in 1 or 2 days and hikers who had acclimated and crossed the John Muir Trail before they climbed Mount Whitney and then exited at Whitney portal. Subjects were referred to the South Inyo Hospital in Lone Pine at the base of the mountain, which graciously permitted us to obtain questionnaires and perform TCD bubble studies in a side room. Hikers who completed the study were given a \$25 gift card to spend at the local pizza and beer restaurant in Lone Pine. What ravenously hungry hiker would scoff at that opportunity? We enrolled 137 subjects. The study demonstrated that 63% of hikers who complained of altitude sickness symptoms had a right-to-left shunt.¹⁷ As the oxygen saturation decreases with increasing altitude, hikers with an inherent PFO would be more likely to have right-to-left shunting and desaturate even further than those without a PFO. Anyone attempting to climb Mount Everest or similar heights may wish to consider obtaining a TCD before their ascent ([Figs. 1 and 2](#)).



Fig. 1. Brian West, MD (*left*), Pooya Banankhah, MD (*middle*), and Bashar Al Hemyari, MD (*right*) at Whitney Portal to recruit hikers before or after their ascent to Mount Whitney.

Platypnea–Orthodeoxia and Patent Foramen Ovale

Another fascinating condition associated with PFO is unexpected profound hypoxemia, often with sudden onset such as following surgery, in people who have dilatation or uncoiling of the aorta or other thoracic abnormalities such as pulmonary lobectomy or hemidiaphragm paralysis. These people have no dyspnea and normal arterial saturation when they lie supine but become short of breath and desaturate to 75% to 85% oxygen saturation as soon as they stand up. It is often difficult to make this diagnosis unless you are thinking about it in your differential for hypoxemia out of proportion to the amount of pulmonary disease (if any), but the patients are completely relieved of their orthodeoxia and shortness of breath after the PFO is closed.^{18,19} Using TEE, we have demonstrated that the PFO height between the septum primum



Fig. 2. Jonathan Tobis recruiting hikers along the John Muir Trail at 12,000' Trail Camp.

and secundum is wider in the upright position when compared with the supine position (Tobis and Yang, unpublished data).

Sleep Apnea and Patent Foramen Ovale

Another area of significant clinical hypoxemia that is associated with PFO is in people who have sleep apnea. PFO occurs in a higher frequency of patients who have obstructive sleep apnea. In one study of 100 patients with sleep apnea, the frequency of PFO was 43% versus the control population of 200 individuals where the incidence of PFO was 20% ($P < .02$).²⁰ There are other reports of sleep apnea patients with a PFO who have significant improvement in their hypoxemia and clinical symptoms of sleep apnea after their PFO is closed.²¹ This topic should be addressed in a prospective randomized double-blinded clinical trial of PFO closure in patients who have sleep apnea with a PFO.

Coronary Artery Spasm and Patent Foramen Ovale

A last topic that I would like to touch upon is a recently described syndrome of severe chest pain plus migraine (usually with aura), in women who have a PFO. I have seen 10 patients like this, which is a rare occurrence for people with PFO, but we have documented angiographic evidence of coronary artery spasm with an abnormal response to intracoronary acetylcholine. These women have recurrent episodes of severe angina-like chest pain which can occur intermittently over several years. This condition is not benign; two of the patients had an episode of ventricular fibrillation associated with severe chest pain from which they were resuscitated. All had a PFO and in those 7 who had their PFO closed, both chest pain and migraine symptoms resolved.²² We believe that there is some vasoactive substance which normally gets detoxified in passage through the pulmonary circulation, but when exposed to the arterial blood in high concentration, can induce coronary spasm and/or migraine in susceptible individuals. It is my hope that those researchers who are currently studying Ischemia with Non Obstructive Coronary Arteries (INOCA) (myocardial ischemia with no obstructive coronary arteries) will also assess the frequency of PFO in this unusual population of coronary spasm or microvascular ischemia (Figs. 3 and 4).

Complications of Patent Foramen Ovale Closure

With improved occluder devices available today and techniques standardized, the complication

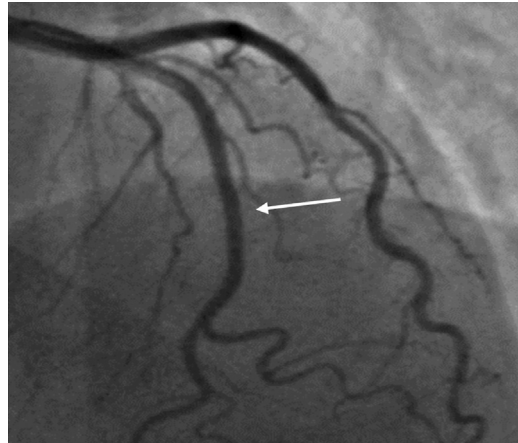


Fig. 3. Baseline coronary angiogram in a 68 year old woman with angina symptoms at rest, migraines, and a PFO. The *white arrow* identifies the Left Anterior Descending artery.

rate of percutaneous PFO closure should be close to zero, making it the safest therapeutic interventional cardiology procedure. Bleeding from the femoral vein can be reduced by placing a Perclose suture prior to insertion of the 11-French sheath. However, there are 2 complications that are worthy of comment.

Atrial Fibrillation Following Patent Foramen Ovale Closure

There is an increased incidence of new-onset atrial fibrillation (AF) after a closure device is placed across the atrial septum. It is believed that this is due to the pressure applied to the interatrial tissue and the presence of a foreign body in the heart. Post-closure AF appears to be relatively benign

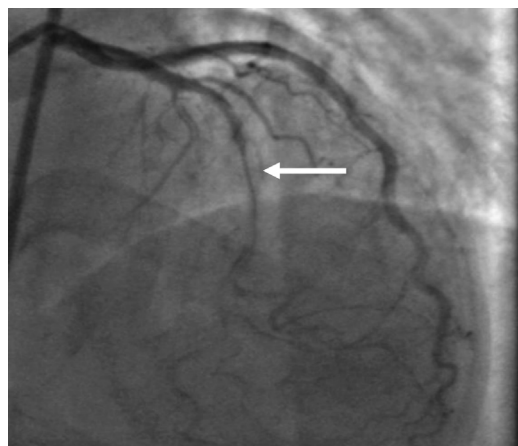


Fig. 4. Intense left anterior descending artery spasm after intracoronary administration of 100 µg acetylcholine. The *white arrow* identifies the same location as in the baseline picture.

and usually does not need long-term anticoagulation since it is not associated with recurrent stroke. However, the symptoms of tachycardia and chest thumping are uncomfortable for the patient and produces anxiety unless they are forewarned of this possibility. To prevent thrombus forming in the left atrium, I treat post-closure AF with short-term apixaban and amiodarone for 6 to 8 weeks. There is no standard therapy and other operators have a variety of approaches. The good news is that the AF is intermittent and transient, always resolving spontaneously. Onset of AF is typically 10 to 14 days post-device closure and it dissipates within 1 month of onset. In our series of 445 patients, older age was not a predictor of developing AF, but male sex was.²³ The REDUCE trial also found male sex to be an independent predictor of postprocedural AF in patients who underwent closure with either Gore Cardioform or Helex devices (OR = 3.45, $P < .01$).²⁴ The rate of AF is approximately 4% with the Amplatzer PFO device but is 16% for the Cardioform occluder, presumably due to greater pressure exerted on the septum with the Gore device. The trade-off is that the complete closure rate with the Cardioform device is 98%, whereas the Amplatzer PFO device has a 15% incidence of residual shunting.²⁵

Need for Surgical Removal of the Device

The second potential complication with PFO closure is significant, but fortunately rare. About 1 in 500 cases develop some complication with the device or the patient has such severe chest pain that surgical removal is required. The mechanism appears slightly different for the 2 major devices. The Amplatzer device seems to leach more nickel from the nitinol wires. Since 12% of people are allergic to nickel, it should be expected that some might react to this product.²⁶ In a survey of close to 14,000 cases around the world, the reported need for surgical removal was 0.2% for either the Amplatzer or the Cardioform device.²⁷ The Amplatzer atrial septal defect (ASD) or PFO device can erode the atrial wall and the Cardioform nitinol wires may fracture and rarely, perforate the heart causing hemopericardium.²⁸ This low risk appears justified if the indication for closure was to prevent recurrent stroke. However, if closure for migraine is approved by the Food and Drug Administration, then we will be placing these devices in younger patients. There is still room for clever bioengineers to develop devices that are as effective as the current ones, but without the need for any surgical removal.

We hope you enjoy reading the chapters presented in this edition of Clinics in Cardiology that

explore the broad clinical spectrum of this residual embryologic cardiac defect called PFO.

CLINICS CARE POINTS

- The echocardiographic criteria for the diagnosis and sizing of a patent foramen ovale (PFO) need to be updated by the appropriate society's guideline committees. Echocardiography underestimates the size of a PFO and the statement on the echo reports that there is "a small PFO" should not be interpreted as "this PFO is too small to cause a stroke."
- Similarly, the late appearance of bubbles in the left atrium does not mean that there is a transpulmonary shunt or pulmonary arteriovenous malformation; 99 times out of 100, late bubbles are due to a PFO.
- I believe that the following hypotheses will eventually be proven to be correct:

Hypothesis #1

Almost all strokes that occur in young patients with migraine are caused by a paradoxical embolus through a PFO. Migraines do not cause stroke from intense vasospasm; they are the clinical clue that a PFO may be present.

Corollary: the increased risk of stroke in migraineurs who take estrogen is due to the more likely presence of a PFO in migraineurs.

- Hypothesis #2

Almost all strokes that occur in young women who take birth control pills are caused by a paradoxical embolus through a PFO. Estrogen does not cause arterial cerebral thrombosis, but rather, predisposes to venous thrombosis which then embolizes through the PFO pathway.

- Unexplained hypoxemia, especially after surgery, may be due to severe right-to-left shunting through a PFO. The clinician has to consider this possibility and then look for it with the appropriate test of an agitated saline bubble study, of which a transcranial Doppler is the most sensitive test and therefore the preferred screening modality.
- Angina with No Obstructive Coronary Arteries (ANOCA) with documented coronary artery spasm may be associated with a PFO. The right-to-left shunt of vasoactive substances may precipitate coronary artery spasm in susceptible people. Unless one looks for the right-to-left shunt, you will never know if it is there and that it could be causally related.

DISCLOSURE

Dr J.M. Tobis is a consultant and proctor for WL Gore, Inc.

REFERENCES

1. Elgendy A, Saver J, Tobis JM, et al. Proposal for updated nomenclature and classification of potential Causative mechanism in patent foramen ovale-associated stroke. *JAMA Neurol* 2020;77(7):878–86.
2. Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment Effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA* 2021;326(22).
3. Mahmoud AN, Elgendy IY, Agarwal N, et al. Identification and Quantification of patent foramen ovale-Mediated shunts: echocardiography and transcranial Doppler. *Interv Cardiol Clin* 2017;6(4):495–504.
4. Mojadidi MK, Mahmoud AN, Elgendy IY, et al. Transesophageal echocardiography for the detection of patent foramen ovale. *J Am Soc Echocardiogr* 2017;30(9):933–4.
5. Mojadidi MK, Zhang L, Chugh Y, et al. Transcranial Doppler: does addition of blood to agitated saline Affect Sensitivity for Detecting cardiac right-to-left shunt? *Echocardiography* 2016;33(8):1219–27.
6. Mojadidi MK, Winoker JS, Roberts SC, et al. Accuracy of Conventional transthoracic echocardiography for the diagnosis of Intracardiac right-to-left shunt: a meta-analysis of prospective studies. *Echocardiography* 2014;31(9):1036–48.
7. Mojadidi MK, Bogush N, Caceres JD, et al. Diagnostic accuracy of transesophageal echocardiogram for the detection of patent foramen ovale: a meta-analysis. *Echocardiography* 2014;31(6):752–8.
8. Gevorgyan R, Perlowski A, Shenoda M, et al. Sensitivity of Brachial versus femoral vein injection of agitated saline to Detect right-to-left shunts with transcranial Doppler. *Catheter Cardiovasc Interv* 2014. <https://doi.org/10.1002/ccd.25391>.
9. Turc G, Lee J-Y, Brochet E, et al, on behalf of the CLOSE and DEFENSE-PFO Trial Investigators. Atrial aneurysm, ShuntSize, and recurrent stroke risk in patients with patent foramen ovale. *J Am Coll Cardiol* 2020;75(18):2312–20.
10. Kijima Y, Gevorgyan R, McWilliams JP, et al. Usefulness of transcranial Doppler for Detecting pulmonary Arteriovenous malformations in hereditary hemorrhagic telangiectasia. *Am J Cardiology* 2016;117(7):1180–4.
11. Saver JL, Carroll JD, Thaler DE, et al. For the RESPECT Investigators* long-term Outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377.
12. Greep NC, Liebeskind DS, Gevorgyan R, et al. Association of ischemic stroke, hormone therapy, and right to left shunt in Postmenopausal women. *Catheter Cardiovasc Interv* 2014;84(3):479–85.
13. Subrata Kar DO, Nabil Nouredin MD, Jamil Aboulhosn MD, et al. Percutaneous closure of patent foramen ovale or atrial septal defect in the presence of thrombophilia. *Journal of Structural Heart Disease* 2017;3(5):135–40.
14. West BH, Nouredin N, Mamzhi Y, et al. Frequency of patent foramen ovale and migraine in patients with cryptogenic stroke. *Stroke* 2018;49(5):1123–8.
15. Charles A, Hansen J. Migraine aura: new ideas about cause, classification, and clinical significance. *Curr Opin Neurol* 2015;28(3):255–60.
16. Anzola G. Potential Source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 1999;52(8):1622–5.
17. West BH, Fleming RG, Al Hemyari B, et al. Relation of patent foramen ovale to Acute mountain sickness. *Am J Cardiol* 2019;123(12):2022–5.
18. Tobis JM, Abudayyeh I. Platypnea-orthodeoxia syndrome: an Overlooked cause of hypoxemia. *JACC Cardiovasc Interv* 2016;9(18):1939–40.
19. Mojadidi MK, Gevorgyan R, Nouredin N, et al. The effect of patent foramen ovale closure in patients with platypnea-orthodeoxia syndrome. *Catheter Cardiovasc Interv* 2015;86(4):701–7.
20. Mojadidi MK, Bokhoor PI, Gevorgyan R, et al. Sleep apnea in patients with and without a right-to-left shunt. *J. Clin Sleep Medicine* 2015;11(11):1299–304.
21. White JM, Veale AG, Ruygrok PN. Patent foramen ovale closure in the treatment of obstructive sleep apnea. *J Invasive Cardiol* 2013;25:E169–71.
22. Ravi D, Parikh R, Aboulhosn J, Tobis JM. A new syndrome of patent foramen ovale inducing Vaso-spastic angina and migraine. *JACC Case Reports* 2023;28:102132.
23. Incidence of Atrial Fibrillation or Arrhythmias After Patent Foramen Ovale Closure Keeley Ravellette, Jeff Gornbein, Jonathan M. Tobis; *JSCAI* 2023.
24. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or Antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033–42.
25. Matsumura K, Gevorgyan R, Mangels D, et al. Comparison of residual shunt rates in five devices used to treat patent foramen ovale. *Catheter Cardiovasc Interv* 2014;84(3):455–63.
26. Brett Wertman MD, Babak Azarbal MD, Marc Riedl MD, et al. Adverse events associated with nickel Allergy in patients Undergoing percutaneous ASD or PFO closure. *J Am Coll Cardiol* 2006;47(6):1226–7.
27. Verma SK, Tobis JM. Explantation of PFO closure devices: a Multicenter survey. *JACC Cardiovasc Interv* 2011;4(5):579–85.
28. Kumar P, Orford J, Tobis JM. Two cases of pericardial tamponade due to nitinol wire fracture of a gore septal occluder. *Catheter Cardiovasc Interv* 2019;1–6.